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Original Research

Comparison of the expression levels of TNF-α, IL-6, hsCRP and sICAM-1 inflammatory factors, bone mineral density and nutritional status between diabetic and normal pregnant women

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Abstract: To compare the ultrasound bone mineral density, nutritional status and inflammatory state of pregnant women with gestational diabetes mellitus (GDM) and those with normal blood glucose. Retrospective analysis of pregnant women who were prenatally examined and delivered in The 5th People's Hospital of Ji'nan from May 2015 to July 2017 was performed, including 68 subjects with normal blood glucose in the control group and 74 subjects with GDM in the experiment group. The bone mineral density, nutritional status and inflammatory state were measured by enzyme-linked immune sorbent assay (ELISA). The bone mineral density of pregnant women with GDM was lower than that of the control group; the incidence of osteoporosis in GDM pregnant women was higher than that in the control group. The energy intake of GDM pregnant women was high, and the usage rate of fruits, sweets, deep-fried products and night snack was higher than that of normal pregnant women. The expression levels of TNF-α, IL-6, hsCRP and sICAM-1 inflammatory factors in GDM pregnant women were significantly higher than those with normal blood glucose. The bone mineral density of pregnant women with GDM is lower than that with normal blood glucose. Therefore, the prevention of GDM in pregnant women is also important for their bone health. GDM pregnant women's health education should be strengthened and reasonable dietary interventions should be carried out as soon as possible. TNF-a, IL-6, hsCRP, and sICAM-1 may be involved in the inflammatory process of GDM.

Key words: Gestational diabetes; Bone mineral density; Nutritional status; Inflammation state.

Introduction

Glucose intolerance (regardless of the degree) of the first identification or onset during pregnancy is called gestational diabetes mellitus (GDM) (1). GDM, one of the most common types of pregnancy disorders, without timely treatment, may increase the risk of pre-eclampsia and preterm birth (2). Clinically, diet and exercise therapy are generally used to control blood sugars, When the above two methods failed, insulin should be used to control blood glucose (3).

Islet B cell defects and peripheral insulin resistance may be the cause of GDM (4). In the study of Leipold et al (5), the C-reactive protein and TNF-α are the main inflammatory mediators associated with GDM, the degree of resistance to human insulin changed with the changes of the level of these inflammatory factors. It believe that the imbalance in the expression between pro-inflammatory and anti-inflammatory factors will destroy the glucose homeostasis in pregnant women (6).

Also, studies have shown that (7), pregnant women may experience varying degrees of bone loss or osteoporosis; some pregnant women may have symptoms such as back pain, therefore abnormal glucose metabolism is likely to be associated with abnormal bone metabolism, which is more obvious in patients with gestational diabetes. The diet of pregnant women has an important impact on GDM (8), and their nutritional status also affects the development of the fetus (9). The impact of nutritional status on GDM patients is complex and comprehensive. It has been reported that women are at increased risk of vitamin D deficiency during pregnancy (10). Vitamin D induces insulin receptor expression through vitamin D receptors, thereby increasing the insulin-dependent glucose transport rate (11), therefore vitamin D deficiency is closely related to GDM. Vitamin D promotes intestinal calcium absorption and maintains serum calcium and phosphate concentrations to ensure normal bone mineralization (11). Vitamin D may also be an immunosuppressive agent that down-regulates the expression of inflammatory cytokines such as TNF-α and IL-2 in GDM patients (12), thereby affecting the inflammation in GDM patients. The bone mineral density, nutritional status and inflammatory status of pregnant women with GDM and pregnant women with normal blood glucose levels were compared in this study, in order to provide support for the establishment of predictive GDM indicators and promote the further development of early diagnosis and treatment of GDM.

Materials and Methods

General information

142 pregnant women in The 5th People's Hospital of Ji'nan from May 2015 to July 2017 were selected, including 74 pregnant women with GDM in the experiment

Table 1. General information about pregnant women between both groups.

