ORIGINAL ARTICLE

Adipokines and β-cell dysfunction in normoglycemic women with previous gestational diabetes mellitus

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KEY WORDS

adipokines, β-cell function, previous gestational diabetes mellitus, subclinical inflammation

ABSTRACT

INTRODUCTION An increased risk of developing type 2 diabetes in women with a history of gestational diabetes mellitus (*gestational diabetes mellitus* – GDM) may be associated with increased insulin resistance and subclinical inflammation. However, approximately half of women with previous GDM (pGDM) do not develop diabetes. These women were the population of focus in the present study.

OBJECTIVES The aim of the study was to assess β-cell function, insulin resistance, and the levels of pro- and anti-inflammatory adipokines in normoglycemic women with pGDM.

PATIENTS AND METHODS A study group included 199 women with pGDM; the mean time after delivery was 7.4 years. A control group included 50 women without pGDM. All patients underwent an oral glucose tolerance test (OGTT) with the assessment of glycemia and insulinemia, β-cell function (HOMA-%β), and insulin resistance (HOMA-IR), as well as the levels of soluble tumor necrosis factor α receptor (sTNF-α-R2), interleukin 6 (IL-6), adiponectin, and visfatin.

RESULTS Normal glucose tolerance was found in 113 women with pGDM (56.8%; the NGT-GDM[+] group) and in 44 control subjects (88.0%). In comparison with controls, the NGT-GDM[+] group had significantly higher glycemia in the OGTT and significantly lower HOMA-%β values, with comparable HOMA-IR and body mass index values. The NGT-GDM(+) group was shown to have significantly higher levels of sTNF-α-R2 and IL-6, with similar adiponectin and visfatin levels.

CONCLUSIONS Normoglycemic women with a history of GDM are characterized by concomitant disturbances in insulin secretion and subclinical inflammation, with normal body weight and insulin sensitivity. It is not known whether these disturbances were present before a GDM-complicated pregnancy or whether they were induced by pregnancy.

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INTRODUCTION The results of current population studies suggest that the incidence of gestational diabetes mellitus (GDM) in various populations of pregnant women ranges from 3.5% to 32.5%, depending on the selection criteria.[1,2] The incidence of GDM has been increasing recently, most likely owing to the growing prevalence of overweight and obesity. GDM is an important risk factor for developing type 2 diabetes, with 4% to 18% of women diagnosed with diabetes within several months after a pregnancy complicated by GDM, and 7% to 40% of women diagnosed within 10 years.[1,3] The development of GDM is believed to be the result of β-cell dysfunction due to increased insulin resistance associated with the physiological effects of placental hormones. Metabolic disturbances in women with previous GDM (pGDM) include reduced insulin secretion and increased insulin resistance, which are typically associated with overweight or obesity.[4-7] Approximately 30% of those women develop signs of metabolic syndrome. During GDM and for a relatively long period of time afterwards, signs of subclinical inflammation are also present in this population.[8,9] Thus, the types of disturbances found in women with GDM are very similar to the pathogenetic abnormalities observed in type 2 diabetes: in addition to insulin secretion disturbances

and insulin resistance, evidence of subclinical inflammation can be also found.[10] The vast majority of studies on metabolic disturbances in women with a history of GDM include either the entire population of women with GDM, regardless of their current carbohydrate metabolism rates, or women who developed type 2 diabetes or glucose intolerance following pregnancy. Only a few reports focused on women with pGDM who remain normoglycemic for a number of years following pregnancy complicated by GDM.[10-18] The results of such studies, typically conducted in very small study populations, indicate that these women are not obese, typically have a normal body weight and show disturbances in insulin secretion in response to a glucose stimulus. The available insulin sensitivity findings are inconclusive; they indicate a possibility of either normal[11-13] or reduced insulin sensitivity.[12,14-19] The reasons for the abnormal insulin secretion and reduced insulin sensitivity observed in normoglycemic nonobese women with pGDM remain unclear. There are no data concerning this particular group of women in terms of anti-inflammatory or proinflammatory adipokines, confirming that these adipokines may be involved in inducing insulin resistance and abnormal insulin secretion, leading to type 2 diabetes.[9,10,20]

The aim of this study was to assess β-cell function, insulin resistance, and selected adipokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), as well as adiponectin and visfatin levels in women with pGDM with no current disturbances in carbohydrate metabolism and no antibodies against pancreatic β cells.

