Surfactant Protein D Gene Polymorphism was Associated with the Susceptibility of Gestational Diabetes Mellitus: A Case Control Study

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Abstract

Background

Surfactant protein D (SP-D) is a critical component of the innate immune system intrinsically linked to energetic metabolism. However, the relationship of SP-D gene polymorphisms and gestational diabetes mellitus (GDM) remains unclear yet. In this study, we analyzed SP-D gene polymorphisms in GDM patients and non-diabatic controls, and then determined the association of SP-D gene polymorphisms with GDM.

Methods

We examined a common genetic polymorphism located in the SP-D coding region (rs721917, Met31Thr) with GDM patients (n = 147) and healthy pregnant controls (n = 97) by using a PCR-RFLP technique. The level of SP-D protein in serum of GDM patients and non-diabetic controls was determined by ELISA method. The gene and allele frequencies od SP-D and their association with GDM as well as SP-D protein level were analyzed using SPSS software.

Results

We found that there exists a significant association of the SP-D polymorphism (rs721917) with GDM. SP-D (T/T) genotype had 11.6% and 21.6% in GDM and matched healthy controls, respectively ($P<0.05$); indicating women with (T/T) genotype have lower prevalence of GDM (OR = 0.473). Women with T/C genotypes showed an increased risk of GDM (OR = 2.440). We did not observe corrections between glucose homeostasis markers and SP-D genotypes in the women patients with GDM. Furthermore, serum SP-D level was higher in the GDM compared to matched healthy controls.

Conclusions

This study has found the first evidence that SP-D gene polymorphism (rs721917) was associated with GDM, which may provide the basis for further study how SP-D plays a regulatory role in GDM.

Background

Gestational diabetes mellitus (GDM), defined as hyperglycemia with onset or first recognition during pregnancy, has recently been recognized and showed dramatical increase. According to the recent reports, the incidences of GDM in the USA and Europe are 2–10% (1), and in the Chinese population approximately 17.5% (2). It has been acknowledged that GDM not only increases the risk of a series of current fetal and maternal complications, including dystocia, polyhydramnios, preterm birth, neonatal hypoglycemia, and hyperinsulinemia, but also results in various severe long-term consequences for both baby and mother, such as predisposition to obesity, metabolic syndrome, and persistent diabetes (3). Recently, several adipokines have been found to be involved in the pathophysiology of GDM. They were proven to participate in various metabolic processes, including insulin sensitivity, insulin secretion,

appetite control, fat distribution, energy expenditure, inflammation, regulation of adipogenesis, and chemoattraction of immune cells into adipose tissue (4). Moreover, the alteration of adipokine secretion might contribute to changes in glucose homeostasis in pregnancy, subsequently causing GDM (4).

Surfactant protein D (SP-D, gene name as *SFTPD*) is initially identified to be expressed and secreted in lung alveolar epithelial type II cells (5), which plays a crucial role in protecting the lung from inhaled microorganisms, organic antigens, and toxins by recruiting the innate immune system and consequently regulating inflammation activities (6). Except for the pulmonary system, SP-D is also expressed in several other tissues/organs, such as the brain, pancreas, kidney, gut, and endothelium, and reproductive system (7–9). Previous studies have revealed the association between low expression of circulating SP-D and increased fat accumulation (10) combined with decreased insulin sensitivity (11), which suggests that SP-D may affect not only the specific inflammatory response but also systemic metabolism (12).

The human SP-D gene located in chromosome 10q22.2-q23.1 contains several single nucleotide polymorphisms (SNP) (13). The SP-D single nucleotide polymorphism (SNP) rs721917 (NC_000010.10: g.81706324A>G) is a missense substitution that leads the replacement in position 31 of an ancestral methionine by a threonine (Met31Thr) (14). The change from methionine to threonine can cause the SP-D oligomeric difference of two common genetic variants.

Many progresses were made in elucidating possible genetic predisposition to GDM through a genome-wide association strategy (15). According to the GWAS, many gene defects of coding sequence changes play a role in metabolic disease (16), and compelling data suggest that genetic factors contribute to GDM (17). However, the study about the genetic susceptibility to GDM lacks relatively (18). The research strategies for the GDM candidate genes are mainly from the genes associated with type 2 diabetes or obesity, which limits the capacity of discovering novel genetic variants of GDM beyond the candidate SNPs of T2D. Therefore, this study aims to investigate whether SP-D polymorphisms are associated with susceptibility to GDM.

