VIA MEDICA
ORIGINAL PAPER / OBSTETRICS
Ginekologia Polska
2017, vol. 88, no. 5, 249–254

ISSN 0017–0011
DOI: 10.5603/GP.a2017.0047

IL16 and *IL18* gene polymorphisms in women with gestational diabetes

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ABSTRACT

Objectives: Gestational diabetes mellitus is a carbohydrate intolerance that occurs during pregnancy. Various inflammatory mediators are considered to be risk factors leading to GDM development. Among them are pro-inflammatory cytokines, such as *IL16* and *IL18*. The aim of this study was to examine the association between *IL16* and *IL18* polymorphisms and GDM.

Material and methods: This study included 204 pregnant women with GDM and 207 pregnant women with normal glucose tolerance (NGT). All samples were genotyped in duplicate using allelic discrimination assays with TaqMan® probes.

Results: We observed that there was a decreased frequency of *IL16* rs4778889 CC genotype carriers among women with GDM (CC *vs.* CT + TT: OR = 0.14; 95% CI = 0.02–1.15; p = 0.034). However, there was no significant difference in the distribution of alleles (C *vs.* T: OR = 0.81; 95% CI = 0.54–1.21; p = 0.30). There was a decreased frequency of the *IL18* rs187238 G allele among GDM women (G *vs.* C: OR = 0.71; 95% CI = 0.53–0.96; p = 0.027). We also observed a decreased frequency of the *IL18* rs1946518 T allele among women with GDM; however, this difference had only borderline statistical significance. We observed an association between *IL18* rs187238, rs1946518 and BMI in pregnant women.

Conclusions: The results of this study suggest that *IL18* rs187238 and rs1946518 polymorphisms may be associated with an increased risk of GDM as well as with BMI in pregnant women.

Key words: polymorphism, SNP, gestational diabetes, genes, metabolism

Ginekologia Polska 2017; 88, 5: 249–254

INTRODUCTION

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance caused by decreased insulin synthesis and action, which is diagnosed in the second or third trimester of pregnancy. The important risk factors of GDM include advanced maternal age, obesity and a family history of type 2 diabetes (T2DM) [1, 2]. This disorder is associated with several maternal and neonatal metabolic and cardiovascular complications [3, 4]. Recent studies suggest that genetic factors play important role in pathogenesis of GDM [5]. The role of the inflammatory response in the pathogenesis of GDM has been recently investigated [6]. Various inflammatory mediators are considered to be risk factors leading to GDM development [7, 8], including cytokines. Cytokines are a group of proteins produced by cells involved in the immune response, and they act as immune regulators and mediators. Cytokines may perform both pro-inflammatory as well as anti-inflammatory actions. Diabetes, carbohydrate intolerance and insulin resistance are associated with an increased synthesis of pro-inflammatory cytokines, such as *IL16* and *IL18* [9]. Recent studies suggest that pro-inflammatory cytokines also play an important role in GDM pathogenesis [10]. The inflammatory response and an imbalance between pro-inflammatory and anti-inflammatory cytokines may lead to the development of pregnancy-induced glucose intolerance and insulin resistance [11]. Previous studies

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have revealed that cytokine production may be associated with polymorphisms in cytokine-encoding genes [12]. These polymorphisms may alter gene expression and cytokine synthesis, and have been investigated in patients with type 1 and type 2 diabetes [13]. These polymorphisms may be associated with increased *IL16* and *IL18* synthesis in some patients and enhanced inflammatory response. Previous studies have shown that these polymorphisms may be associated with increased risk of inflammatory diseases [14]. The aim of this study was to examine the association between *IL16* and *IL18* gene polymorphisms and GDM.

MATERIAL AND METHODS

Patients

This 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, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [15]. The diagnosis of GDM was made when one of the following plasma glucose values in the OGTT was met or exceeded: fasting plasma glucose of 92 mg/dL (5.1 mmol/L); 1 h plasma glucose of 180 mg/dL (10.0 mmol/L); 2 h plasma glucose of 153 mg/dL (8.5 mmol/L) [15]. Exclusion criteria were: type 1 and type 2 diabetes, autoimmune and inflammatory diseases, neoplastic diseases and chronic infections. 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. The study was approved by the ethics committee in Pomeranian Medical University, Szczecin, Poland, and written informed consent was obtained from all subjects.

Methods

All samples were genotyped in duplicate using allelic discrimination assays with TaqMan® probes (Applied Biosystems, Carlsbad, California, USA) on a Real-Time PCR Detection System (Applied Biosystems). To discriminate the *IL16* rs4778889 and *IL18* rs187238, rs1946518 gene polymorphisms, TaqMan® Pre-Designed SNP Genotyping Assays were used (the assay IDs were C__31837550_10, C___2408543_10 and C___2898460_10 respectively). Appropriate primers were included and fluorescently labelled (FAM and VIC) MGB™ probes were used to detect the alleles.

