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Secreted Frizzled-Related Protein 5 in Serum and Urine of Post-Partum Women with Gestational Diabetes Mellitus

Marcin Trojnar [1]*, Żaneta Kimber-Trojnar[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;

* Correspondence: marcin.trojnar@umlub.pl

Abstract

Secreted frizzled-related protein 5 (SFRP5) is a newly identified member of the SFRP family produced by the adipose tissue which can act as an anti-inflammatory adipokine. The aim of the study was to assess SFRP5 levels in the serum and urine of women with 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 included two groups: 22 GDM patients and 24 healthy controls. Maternal body composition and hydration status were evaluated by the bioelectrical impedance analysis (BIA) method. The serum and urine SFRP5, leptin and ghrelin concentrations were determined via enzyme-linked immunosorbent assay (ELISA).

No significant differences were observed between the GDM and healthy groups with regard to the serum and urine SFRP5 concentrations. In the GDM group serum and urine SFRP5 levels correlated positively. The serum SFRP5 concentrations correlated negatively with hemoglobin A1c (HgbA1c) and leptin serum levels in the controls. In the control and GDM groups the serum and urine SFRP5 levels correlated negatively with the serum ghrelin levels.

It appears that ghrelin as well as SFRP5 could influence the metabolic homeostasis 48 hours after delivery.

A significant correlation between concentrations of SFRP5 in the serum and urine seems to suggest that urine sampling may represent an alternative to the current standard of management i.e. blood sampling. Further research in this field is required.

Keywords: adipokines; secreted frizzled-related protein 5; leptin; gestational diabetes mellitus; bioelectrical impedance analysis; body composition; hydration status

INTRODUCTION

At present, gestational diabetes mellitus (GDM) represents a risk factor which accounts for post-partum complications both in the mother and child, thereby increasing their risk of developing chronic diseases later in life [1-4]. Women who had prior GDM were at risk, assessed at 36-70%, developing type 2 diabetes mellitus (T2DM) later in life, depending on risk factors and length of follow-up [5].

The presented study focuses on a recently introduced adipokine, the role of which is strictly linked to metabolic disorders ranging from insulin resistance to obesity and metabolic syndrome [6,7-11]. Secreted frizzled-related protein 5 (SFRP5) is secreted by the adipose tissue and is known to show anti-inflammatory properties [6,12]. The gene that codes the mentioned protein is localized on chromosome 10 [13]. By interfering with the Wnt signaling, SFRP5 affects a wide range of actions including fetus development, immune responses and inflammation [14,15]. The detailed mechanism of action deals with interaction with Wnt5a, which in turn inhibits c-Jun N-terminal kinase (JNK) activation in adipocytes. The outcome of this cascade of events is downregulation of pro-inflammatory cytokines and macrophage accumulation. Another clinically significant aspect of SFRP5 activity is the negative interaction with the insulin receptor substrate-1 (IRS-1) [6,12,16]. For this reason the ability of SFRP5 to modulate the progression of T2DM has been proposed by several authors. This indeed was confirmed in a series of experiments in diabetic and obese mice in which administration of SFRP5 improved the insulin sensitivity. Moreover other authors also reported beneficial outcomes and protective role of SFRP5 in case of hepatic steatosis, glucose intolerance and fibrosis [17].

There are few studies on the urine SFRP5 concentrations in humans. Such analyses were only performed in patients with urinary bladder cancer [18,19]. However, till date no data regarding SFRP5 in the post-partum period exist. Our research seems to be the first one in this respect.

As far as we know, the SFRP5 levels in the urine of GDM patients have not been investigated before.

The relationship between SFRP5 and various biochemical and biophysical measurements in women with GDM after delivery still remains vague. In our study the evaluation of body composition and hydration status with the use of the bioelectrical impedance analysis (BIA) method was taken into consideration.