Materials And Methods

Subjects

For this study, we collected data and blood samples from pregnant women diagnosed GDM and matched healthy pregnant women as controls. Briefly, 147 pregnant women with gestational diabetes, singleton, aged 24–40 years were admitted in the Department of Obstetrics of Second Hospital Affiliated to Zhejiang University Medical College, Hangzhou, Zhejiang Province, between October 2016 and October 2018; and 97 age-matched healthy singleton pregnancies in the same hospital were recruited as controls. All of the participants recruited were Han Chinese. The diagnosis of GDM was established following the International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria. GDM should be diagnosed at any time in pregnancy if one or more of the listed criteria are met following a 75-gram glucose load: fasting PG ≥ 5.1 mmol/l; 1-hour PG ≥ 10.0mmol/l; 2-hour PG 8.5–11.0 mmol/l.

Those women diagnosed with DM or pre-diabetes (impaired fasting glucose or impaired glucose tolerance) before pregnancy were excluded from the study. A total of 97 matched healthy pregnant women as controls were recruited in this study. The study protocol(I2018001239) was approved by the clinical research ethics committee of The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China. The informed consents were signed and obtained from all pregnancies and subjects before initiation of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Specimen collection

Peripheral blood (2ml) sample was collected from each GDM patient or matched healthy control. The samples were stored at room temperature for 1h, then centrifuged at 5000 rpm/min for 5 min to separate white blood cells and serum. Serum and white blood cells were saved at -20℃ for following analysis.

Analysis of SP-D Thr31Met polymorphism

The SP-D gene polymorphism rs721917 (NC_000010.10: g.81706324A>G) was analyzed using the instructions of the genome DNA extraction kit (Slolarbio, Beijing, China). The remaining procedure to exam the SP-D polymorphism Thr31Met was similar to a described method for sequence-specific primer-polymerase chain reaction (PCR-SSP) previously (20). This method provided the reproducible results as follows: initial denaturation 1 min at 94 ℃; followed by 5 cycles of 20s at 94 ℃,45 s at 65 ℃, 25 s at 72 ℃; 21 cycles of 25 s at 94 ℃, 50 s at 55 ℃, 30 s at 72 ℃, 4 cycles of 30s at 94 ℃, 60s at 50 ℃, 120 s at 72 ℃; and a final extension at 72 ℃ for 3 min. Then PCR products were separated and identified using 2%-agarose gel electrophoresis. The genotype of SP-D was determined as described previously (20).

ELISA of SPD level in serum

Serum SP-D protein levels in GDM patients and controls were detected by ELISA (CUSABIO, Shanghai, China) according to the manufacture's instructions.

Statistical analysis

The statistical association between the SP-D gene polymorphism rs721917 and GDM was performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). Departures from Hardy-Weinberg equilibrium(HWE) were tested to determine whether the genotype and allele frequencies were consistent with the genetic balance. Quantitative data were expressed as X ± SEM and compared by standard one-way ANOVA test or Student's t-test where appropriate. $P < 0.05$ was considered to be statistically significant. Allele and genotype frequencies were compared by Pearson's two-tailed chi-square test or Fisher exact test. The risk of developing GDM under exposure to this SP-D SNP was evaluated using logistic regression to estimate Odd Ratios (OR) with a 95% confidence interval, considering the TT genotype as the reference group.

Results

Baseline characteristics of GDM patients and healthy controls

Clinicopathological characteristics of a total of 147 pregnant women with GDM, and 97 healthy pregnant women (controls) in our study are presented in Table 1 (SI Appendix, GDM and controls). The mean age of GDM patients and the controls was 31.59 ± 3.77 and 29.80 ± 3.85 years, respectively. Although BMI levels, delivery age, and infant birth age were not different, several makers of glucose homeostasis, including Fasting glucose, Glucose 1h post overload, Glucose 2h post overload (mmol/L), HbA1c (%), differed significantly between GDM and healthy controls ($p < 0.001$) (Table 1).

Table 1
Baseline characteristics of GDM patients and healthy pregnant controls

	GDM	Controls	p value
N	147	97	
Age(yr)	31.59 ± 3.77	29.80 ± 3.85	
BMI(kg/m2)	26.43 ± 2.58	25.97 ± 2.74	0.182
Fasting glucose(mmol/L)	4.70 ± 0.48	4.35 ± 0.52	**< 0.001**
Glucose 1h post overload(mmol/L)	9.78 ± 1.44	7.48 ± 1.32	**< 0.001**
Glucose 2h post overload(mmol/L)	8.66 ± 1.30	6.43 ± 1.09	**< 0.001**
HbA1c(%)	4.95 ± 0.35	4.77 ± 0.32	**< 0.001**
Gestational age at delivery(w)	38.37 ± 1.19	38.47 ± 1.15	0.520
Infant birth weight(g)	3312.59 ± 440.52	3289.48 ± 379.75	0.673