PATIENTS AND METHODS

Study population

The primary study group consisted of 204 women. All of the studied participants were examined for the presence of antiglutamic acid decarboxylase antibodies (anti-GAD), and 5 of them were excluded from further analysis because they were anti-GAD positive. Thus, the final study group included 199 women at a mean age of 38.4 ±6.6 years, who had given birth within the last 5 to 12 years and had been diagnosed with GDM based on results of the oral glucose tolerance test (OGTT) conducted during the index pregnancy (the GDM[+] group). The control group included 50 women of comparable age (mean age, 36.8 ±5.6 years), who had given birth during the same period of time and in whom GDM was excluded based on OGTT results during pregnancy (the GDM[–] group). Both groups were also matched in terms of the body mass index (BMI) and the number of pregnancies. This study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland, and written informed consent was obtained from each subject.

Methods

A detailed medical history was taken from study participants, including the date, number, and course of their pregnancies as well as their body weight before pregnancy. A physical examination included the measurement of weight and height for BMI (kg/m^2) calculation and waist and hip circumference for waist-to-hip ratio (WHR) calculation, as well as the assessment of adipose tissue content (mass and percentage) by the bioelectrical impedance method, using the Tanita SC-330S scale (Tanita Corporation, Tokyo, Japan). All participants underwent an OGTT (75 g) to measure the levels of blood glucose (enzymatic method; PZ Cormay S.A., Warsaw, Poland) and insulin (immunoradiometric assay; BioSource Europe S.A., Nivelles, Belgium). The measurements were taken at baseline and after 60 and 120 minutes, and the following parameters were calculated using the homoeostasis model assessment (HOMA) calculator, version 2.2.2: insulin resistance (HOMA-IR; glucose level [mmol/l] × insulin level [μIU/ml/22.5]) and β-cell function (HOMA-%β).[21] Additional measurements included glycated hemoglobin (HbA_{1c}) levels (high-performance liquid chromatography method, Bio-Rad Laboratories, Munich, Germany) and anti-GAD antibodies (enzyme-linked immunosorbent assay [ELISA], Euroimmun, Lübeck, Germany) as a marker of immune response indicative of type 1 diabetes. Serum adipokine levels were determined as follows: soluble TNF-α receptor 2 (sTNF-α-R2), which reflects TNF-α levels, via ELISA (MyBiosource, San Diego, California, United States); IL-6, via ELISA (Bender-Systems, Vienna, Austria); adiponectin, via radioimmunoassay (Linco Research Inc., St. Charles, Missouri, United States); visfatin, via enzyme immunoassay (Phoenix Pharmaceuticals, Burlingame, California, United States).

Statistical analysis

The STATISTICA software version 7.1 (StatSoft Inc., Tulsa, Oklahoma, United States) was used for database management and statistical analyses. The Mann–Whitney and χ^2 tests were used for the comparison of continuous and nominal variables, respectively. Correlations between the continuous variables in each group were analyzed using the Spearman rank correlation coefficient (r). A P value of less than 0.05 was considered statistically significant.

