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SFRP5-leptin ratio as a promising index in post-partum women with gestational diabetes mellitus

Żaneta Kimber-Trojnar, Jolanta Patro-Małysza, Bożena Leszczyńska-Gorzelak

MD PhD Żaneta Kimber-Trojnar; zkimber@poczta.onet.pl; https://orcid.org/0000-0001-7295-0409
MD PhD Jolanta Patro-Małysza; jolapatro@wp.pl; https://orcid.org/0000-0002-4118-7698
Prof. Bożena Leszczyńska-Gorzelak; b.leszczynska@umlub.pl; https://orcid.org/0000-0002-0221-1982

Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Poland

Abstract:

INTRODUCTION: Gestational diabetes mellitus (GDM) has often been referred to as the "marker" for the development of diabetes, obesity and cardiovascular diseases in future lives of women. In the current literature the adiponectin-leptin ratio is presented as a valuable index to estimate adipose tissue dysfunction.
OBJECTIVES: The aim of the study was to investigate the significance of a novel parameter, i.e. the ratio of serum concentration of secreted frizzled-related protein 5 (SFRP5) to that of leptin in the early post-partum period. The associations between SFRP5/leptin ratio and maternal laboratory test results, body composition and hydration status were also assessed.
PATIENTS AND METHODS: 26 mothers diagnosed with gestational diabetes mellitus (GDM) and 28 healthy controls were enrolled in the study. Body composition and hydration status of the patients were evaluated with the use of bioelectrical impedance analysis (BIA) method. The serum concentrations of SFRP5, leptin, fatty acid-binding protein 4 (FABP4)

and ghrelin were determined via enzyme-linked immunosorbent assay (ELISA).
RESULTS: SFRP5/leptin ratio was lower in the GDM mothers in comparison to that of the control group. There were positive correlations between SFRP5/leptin ratio and total cholesterol and low-density lipoprotein cholesterol (LDL) levels. The SFRP5/leptin ratio correlated negatively with total body water (TBW) and extracellular water (ECW).
CONCLUSIONS: The SFRP5/leptin ratio appears to be a promising index for evaluating of metabolic disturbances in mothers with a history of GDM.

Keywords: adipokines, secreted frizzled-related protein 5, leptin, bioelectrical impedance analysis, gestational diabetes mellitus

INTRODUCTION

Among various adipokines, leptin and fatty acid-binding protein 4 (FABP4) were described as markers that are positively related to body weight, fat mass, insulin resistance, and pro-inflammatory properties [1]. Leptin, representing the first adipokine that has been discovered, influences many metabolic processes, as well as immunological and inflammatory status [2,3]. Apart from many pro-inflammatory cytokines, adipose tissue also secretes a variety of anti-inflammatory adipokines, including adiponectin and secreted frizzled-related protein 5 (SFRP5), which play crucial protective roles in inflammation. SFRP5 is a relatively new adipokine, which has been identified as a negative modulator of the wingless-type MMTV integration site family member (Wnt) signaling transduction pathway [4,5]. It has been demonstrated that SFRP5 expression is decreased, whereas Wnt5a expression is increased in the white adipose tissue of obese mice and humans [6]. SFRP5 seems to have the ability to modulate the progression of type 2 diabetes mellitus (T2DM) [7]. Nevertheless, there is still limited data available regarding the SFRP5 concentrations in obstetric aspects [8,9].

Any imbalance between pro- and anti-inflammatory adipokines triggers abnormal expansion of the adipose tissue, the leading cause of obesity, and induces local and systemic inflammation [1].

In the current literature the adiponectin/leptin ratio seems to be a valuable index estimating the adipose tissue dysfunction [10]. We were interested in evaluating the novel anti-inflammatory adipokine, i.e. SFRP5 instead of adiponectin. The aim of our study is to assess the ratio of serum levels of SFRP5 to those of leptin in mothers with a history of gestational diabetes mellitus (GDM).

