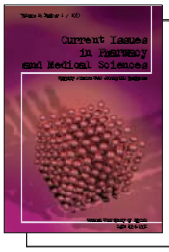

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Does adiponectin play a role in gestational diabetes?

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ABSTRACT

Current literature provides contradictory information on the role of adiponectin (AdipoQ) in the course of gestational diabetes (GDM). The aim of the study was to measure AdipoQ concentration in blood of women with GDM and to find relationships between this adipokine and clinical and biochemical parameters. The study group included 50 women diagnosed with GDM between 24 and 28 weeks of gestation who underwent routine prenatal tests for GDM in compliance with the guidelines of the Polish Diabetes Association. All patients underwent clinical and laboratory evaluation at GDM diagnosis. Laboratory tests included serum AdipoQ concentration, fasting glucose, fasting insulin, OGTT and lipid parameters in serum. AdipoQ concentrations did not differ significantly between the groups during gestation (p=0.7054). In the subgroup (2h glucose level in the OGTT 200 mg/dl) the concentration of AdipoQ tended to be decreased as compared to the remaining patients from the study and control groups, though the decline was insignificant (p=0.0541). The concentration of AdipoQ in the subgroup was about 20% lower than in the other patients from the study group. No correlations, except with the neonatal weight (r= - 0.29, p<0.05), were found between AdipoQ and the studied parameters. The GDM group showed significantly elevated fasting glucose, insulin, HOMA-IR values, total cholesterol, LDL-cholesterol and triglicerydes, as compared with the control group (p.05). These results lead to the conclusion that women with newly diagnosed and promptly treated GDM have normal adiponectin level. A negative correlation between AdipoQ level and the birth weight may suggest that this adipokine plays a role in the control of the birth weight especially in the incidence of macrosomia.

Keywords: adiponectin, gestational diabetes, insulin resistance, birth weight, macrosomia

INTRODUCTION

Gestational diabetes mellitus (GDM) is any carbohydrate intolerance (impaired fasting glucose, impaired glucose tolerance or diabetes) diagnosed for the first time during pregnancy [24]. Current data indicate that GDM is a slowly developing form of type 2 diabetes in the stage of increasing insulin resistance arising from the hormonal activity of the placenta. GDM usually subsides after pregnancy but it remains a type 2 diabetes risk factor for the mother in the future as a woman once diagnosed with GDM has a sevenfold increased risk of developing type 2 diabetes [10].

The key role of insulin resistance, which is the pathogenic mechanism common for obesity, type 2 diabetes and GDM, points to the need to find characteristic alterations in the factors that affect this phenomenon. It has been proven that a crucial role in the regulation of insulin sensitivity in tissues is played by adipokines i.e. compounds secreted by the visceral adipose tissue [6]. Among many discovered adipokines, in recent years adiponectin (AdipoQ) has been an object of great interest. AdipoQ is the main adipokine of adipose tissue largely known for its insulin sensitizing properties [7]. It has been reported that low AdipoQ in serum correlates with elevated insulin resistance and development of metabolic disorders, including type 2 diabetes and cardiovascular complications [12]. Current literature provides not only little but also contradictory information on the role of AdipoQ in the course of GDM and the changes after delivery. Retnakaran et al. have shown a decline in its concentration accompanied with increased insulin resistance during gestation, which would corroborate the fact that this cytokine participates in the pathogenesis of insulin resistance [26]. However, the studies of others demonstrate that the concentration of AdipoQ may depend on the severity of insulin resistance and carbohydrate metabolism disorders [28].

Therefore, the aim of the study was to measure AdipoQ concentration in blood of women with GDM and to search for correlations of this adipokine with selected clinical and biochemical parameters.

