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Pre- and Post-partum Levels of Serum Visfatin in Pregnant Women with Gestational Diabetes Mellitus: A Correlation

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ABSTRACT

Introduction: Gestational diabetes mellitus is glucose intolerance diagnosed or detected for the first-time during pregnancy and has serious implications for fetal and maternal health if left untreated. Hyperglycemia during pregnancy is caused by the progressive increase in insulin resistance from mid to third trimester. Increased insulin resistance is a consequence of an increase in adipose tissue in mother and desensitizing effect to insulin by placental factors. Adipokine, visfatin, is multifunctional protein. Its levels are much higher in pregnant women.

Aims and Objectives: To determine and compare levels of serum visfatin and insulin resistance before and after delivery in gestational diabetics.

Place and Duration of Study: Lahore General Hospital Lahore/ PGMI, Lahore, during 2024.

Materials and Methods: It was a Case control study. 21 Pregnant females at gestational age of 32-36 weeks were selected using non-probability purposive sampling as diagnosed cases of GDM (OGTT) matched with 21 control without GDM. Serum levels of Visfatin, Insulin, fasting blood Glucose and HOMA IR were determined. Data was analyzed by using SPSS version 20. Results were checked for normality. Paired t test was used to compare normally distributed data before and after delivery in the both groups. The Wilcoxon sign rank test was used to compare non normally distributed data before and after delivery. Spearman's and Pearson correlation was used to correlate data. A p-value of <0.05 was considered significant.

Results: A statistically significant difference (p-value=0.000) was determined between Serum visfatin and fasting insulin levels. A Statistically significant correlation (p-value=0.000) was found between Serum visfatin, insulin, FBG and HOMAIR before and after delivery.

Conclusion: In GDM women comparison of visfatin before and after delivery showed a significant difference indicating that source of visfatin is likely the placenta, which due to prolonged hyperglycemia causes the release of visfatin. A significant correlation supporting the belief that enhanced insulin resistance during pregnancy leads to hyperglycemia causing an increased level of visfatin.

Key words: Visfatin, Gestational Diabetes Mellitus, Insulin

INTRODUCTION

Gestational diabetes mellitus is glucose intolerance diagnosed or detected for the first-time during pregnancy affecting 3 - 14 % of pregnant women. The prevalence of GDM has doubled in the last 8 years with an average increase of 12% per year.[1] The prevalence of GDM in Pakistan is 8% 2 while the incidence of GDM is increasing as the pregnancy population is becoming older and obese/overweight.[3] The WHO diagnostic criteria for GDM is fasting plasma glucose ≥ 7.0mmol/l (126mg/dl), two hour plasma glucose level ≥ 11.1mmol(200mg/dl) after 75 g oral glucose load and random plasma glucose level ≥ 11 mmol/l (WHO 2013).Consequences of GDM on both baby and mother are reported by various studies that documented an increase in perinatal mortality if left untreated.[4] Hyperglycemia during pregnancy is caused by the progressive increase in insulin resistance from mid to third trimester. Increased insulin resistance is a consequence of an increase in adipose tissue in mother and desensitizing effect to insulin by placental factors[5]. It is suggested that as the pregnancy advances there is a gradual elevation in release of insulin[6] but the reduced responsiveness

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to insulin action causes impaired expression of GLUT4 (glucose transporter 4) on cell membrane. In pregnancy, adipose tissue mass increases [7] and this adipose tissue secretes various factors/hormones /adipokines.[8] Adipokine, visfatin, is multifunctional protein having activities like cytokine, phosphoribosyl transferase and adipokine.[9] Its levels are much higher in pregnant women.[10] Regarding the regulation of glucose metabolism it has insulin like activity. Administration of visfatin resulted in a reduced blood glucose levels similar to insulin.[11]

Visfatin levels are increased during normal pregnancy to compensate for insulin resistance by its insulin mimetic properties.[12] Excess visfatin ensures sufficient delivery of glucose to the fetus.[13]

There are several contrasting reports regarding the levels of visfatin in GDM women with some reporting elevated levels[14,15,16,17], whereas decreased levels of visfatin seen in many other studies.[18, 19, 20] This conflict may be caused by variance regarding sampling size and duration of pregnancy, various diagnostic criteria or racial differences and laboratory determination methods. The role of visfatin is conflicting and not well defined hence the aim of this study was to determine, compare and find any correlation between these parameters in our population.

In future if the role of visfatin becomes defined then it can be targeted for the management of health of both mother and child.

