Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: A randomized controlled trial

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Abstract. It has previously been reported that the influence of vitamin D on the metabolism of calcium and phosphorus is associated with diabetes, cardiovascular disease, Alzheimer's disease, cancer and other systemic diseases, and is considered an important indicator of general health. The present study was conducted to determine the effect of various doses of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation and the levels of oxidative stress of pregnant women with gestational diabetes mellitus (GDM). The present randomized, double-blind placebo-controlled clinical trial was conducted on 133 pregnant women with GDM during weeks 24-28 of pregnancy. The patients were randomly divided into four groups. The control group (n=20) received a placebo (sucrose; one granule/day), the low dosage group (n=38) received the daily recommended intake of 200 IU vitamin D (calciferol) daily, the medium dosage group (n=38) received 50,000 IU monthly (2,000 IU daily for 25 days) and the high dosage group (n=37) received 50,000 IU every 2 weeks (4,000 IU daily for 12.5 days). The general characteristics and dietary intakes of the patients with GDM were similar between each group. Using ELISA kits, it was determined that insulin, homeostatic model assessment-insulin resistance and total cholesterol were significantly reduced by high dosage vitamin D supplementation ($P<0.05$). Total antioxidant capacity and total glutathione levels were significantly elevated as a result of high dosage vitamin D supplementation ($P<0.01$). In conclusion, high-dose vitamin D supplementation (50,000 IU every 2 weeks) significantly improved insulin resistance in pregnant women with GDM.

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Introduction

Gestational diabetes mellitus (GDM) is defined as an abnormal glucose metabolism that initially occurs or is first recognized during the pregnancy period, and is a relatively common complication of pregnancy in China (1). In recent years, with the improvement of medical diagnostic technology and the living standards of the human population, GDM incidence has increased (2,3). Patients with GDM are prone to pregnancy-induced hypertension, polyhydramnios, infections, ketoacidosis and other complications; if the control of blood glucose levels remains unfavorable for a prolonged duration of time, it may result in chronic intrauterine fetal hypoxia, growth abnormalities, malformations, neonatal hyperbilirubinemia and hypoglycemia respiratory distress syndrome, amongst others (4,5).

Previous studies have revealed that GDM may increase fetal growth restriction, fetal distress, preterm delivery and polyhydramnios during pregnancy, in addition to an increase in the risk of type 2 diabetes and the incidence of cesarean pain (6,7). Furthermore, GDM may result in adverse effects in the offspring, including fetal macrosomia, defects associated with premature birth, low birth weight, neonatal respiratory distress syndrome and neonatal jaundice (8). Additional research has revealed that the aforementioned adverse pregnancy outcomes are associated with maternal blood glucose levels; thus the effective control of blood sugar levels in pregnant women has the ability to successfully reduce adverse pregnancy outcomes (9). Therefore, the primary goal for successful medical management of GDM is to maintain the concentration of maternal blood glucose, particularly postprandial blood glucose levels, within the ideal range (10). It has been hypothesized that the mechanism of GDM involves an increase in the hormones produced by the placenta known to resist insulin, which results in a decreased sensitivity to insulin in pregnant women (11,12). This consolidates the scientific basis of medical nutrition therapy for the treatment of GDM (13). Medical nutrition therapy aims to treat high blood sugar through scientific dietary adjustments in combination with exercise and blood glucose level monitoring. The American Diabetes Association recommends that all patients be evaluated for GDM risk according to their food intake,

metabolic status and lifestyle by a professional nutritionist, who can develop an individualized medical nutrition therapy according to the patients height, weight and gestational age (14). As the primary method for the treatment of GDM, medical nutrition therapy has gained increasing clinical attention.