METHODOLOGY

The study comprised women who were in a singleton term pregnancy (after 37 weeks of gestation) hospitalized in the Chair and Department of Obstetrics and Perinatology, the Medical University of Lublin. The data collection was performed between March, 2016

and February, 2017. The studied group included 26 mothers diagnosed with GDM, who followed diabetic diet and were treated with insulin. Diagnostic criteria for GDM were based on the oral glucose tolerance test (OGTT)performed at 24-28 weeks of gestation: fasting glucose ≥ 5,1mmol/l (92 mg/dl), or/and one hour plasma glucose result of ≥ 10.0 mmol/l (180 mg/dl), or a two-hour plasma glucose result of ≥ 8,5 mmol/l (153 mg/ dl).

The control group was represented by 28 healthy controls, i.e. mothers without any metabolic disorders. Three normal standard OGTT results at 24–28 weeks of gestation were documented in these subjects. This subgroup had no history of concomitant diseases, received only vitamin-iron supplementation and presented normal pre-pregnancy BMI values (i.e., between 18.5 and 24.99 kg/m^2), normal gestational weight gain (i.e., 11.5–16 kg) as well as proper gestational age.

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 (GFR) findings), metabolic disorders (such as polycystic ovarian syndrome; except for those listed in the inclusion criteria for the studied groups), mental illness, 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-hour fasting in the early post-partum period (i.e. within 48 hours after delivery). The maternal body composition and hydration status were evaluated by the BIA method (body composition monitor (BCM); Fresenius Medical Care). The serum levels of albumin, hemoglobin A1c and lipid profile were evaluated by a certified laboratory. Following centrifugation, the collected maternal serum samples were stored at –80 °C. The serum concentrations of SFRP5 (Wuhan EIAab Science Co., Wuhan, China), leptin (R&D Systems, Inc., Minneapolis, MN, USA), FABP4 (R&D Systems, Inc., Minneapolis, MN, USA) and ghrelin (Wuhan EIAab Science Co., Wuhan, China) 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 the patients were informed of the study protocol and the aim of the study. Written informed consent was obtained from each subject who agreed to participate in the study.

The study protocol was approved by the Bioethics Committee of the Medical University of Lublin (no. KE-0254/221/2015 [25th June, 2015] and no. KE-0254/348/2016 [15th December, 2016]).