MATERIALS AND METHODS

Twenty-one pregnant women at 32-36 weeks of gestation were taken after written informed consent using non-probability purposive sampling. All were diagnosed cases of GDM (Diagnosis based on OGTT). IRB approval taken from PGMI Ethical review committee and LGH review committee and IRB No: AMC/PGMI/LGH/Article/Research No:00-24-S. The sample size was calculated using formula:

$$n = \left(\frac{r+1}{r}\right)\frac{\sigma^2\left(Z_{1-\beta}+Z_{1-\alpha/2}\right)^2}{d^2}$$

21 Normal, healthy pregnant females with Fasting blood glucose level < 126 mg/dl were taken for comparison. History and general physical examination was recorded on predesigned proforma. 5ml venous blood was drawn under aseptic measures. 1st sample was drawn at 32 to 36 weeks of gestation and 2nd sample was drawn at 36-48 hours after delivery. Blood was centrifuged at 3000rmp for 15 minutes and serum was stored at -20°C till further analysis.

Statistical Analysis: Data was analyzed by using IBM SPSS version 20. Results were checked for normality and the Paired t test was used to compare normally distributed variables before and after delivery. The Wilcoxon sign rank test was used to compare non normally distributed data before and after delivery. Spearman's and Pearson correlation was used to correlate the non-normal and normally distributed data respectively. A p value of <0.05 was considered significant.

RESULTS

Median (IQR) of age was 30 (25.00-35.00) years. 47.6% were more than 30 years of age. 47.6% subjects had normal BMI. 52.4% subjects were obese. The mean ±SD was 24.8±5.5 Kg/m^2.

Biochemical Parameters of the GDM Population: Before delivery 67% females had blood sugar above 100mg/dl. After delivery 43% of females had blood glucose between 70-100mg/dl and 52% had blood glucose above 100mg/dl. 52% had levels serum insulin levels above $20\mu IU/mL$ before delivery and after delivery they were found to be in the normal range of 10-$20\mu IU/mL$ in 48% of cases. Only one subject had serum insulin above $20\mu IU/mL$. Before delivery 19% had HOMA IR below 2.37 while 81% had HOMA IR above 2.38. After delivery 42% subjects had HOMA IR above 2.38. The mean serum visfatin level before delivery was $34.64\pm6.06 ng/ml$. After delivery it was 23.97±7.58 ng/ml.

Comparison Of Biochemical Parameters Before Delivery and After Delivery

When compared by applying paired t test, a statistically significant difference (p=0.00) was seen in serum visfatin levels of the study population when compared before and after delivery.

By applying Wilcoxon sign rank test, a non-significant difference (0.74) was observed in FBG of study population before and after delivery. A statistically significant difference was observed in fasting serum insulin levels before and after delivery in the study population (p=0.00) when compared by applying paired t test.

Table 1: Comparison Of Biochemical Parameters before and after delivery

Parameters	Before delivery	After Delivery	P-value
Glucose (mg/dl)●	104(89-107)	102(83-152)	0.74
Insulin ($\mu IU/mL$)▲	20.81 ±11.22	11.18±5.20	0.00***
HOMAIR▲	5.16±2.73	3.34±2.66	0.06

Visfatin(ng/dl) ▲	34.64±6.06	23.97±7.58	0.00***

***p considered highly significant
▲-compared by paired t test
●-compared by Wilcoxon sign rank test

Comparison of fasting serum visfatin levels in GDM patients showed a statistically significant difference (p=0.00) before and after delivery Figure 1. Blood glucose when compared by applying Wilcoxon sign rank test, a statistically a non-significant difference (0.74) was observed in FBG before and after delivery. A statistically significant difference was observed in fasting serum insulin levels before and after delivery (p=0.00) when compared by applying paired t test.

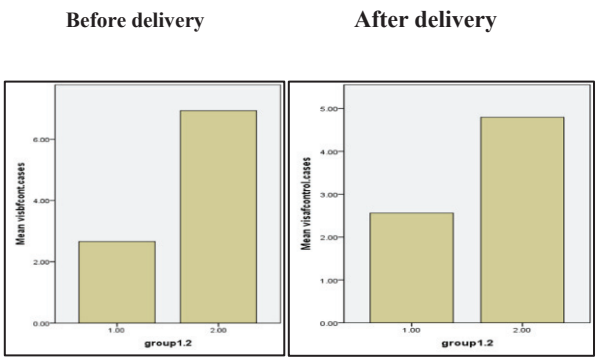


Figure 1: Serum visfatin levels in the study population before and after delivery.

Correlation between serum visfatin and glycemic parameters Before Delivery

A significant correlation was observed between serum visfatin with blood glucose (p<0.001), serum insulin (p<0.001) and HOMA IR(p<0.001) in the study population as shown in (Table1)

Statistically significant correlation was also observed when serum visfatin was correlated with blood glucose, serum insulin, and HOMA IR after delivery with a p<0.001, 0.01 and p<0.001 respectively (Table 2).