Vitamin D is a fat-soluble steroid hormone. Recent studies have indicated its involvement in cardiovascular disease, cancer, autoimmune diseases and diabetes. This is an effect of the widespread distribution of its receptor, vitamin D receptor (VDR), which interacts with the active form of vitamin D, 1,25-dihydroxyvitamin D_3, *in vivo*, in addition to the classic role of VDR in the regulation of calcium and phosphate metabolism (15). VDR is also present in islet β cells. As vitamin D affects insulin secretion and function by acting on the VDR of β cells, it has become a novel hotspot of diabetes research. Numerous studies have confirmed that vitamin D is associated with diabetes in patients that are not pregnant, and further investigation to determine its mechanism of action has been conducted (16,17).

The present study evaluated the effect of different doses of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation and the oxidative stress levels of pregnant women with GDM, in order to assess whether vitamin D may improve the treatment of GDM.

Patients and methods

Participants. In the present randomized, double-blind, controlled clinical trial, 283 pregnant women were recruited from the Obstetrics and Gynecology Hospital of Fudan University (Shanghai, China), between September 2009 and November 2014 (Fig. 1). The exclusion criteria included women with: Diabetes or GDM treated with insulin, thyroid or parathyroid disorders, polycystic ovary disease prior to pregnancy, a body mass index (BMI) of >30 kg/m^2 prior to pregnancy and women who had received vitamin D supplementation in the 6 months that preceded the trial. In addition, a GDM diagnosis of <12 weeks was required for eligibility. To detect a minimum of 7 ng/ml difference in the mean of vitamin D between groups with 80% power, a standard deviation of 10.5 was assumed, as determined in previous studies (18,19), and α=0.05 was used. The present study therefore aimed to recruit 133 patients to allow for a 10% dropout throughout the duration of the study.

Study design. All patients provided written informed consent for participation in the present study, which was approved by the Institutional Ethics Committee [approval no. (2009)21]. During the initial antenatal visit between 24 and 28 weeks of pregnancy, a blood sample was obtained to measure fasting blood sugar (FBS), insulin, 25-hydroxyvitamin D [25(OH)D] and calcium levels. The patients (n=133) were then randomly divided into four groups (Fig. 1). Computer-generated random number lists were produced by an independent researcher. Patients and researchers were blind to treatment assignment. All dosing was performed via the oral route. The control group (n=20) received a placebo (sucrose; one granule/day), the low dosage group (n=38) received the daily recommended intake of 200 IU vitamin D (calciferol; Costco Wholesale Corporation, Issaquah, WA, USA) daily, the medium dosage group (n=38) received 50,000 IU monthly (2,000 IU daily for 25 days) and the high dosage group (n=37) received 50,000 IU every 2 weeks (4,000 IU daily for 12.5 days). Supplementation commenced at 24-28 weeks of pregnancy and continued until delivery. Patients received a follow-up examination every month during pregnancy and were evaluated for indications of adverse effects to vitamin D, including headaches and vomiting. A blood sample for the measurement of fasting plasma glucose (FPG), insulin, vitamin D and calcium levels was retrieved from each participant at the end of pregnancy.

Assessment of variables. Height and prepregnancy weight were obtained from the records of the patients that existed within the clinic. A midwife at the maternity clinic performed anthropometric measurements at the study baseline and 9 weeks subsequent to the intervention. The height of patients was measured to the nearest 0.1 cm with a nonstretched tape measure (Seca GmbH & Co. KG, Hamburg, Germany). The body weight of pregnant women was measured to the nearest 0.1 kg following overnight fasting and wearing minimal clothing, by the use of a digital scale (Seca GmbH & Co. KG). BMI was determined as weight (kg) / height (m^2). Venous blood samples were harvested and immediately centrifuged at 10,000 x g for 15 min (Wuxi Ruijiang Analysis Instrument Co., Ltd., Wuxi, China) to separate the serum. Serum samples were then stored at -80˚C prior to analysis.

