ORIGINAL ARTICLE

VISFATIN AS A BIOMARKER FOR EARLY DETECTION OF GESTATIONAL DIABETES MELLITUS

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Background: The increased levels of visfatin in response to slowly developing resistance to insulin and impairment of glucose metabolism in human body is a well-documented process, beginning early in with uncontrolled diabetes and obesity The objective of present study was to determine the difference between levels of visfatin in the gestational diabetes mellitus cases and pregnancies with normal OGTT. **Methods:** It was a case control study conducted in Ayub Teaching Hospital Abbottabad. Twenty-eight (n=28) diagnosed cases of gestational diabetes mellitus at various gestational ages (ranging from 11 weeks to 33weeks of pregnancy) were included in the Group I and their levels were compared with non-diabetic normal antenatal cases, Group II (n=32). Blood samples were collected for blood glucose and visfatin levels. Visfatin levels were measured by enzyme-linked immunosorbent assay (ELIZA). Statistical analysis was performed on SPSS-20, and $p<0.05$ was taken as significant. **Results:** Pregnant women (n=60) of different gestational age ranging from 4–36 weeks of pregnancy when subdivided into three categories (4–12 weeks, 13–24 weeks, 24–36 weeks respectively), showed statistically significant ($p=0.003$) differences of serum visfatin levels (10.11±2.982, 1.01±2.634, 1.17±3.102 ng/ml respectively). There were no significant differences in mean value of serum visfatin ($p=0.763$) according to parity of the patients (0.16±2.892, 0.19±2.883, 1.01±2.736 respectively) in the three trimesters of pregnancy. **Conclusion:** Visfatin levels were significantly raised in gestational diabetes mellitus as early as first trimester of pregnancy. Increased levels of visfatin can be used as a novel biomarker for early detection of gestational diabetes mellitus.

Keywords: Visfatin, insulin resistance, gestational diabetes mellitus

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INTRODUCTION

Various adipokines like resistin, adiponectin, IL-6, leptin, TNF and visfatin play quite significant roles in regulation of glucose, lipids and energy metabolism leading to the development of abnormal cascade of metabolism in cardiovascular, reproductive immune system.[1] Due to unique mechanism of action of visfatin on insulin resistance it initiates the cascade of intracellular signalling of insulin like stimulation of phosphorylation of tyrosine kinase and activation of protein kinase B but in different manner than insulin itself leading to development of Gestational Diabetes Mellitus (GDM).[1,2]

Visfatin has been implicated in many disease entities including atherosclerosis, obesity due to visceral fat mass[3], type II diabetes mellitus[4], renal and, beta cell functional impairment and metabolic syndrome[3,4] and tumour replication[5]. During pregnancy the level of visfatin which is complicated by glucose intolerance may sometimes be increased or decreased.[1]

GDM is the glucose intolerance which is diagnosed for the first time during pregnancy.[6] Visfatin is found to be produced by adipocytes, placental tissues and the membranes of the fetus.[7] Some international studies suggest that there is significant increase in visfatin levels in pregnancies with GDM compared to the controls suggest that there might be a role of this peptide in the worsening of insulin resistance in normal pregnancies ultimately progressing to gestational diabetes mellitus.[8]

The finding of increased serum levels of visfatin at early pregnancy (11–13 weeks) in pregnant women is a new one, who subsequently develop GDM in later pregnancy.[7] There is evidence that, in pregnancy, the source of circulating visfatin is not only visceral fat, but also the placenta and the increased serum concentration observed in GDM may be the consequence of placental over-secretion.[9]

Visfatin may have a role in development of gestational diabetes and can worsen the consequences if not detected and treated earlier. With timely risk factors manipulation and intervention, the worsening of disease and development of maternal and foetal complications could be avoided. This study aimed to see the difference between levels of visfatin in the gestational diabetes mellitus cases and pregnancies with normal OGTT.

MATERIAL AND METHODS

This was an observational cross-sectional study. We sought to determine the levels of maternal serum visfatin in pregnancy as a biomarker for the detection of uncontrolled diabetes mellitus (gestational diabetes mellitus GDM). Written informed consent was taken from women who agreed to participate in the study.

Sampling was done through technique of convenience sampling.

