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Assessment of serum mid-regional pro-adrenomedullin level in gestational Diabetes Mellitus in Iraqi women

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ABSTRACT: Adrenomedullin (ADM) is a strong vasodilator peptide that was first identified in human pheochromocytoma and known to expressed in numerous cell types and believed to have pleiotropic impacts on pregnancy-related vascular adaptations and fetal growth. Mid-regional pro-adrenomedullin (MR-proADM) peptide which secreted in an equimolar concentration to ADM used to quantify ADM in plasma since it has longer half-life with more availability than ADM and for that reason the present study determine the serum MR-proADM level in the plasma of pregnant women with and without GDM and determine any potential correlation between MR-proADM and gestational diabetes mellitus (GDM) in an observational case–control study conducted on 90 pregnant women in the third trimester of pregnancy who were divided into two groups: 45 pregnant women with GDM as patient and 45 apparent healthy pregnant women without GDM as control and the levels of MR-proADM, and the diabetic markers that include fasting serum insulin (FSI), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were determined and results revealed that the serum levels of MR-proADM were significantly higher in patients with GDM compared with those of controls, and also showed that MR-proADM levels were significantly and directly correlated with all studied diabetic parameters which lead to conclude that MR-proADM can serve as prognostic indicator for GDM.

KEYWORDS: Adrenomedullin; gestational diabetes; Mid-regional pro-adrenomedullin; pregnant women; insulin resistance; fasting blood glucose.

1. INTRODUCTION

Diabetes mellitus (DM) is the most prevalent metabolic disease characterized by increase in blood glucose levels and variable degrees of impaired protein, lipid, and carbohydrate metabolism [1, 2]. Diabetes has been linked to a long-term hyperglycemia, which can cause numerous malfunctions, and even organ failure in the kidneys, heart, blood vessels, eyes, and nerves [3]. Gestational Diabetes Mellitus (GDM) is defined as a condition characterized by impaired glucose tolerance that begins or is initially detected during pregnancy [4, 5]. In pregnancy, up to 25% of women may be influenced by GDM, the most prevalent metabolic condition [6]. GDM is a severe medical condition that develops within the second or third trimester of pregnancy and has many health complications for the mother as well as the child, such as premature birth, rapid fetal development, an elevated insulin level in newborns, hypoglycemia, and hyperbilirubinemia, among other conditions [7-9]. The metabolic state undergoes major changes during pregnancy, which impacts the action and sensitivity of insulin. This effect is more pronounced in the second part of pregnancy because of hyperglycemia brought on by insulin resistance [10].

Gestational diabetes mellitus progresses more quickly in women who are older than 25 years, have had GDM since their last pregnancy, and who also have a history of polycystic ovarian syndrome (PCOS) and type 2 diabetes mellitus (T2DM) [11]. There is still much to discover about the etiology of GDM, although it has been observed that certain ethnic groups of women, obesity, and older mothers are at greater risk for the disease [6]. To meet the fetus's energy needs, a woman's body goes through many physiological changes throughout pregnancy. In an attempt to improve the fetus's glucose supply insulin resistance increases. Pancreatic β-cells compensate for the increased demand for glucose, resulting in the development of a normoglycemic state. Conversely, women who have had GDM before are experiencing an inadequate β-cell response, which results in decreased insulin production and eventually, hyperglycemia. Thus, when β-

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cells lose their ability to control insulin resistance, glucose sensitivity may result [12]. The American Diabetes Association (ADA) suggests an oral glucose tolerance test (OGTT) for expectant mothers between 24 and 28 weeks of pregnancy, despite disagreements on the most effective GDM screening test [6]. According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines, routine GDM screening and diagnosis may take place in weeks 24 and 28 of pregnancy [13]. Furthermore, based on large gestational age (LGA) concerns that refer to fetus who are larger than expected for their age and gender, the IADPSG published updated diagnosis criteria for GDM in 2010. The concentrations of plasma glucose measured by 1-h, 2-h OGTT, and fasting blood glucose (FBG) were found to be 7.4, 6.2, and 4.5 mmol/l, respectively [14,15].