RESULTS

The study groups did not differ in terms of age, gravidity and parity, the period of time after the index pregnancy (whether complicated or uncomplicated by GDM), pregravid body weight, current anthropometric parameters (BMI, waist and hip circumference, WHR), body composition, or blood pressure. Mean HbA_{1c}, fasting glucose, and 60- and 120-minute OGTT glucose levels in women with a history of GDM were significantly higher than those in women without pGDM; nonetheless, they were within the normal range. In addition, women with pGDM had a significantly lower insulin secretion rate as determined by the homeostasis model assessment (HOMA-%β) but had comparable levels of insulin resistance. Women with pGDM had significantly higher levels of proinflammatory cytokines

TABLE 1 Characteristics of women with and without previous gestational diabetes mellitus

Parameter	GDM[+] n = 199	GDM[–] n = 50	*P* value
age, y	38.4 ±6.6	36.8 ±5.6	NS
number of pregnancies	2.4 ±1.4	1.9 ±2.1	NS
number of deliveries	2.1 ±1.2	1.8 ±2.4	NS
time since previous GDM/ pregnancy, y	7.4 ±0.7	7.8 ±1.0	NS
body weight before pregnancy, kg	63.3 ±13.1	61.6 ±11.1	NS
body weight, kg	67.9 ±15.2	68.7 ±14.9	NS
BMI, kg/m^2	25.5 ±5.6	25.4 ±5.0	NS
WHR	0.86 ±0.09	0.84 ±0.07	NS
adipose tissue mass, %	31.0 ±8.0	31.2 ±8.9	NS
lean body mass, kg	45.5 ±6.1	46.1 ±4.8	NS
HbA_{1c}, %	5.6 ±0.4	5.4 ±0.4	<0.01
glucose 0′, mmol/l	5.3 ±0.7	4.9 ±0.6	<0.0001
glucose 60′, mmol/l	8.3 ±2.6	5.8 ±1.9	<0.0001
glucose 120′, mmol/l	6.4 ±2.2	4.8 ±1.1	<0.0001
insulin 0′, μIU/ml	13.7 ±8.7	13.7 ±8.5	NS
insulin 60′, μIU/ml	106.8 ±62.6	83.8 ±41.1	<0.03
insulin 120′, μIU/ml	74.6 ±58.7	47.5 ±30.6	<0.002
HOMA-IR	1.76 ±1.05	1.73 ±1.03	NS
HOMA-%β	125.4 ±52.7	145.7 ±49.2	<0.002
sTNF-α-R2, ng/ml	4.7 ±1.6	4.1 ±1.3	<0.003
IL-6, pg/ml	3.5 ±3.2	2.2 ±1.2	<0.0001
adiponectin, ng/ml	14.4 ±6.5	14.7 ±8.0	NS
visfatin, ng/ml	1.9 ±1.3	2.1 ±1.5	NS

Data are presented as mean ± standard deviation.

Abbreviations: BMI, body mass index; GDM[+], women with previous gestational diabetes; GDM[–], women without previous gestational diabetes; HbA_{1c}, hemoglobinA_{1c}; HOMA-IR, homoeostasis model assessment, insulin resistance; HOMA-%β, homoeostasis model assessment, β-cell function; IL-6, interleukin 6; NS, nonsignificant; sTNF-α-R2, soluble tumor necrosis factor α receptor type 2; WHR, waist-to-hip ratio