Groups	The experiment group(n=74)	The control group(n=68)	t/α^2	*p*
Age (Years)	30.13±2.87	29.43±1.97	1.680	0.095
BMI(kg/m^2)	26.87±2.54	23.86±2.71	0.365	0.716
Gestational age (week)	27.36±3.13	27.73±2.96	0.722	0.471
Vomiting During Pregnancy [n (%)]				
Vomit	34(45.95)	37(54.41)	1.016	0.314
Non-vomit	40(54.05)	31(45.59)		
constipation [n (%)]				
With consipation	36(48.65)	35(51.47)	0.113	0.737
Without-constipation	38(51.35)	33(48.53)		
Glycated hemoglobin (%)	6.74±0.79	5.14±0.62	13.35	< 0.001
fasting blood glucose (mmol/L)	5.76±1.34	3.28±0.58	8.411	< 0.001

group, with a mean age of (30.13±2.87) years. Another 68 pregnant women with normal blood glucose in The 5th People's Hospital of Ji'nan were selected as the control group, with a mean age of (29.43±1.97) years. People in the experiment group were diagnosed with GDM during the gestational period of 24-28 weeks. The diagnosis of GDM patients is based on the 2010 International Diabetes Diagnostic Criteria (13).

Inclusion criteria: pregnant women under 35 years old; diagnosed with GDM; informed and cooperated with the treatment. Pregnant women with normal blood glucose levels in the same period. The study was approved by the patient and their families, and informed consent was signed. Exclusion criteria: patients with malignant tumors; patients with glucocorticoids; patients with severe liver damage, hyperthyroidism, hypothyroidism, rheumatism, etc.; without screening glucose tolerance, patients have been diagnosed with impaired glucose tolerance or type 2 diabetes before pregnancy; patients with pregnancy-induced hypertension; patients with chronic bronchial asthma, emphysema, bronchitis and other respiratory diseases; patients with hepatorenal dysfunction; patients with mental disorders; patients with a history of habitual abortion; patients who were unwilling to participate in the survey. There were no significant differences in the age, body mass index, and gestational age between the two groups (P> 0.05). The glycated hemoglobin and fasting blood glucose were significantly different between both groups (P< 0.05) based on Table 1.

Research methods

(A) Subjects fasted for 8 to 14 hours, and 4 ml of venous blood was taken between 8 am and 10 am on the next day. The blood was collected into the vacuum blood collection device, a glass tube without anticoagulant. 6 hours later, the serum was separated and stored at -20°C. Enzyme-linked immune sorbent assay (ELISA) was used to detect TNF-α, IL-6 and sICAM-1 levels, and the operation was carried out in strict accordance with the instructions; automatic biochemical analyzer was used to detect hsCRP levels.

(B) The ultrasonic bone tester was used to detect the bone density of the right heel bone of pregnant women, including attenuation of ultrasonic amplitude (BUA), bone ultrasound conduction velocity (SOS), and bone hardness index (STI).

(C) The proportion of food intake in the two groups of pregnant women was investigated by questionnaires, including cereals, beans, vegetables, milk, meat and poultry. Meal nutrition analysis software was used to record dietary data and calculate the dietary anti-inflammatory index.

Equipment and kits

UBIS3000 ultrasonic bone tester and supporting imager (CHKSILTP and DMS); automatic biochemical analyzer (GE); dietary nutrition analysis software (Shanghai Zhending Software Company); tumor necrosis factor α (TNF-α) kit (Shanghai Enzyme-linked Biotechnology Co., Ltd.); human interleukin 6 (IL-6) quantitative detection kit (Shanghai Biosh Biotechnology Co., Ltd.); human soluble intercellular adhesion molecule 1 (sICAM-1) kit (Shanghai HZ Biological Technology Co., Ltd.).

Calculation of the dietary inflammatory index (DII)

DII of a certain dietary ingredient= (the daily intake of the ingredient - the global per capita daily intake of the ingredient) / the standard deviation of the per capita intake of the ingredient × inflammatory effect index of the ingredient. The sum of all dietary ingredients DII was the DII total score (14). The greater the positive value of DII, the greater the pro-inflammatory potential of the dietary; the greater the negative value of DII, the greater the anti-inflammatory potential of the dietary. The experimental group and the control group were grouped according to the DII total quartile and divided into 3 groups by P25 and P75: pro-inflammatory group (DII>-2.55), middle group (-5.10< DII< -2.55), anti-inflammatory group (DII< -5.10).

