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Early Pregnancy Serum Concentration of Secreted Frizzled-Related Protein 4, Secreted Frizzled-Related Protein 5, and Chemerin in Obese Women Who Develop Gestational Diabetes Mellitus

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Abstract: Background: The aim of this study was to evaluate whether secreted frizzled-related protein 4 (sFRP4), secreted frizzled-related protein 5 (sFRP5), and chemerin serum concentrations in early pregnancy are associated with the development of gestational diabetes mellitus (GDM) in an obese cohort. In previous studies, increased sFRP4 and chemerin, and decreased sFRP5 concentrations were associated with the development of GDM in normal and overweight women. Methods: In this exploratory case control study, sFRP4, sFRP5, and chemerin serum concentrations were determined by ELISA in 50 obese women who developed GDM and 100 uncomplicated control pregnancies. Serum samples were obtained between 15^{+0}–18^{+6} weeks' gestational age and based on a priori known associations with the development of GDM, body mass index (BMI) and maternal age were selected for adjustment in multivariate analyses. Results: In this obese cohort (median BMI 35.7 kg/m^2, IQR 33.2–40.3 kg/m^2), the biochemical markers showed no association with GDM: sFRP5 odds ratio (OR) 0.44 (95% confidence interval (CI) 0.01–23.18, p = 0.687), sFRP4 OR 0.55 (95% CI 0.09–3.52, p = 0.528), and chemerin OR 3.47 (95% CI 0.05–227.72, p = 0.560). Adjustment for BMI and maternal age did not influence the association. None of the markers were significantly correlated with insulin resistance (HOMA2-IR). Conclusion: No association was found between sFRP4, sFRP5, or chemerin concentration and the development of GDM in a cohort of obese pregnant women. The absence of the association may indicate that these proteins play a lesser biological role in the pathophysiology of GDM in obese women.

Keywords: secreted frizzled-related protein 4 (sFRP4); secreted frizzled-related protein 5 (sFRP5); chemerin; gestational diabetes mellitus; obesity

1. Introduction

Gestational diabetes mellitus (GDM) is defined as the first identification of hyperglycemia during pregnancy, in which diagnostic glucose tolerance thresholds are lower than those for diabetes in non-pregnant individuals [1]. The disorder is associated with multiple short- and long-term risks, such as an increased risk of preeclampsia and preterm birth and an increased likelihood of developing type 2 diabetes and cardiovascular disease

later in life, for both mother and offspring [1]. Good glucose management by behavioral modifications and/or therapeutic intervention can significantly reduce these adverse pregnancy outcomes [2].

Recognition that abnormal fetal growth predates the conventional time for diagnosis of GDM in the late second/early third trimester have driven the search for earlier prediction of GDM [3]. Current early screening approaches are mainly based on one or more demographic risk factors, such as maternal age, first degree relative with a history of diabetes, and high body mass index (BMI) [4]. Studies have already demonstrated improved risk assessment with the inclusion of one or more biochemical markers [5,6], likely because they provide a more precise way of identifying pathophysiological pathways for hyperglycemia in pregnancy.

One intensively researched biochemical group for the prediction of GDM is adipokines, which are proteins secreted by adipocytes in white adipose tissue and commonly associated with metabolic diseases [7]. Well-described adipokines include adiponectin and leptin; they are involved in various endocrine processes, including insulin resistance [8]. Next to these well-described adipokines, the list is still expanding. Among them is chemerin: an adipokine, yet also produced by the pancreas and placenta, and involved in the onset of metabolic disorders through inducing an insulin-resistant state in both adipocytes and skeletal muscles [9,10]. Another adipokine additionally secreted by the pancreas is the anti-inflammatory secreted frizzled-related protein 5 (sFRP5) [11]. Through its antagonistic action on the wingless-type (Wnt) signaling pathway, sFRP5 has been associated with obesity-related metabolic disorders through its role in the fetal development of the pancreas, beta cell proliferation, inflammation, and insulin action [12,13].

Secreted frizzled-related protein 4 (sFRP4), another member of the Wnt antagonizing protein family, has also been associated with metabolic disorders and specifically the development of type 2 diabetes [14]. Although physiologically widespread, it has been described to a lesser extent as an adipokine and is also produced by the endometrium and α and β cells of the pancreas [15,16]. However, increased sFRP4 has been identified as a marker for early pancreatic beta cell dysfunction, as it has been shown to suppress insulin secretion, and it also downregulates adiponectin (a marker of insulin sensitivity) and upregulates leptin in murine adipose tissue [16,17].

In a previous study, we showed that increased levels of sFRP4 and chemerin in the first trimester are associated with the development of GDM [18], and a study from Oztas et al. [19] showed decreased sFRP5 expression in women who later developed GDM. Women with GDM in these two studies had a mean BMI in the normal and overweight weight range: 24.3 ± 3.7 and 26.2 ± 5.6 kg/m^2, respectively. Since BMI is one of the major predictors for GDM, the aim of this study was to evaluate whether sFRP4, sFRP5, and chemerin are associated with the development of GDM when measured early in pregnancy in an obese cohort.

