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Evaluating Serum Adiponectin Levels with Respect to the Results of Oral Glucose Tolerance Test in Dysglycemic Pregnant Females

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Abstract:

The hormone adiponectin has antidiabetic and anti-inflammatory effects. Gestational diabetes is hyperglycemia that develops in middle of pregnancy. The oral glucose tolerance test is used to screen for gestational diabetes. As a measure for insulin resistance, the (QUICKI-index), utilizes fasting insulin and fasting glucose levels to evaluate the sensitivity to insulin. Pregnancy is a state of insulin resistance and the role played by the adiponectin in the progression from euglycemia into prediabetes is a matter of conflict.

Aim: to evaluate adiponectin levels in pregnancy and to find out if it can be used as a marker for developing GDM.

Subjects and methods: a cross-sectional study involved 40 pregnants of 18–40 years of age at their second trimester and having BMI of 25-30 Kg/m2. After performing the OGTT, pregnants were divided into:

A. Impaired glucose tolerance (IGTT) group: 23 pregnant with a mean age of 25.9 ± 6.1 years. *B. Gestational diabetes (GDM) group:* 13 pregnant with an age of 29.5 ± 3.9 years. The following parameters were measured: FBG, 2-hour RBG, fasting insulin, serum adiponectin, QUICKI-index.

Results: There was no significant statistical difference with respect to; age (p= .855), BMI (p= .071), and gestational age (p= .239). Serum adiponectin was significantly lower in the GDM group (p= .028). The FBG was significantly higher in the GDM group, (p<0.0001). Similarly, the 2-hour BG, (p<0.001). The fasting serum insulin was significantly higher in the GDM group, (p<0.0001). Pregnant with GDM had significantly lower QUICKI-index in comparison to those with IGTT (p<0.0001). Finally, the blood level of adiponectin showed positive correlation with QUICKI-index of insulin resistance, r (38) = ,499,

p <0.0001.
Conclusions: serum adiponectin is reduced in pregnant with insulin resistance and might be an independent risk factor for developing diabetes. It might be of help in predicting the progression from euglycemic into overt diabetic states.
Abbreviations: OGTT = oral glucose tolerance test, FBG = fasting blood glucose, RBG = random blood glucose, GDM = gestational diabetes mellitus, IGT = impaired glucose tolerance, BMI = body mass index, T2DM = type 2 diabetes mellitus.

Introduction:
Adiponectin is 30 KDa hormone produced by adipocytes [1]. It has potent antidiabetic activities as well as anti-inflammatory actions where it down-regulates several mediators of inflammation like TNF-α and interleukin-6 [2]. Researches had demonstrated a positive correlation between adiponectin and the tissue sensitivity to insulin as well as a negative correlation with developing type 2 diabetes (T2DM) [3, 4]. The adipokine increases the tissue`s sensitivity to insulin and the metabolism of glucose beside its anti-inflammatory effects [4]. Studies reported a decrease in serum adiponectin in insulin-resistant states, suggesting using it as a surrogate for insulin resistance [5]. The T2DM at those with genetic predisposition may present itself as a prediabetes which is a condition that involves a higher-than-normal blood glucose, but not to the point that can be designated as T2DM [6]. Prediabetes may be presented as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). About third of the population have prediabetes but the vast majority of them are zero symptomatic and are unaware of having such a condition. Prediabetes, if untreated, may progress into T2DM with a rate of about 10% per year, and by itself can increase the cardiovascular risk and cerebrovascular events [7].
Gestational diabetes mellitus (GDM) is the hyperglycemia that develops in middle of pregnancy. The risk factors for developing GDM being advanced age and having increased body mass index (BMI). Pregnant females with GDM have increased risk to have GDM during further pregnancies, and to develop T2DM at some point in their lives [8].
The oral glucose tolerance test (OGTT) is very useful test for screening gestational diabetes or insulin resistance during pregnancy. In this test, a drink of standardized concentration of glucose is given to the patient via mouth, and two hours later, blood glucose levels are measured beside those taken before starting the test [9]. There are several parameters that measure the resistance to insulin action like fasting insulin levels, Matsuda-index, Homeostatic model assessment (HOMA), Glucose/insulin ratio (G/I ratio), and the Quantitative Insulin Sensitivity Check Index (QUICKI-index). QUICKI-index utilizes the fasting insulin and fasting glucose levels to evaluate the sensitivity to insulin and the resistance to its actions. It is inversely correlated with fasting insulin levels. The normal reference range of QUICKI-index is > 0.45, values suggesting insulin resistance ranges from 0.30 - 0.45, and values suggesting the diagnosis of diabetes are < 0.30 [10].
Despite the strong evidences connecting the development of overt diabetes with reduced adiponectin levels, yet, the exact role played by the adipokine in the progression from euglycemia into prediabetes is a matter of conflict. As the prevalence of type-2 diabetes mellitus (T2DM) and the blood`s adiponectin levels vary significantly among different population of various races and ethnicities, it is vital to assess the fidelity of adiponectin and dysglycemia interaction in various population including pregnant women [11].
Aim of the study: to evaluate the serum adiponectin levels in a cohort of dysglycemic pregnant and to find out if it has a correlation with insulin resistance, and if so, can it be used as a marker for developing GDM?

