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GENETICS

Adiponectin and leptin gene polymorphisms in women with gestational diabetes mellitus

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Abstract
Purpose Gestational diabetes mellitus (GDM) is the glucose intolerance occurring during pregnancy. The prevalence of GDM is increased in obese women. Leptin and adiponectin are adipokines that play an important role in the regulation of insulin secretion and glucose and lipid metabolism. The aim of this study was to examine the association between adiponectin and leptin gene polymorphisms and the development of GDM.
Methods This case–control study included 204 pregnant women with GDM and 207 pregnant women with normal glucose tolerance (NGT). The diagnosis of GDM was based on a 75-g oral glucose tolerance test (OGTT) at 24–28 weeks' gestation. To discriminate the *ADIPOQ* rs266729, rs1501299 and *LEP* rs2167270 alleles, TaqMan® Pre-Designed SNP Genotyping Assays were used.
Results There was a statistically significant association between the *ADIPOQ* rs266729 gene polymorphism and GDM. Among women with GDM, a higher prevalence of the G allele was observed (GG and CG genotypes). Multivariate logistic regression analysis, taking into account age, BMI before pregnancy, past pregnancies and the *ADIPOQ* rs266729 gene polymorphism, revealed that the presence of a G allele is an independent risk factor for GDM. Moreover, there was the association between the *LEP* rs2167270 polymorphism and the requirement for daily insulin, which was significantly higher in women with the A allele (AA and GA genotypes).
Conclusions The results of our study suggest an association between adiponectin gene rs266729 as well as leptin gene rs2167270 polymorphisms and GDM.

Keywords Gestational diabetes · Adiponectin · Leptin · Polymorphism

Capsule This study examined the association between adiponectin and leptin gene polymorphisms and the development of GDM.

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Introduction

Gestational diabetes mellitus (GDM) is the glucose intolerance occurring during pregnancy. This disorder is associated with significant neonatal and maternal complications [1]. GDM occurs due to decreased pancreatic β-cell function and increased insulin resistance. GDM is the metabolic complication occurring especially in women with obesity which is associated with insulin resistance [2, 3].

Leptin and adiponectin are adipokines regulating the insulin secretion, insulin sensitivity as well as glucose and lipid metabolism. Leptin, the product of ob gene, is secreted by adipocytes. This adipokine regulates lipid metabolism and leptin serum levels positively correlate with body mass [4]. Moreover, leptin also regulates the function of the immune system. Numerous studies indicate that increased serum leptin levels are associated with diabetes, lipid disorders and are a risk factor for cardiovascular disease [5]. The synthesis of this

hormone has genetic background and is regulated by genetic polymorphisms in leptin gene. Leptin gene polymorphisms were studied in patients with diabetes mellitus, lipid disorders and diseases of circulatory system [6].

Adiponectin is produced in adipose tissue and modulates various metabolic processes, including glucose and lipid metabolism and fatty acid oxidation. This hormone decreases insulin resistance, improves lipid metabolism and exerts anti-inflammatory properties. Decreased plasma adiponectin levels were observed in patients with metabolic syndrome, diabetes mellitus, dyslipidaemia and obesity [7]. Previous studied suggest also significant associations between adiponectin gene polymorphisms and diabetes mellitus, metabolic syndrome, and obesity [8, 9]. The aim of this study was to examine the association between adiponectin and leptin gene polymorphisms and the development of gestational diabetes.

Materials and methods

This case–control study included 204 pregnant Caucasian women with GDM and 207 pregnant women with normal glucose tolerance (NGT). Clinical and demographic parameters of women with and without GDM are shown in Table 1. The cases and controls were recruited consecutively in years 2013–2014 in Department of Obstetrics and Gynecology county Hospital in Zielona Gora, Poland. All pregnancies were achieved by natural conception. Exclusion criteria were diabetes type 1 and type 2, autoimmune and inflammatory diseases, neoplastic diseases and chronic infections. The control group included 207 women with normal values of oral glucose tolerance test (OGTT) without diabetes type 1 and type 2, GDM in previous pregnancies, autoimmune and inflammatory diseases, neoplastic diseases and chronic infections. The diagnosis of GDM was based on a 75-g oral glucose tolerance test at 24–28 weeks' gestation, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [10]. The diagnosis of GDM was made when one of the following plasma glucose values in the OGTT was met or exceeded: fasting plasma glucose 92 mg/dL (5.1 mmol/L), 1-h plasma glucose 180 mg/dL (10.0 mmol/L) and 2-h plasma glucose 153 mg/dL (8.5 mmol/L) [10]. Among the pregnant women with GDM, 152 (75%) were treated with diet control alone throughout the pregnancy, whereas the remaining 52 (25%) were treated with diet control and insulin until delivery [11]. The study was approved by the ethics committee in Pomeranian Medical University, Szczecin, Poland, and written informed consent was obtained from all subjects.