Association between SP-D genotype and the susceptibility to GDM

The distribution of SP-D Thr31Met genotypes and alleles obtained in this study were consistent with HWE ($p>0.05$). Compared with healthy controls, the frequency of SP-D 31Met/Met (T/T) genotype was significantly lower in GDM patients ($p = 0.033$), indicating that homozygous SP-D 31Met/Met (T/T) women are resistance to GDM incidence; the frequency of SP-D 31Met/Thr (T/C) genotype was significantly high in GDM patients compared to healthy controls ($p = 0.017$), suggesting that the heterogenous SP-D 31Met/Thr (T/C) women are sensitive to GDM incidence (Table 2). However, the frequencies of SP-D 31 Thr (C) and 31 Met (T) alleles were not significantly different in women with GDM and healthy controls ($p = 0.859$) (Table 2). Furthermore, we examined whether there are corrections between SP-D 31Met/Thr genotypes and glucose homeostasis in the GDM patients. The results indicated that the markers of glucose homeostasis have no difference among the three SP-D genotypes ($p>0.05$) (Table 3,Figure 1). When study participants with extreme levels of markers of glucose homeostasis in our cohort were analyzed separately, it was no significant difference to be found ($p>0.05$) (SI Appendix, Table 1–4).

Table 2
Surfactant protein D gene polymorphisms in GDM patients and healthy controls

Model	GDM		Controls		OR	95%CI	p value
	N %		N	%			
Genotype (Met31Thr)							
T/T	17	11.6	21	21.6	0.473	0.235–0.952	**0.033**
C/T	81	55.1	41	42.3	2.440	1.162–5.123	**0.017**
C/C	49	33.3	35	36.1	1.729	0.799–3.745	0.163
Allele							
T	115	39.1	83	42.8	0.859	0.594–1.242	0.419
C	179	60.9	111	57.2			

Table 3
Baseline serum markers of glucose homeostasis levels and different genotypes among patients with GDM

	TT(17)	TC(81)	CC(49)	p value	p* value
Fasting glucose(mmol/L)	4.68 ± 0.47	4.71 ± 0.45	4.69 ± 0.54	0.393	0.448
Glucose 1h post overload(mmol/L)	9.63 ± 0.86	9.74 ± 1.50	9.88 ± 1.52	0.232	0.522
Glucose 2h post overload(mmol/L)	8.77 ± 1.19	8.68 ± 1.19	8.58 ± 1.51	0.786	0.646
HbA1c(%)	4.86 ± 0.26	5.01 ± 0.37	4.89 ± 0.36	0.110	0.591
BMI(kg/m2)	26.24 ± 2.01	26.42 ± 2.59	26.52 ± 2.78	0.791	0.706

Serum SP-D level in GDM patients and healthy controls

In this study we measured the SP-D level in serum collected from GDM and healthy controls. The results indicated that serum SP-D level of healthy controls ranged from 14.63 ng/ml to 36.47 ng/ml (median 24.68 ng/ml; 25-75th IQR 19.22–27.63 ng/ml). Serum SP-D levels of GDM patients ranged from 9.44

ng/ml to 60.14 ng/ml (median 31.06 ng/ml; 25-75th IQR 14.70-48.65 ng/ml). Compared with healthy controls, serum SP-D levels in GDM patients were significantly increased ($p<0.01$) (Table 4).

Table 4
Serum SP-D levels in GDM patients and healthy controls

	GDM patients	Healthy controls	p value
Median (25th -75^{thl}IQR) serum SP-D (ng/ml)	31.06(14.70-48.65)	24.68(19.22–27.63)	**0.002**

Analysis of correlations between SP-D genotypes and serum SP-D level in GDM patients

We further examined whether there exists a correlation between SP-D genotypes and serum SP-D level. The results indicated that no difference in serum SP-D levels between GDM patients was observed among three genotypes i.e. Thr31Thr, Met31Thr and Met31Met genotypes (Table 5).

Table 5
Basal serum SP-D levels and different genotypes among GDM patients

Genotype	Median (25th -75^{thl}IQR) baseline serum SP-D(ng/ml)	p value
Met31Thr		
T/T	34.88(26.51–54.04)	
C/T	23.86(12.27–43.29)	0.125
C/C	38.41(21.71–56.31)	0.630

IQR interquartile range

Discussion

The objective of this study was to study the relationship between SP-D Met31Thr (T/C) polymorphism and the susceptibility of GDM in Chinese patients.