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MATERIALS AND METHODS

Patients. The study was conducted on pregnant women from the Lublin region who underwent routine prenatal tests for GDM in compliance with the guidelines of the Polish Diabetes Association [24]. The study group included 50 women diagnosed with GDM between 24 and 28 weeks of gestation. The control group comprised 21 healthy pregnant women with a normal OGTT. The patients enrolled into the study gave written informed consent to participate and filled out a questionnaire which included the following information: patient's age, height, pregestational weight, medical, family and obstetric history. The study protocol was accepted by the Bioethics Committee of the Medical University in Lublin.

Study design. All patients underwent clinical and laboratory evaluation at GDM diagnosis i.e. between 24 and 28 weeks of gestation. Anthropometric measurements were obtained from all participants. The weight was taken in light clothes while the height without shoes. Body mass index BMI was calculated according to the formula: weight (kg)/height (m^2). Additionally, a retrospective analysis of anthropometric measurements was performed before gestation. Laboratory evaluation at GDM diagnosis included routine laboratory tests (fasting glucose, fasting insulin, total cholesterol, HDL cholesterol and triglycerides in serum). AdipoQ concentration was measured in serum at GDM diagnosis.

The assays were performed with the use of a routine laboratory method with a biochemical analyzer ADVIA 1650 with the Siemens' Advia Chemistry reagent sets. The atherogenic index was calculated based on the concentration of triglycerides and HDL cholesterol [5]. The index above 0.5 indicated an increased risk of cardiovascular complications. The LDL cholesterol con- centration was calculated with the Friedewald equation [21]. Additionally, the indirect index of insulin resistance – HOMA–IR (Homeostasis Model Assessment – Insulin Resistance) was calculated [16]. Adiponectin concentration measurement was performed with the use of Human Adiponectin ELISA, High Sensitivity from BioVendor according to the recommendations of the manufacturer. The results were read on a microtiter plate reader ELx 800 (Bio-Tek Co Ltd, USA). The laboratory analyses were carried out in the Central Laboratory of the Clinical Hospital no. 4 (SPSK4) and the Department of Laboratory Diagnostics of the Medical University in Lublin.

RESULTS

Clinical characteristics of the study and control groups

Table 1 shows the clinical characteristics of the study and control groups. No significant differences were found between the groups in terms of the patients' weight and BMI before and during pregnancy i.e. at GDM diagnosis. The GDM group included more multipara women than the control group. No significant differences were found between the study and control groups in terms of the neonatal weight and medical history concerning the number of miscarriages and diabetes in previous pregnancies. More patients had family history of diabetes in the study than in the control group.

Table 1. Clinical characteristics of the study and control groups

Studied parameter		Study group	Control group
Age (years)		31.0 (29.0-32.0)	29.0 (26.0-33.0)
Height (m)		1.63 (1.6-1.67)	1.64 (1.6-1.69)
Weight (kg)	before gestation	61.5 (58.0-66.0)	58.0 (54.7-61.7)
	during gestation	71.0 (66.7-75.0)	69.0 (63.2-75.0)
BMI (kg/m^2)	before gestation	23.0 (21.6-25.8)	21.6 (20.7-23.2)
	during gestation	26.9 (24.8-30.0)	25.6 (24.0-28.1)
Pregnancy	first	20 (40%)*	15 (72%)
	second	19 (38%)	4 (19%)
	third and subsequent	11 (22%)	2 (9%)
Birth weight (g)		3205.0 (3100.0-3650.0)	3300.0 (3245.0-3475.0)
Gestational age (weeks)		26.0 (25.0-28.0)	28.0 (24.0-28.0)
History of miscarriage	no	31 (62%)	15 (72%)
	one	15 (30%)	6 (28%)
	two	4 (8%)	0 (0%)
History of GDM	no	43 (86%)	21 (100%)
	yes	7 (14%)	0 (0%)
Family history of diabetes	no	22 (44%)*	18 (85.7%)
	yes	28 (56%)	3 (14.3%)

Quantitative variables – median (interquartile range)
Qualitative variables – number of observations (percentage)
* $p<0.05$ in comparison with the control group

Evaluation of metabolic parameters in the study and control groups

The evaluation of glycemia, insulin resistance and lipids in both groups is shown in Table 2. At GDM diagnosis the study group showed significantly elevated fasting glucose, fasting insulin and HOMA-IR values as compared with the control group. Significant changes in the lipid profile were found in the study group during pregnancy as compared to the control group. What is more, the concentration of total, LDL cholesterol and triglycerides was higher while HDL cholesterol was significantly lower than in the healthy subjects.