(sTNF-α-R2 and IL-6) with comparable levels of anti-inflammatory adipokines (adiponectin and visfatin) (TABLE 1). Disturbances in carbohydrate metabolism detected with the OGTT were significantly more common in the GDM[+] group than in the GDM[–] group; normal glucose tolerance was observed in 113 women (56.8%) and 44 women (88%), respectively; abnormal fasting blood glucose, in 40 women (20.1%) and 5 women (10%), respectively; and abnormal glucose tolerance, in 33 women (16.6%) and 1 woman (2.0%), respectively. However, diabetes was found only in the GDM[+] group (in 13 subjects [6.5%]; χ^2 = 18.7; *P* <0.001). A group of 113 normoglycemic women with a history of GDM (the NGT-GDM[+] group) and 44 normoglycemic women with no previous GDM (the NGT-GDM[–] group) underwent further analysis. The evaluated subgroups did not differ in terms of age, gravidity and parity, time after the index pregnancy (with or without GDM), pregravid body weight, anthropometric parameters (BMI, waist circumference, WHR), or blood pressure. The NGT-GDM[+] group was found to have significantly lower lean body mass than the NGT-GDM[–] group (44.1 ±4.6 vs 46.2 ±4.7 kg; *P* <0.05), with comparable body weight and body fat percentage (TABLE 2). Although within the normal range, the blood glucose levels at all OGTT time points (fasting, 60 minutes, and 120 minutes) were significantly higher in the subgroup of normoglycemic women with pGDM. Moreover, significantly higher 120-min OGTT insulin levels were observed in the NGT-GDM[+] group (64.5 ±50.6 vs 42.0 ±25.6; *P* = 0.003), with identical fasting insulinemia values and nonsignificantly higher insulinemia at 60 minutes. Women from the NGT-GDM[+] group showed significantly lower HOMA-%β values (131.1 ±51.1 vs 144.7 ±47.1; *P* <0.04), with similar HOMA-IR levels. The 2 groups did not differ in terms of lipid profiles, with the exception of high-density lipoprotein cholesterol levels, which were significantly higher in the NGT-GDM[+] group (TABLE 2). A comparison of adipokine levels in normoglycemic women revealed significantly higher levels of proinflammatory cytokines in the NGT-GDM[+] group compared with those in the NGT-GDM[–] group (sTNF-α-R2, 4.7 ±2.0 vs 4.1 ±1.2 ng/ml; *P* <0.03; IL-6, 3.2 ±2.6 vs 2.3 ±1.2 pg/ml; *P* <0.01). However, no significant intergroup differences were observed in terms of either adiponectin or visfatin levels (TABLE 2). The NGT-GDM[+] subgroup was evaluated for any relationship between adipokine levels and anthropometric and metabolic parameters. The levels of sTNF-α-R2 did not reveal any significant correlation with either anthropometric or metabolic parameters, except for a positive correlation between HbA_{1c} and visfatin levels. IL-6 levels showed a negative correlation with fasting and 120-minute insulin levels, as well as HOMA-IR values. The adiponectin concentration was negatively correlated with anthropometric parameters (BMI, body weight, WHR), body fat percentage, blood glucose and insulin levels in the OGTT, and HOMA-IR and HOMA-%β values. Conversely, visfatin was positively correlated with insulin levels in the OGTT, fasting insulin levels, and HOMA-%β values. The results are presented in TABLE 3.

DISCUSSION In the evaluated group of women, the period of time between the pregnancy complicated by GDM and enrollment to the study was from 5 to 12 years. We selected this time period because it is the period with the highest incidence of type 2 diabetes in women with pGDM; after this period, the incidence of type 2 diabetes in this group reaches a plateau.[3] At the same time, cardiovascular complications are not yet present; thus, there is no potential for their influence on inflammatory mediators and confounding the study results. Conducting research in this study group was also important because earlier studies evaluating adipokines and β-cell function were typically conducted in women soon after delivery (up to approximately a dozen weeks

TABLE 2 Characteristics of normoglycemic women with and without previous gestational diabetes mellitus

