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The Correlation between Insulin Resistance and Urotensin II in Patients with Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus is glucose intolerance of varying degree with onset or first detection duringpregnancy, it can causelong and short term morbidities in both the mother and the child, such as shoulder dystocia, preeclampsia, and high blood pressure. The most powerful endogenous vasoconstrictor peptide, urotensin II, and its receptor are involved in the etiology of gestational diabetes mellitus.

Aim of the study: The study's goal was to see if there is a link between Urotensin II levels and insulin resistance in pregnant women with gestational diabetes.

Patients and method: A case-control study that was conducted in obstetrics and gynecology department at Baghdad Teaching hospital from the first of January 2019 to the end of December 2019. A sample of 80 pregnant women participated in the study fulfilling inclusion criteria. 40 of them diagnosed with gestational diabetes mellitus by (2 hours 75 gm. Oral glucose tolerance test) and 40 women as control group.

Results: The mean age of the gestational diabetes mellitus group was 29.8±6.9 years and control was 29.7±6.6 years with no significant differences. The study showed highly significant increase infasting Insulin, fasting blood glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), of the GDM group than that in the group without disease. Significant difference was found regarding high-sensitivity C-reactive protein hs-CRP (p=0.004). The level of Urotensin II in subjects with gestational diabetes was (109±33.22) highly increased than that in healthy subjects (78±22.6). There is a positive correlation between circulating Urotensin II levels with fasting insulin, and HOMA-IR. While negative correlation found with fasting blood glucose.

Conclusion: The level of UII was found to be raised in gestational diabetes pregnant women

Keywords: Diabetes; insulin resistance; urotensin II.

Introduction

"Gestational diabetes mellitus (GDM), is a state of carbohydrate intolerance, first diagnosed during pregnancy, it is a glucose metabolism disorder which can cause long & short term morbidities in both mother & fetus asdifficulty in delivery of shoulder & preeclampsia.[1] It is one of the common complication

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that can occur during pregnancy, in which increase in blood sugar occur during pregnancy.[2] "GDM affects about 14% of pregnancies worldwide, representing nearly 18 million births every year".[3]

"The American Diabetes Association (ADA) formally categorizes Gestational diabetes mellitus as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation."[2] "The exact threshold for a diagnosis of GDM, however, is dependent on the criteria utilized, and there has been no unanimity among health specialists thus far''.[4]

The considerable decline in insulin sensitivity that occurs late in pregnancy reveals the lower insulin sensitivity that occurs before to pregnancy. Furthermore, abnormalities in insulin production have been linked to the degree of glucose intolerance throughout pregnancy. Beta-cell dysfunction persisted after birth and is linked to the severity of glucose intolerance throughout pregnancy. Interleukin 6 (IL6) and circulating tumor necrosis factor alpha (TNFa) have been found to be inversely associated to insulin sensitivity in people with GDM, proposing that inflammatory factors play a role in the disease's etiology. Other cytokines, like as leptin, have been reported to be elevated in people with GDM.[5]

The endogenous vasoconstrictor peptide urotensin II (UII) and its receptor (UTR) are both implicated in the etiology of essential hypertension. This human receptor G-protein receptor (GPR14) was then renamed urotensin II (UII) and its receptor recovered the interest in this field. "The U-II gene is found on chromosome 1p36U-II, and the length of the peptide differs between species due to distinct cleaving sites positioned at different places. The length of U-II in humans is 11 amino acids. The core is the peptide sequence required for biological function in both U-II and urotensin II-Related Peptide (URP). It's a hexa peptide (-CYS-TYR-LYS-TRP-PHE-CYS-) with a disulfide link connecting the two ends. Similarly, to URP, the amino terminus can be changed with keeping its pharmacological action, implying that it is not required for receptor activation.In contrast to URP, U-II contains an acidic amino acid (Aspartic or Glutamic) before the core sequence. While the amino acid isn't required for urotensin II receptor activation, its conservation across species proposes it has a biological purpose which has yet to be uncovered".[6]

UII is found in the pancreas that blocks insulin from being released. Increased UII plasma levels and expression have been found in a variety of diseases, including hypertension, atherosclerosis, pulmonary hypertension, heart failure, pregnancy kidney failure, diabetes, and the metabolic syndrome.

"Type 2 diabetes mellitus (T2DM), insulin resistance, and diabetic complications as carotid atherosclerosis and diabetic retinopathy have all been linked to polymorphisms in the UTS2 gene. The UTS2 gene regulates skeletal muscle fat storage and fatty acid metabolism, two biological processes linked to T2DM in humans."[7]

Insulin resistance is defined as a failure of insulin signaling which lead toinadequate plasma membrane translocation of glucose transporter 4 (GLUT4), the primary transporter which transports glucose inside the cell to be used as energy. In GDM, glucose absorption which is stimulated by insulin is reduced by 54% in comparison to normal pregnancy.[8]

Aim of the study:

our goal was to see if there is a link between Urotensin II levels and insulin resistance in pregnant patientswho have gestational diabetes.