Statistical processing

This study used the SPSS20.0 software package (Bo Yi Zhixun (Beijing) Information Technology Co. Ltd.) for the statistical analysis of experimental data; the graph was plotted by GraphPad Prism 7. The measurement data were expressed with mean±standard deviation (Mean±SD). The analysis between the two groups was performed using a t-test. Counting data were analyzed using the Chi-square test. P< 0.05, considered as the difference was statistically significant. Spearman correlation analysis was used to analyze the categorical variables.

Results

Comparison of bone mineral density measurements between both groups of pregnant women

The results of bone mineral density measurement

in the two groups showed that the BUA, SOS and STI indices of the experiment group were (64.12±10.34), (1518±90.73) and (81.21±8.43), respectively. The BUA, SOS, and STI indices of the control group were (71.86±12.37), (1553±97.65) and (90.76±8.65), respectively. The bone mineral density indices of the experiment group were significantly lower than that of the control group. The difference between the two groups was statistically significant (P< 0.05) based on Table 2.

Comparison of the osteoporosis morbidity in two groups of pregnant women

Comparing the osteoporosis morbidity between both groups of pregnant women, the experiment group included 56 patients (75.68%) with normal bone mass, 11 patients (14.86%) with less bone mass and 7 patients (9.46%) with osteoporosis. The control group included 64 patients (94.21%) with normal bone mass, 3 patients (4.41%) with less bone mass, and 1 patient (1.47%) with osteoporosis. Comparing the osteoporosis morbidity between both groups, the number of normal bone mass in the experiment group was higher than that in the control group. The number of bone mass in the experiment group was lower than that in the control group, and the osteoporosis morbidity in the control group was significantly higher than that in the experiment group (P< 0.05) according to Table 3.

The proportion of food intake of pregnant women between both groups

The proportion of food intake between both groups of pregnant women was investigated through questionnaires. The results showed the difference in the usage rate of cereals, vegetables, poultry, eggs, fish and shrimp, beans, and dairy products between both groups was not statistically significant(P> 0.05). The usage rate of fruits, sweets, deep-fried precuts and night snack were significantly higher than that of the control group. The difference between both groups was statistically significant (P< 0.05) based on Table 4.

The relationship between the dietary and inflammation in the two groups of pregnant women was compared (Table 5). The results showed that there were 11 cases (14.86%) in the anti-inflammatory group, 44 cases (59.46%) in the middle group, and 19 cases (25.68%) in the pro-inflammatory group. There were 12 cases (17.68%) in the anti-inflammatory group, 49 cases (72.06) in the middle group, and 7 cases (10.94%) in the pro-inflammatory group. The number of cases in the pro-inflammatory group in the experimental group was significantly higher than that in the control group (P< 0.05, Table 5).

Table 2. Comparison of bone mineral density measurements between two groups of pregnant women.

Groups	BUA(dB/MHz)	SOS(m/s)	STI
The experiment group (n=74)	64.12±10.34	1518±90.73	81.21±8.43
The control group (n=68)	71.86±12.37	1553±97.65	90.76±8.65
t	4.057	2.214	6.660
p	<0.001	0.028	< 0.001

Table 3. Comparison of the osteoporosis morbidity between both groups of pregnant women [n (%)].

Groups	Normal bone mass	Less bone mass	osteoporosis morbidity
The experiment group (n=74)	56（75.68）	11（14.86）	7 (9.46)
The control group (n=68)	64（94.12）	3（4.41）	1 (1.47)
X^2	9.205	4.357	4.254
p	0.002	0.037	0.039

Table 4. The proportion of various food intakes between the two groups of pregnant women.