Serum 25(OH)D concentrations were assayed using a commercial ELISA kit (H191; Jiancheng Bioengineering Institute, Nanjing, China). Vitamin D sufficiency was defined as >30 ng/ml 25(OH)D, insufficiency as 25(OH)D levels of 20-30 ng/ml and deficiency as serum 25(OH)D levels of <20 ng/ml. Serum calcium (C004-2), phosphorus, (C006) magnesium (C005), zinc (E011; all Jiancheng Bioengineering Institute) and selenium (E-EL-H2065c; Elabscience Bioengineering Co., Ltd., Wuhan, China) concentrations were also assayed using commercial ELISA kits. FPG (R057), serum insulin (H203), insulin resistance (R056) [as determined by homeostatic model assessment-insulin resistance (HOMA-IR)], total cholesterol change (F002-1), triglyceride levels (A110-1), high-sensitivity C-reactive protein (hs-CRP; E024), plasma total antioxidant capacity (TAC; A015) and glutathione (GSH; A005) changes were measured with commercial ELISA kits purchased from Beyotime Institute of Biotechnology (Haimen, China).

Statistical analysis. To ensure the normal distribution of variables, the Kolmogorov-Smirnov test was applied. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as means ± standard deviation (SD). Non-parametric tests were employed to compare the groups, and to compare baseline and endpoint measurements. For comparisons within groups, the Wilcoxon test was used. P<0.05 was considered to indicate a statistically significant difference.

Results

General characteristics of pregnant women with GDM. In the present randomized controlled trial, 37 cases from the

Table I. General characteristics of patients with GDM.

Characteristic	Control (n=20)	Low dosage (n=38)	Medium dosage (n=38)	High dosage (n=37)	P-value
Age, year	29.8±4.7	30.3±5.1	29.4±4.9	30.1±4.5	0.87
Height, cm	160.1±5.1	158±5.7	157.8±6.6	159.1±5.1	0.62
Prepregnancy weight, kg	70.5±9.4	69.1±8.9	69.7±8.8	70.1±9.2	0.71
Weight at study baseline, kg	79.1±10.1	79.6±10.6	78.2±9.9	78.8±12.1	0.76
Weight at end of trial, kg	81.8±11.8	81.1±11.2	80.4±12.5	80.9±10.3	0.87
Prepregnancy BMI, kg/m^2	27.1±3.6	27.4±4.6	26.9±4.1	27.2±4.3	0.89
BMI at study baseline, kg/m^2	31.1±3.9	30.6±4.1	31.1± 3.9	30.6±4.1	0.63
BMI at end of trial, kg/m^2	32.3±4.3	31.1±5.2	32.8±3.8	31.8±4.4	0.87

GDM, gestational diabetes mellitus; BMI, body mass index.

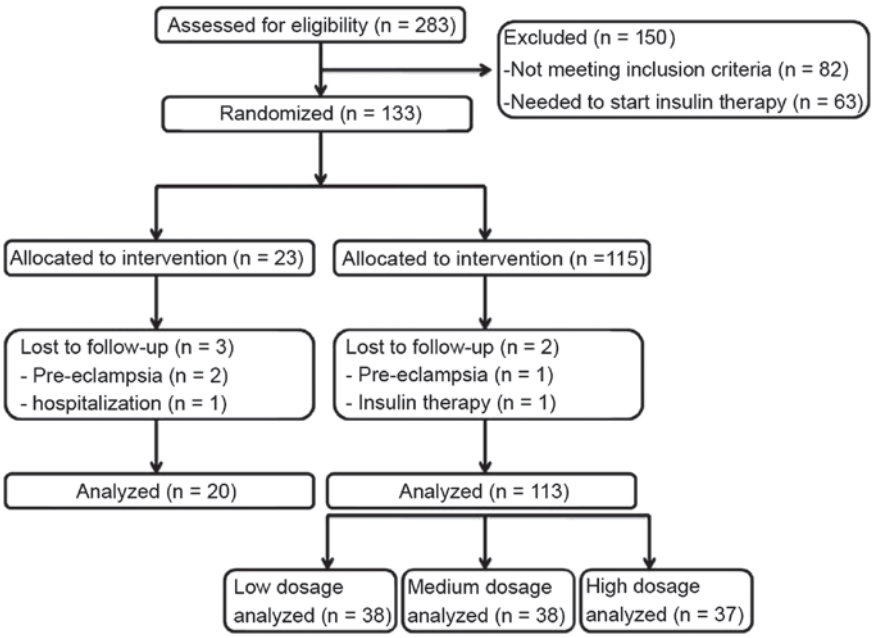

Figure 1. Flow diagram summarizing patient progress through the trial.