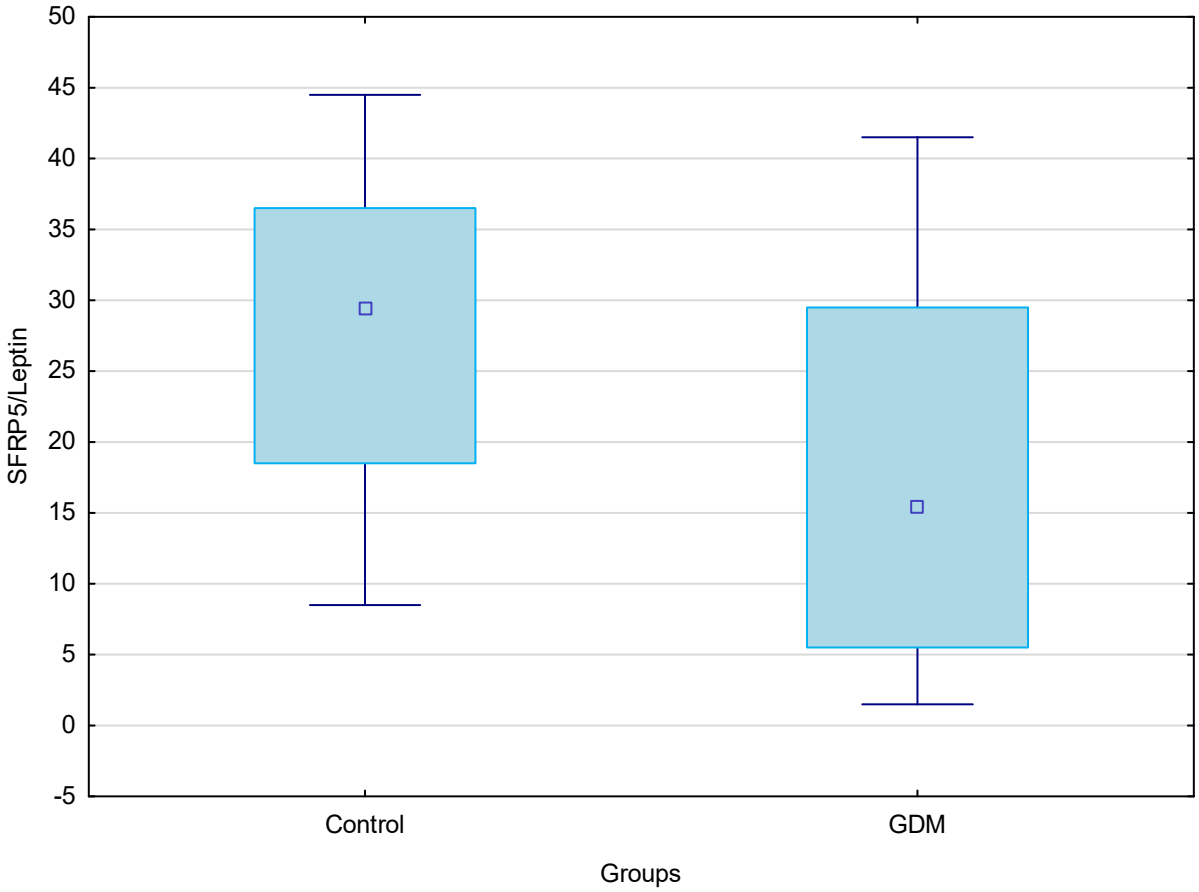
The values of the analyzed parameters were reported as the median (interquartile range 25–75%). The differences between the three studied subgroups were tested for significance using the Kruskal-Wallis analysis of variance. The post-hoc analysis of differences between two subgroups were tested for significance. 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 characteristics of the study subjects was previously presented in our recent studies [9,11,12].

The median of SFRP5/leptin ratio was significantly higher in the healthy subjects in comparison to the GDM mothers ($p<0,05$). Figure 1 compares the SFRP5/leptin ratio in the control and GDM groups in the early post-partum period.

Figure 1. The serum SFRP5/leptin ratio in the control and GDM groups in the early post-partum period



Positive correlations were found between the SFRP5/leptin ratio and total cholesterol and low density cholesterol (LDL) concentrations. The SFRP5/leptin ratio correlated negatively with total body water (TBW) and extracellular water (ECW) (Table 1).

Table 1. Correlation coefficient between the serum ratio of SFRP5 to leptin and selected parameters in the all groups

SFRP5/leptin ratio	R Spearman	*p*
gestational weight gain	0,091	0,548
pre-pregnancy BMI	-0,152	0,323
BMI at delivery	-0,115	0,459
gestational BMI gain	0,036	0,814
BMI loss after delivery	0,066	0,665
BMI after delivery	-0,261	0,088
ΔBMI	-0,263	0,084
albumin	0,086	0,568
total cholesterol	0,725	**<0,001**
HDL	0,279	0,078
LDL	0,649	**<0,001**
triglycerides	-0,039	0,801
hemoglobin A1c	-0,275	0,065
serum FABP4	-0,044	0,771
serum ghrelin	-0,275	0,065
BCM index	0,005	0,974
body cell mass	-0,002	0,992
lean tissue index	0,011	0,945
fat tissue index	-0,265	0,061
total body water	-0,315	**<0,05**
extracellular water	-0,404	**<0,01**
intracellular water	-0,188	0,211

Statistically significant values are given in the bold type. BCMI—body cell mass index; BMI—body mass index; ΔBMI—BMI gain in the period from pre-pregnancy to 48 h after delivery; FABP4—fatty acid-binding protein 4; HDL—high-density lipoprotein cholesterol; LDL—low-density lipoprotein cholesterol; SFRP5—secreted frizzled-related protein 5

