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Fatty Acid-Binding Protein 4 Serum/Urine Gradient of Post-Partum Women with Metabolic Disturbances

Marcin Trojnar[1], Jolanta Patro-Małysza[2], Bożena Leszczyńska-Gorzelak[2]

[1] Chair and Department of Internal Medicine, Medical University of Lublin, Lublin 20-081, Poland

[2] Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Lublin 20-090, Poland

Abstract:

Among novel adipokines fatty acid binding protein 4 (FABP4) seems to be one of the most promising predictors of long-term metabolic pregnancy complications.

The aim of the study was to evaluate FABP4 serum/urine gradients which are quotients of the serum FABP4 concentrations to the urine in women with excessive gestational weight gain (EGWG) and gestational diabetes mellitus (GDM) in the early post-partum period, with reference to their laboratory test results, body composition and hydration status.

The study subjects were divided into three groups: 24 mothers with EGWG, 22

GDM patients and 24 healthy controls. Maternal body composition and hydration status were evaluated by the bioelectrical impedance analysis (BIA) method. Concentrations of FABP4, leptin, and ghrelin were determined via ELISA.

The FABP4 serum/urine gradients were comparable in the three studied groups. This parameter was positively associated with the serum FABP4 level only in the control group, whereas it was highly negatively related to the urine FABP4 concentrations in all the three studied groups. We found positive correlations between the FABP4 serum/urine gradients with albumin and LDL concentrations but only in the healthy controls. No correlation was found between the FABP4 serum/urine gradient and biochemical results in the EGWG and GDM groups. The FABP4 serum/urine gradient positively correlated with all the studied BIA variables with the exception of extracellular water (ECW) in the healthy group. The EGWG group was characterized by positive correlations between the FABP4 serum/urine gradient and lean tissue index as well as negative correlations with ECW. No correlations were observed between this parameter and BIA findings in the GDM group.

Our results seem to confirm that further studies should not be limited to evaluation of serum FABP4 levels only.

Keywords: adipokines, fatty acid binding protein 4, gestational diabetes mellitus; excessive gestational weight gain, bioelectrical impedance analysis; body composition; hydration status

INTRODUCTION

In one of the most recent systematic reviews by Bellos et al., targeting the potential association of 10 novel adipokines (i.e. apelin, chemerin, fatty acid binding protein 4 (FABP4), fibroblast growth factor-1, monocyte chemoattractant protein-1, nesfatin-1, omentin-1, resistin, vaspin, and visfatin) with gestational diabetes mellitus (GDM), only FABP4 was found to be the most promising predictor of this metabolic pregnancy complication [1].

Our previous study evaluated FABP4 levels in the serum and urine of the GDM and excessive gestational weight gain (EGWG) mothers in comparison to the healthy women in the early post-partum period [2]. Our study showed that the highest serum FABP4 levels were present in the GDM mothers. We did not find any statistical differences in the FABP4 urine concentrations between the three studied groups [2].

The aim of this study was to evaluate FABP4 serum/urine gradients which are quotients of the serum FABP4 concentrations to the urine FABP4 concentrations in mothers in the study that is with EGWG and GDM in comparison to the healthy women in the early post-partum period. We also assessed the relationship between this new parameter and maternal laboratory test results, body composition and hydration status.

We hypothesized that due to certain disturbances occurring in pregnancy and post-partum period, including changes in the body composition and hydration status in GDM and EGWG, the FABP4 serum/urine gradient would probably be helpful in better understanding of pathophysiology of the abovementioned complications.

METHODS

The study comprised women in a singleton term pregnancy hospitalized at the Chair and Department of Obstetrics and Perinatology, at the Medical University of Lublin. All of the study subjects included in this study were Caucasian and were divided into three groups. The first group consisted of 24 healthy controls, i.e. women without any metabolic disorders and with three normal results of the standard glucose tolerance test (OGTT) at 24–28 weeks of gestation. This subgroup had no concomitant diseases, received only vitamin-iron supplementation and presented normal values of pre-pregnancy body mass index (BMI) and normal gestational weight gain.

The second group included 24 patients with EGWG, i.e. with normal pre-pregnancy BMI, three normal results of the OGTT at 24-28 weeks of gestation and gestational weight gain of at least 20 kilograms.

The third studied group consisted of 22 patients with diagnosed GDM who were on a diabetic diet and were treated with insulin. Diagnostic criteria for GDM were based on the OGTT at 24-28 weeks of gestation.