high dosage group, 38 cases from the medium dosage group, 38 cases from the low dosage group and 20 pregnant women from the control group completed participation (Fig. 1). Table I displays the general characteristics of the pregnant female patients with GDM in each of the groups prior to intervention. In the control group, the mean age ± SD was 29.8±4.7 years, the mean height ± SD was 160.1±5.1 cm, the mean prepregnancy weight ± SD was 70.5±9.4 kg and the mean prepregnancy BMI ± SD was 27.1±3.6 kg/m^2. Prior to intervention, the mean age, height, FBS, prepregnancy weight and prepregnancy BMI were not significantly different between the three groups (P>0.05).

Dietary intakes of pregnant women with GDM. Dietary intakes of patients with GDM are displayed in Table II, as determined by ELISA of serum blood samples. The mean energy, carbohydrate, protein, dietary fiber, vitamin D, calcium, phosphorus, magnesium, zinc and selenium levels in the control group were similar to those in each of the treatment groups (P>0.05).

High and medium doses of vitamin D supplementation reduces insulin and HOMA-IR levels in patients with GDM. Fig. 2 revealed that FPG levels were not significantly affected by any of the low, medium and high vitamin D supplementation groups (96.12, 88.59 and 84.73 mg/dl, respectively), as compared with the control group (92.49 mg/dl) (Fig. 2A; P>0.05). Conversely, as compared with the control group, the high and medium vitamin D supplementation groups effectually reduced insulin (Fig. 2B; 9.21 vs. 5.01 and 4.2 IU/ml, respectively) and HOMA-IR (Fig. 2C; 2.87 vs. 1.52 and 1.18, respectively) concentration levels in patients with GDM (P<0.01).

High and medium doses of vitamin D supplementation decreases total cholesterol in patients with GDMs. Fig. 3A revealed that the medium and high vitamin D supplementation

Table II. Dietary intakes of pregnant women with GDM.

Dietary intake	Control (n=20)	Low dosage (n=38)	Medium dosage (n=38)	High dosage (n=37)	P-value
Energy, kcal/day	2,411±189	2,392±211	2,388±198	2,396±192	0.75
Carbohydrate, g/day	329±51	338±44	333±48	335±46	0.82
Protein, g/day	84±17	86±16	81±19	83±18	0.36
Dietary fiber, g/day	19.5±4.6	20.1±4.6	19.7±4.4	20.7±4.1	0.24
Vitamin D, mg/day	2.9±0.5	2.8±0.9	2.9±0.6	2.8±0.7	0.37
Calcium, g/day	1.15±0.17	1.15±0.14	1.15±0.16	1.15±0.15	0.91
Phosphorus, g/day	1.18±0.22	1.22±0.12	1.20±0.16	1.19±0.19	0.76
Magnesium, mg/day	296±73	294±66	292±71	291±69	0.66
Zinc, mg/day	9.3±2.7	9.0±2.4	9.1±2.1	8.9±2.7	0.79
Selenium, mg/day	118±31.9	116±29.5	123±29.1	121±28.9	0.39

GDM, gestational diabetes mellitus.