Table 1 Clinical and demographic parameters of women with and without GDM

Parameters	Control group $N = 207$ Mean ± SD	GDM group $N = 204$ Mean ± SD
Age [years]	29.2 ± 5.0	31.7 ± 4.5
Height [cm]	165.5 ± 5.7	164.7 ± 5.9
Body mass before pregnancy [kg]	63.3 ± 12.4	68.3 ± 16.4
Body mass at birth [kg]	78.1 ± 14.2	79.5 ± 17.1
Body mass increase during pregnancy [kg]	14.8 ± 5.4	11.1 ± 5.2
BMI before pregnancy [kg/m^2]	23.0 ± 4.0	25.1 ± 5.5
BMI at birth [kg/m^2]	28.4 ± 4.5	29.3 ± 5.9
BMI increase during pregnancy [kg/m^2]	5.4 ± 1.9	4.1 ± 2.0
Current number of pregnancy	1.8 ± 1.1	2.0 ± 1.0
HbA1c [%]	–	5.56 ± 0.48
Gestational age at delivery [weeks]	39.1 ± 1.6	38.5 ± 1.9
Newborn body mass [g]	3362 ± 530	3265 ± 631
APGAR [0–10]	9.9 ± 0.4	9.7 ± 1.0

BMI body mass index, *HbA1c* glycated haemoglobin

Methods

All samples were genotyped in duplicate using allelic discrimination assays with TaqMan® probes (Applied Biosystems, Carlsbad, California, USA) on a CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad, Hercules, California, USA). To discriminate the *ADIPOQ* rs266729, rs1501299 and *LEP* rs2167270 alleles, TaqMan® Pre-Designed SNP Genotyping Assays were used (assay IDs: C___2412786_10, C___7497299_10 and C__15966471_20, respectively), including appropriate primers and fluorescently labelled (FAM and VIC) MGB™ probes to detect the alleles. Genotypes were assigned using all of the data from the study simultaneously.

Statistical analysis

The consistency of the genotype distribution with Hardy–Weinberg equilibrium (HWE) was assessed using the exact test. A chi-square test was used to compare genotype and allele distributions between groups. Quantitative variables were compared between genotype groups with the Mann–Whitney test. A multivariate logistic regression model was used to find independent predictors of GDM risk. A p value of <0.05 was considered to indicate a statistically significant result.

Results

The distributions of the studied *ADIPOQ* and *LEP* genotypes were in HWE ($p > 0.05$). The genotype/allele

frequencies in the groups with and without GDM are shown in Table 2. GDM was not statistically significantly associated with genotypes or alleles of the *ADIPOQ* rs1501299 or *LEP* rs2167270 polymorphisms, whereas there was a statistically significant association between *ADIPOQ* rs266729 polymorphism and GDM (Table 2). Among women with GDM, a higher prevalence of the G allele (GG and CG genotypes) was observed. Multivariate logistic regression analysis, taking into account age, BMI before pregnancy, past pregnancies and the *ADIPOQ* rs266729 gene polymorphism revealed that this polymorphism is an independent risk factor for GDM. In this analysis, older age, higher BMI and presence of the G allele were independent significant predictors of a higher risk of GDM (Table 3).

We also analysed the association between the studied polymorphisms and clinical parameters, such as BMI before pregnancy, BMI at birth, weight increase during pregnancy, BMI increase during pregnancy, HbA1c (%), daily insulin requirement, gestational age at delivery, newborn body mass and APGAR score in women with GDM. There were no statistically significant associations between the studied polymorphisms and any of these parameters except for the association between the *LEP* rs2167270 polymorphism and daily insulin requirement, which was significantly higher in women with GDM who carried the A allele (AA and GA genotypes, Table 4). Accordingly, the proportion of women with GDM who were treated with insulin was higher in A allele carriers (31.5%) than in GG homozygotes (15.6%) and this association was

Table 2 Distribution of *ADIPOQ* and *LEP* genotypes in GDM women and control group