Groups	The experiment group (n=74)		The control group (n=68)		X^2	*p*
	NO. of people	Usage rate	NO. of people	Usage rate		
Cereals	74	100%	67	98.53%	1.096	0.295
Fruits	73	98.65%	59	85.50%	7.645	0.006
Vegetables	72	97.30%	66	95.65%	0.007	0.932
Poultry	35	47.30%	27	39.13%	0.830	0.362
Eggs	33	44.59%	29	42.65%	0.546	0.815
Fish and shrimps	31	41.89%	27	39.71%	0.070	0.791
Beans	35	47.30%	36	52.94%	0.582	0.445
Dairy products	39	52.70%	35	51.47%	0.021	0.883
Sweets	23	31.08%	6	8.82%	10.80	0.001
Deep fried	7	9.46%	1	1.47%	4.254	0.039
Night snack	17	22.97%	2	2.84%	12.27	0.001

Table 5. Comparison of dietary structure and inflammation between the two groups of pregnant women [n (%)].

	The experimentgroup (n=74)	The control group (n=68)	χ^2	*p*
The anti-inflammatory group	11 (14.86)	12 (17.68)	0.202	0.820
The middle group	44 (59.46)	49 (72.06)	2.489	0.157
The pro-inflammatory group	19 (25.68)	7 (10.94)	5.605	0.029

Comparison of TNF-a, IL-6, hsCRP and sICAM-1 levels between experiment group and control group

The expression levels of TNF-a, IL-6, hsCRP and sICAM-1 in the experiment group were (7.75±0.87) ng/L, (9.89±3.76) ng/L, (9.12±5.21) ng/L and (532.53±181.77) ng/L, respectively. The expression levels of TNF-a, IL-6, hsCRP and sICAM-1 in the control group were (5.64±0.76) ng/L, (8.63±1.30) ng/L, (5.32±3.15) ng/L and (365.75±121.77) ng/L, respectively. The levels of TNF-a, IL-6, hsCRP and sICAM-1 in the experiment group were significantly higher than those in the control group. The difference between the two groups was statistically significant ($P< 0.05$) based on Table 6.

Spearman analysis of food factors, bone mineral density and inflammatory cytokine levels in the experimental group

The results in Table 7 indicated that there was no correlation between fruit and bone mineral density, inflammatory cytokine levels. Sweets, fried food and midnight snacks were not only negatively correlated with bone density but also negatively correlated with inflammatory cytokine levels.

Discussion

The incidence of congenital malformation in early pregnancy is 6 to 10% (15). A previous study has shown that 35 to 60% of GDM patients will develop into diabetic patients within 10-20 years after delivery (16). GDM can easily lead to adverse pregnancy outcomes in mothers and children, therefore, pregnant women should be regularly inspected according to the requirements of The 5th People's Hospital of Ji'nan, and timely detection of treatment should be applied to prevent serious consequences. However, the complex condition of gestational diabetes is easily misdiagnosed or undiagnosed (17).

Hyperinsulinemia in pregnant women can increase fetal oxygen consumption and reduce the blood supply

Table 6. Comparison of inflammatory cytokine levels in two groups of pregnant women.

	The experiment group (n=74)	The control group (n=68)	t	*p*
TNF-α (ng/L)	7.75±0.87	5.64±0.76	15.33	0.001
IL-6 (ng/L)	9.89±3.76	8.63±1.30	2.622	0.010
hsCRP (ng/L)	9.12±5.21	5.32±3.15	5.203	0.001
sICAM-1 (ng/L)	532.53±181.77	365.75±121.77	6.366	0.000

Table 7. Spearman analysis of food factors, bone mineral density and inflammatory cytokine levels in the GDM group.

Factors	r	*p*
Food factors and BUA		
Fruits	0.140	0.235
Sweets	-0.066	0.035
Fried foods	-0.098	0.044
Midnight snack	-0.071	0.025
Food factors and SOS		
Fruits	0.173	0.141
Sweets	-0.046	0.038
Fried foods	-0.044	0.028
Midnight snack	-0.148	0.015
Food factors and STI		
Fruits	0.129	0.274
Sweets	-0.064	0.041
Fried foods	-0.083	0.048
Midnight snack	-0.067	0.021
Food factors and TNF-α		
Fruits	0.058	0.626
Sweets	-0.013	0.013
Fried foods	-0.182	0.048
Midnight snack	-0.082	0.042
Food factors and IL-6		
Fruits	0.189	0.107
Sweets	-0.076	0.021
Fried foods	-0.577	0.037
Midnight snack	-0.052	0.034
Food factors and hsCRP		
Fruits	0.014	0.908
Sweets	-0.032	0.036
Fried foods	-0.597	0.044
Midnight snack	-0.018	0.031
Food factors and sICAM-1		
Fruits	0.058	0.626
Sweets	-0.148	0.027
Fried foods	-0.075	0.028
Midnight snack	-0.109	0.036