Pregnant women (60) of different parity and gestational age were divided into two groups. Twenty-eight diagnosed cases of gestational diabetes mellitus at various gestational ages (11–33 weeks) were included in Group I and their levels were compared with non-diabetic normal antenatal cases, Group II (controls, n=32). Weight (Kg), height (m), and body mass index (BMI) (Kg/m^2) were recorded. Subjects were divided into four sub-groups according to their BMI. Normal weight (18.5–22.9), underweight (<18.5), overweight (23–24.4) and obese (>25). BMI was classified according to the static requirements for Asian population.[10]

Blood pressure, and period of gestation were recorded as their routine antenatal examination, and previous or family history of gestational diabetes was taken. The fasting blood samples were collected through venepuncture for levels of blood glucose and serum visfatin. Women were categorized into two groups (cases and controls) with blood glucose levels >6.75 mmol/L suspected for gestational diabetes with positive family or previous history of DM. In order to confirm the diagnosis of GDM an oral glucose tolerance test was performed by giving 75 gm oral glucose and measurement of plasma glucose level after two hours. Levels more than 7.8 mmol/L were taken as confirmed cases of GDM.[11] The cases and controls were further analyzed for serum visfatin levels. Maternal serum visfatin concentration was measured quantitatively by ELISA technique using eNampt/PBEF ELISA kit for visfatin of Alpco Diagnostics.

Statistical data analysis was performed on SPSS-20. For continuous variables like serum visfatin, Mean±SD was calculated and for categorical variables like BMI, period of gestation, and parity, frequencies and percentages were calculated. Two-way Student's *t*-test was applied for comparison of serum visfatin in various sub-groups of pregnant women, and $p<0.05$ was taken as statistically significant.

RESULTS

The mean age of women in our study group was 32.8 (26.4–39.2) in years. Weight and height of all patients were recorded to calculate BMI; 35 (58.33%) women were of normal weight, 2 (3.33%) were under weight, 15 (25%) were overweight and 8 (13.33%) were obese. There were statistically significant differences ($p=0.001$) among four subgroups of women according to their BMI (1.06±0.025, 1.05±0.031, 3.53±0.094, 3.92±0.193). Pregnant women (n=60) of different gestational age ranging from 4–36 weeks of pregnancy when subdivided into 3 categories (4–12 weeks, 13–24 weeks, 24–36 weeks respectively), showed statistically significant ($p=0.003$) differences of serum visfatin levels (10.11±2.982, 1.01±2.634, 1.17±3.102 ng/ml respectively). Among all pregnant cases 12 (20%) were primipara, 22 (36.66%) were multigravida, and 26 (43.33%) were grand multigravidas with more than five pregnancies. There were no significant differences in mean value of serum visfatin ($p=0.763$) according to parity of the patients (0.16±2.892, 0.19±2.883, 1.01±2.736 respectively) in the three trimesters of pregnancy. In our study 32 (53.33%) were non-diabetic, and 28 (46.66%) were cases of gestational diabetes having significant ($p=0.0001$) differences in mean serum visfatin levels (1.06±0.013 and 3.82±0.193) (Table-1).

Trimester-wise stratification of study population into diabetic and non-diabetic (cases and controls) showed high percentage of impaired glucose tolerance in pregnant women in 1st trimester (61.53%) and 2nd (35.7%), and 3rd trimester (52.63%) respectively (Table-2).

The differences of mean values of serum visfatin, blood glucose and glycosylated haemoglobin between group I and II and their statistical significance ($p=0.0001$) in each case showing the positive correlation between gestational diabetes and visfatin metabolism are tabulated as Table–3.

Table-1: Pregnancy variables and descriptive characteristics of subjects

Parameter	n (%)	Serum visfatin (ng/ml)	*p*
BMI (Kg/m^2)			
Normal (18.5–22.9)	35 (58.33)	1.06±0.025	0.001
Underweight (<18.5)	2 (3.33)	1.05±0.031	
Overweight (23–24.4)	15 (25)	3.53±0.094	
Obese (>25)	8 (13.33)	3.92±0.193	
Period of Gestation			
4–12 weeks	13 (21.66)	0.11±2.982	0.003
13–24 weeks	28 (46.66)	1.01±2.634	
24–36 weeks	19 (31.66)	1.17±3.102	
Parity			
Primipara (1st)	12 (20)	0.16±2.892	0.763
Multigravida (2–4)	22 (36.66)	0.19±2.883	
Grand multigravida (≥5)	26 (43.33)	1.01±2.736	
Diabetic status			
Non-Diabetic	32 (53.33%)	1.06±0.013	0.0001
GDM	28 (46.66%)	3.82±0.193	

Table-2: Trimester-wise stratification of study population into two groups (cases and controls)