Parameter	NGT-GDM[+] n = 113	NGT-GDM[–] n = 44	*P* value
age, y	37.3 ±6.4	36.4 ±5.5	NS
number of pregnancies	2.3 ±1.4	2.0 ±1.1	NS
number of deliveries	2.0 ±1.1	1.9 ±1.1	NS
time since previous GDM/ pregnancy, y	7.5 ±2.3	8.1 ±2.5	NS
body weight before pregnancy, kg	60.5 ±12.4	61.6 ±10.3	NS
body weight, kg	63.7 ±12.1	68.3 ±14.6	NS
BMI, kg/m^2	23.9 ±4.3	25.1 ±4.7	NS
WHR	0.84 ±0.06	0.84 ±0.07	NS
adipose tissue mass, %	29.5 ±7.0	30.6 ±8.5	NS
lean body mass, kg	44.1 ±4.6	46.2 ±4.7	<0.05
HbA_{1c}, %	5.5 ±0.4	5.4 ±0.3	NS
glucose 0′, mmol/l	4.9 ±0.4	4.7 ±0.4	<0.02
glucose 60′, mmol/l	7.0 ±1.7	5.6 ±1.5	<0.0001
glucose 120′, mmol/l	5.3 ±1.0	4.6 ±1.0	<0.0001
insulin 0′, μIU/ml	12.0 ±8.0	12.1 ±4.9	NS
insulin 60′, μIU/ml	102.7 ±62.3	83.4 ±39.8	NS
insulin 120′, μIU/ml	64.5 ±50.6	42.0 ±25.6	0.003
HOMA-IR	1.51 ±0.9	1.53 ±0.6	NS
HOMA-%β	131.1 ±51.1	144.7 ±47.1	<0.04
sTNF-α-R2, ng/ml	4.7 ±2.0	4.1 ±1.2	<0.03
IL-6, pg/ml	3.2 ±2.6	2.3 ±1,2	<0.01
adiponectin, ng/ml	15.4 ±6.4	13.8 ±5.9	NS
visfatin, ng/ml	1.7 ±1.0	2.1 ±1.5	NS

Data are presented as mean ± standard deviation.

Abbreviations: NTG-GDM[+], normoglycemic women with previous gestational diabetes; NTG-GDM[–], normoglycemic women without previous gestational diabetes; others, see TABLE 1

following pregnancy). In a few studies, this period was longer but did not exceed 1 to 4 years.[22-24]

After a mean period of 7 years following the index pregnancy, disturbances in carbohydrate metabolism were found in approximately 43% (including diabetes in 6.5%) of the group of nearly 200 women with pGDM, in comparison with only 12% in the group of women without pGDM. The group of 113 women with pGDM and normal glucose tolerance in a recent OGTT did not differ significantly from the control group in terms of body weight, BMI (mean, 23.9 kg/m^2), body fat percentage, blood pressure, lipid profile, or insulin resistance. Despite the similar current and pregravid body weight values, women with pGDM showed impaired β-cell function (as assessed by HOMA-%β) in comparison with the control group. Blood glucose levels in the OGTT in women with pGDM were, although within the normal range, significantly higher than those in the control group.

The causative factors for abnormal insulin secretion in women with pGDM remain unclear. They cannot be associated with an autoimmune process directed against β cells because this process has been excluded based on negative anti-GAD antibody tests. Additionally, β-cell impairment seems unlikely to be a result of compensatory hyperstimulation, as the evaluated women were not obese and did not have abnormal insulin resistance. However, undiagnosed mild genetic predisposition to diabetes (eg, maturity-onset diabetes of the young) in some of these women cannot be excluded. In the period of increased physiological insulin resistance during the second and third trimesters of pregnancy, impaired insulin secretion associated with a genetic defect could lead to hyperglycemia and diagnosis of GDM. Monogenic diabetes is estimated to account for approximately 10% of all GDM cases.[25] Genetic testing in this study subgroup, that is, normoglycemic women with pGDM without obesity or overweight (approximately 57% of women with pGDM), would allow to identify a much greater proportion of genetically determined diabetes mellitus.

The study group was evaluated for the levels of adipokines, proteins secreted by adipose tissue, because TNF-α and IL-6 are believed to be associated with obesity, type 2 diabetes, and subclinical inflammation, and adiponectin is believed to be an anti-inflammatory adipokine, while the role of visfatin in inflammatory process is not clear. The levels of TNF-α and IL-6, that is, adipokines with proinflammatory and proatherosclerotic properties, were significantly higher in women with pGDM. The reasons for this phenomenon are not clear.