Subjects and methods:
After the clearance of Warith Al-Anbyaa College of Medicine, the study was conducted as a prospective

cross-sectional type at the Imam Zain-ul-abiden hospital/ Kerbala/ Iraq for the period from October 2021 to June 2023. The study involved 40 pregnant at their 24-28 gestational week and with no diabetic history of any kind. The study included pregnant females between the age of 18–40 years, at their second trimester and of BMI that ranged from 25-30 Kg/m^2.

Exclusion criteria: any participant with confirmed diabetes of any type including the known gestational diabetes at previous pregnancy, preeclampsia, high blood pressure, polycystic ovary syndrome, and those taking medications such as oral hypoglycemic agents, or recovering from a major trauma or serious disease.

The participants were referred to the diabetology center to perform OGTT for a variety of reasons including suspicion of being prediabetics, having macrosomic babies before, HbA1C $\geq$ 5.7%, polyhydramnios, being obese with more than 25 kg/m^2 BMI, having signs of insulin resistance like acanthosis nigricans, and so on. For each participant, a two hours OGTT was done in which after 12 hours period of water only fasting, two milliliters of venous blood were withdrawn at time zero. Pregnant patients were instructed to drink a 250 ml of syrup containing 75 mg of anhydrous glucose and remain seated the entire procedure. Then samples were collected and indexed as per collection time into 120-minute samples. The samples allowed to clot for one hour at 25 ℃ prior to centrifugation at 1000×g for 20 minutes. The precipitant was discarded and only the supernatant was utilized for chemical assessment. After performing the OGTT, the participants were divided into two groups basing on their OGTT results as follows:

A. Impaired glucose tolerance (IGTT) group: this group included all the pregnant participants with an impaired GTT. It included 23 females with a mean age of (25.9 ± 6.1) years.

B. Gestational diabetes (GDM) group: this involved all the participants whom returned to be of diabetics after the OGTT. It comprised 13 pregnant with a mean age of 29.5 ± 3.9 years. The GDM was diagnosed based on the criteria published by the World Health Organization (WHO) which, in turn, were recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in which fasting blood glucose (FBG) exceeds 125 mg/dl or a blood glucose level of 199 mg/dl two hours after a 75 g oral glucose tolerance test (OGTT). The diagnosis of IGTT was implied when the OGTT gave a FBG level of 100-125 mg/dl or/and a 2-hour blood glucose level of 140-199 mg/dl [12].

The QUICKI-index was calculated according to the following equation: 1 / [log (Fasting insulin in mIU/L) + log (Fasting glucose in mg/d)] [13].

The plasma glucose level estimated by glucose oxidase method and the adiponectin level was measured using sandwich enzyme-linked immunosorbent assay (ELISA) technique utilizing human ADP/Acrp30 (Adiponectin) provided by (Elabsciences Biotechnology Inc., Houston, Texas, USA). The test`s sensitivity to adiponectin was 0.1 pg/ml according to the manufacturer instructions.