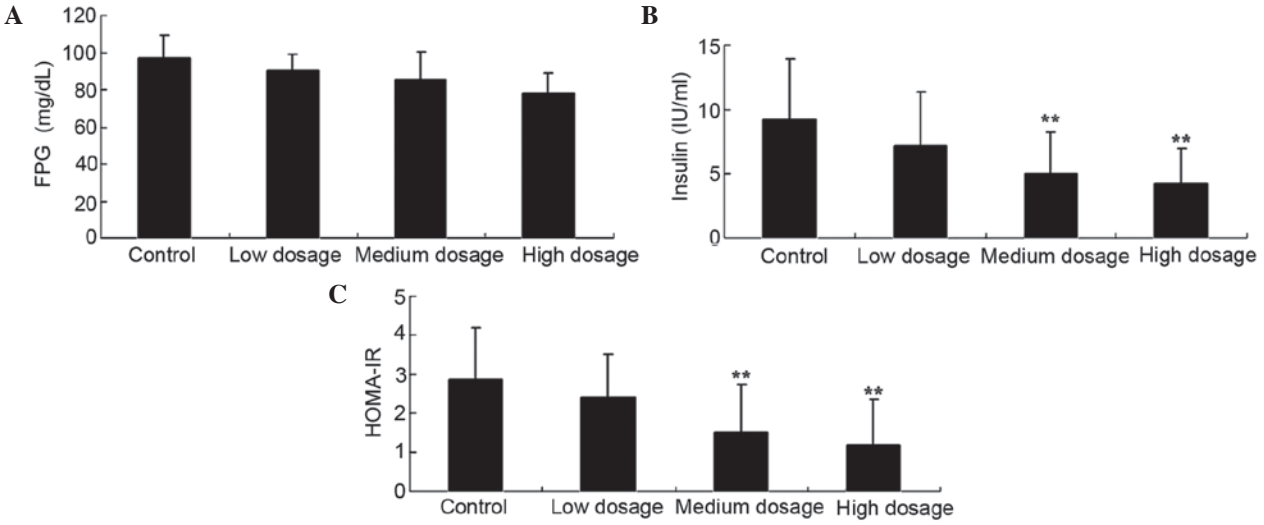

Figure 2. Effect of different doses of vitamin D supplementation on (A) FPG (B) insulin and (C) HOMA-IR in patients with gestational diabetes mellitus. Data are presented as mean ± standard deviation. **P<0.01 vs. control group. FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment-insulin resistance.

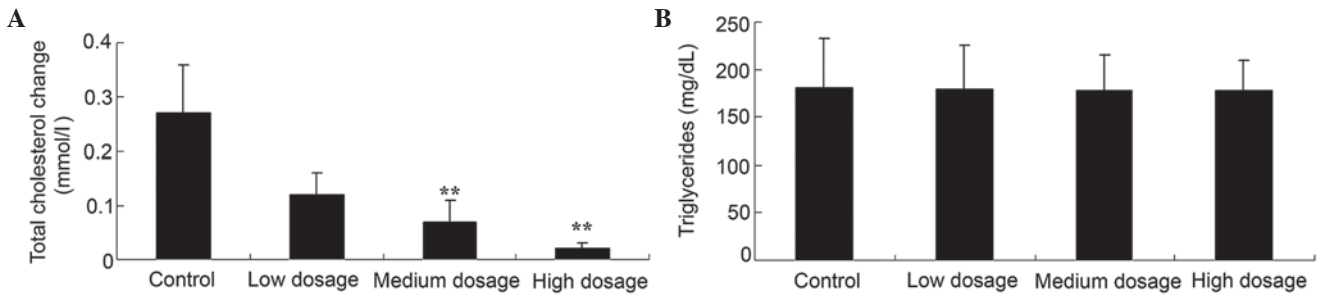

Figure 3. Effect of different doses of vitamin D supplementation on lipid concentrations, including (A) total cholesterol change and (B) triglyceride levels, in patients with gestational diabetes mellitus. Data are presented as mean ± standard deviation. **P<0.01 vs. control group.

groups displayed significantly decreased total cholesterol change in pregnant women with GDM, as compared with the control (0.07 and 0.02 vs. 0.27 mmol/l; P<0.01). By contrast, the levels of triglycerides in the low, medium and high vitamin D dosage groups (179, 178 and 178 mg/dl, respectively) were not significantly different, as compared with the control group (180 mg/dl) (Fig. 3B; P>0.05).

