CLINICAL STUDY

Serum levels of adipocyte fatty acid binding protein are increased in gestational diabetes mellitus

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Abstract

Objective: Adipocyte fatty acid binding protein (AFABP) was recently introduced as a novel adipokine, serum levels of which independently correlate with the development of the metabolic syndrome and cardiovascular disease in humans. In the current study, we investigated serum concentrations of AFABP in patients with gestational diabetes mellitus (GDM) as compared with healthy pregnant controls matched for gestational age and fasting insulin.

Design and methods: AFABP was determined by ELISA in controls ($n=80$) and GDM patients ($n=40$) and correlated to clinical and biochemical measures of renal function, glucose and lipid metabolism, as well as inflammation, in both groups.

Results: Median serum AFABP concentrations were significantly elevated in subjects with GDM ($22.9 \mu\text{g/l}$) as compared with healthy pregnant controls ($18.3 \mu\text{g/l}$; $P<0.05$). Furthermore, GDM was independently associated with AFABP concentrations in multiple regression analysis ($P<0.05$). In addition, markers of adiposity (body mass index, serum leptin), triglycerides and serum creatinine were independently associated with circulating AFABP ($P<0.05$).

Conclusions: Maternal AFABP concentrations are significantly increased in GDM. The adipokine might contribute to the increased metabolic and cardiovascular risk of the disease.

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Introduction

Gestational diabetes mellitus (GDM) is a serious complication in pregnancy that is characterized by glucose intolerance with onset or first recognition during pregnancy (1). As a consequence of a diabetic pregnancy, mother and newborn have a significantly increased future risk of metabolic and cardiovascular diseases. Thus, the 8 year *post partum* diabetes mellitus risk was $>50\%$ in patients with previous GDM (2). Furthermore, cardiovascular risk factors including intima-media thickness (IMT), circulating levels of E-selectin, and intercellular adhesion molecule-1 were significantly increased in previous GDM patients 6.5 years after delivery as compared with controls (3).

The pathogenetic mechanisms underlying GDM have been better elucidated in recent years and are similar to obesity-associated type 2 diabetes mellitus (T2DM). Thus, insulin resistance during pregnancy and a limitation in the pancreatic β -cell reserve contribute to the development of the disease. Furthermore, adipocyte-secreted factors – so-called adipokines – that influence insulin sensitivity might play an important role in the

pathogenesis of GDM. Here, decreased levels of the insulin-sensitizing and vasoprotective adipokine adiponectin have been found in GDM in several independent studies (4–6). Furthermore, adiponectin was lower in women in early pregnancy who later developed GDM (7). Interestingly, a positive association between circulating adiponectin and β -cell function existed in pregnant women (8). Studies on regulation of the appetite-suppressive adipokine leptin in GDM have been less clear. Thus, increased serum levels of leptin during early pregnancy predicted the clinical onset of GDM (9, 10). By contrast, women with mild GDM presented with relative hypoleptinaemia as compared with controls in another study (11). Furthermore, leptin administration prevented spontaneous GDM in heterozygous leptin receptor-deficient mice (12).

Adipocyte fatty acid binding protein (AFABP, also known as aP2 and FABP4) has recently been described as a novel adipokine associated with insulin resistance, T2DM, and cardiovascular disease. Thus, AFABP serum levels were significantly increased in overweight and obese subjects as compared with lean controls and correlated positively with waist circumference, blood

pressure, and insulin resistance (13). Higher baseline levels of circulating AFABP independently predicted the risk to develop a metabolic syndrome during a follow-up of 5 years (14). Similarly, baseline AFABP concentrations were predictive of T2DM independent of obesity, insulin resistance or glycemic indexes (15). Work from the same group showed that serum AFABP levels were positively linked with carotid IMT and presence of plaques in women (16). These results indicate that AFABP might have a central role in the development of metabolic and cardiovascular disease.