Adrenomedullin (ADM) is a strong vasodilator peptide consisting of 52 amino acid residues that was first identified in human pheochromocytoma [16, 17]. ADM belongs to the calcitonin peptide superfamily, and calcitonin receptor-like receptor (CRLR) is the receptor that mediates its signal. In order to provide high affinity for ADM, CRLR interacts with receptor activity-modifying proteins (RAMPs), of which RAMP2 and RAMP3 are two examples. These RAMPs transport CRLR from the endoplasmic reticulum to the cell membrane [18]. Numerous cell types express ADM, which is believed to have pleiotropic impacts on pregnancy-related vascular adaptations, fetal growth, inflammation, and hormone secretion [17]. During pregnancy, the placenta, chorion, and amnion can synthesis and release ADM. It is initially generated as a preprohormone and cleaves peripherally to its active type. ADM cleavage results in the physiologically inactive prohormone fragment known as the mid-region pro-adrenomedullin (MR-proADM) peptide, which has a 1:1 ratio. ADM's short half-life (22 minutes) and the presence of binding proteins make it difficult to quantify in plasma, which is why the more stable MR-proADM protein has been used as a replacement marker for ADM in several research. Due to its extended half-life of several hours and the ability to quantify its plasma levels in clinical settings [19].

The objective of this study is to measure the concentration of Mid-regional pro-adrenomedullin (MR-pro ADM) in the blood serum of pregnant women, both with and without GDM. Additionally, the study seeks to explore any possible connections between MR-proADM levels and the presence of GDM during the third trimester of pregnancy.

2. RESULTS

Results illustrated in Table 1 showed that the age, BMI and number of pregnancies in GDM patients were significantly higher ($p \leq 0.05$) than those in NGDM subjects whereas a gestational age of GDM patients was significantly lower ($p \leq 0.05$) than that of NGDM subjects

Table 1. Demographic Data for all participants

Characteristics	NGDM (N=45)	GDM (N=45)	*P*-value
Age (Years)	27.76±4.86	31.56±6.91	0.003*
BMI (kg/m2)	23.28±2.56	26.30±2.47	0.0001*
Gestational age (weeks)	35.40±3.87	33.36±4.35	0.021*
No. of pregnancy	3.42±1.56	4.78±2.34	0.002*

* Significance at $P<0.05$ NGDM: pregnant women with no gestational diabetes, GDM: pregnant women with gestational diabetes, N: number, BMI: body mass index, SD: standard deviation, No. of pregnancy: number of pregnancy

Results Illustrated in Table 2 showed that the levels of all studied diabetes markers which include fasting serum insulin (FSI), FBG, Glycosylated hemoglobin (HbA1c) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were significantly higher in pregnant women with GDM than those of controls.

Moreover, the levels of MR-proADM in GDM females were significantly higher than those of controls in a parallel with the elevations in the diabetic marker studied.

A statistically significant difference was seen in the serum MR-proADM levels between the two participating groups ($p<0.05$, unpaired t-test). MR-proADM serum levels were significantly higher in GDM patients (mean= 455.92±71.20 pg/mL) than in the non-GDM groups (258.24 ± 22.10 pg/ml; $p<0.05$). These results indicated a relationship between higher serum MR-proADM levels and the development or progression of GDM. Additionally, a correlation has been observed between blood levels of MR-proADM and the severity of GDM.

The results illustrated in Table 3 show the Pearson's correlation analysis for the association between the serum biomarker levels. A significant positive association was found among serum levels of MR-proADM and studied variables.

Table 2. Biochemical characteristics for pregnant women with no gestational diabetes (NGDM) and pregnant women with gestational diabetes (GDM)

Marker	NGDM (N=45)	GDM (N=45)	*P*-value
FSI (mU/L)	3.24±0.67	7.76±3.52	<0.001***
FBG (mmol/L)	4.74±0.63	8.12±3.10	<0.001***
HbA1c (%)	4.76±0.35	6.91±1.19	<0.001***
HOMA-IR	0.68±0.15	2.82±1.68	<0.001***
MR-proADM (pg,/ml)	258.24±22.10	455.92±71.20	<0.001***