Table 2. Evaluation of metabolic parameters in the study and control groups at 24-28 week of gestation

Studied parameter		Study group	Control group
Fasting glucose (mg/dl)		87.0 (79.0-93.0)*	78.0 (74.0-81.0)
Fasting insulin (mU/l)		10.9 (7.0-15.0)*	6.5 (5.4-7.3)
HOMA-IR		2.4 (1.9-3.5)*	1.2 (1.1-1.4)
glucose in OGTT (mg/dl)	0 min.	87.0 (79.0-93.0)*	78.0 (74.0-81.0)
	120 min.	167.0 (156.0-189.0)	–
Cholesterol (mg/dl)		268.0 (250.0-289.0)*	210.0 (194.5-230.7)
LDL cholesterol (mg/dl)		150.1 (134.6-165.0)*	105.0 (91.5-113.0)
HDL cholesterol (mg/dl)		70.1 (65.0-76.0)*	80.0 (70.7-86.5)
Triglycerides (mg/dl)		245.0 (223.0-268.0)*	180.0 (167.25-198.5)

Quantitative variables – median (interquartile range)
* $p<0.05$ in comparison with the control group

Evaluation of adiponectin concentration in the study and control groups

No significant differences were found in terms of AdipoQ concentration in pregnancy between the groups.

Figure 1. shows the median with the interquartile range for the study and control groups 15.8 (12.8-17.8) μg/ml and 15.9 (10.4-18.4) μg/ml respectively.

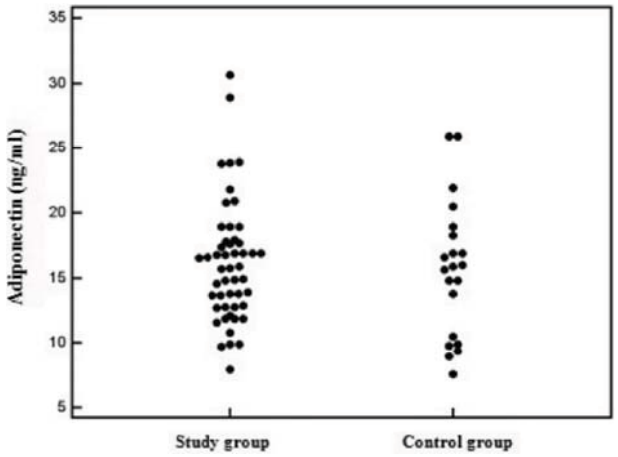

Fig. 1. Comparison of adiponectin levels in the study and control groups in gestation (p=0.7054)

Evaluation of the correlations between adiponectin concentration and clinical features in the study and control groups

Tables 3 and 4 present relations between adiponectin concentration and the studied parameters in the study and control groups. In the GDM group AdipoQ concentration significantly negatively correlated with the neonatal weight (r=-0.29, p.05); no other correlations between the adiponectin concentration and the studied clinical features were found in the study and control groups (Table 3). In both groups during pregnancy no significant correlations were observed between the concentration of AdipoQ and glycemia and HOMA-IR values. No differences were detected between the studied adipokine and the lipid parameters (Table 4.).