Results

For the 40 participants underwent OGTT, 13 (32.5%) of them turned to have gestational diabetes mellitus (GDM) and 27 (67.5%) were having impaired glucose tolerance (IGTT) as shown in figure (1).

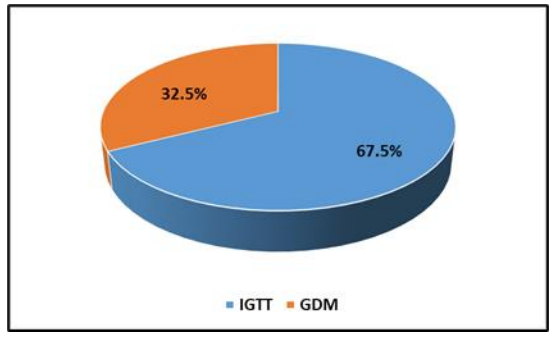

Figure 1: the distribution of pregnant participants after the results of the OGTT. The majority of pregnant (67.5%) were having impaired glucose tolerance (IGTT) whereas the remaining pregnant females (i.e., 32.5%) were diagnosed as having gestational diabetes mellitus (GDM).

Table (1) summarizes the results of comparing means of different study parameters between both groups. The study results revealed the following: pregnant females with IGTT had a mean age of (26.9 ± 5.2) years while those with GDM had their mean age around (27.2 ± 3.9) years. There was no significant statistical difference with respect to age (p= .855). Additionally, the BMI in both groups showed no significant statistical difference as well, (p= .071) where those with IGTT had their BMI around (27.3 ± 2.3) kg/m^2 whereas those with diabetes had BMI of (25.5 ± 4.1) kg/m^2. The results revealed no significant statistical difference with respect to gestational age (p= .239) where it was (21.3 ± 2.2) weeks in the IGTT group versus (22.1 ± 1.4) weeks in the GDM group.

Pregnant females with GDM expressed significantly lower adiponectin levels than those with IGTT, (9.73 ± 2.16) µg/ml versus (12.03 ± 3.3) µg/ml, respectively, (p= .028).

The FBG was significantly higher in the GDM group in relation to IGTT group, (p<0.0001) where it was (198.7 ± 20.6) mg/dl in pregnant with GDM compared to (114.8 ± 9.9) mg/dl in the IGTT pregnant. Similarly, the 2-hour blood glucose was significantly higher in the GDM group (198.7 ± 20.6) mg/dl compared to the (162.2 ± 17.3) mg/dl in the IGTT group (p<0.001).

The fasting serum insulin was significantly higher in the GDM group compared to the IGTT group, (21.1 ± 2.06) mIU/ml versus (16.1 ± 1.63) mIU/ml for the GDM and IGTT groups respectively, (p<0.001).

Pregnant females with GDM had significantly higher levels of insulin resistance as reflected by the significantly lower QUICKI-index in comparison to those with IGTT (p<0.001), where it was (0.268 ± 0.04) versus (0.297 ± 0.01) for the GDM and IGTT groups, respectively.

Table 1: summary of results after comparing the IGTT participants with those of GDM. Values are expressed as mean and standard deviation unless mentioned otherwise. The level of significance was set at 0.05.

Parameter	***IGTT (n=27)***	***GDM (n=13)***	***p value***
Age (years)	26.9 ± 5.2	27.2 ± 3.9	0.855
BMI (kg/m^2)	27.3 ± 2.3	25.5 ± 4.1	0.082
Gestational age (weeks)	21.3 ± 2.2	22.1 ± 1.4	0.239
Serum adiponectin (µg/ml)	12.03 ± 3.3	9.73 ± 2.16	0.028*
FBG (mg/dl)	114.8 ± 9.9	154.1 ± 17.6	<0.0001*
2-hour blood glucose (mg/dl)	162.2 ± 17.3	198.7 ± 20.6	<0.0001*
Fasting serum insulin (µU/ml)	16.1 ± 1.63	21.1 ± 2.06	<0.0001*
QUIKI-index	0.297 ± 0.01	0.268 ± 0.04	<0.0001*

- * Significant statistical difference.
- BMI = body mass index, FBG = fasting blood glucose, QUICKI = Quantitative Insulin Sensitivity Check Index

The results revealed a significant positive correlation between serum adiponectin level and QUICKI-index of insulin resistance, r (38) = ,499, p <0.001, as depicted in figure (2).