The exclusion criteria were as follows: multiple pregnancy, chronic infectious diseases, current urinary infections, abnormal laboratory results (e.g. the complete blood count, urine test, creatinine, glomerular filtration rate findings), metabolic disorders (such as polycystic ovarian syndrome; except for those listed in the inclusion criteria for the studied groups), mental illnesses, cancer, liver diseases, cardiovascular disorders, fetal malformation, premature membrane rupture, intrauterine growth retardation, the presence of metallic prostheses, and pacemakers or cardioverter-defibrillators.

Anthropometric measurements and sampling were performed after a 6-h fasting in the early post-partum period (i.e. within 48 hours after delivery). The maternal body composition and hydration status were evaluated with the use of bioelectrical impedance analysis (BIA) method (BCM; Fresenius Medical Care). The serum levels of albumin, hemoglobin A1c and lipid profile were measured by a certified laboratory. After centrifugation, all of the collected maternal serum and urine samples were stored at –80 °C. The concentrations of FABP4 (R&D Systems, Inc., Minneapolis, MN, USA), leptin (R&D Systems, Inc., Minneapolis, MN, USA) and ghrelin (Wuhan EIAab Science Co., Wuhan, China) in these materials were determined using commercially available kits and in compliance with the manufacturer's instructions via traditional enzyme-linked immunosorbent assay (ELISA). The survey was performed in duplicates for each patient.

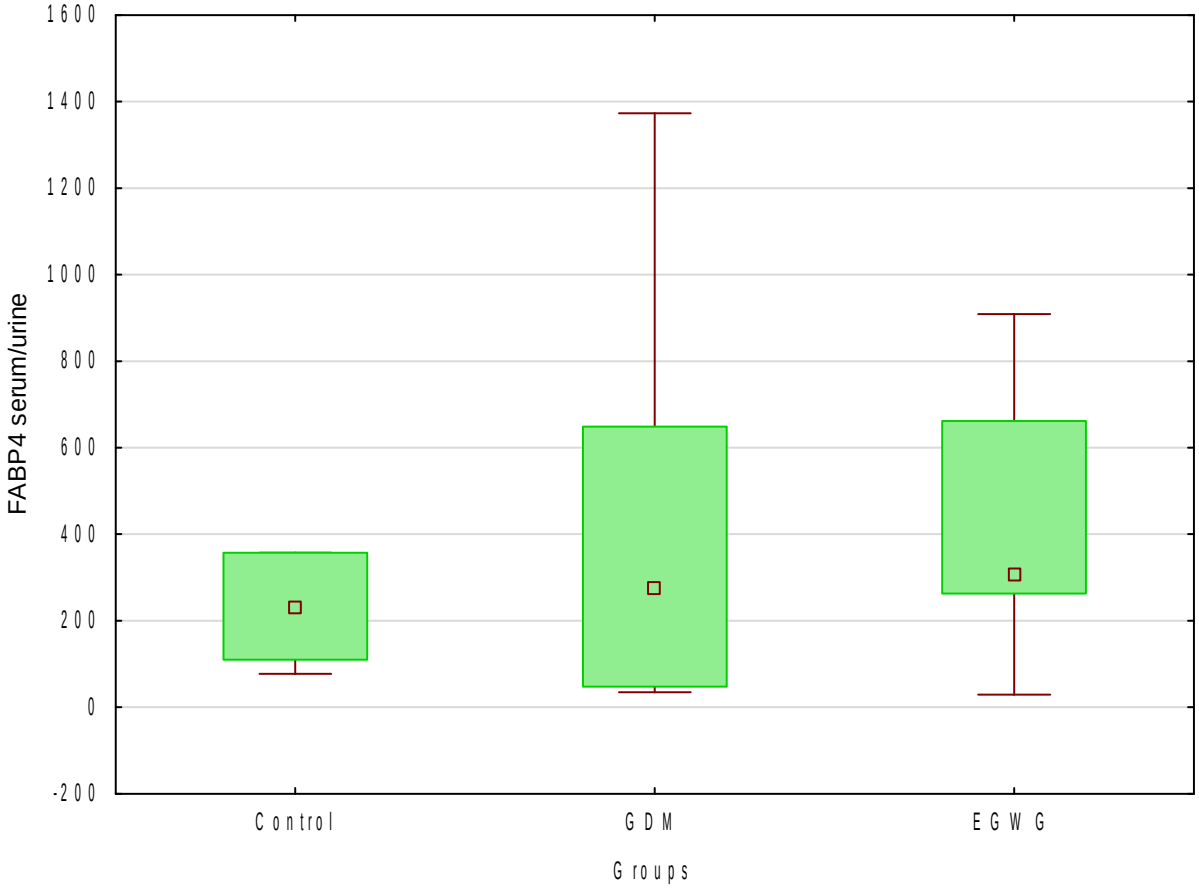
All of the patients were informed about the study protocol, and a detailed written consent was obtained from each patient who agreed to participate in the study. The study protocol was approved by the Bioethics Committee of the Medical University of Lublin.