*** Very highly significant at P<0.001. NGDM: pregnant women with no gestational diabetes, GDM: pregnant women with gestational diabetes, FBG: Fasting blood glucose, FSI: Fasting serum insulin, HbA1c: glycated hemoglobin, MR-proADM: mid-regional pro-adrenomedullin , HOMA-IR: Homeostasis model assessment of insulin resistance, N: number, SD: standard deviation, ml: milliliter, mmol: milli mole, L: Liter, pg: picogram,

Table 3. Spearman's correlation of MR-proADM serum with the studied variables for pregnant women with and with no GDM

Variables	r- value	*p*- value
FBG mmol/L	0.538	<0.001***
HbA1c%	0.687	<0.001***
FSI mU/L	0.601	<0.001***
HOMA-IR	0.598	<0.001***

*** very highly significant at P<0.001. FBG: fasting blood glucose, HbA1c: glycated hemoglobin, FSI: fasting serum insulin, HOMA-IR, Homeostasis model assessment of insulin resistance.

3. DISCUSSION

Although the pathophysiology of impaired β-cell activity is yet unknown, GDM is thought to be a state of insufficient insulin synthesis by pancreatic β-cells in an insulin resistance situation. The current investigation found that MR-proADM levels in the serum were greater in GDM affected women than in healthy pregnant women. This study supports previous research which showed that pregnant women in good health had lower serum MR-proADM concentrations than those with GDM. Suggesting that there may be a connection between the pathophysiology of GDM and increased circulating ADM [17]. Obese people exhibit greater plasma ADM concentrations and also patients with type 2 diabetes mellitus [20]. In addition, amniotic fluid from diabetic pregnancies has higher ADM concentrations than control studies [21]. When considered collectively, these findings suggest that adipose tissue contains ADM and its receptors and that ADM may play a role in the etiology of insulin resistance in GDM, a condition commonly associated with diabetes. Thus, we postulated that the excessive production of ADM by adipose tissue could have negative effects on lipogenesis, reducing the amount and quality of lipids in the maternal circulation available for transfer to the fetus. This, in turn, could lead to fetal overgrowth and excessive adiposity. These include modulating the effects of tumor necrosis factor (TNF)-α and opposing the effects of insulin. Therefore, adjusting ADM and studying its impact in adipose tissues could be a unique way to lower the risk of GDM and fetal overgrowth [18]. Finding from the current study, reports that FBG, FSI, and insulin resistance were significantly higher in GDM patients than in women with healthy pregnancy, which agreed with the previous studies [22, 23].

Elevated insulin resistance may arise from decreased insulin sensitivity, which is typically observed during pregnancy in order to protect the fetus's glucose reserves. Consequently, this is linked to the impact of hormones secreted by the placenta, as well as physiological changes in some pregnant women that result in impairment to their glucose tolerance, which may cause GDM [24]. Physiological insulin resistance can be shown with increasing gestational age due to the placenta's production of lactose, estrogens, progesterone, and maternal adrenocorticotropic hormones [23]. However, other research suggested that the primary cause of insulin resistance in GDM is post-cellular damage, which is shown by decreased tyrosine phosphorylation in insulin receptors and insulin receptor substrate-1, while increased serine phosphorylation inhibits insulin signaling by preventing glucose transporter type 4 (GLUT4)-translocation [25]. Additionally, compared to pregnant women without GDM, pregnant women with GDM may have worse insulin sensitivity by 30–40%

and increased peripheral insulin resistance, primarily in skeletal muscle, as well as reduced insulin secretion. Additionally, the secretion of insulin is significantly reduced in response to hyperglycemia, suggesting a primary beta cell deficiency that complicates the process of compensating for elevated insulin resistance and suggests multiple insulin action deficiencies in the long term. These factors contribute to the etiology of gestational diabetes [25].

As illustrated in Table 3, results indicated a significant positive correlation between the MR-proADM concentration and the previously described parameters. Serum MR-proADM concentration increased in parallel with increases in FBG, FSI, HbA1c, and HOMA-IR concentrations. It is thought that increased MR-proADM concentrations may promote the development of insulin resistance and beta cell dysfunction, even if the exact mechanism underlying this process is still unknown [17]. Some limitations were encountered in the present study including that this study was carried out at a single center so additional long-term clinical studies are required to assess whether MR-proADM level detection aids in early diagnosis and prognosis, and whether higher serum levels of MR-proADM increases the risk of GDM in pregnant women. Secondly, lifestyle factors like exercise and diet were not considered. Third, difficulties with getting pregnant women to provide information and a blood sample.