METHODS

The studied group included Caucasian women in a singleton term pregnancy (after 37 weeks of gestation). The patients were divided into two groups. The first group consisted of 22 mothers with previously diagnosed GDM who were treated with insulin and followed low carbohydrate diet. Intensive insulin-therapy was used in 27% of the above mentioned GDM women, while 73% of them received only one basal insulin injection daily. The diagnosis of GDM was based on the 2-h-75 g-oral glucose tolerance test (OGTT), which was performed at 24-28 weeks of gestation. The diagnostic criteria of GDM included: fasting glucose ≥5.1mmol/L (92 mg/dL), or glucose plasma concentration of ≥10.0 mmol/L (180 mg/dL) at 60 minutes, or glucose plasma concentration of ≥8.5 mmol/L (153 mg/dL) at 120 minutes [20,21].

The second group was represented by 24 healthy controls, i.e. women in whom no metabolic disorders were diagnosed and who had normal OGTT result at 24–28 weeks of gestation. The pregnant women in this group had no concomitant diseases, they were following vitamin supplementation and presented normal values of pre-pregnancy body mass index (BMI) (i.e., between 18.5 and 24.99 kg/m^2), normal gestational weight gain (i.e., 11.5–16 kg) [22] and proper gestational age.

The exclusion criteria included: multiple pregnancy, chronic infectious diseases, current urinary infection or abnormal results of laboratory tests (e.g. the complete blood count, urine test, creatinine, glomerular filtration rate), mental illness, cancer, liver diseases, cardiovascular disorders, fetal malformation, premature membrane rupture, intrauterine growth retardation, the presence of metallic prostheses, pacemakers or cardioverter-defibrillators.

Blood and urine collection was performed 48 hours after delivery. The serum levels of albumin, hemoglobin A1c (HgbA1c) and lipid profile were measured by a certified laboratory. Following centrifugation, all of the serum and urine specimens were stored at –80 °C. The concentrations of SFRP5, ghrelin (Wuhan EIAab Science Co., Wuhan, China) and leptin (R and D Systems, Inc., Minneapolis, MN, USA) in the studied materials were determined with the use of commercially available kits and remained in compliance with the manufacturer's instructions via traditional enzyme-linked immunosorbent assay (ELISA). The procedure was performed twice for each patient. Additionally, the anthropometric measurements of mothers were carried out. The body composition including the hydration status of the study subjects was assessed using BIA method (Fresenius Medical Care).

Written informed consent for the study-related procedures was obtained from all the patients in the experiment. The study received approval of the Bioethics Committee of the Medical University of Lublin (KE-0254/221/2015 and KE-0254/348/2016).

All of the values were reported as the median (interquartile range 25–75%). The differences between the two studied groups were tested for significance using the Mann-Whitney *U*-test. 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

Comparing the characteristics of the study groups (Table 1) revealed that the healthy women were younger as well as had lower BMI before pregnancy, at and after delivery. The GDM mothers were characterized by lower levels of total cholesterol, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) as well as higher serum leptin concentrations, total body water (TBW), extracellular water (ECW) and fat tissue index (FTI).

No significant differences were observed between the groups with regard to other analyzed parameters (Table 1).

Since the values of the urine leptin levels detected in most of the studied GDM patients turned out to be below the threshold of sensitivity of the ELISA test, the “urine leptin” parameter is not present in this group. The minimum detectable dose of human leptin is typically less than 7.8 pg/mL.

Table 1. Comparison of characteristics of the subjects.