2. Materials and Methods

2.1. Study Design

Samples analyzed in this sub-study were collected prospectively from participants recruited to the UK Pregnancies Better Eating and Activity Trial (UPBEAT, ISRCTN 89971375) between 2009 and 2014. The trial was approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 09/H0802/5). Exclusion criteria for women participating in this study were as follows: pre-existent diabetes, currently prescribed metformin, essential hypertension, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease, thalassemia, coeliac disease, thyroid disease, or current psychosis. All women had a BMI of $\geq$30 kg/m^2. Demographic parameters, clinical information, and serum samples were collected at trial entry (15^{+0}–18^{+6} weeks gestational age). Skinfold thicknesses were measured in triplicate by Harpenden skinfold calipers, and the mean of the triplicate was used for analyses. Sum of skinfold thicknesses was determined by summing subscapular, suprailiac, triceps, and biceps and is a measure

of adiposity. GDM was defined according to the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG); fasting glucose $\geq$ 5.1 mmol/L and after a 75 g oral glucose tolerance test (OGTT), glucose levels of $\geq$ 10.0 mmol/L after 1 h or $\geq$ 8.5 mmol/L after 2 h. Insulin resistance was calculated by homeostatic model assessment of insulin resistance (HOMA2-IR) [20].

In this exploratory case-control study, 150 obese women were included with a BMI of $\geq$30 kg/m^2 (median BMI 35.7 kg/m^2, IQR 33.2–40.3 kg/m^2); 50 who developed GDM and 100 who did not develop GDM diagnosed in the late second or early third trimester.

2.2. Adipokine Analysis

Adipokine concentrations were analyzed by enzyme-linked immunosorbent assay (ELISA) for human sFRP4 (SEF878Hu, Cloud-Clone Corp., Houston, TX, USA), sFRP5 (SEC842Hu, Cloud-Clone Corp., Houston, TX, USA), and chemerin (DT2324, R&D Systems, Minneapolis, MN, USA). All kits were used according to the protocol supplied. In short, a microtiter plate coated with an antibody specific to the antigen was incubated with the standards and serum samples, and serum samples were diluted 1:20 for sFRP5, 1:50 for sFRP4, and 1:500 for chemerin. After incubation and washing, the wells were incubated with a biotin-conjugated antibody specific to the adipokine antigen. Subsequent to a further wash, the biotin-conjugated antibody was detected by horseradish peroxidase (HRP) conjugated to streptavidin. After the addition of 3,3′,5,5′-tetramethylbenzidine (TMB), the TMB was enzymatically converted by the HRP, and this was stopped by sulfuric acid after sufficient conversion. The antigen concentration in the samples was calculated by optical density interpolation to the standard curve. The lower limits of quantification of the assays were 31.2, 650, and 1500 pg/mL for, respectively, sFRP5, sFRP4, and chemerin, and all intra- and inter-assay variations were below 15%. Before analysis, all serum samples were coded to blind the investigator to the clinical outcome of the subjects.

2.3. Statistical Analysis

Demographic variables are presented as median values and interquartile ranges for continuous data and numbers and percentages for categorical data, respectively. Adipokine levels were checked for normality, and all protein levels were log-transformed to obtain a Gaussian distribution for further statistical analysis. Statistical comparisons between cases and controls were performed using Mann–Whitney U or Chi-square tests for baseline characteristics. The association of the variable(s) with GDM was determined by univariate binary logistic regression analysis. Based on a priori known associations with the development of GDM, BMI and maternal age were selected for adjustment in multivariate analyses. All statistical analyses were performed using SPSS (IBM version 26, Armonk, NY, USA), and p-values < 0.05 were considered statistically significant.

3. Results

The baseline characteristics of this obese cohort (median BMI 35.7 kg/m^2, IQR 33.2–40.3 kg/m^2) are shown in Table 1.

Maternal age (p = 0.007), ethnicity (p = 0.020), birthweight (p = 0.017), and sum of skinfolds (p = 0.024) were significantly different between women who developed GDM and those who did not. Glucose parameters were, by definition, significantly different: fasting, 1-h glucose after OGTT, and 2-h glucose after OGTT (all p < 0.001). Absolute concentrations of sFRP4, sFRP5, and chemerin are shown in Table 2. After logarithmic transformation, univariate logistic regression of the biochemical markers showed no differences for sFRP5 (odds ratio (OR) 0.44; 95% confidence interval (CI) 0.01–23.18, p = 0.687), sFRP4 (OR 0.55; 95% CI 0.09–3.52, p = 0.528), and chemerin (OR 3.47; 95% CI 0.05–227.72, p = 0.560) (Table 2).