Table 3. Evaluation of the correlations between adiponectin concentration and clinical features in the study and control groups

Studied parameter		Study group	Control group
Age (years)		-0.221	0.025
Height (m)		0.149	-0.286
Weight (kg)	at 24-28 weeks	0.213	-0.043
BMI (kg/m^2)	at 24-28 weeks	0.015	0.095
Sequence of pregnancy		-0.038	-0.208
Birth weight		-0.290*	-0.012
Week of gestation		0.070	0.053
History of miscarriage		0.057	-0.183
History of GDM	no	15.8 (12.8-17.9)	-
	yes	16.6 (13.2-16.9)	-
Family history of diabetes	no	14.3 (11.9-16.9)	-
	yes	16.6 (13.9-18.4)	-

With yes/no categories the Mann–Whitney U test was used to compare the values

* p<0.05 in the Spearman's rank correlation

Table 4. Evaluation of the correlations between adiponectin concentration and metabolic parameters in the study and control groups during gestation in the Spearman's rank correlation test

Studied parameter		Study group	Control group
Fasting glucose (mg/dl)		0.065	-0.253
Fasting insulin (mU/l)		-0.053	-0.213
HOMA-IR		0.053	-0.290
glucose in OGTT (mg/dl)	0 min.	0.065	-0.253
	120 min.	-0.040	–
Cholesterol (mg/dl)		-0.124	0.319
LDL cholesterol (mg/dl)		-0.120	0.261
HDL cholesterol (mg/dl)		-0.050	0.287
Triglycerides (mg/dl)		-0.054	0.224

DISCUSSION

Despite the fact that many authors have emphasized the multidirectional role of AdipoQ in obesity, diabetes type 2, metabolic syndrome or GDM, especially the link between hypoadiponectinemia and those disorders, pathophysiological implications of this adipokine have not been fully explained [2,8,31]. Current studies show that AdipoQ concentration in serum of women with GDM does not differ from its level in healthy pregnant subjects, which corroborates the findings of some authors [19,28] but contradicts the results of others [17,26]. Thyfault et al. explicitly showed that AdipoQ concentration may depend on the severity of insulin resistance and carbohydrate metabolism disorder [28]. In the literature to date, the results of AdipoQ determination are not clear. Some authors who showed hypoadiponectinemia often demonstrated a slightly different metabolic phenotype of the population with GDM. Hypoadiponectinemia significantly correlated with insulin resistance parameters and consequently with the severity of carbohydrate metabolism disorders [18, 26]. What is more, the authors of the Hyperglycemia and Adverse Pregnancy Outcome Study also demonstrated depressed AdipoQ concentration with accompanying increased maternal glucose level [15]. No clear-cut criteria, neither the diagnostic, nor the treatment ones, may underlie the discrepancy in the results of the studies from various parts of the globe, which means that the populations of GDM women are heterogeneous and metabolically incomparable. In both Americas this disorder is diagnosed with at least two abnormal values of the 100g 3h oral glucose tolerance test. Whereas impaired glucose tolerance (IGT) is diagnosed when only one value is abnormal. Therefore, a group of GDM diagnosed this way is more homogeneous metabolically than the pregnant women in Poland where the doctors follow the WHO guidelines modified by the Polish Diabetes Association. According to these recommendations, GDM is diagnosed when any impaired carbohydrate metabolism is found, including IGT. That is why this group has a heterogeneous metabolic phenotype. It is worth emphasizing the aspect of completely dissimilar diagnostic thresholds for glucose tested while fasting and after glucose load. Retnakaran et

al. revealed high heterogeneity of the group of IGT pregnant women as the patients with abnormal glucose level after one hour had metabolic features similar to those of the GDM patients, while after two and three hours the results were close to those of the healthy pregnant women [25]. Di Cianni et al. demonstrated parallel correlations and showed that the patients with one abnormal glucose tolerance test value placed somewhere between normal glucose tolerance and GDM are characterized by impaired insulin secretion and decreased insulin sensitivity, which makes them metabolically close to the phenotype of GDM [4].