	Control group		GDM		*p* value[a]		*p* value[a]	OR (95% CI)
	n	%	*n*	%				
ADIPOQ rs266729 genotype								
CC	115	55.56	92	45.10	0.11	GG + CG vs CC	0.034	1.52 (1.03–2.25)
CG	75	36.23	91	44.61		GG vs CG + CC	0.47	1.28 (0.66–2.51)
GG	17	8.21	21	10.29		GG vs CC	0.22	1.54 (0.77–3.10)
						CG vs CC	0.046	1.52 (1.01–2.29)
						GG vs CG	0.96	1.02 (0.50–2.07)
Allele								
C	305	73.67	275	67.40				
G	109	26.33	133	32.60		G vs C	0.049	1.35 (1.00–1.83)
ADIPOQ rs1501299 genotype								
GG	106	51.21	98	48.04	0.76	TT + GT vs GG	0.52	1.14 (0.77–1.67)
GT	83	40.10	85	41.67		TT vs GT + GG	0.58	1.20 (0.62–2.33)
TT	18	8.70	21	10.29		TT vs GG	0.51	1.26 (0.63–2.51)
						GT vs GG	0.62	1.11 (0.74–1.67)
						TT vs GT	0.71	1.14 (0.57–2.29)
Allele								
G	295	71.26	281	68.87				
T	119	28.74	127	31.13		T vs G	0.46	1.12 (0.83–1.51)
LEP rs2167270 genotype								
GG	76	36.71	77	37.75	0.83	AA + GA vs GG	0.83	0.96 (0.64–1.43)
GA	102	49.28	95	46.57		AA vs GA + GG	0.63	1.14 (0.66–1.97)
AA	29	14.01	32	15.69		AA vs GG	0.78	1.09 (0.60–1.97)
						GA vs GG	0.70	0.92 (0.60–1.40)
						AA vs GA	0.56	1.18 (0.67–2.11)
Allele								
G	254	61.35	249	61.03				
A	160	38.65	159	38.97		A vs G	0.92	1.01 (0.77–1.34)

HWE: control group $p = 0.37$, GDM $p = 0.87$ for *ADIPOQ* rs266729

HWE: control group $p = 0.74$, GDM $p = 0.74$ for *ADIPOQ* rs1501299

HWE: control group $p = 0.66$, GDM $p = 0.77$ for *LEP* rs2167270

[a] χ^2 test

Table 3 Multivariate logistic regression analysis assessing predictors of a higher hazard of GDM

Parameter	OR (95% CI)	*p*
Age (years)	1.12 (1.07–1.18)	0.0000027
BMI before pregnancy (kg/m^2)	1.10 (1.05–1.15)	0.000088
Past pregnancy[a]	0.86 (0.54–1.35)	0.51
ADIPOQ rs266729 (G allele carrier)	1.78 (1.17–2.71)	0.0068

[a] Anamnesis of at least one past pregnancy

statistically significant (OR = 2.49, 95% CI = 1.21–5.12, $p = 0.011$).

Discussion

In this study, we examined the association between adiponectin and leptin gene polymorphisms and the development of GDM. Our results suggest that the *ADIPOQ* gene rs266729 polymorphism allele G is associated with an increased risk of GDM. This association was confirmed by multivariate logistic regression analysis. This analysis showed that the presence of the G allele is associated independently of age, BMI before pregnancy and past pregnancies with an increased risk of GDM. Previous studies have indicated that this allele is associated with lower plasma adiponectin levels and is considered a risk factor for developing type 2 diabetes [12–15]. Moreover, the requirement for insulin was more frequent and higher in women with GDM who carried the *LEP* rs2167270 A allele, which is associated with increased serum leptin levels [16, 17].

Adipokines are the hormones of adipose tissue involved in insulin resistance in pregnancy and GDM. Adiponectin regulates glucose and lipid metabolism, decreases insulin resistance as well as has anti-inflammatory properties [18]. The presence of adiponectin and its receptors has been detected in the human placenta [19, 20]. Previous studies have indicated lower plasma adiponectin levels in women with GDM [21]. The serum levels of adiponectin in pregnancy correlated with insulin sensitivity, insulin levels and glucose metabolism. The studies have shown that adiponectin has insulin-sensitizing properties and exerts significant effect on glucose and lipid metabolism in pregnant women. This hormone reduces hepatic glucose production and increases glucose uptake in skeletal muscle. Furthermore, adiponectin reduces the gluconeogenesis, as well as decreases synthesis of triglycerides and fatty acid oxidation in the liver. Plasma adiponectin levels were positively correlated with plasma HDL cholesterol levels and inversely correlated with triglyceride levels [22, 23]. The above reports indicate that adiponectin improves glucose metabolism and prevents the development of insulin resistance and diabetes.

Previous studies have indicated that leptin has an inhibitory effect on insulin gene expression and insulin secretion in pancreatic β-cells [24]. Leptin also suppresses insulin secretion induced by cAMP, glucagon-like peptide 1 and protein kinase C [25]. Moreover, leptin inhibits the phosphorylation of glucose transporter 2 (GLUT2) and impairs glucose transport in tissues increasing insulin resistance. Furthermore, leptin increases the activity of adrenergic nervous system. Plasma

Table 4 The association between *LEP* rs2167270 genotypes and clinical parameters