Table 2: Correlation between serum visfatin, insulin, blood glucose, and HOMA IR Before Delivery

Parameter		Before Delivery n = 42	
		Rho	p-value
Visfatin	Glucose ●	0.367	0.01*
	Insulin ▲	0.531	0.00***
	HOMA IR ▲	0.569	0.00***

* p considered significant
***p considered highly significant
● Correlated by spearman test
▲ Correlated by Pearson test

Table 3: Correlation between serum visfatin, insulin, blood glucose and HOMA IR After Delivery

Parameter		After Delivery n = 42	
		Rho	p-value
Visfatin	Glucose ●	0.567	0.00***
	Insulin ▲	0.394	0.01*
	Homa IR ▲	0.399	0.00***

*p considered significant
***p considered highly significant
● Correlated by spearman test
▲ Correlated by Pearson test

Fig 2: Scatter plot showing significant correlation between serum visfatin and fasting glucose levels before delivery in the study population

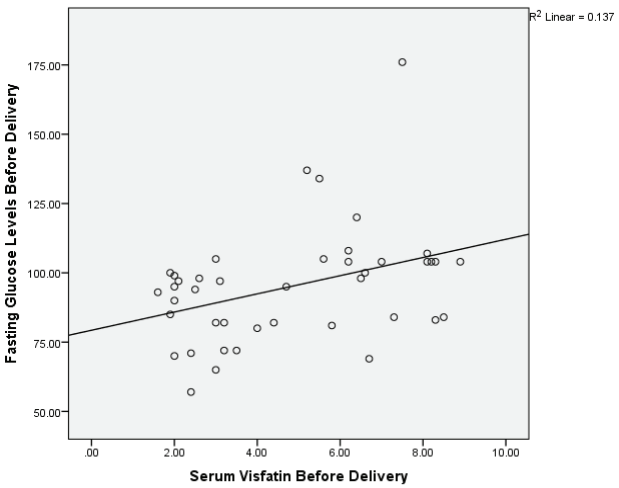


Fig 3: Scatter plot showing significant correlation between serum visfatin and insulin levels before delivery in the study population.

Fig 4: Scatter plot showing significant correlation. between serum visfatin and HOMA IR before delivery in the study population.

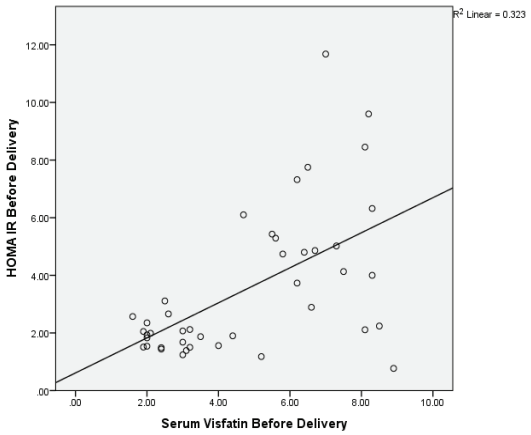


Fig 5: Scatter plot showing significant correlation between serum visfatin and fasting glucose levels after delivery in the study population.

Fig 6: Scatter plot showing significant correlation between serum visfatin and insulin levels after delivery in both groups.

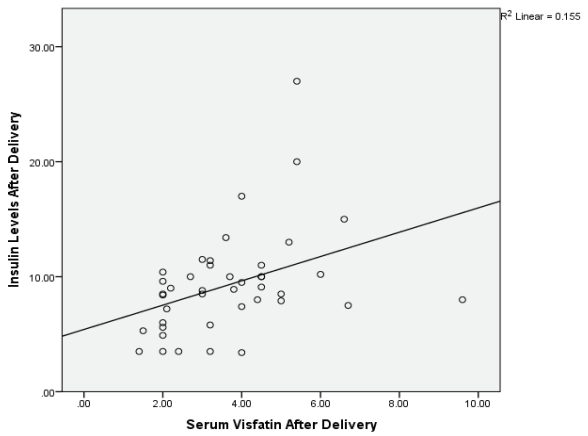
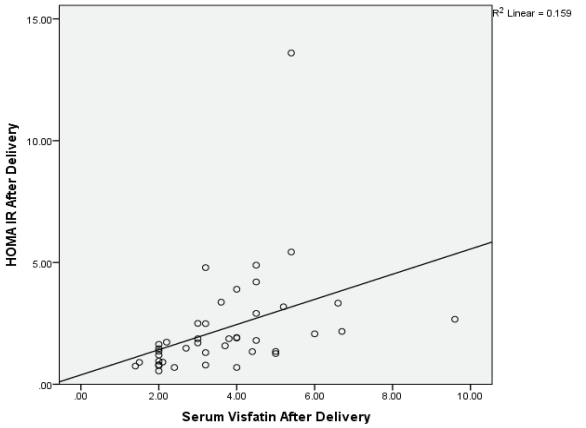


Fig 7: Scatter plot showing significant correlation between serum visfatin and HOMA IR after delivery in study population.