Patients and Methods

Study design and setting: A case-control study that carried out in department of Obstetrics and Gynecology at Baghdad Teaching Hospital from the first of January 2019 to the end of December 2019. A sample of 80 pregnant women participated in the study after fulfilling inclusion criteria.

Ethical consideration: Approval of the Obstetrics and Gynecology Department of Baghdad Teaching Hospital/Medical city.

Inclusion criteria: (40 with gestational DM and 40 without) which is diagnosed by two hours 75gm oral glucose tolerance test at 24-28-weekgestational age which they have risk factors for doing OGTT as a NICE guideline criterion Exclusion criterion:

1. Patients have history of DM 1 or 2
2. If they have impaired glucose tolerance (IGT) before pregnancy,
3. Previous complication of pregnancy (HT, PE, IUGR….)

4. Twin or triple pregnancy
5. Taking medication that affect the level of glucose (steroid, anti-inflammatory drugs, carbohydrate metabolism-regulating obesity)
6. Previous medical history: CA, acute or chronic systematic disease, hypo or hyper-thyroidisim.

Consent taken from all participants, history was taken and physical examination, Blood pressure and obstetric examination were performed. last menstrual period and/or early ultrasonography were used to determine their gestational age.

Method

5 cc sample of blood was taken from the participants in the morning who were fasting for at least ten hours. Then separation of the sample was done by 15 minutes centrifuging of the blood at 2000x, before the analysis of UII the serum sample were kept in aliquots at − 80 °C. Urotensin II were measured via the ELISA technique by using Ray Biotech ELISA Kits. "Homeostasis model assessment: insulin resistance (HOMA-IR): HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mg/dl)/405"

Statistical analysis: After the data entered in a table, the analysis done by using the Statistical Package for Social Science (SPSS) program, version 23 and for qualitative variables, we used frequencies & percentages, and for the quantitative variables, we used measures of central tendency and dispersion (standard deviation). For the inferential statistics, the tests used of chi-square test (with a significance of $P \leq 0.05$)

Results

Eighty pregnant women between 24 and 28 weeks' gestational age wereenrolled in the study, 40 patients were taken as a study group with diagnosed of GDM and 40 women as control group. The mean age of the GDM group was 29.8±6.9 years & control was 29.7±6.6 years. All these findings were shown in table1.

Table 1: Demographic characteristics of the studied groups

Variable	GDM (Cases) (n=40)		Normal (control) (n=40)	
	Number	%	No.	%
Age				
<20 years	9	22.5	2	5.0
20-29 years	14	35.0	18	45.0
≥30 years	17	42.5	20	50.0
Age (mean±SD)	29.8±6.9		29.7±6.6	

Fisher exact test

In Table 2, there is highly significant difference were found between the studied group among parity ($p<0.001$) and there was no significant association between other demographic criteria found between control group and GDM group ($p >0.05$).

Table 2: Comparison between demographic criteria of the studied groups (mean±SD)

	GDM group (n=40)	Control group(n=40)	P value
Age	29.8±6.9	29.7±6.6	0.9
GA	26.87±1.09	26.69±1.24	0.5
parity	3±1	2±1	<0.001
SBP	114.3±12.2	112.1±9.6	0.3
DBP	72.4±4.2	71.2±4.5	0.2

Table 3 showed highly significant increase in FBG, fasting Insulin, HOMA-IR, of the GDM group than that in control group (P<0.001).

Table 3: Relationship between fasting blood glucose, fasting insulin and IR among studied group. (mean±SD)

	GDM group (n = 40) Mean±SD	Control group (n=40) Mean±SD	P value
FBG	83.0±13.9	71.7±9.2	<0.001
Fasting Insulin	14.82±7.9	9.78±4.3	<0.001
HOMA-IR	3.10±2.05	1.82±0.99	<0.001

As shown in table 4, the level of Urotensin II in subjects with GDM was (109±33.22) and in healthy subjects was (78±22.6) there was a highly significant association between mean of Urotensin II than the women withno GDM (p<0.001).

Table 4: Distribution of Urotensin II mean in the studied group

Variable	GDM	Normal	P
	Mean±SD	Mean±SD	
Urotensin II (ng/mL)	109±33.22	78±22.6	<0.001*S

***Independent sample t-test*, *S=Significant*.**

As shown in Table 5 the marker has high sensitivity and lesser specificity So the accuracy about 87.5%.