4. CONCLUSION

The study's findings support MR-proADM as a biomarker for the early detection of GDM. An elevated serum level of MR-proADM may play a role in the etiology of GDM. When compared to healthy controls, women with GDM had high levels of MR-proADM. Furthermore, MR-pro-ADM was positively correlated with HbA1c, FSI, HOMA-IR, and FBG. The MR-proADM exact mechanism in glucose metabolism remain unclear as of the moment.

5. MATERIALS AND METHODS

Patients

An observational case-control study was conducted on a cohort of Iraqi pregnant women with normal glycemic control and those with GDM. The participants in this study were chosen from pregnant women seeking medical care at AL Alawiya Maternity Hospital in Baghdad, Iraq in the duration from February 1st to the 30 of July 2023. The research protocol has been approved by the College of Pharmacy Scientific and Ethical Committee, University of Baghdad (RECAUBCP542023K), after the participant was given full information about the study's goal, they gave their informed consent. All the participants were interviewed by the researcher and demographic data were obtained from them and recorded in a data collecting sheet, including age, body weight and height, number of pregnancies, gestational age, past medical history. A total number of 100 participants initially participated in the study. Nevertheless, the blood samples from ten patients were omitted from the study because of their hemolysis. The remaining ninety patients were categorized into two group: **Group A** consisted of forty-five pregnant women who were diagnosed with GDM, representing the patient group. And **Group B** consisted of forty-five healthy pregnant women without GDM, representing the control group.

Inclusion criteria

Patients were selected to be previously diagnosed with GDM diagnostic criteria [13-15]. The diabetic pregnant patients must be within age above 18 years. HbA1c equal or more than (5.9%).

Exclusion criteria

- Women suffer from other endocrinopathies rather than diabetes, women with cardiac, renal, liver and autoimmune disease. Women with malignancy or taking drugs that may interferes with glycemic control.
- Women who have inborn errors of metabolism, such as lysosomal storage disease or glycogen storage disease.

Specimen collection

Ten milliliters of venous blood were taken by venipuncture from each participant. A volume of 2 milliliters of the blood sample were placed into EDTA tube for the purpose of conducting the HbA1c assay. After transferring the rest of the blood sample (8 mL) to a gel tube, it was centrifuged at a speed of 3000 rpm

for 10 minutes. Subsequently, the tube was left undisturbed for 30 minutes to allow the blood to clot and separate the serum. The hospital's laboratory utilized a fraction of the serum to quantify FBG. The serum was stored in Eppendorf tubes at -20°C until the MR-proADM level was tested.

Measurement of MR-proADM levels

Plasma MR-proADM levels were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA). MR-proADM can be identified using this "sandwich enzyme immunoassay," which has a detection range of 15.63-1000pg/ml. The procedures have been carried out according to the manufacturer's instructions. Within and between assays, variations were less than 10%.

Other Biochemical Parameter

An enzymatic colorimetric approach was used to assess FBG [26]. HbA1c is biomarker of glycemic control in DM condition because it describes blood glucose levels in the last 60-90 days [27]. The measurement FSI was conducted using Commercial competitive inhibition ELISA kits provided by Cloud-Clone-Corp. An index of insulin resistance was calculated using the FSI and FBG concentrations. HOMA-IR, also known as Homeostasis Model Assessment—Insulin Resistance, is a method used to assess insulin resistance in the body. The formula for calculating HOMA-IR is as follows: HOMA-IR equals the product of glycemic level in millimoles per litre and fasting insulin level in milliunits per litre, divided by 22.5 [28].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS, IBM, USA, version (25). The Shapiro–Wilk test was used to test the normality of the results. Continuous variables were expressed as mean ± SD of the values. For normally distributed groups, the mean differences of two independent groups were measured by unpaired t-test. Pearson correlation was performed to determine the relation between MR-proADM and study variables, and the correlation coefficient (*r*) was used to assess the association strength among parameters. A probability that equals or less than (0.05) indicates a significant difference, less than (0.01) means a highly significant difference, and less than (0.001) is considered very highly significant [29,30].

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