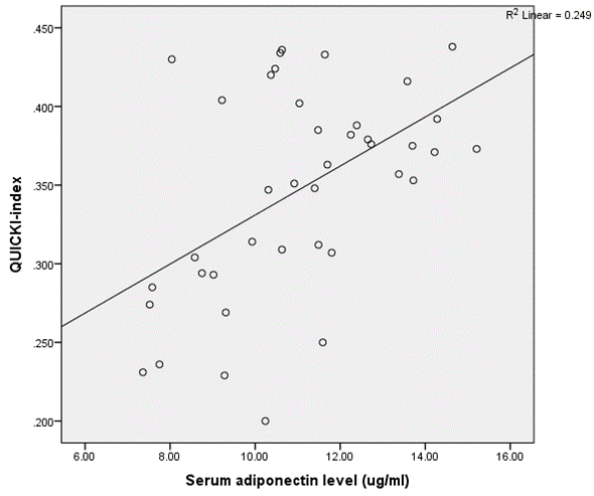

Figure 2: the positive correlation between insulin resistance as expressed by the QUICKI-index and the blood level of adiponectin in all participants. The correlation was significant (p<0.001).

Discussion:

The results of the current study revealed that serum adiponectin levels are reduced in pregnant females with IGTT as well as in those with GDM, nevertheless, the reduction was more pronounced in the diabetics. This observation is in concordance with that reported by other studies [14, 15]. For instance, a study conducted by Irving *et. al*., concluded that circulating levels of adiponectin were reduced in pregnant women with GDM, which they thought it could have been secondary to resistance to insulin action [16]. Similar results were obtained by a study that revealed a decline in the adipokine level in the sera of pregnant females with GDM at their second trimester [17]. On the other hand, some other studies had contradicted our results by showing a steady level of adiponectin in GDM throughout pregnancy [18, 19] or a reduced level at the end of pregnancy rather than the second trimester [20]. This controversy in the reported figures might be attributable to the fact that the surveyed participants were having different body mass indices, or because of the different methodologies in ruling in or out patients and to different study settings. Adiponectin stimulates the activity of skeletal muscles and hepatocytes adenosine monophosphate-activated protein kinase (AMPK), inhibits the enzymes of gluconeogenesis, and enhances the β oxidation of fatty acids [21]. Owing to the aforementioned effects of adiponectin, the latter reduces blood glucose levels. Therefore, an inverse association between low adiponectin levels and insulin resistance is postulated. Several researches indicated an increase in GDM risk in females with reduced adiponectin [22, 23].

The current study also demonstrated that low serum adiponectin level is an independent correlate of beta-cell function, as evidenced by the significantly reduced QUICKI-index, in the second trimester of pregnancy. The mean level of adiponectin was significantly lower in the diabetic pregnant in comparison to those with IGTT. These significant differences in the adiponectin levels can't be attributed to the wights or the gestational period of participants since we controlled both of these two confounders by the strict inclusion criteria which took into consideration the matching in BMI and gestational age. The lower the adiponectin level the higher the resistance to insulin action and consequently the lower the QUICKI-index, the same results were reported by an Iranian study [24]. Another research reported that upon the progression of pregnancy, the patients with GDM revealed reducing levels of the adipokine compared to those who were glucose tolerant [25].

Conclusions:

Serum adiponectin level is reduced in both GDM and IGTT. The reduction of the adipokine reflects the

increased level of insulin resistance in such affected pregnancies. Adiponectin can be used as an independent risk factor for the development of GDM, yet further researches are required.

Conflict of interests: none to be declared by authors.

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