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Correlation between atherogenic risk and adiponectin in gestational diabetes mellitus

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Abstract

Introduction and objective. Gestational diabetes mellitus (GDM) is a pregnancy complication which increases the risk for maternal and foetal complications during pregnancy, and also significantly increases the cardiovascular risk for women's health in the postpartum. Current literature provides contradictory information on the role of adiponectin (AdipoQ) in the course of GDM. The aim of the study was to measure AdipoQ concentration in blood of women with GDM and to find correlations between this adipokine and clinical and biochemical parameters of the atherogenic risk.

Material and methods. The GDM group included 50 women diagnosed with GDM between 24 – 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 and insulin, OGTT, lipid parameters, C-reactive protein and fibrinogen in serum.

Results. The GDM group showed significantly elevated fasting glucose, insulin, HOMA-IR values, total cholesterol, LDL-cholesterol and triglicerydes as compared with the control group ($p<0.05$). The atherogenic index, CRP, fibrinogen in women with GDM were significantly higher than in the control group ($p<0.05$). AdipoQ concentrations did not differ significantly between the groups during gestation ($p=0.7054$). No correlations, except with the neonatal weight ($r= – 0.29$, $p<0.05$), were found between AdipoQ and the studied parameters.

Conclusions. Based on the conducted studies, it may be conclude that women with early diagnosed and promptly treated GDM have a normal adiponectin level, although insulin resistant changes and increased cardiovascular risk in basic metabolic parameters are observed. Moreover, adiponectin does not reflect the atherogenic risk in pregnant women with GDM.

Key words

Adiponectin, gestational diabetes, insulin resistance, atherogenic risk, fibrinogen, CRP

INTRODUCTION

Gestational diabetes mellitus (GDM) is any impaired carbohydrate tolerance (impaired fasting glucose, impaired glucose tolerance or diabetes) diagnosed during pregnancy [1]. Current data indicate that GDM is a slowly developing form of type 2 diabetes (T2DM) in the stage of increasing insulin resistance arising from the hormonal activity of the placenta. GDM usually subsides after pregnancy, but it remains a T2DM risk factor for the mother in the future as a woman once diagnosed with GDM has a sevenfold increased risk of developing T2DM [2]. In the light of the growing epidemic problem of T2DM incidence in developed countries, with accompanying obesity and insulin resistance, as well as a higher prevalence of GDM, which is a precursor of higher incidence of T2DM in the future, active and multidisciplinary search for markers of this disease in the population of young women diagnosed with GDM is necessary [3, 4]. Several studies have demonstrated evidence of the increased cardiovascular risk and higher prevalence of cardiovascular events later in life in the population of women with a history of GDM [5, 6, 7].

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The key role of insulin resistance, which is the main pathogenic mechanism for obesity, T2DM and GDM, points to the need to find characteristic alterations in the factors that affect this phenomenon. It has been proved that adipokines, i.e. compounds secreted by the visceral adipose tissue, play a vital role in the regulation of insulin sensitivity in tissues [8]. 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 [9]. It has been reported that low AdipoQ in serum correlates with increased insulin resistance, obesity and development of metabolic and cardiovascular disorders [10]. Furthermore, AdipoQ is involved in multiple physiological processes including energy metabolism, inflammation and vascular physiology, by acting directly in the liver, skeletal muscle, and vascular endothelium. A lot of research has revealed that AdipoQ also has anti-inflammatory, anti-atherogenic and cardioprotective effects [11, 12]. Decreased plasma AdipoQ levels are associated with atherosclerosis, low-grade metabolic inflammation and cardiovascular complications [12].

The data on AdipoQ concentration in GDM and future cardiovascular risk of women with prior history of GDM are contradictory. Therefore, the aim of the presented 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 of the atherogenic risk.

MATERIAL 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 [1]. The GDM group included 50 women diagnosed with GDM between 24 – 28 weeks of gestation. GDM was diagnosed with the use of a 75-gram glucose oral glucose tolerance test (OGTT), if, when 1 – 2 plasma glucose levels met or exceeded the following thresholds: fasting glucose concentration of 100 mg/dl and/or a 2-hour glucose concentration of 140 mg/dl. The control group comprised 21 healthy pregnant women with normal OGTT results. 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 – 28 weeks of gestation. Anthropometric measurements were obtained from all participants. The weight was taken in light clothes and 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, C-reactive protein, fibrinogen, 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 [13]. An index above 0.5 indicated an increased risk of cardiovascular complications. The LDL cholesterol concentration was calculated with the Friedewald equation [14]. Additionally, the indirect index of insulin resistance – HOMA-IR (Homeostasis Model Assessment – Insulin Resistance) was estimated [15]. Serum AdipoQ concentrations were measured with a commercial enzyme-linked immunosorbent assay kit: 'Adiponectin Human ELISA', Cat. No.: RD195023100 (BioVendor Laboratory Medicine, Modrice, Czech Republic), according to manufacturer's instructions. The limit of detection was 26 ng/mL. The intra- and inter-assay coefficients of variation (CVs) were 4.9% and 6.7%, respectively. The results were read on a microtiter plate reader ELx 800 (Bio-Tek, USA). Laboratory analyses were carried out in the Central Laboratory of the Clinical Hospital No. 4 (SPSK4) and in the Department of Laboratory Diagnostics of the Medical University in Lublin.