Statistical analysis

The agreement of the genotype distribution with the Hardy-Weinberg equilibrium (HWE) was assessed using the exact test. A chi-square test was used to compare genotype and allele distributions between groups. Clinical parameters were compared between genotype groups using the Mann-Whitney test. Statistical significance was assessed at the value of $p < 0.05$.

RESULTS

Clinical parameters of women with and without GDM are shown in Table 1. The family history of type 2 diabetes in women with GDM was noted in 82 cases (40%).

The studied genotypes were distributed according to HWE and are shown in Table 2.

We observed that there was a decreased frequency of *IL16* rs4778889 CC genotype carriers among women with GDM (CC *vs.* CT + TT: OR = 0.14; 95% CI = 0.02–1.15; p = 0.034). However, there was no significant difference in the distribution of alleles (C *vs.* T: OR = 0.81; 95% CI = 0.54–1.21; p = 0.30).

Regarding the *IL18* rs187238 polymorphism, there was a decreased frequency of the G allele among GDM women (G *vs.* C: OR = 0.71; 95% CI = 0.53–0.96; p = 0.027; GG *vs.* CG + CC: OR = 0.49; 95% CI = 0.25–0.97; p = 0.037). We also observed a decreased frequency of the *IL18* rs1946518 T allele among women with GDM; however, this difference had only borderline statistical significance (T *vs.* G: OR = 0.77; 95% CI: 0.59–1.02; p = 0.071; Table 2).

Additionally, we examined the association between the studied genotypes and the following clinical parameters in women with GDM: body mass before pregnancy, body mass at birth, body mass increase during pregnancy, BMI (body mass index) before pregnancy, BMI at birth, BMI increase

Table 1. Clinical parameters of women with and without GDM

Parameters	Control group N = 207	GDM group N = 204
	Mean ± SD	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
HbA_{1c} [%]	–	5.56 ± 0.48
Daily insulin requirement [unit]	–	5.28 ± 11.45
Childbirth [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; HbA_{1c} — glycated haemoglobin

Table 2. Distribution of *IL16* and *IL18* genotypes and alleles in women with GDM and controls

	Control group		GDM		p value^		OR (95% CI)	p value^
	N	%	N	%				
***IL16* rs4778889 genotype**								
TT	153	73.91%	155	75.98%	0.11	CC + CT *vs.* TT	0.90 (0.57–1.40)	0.63
CT	47	22.71%	48	23.53%		CC *vs.* CT + TT	0.14 (0.02–1.15)	0.034
CC	7	3.38%	1	0.49%		CC *vs.* TT	0.14 (0.02–1.16)	0.035
						CT *vs.* TT	1.01 (0.64–1.60)	0.97
						CC *vs.* CT	0.14 (0.02–1.18)	0.039
Allele								
T	353	85.27%	358	87.75%		C *vs.* T	0.81 (0.54–1.21)	0.30
C	61	14.73%	50	12.25%				
***IL18* rs187238 genotype**								
CC	94	45.41%	109	53.43%	0.069	GG + CG *vs.* CC	0.73 (0.49–1.07)	0.10
CG	86	41.55%	81	39.71%		GG *vs.* CG + CC	0.49 (0.25–0.97)	0.037
GG	27	13.04%	14	6.86%		GG *vs.* CC	0.45 (0.22–0.90)	0.022
						CG *vs.* CC	0.81 (0.54–1.22)	0.32
						GG *vs.* CG	0.55 (0.27–1.12)	0.098
Allele								
C	274	66.18%	299	73.28%		G *vs.* C	0.71 (0.53–0.96)	0.027
G	140	33.82%	109	26.72%				
***IL18* rs1946518 genotype**								
GG	62	29.95%	73	35.78%	0.15	TT + GT *vs.* GG	0.77 (0.51–1.16)	0.21
GT	105	50.72%	105	51.47%		TT *vs.* GT + GG	0.61 (0.36–1.04)	0.069
TT	40	19.32%	26	12.75%		TT *vs.* GG	0.55 (0.30–1.00)	0.051
						GT *vs.* GG	0.85 (0.55–1.31)	0.46
						TT *vs.* GT	0.65 (0.37–1.14)	0.13
Allele								
G	229	55.31%	251	61.52%		T *vs.* G	0.77 (0.59–1.02)	0.071
T	185	44.69%	157	38.48%				

^χ^2 test
HWE: control group p = 0.17, GDM p = 0.32 for *IL16* rs4778889
HWE: control group p = 0.35, GDM p = 1.00 for *IL18* rs187238
HWE: control group p = 0.78, GDM p = 0.24 for *IL18* rs1946518

during pregnancy, glycated haemoglobin HbA_{1c}, daily insulin requirement, duration of pregnancy, newborn body mass and Apgar score. Among women with the CT genotype *IL16* rs4778889, we observed a lower increase of body mass and BMI during pregnancy compared with the TT genotype (Table 3). Women with the CG genotype *IL18* rs187238 had a higher increase of body mass and BMI during pregnancy than the CC genotype (Table 4). Women with the GT genotype *IL18* rs1946518 had a higher body mass and BMI before pregnancy and at birth compared with the GG genotype (Table 5).