By contrast to adipokines including adiponectin and leptin, AFABP serum concentrations have not been evaluated so far in GDM. In the current study, we therefore, sought to investigate for the first time whether maternal AFABP levels are altered in GDM and might potentially contribute to the present and future metabolic and cardiovascular risk of the disease. We determined AFABP levels in 80 control and 40 GDM patients who were matched for gestational age and fasting insulin (FI) and correlated serum concentrations of this adipocyte-expressed factor to clinical and biochemical measures of renal function, glucose and lipid metabolism, as well as inflammation.

Subjects and methods

Subjects

Forty pregnant women with GDM and eighty controls matched for gestational age and FI were recruited. GDM was diagnosed if one or more plasma glucose levels were elevated during a 75 g, 2 h oral glucose tolerance test (OGTT) according to the criteria of the Austrian Diabetes Association (17). The following threshold plasma glucose levels were used: fasting ≥ 5.3 mmol/l; 1 h ≥ 10.0 mmol/l; 2 h ≥ 8.6 mmol/l (17). Body mass index (BMI) was calculated as weight before pregnancy divided by squared height. Age of the patients ranged from 18 to 45 years and BMI from 15.6 to 38.2 kg/m². Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described (18). Patients with renal diseases, preeclampsia, and generalized inflammation were excluded from the study. The study protocol was approved by the local Ethics Committee. All patients gave written informed consent before taking part in the study.

Assays

Blood samples were taken after an overnight fast. At the time of the blood sampling, none of the women was in labor. Serum insulin was determined with a two-site chemiluminescent enzyme immunometric assay for the Immulite automated analyzer (Diagnostic Products, Los Angeles, CA, USA). AFABP (Biovendor, Modrice, Czech Republic), adiponectin, resistin, and leptin (all

Mediagnost, Reutlingen, Germany) were determined with ELISAs according to the manufacturers' instructions. Serum creatinine, cholesterol, triglycerides (TG), and C reactive protein (CRP) were measured by standard laboratory methods in a certified laboratory.

Statistical analysis

SPSS software version 11.5 (SPSS, Chicago, IL, USA) was used in all statistical analyses. Differences between controls and GDM patients were assessed by Mann–Whitney-*U* test. Correlations were performed using the Spearman's rank correlation method. To adjust the effects of covariates and identify independent relationships, multivariate linear regression analyses were performed. Before performing multivariate analyses, distribution was tested for normality using Shapiro–Wilk *W* test and non-normally distributed parameters were logarithmically transformed. A *P*-value of <0.05 was considered as statistically significant in all analyses.

Results

AFABP serum levels are increased in GDM patients as compared with controls

Table 1 summarizes the clinical characteristics of the subgroups studied (Control, GDM). All continuous variables are given as median $\pm$ interquartile range. Maternal serum AFABP concentrations were significantly elevated in

Table 1 Baseline characteristics of the study population.

	Control	GDM
<i>N</i>	80	40
AFABP (μ g/l)	18.3 $\pm$ 12.9	22.9 $\pm$ 12.2*
Age (years)	28 $\pm$ 5	33 $\pm$ 10*
BMI (kg/m ²)	22.3 $\pm$ 7.0	24.9 $\pm$ 4.9
SBP (mmHg)	125 $\pm$ 16	121 $\pm$ 23
DBP (mmHg)	75 $\pm$ 13	71 $\pm$ 17
Gestational age at blood sampling (days)	198 $\pm$ 39	205 $\pm$ 30
Glucose 0 h (mmol/l)	4.2 $\pm$ 0.4	4.5 $\pm$ 0.9*
Glucose 1 h (mmol/l)	7.5 $\pm$ 1.6	10.3 $\pm$ 1.6*
Glucose 2 h (mmol/l)	6.2 $\pm$ 1.8	9.0 $\pm$ 2.3*
FI (pmol/l)	56.5 $\pm$ 39.3	60.3 $\pm$ 37.1
HOMA-IR	1.4 $\pm$ 1.0	1.6 $\pm$ 1.3
Creatinine (μ mol/l)	49 $\pm$ 12	46 $\pm$ 11
TG (mmol/l)	2.1 $\pm$ 1.4	2.2 $\pm$ 1.3
Cholesterol (mmol/l)	6.3 $\pm$ 1.8	6.6 $\pm$ 2.2
HDL cholesterol (mmol/l)	1.9 $\pm$ 0.5	1.7 $\pm$ 0.7
LDL cholesterol (mmol/l)	3.7 $\pm$ 1.6	3.8 $\pm$ 1.9
Leptin (μ g/l)	23.1 $\pm$ 11.7	24.9 $\pm$ 13.9
Adiponectin (mg/l)	7.0 $\pm$ 3.9	7.3 $\pm$ 5.6
Resistin (μ g/l)	7.4 $\pm$ 4.5	6.5 $\pm$ 3.6
CRP (mg/l)	4.3 $\pm$ 4.5	4.2 $\pm$ 4.9