Statistical analysis. Fisher's exact test and Mann–Whitney test were employed to compare proportions and quantitative variables, respectively. Partial Spearman correlation coefficients between AdipoQ serum concentrations and other laboratory parameters were calculated. Results were expressed as median (interquartile range). All tests were considered significant with $p<0.05$. All analyses were performed with the MedCalc ver. 11.4.3.0.

RESULTS

Clinical characteristics of GDM and control groups. Table 1 shows the clinical characteristics of the GDM 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 GDM and control groups in terms of neonatal weight and medical history concerning the number of miscarriages and diabetes in previous pregnancies. More patients had a family history of diabetes in the GDM than in the control group (Tab. 1).

Table 1. Clinical characteristics of GDM and control groups

Studied parameter		GDM 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 adiponectin and metabolic parameters in GDM and control groups. Evaluation of glycaemia, insulin resistance and lipids in both groups is shown in Table 2. At GDM diagnosis, the GDM group showed significantly elevated fasting glucose and insulin levels HOMA-IR values, compared with the control group ($p<0.05$). In the lipid profile, significant changes were found in the GDM group during pregnancy, compared to the control group ($p<0.05$). What is more, the concentration of total, LDL cholesterol and triglycerides was higher while HDL cholesterol was significantly lower than in the healthy subjects ($p<0.05$). The atherogenic index, C-reactive protein and fibrinogen

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

Studied parameter		GDM 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)
Atherogenic index		0.536 (0.506-0.595)*	0.350 (0.324-0.409)
C-reactive protein (mg/l)		4.0 (2.7-5.8)*	2.1 (1.2-3.0)
Fibrinogen (g/l)		4.8 (4.2-5.6)*	3.8 (3.5-5.2)
Adiponectin (ug/ml)		15.8 (12.8-17.8)	15.9 (10.4-18.4)

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

in women with GDM was significantly higher than in the control group ($p<0.05$).

No significant differences were found in terms of AdipoQ concentration in pregnancy between the groups. The median adiponectin concentrations with the interquartile range for the GDM and control groups were 15.8 (12.8–17.8) μg/ml and 15.9 (10.4–18.4) μg/ml; $p=0.7054$, respectively.

Evaluation of correlations between adiponectin concentration and clinical features in the GDM and control groups. Tables 3 and 4 present correlations between adiponectin concentration and the studied parameters in the GDM and control groups. In the GDM group, AdipoQ concentration significantly negatively correlated with the neonatal weight ($r=-0.29$; $p<0.05$); no other correlations between the adiponectin concentration and the studied clinical features were found in the GDM and control groups (Tab. 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 (Tab. 4).

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

Studied parameter		GDM 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 GDM and control groups during gestation in the Spearman's rank correlation test

Studied parameter		GDM 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
Atherogenic index		–0.019	–0.061
C-reactive protein (mg/l)		–0.124	–0.077
Fibrinogen (g/l)		–0.039	0.335

DISCUSSION

Despite the fact that many authors have emphasized the multidirectional role of AdipoQ in obesity, T2DM, metabolic syndrome or GDM, especially the link between hypoadiponectinaemia and those disorders, pathophysiological implications of this adipokine have not yet been fully explained [16, 17, 18]. Diagnosed GDM not only increases the risk of maternal and foetal complications during pregnancy, but also significantly increases a woman's risk of both T2DM and cardiovascular disease (CVD) in the postpartum. Even women with milder forms of abnormal glucose homeostasis during pregnancy, specifically gestational impaired glucose tolerance, are at increased risk, which justifies the recent recommendation to tighten the diagnostic criteria for GDM, thus including many more women. The factors that increase the risk of future CVD among women with a history of GDM include: postpartum progression to T2DM metabolic syndrome, obesity, hypertension, and altered levels of circulating inflammatory markers, particularly AdipoQ, dyslipidaemia, CRP, fibrinogen [19].