The main source of TNF-α during pregnancy is the placenta. Normoglycemic women with a history of GDM were found to have significantly higher levels of this cytokine in comparison with women with normal carbohydrate metabolism and no GDM.[26-28] Only a few studies have evaluated TNF-α levels in women with pGDM. Non-significantly elevated levels of this cytokine have been reported 3 to 12 months after a pregnancy complicated by GDM.[8] At the same time, other inflammatory markers, IL-6, C-reactive protein, and plasminogen activator inhibitor, were significantly elevated; however, these differences disappeared when only the data from insulin-sensitive subjects with normal body weight were analyzed. According to other reports, TNF-α levels during GDM-complicated pregnancy at 6 weeks or 6 months after delivery did not differ from the levels observed in pregnancies without GDM, despite the presence of markers of insulin resistance. TNF-α is considered to be a marker of subclinical inflammation, which is a risk factor for both type 2 diabetes and cardiovascular events.[29]

Higher levels of TNF-α have been associated mainly with insulin resistance and metabolic syndrome and have been attributed to concomitant obesity.[30,31] However, normoglycemic women in our study had normal body weight and showed no evidence of metabolic syndrome or insulin resistance. The positive correlation between TNF-α

TABLE 3 Correlations between adipokine concentrations and anthropometric and metabolic parameters in normoglycemic women with previous gestational diabetes

Parameter	sTNF-α-R2	IL-6	Adiponectin	Visfatin
body mass	NS	NS	$r = -0.21$; $P < 0.03$	NS
BMI	NS	NS	$r = -0.25$; $P < 0.008$	NS
WHR	NS	NS	$r = -0.27$; $P < 0.005$	NS
adipose tissue mass	NS	NS	$r = -0.22$; $P < 0.02$	NS
lean tissue mass	NS	NS	NS	NS
glucose 0′	NS	NS	NS	NS
glucose 60′	NS	NS	$r = -0.21$; $P < 0.03$	NS
glucose 120′	NS	NS	NS	NS
insulin 0′	NS	$r = -0.24$; $P < 0.02$	$r = -0.38$; $P < 0.0001$	$r = 0.20$; $P < 0.04$
insulin 60′	NS	NS	$r = -0.22$; $P < 0.03$	$r = 0.21$, $P < 0.03$
insulin 120′	NS	$r = -0.25$; $P < 0.01$	$r = -0.21$; $P < 0.03$	NS
HbA_{1c}	$r = 0.21$; $P < 0.03$	NS	NS	NS
HOMA-IR	NS	$r = -0.20$; $P < 0.03$	$r = -0.38$; $P < 0.0001$	NS
HOMA-%β	NS	NS	$r = -0.35$; $P < 0.0005$	$r = 0.28$; $P < 0.003$
sTNF-α-R2	–	NS	NS	$r = 0.22$; $P < 0.02$
IL-6	NS	–	NS	NS
adiponectin	NS	NS	–	NS
visfatin	$r = 0.22$; $P < 0.02$	NS	NS	–

Data are presented as Spearman rank correlation coefficient and *P* values.

Abbreviations: see TABLES 1 and 2

and HbA_{1c} levels may indicate an association between subclinical inflammation and mild chronic hyperglycemia. It is possible that normoglycemic women with pGDM have subclinical inflammation, leading to an increase in inflammatory markers and abnormalities in secondary insulin secretion, which seems to be suggested by in-vitro studies showing that TNF-α inhibits insulin secretion by insulinoma cells.[32] The potential primary site of inflammation in this group of women remains unknown. However, a reverse situation with β-cell dysfunction as the primary disorder and a secondary slight increase in blood glucose levels (still within the normal range for the population) that activates or promotes subclinical inflammation cannot be excluded. The latter correlation is indicated by a significant reduction in TNF-α levels and improved β-cell function in response to aggressive insulin therapy in patients with new-onset type 2 diabetes.[33] Enhanced gene expression and increased proinflammatory cytokine secretion (including TNF-α and IL-6) by monocytes are also known to result from hyperinsulinemia.[34]