Variables	Control Group (n = 24)	GDM Group (n = 22)	p
Pregnancy & Delivery			
Age (years)	30.5 (30-36)	36.1 (32-41)	**0.018 ***
Pre-pregnancy BMI (kg/m^2)	21.77 (20.2-24.4)	28.1 (26.6- 30.1)	**0.000003 *****
Gestational weight gain (kg)	14.5 (8-15)	11 (7-15)	0.889
ΔBMI-1 (kg/m^2)	5.44 (2.97-5.6)	3.9 (2.23-5.19)	0.605
BMI at delivery (kg/m^2)	26.4 (25.1-29.1)	32.2 (30.5-33.9)	**0.000001 *****
2nd Day of Post-Partum Period			
Post-partum BMI (kg/m^2)	22.9 (21-23.9)	29.8 (27.7-31.2)	**0.000002 *****
ΔBMI-2 (kg/m^2)	2.53 (2.08-4.16)	2.2 (1.28-2.7)	0.112
ΔBMI (kg/m^2)	0.51 (-1.23-2.6)	2.2 (0.1-2.9)	0.467
Albumin (g/dL)	3.68 (3.43-3.73)	3.46 (3.37-3.64)	0.0689
Total cholesterol (mg/dL)	257 (207-287)	199.5 (192-242)	**0.012 ***
HDL (mg/dL)	78 (75-79)	65 (54-73)	**0.006 ***
LDL (mg/dL)	131 (102-152)	100 (84-127)	**0.011 ***
Triglycerides (mg/dL)	190 (150-254)	240.5 (155-252)	0.3797
Hemoglobin A1c (%)	5.35 (5.2-5.4)	5.6 (5.2-5.8)	0.0814
Serum ghrelin (ng/mL)	0.93 (0.65-1.11)	0.4 (0.19-1.23)	0.0624
Urine ghrelin (ng/mL)	0.1 (0.1-0.29)	0.21 (0.07-6.6)	0.3292
Serum SFRP5 (ng/mL)	3.01 (2.06-7.98)	4.42 (1.0-7.76)	0.287
Urine SFRP5 (ng/mL)	3.09 (0.66-15.72)	2.99 (1.0-7.82)	0.088
Serum leptin (ng/mL)	10.43 (6.04-14.88)	18.15 (10.84-51.91)	**0.003 ***
Urine leptin (ng/mL)	0.16 (0-4.01)	ND	-
Total body water (L)	29.9 (26-32.9)	33.9 (32.3-36.2)	**0.004 ***
Extracellular water (L)	14.5 (13-15.7)	16.6 (15-17.8)	**0.0002 ****
Intracellular water (L)	15.4 (13.5-17.1)	17.3 (16.8-18.4)	0.095
Lean tissue index (kg/m^2)	10 (9.4-13.1)	12.1 (11-13.2)	0.187
Fat tissue index (kg/m^2)	11.1 (9.9-13.8)	17 (13.3-18.8)	**0.00002 *****
BCMI (kg/m^2)	5.1 (4.8-7.2)	6.2 (5.5-7.3)	0.215

The results are shown as the median (interquartile range 25–75%). 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 hours after delivery; ΔBMI – BMI gain in the period from pre-pregnancy to 48 hours after delivery; SFRP5 - secreted frizzled-related protein 5; GDM – gestational diabetes mellitus; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol, ND – detected below the threshold of the sensitivity of the ELISA test.

Positive correlations were found between the serum and urine SFRP5 concentrations only in the GDM group (Table 2).

Table 2. Correlation coefficient between the maternal serum and urine SFRP5 levels and clinical and neonatal parameters in the control and GDM groups.

Variables	Control group		GDM group	
	Serum SFRP5	Urine SFRP5	Serum SFRP5	Urine SFRP5
Age	0.377	**0.463***	-0.012	-0.231
Pre-pregnancy BMI	**0.657****	0.028	-0.079	-0.030
Gestational weight gain	**-0.464***	**-0.522***	**0.560***	**0.695****
ΔBMI-1	-0.086	**-0.543***	0.191	**0.446***
BMI at delivery	**0.543***	-0.086	**0.527***	0.407
Post-partum BMI	0.086	-0.143	0.261	**0.663***
ΔBMI-2	-0.028	0.257	0.360	-0.103
ΔBMI	**-0.543***	**-0.486***	0.285	**0.699****
Albumin	-0.257	**-0.657****	-0.405	**-0.428***
Total cholesterol	**0.812*****	**-0.493***	0.194	-0.231
HDL	0.116	**0.725*****	**0.669***	-0.292
LDL	**0.771*****	**-0.543***	-0.097	0.079
Triglycerides	**0.464***	**-0.406***	-0.334	-0.407
Haemoglobin A1c	**-0.667****	-0.116	-0.032	**0.424***
Urine SFRP5	0.086	-	**0.470***	-
Serum ghrelin	**-0.486***	**-0.428***	**-0.410***	**-0.537***
Urine ghrelin	-0.200	-0.314	0.073	**-0.615***
Serum leptin	**-0.543***	-0.086	0.337	0.287
Urine leptin	0.152	0.395	-	-
Total body water	-0.086	0.143	-0.041	**0.469***
Extracellular water	-0.200	0.371	-0.014	**0.465***
Intracellular water	-0.257	-0.143	0.174	**0.622***
Lean tissue index	-0.200	0.086	0.324	0.336
Fat tissue index	0.086	**-0.600***	0.168	**0.469***
BCMI	-0.086	0.143	0.241	0.383