Parameters	*LEP* rs2167270 genotype								
	GG *n* = 77 Mean ± SD	GA *n* = 95 Mean ± SD	AA *n* = 32 Mean ± SD	AA + GA *n* = 127 Mean ± SD	GG + GA *n* = 172 Mean ± SD	GG vs GA *p*[a]	GG vs AA	GA vs AA	GG vs AA + GA	GG + GA vs AA
BMI before pregnancy [kg/m^2]	24.6 ± 4.5	25.3 ± 6.0	25.8 ± 6.4	25.5 ± 6.1	25.0 ± 5.4	0.87	0.52	0.72	0.71	0.60
BMI at birth [kg/m^2]	28.7 ± 4.6	29.5 ± 6.4	30.1 ± 7.0	29.6 ± 6.5	29.1 ± 5.6	0.93	0.74	0.67	0.84	0.68
Weight increase during pregnancy [kg]	11.0 ± 5.0	11.1 ± 4.8	11.6 ± 6.9	11.2 ± 5.4	11.1 ± 4.9	0.86	0.78	0.72	0.97	0.73
BMI increase during pregnancy [kg/m^2]	4.1 ± 1.9	4.1 ± 1.8	4.3 ± 2.7	4.2 ± 2.1	4.1 ± 1.8	0.81	0.80	0.61	0.92	0.67
HbA1c [%]	5.54 ± 0.43	5.59 ± 0.51	5.52 ± 0.48	5.57 ± 0.50	5.57 ± 0.47	0.58	0.81	0.64	0.72	0.70
Daily insulin requirement [unit]	3.53 ± 9.41	6.26 ± 12.00	6.56 ± 13.88	6.34 ± 12.45	5.04 ± 10.97	0.019	0.14	0.74	0.019	0.66
Gestational age at delivery [weeks pregnant]	38.4 ± 2.3	38.6 ± 1.5	38.4 ± 2.1	38.5 ± 1.7	38.5 ± 1.9	0.66	0.95	0.68	0.75	0.79
Newborn body mass [g]	3250 ± 617	3276 ± 625	3271 ± 698	3275 ± 641	3264 ± 619	0.85	0.59	0.54	0.96	0.53
APGAR	9.8 ± 0.8	9.7 ± 1.1	9.5 ± 1.1	9.6 ± 1.1	9.7 ± 1.0	0.30	0.10	0.40	0.17	0.19

[a] Mann–Whitney *U* test

leptin levels and placental leptin expression in women with GDM were significantly increased in comparison with healthy pregnant women [26, 27].

Adiponectin and leptin gene polymorphisms have been intensively investigated in patients with diabetes mellitus in various populations. The results are variable and are dependent on the studied population. In the majority of studies, these polymorphisms seem to be predisposing factors to diabetes mellitus or diabetic complications. Previous studies investigated the association between adiponectin and leptin gene polymorphisms and gestational diabetes. Beltcheva et al. have indicated a significant association between the adiponectin gene rs266729 polymorphism and GDM [28], while there were no associations between rs2241766 and rs1501299 adiponectin gene polymorphisms and GDM. Han et al. examined *ADIPOQ* rs2241766 gene polymorphisms in women with GDM from the Nantong area in China [29]. The G allele and TG and GG genotypes were significantly more frequent than the T allele in the GDM group. Moreover plasma adiponectin concentrations in women with TG and GG genotypes were significantly lower than those of TT homozygotes. Takhshid et al. investigated the relationships between the rs2241766 polymorphism in the adiponectin gene, serum adiponectin levels, insulin resistance and the risk of GDM in an Iranian population [30]. The G allele was more frequent than the T allele in GDM patients. There were not the associations between studied genotypes and plasma levels of adiponectin [30]. Low et al. also found an association between the adiponectin rs2241766 gene polymorphism and GDM in a Malaysian population [31]. Women with GDM with the TG and GG genotypes had significantly lower plasma adiponectin levels than healthy women with the TT genotype.

With respect to the leptin gene rs2167270 polymorphism, in a study by Vaskú et al., the A allele was associated with an increased risk of GDM [32]. In our study, women with the *LEP* rs2167270 A allele had an increased daily insulin requirement. Sahin et al. and Mammès et al. suggested that the *LEP* rs2167270 A allele is associated with increased serum leptin levels [16, 17]. Hoffstedt et al. have shown that the rs2167270 leptin gene polymorphism influences leptin expression at the transcriptional level and, therefore, also affects the secretion of this hormone [33].

Previous studies indicate that polymorphisms in adiponectin and leptin genes are associated with GDM. This association may depend on ethnic and genetic differences in the studied population. The results of our study suggest an association between the adiponectin gene rs266729 polymorphism and GDM risk as well as between the leptin gene rs2167270 polymorphism and the need for insulin treatment of GDM. Nevertheless, this hypothesis requires further investigation.

Compliance with ethical standards The study was approved by the ethics committee in Pomeranian Medical University, Szczecin, Poland, and written informed consent was obtained from all subjects.

Conflict of interest The authors declare that they have no conflict of interest.

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