AFABP, adipocyte fatty acid binding protein; BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; FI, fasting insulin; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure and TG, triglycerides. Values for median $\pm$ interquartile range are shown. **P* <0.05 as compared to control as assessed by Mann–Whitney-*U* test.

subjects with GDM ($22.9 \pm 12.2 \mu\text{g/l}$) as compared with healthy pregnant controls ($18.3 \pm 12.9 \mu\text{g/l}$; $P < 0.05$; Table 1). Furthermore, AFABP levels were significantly higher in overweight-obese ($\text{BMI} \geq 25 \text{ kg/m}^2$, $22.4 \pm 15.3 \mu\text{g/l}$) as compared with lean ($\text{BMI} < 25 \text{ kg/m}^2$, $15.3 \pm 11.2 \mu\text{g/l}$) controls ($P < 0.001$; Fig. 1). Patients with GDM were significantly older (33 ± 10 years) as compared with control subjects (28 ± 5 years; $P < 0.05$; Table 1). However, the significant difference in AFABP serum levels between GDM and control patients persisted after adjustment for maternal age ($P < 0.05$; data not shown). Both groups were matched for FI (60.3 ± 37.1 vs $56.5 \pm 39.3 \text{ pmol/l}$) and gestational age at blood sampling (205 ± 30 vs 198 ± 39 days; Table 1). Fasting plasma glucose, as well as 1 and 2 h glucose values during 75 g OGTT were significantly higher in GDM patients as compared with controls ($P < 0.001$; Table 1). By contrast, BMI, as well as markers of lipid metabolism (TG, cholesterol), inflammation (CRP), and renal function (creatinine) were not significantly different between the two groups (Table 1).

Univariate correlations

Serum AFABP levels positively correlated with BMI, systolic blood pressure (SBP), FI, HOMA-IR, creatinine, TG, leptin, and CRP ($P < 0.05$; Table 2). By contrast, AFABP concentrations did not show an association with age, diastolic blood pressure, gestational age at blood sampling, fasting glucose, 1 and 2 h glucose during 75 g OGTT, cholesterol, resistin, and adiponectin (Table 2).

Figure 1 AFABP serum levels in lean ($\text{BMI} < 25 \text{ kg/m}^2$) and overweight/obese ($\text{BMI} \geq 25 \text{ kg/m}^2$) pregnant controls. Boxplot graphs are shown. Differences between the two groups were analyzed by Mann-Whitney-*U* test.

Table 2 Univariate correlations with serum adipocyte fatty acid binding protein (AFABP) concentrations.