In the multivariate logistic regression analysis, taking into account maternal age, BMI before pregnancy as well as *IL18* rs1946518 and *IL16* rs4778889 polymorphisms we examined the independent risk factors of GDM. In this analysis, older age and higher BMI before pregnancy were independent significant predictors of a higher risk of GDM, while higher number of *IL18* rs1946518 T alleles was a protective factor against GDM (Table 6).

DISCUSSION

In this study we examined the associations between *IL16* and *IL18* gene polymorphisms and GDM. Our results have indicated decreased frequency of *IL16* rs4778889 CC genotype among women with GDM, decreased frequency of the *IL18* rs187238 G allele, as well as decreased frequency of the *IL18* rs1946518 T allele; however, this difference had borderline statistical significance (p = 0.071). In the multivariate logistic regression analysis older age and higher

Table 3. Clinical parameters of women with GDM stratified according to *IL16* rs4778889 genotype

Parameters	*IL16* rs4778889 genotype		
	TT N = 155	CT N = 48	TT *vs.* CT
	Mean ± SD	Mean ± SD	p[&]
Body mass before pregnancy [kg]	69.0 ± 16.9	66.4 ± 14.6	0.36
Body mass at birth [kg]	80.6 ± 17.6	76.1 ± 15.2	0.091
Body mass increase during pregnancy [kg]	11.5 ± 5.3	9.8 ± 4.8	0.027
BMI before pregnancy [kg/m^2]	25.4 ± 5.8	24.4 ± 4.8	0.31
BMI at birth [kg/m^2]	29.7 ± 6.1	28.0 ± 5.1	0.053
BMI increase during pregnancy [kg/m^2]	4.3 ± 2.0	3.6 ± 1.8	0.021
HbA_{1c} [%]	5.56 ± 0.48	5.57 ± 0.45	0.99
Daily insulin requirement [unit]	5.07 ± 10.93	6.06 ± 13.17	0.97
Childbirth [weeks]	38.5 ± 1.8	38.4 ± 2.2	0.75
Newborn body mass [g]	3267 ± 627	3272 ± 649	0.90
APGAR (0–10)	9.7 ± 1.0	9.8 ± 1.0	0.41

[&]Mann-Whitney U test

Table 4. Clinical parameters of women with GDM stratified according to *IL18* rs187238 genotype

Parameters	*IL18* rs187238 genotype					
	CC N = 109	CG N = 81	GG N = 14	CC *vs.* CG	CC *vs.* GG	CG *vs.* GG
	Mean ± SD	Mean ± SD	Mean ± SD	p[&]		
Body mass before pregnancy [kg]	67.6 ± 15.9	70.2 ± 17.6	62.9 ± 12.1	0.27	0.31	0.11
Body mass at birth [kg]	78.3 ± 16.4	82.2 ± 18.5	72.8 ± 12.1	0.11	0.28	0.059
Body mass increase during pregnancy [kg]	10.6 ± 5.4	12.0 ± 5.1	9.9 ± 3.9	0.013	0.91	0.12
BMI before pregnancy [kg/m^2]	24.9 ± 5.0	25.8 ± 6.2	23.6 ± 4.9	0.41	0.29	0.17
BMI at birth [kg/m^2]	28.8 ± 5.4	30.2 ± 6.5	27.3 ± 5.0	0.23	0.30	0.12
BMI increase during pregnancy [kg/m^2]	4.0 ± 2.1	4.4 ± 1.8	3.7 ± 1.5	0.019	0.94	0.14
HbA_{1c} [%]	5.57 ± 0.45	5.59 ± 0.50	5.29 ± 0.51	0.61	0.051	0.049
Daily insulin requirement [unit]	5.17 ± 11.05	5.64 ± 12.09	4.07 ± 11.45	0.51	0.32	0.54
Childbirth [weeks]	38.3 ± 2.3	38.7 ± 1.2	38.9 ± 1.2	0.79	0.38	0.48
Newborn body mass [g]	3189 ± 713	3381 ± 505	3182 ± 527	0.094	0.56	0.14
APGAR (0–10)	9.6 ± 1.2	9.8 ± 0.6	10.0 ± 0.0	0.26	0.13	0.22

[&]Mann-Whitney U test

BMI before pregnancy were independent significant predictors of a higher risk of GDM, while higher number of *IL18* rs1946518 T alleles was a protective factor against GDM.