Surfactant collectin such as SP-D is well known to be involved in lung innate immunity to prevent respiratory infections (21). The SP-D Met31Thr polymorphism has been demonstrated correlating with susceptibility to increased incidence or risk of various disorders, including chronic obstructive pulmonary disease (22), allergic rhinitis (23), asthma (24), acute kidney injury (25), obesity and accompanying T2D (26). Interestingly, one C-allele carriers showed decreased circulating SP-D, fasting glucose and lower prevalence of T2D (26). However, in our study TT homozygotes had 11.6% ($P<0.05$) lower prevalence of GDM than C-allele carriers (OR = 0.473), and the T/C genotypes showed a higher risk of GDM (OR =

2.440). However, the levels of glucose homeostasis markers were not significantly different in women with GDM compared to matched healthy controls. Furthermore, compared with healthy controls, serum SP-D levels in GDM patients were significantly elevated ($p<0.01$), but no difference was observed in serum SP-D levels between GDM patients with Thr31Thr genotype and those with Met31Thr and Met31Met genotypes. To mitigate effects induced by race difference or heterogeneity in region and living environments, all GDM patients and healthy controls in our study were confined the Chinese Han nationality residing in similar geographic locations from Zhejiang Province of China. As a result, frequencies of genotypes at Met31Thr loci in healthy controls were similar to those reported in previous studies conducted in the Chinese population (25) while the distribution of genotypes in the Chinese population differed from the Western counterpart (26). Therefore, we speculated that the SP-D Met31Thr polymorphism might be used as a biomarker to predict patient susceptibility to Chinese GDM patients.

As an intraexonic polymorphism (rs721917) located in codon 11 in the SP-D N-terminal region, the Met31Thr results in changes in amino acid residues of SP-D protein. It has been reported that the polymorphic variation influences oligomerization, function and circulating concentrations (27). Leth-Larsen et al. (27) found that Thr31Thr genotype produces almost exclusively monomers of SP-D, whereas Met31Met genotype shows multimers such as dodecamers and trimers of subunits. These macromolecule polymers of SP-D may bind to viruses and bacteria, while the monomeric species seem to bind LPS almost exclusively. However, it is unclear how these different oligomeric protein molecules influence other biological function. It needs to be further studies in the future.

In the present study, we found that GDM subjects exhibited higher serum SP-D concentrations compared to healthy controls ($p = 0.002$), particularly among subjects with Thr31Thr genotype, which might contribute to individual susceptibility. However, no difference was observed in serum SP-D levels between GDM subjects with Thr31Thr genotype and those with Met31Thr and Met31Met genotypes. Neus Pueyo *et al*. (11) found cross-sectional and longitudinal associations of circulating SP-D concentrations within insulin resistance and T2D, and also described that the Met31Thr SP-D gene SNP rs721917 was associated with insulin resistance and the prevalence of T2D (28). In this study, GDM partially shares the same mechanism with T2D, and the possible influence of the Met31Thr SP-D gene SNP on GDM may arise from changes in the molecular structure and/or functional properties of SP-D protein rather than through changes in its circulating concentrations. Jie Yan et al. (29) verified twenty genes associated with T2D and obesity in a Chinese population and found only four SNPs were significantly correlated with GDM, and those risk alleles were associated with lipid profiles and glucose level. Ming et al. (30) genotyped one hundred and twelve susceptibility genetic variants confirmed by genome-wide association studies for T2D from two independent populations, and identified only eleven SNPs associated with the risk of GDM. These findings might be explained by two possible reasons. Firstly, mechanisms responsible for incidence or progression vary from gestational diabetes mellitus (GDM) and obesity or its accompanying T2D. Besides, as one of the metabolic diseases, GDM is involved in interactions between genetic and environmental or nutritional factors, which indicates that GDM pathogenesis could be attributed to various elements besides genetic polymorphisms. Secondly, our study was carried only in

the Chinese Han population, which expressed different genetic variants due to race, region, and living environments.