	<i>r</i>	<i>P</i>
Age (years)	0.139	0.129
BMI (kg/m^2)	0.519	<0.001*
SBP (mmHg)	0.191	0.040*
DBP (mmHg)	0.133	0.157
Gestational age at blood sampling (days)	0.175	0.059
Glucose 0 h (mmol/l)	0.129	0.163
Glucose 1 h (mmol/l)	0.171	0.070
Glucose 2 h (mmol/l)	0.037	0.699
FI (pmol/l)	0.266	0.004*
HOMA-IR	0.264	0.004*
Creatinine ($\mu\text{mol/l}$)	0.235	0.010*
TG (mmol/l)	0.345	<0.001*
Cholesterol (mmol/l)	0.111	0.230
HDL cholesterol (mmol/l)	-0.090	0.328
LDL cholesterol (mmol/l)	0.060	0.518
Leptin ($\mu\text{g/l}$)	0.437	<0.001*
Adiponectin (mg/l)	-0.107	0.244
Resistin ($\mu\text{g/l}$)	-0.009	0.926
CRP (mg/l)	0.201	0.031*

r and *P*-values are given. Abbreviations are indicated in Table 1. *Significant correlation as assessed by Spearman's correlation method.

Multivariate correlations

In multiple regression analysis, the positive association between AFABP serum concentrations on one hand and BMI, creatinine, and TG on the other hand persisted after adjustment for SBP, HOMA-IR, and CRP (Table 3, model 1). When circulating leptin instead of BMI and FI instead of HOMA-IR were included in multivariate analysis, leptin but not FI remained independently associated with serum AFABP concentrations (Table 3,

Table 3 Multivariate linear regression analyses between adipocyte fatty acid binding protein (AFABP; dependent variable) and body mass index (BMI), systolic blood pressure (SBP), homeostasis model assessment of insulin resistance (HOMA-IR), creatinine, triglycerides (TG), C reactive protein (CRP), and gestational diabetes mellitus (GDM; Model 1), as well as between AFABP (dependent variable) and leptin, SBP, fasting insulin (FI), creatinine, TG, CRP, and GDM (Model 2).

Model	Independent variable	β	<i>P</i>
Model 1	BMI	0.317	0.001*
	SBP	0.040	0.645
	HOMA-IR	0.155	0.107
	Creatinine	0.346	<0.001*
	TG	0.232	0.006*
	CRP	0.056	0.481
	GDM	0.165	0.042*
Model 2	Leptin	0.259	0.008*
	SBP	0.098	0.259
	FI	0.067	0.510
	Creatinine	0.306	<0.001*
	TG	0.259	0.003*
	CRP	0.065	0.427
	GDM	0.230	0.005*

β -coefficients and *P*-values are given, * indicates significant correlation.

model 2). GDM remained significantly correlated with serum AFABP levels independent of BMI/leptin, SBP, HOMA-IR/FI, creatinine, TG, and CRP in multivariate analyses (Table 3).

Discussion

In the current study, we demonstrate for the first time that maternal-serum levels of the adipokine AFABP are significantly increased in GDM patients as compared with healthy pregnant controls who are matched for gestational age and FI. Moreover, GDM remains significantly associated with serum AFABP concentrations independent of markers of adiposity (BMI, leptin), insulin resistance (FI, HOMA-IR), TG, CRP, and serum creatinine. Three recent well-controlled studies demonstrate that AFABP serum levels independently predict the risk to develop a metabolic syndrome (14), as well as T2DM (15), and are independently related to IMT in women (16). Furthermore, several independent studies in animals and humans indicate that AFABP is not only related to metabolic and cardiovascular disease but also directly promotes these conditions. Thus, targeted ablation of AFABP protects mice from obesity-associated insulin resistance and T2DM (19). AFABP-deficient ob-ob mice are more insulin-sensitive compared with controls and show lower plasma glucose and insulin levels, better performance in insulin and glucose tolerance tests, as well as lower plasma TG and cholesterol concentrations (20). AFABP ablation in ApoE-knockout mice significantly reduces mean atherosclerotic lesion size in the proximal aorta as compared with ApoE-deficient controls (21, 22). These proatherogenic effects of AFABP appear to be mediated via direct actions in macrophages, through modification of cholesterol trafficking, and through activation of inflammatory signaling molecules including nuclear factor κ B (23). AFABP inhibition by the orally active small-molecule inhibitor BMS309403 in mice reduces the extent of atherosclerotic lesion area in the proximal aorta (24). Furthermore, this AFABP inhibitor decreases blood glucose and insulin levels and increases concentrations of the insulin-sensitizing adipokine adiponectin in ob-ob mice (24). In humans, subjects with a functionally significant genetic variation of the AFABP locus leading to decreased adipose tissue AFABP expression have lower TG levels, as well as a significantly reduced risk for coronary heart disease and T2DM (25). In agreement with these findings, lower expression of AFABP is found in adipose tissue of lean and weight-reduced individuals as compared with obese subjects (26). Taking these studies into consideration, increased AFABP concentration in GDM might contribute to the increased metabolic and cardiovascular risk of the disease. It needs to be tested in future studies whether increased AFABP levels persist in GDM patients after delivery.