Table 5: Validity test

Cutoff value of Urotensin II	Sensitivity	Specificity	PPV	NPV	Accuracy
92 ng/ml	95%	80%	90%	82%	87.5%

In table 6 No relation wasestablished between the Urotensin II & Age, lipid profile and creatinine in GDM patients, while significant correlation were found regarding the hs-CRP. The correlation analysis between serum Urotensin II and various parameters showed that there is a positive relation between circulating Urotensin II levels with fasting insulin, and HOMA-IR. While negative correlation found with fasting blood glucose.

Table 6: Statistical correlation between many variables in GDM group with Urotensin II

	Urotensin II	
	GDM	
	r	P
Age	0.17	0.5
Cholesterol	0.441	0.7
hs-CRP	0.717	0.04
low-density lipoprotein	0.0941	0.08
High-density lipoprotein	0.0805	0.9
Triglycerides	-0.051	0.7
Creatinine	0.234	0.07
FBG	-0.086	0.6
Insulin	0.73	<0.001
HOMA-IR	0.820	<0.001

"Pearson's correlation analysis was used. r: Pearson's correlation coefficient. A P value of < 0.05 was considered significant".

Discussion

Numerous polymorphic areas of the UII gene producing the UII peptide, including the Rs.228648 polymorphism, have been identified and linked to a variety of disorders, including diabetes, diabetic retinopathy[9], breast cancer,[10] Behcet's disease,[11] and systemic sclerosis.[12] Yumrutas et al. discovered that the "Thr21Met (143G>A, rs228648) polymorphism in

the UII gene was linked to the likelihood of developing breast cancer, and that the variant genotype was linked to lower UII plasma expression, suggesting a putative mechanism for UII participation in disease risk".[10]

"Gestational diabetes mellitus is a metabolic condition linked to insulin resistance", according to Desoye G.[13] Until date, the basic biological processes underlying the reduction of insulin resistance in pregnant individuals with GDM were unknown. Despite the fact that a variety of chemicals are expected to prevent the signaling pathway of insulin, there is no evidence of anassociation between insulin resistance and UII in pregnant patient with GDM. [14,15]

"UII is a multi-functional peptide that plays a key role in metabolism of glucose and the occurrence of insulin resistance", according to Gruson D et al., and levels of circulating UII were observed to be greater in patients who had metabolic syndrome than in the control group.[16]

The current investigation demonstrated a negative connection between FBG and UII levels, which is consistent with Totsune et alwork's which reported no link between HgbA1Cor FBG and UII levels.[17] "In a research by Totsune et al., UII levels were observed to be higher in type 2 diabetics with and without proteinuria in comparison to healthy patients".

The current study shows a positive correlation between HOMA-IR and UII in GSD patients group. Which is same that in Yilmaz Ö, et al, study and Suguro T et al., study, which confirmed that there was a positive relation, were found between HOMA-IRand UII in a variety of disorders.[18,19]

Pregnant women with high UII levels are more prone to develop GDM. These data imply that UII may contribute to the occurance of insulin resistance in women with GDM. Surprisingly, a small number of investigators have looked at "the consequences of the UII genetic polymorphism on the development of T2DM.[20] Furthermore, as compared to controls, the genetic polymorphism of UII was shown to be greater in diabetic retinopathy patients.[9] GDM is linked to low-grade chronic inflammation, which causes insulin resistance.[21]

According to Yilmaz et al.[18]," there is a link between UII and inflammatory indicators. In the current investigation, we discovered that levels of the circulating inflammatory marker hs-CRP were greater in pregnant women with GDM than in controls".

In addition, UII demonstrated a favorable correlation with hs- CRP. These findings imply that UII may play a role in the development of insulin resistance in pregnant women with GDM via an indirect effector. In patients with essential hypertension, the most powerful vasoconstrictor peptide, UII, was shown to be raised.

We discovered no link between lipid parameters and UII in this study, which contradicts findings from a small number of preclinical investigations that held the concept that there is a linkage between lipid imbalance & UII.[22,23]

We also discovered that circulating levels of UII were greater in women with GDM than in controls in the current investigation. Insulin resistance was observed to be greater in pregnant women with GDM in comparison with controls. Furthermore, UII levels were positively correlated with HOMA-IR or insulin, but not with lipid profile or age. UII had an independent relationship with HOMA-IR. In his study, Hursitoglu M discovered that levels of UII were greater in women with GDM.[6]

In this study, patients with GDM had considerably greater levels of circulating U II than those without the condition (healthy group). "This is in line with a Turkish study published in 2019 by Calan M et al., which demonstrated that elevated UII levels are linked to insulin resistance in patients with GDM".[1]

Conclusion

Level of UII was found to be raised in GDM pregnant women and independently related with insulin resistance

Recommendations:

1. Urotensin II can be used as biomarker for screening of GDM women.
2. Further investigations were required to identify the role of Urotensin in women with gestational diabetes.

Conflict of Interest: There is no any conflict of interest.

Source of Funding: Self-funded study

Ethical Clearance: Ethical approval was obtained the form the Baghdad Teaching Hospital

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