It has been shown that *IL18* promoter gene polymorphisms rs187238 and rs1946518, may influence promoter activity and *IL18* production [12, 16, 17]. Previous studies have indicated that *IL16* and *IL18* are pro-inflammatory cytokines involved in the pathogenesis of diabetes [13, 18–20]. The significant role of low-grade inflammation has been confirmed in type 2 diabetes. Due to the similarity between T2DM and GDM, and the association between T2DM and inflammation, it has been hypothesised that inflammation could also be implicated in the pathophysiology of GDM [6, 7]. Several studies have examined cytokine production in pregnant women and it has been shown that during pregnancy, the imbalance between the production of anti-inflammatory and pro-inflammatory cytokines may induce low-grade inflammation and insulin resistance [21].

Previous studies have indicated that women with GDM have increased plasma *IL16* and *IL18* levels. This increase in *IL16* in pregnant women was found to be associated with pre-eclampsia and preterm birth [22–24]. Kuzmicki et al. have shown that the balance between circulating pro- and anti-inflammatory cytokines is impaired in patients with GDM.

Table 5. Clinical parameters of women with GDM stratified according to *IL18* rs1946518 genotype

Parameters	*IL18* rs1946518 genotype					
	GG N = 73	GT N = 105	TT N = 26	GG *vs.* GT	GG *vs.* TT	GT *vs.* TT
	Mean ± SD	Mean ± SD	Mean ± SD	p[&]		
Body mass before pregnancy [kg]	65.8 ± 15.8	70.3 ± 17.2	67.5 ± 13.9	0.022	0.34	0.50
Body mass at birth [kg]	76.4 ± 16.4	81.7 ± 17.9	79.0 ± 14.8	0.015	0.32	0.54
Body mass increase during pregnancy [kg]	10.6 ± 5.0	11.4 ± 5.3	11.5 ± 5.7	0.25	0.36	0.91
BMI before pregnancy [kg/m^2]	24.2 ± 4.8	25.8 ± 6.0	25.2 ± 5.4	0.049	0.41	0.64
BMI at birth [kg/m^2]	28.1 ± 5.0	30.0 ± 6.4	29.5 ± 5.7	0.045	0.33	0.82
BMI increase during pregnancy [kg/m^2]	3.9 ± 1.9	4.2 ± 2.0	4.3 ± 2.1	0.34	0.36	0.93
HbA_{1c} [%]	5.56 ± 0.49	5.57 ± 0.45	5.49 ± 0.55	0.62	0.64	0.49
Daily insulin requirement [unit]	4.42 ± 10.33	5.97 ± 12.15	4.88 ± 11.80	0.53	0.71	0.44
Childbirth [weeks]	38.1 ± 2.5	38.7 ± 1.4	38.7 ± 1.3	0.36	0.40	0.81
Newborn body mass [g]	3154 ± 747	3344 ± 522	3258 ± 650	0.084	0.85	0.37
APGAR (0–10)	9.5 ± 1.2	9.8 ± 0.9	9.8 ± 0.7	0.11	0.51	0.66

[&] Mann-Whitney U test

Table 6. Multivariate logistic regression analysis for presence of GDM as the dependent variable

Parameters	OR (95% CI)	p
Age [years]	1.11 (1.06–1.16)	0.0000034
BMI before pregnancy [kg/m^2]	1.09 (1.04–1.15)	0.00018
IL18 rs1946518 (number of T alleles)	0.73 (0.54–1.00)	0.0499
IL16 rs4778889 (CC *vs.* CT+TT)	0.15 (0.018–1.27)	0.081

Increased *IL18* levels were detected in women with GDM and correlated with maternal obesity [25]. Fatima et al. found that increased *IL18* levels in women with GDM were correlated with low-grade inflammation and insulin resistance [26]. *IL18* gene polymorphisms have been investigated among patients with type 1 and type 2 diabetes [27–31]. Several studies suggest that these polymorphisms may be associated with an increased risk of diabetes and its cardiovascular complications. These polymorphisms were also studied in patients with obesity and it has been found that *IL18* gene polymorphisms may be associated with obesity and low-grade inflammation [32, 33]. In our study, we also observed the associations between *IL18* rs187238 and rs1946518 gene polymorphisms and BMI in pregnant women.

CONCLUSIONS

The results of this study suggest that *IL16* rs4778889, *IL18* rs187238 and rs1946518 polymorphisms may affect the risk of GDM as well as BMI in pregnant women. However, this observation requires further investigation in women of other populations.

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