Table 1. Baseline characteristics of pregnancies affected by gestational diabetes (GDM) and uncomplicated pregnancies (controls).

		Non GDM (n = 100)	GDM (n = 50)	p-Value	
Maternal age (years)		29 (25–35)	32 (29–36)	0.007	#
Maternal BMI (kg/m^2)		34.5 (33.2–39.2)	37.2 (33.5–42.6)	0.120	#
Gestational age sampling (days)		117.5 (112.0–125.0)	121.0 (116.0–125.0)	0.060	#
Maternal ethnicity	White Black Asian Other	77 (77%) 15 (15%) 5 (5%) 3 (3%)	26 (52%) 15 (30%) 5 (10%) 4 (8%)	0.020	##
Parity	0 1 2 3 4	45 (45%) 31 (31%) 20 (20%) 3 (3%) 1 (1%)	16 (32%) 17 (34%) 10 (20%) 4 (8%) 3 (6%)	0.172	##
Delivery mode	Cesarian section in labor Prelabor cesarian section Operative vaginal Unassisted vaginal	20 (20%) 15 (15%) 9 (9%) 56 (56%)	11 (22%) 11 (22%) 5 (10%) 23 (46%)	0.642	##
Infant sex	Female Male	45 (45%) 55 (55%)	26 (52%) 24 (48%)	0.418	##
Birthweight (g)		3580 (3333–3821)	3370 (3020–3700)	0.017	#
Birth weight percentile		45.1 (27.9–65.4)	52.5 (23.7–77.0)	0.649	#
Mean sum of skinfolds (mm) *		117 (102–138)	135 (108–147)	0.024	#
Waist circumference (cm) *		105 (100–112)	108 (102–115)	0.095	#
Fasting glucose (mmol/L)		4.5 (4.3–4.8)	5.2 (5.0–5.7)	<0.001	#
1-h glucose after OGTT (mmol/L) *		7.0 (6.3–8.3)	9.9 (8.7–11.0)	<0.001	#
2-h glucose after OGTT (mmol/L) *		5.7 (4.8–6.3)	6.9 (6.0–7.8)	<0.001	#
HOMA2-IR score (units) *		2.6 (1.9–4.2)	3.5 (2.2–5.4)	0.074	#

Data are presented as respectively median values and interquartile ranges for continuous data, and as numbers and percentages for categorical data. # Analysis by Mann–Whitney U test. ## Analysis by Chi-square test. * Missing data at baseline; Mean sum of skinfolds (n = 2), waist circumference (n = 1), 2-h glucose after OGTT (n = 5), and HOMA2-IR score (n = 4). OGTT: oral glucose tolerance test; BMI: body mass index.

Table 2. Absolute mean concentrations and standard deviation (SD) and logistic regression analysis of logarithmic transformed sFRP4, sFRP5, and chemerin concentrations in gestational diabetes (GDM) and uncomplicated (control) pregnancies.

	Mean Concentrations ± SD (ng/mL)		OR (95% CI)	Significance
	Control (n = 100)	GDM (n = 50)		
sFRP4	45.78 ± 21.89	42.00 ± 14.87	0.550 (0.086–3.517)	0.528
sFRP5	42.76 ± 8.91	42.00 ± 7.87	0.444 (0.008–23.180)	0.687
Chemerin	185.16 ± 33.02	189.68 ± 39.53	3.466 (0.053–227.723)	0.560

Adjustment for BMI and maternal age (and ethnicity/HOMA2-IR; data not shown) in multivariate analyses did not influence the association between adipokines and the development of GDM (Table 3). None of the markers were significantly correlated with HOMA2-IR (data not shown).

Table 3. Multivariate analysis of logarithmic transformed sFRP4, sFRP5, and chemerin concentrations, maternal age, and BMI in gestational diabetes (GDM) and uncomplicated (control) pregnancies.

	sFRP4	
Variables *	**OR (95% CI)**	**Significance**
sFRP4	0.749 (0.109–5.162)	0.769
Maternal age	1.075 (1.013–1.141)	0.017
sFRP4	0.313 (0.043–2.271)	0.250
Maternal BMI	1.075 (1.005–1.148)	0.034
sFRP4	0.431 (0.055–3.376)	0.431
Maternal age	1.074 (1.011–1.141)	0.020
Maternal BMI	1.073 (1.002–1.149)	0.043
	sFRP5	
Variables *	**OR (95% CI)**	**Significance**
sFRP5	0.247 (0.004–14.511)	0.501
Maternal age	1.079 (1.017–1.145)	0.012
sFRP5	0.496 (0.009–26.614)	0.730
Maternal BMI	1.063 (0.998–1.133)	0.059
sFRP5	0.268 (0.004–16.288)	0.530
Maternal age	1.080 (1.017–1.147)	0.012
Maternal BMI	1.064 (0.997–1.136)	0.060
	Chemerin	
Variables *	**OR (95% CI)**	**Significance**
Chemerin	1.683 (0.023–121.774)	0.812
Maternal age	1.076 (1.013–1.142)	0.016
Chemerin	1.175 (0.015–94.188)	0.942
Maternal BMI	1.063 (0.995–1.135)	0.070
Chemerin	0.524 (0.006–47.136)	0.778
Maternal age	1.079 (1.016–1.146)	0.014
Maternal BMI	1.068 (0.998–1.143)	0.058