In the current study, we demonstrate that markers of adiposity (BMI, leptin) are independently correlated with serum AFABP levels. These findings support previous data from our group showing an independent association between AFABP and BMI in a study with preeclamptic patients (27). A similar association has also been shown in several non-pregnant populations. Thus, baseline age- and sex-adjusted serum AFABP concentrations correlate with BMI after 5-year follow-up in 495 non-diabetic adults (14). Similarly, circulating AFABP levels are correlated with BMI in 67 non-obese and healthy subjects and 71 patients with the metabolic syndrome (28). Furthermore, AFABP concentrations are significantly associated with BMI before and 6 months after gastric banding in 33 morbidly obese patients (29). In addition, we have recently shown that BMI is independently correlated with circulating AFABP in patients on chronic hemodialysis (30). Taking this published evidence into consideration, circulating AFABP appears to be regulated in a body weight-dependent manner similar to the adipokine leptin. It is tempting to speculate that hyperplastic and hypertrophic fat tissue developing during weight gain directly leads to increased AFABP production. In accordance with this hypothesis, serum AFABP levels closely and positively correlate with AFABP synthesis in adipose tissue (14).

In the current study, we demonstrate that renal function assessed as serum creatinine is strongly and independently correlated with circulating AFABP concentrations. These findings are in accordance with previous data from our group showing that serum creatinine and AFABP are independently associated in preeclampsia (27). Furthermore, we have recently demonstrated that AFABP is more than ten-fold higher in patients on chronic hemodialysis as compared with controls (30). These results further support the notion that renal elimination is a major route by which physiological AFABP serum levels are maintained. In addition, markers of renal function should always be included in studies concerning AFABP physiology and regulation.

In our study, BMI is not significantly different between GDM patients and controls, whereas increased body weight in GDM has been described by various groups (4, 31, 32). However, GDM patients and controls are matched for FI as a marker of insulin resistance in our study, whereas FI has been increased in GDM patients (4, 32) or has not been determined (31) previously. It is well established that FI increases when body weight is gained. Taking these facts into consideration, it appears plausible that BMI is not significantly different between controls and GDM patients in our study since both groups are matched for FI.

Furthermore, downregulation of the insulin-sensitizing adipokine adiponectin has recently been shown in GDM (4–6, 31, 32) in contrast to our current results. Again, these different findings are most probably due to

the fact that insulin resistance was similar in GDM and control patients in our study in contrast to previous reports (4–6, 31, 32). Similar to adiponectin, serum resistin levels are not significantly different between GDM and control patients in our hands. It is interesting to note in this context that both upregulation (33) and downregulation (34) of this adipokine in GDM have been described recently.

Some limitations of the present study have to be pointed out: first, cross-sectional data are presented and the sample size is relatively small. Furthermore, we cannot exclude the possibility that confounding factors that influence circulating AFABP have not been considered.

Taken together, we present evidence that maternal AFABP levels are significantly increased in GDM which might contribute to increased metabolic and cardiovascular risk in these patients. Furthermore, we show that body weight, renal function, and TG are independently associated with serum AFABP concentrations. More work is needed to better elucidate the mechanisms by which circulating AFABP influences metabolic and cardiovascular health.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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