to the fetus, which leads to intrauterine hypoxia and increased incidence of premature infants (18). Pregnancy osteoporosis is a type of idiopathic osteoporosis that occurs during pregnancy (19). In this study, quantitative ultrasound was used to detect bone mineral density in pregnant women. Quantitative ultrasonic bone measurement is widely used in Europe and Asia and has the advantages of convenient carrying, low cost, and no radiation (20). Therefore, quantitative ultrasound measurement is of great value in the diagnosis of osteoporosis and the prediction of fractures.

A previous study has shown that (21) dietary intervention for gestational diabetes is very important, and dietary adjustment is significant to the prevention of gestational diabetes. Therefore, dietary intervention should be carried out as soon as possible. The results of the food intake ratio of the two groups of pregnant women showed that subjects in the experimental group were not aware of the diet; the DLL grouping showed that the dietary of patients in the experimental group was pro-inflammatory, and there was an increased possibility of the risk of inflammation. Vitamin D promotes calcium absorption to maintain bone mineralization and down-regulates the expression of inflammatory cytokines (11), therefore GDM pregnant women are recommended to appropriately increase the intake of vitamin D.

William et al. (22) used quantitative ultrasound to compare the difference between the GDM group and pregnant women with normal blood glucose, and it was found that the loss of bone mineral density in the GDM group was more serious. This study also used quantitative ultrasound to measure the bone mineral density in pregnant women and analyzed the prevalence of osteoporosis in both groups. Compared with the control group, the experimental group had a lower BMD. The prevalence of osteoporosis in the experimental group was significantly higher than that in the control group. The results of this study are similar to those of William et al. The reason for the above results may be that GDM patients shoulder the burden of abnormal glucose metabolism and pregnancy, both of which can affect the bone metabolism of patients, thus leading to an increased incidence of osteoporosis, decreased bone mass and increased bone density loss (23). The results of Spearman correlation analysis in this study showed that sweets, fried foods and midnight snack may reduce bone density (24-34).

It has been reported that (35), the levels of various acute-phase proteins (such as CRP) in patients with type 2 diabetes were significantly elevated; therefore, the levels of inflammatory cytokines in the two groups of pregnant women were compared in this study. The results showed that the inflammatory cytokine levels in the experimental group were higher than those in the control group. This may be related to pro-inflammatory dietary in the experimental group. The results of the Spearman correlation analysis also indicate that sweets, fried foods and midnight snacks may stimulate the expression of inflammatory cytokines. Yu et al. (36) showed that there are a large number of macrophages in the placenta of GDM patients. Macrophages, as inflammatory cells, can secrete a large number of inflammatory cytokines such as TNF-α and IL-6, which may lead to higher inflammatory cytokine levels in the experimental group.

However, there are certain limitations to this study. Long-term follow-up of the experimental group was not performed to explore the long-term effects of GDM on pregnant women, and the impact of GDM on new births was not recorded. The pathological mechanism of GDM has not been explored. Therefore, it expected that most scholars will increase the sample sizes, which further explores the role of GDM.

Diabetes is a type of hyperglycemic disease, also a type of inflammatory disease. GDM is harmful to the bone health of pregnant women and rationalization of the diet of GDM pregnant women should be strengthened. The increasing intake of nutrients such as vitamin D can promote bone health.

Authors' contributions

QW put forward the proposition, designed the study, provided statistical methods, performed the research, collected and analyzed the data of this study. CW was responsible for carrying out additional analysis, interpreting the results, writing the initial draft of the paper, revising and finalizing this paper. Both authors read and approved the final manuscript.

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