Vitamin D supplementation does not reduce inflammation in patients with GDM. Fig. 4 revealed that low, medium and

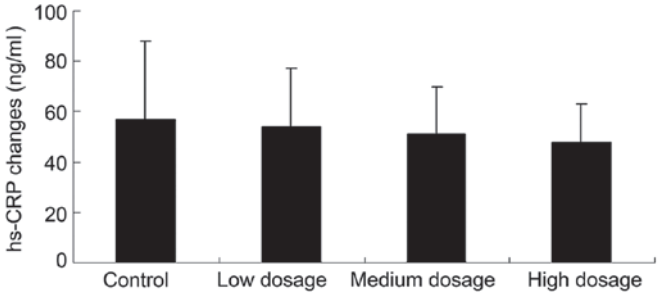

Figure 4. Effect of different doses of vitamin D supplementation on inflammation, as measured by hs-CRP concentration, in patients with gestational diabetes mellitus. Data are presented as mean ± standard deviation. hs-CRP, high-sensitivity c-reactive protein.

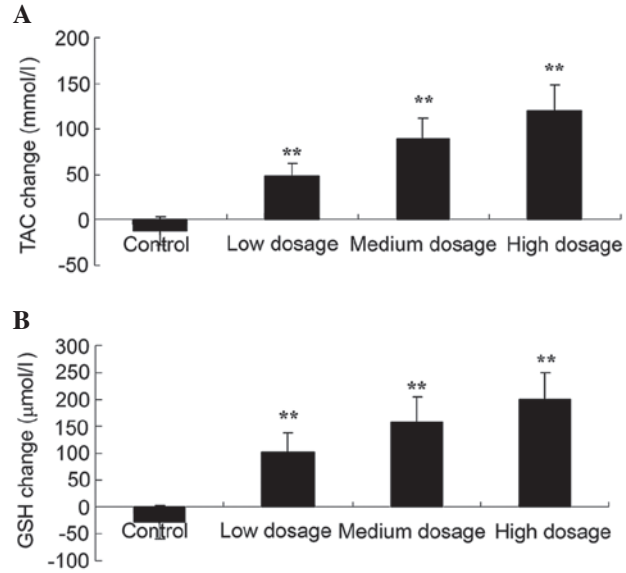

Figure 5. Effect of different doses of vitamin D supplementation on oxidative stress, as assessed by (A) TAC and (B) GSH levels, in patients with gestational diabetes mellitus. Data are presented as mean ± standard deviation. **P<0.01 vs. control group. TAC, total antioxidant capacity; GSH, total glutathione.

high dose vitamin D supplementation (54, 51 and 48 ng/ml, respectively) does not significantly reduce the hs-CRP levels of patients with GDM, as compared with the control group (57 ng/ml; P>0.05).

Vitamin D supplementation increases TAC and total GSH in patients with GDM. Fig. 5 revealed that high, medium and low doses of vitamin D supplementation all significantly increased TAC (120, 89 and 49 mmol/l, respectively; Fig. 5A) and total GSH (199, 158 and 102 μmol/l, respectively; Fig. 5B) levels in patients with GDM, as compared with the control groups (12 mmol/l and -28 μmol/l, respectively; P<0.01).

Discussion

Medical nutrition therapy (MNT) is the foundation of treating diabetes and is an essential measure for the prevention of phase and control phase in the natural course of diabetes. In 2002, the American Diabetes Association (ADA) proposed the evidence-based diabetes nutrition supply standard and and established a classification standard for scientific evidence (20). ADA indicated that patients with GDM who adhered to personalized nutrition therapy from a registered dietitian were more likely to achieve treatment goals. The pathophysiological features of GDM are unique and require close management; if poorly managed, maternal hypoglycemia, ketoacidosis and high blood sugar, in addition to other complications, may occur (21). The high blood sugar levels often observed in patients with GDM can lead to fetal hyperglycemia, while GDM-induced hyperosmolarity is typically treated with diuretics, resulting in increased urination; consequently, sugar levels are high in the amniotic fluid, which in turn stimulates the secretion of amniotic membrane and may eventually lead to excessive amniotic fluid (22). Additionally, hyperglycemia stimulates fetal insulin secretion. Excessive insulin levels may reduce fetus alveolar surface material, resulting in delayed fetal lung maturity and therefore increasing the incidence of neonatal respiratory distress syndrome (23). Furthermore, hyperinsulinemia persists in the newborn following birth and removal from the environment of the mother's hyperglycemia; thus, the newborn is prone to neonatal hypoglycemia (24). The present study involved a randomized, double-blind, placebo-controlled clinical trial conducted on 133 patients with a GDM diagnosis of <12 weeks. The general characteristics and dietary intakes of patients with GDM in each group of the trial were similar, which demonstrated that these patient charcteristics did not differ prior to intervention.