Our study showed significantly higher oral glucose-induced insulin levels in women with pGDM. Brief postprandial alterations in insulin levels may be involved in inducing subclinical inflammation. Another finding of unclear significance is a positive correlation between visfatin and sTNF-α-R2 levels. Visfatin, previously known as pre-β-cell colony enhancing factor 1, is known to increase TNF-α expression.[35] However, because the level of visfatin was comparable in both groups, there must be a different reason for the elevation of TNF-α levels in one of the groups. The inflammatory mediator IL-6 is known as a risk factor for type 2 diabetes.[36] Only a very few studies have reported on the levels of this cytokine in women with GDM. IL-6 levels have been found to be elevated during a pregnancy complicated by GDM.[27,37] This elevation also occurs in women with pGDM 2 to 12 months after delivery.[8,23] Increased IL-6 levels were found 2 to 3 years following a pregnancy complicated by GDM, especially in women with coexisting metabolic syndrome.[24] A follow-up of women with pGDM showed significantly higher levels of IL-6 (also in women with normal body weight) at 4 years after delivery; however, the study was conducted in a very small group of subjects.[8] The present study, conducted approximately 7 years after delivery, demonstrates that this abnormality persists for many years after pregnancy.

As in the case of TNF-α, the cause of increased IL-6 levels in normoglycemic women with pGDM remains unclear. A negative correlation between IL-6 levels and insulinemia in the OGTT may suggest an inhibitory effect of this cytokine on insulin secretion. The negative correlation between IL-6 levels and insulin resistance (assessed by HOMA-IR) found in our study is surprising and difficult to explain, as the relationship between IL-6 levels and the increased risk of type 2 diabetes has been explained by the effect of this cytokine on insulin resistance.[33] As in the case of TNF-α, it is very difficult to determine whether elevated IL-6 levels are the cause or the effect of

the observed abnormalities in insulin secretion. Adiponectin, which is secreted by adipose tissue, improves insulin sensitivity (especially glucose uptake in the tissues), reduces hepatic glucose production, and exerts an anti-inflammatory effect. Increased visceral fat leads to reductions in the adiponectin level; thus, hypoadiponectemia is observed in abdominal obesity, metabolic syndrome, and type 2 diabetes.[38,39] During a GDM-complicated pregnancy, adiponectin levels may be low regardless of body weight or insulin resistance.[40,41] Lower adiponectin levels during pregnancy may be associated with β-cell dysfunction.[42] The few studies conducted in women with pGDM have demonstrated reduced adiponectin levels after 1 to 4 years.[8,43] This phenomenon seems to be mainly a result of higher body weight of the study subjects. Isolated reports indicate comparable adiponectin levels in women with and without pGDM (at 6 months after delivery).[22] Our study conducted in normoglycemic women with pGDM and normal body weight demonstrated adiponectin levels to be the same as those in healthy women of comparable age with the same body weight and no history of GDM. Despite the normal body weight in this group, we observed a characteristic negative correlation between adiponectin levels and BMI, body weight, body fat percentage, insulin resistance (HOMA-IR), blood glucose levels, and insulinemia. The negative correlation between adiponectin levels and HOMA-%β values also indicates a possible relationship between reduced adiponectin-levels and β-cell dysfunction.

Visfatin, which is secreted mainly by visceral fat tissue, had been initially described as an insulinmimetic cytokine that binds to insulin receptors.[44] Subsequent studies have demonstrated a relationship between visfatin and metabolic syndrome and suggested its possible role in the pathogenesis of type 2 diabetes.[45,46] Both increased and decreased levels of this cytokine have been described in GDM.[47,48] Only 1 study evaluated visfatin levels following GDM.[49] It included 23 subjects who were observed at 6 to 10 weeks after delivery. It showed that the visfatin level that had been elevated during pregnancy normalized after delivery and did not differ from that observed in women without pGDM. The analysis of visfatin levels in our study revealed no differences between normoglycemic women with and without pGDM. However, a positive correlation was observed between visfatin levels and fasting and oral glucose-induced blood insulin levels as well as β-cell function indicated by HOMA-%β. It is not clear whether this correlation results from a possible direct effect on β cells or whether it may have a protective or compensatory effect on β-cell function, which has been found to be slightly impaired in this group.