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 hours after delivery; ΔBMI – BMI gain in the period from pre-pregnancy to 48 hours after delivery; SFRP5 - secreted frizzled-related protein 5; GDM – gestational diabetes mellitus; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol.

In the control and GDM groups the serum and urine SFRP5 levels correlated negatively with the serum ghrelin levels. There was also a negative correlation between the urine ghrelin and SFRP5 levels in the GDM mothers. As far as leptin concentrations are concerned, negative correlations occurred between the serum SFRP5 and leptin levels in the control group (Table 2).

In the control group we found positive correlations between the serum SFRP5 and pre-pregnancy BMI, BMI at delivery, total cholesterol, LDL and triglycerides levels. Negative correlations between the serum SFRP5 concentration and gestational weight gain, BMI gain in the period from pre-pregnancy to 48 hours after delivery (ΔBMI) as well as HgbA1c were observed in the healthy mothers. In the healthy group the urine SFRP5 correlated negatively with gestational weight gain, gestational BMI gain (ΔBMI-1), ΔBMI, FTI and a majority of laboratory parameters (i.e. albumin, total cholesterol, LDL, triglycerides) and positively only with maternal age and HDL (Table 2).

In the GDM group we found positive correlations between gestational weight gain and the serum and urine SFRP5 concentrations and also between the serum SFRP5 levels and BMI at delivery and HDL as well as between the urine SFRP5 concentrations and ΔBMI-1, post-partum BMI, ΔBMI, HgbA1c, TBW, ECW, ICW and FTI. The urine SFRP5 levels correlated negatively with albumin concentrations in the GDM mothers (Table 2).

DISCUSSION

To the best to our knowledge, our study is the first one to report the SFRP5 levels in the early puerperal mothers. However, we did not find any significant differences between the serum or urine SFRP5 concentrations in GDM women and those of healthy controls.

Previous research on this novel adipokine was performed mainly in the elderly. SFRP5 is a recently defined adipokine with probable anti-inflammatory and diabetes protective features [6,23]. SFRPs act as soluble modulators of Wnt signaling pathway which is known to be involved in pancreatic development, β-cell proliferation, adiposity, insulin resistance and inflammation [24]. Additionally, Wnt signaling is engaged in placental vascularization and angiogenesis as well as in extraembryonic development [23]. Although, previous studies investigating the role of SFRP5 were controversial, a number of in vitro and in vivo studies have proposed a negative relationship between SFRP5 and the risk of disturbed glucose metabolism [7,8]. Oztas et al. suggested that its altered levels may contribute to the development of GDM [23]. The cited authors found that the serum SFRP5 concentrations were significantly lower in pregnant women who subsequently developed GDM than in healthy pregnant women [23]. There was no statistically significant difference in the first trimester maternal serum SFRP5 levels between the diet- and insulin-treated GDM groups. The authors explained that it might have been caused by the small number of patients in the only diet-treated GDM group (n=14) in comparison with the ones in the insulin group (n=26) in their study. Oztas et al. [23] noted that further studies investigating the relationship between the serum SFRP5 levels and the severity of the disease in GDM patients are needed to establish such a relationship, primarily in the third trimester or at the time of diagnosis, namely at 24–28 weeks of pregnancy. Moreover, Hu et al. observed that the serum SFRP5 levels were similar in patients with the impaired glucose tolerance and with newly diagnosed T2DM [8]. This may be the another explanation for the similar results in the diet- and insulin-treated groups in Oztas et al.'s study since SFRP5 might be involved in the pathogenesis but not correlated with the severity of the disease.