Thus, it seems that international unification of diagnostic criteria in GDM proposed by the International Association of the Diabetes and Pregnancy Study Groups based on the results of the HAPO Study could help make the populations of pregnant women with GDM more homogeneous in terms of metabolic markers and therefore make the observations of researchers and the work of clinicians more efficient [14]. In order to address the problem of diverse AdipoQ concentrations in populations from different parts of the world, the authors suggest that ethnicity may condition adiponectinemia in pregnant women. Non-Caucasian women (Afro-Americans) had significantly lower AdipoQ concentration than the Caucasian ones. What is more, the latter group of women with GDM experienced no changes in AdipoQ concentration irrespective of the treatment type. However, the studied hypoadiponectinemia was found only in the non-Caucasian women with GDM [28]. Many authors have addressed the issue of ethnicity in pregnant women and have been proven that Asian subjects have higher risk of developing GDM than their Caucasian equivalents. Consequently, ethnic background seems to be a factor modulating the severity of insulin resistance in pregnant women [27,32]. Our studies were conducted only on Caucasian women, while in the study by Mazaki-Tovi et al. they comprised only 5% of the studied population, while the black women dominated, which may have affected the final AdipoQ concentration [18]. Though, it should be noted that the ethnicity may be an insignificant factor blurring the evaluation of AdipoQ level in GDM as the results in non-pregnant women did not corroborate the differences in the level of this adipokine between the Caucasian and Afro-American women [9].

The study group of women with GDM had typical biochemical disorders especially in terms of impaired carbohydrate and lipid metabolism as well as insulin sensitivity parameters compared to healthy pregnant women. The observed changes most probably reflected already existing metabolic disorders which arose from GDM [1,2]. In terms of the body weight we found that pregestational and gestational BMIs were comparable, which may suggest a similar growth of adipose tissue during pregnancy in both groups. This phenomenon may serve as an additional argument for the lack of differences between AdipoQ concentrations in pregnant women since a negative correlation between this adipokine and BMI has been suggested by other authors, including with regard to non-pregnant women [13,33]. Insulin resistance determined with the rise in the HOMA-IR values in the study group of patients with GDM, which most certainly was affected by higher glucose levels and fasting hyperinsulinemia, did not correlate with AdipoQ concentrations or with the above parameters in the study group. Owecki et al. obtained comparable results from a group of obese adults [23]. Nevertheless, there have been many reports which confirm a strong correlation between hypoadiponectinemia and insulin resistance in GDM [3, 30].

Carbohydrate metabolism disorders in women with GDM may be short-term thanks to quick diagnosis and effective treatment. However, it seems that these types of disorders may not be reflected in AdipoQ concentrations or they may manifest themselves adequately to the severity of insulin resistance and carbohydrate metabolism disorders. Therefore, it should be stressed that positive GDM diagnosis following the Polish guidelines translates into a quick therapeutic intervention; at first only with diet management or enriched with insulin to provide a normal maternal and fetal glucose levels.

An interesting and important relation following from our study is a negative correlation between maternal AdipoQ concentration and birth weight, which has been confirmed by the results of other parallel studies including ours [15,29]. It may suggest an important role of maternal AdipoQ in birth weight control. If the rise of fetal AdipoQ level is also taken into consideration, the above correlation may point to two sources of adipose tissue development in the fetus and the newborn and also to other disorders in adult life [11]. Nanda et al. proposed that AdipoQ concentration in early pregnancy, determined between 11 and 13 weeks, could serve as a practical marker for predicting macrosomia in newborns [20]. Nonetheless, this dependence requires further and more detailed analysis to comprehend this disorder as some authors have not confirmed it, but have suggested the body length of a newborn as a potential factor interfering with AdipoQ level in Japanese babies [22].

In the light of contradictory findings about the role of AdipoQ in GDM and its predictive function in the incidence of type 2 diabetes, there is a need for further and more detailed research in this field. It is necessary to find important mediators which play a role in insulin resistance pathogenesis whose analysis would allow us to comprehend the nature of the disorders underlying GDM.

CONCLUSIONS

Based on the conducted studies we may conclude that women with newly diagnosed and promptly treated GDM have normal adiponectin level. A negative correlation between AdipoQ level and the birth weight may suggest that this adipokine plays a role in the control of the birth weight, especially in the incidence of macrosomia.

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