DISCUSSION

GDM has been called a "marker" for future diabetes and cardiovascular diseases. Women with GDM in their prior pregnancy are more likely to have metabolic syndrome, an atherogenic lipid profile, and early vascular dysfunction at ≥3 months postpartum than women without previous GDM [13]. In one study of women with GDM, approximately one-third developed metabolic syndrome within 5 to 10 years of delivery [13]. In a 2009 systematic review and meta-analysis, women with GDM were at significantly higher risk of developing subsequent T2DM than women with normoglycemic pregnancies (RR 7.43, 95% CI 4.79-11.51; 20 cohort studies including 675,455 women of whom 10,859 had T2DM) [14].

The relative risk was 4.69 within the first five years after delivery and 9.34 more than five years after delivery. The absolute risks were illustrated in a population-based study: the incidence of T2DM in women with previous GDM was 3.7 percent 9 months postpartum, 4.9 percent 15 months postpartum, 13.1 percent 5 years postpartum, and 18.9 percent 9 years postpartum (versus 2 percent in controls without GDM) [15].

It was not without reason that SFRP5 was chosen by us out of the new adipokines to calculate the new parameter, i.e. the SFRP5/leptin ratio for evaluating in the serum in women with GDM in the early post-partum period in comparison to the healthy mothers. SFRP5 and leptin have been reported to be implicated in insulin resistance, obesity and metabolic syndrome [16-20].

There are very limited data regarding SFRP5 in obstetrics [8,9]. Oztas et al. [8] revealed that the serum SFRP5 concentrations were significantly lower in pregnant women who subsequently developed GDM than in healthy pregnant women.

Ouchi et al. [21] reported that after being put on a high-fat diet, genetically engineered SFRP5-lacking mice showed greater insulin resistance and adipose tissue inflammation due to an unrestrained wingless type MMTV integration site family member 5a (Wnt5a) activity. Interestingly, over-expression of SFRP5 in the adipocytes of these animals blocked the Wnt5a activity so that an inflammatory and insulin-resistant state could be prevented [21]. The cited authors concluded that the SFRP5 secretion by adipocytes exerts salutary effects on metabolic dysfunction with anti-inflammatory properties within the adipose tissue [21]. It seems that our findings may prove this observation. In our study the SFRP5/leptin ratio was positively associated with lipid profile, i.e. with levels of total and low density cholesterol.

In our previous study the serum leptin concentrations were lower in the healthy women [9]. This result is consistent with the observations made by other authors [22]. Previous studies also reported that the serum concentrations of SFRP5 and leptin were related to each other [23,24]. Moreover, it has been shown that a high leptin standard indicates a succedent development of T2DM [24,25]. Taking into account lower SFRP5/leptin ratio in the GDM group while comparing them to the healthy subjects, it seems that these women should be kept under metabolic supervision.

Our current findings may suggest that both leptin and SFRP5 seem to have a significance in the metabolic homeostasis at 48 hours after delivery. These results could be a consequence of disturbances developing during pregnancy and connected with the glucose intolerance or excess of gestational weight gain as well as of the early postpartum period in which maternal physiological changes related to pregnancy are beginning to return to the nonpregnant state.

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 [9,26,27]. The physical properties of BIA, its measurement variables, and their clinical significance, have well been described in many published reports [9,26,28]. Our previous 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 [9]. These results might suggest that the GDM mothers presented some disturbances in the BIA findings in the early puerperium in comparison to the healthy

subjects. In current study the SFRP5/leptin ratio correlated negatively with TBW and ECW. It may indicate that this new index is associated with hydration status.

CONCLUSIONS

The SFRP5/leptin ratio was statistically lower in the GDM mothers in comparison to that of the control group. This new parameter was associated with lipid profile as well as with the selected parameters of hydration status.

The SFRP5/leptin ratio appears to be a promising index for evaluating of metabolic disturbances in mothers with a history of GDM.

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