All of the values were reported as the medians (interquartile range 25–75%). The differences between the three studied groups were tested for significance using the Kruskal-Wallis analysis of variance. The Spearman's coefficient test was used for the correlation analyses. All of the analyses were performed using the Statistical Package for the Social Sciences software (version 19; SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

The results regarding the characteristics of the study subjects were previously presented by us [2]. Taking into account the difference in the maternal FABP4 concentrations between the studied groups, which is a finding of our previous study, for the sake of investigating the relationship between the selected biochemical and biophysical variables, we introduced the FABP4 serum/urine gradient. This new parameter is a ratio of the serum FABP4 concentration to that in urine. We did not reveal any significant differences in the FABP4 serum/urine gradient between our three groups (Figure 1).

Figure 1. The FABP4 serum/urine gradient in three studied groups.



The FABP4 serum/urine gradient correlated positively with all the evaluated BMIs (i.e. pre-pregnancy, at delivery and post-partum BMIs), BMI gain in the period from pre-pregnancy to 48 hours after delivery (ΔBMI), albumin, low-density lipoprotein cholesterol (LDL), serum FABP4 and all the studied BIA variables (with the exception of extracellular water (ECW)) in the healthy group. Negative correlations were found between the FABP4 serum/urine gradient and BMI loss at 48 h after delivery (ΔBMI 2) and urine FABP4 concentrations in the control group (Table 1).

The EGWG group was characterized by positive correlations between the FABP4 serum/urine gradient and lean tissue index (LTI) as well as by negative correlations with

the BMI at delivery, serum ghrelin and leptin levels, urine FABP4 concentration and ECW (Table 1).

Negative relationships were observed between the FABP4 serum/urine gradient and BMI at delivery as well as urine ghrelin and FABP4 levels in the GDM group (Table 1).

Table 1. Correlations between the maternal FABP4 serum/urine gradient and the selected parameters.

Variables	Healthy Group	EGWG Group	GDM Group
age	0.290	0.081	-0.346
pre-pregnancy BMI	**0.600***	-0.007	-0.333
gestational weight gain	0.290	-0.324	-0.215
ΔBMI 1	0.257	0.017	-0.009
BMI at delivery	**0.486***	**-0.410***	**-0.624***
post-partum BMI	**0.771*****	-0.341	-0.212
ΔBMI 2	**-0.543***	0.014	-0.102
ΔBMI	**0.543***	-0.378	0.079
albumin	**0.943*****	0.168	0.018
total cholesterol	0.377	0.175	-0.188
HDL	0.377	0.168	-0.006
LDL	**0.486***	0.175	0.248
triglycerides	0.116	0.259	-0.345
hemoglobin A1c	0.116	0.011	0.193
serum ghrelin	-0.314	**-0.608***	0.136
urine ghrelin	-0.314	0.056	**-0.473***
serum FABP4	**0.543***	0.336	-0.064
urine FABP4	**-1.0*****	**-0.811*****	**-0.964*****
serum leptin	0.143	**-0.475***	-0.282
total body water	**0.486***	-0.217	0.209
extracellular water	0.371	**-0.508***	0.218
intracellular water	**0.771*****	-0.049	0.278
lean tissue index	**0.543***	**0.504***	0.155
fat tissue index	**0.543***	-0.263	-0.127
BCMI	**0.486***	0.385	0.336

Statistically significant values are given in the bold type. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$. BCMI—body cell mass index; BMI—body mass index; ΔBMI 1—gestational BMI gain; ΔBMI 2—BMI loss at 48 h after delivery; ΔBMI – BMI gain in the period from pre-pregnancy to 48 hours after delivery; EGWG – excessive gestational weight gain; FABP4 – fatty acid binding protein 4; FABP4 S/U gradient – FABP4 serum/urine gradient; GDM — gestational diabetes mellitus; HDL—high-density lipoprotein cholesterol; LDL—low-density lipoprotein cholesterol.