Our study is the first to evaluate insulin secretion and adipokine levels after such a long period of time following a GDM-complicated pregnancy. It is also the first study of this type conducted in women with long-term normoglycemia following such pregnancy. We would also like to emphasize that our analysis involved a large group of women.

In conclusion, the results of our study suggest a simultaneous presence of abnormal insulin secretion and subclinical inflammation in normoglycemic women with a history of GDM many years earlier, despite normal body weight and maintained normal insulin sensitivity. The possible causative relationship between the observed abnormalities remains unclear. Moreover, it is unknown whether these abnormalities were primary and developed before the index pregnancy or were induced by pregnancy complicated by GDM.

Contribution statement PM participated in study design, collected the data, and prepared the manuscript. AF collected the data and helped to draft the manuscript. KS performed the statistical analysis and helped to draft the manuscript. LM conceived the idea of the study, participated in its design and coordination and helped to draft the manuscript.

All authors edited and approved the final version of the manuscript

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ARTYKUŁ ORYGINALNY

Adipokiny i funkcja komórek β u kobiet z cukrzycą ciążową w wywiadzie

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adipokiny, funkcja komórek β, przebyta cukrzyca ciążowa, subkliniczny stan zapalny

STRESZCZENIE

WPROWADZENIE Zwiększone ryzyko rozwoju cukrzycy typu 2 u kobiet z cukrzycą ciążową (GDM) w wywiadzie może być związane ze zwiększoną insulinoopornością oraz subklinicznym stanem zapalnym. Niemniej jednak u około połowy kobiet z przebytą GDM (pGDM) nie rozwija się cukrzyca. W niniejszej pracy skupiono się głównie na tej populacji kobiet.

CELE Celem badania była ocena funkcji komórek β, insulinooporności oraz poziomów adipokin pro- i przeciwzapalnych u normoglikemicznych kobiet z pGDM.

PACJENCI I METODY Grupa badana liczyła 199 kobiet z pGDM; średni czas po porodzie wynosił 7,4 roku. Grupa kontrolna liczyła 50 kobiet bez GDM w wywiadzie. U wszystkich pacjentek przeprowadzono doustny test tolerancji glukozy (*oral glucose tolerance test* – OGTT) z oceną glikemii oraz insulinemii, wyliczeniem wskaźnika funkcji komórek β (HOMA-%B) i insulinooporności (HOMA-IR), a także stężenia rozpuszczalnego receptora czynnika martwicy guza α (soluble tumor necrosis factor α – sTNF-α-R2), interleukiny 6 (IL-6), adiponektyny oraz wisfatyny.

WYNIKI Prawidłową tolerancję glukozy stwierdzono u 113 kobiet z pGDM (56,8%; grupa NTG-GDM[+]) oraz u 44 kobiet z grupy kontrolnej (88,0%). W porównianiu z grupą kontrolną grupa NGT-GDM[+] charakteryzowała się znamiennie wyższą glikemią w OGTT oraz znamiennie niższym poziomem HOMA-%β przy porównywalnym HOMA-IR oraz wskaźniku masy ciała. W grupie NTG-GDM[+] stwierdzono istotnie wyższe stężenia sTNFα-R2 i IL-6 przy podobnych stężeniach adiponektyny oraz wisfatyny.

WNIOSKI U normoglikemicznych kobiet z GDM w wywiadzie charakterystyczne jest współistnienie zaburzeń wydzielania insuliny oraz subklinicznego stanu zapalnego, przy prawidłowej masie ciała i wrażliwości na insulinę. Nie jest jasne czy zaburzenia te obecne były jeszcze przed ciążą powikłaną GDM, czy też zostały wyindukowane przez ciążę.

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