In conclusion, we found at first time that SP-D gene polymorphism (rs721917) was associated with GDM and there is higher serum SP-D level in the GDM compared to matched healthy controls.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the clinical research ethics committee of The Second Affiliated Hospital, School of Medicine, Zhejiang University, (I2018001239), Hangzhou, China. The informed consents were signed and obtained from all patients and subjects before initiation of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets created during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JWX and LQW contributed to conception and design, JWX acquired data and performed SP-D polymorphisms analysis, also was a major contributor in drafting the manuscript, YC acquired and analyzed the patient data and detected the serum SP-D protein level, LFT and XYT were contributors in writing the manuscript and performing the statistical analyses, LF and LGJ performed the statistic analysis, GRW and LQW revised the crude manuscript, LQW was a major contributor in coordinating the corhort and designing the experiment. All authors have reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Figures

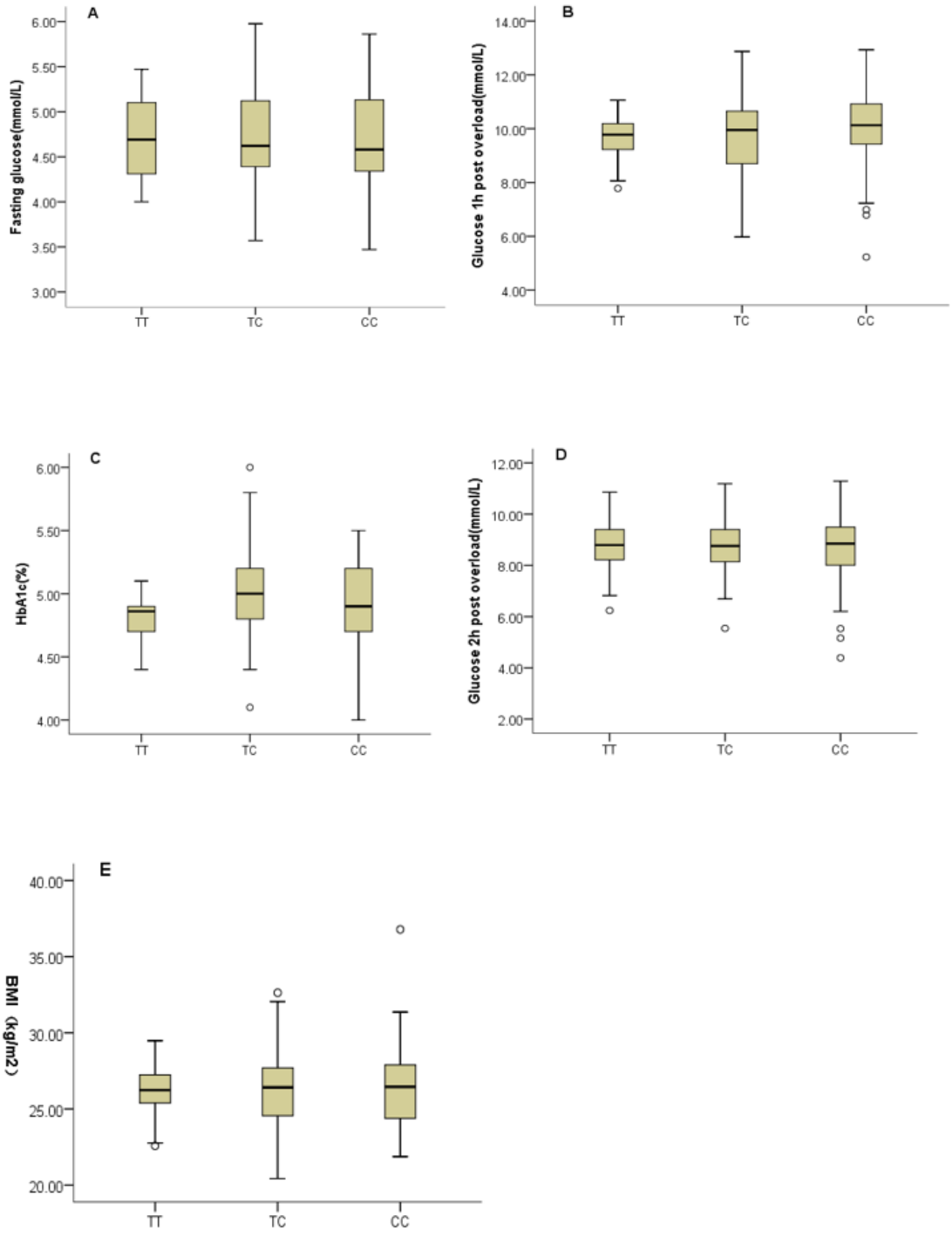

Figure 1

Genotypes for Met31Thr and measures of impaired glucose tolerance. Mean and 95% confidence interval for fasting glucose (Fig. A), glucose 1h post overload (Fig. B), glucose 2h post overload (Fig. C), HbA1c (Fig. D), and BMI (Fig. E).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- controls.xls
- NGDM001.xls