* All biochemical variables were log transformed

4. Discussion

In this exploratory study in an obese cohort of pregnant women, no association was found between sFRP4, sFRP5, or chemerin and the development of GDM. This is in contrast with other available studies in which mainly normal weight and overweight women were included [18,19]. The absence of this association may indicate that the studied proteins play a lesser biological role in the pathophysiology of GDM in obese women.

In our previous study, a significantly increased sFRP4 was observed in the GDM group compared to the control pregnancies [18]. The lack of association found in this cohort might relate to the higher BMI; in women of normal weight, it is hypothesized that insufficient insulin secretion may play a more prominent role in the development of GDM [21,22].

sFRP4 causes a decrease in the expression of calcium ion channels in pancreatic beta cells, which in turn are responsible for the exocytosis of insulin [16,23], and as such, is a marker of early pancreatic beta cell dysfunction. Therefore, the increased sFRP4 expression as found in normal weight GDM women might be related to a higher prevalence of GDM caused by insufficient insulin secretion. Based on available data of non-pregnant women, increased sFRP4 levels could be expected in obese pregnant women, since obesity is a chronic mild inflammatory condition and pancreatic sFRP4 overexpression is induced by the pro-inflammatory IL-1β [14]. Nevertheless, the average sFRP4 level in this obese cohort was lower overall compared to our previous study: 43.9 vs. 116.9 ng/mL [18]. A reason for this observation might be the difference in gestational age at sampling: average 120 in this study vs. 81 days previously. This is a time interval in which the maternal immune and hormonal system undergoes major adaptations, and multiple studies have showed that IL-1β significantly decreases between the first and second trimester [24–26]. In addition, Pantham et al. conclude from various studies that obesity during pregnancy does not always show the same inflammatory profile as in non-pregnant obese women [25].

As well as higher concentrations of sFRP4, increased levels of chemerin have also been observed in normal weight GDM women [27]. Since chemerin is mainly produced by adipose tissue, this might reflect the presence of more (visceral) adipose tissue in normal weight women with GDM as opposed to those without GDM [28]. It is noteworthy that, compared to our previous study of normal weight women [18], the average absolute concentration of chemerin detected in this obese cohort was higher: 186.7 vs. 154.3 ng/mL, potentially due to the presence of a higher quantity of adipokine-producing adipose tissue, yet no association with GDM was found; it is feasible that, as previously demonstrated with leptin [29], there is a reduction in sensitivity at higher chemerin concentrations, and such resistance to chemerin has already been hypothesized [30,31].

In contrast, a lower concentration of sFRP5 is hypothesized to be associated with GDM in normal weight women [19]. This is most likely related to a decrease in sFRP5 levels resulting in activation of the Wnt pathway, which in turn is associated with insulin resistance and inflammation [12]. Of note, higher absolute sFRP5 levels were observed in this study compared to the study of Oztas et al. (average 42.5 vs. 16.2 ng/mL), although diverse results have been published for both obesity and diabetes [13].

In conclusion, we did not find an association between sFRP4, sFRP5, or chemerin and the development of GDM in an obese cohort of pregnant women, and to the best of our knowledge, no previous study has investigated this. A limitation to this study is that the cohort was small and may lack power to identify differences. In addition, it is important to note that although glycaemia, age, ethnicity, and sum of skinfolds differed between women who developed GDM and those who did not, neither BMI nor HOMA2-IR levels differed significantly in this case-control sub-study. A failure to find an association between GDM and these adipokines may therefore relate to only small differences in adiposity between the groups, although a lack of correlation between HOMA2-IR and the adipokines points to a diverse pathophysiology. Of note, women included in our previous study were matched on maternal age and BMI, and significant differences in GDM pregnancies were observed for both sFRP4 and chemerin [18]. Thus, these adipokines may not only reflect adiposity, but could also have a biological role in the pathophysiology of GDM in non-obese women. These observations and the results from this study warrant further investigation in a larger and more weight heterogeneous cohort in order to explore the mechanism of these adipokines in GDM.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author, R.H.J.B., upon reasonable request.

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Conflicts of Interest: R.H.J.B. and J.H.N.S. are employed by IQ Products. The remaining authors report no conflict of interest.

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