DISCUSSION

Our previous study showed that the highest serum FABP4 levels were present in the GDM mothers [2]. These results are consistent with the observations made by other authors that FABP4 is directly involved in the pathophysiology of GDM and its long-term post-partum complications[3,4].

Taking into account the difference in the maternal serum FABP4 between the studied groups, we introduced the FABP4 serum/urine gradient which was calculated as a quotient of FABP4 concentrations in the serum to those in the urine. This novel parameter was positively associated with the serum FABP4 level in this group, whereas it was highly negatively related to the urine FABP4 concentrations in all three studied groups. These above mentioned findings may suggest that there are some differences in the FABP4 production or elimination in patients both with EGWG and GDM in comparison to healthy mothers.

After calculating the relationship between the FABP4 serum/urine gradient and ghrelin concentrations, we obtained significant negative correlations with the serum ghrelin levels in the EGWG group and with the urine ghrelin concentrations in the GDM mothers.

The FABP4 serum/urine gradient correlated positively with almost all the studied BMI values (i.e. before pregnancy, at delivery and after delivery) as well as negatively with BMI loss after delivery in the healthy mothers. In the EGWG and GDM groups, this parameter was negatively associated only with the post-partum BMI, i.e. with BMI, which was valid for the time of blood and urine sample collection to determine FABP4 levels in our patients.

We found positive correlations between the FABP4 serum/urine gradient with albumin and LDL concentrations but only in the healthy subjects. No correlation was found between the FABP4 serum/urine gradient and biochemical results in the EGWG and GDM groups.

It has been reported that FABP4 expression is not detected in podocytes [5,6]. Understanding the role of podocytes as a glomerular filtration barrier has progressed in the past decade [7]. However, the importance of the glomerular endothelial cells in the pathogenesis of proteinuria has recently received much attention [8,9]. Loss of the glycocalyx in the glomerular endothelial cells was shown to promote passage of albumin across the glomerular filtration barrier [8,10]. The glomerular endothelial cell damage preceded a podocyte injury in different types of renal diseases and decreased eNOS [9,11,12]. Interestingly, FABP4 expression decreased phosphorylation of eNOS and nitric oxide production in the microvascular endothelial cells, thereby contributing to endothelial dysfunction. Thus, it is quite possible that that the glomerular FABP4, which is upregulated by endothelial damage, compromises nitric oxide production leading to a vicious cycle of glomerular injury and an increase in the protein permeability [13]. Okazaki et al. [13] concluded that the urine FABP4 level correlated independently with the level of albuminuria and it seems to be a biomarker of glomerular damage.

On the other hand, pregnancy affects essentially all aspects of the kidney

physiology. The orchestration of changes that occur in pregnancy is a physiologic feat. The kidney and systemic hemodynamics are marked by significant volume expansion and vasodilation. GFR increases by 50% and renal plasma flow increases by up to 80% as compared with non-pregnant levels. In normal pregnancy there is an increase in total urinary protein and albumin excretion, especially notable after 20 weeks. The protein content in urine is mostly Tamm-Horsfall, with a small amount of albumin and other circulating proteins. The rise in proteinuria during pregnancy is often attributed to the rise in GFR, although the timing does not fall within the peak increase in GFR. There is evidence that the amount of albuminuria increases in late pregnancy, albeit with levels that do not exceed the upper limit of the norm. Circulating soluble antiangiogenic factors, which are found at unusually high levels in preeclampsia and are known to disrupt the slit diaphragm, are also increased late in normal pregnancy and may explain late-term elevations in proteinuria. Another potential factor includes selective alterations in the glomerular charge or the presence of other protein material which is seen in the third trimester [14].

The FABP4 serum/urine gradient positively correlated with all the studied BIA variables with the exception of ECW in the healthy group. The EGWG group was characterized by positive correlations between the FABP4 serum/urine gradient and LTI as well as negative correlations with ECW. No correlations were observed between this parameter and BIA findings in the GDM group.

CONCLUSIONS

The FABP4 serum/urine gradient was comparable in the three studied groups of the post-partum mothers. However, this novel parameter was positively associated with the serum FABP4 level in the healthy group, whereas it was highly negatively related to the urine FABP4 concentrations in all three studied groups. These above mentioned findings may suggest that there are some differences in the FABP4 production or elimination in patients with both EGWG and GDM in comparison to healthy mothers.

Our results seem to confirm that further studies should not be limited to the evaluation of the serum FABP4 levels only.

It appears that urine sampling should also be taken into account since this biological material may provide additional useful information and help to explain the pathogenesis of type 2 diabetes mellitus.

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