	Trimester		
GROUPS	**I (4–12 weeks)**	**II (13–24 weeks)**	**III (25–36 weeks)**
GDM	8 (61.53%)	10 (35.7%)	10 (52.63%)
Non Diabetic	5 (38.46%)	18 (64.28%)	9 (47.37%)

Table-3: Differences between serum visfatin, plasma glucose level, and glycosylated haemoglobin in two groups (Mean±SD)

Variable	Groups I (Cases)	Group II (Controls)	*p*
Serum visfatin (ng/ml)	3.82±0.193	1.06±0.013	<0.01
Blood Glucose (mmol/l)	14.5±1.20	5.6±0.58	<0.01
Glycosylated haemoglobin (%)	6.79±0.62	4.53±0.17	<0.01

DISCUSSION

The role of visfatin in development of type II Diabetes Mellitus is well established entity supported by many researches.[2–5] However, the concept of raised serum visfatin levels at early (4–12 weeks) of pregnancy in the women who subsequently develop gestational diabetes mellitus (GDM) is new.[7,9] Although the source of circulating visfatin in obesity and diabetes is visceral fat but some other studies support the fact that placenta may be implicated in raised serum concentration of visfatin in gestational diabetes.[8] During the course of normal pregnancy, the resistance to insulin increases physiologically and many studies suggest that visfatin possesses insulinomimetic properties.[10,11] which enables visfatin to bind to insulin receptors and increase intracellular uptake of glucose thus, leading to conclusion by Liang *et al*, that visfatin has an association with metabolic disorders of lipids, insulin and glucose in GDM.[12] This finding is consistent with our study finding that visfatin starts increasing in as early as first trimester of the pregnancy[7] and shows an increasing trend near term. However it has no association with parity or number of pregnancies whether primipara, multigravida, or grand multigravida.

Raised visfatin levels in GDM may be the reflection of impaired action of visfatin on receptors of target cells leading to dysregulation of glucose and lipid homeostasis leading to development of GDM.[13] Placental tissue could be a source of visfatin over secretion in GDM as one study shows the increased expression of visfatin receptors on placental tissue, mesenchymal cells, amniotic epithelium, parietal decidua and chorionic cytotrophoblastic cells.[14] We also found increased association of GDM and high serum visfatin levels in obese and overweight women with high BMI as compared to normal and underweight women as found by other researchers in recent past.[12]

There is some controversial role of visfatin and other adipocytokines in the development and progression of GDM as reported by Park *et al*, who studied 215 patients of GDM and 531 normal pregnant women and found reduced circulating visfatin and adiponectin level in GDM as compared to the normal pregnancy[15] while this finding was not showing consistency of results with our study where serum visfatin levels were significantly related to BMI and maternal obesity. We cannot draw a conclusion whether raised serum visfatin is a cause or consequence of gestational diabetes. This might be a limitation to the study where we can use visfatin as a biomarker for early detection of gestational diabetes. Study of Kiran *et al*, revealed that levels of visfatin in GDM women were elevated than women who showed normal glucose tolerance, a finding consistent with our study.[16] When the patients were further stratified trimester-wise we found high percentage of impaired glucose intolerance in first trimester as compared to the second and third trimester GDM cases.

Recent studies have shown that visfatin increases weeks before the onset of gestational diabetes and can be of predictive value of the onset of disease not necessarily consistent with the maternal other characteristics. This is similar to a report which found increased visfatin levels weeks before clinical diagnosis of the disease.[1,7] Finding the difference of serum visfatin in GDM and Non GDM is a challenging finding in medicine and obstetrics, leading the researchers to find out an effective, simple, cost effective and less invasive techniques for diagnosis of GDM and many used saliva instead of serum and found a quite significant difference in both groups again showing a relationship between the two variables.[17] The focus of previous studies was primarily on the complex relationship between serum visfatin and Type 2 Diabetes Mellitus[18,19] which now shifts to the GDM in obese women, a finding consistent with our study and supported by international literature.[20]

CONCLUSION

Considering that visfatin participates indirectly in the development of GDM in obese women, visfatin might be a potential predictor for assessing GDM with obesity. Early screening for GDM is effective strategy for reducing the foetal and maternal comorbidities. The sample size limits the generalization of this study, so further well-designed epidemiological studies with larger sample size and strict stratification of other potential confounding factors should be done in order to fully understand the complex pathophysiology of visfatin in gestational diabetes prediction and therapeutics.

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RN: Concept study design and manuscript writing
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