DISCUSSION

In this study serum visfatin levels along markers of insulin resistance were measured and compared in pregnant women diagnosed with GDM before and after delivery. Women with GDM have higher insulin resistance as compared to normal pregnant women ($p<0.001$) and an increase in visfatin secretion occurs due to this chronic insulin resistance. Majority of women suffering from GDM have a β-cell dysfunction[5]. This β cell dysfunction causes maternal glucose intolerance and gestational diabetes[21]. Another reason of higher visfatin levels is the presence of prolonged hyperglycemia which has stimulatory effect on the visfatin release from adipocytes[22]. However, during pregnancy, the source of circulating visfatin is not only the adipose tissue but also the over secretion by placenta. A statistically non-significant difference ($p=0.74$) is seen in serum visfatin levels in normal pregnant women, whereas a statistically significant decrease ($p=0.00$) is seen in GDM pregnant women when levels are compared before and after delivery in each group. A non-significant decrease in postpartum serum visfatin levels in healthy pregnant women and a significant decrease in serum visfatin levels after delivery among the GDM patients has been stated[17]. The increased expression of visfatin from adipose tissue may be responsible for non-significant difference in pre and post-delivery levels of normal pregnant subjects. In GDM women as placenta is a major source of visfatin[16] (Ma et al., 2010) and the removal of placenta thus leads to decrease in serum visfatin levels after delivery in this group. In contrary to this finding[14] Krzyzanowska et al.,2006 has reported an increase in visfatin level after delivery in GDM women. They have attributed this to increased

expression of visfatin from neutrophils under the effect of inflammatory stimuli like interleukin 1β or TNFα released due to parturition. [23] Removal of placenta leads to rapid fall in insulin resistance in patients with pre gestational diabetes [24]. When HOMA IR is compared a statistically significant difference (p=0.046) is seen within GDM pregnant women. These results were also shown by [16] Ma et al.,2010 who reported decrease in HOMA IR after delivery as compared to normal after delivery that favors our study findings. In GDM women comparison of visfatin before and after delivery showed a significant difference thus reflecting that source of visfatin is placenta, which under the influence of prolonged hyperglycemia causes the release of visfatin. When serum visfatin levels are correlated with any of the glycemic parameters in the GDM before and after delivery separately, no significant correlation is found.[25] Liang et al.,2016 and Akturk et al.,2008 have also shown no correlation in insulin resistance parameters in GDM group. In GDM the severe insulin resistance cannot be overcome by secretion of visfatin resulting in hyperglycemia. However the correlation of study parameters in pooled analysis of study population showed a significant correlation of serum visfatin with fasting glucose (r=0.56, 0.36, p=0.00, 0.01), HOMA IR (r=0.39 , 0.56 p=0.00, 0.01) and fasting insulin (r=0.39, 0.53, p=0.01, 0.00) before and after delivery. Haider et al., 2006 reported significant correlation between visfatin and parameters in GDM. So, the results of this study inplicate a strong association of visfatin with glucose metabolism during pregnancy. Increased serum visfatin levels in women with GDM in comparison to normal pregnant women supports that visfatin is released more in GDM patients to compensate the hyperglycemia in these patients. Hyperglycemia and increased insulin resistance in GDM are accompanied by higher levels of serum visfatin. Delivery of placenta in GDM leads to fall in serum visfatin levels which is not observed in normal pregnancy.

CONCLUSION

In GDM women comparison of visfatin before and after delivery showed a significant difference indicating that source of visfatin is likely the placenta, which due to prolonged hyperglycemia causes the release of visfatin. This finding has major clinical implications for maternal health indications and may direct future research in order to reduce mortality and complications due to GDM in both mother and newborns. Pooled analysis of the study shows a significant correlation thus supporting the belief that enhanced insulin resistance during pregnancy leads to hyperglycemia causing an increased level of visfatin.

Recommendations: Serial follow up studies one week and one month after delivery are required to see the pattern of decrease in serum visfatin levels.The increased expression of visfatin in placenta of GDM patients could have been studied. Maternal placenta and cord blood should be used for the detection of visfatin

Limitation: The levels of TNF-α were not measured as it has shown to increase the placental expression of visfatin levels.

Future research directions: Studies in the future including serial follow up of serum visfatin levels at one and three months after delivery could further clarify pattern of changes in its levels.

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