To the best of our knowledge, so far urine as a biological material has only been used in human studies for the assessment of the SFRP5 methylation status in patients with urinary bladder cancers [18,19]. Wang et al. [25], in the study performed in elderly subjects with acute ST-segment elevation myocardial infarction (STEMI) and chronic kidney disease (CKD) stage 4 and 5, observed an inverse correlation between the plasma SFRP5 levels and GFR. The increase in the plasma SFRP5 that occurs when kidney function deteriorates might represent an adaptive response to the altered metabolic profile related to a high cardiovascular risk in CKD patients. The authors concluded that the negative correlation between the SFRP5 concentrations and GFR suggested probable clearance impairment, although they did not test correlations between the urinary SFRP5 levels and eGFR in their patients to support this hypothesis. The cited authors emphasized that further studies are necessary to elucidate this issue. The methodology of our study was based on the evaluation of the SFRP5 concentrations in the serum and urine, but our study exclusion criteria comprised abnormalities in the GFR and urine test.

Our study revealed that although the serum and urine SFRP5 concentrations correlated positively, this relationship was documented only in the GDM mothers. Undoubtedly, urine tests are noninvasive and much better tolerated by patients than blood drawing procedures. It should be pointed out that from this perspective the potential aspect of epidemiological screening for metabolic disorders should be further explored in research.

Lower leptin plasma levels were found in healthy controls. A negative correlation between the serum SFRP5 and leptin concentrations was proved in the healthy mothers. These findings are in line with previously reported results by other authors [2,26,27]. Leptin plays a significant role at a cellular level in the development of a wide range of pathological conditions including coronary artery disease, obesity or T2DM [28]. Its role is strictly related to modification of insulin resistance, lipid metabolism and effect on energy balance [28-30]. Leptin is also engaged in suppression of pro-inflammatory cytokines that trigger lipogenesis. There are reports that link increased leptin concentration with the risk of the development of T2DM [29,31]. Due to this observation it may seem reasonable to consider monitoring GDM subjects for potential metabolic disorders in future life, as their leptin levels were found significantly higher than those in healthy counterparts in our experiment.

In our study the serum SFRP5 levels were negatively associated with the serum ghrelin levels in the healthy and GDM groups. Interestingly, negative correlations were also found between the urine SFRP5 and serum ghrelin levels in the healthy group and the serum and urine ghrelin concentrations in the GDM mothers.

Our previous study showed a positive correlation between the serum and urine ghrelin levels in the healthy mothers in the early post-partum period [2]. This association between the ghrelin concentrations in these two biological materials was not observed in the GDM group. We concluded that an irrelevant difference in favor of greater ghrelin levels in the urine of GDM mothers might be caused by their disturbed metabolism of the circulating ghrelin. This might have resulted from increased renal ghrelin clearance [2].

On the basis of the analyzed data it appears that ghrelin as well as SFRP5 could influence the metabolic homeostasis 48 hours after delivery. Insulin resistance that develops in every pregnancy is associated with increasing BMI values in pregnant women. Several case-control studies have found that increased insulin resistance during pregnancy is associated with abnormalities in the body weight [2,32,33]. Higher pre-pregnant BMI and more advanced maternal age are connected with an increased risk of GDM [34]. Also in our study, the

patients of GDM group were the oldest and were characterized by the highest values of BMIs evaluated before pregnancy.