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 [20, 21], but contradicts the results of others [22, 23]. Thyfault et al. showed that AdipoQ concentration may depend on the severity of insulin resistance and carbohydrate metabolism disorder [23]. In the literature to-date, the results of AdipoQ determination are not clear. Some authors who showed hypoadiponectinaemia often demonstrated a slightly different metabolic phenotype of the population with GDM. Hypoadiponectinaemia significantly correlated with insulin resistance parameters and consequently with the severity of carbohydrate metabolism disorders [22, 24]. What is more, the authors of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study also demonstrated depressed AdipoQ concentration with accompanying increased maternal glucose level [25].

No clear-cut criteria, neither the diagnostic nor the treatment criteria, 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. 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 [26]. Thus, it seems that the international unification of diagnostic criteria in GDM proposed by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), 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 [27, 28].

The GDM group 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 [29, 30]. In terms of the body weight, it was 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 [31, 32]. 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 a positive GDM diagnosis following the Polish guidelines translates into a quick therapeutic intervention, at first only with diet management or diet enriched with insulin to provide a normal maternal and foetal glucose levels. There have been many reports which confirm a strong correlation between hypoadiponectinaemia and insulin resistance in GDM [17, 21]. Insulin resistance determined with the rise in the HOMA-IR values in the GDM group, which most certainly was affected by higher glucose levels and fasting hyperinsulinaemia, 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 [32]. However, it should be noted that HOMA-IR was only surrogate measurement and does not reflect the insulin resistance in full; it is also affected by measurement errors of glucose and insulin. Therefore, incorporating the direct technique of metabolic clamp, unavailable in our conditions, would be a better choice. Although the control and GDM groups had comparable BMIs, women in the latter group had a more atherogenic lipid profile and higher fasting plasma glucose, as well as insulin levels; thus, they seemed to be more insulin resistant. Research conducted by Carr DB et al. provides evidence that a history of GDM is associated with a higher prevalence of CVD in the population with a family history of diabetes. Furthermore, women with a history of GDM experienced cardiovascular events at a younger age compared with the women without a history of GDM [33]. In the GDM group in the presented study, higher fibrinogen levels were observed, in comparison to normal pregnancy, which may indicate increased cardiovascular risk in this group. The results of Ko at al. confirmed close correlations between plasma fibrinogen and cardiovascular risk factors, in particular abnormal lipid and glucose metabolism [34]. Increased CRP levels in GDM compared with healthy controls might indicate an increased risk of subclinical atherosclerosis and future atherosclerotic heart disease, which confirmed the findings of other researchers [35,36]. The data suggest that the high prevalence of impaired glucose levels and fasting hyperinsulinaemia, dyslipidaemia and altered inflammatory markers, with the exception of AdipoQ, make GDM a high-risk situation for T2DM and CVD.

Finally, a negative correlation was noticed between maternal AdipoQ concentration and birth weight, which has been confirmed by the results of other parallel studies including ours [37, 38]. This may suggest an important role of maternal AdipoQ in birth weight control. If the rise in foetal AdipoQ level is also taken into consideration, the above correlation may point to two sources of adipose tissue development in the foetus and the newborn, and also to other disorders in adult life [38]. Nanda et al. proposed that AdipoQ concentration in early pregnancy, determined between 11 – 13 weeks, could serve as a practical marker for predicting macrosomia in newborns [39].

The major limitation of the presented study is the quite small number of GDM subjects. However, it should be noted that the group of women recruited presented a typical phenotype for GDM, and it may be an argument that the results may be representative for GDM subjects, although the small number of women with gestational diabetes reflects a need for further research in this field in a large study population. Another issue is that for atherogenic risk assessment, only CRP, fibrinogen and lipid parameters were used, which may not allow for detailed evaluation of atherosclerotic processes. But what is important, these simple laboratory devices nowadays belong to routinely analyzed parameters in the laboratories and are available to physicians all over the world. Moreover, it should be stressed that these basic parameters may serve as tools for the assessment of atherogenic risk in a large population study.

In the light of contradictory findings about the role of AdipoQ in GDM and its predictive function in the incidence of DMT2 and CVD, 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, it may be concluded that women with early diagnosed and promptly treated GDM have a normal adiponectin level, although insulin resistant changes and increased atherogenic risk in basic metabolic parameters, such as lipids, CRP and fibrinogen are observed. What is more, adiponectin does not reflect the atherogenic risk in pregnant women with GDM.

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