In pregnant women with elevated blood sugar levels, fetuses may experience fetal hyperglycemia, leading to fetal islet cell proliferation, increased insulin secretion and promotion of the synthesis of protein and fat, in addition to the inhibition of lipolysis, thus leading to the occurrence of fetal macrosomia (25). GDM insulin resistance and hyperinsulinemia may cause microvascular disease, resulting in the thickening of the basement membrane in capillary walls. This also contributes to the occurrence of maternal hypertensive disorders in pregnancy (26). In the present study, patients in the groups receiving high and medium doses of vitamin D supplementation were observed to display reduced insulin, HOMA-IR and total cholesterol levels. These results demonstrated that high-dose vitamin D supplementation significantly improved insulin resistance in pregnant women with GDM. However, the levels of FPG and triglycerides exhibited no significant differences in the groups receiving vitamin D supplementation compared with the control group. Senti *et al* reported that vitamin D supplementation was a potential target for patients with GDM (27). Yap *et al* also revealed that the effect of vitamin D supplementation (5,000 IU per day) prevented glucose metabolism during pregnancy (28).

Diabetes is a vascular disease, as well as a disease of hyperglycemia. In addition, diabetes may also be an inflammatory disease (29). Inflammation, immune system activation and the corresponding metabolic changes in an organism are subject to the regulation of the nervous and endocrine systems, which affect organism function through feedback pathways, forming complex nerve-endocrine-immune system networks (30). GDM and obesity involve insulin resistance as a common feature in their disease pathogenesis. A variety of inflammatory cytokines generated by the activation of the immune

system, including tumor necrosis factor-α, interleukin-6 and CRP, can induce insulin resistance (31). In the present study, hs-CRP levels in patients with GDM were not affected by high dosage vitamin D supplementation. Similarly, Asemi *et al* revealed that vitamin D supplementation does not affect inflammation in pregnant women with GDM (17,32).

The oxidative stress imbalance involves excessive oxidative generation and inadequate levels of antioxidants. It has been revealed that oxidative stress imbalance is important in the pathophysiological processes involved in vascular diseases, including diabetes, hypertension and atherosclerosis (33). An oxidative stress imbalance is also present in GDM patients and can cause vascular injury and adverse pregnancy events. Multiple adverse pregnancy outcomes are associated with GDM, including fetal growth restriction, preterm birth, hypertensive disorders of pregnancy, stillbirth and miscarriage, all of which are associated with abnormal placental circulation (34). The present study demonstrated that high, medium and low dosages of vitamin D supplementation resulted in dose-dependent increases in total TAC and GSH levels in patients with GDM, which suggested that high-dose vitamin D supplementation provided the greatest anti-oxidation effects. Asemi *et al* previously presented data in support of this, revealing that vitamin D supplementation significantly increased malondialdehyde and GSH levels (35).

In conclusion, high-dose vitamin D supplementation (50,000 IU) every 2 weeks significantly decreased levels of insulin resistance in pregnant women with GDM. However, it did not affect FPG, triglyceride or inflammation levels. The results of the present study suggest that high-dose vitamin D supplementation (50,000 IU every 2 weeks) is recommended for pregnant women with GDM from the 12th week of pregnancy until delivery.

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