Our study showed that serum SFRP5 levels correlated positively with pre-pregnancy BMI as well as BMI at delivery in the group of healthy mothers. To the contrary, the inverse correlations were found between the serum and urine SFRP5 levels and gestational weight gain and ΔBMI in the healthy group. This observation did not surprise us because of the well-known beneficial metabolic profile of SFRP5, the concentration of which remains low in obese non pregnant individuals.

In contrast, the GDM women were characterized by positive correlations between the serum and urine SFRP5 concentrations and gestational weight gain as well as between the urine SFRP5 levels and ΔBMI. Our results are probably related to the fact that the GDM women, due to their pre-pregnant overweight and obesity and normal carbohydrate results in the first trimester, remained under strict metabolic control from the beginning of gestation so that from 24-28 weeks of pregnancy following the diagnosis of GDM they could have been successfully treated not only with a proper diet but also with insulin.

Our study has demonstrated that healthy mothers had higher levels of total cholesterol, HDL and LDL than the GDM women. These results are consistent with the observations made by other authors [35,36]. Lower HDL concentrations are indicated as a risk factor of cardiovascular diseases for women with a history of GDM when compared with healthy pregnant controls [4,37,38]. Dubé et al. [36] found decreased maternal plasma levels of total cholesterol, LDL and HDL in the GDM patients, which is in agreement with ours and other authors' studies [2,39].

Our findings revealed that the serum SFRP5 concentrations correlated positively with the lipid profile (i.e. total cholesterol, LDL and TG levels) as well as negatively with HgbA1c concentrations in the healthy puerperal mothers. Negative correlations were found between the urine SFRP5 and albumin levels in this group. It should be noted that in our study all abnormalities in the urine analysis, including proteinuria, were excluded. The urine SFRP5 concentrations were also inversely associated with lipid profile (i.e. total cholesterol, LDL and triglycerides) of control subjects. It seems that the lower urine SFRP5 concentrations, the higher the values of the lipid profile in the serum of healthy mothers.

Among the results regarding the correlation between SFRP5 and laboratory findings we would especially like to draw attention to the highly significant associations between the serum SFRP5 and total cholesterol, LDL and HgbA1c levels in the healthy patients. The authors of previous studies also found a relationship between the plasma SFRP5 and lipid profile and HgbA1c [7,25]. We revealed highly statistically significant correlations between the urine SFRP5 and the serum HDL and albumin concentrations in the control group as well.

In order to assess the maternal body composition and hydration status, the BIA method was used in the study. This standardized technique is non-invasive, fast, and well tolerated by patients [2,40-42]. The physical properties of BIA, its measurement variables, and their clinical significance, have well been described in many published reports [2,41,43,44]. Our study showed that mothers with GDM in the early puerperium, when compared with the healthy controls, presented higher levels of not only FTI, which is defined as the adipose tissue mass divided by the square of the body height and expressed in units of kg/m^2, but also of TBW and ECW, where the latter consists of the interstitial water, plasma water, and transcellular water [2].

In the current study, lower results of the analyzed BIA parameters (i.e. TBW, ECW, and FTI) were observed in the healthy subjects.

Evaluation of the associations between SFRP5 and variables of the hydration status and body composition revealed positive correlations between the urine SFRP5 levels and the majority of BIA findings with the exception of lean tissue index (LTI) and body cell mass index (BCMI) in the GDM subjects. The last aforementioned parameter, i.e. BCMI, was introduced in our previous study [2], where we took into account the difference in the BMI in the post-partum period between our patients, and it was calculated as the body cell mass divided by the square of the body height as it seems to be a more precise parameter than body cell mass (BCM). We also observed that the urine SFRP5 correlated negatively with FTI in the healthy mothers.

CONCLUSIONS

In the light of the presented study and previous reports by other authors, SFRP5 should be further investigated with regard to metabolic disorders not only limited to pregnancy but also in future life of female patients.

The fact that there is a significant correlation between concentrations of SFRP5 in serum and urine suggests that urine sampling may represent an alternative to the current standard of management i.e. blood sampling. Further research in this field is required.

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