Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: a double-blind randomized controlled clinical trial1–3

Zatollah Asemi, Teibeh Hashemi, Maryam Karamali, Mansooreh Samimi, and Ahmad Esmaillzadeh

ABSTRACT

Background: To our knowledge, there is no study that has examined the effects of vitamin D supplementation on metabolic status in gestational diabetes mellitus (GDM).

Objective: This study was designed to assess the effects of vitamin D supplementation on metabolic profiles, high-sensitivity C-reactive protein, and biomarkers of oxidative stress in pregnant women with GDM.

Design: This randomized, double-blind, placebo-controlled clinical trial was conducted in 54 women with GDM. Subjects were randomly assigned to receive either vitamin D supplements or placebo. Individuals in the vitamin D group (n = 27) received capsules containing 50,000 IU vitamin D3 2 times during the study (at baseline and at day 21 of the intervention) and those in the placebo group (n = 27) received 2 placebos at the same times. Fasting blood samples were collected at baseline and after 6 wk of the intervention to quantify relevant variables.

Results: Cholecalciferol supplementation resulted in increased serum 25-hydroxyvitamin D concentrations compared with placebo (±18.5 ± 20.4 compared with ±0.5 ± 6.1 ng/mL; P < 0.001). Furthermore, intake of vitamin D supplements led to a significant increase in concentrations of fasting plasma glucose (−17.1 ± 14.8 compared with −0.9 ± 16.6 mg/dL; P < 0.001) and serum insulin (−3.08 ± 6.62 compared with +1.34 ± 6.51 μIU/mL; P = 0.01) and homeostasis model of assessment-insulin resistance (−1.28 ± 1.41 compared with +0.34 ± 1.79; P < 0.001) and a significant increase in the Quantitative Insulin Sensitivity Check Index (+0.03 ± 0.03 compared with −0.001 ± 0.02; P = 0.003) compared with placebo. A significant reduction in concentrations of total (−11.0 ± 23.5 compared with +9.5 ± 36.5 mg/dL; P = 0.01) and low-density lipoprotein (LDL) cholesterol (−10.8 ± 22.4 compared with +10.4 ± 28.0 mg/dL; P = 0.003) was also seen after vitamin D supplementation.

Conclusions: Vitamin D supplementation in pregnant women with GDM had beneficial effects on glycemia and total and LDL-cholesterol concentrations but did not affect inflammation and oxidative stress. This trial was registered at www.irct.ir as IRCT201305115623N7. Am J Clin Nutr 2013;98:1425–32.

INTRODUCTION

Gestational diabetes mellitus (GDM)1 is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. This definition applies whether or not insulin is used for treatment (1). It affects 2–13% of all pregnancies depending on the population screened and the diagnostic criteria (2). This condition affects 4.7% of pregnant women in Iran (3). It is associated with serious adverse maternal outcomes including preeclampsia, higher rates of cesarean section, and increased long-term risk of developing metabolic syndrome and type 2 diabetes mellitus (4). Furthermore, GDM patients have abnormal fetal outcomes such as macrosomia, which is related to shoulder dystocia and newborn asphyxia, infant respiratory distress syndrome, and neonatal hypoglycemia (5).

Various factors, especially severe obesity during pregnancy, strong family history of type 2 diabetes (6), and recent vitamin D deficiency (7), are reported as contributors to increased risk of GDM. Because of rapid fetal development, particularly bone calcification at the end of pregnancy (8), vitamin D deficiency may occur in pregnant women. The prevalence of vitamin D deficiency in pregnant women varies from 18% to 84%, depending on the region and type of clothing (10). Available research indicates that vitamin D might help in maintaining normal glucose homeostasis (11, 12). A few studies have also shown that vitamin D supplementation might improve metabolic profiles, inflammation, and biomarkers of oxidative stress in patients without GDM (13–15). Furthermore, insulin resistance in animal models as well as in humans has been related to...
vitamin D deficiency. This relation is explained by the specific receptors of vitamin D in pancreatic β cells (16). Vitamin D supplementation might influence metabolic profiles of GDM patients because of its effect on apolipoprotein gene expression (17) and parathyroid hormone suppression (18). However, no information is available examining the effect of vitamin D supplementation on the metabolic status of patients with GDM. In an 8-wk clinical trial, vitamin D supplementation (50,000 IU/wk) resulted in a significant decrease in serum insulin concentrations and HOMA-IR in type 2 diabetic patients (19). However, daily intake of 7000 IU vitamin D for 26 wk in obese adults with vitamin D deficiency did not affect HOMA-IR, plasma lipid profiles, or inflammatory biomarkers (20). Other studies have also reached conflicting results. We are aware of no study that has examined the effect of vitamin D supplementation on metabolic profiles, systemic inflammation, and biomarkers of oxidative stress in GDM. The current study was therefore performed to investigate the effects of vitamin D on the metabolic status of pregnant women with GDM.

SUBJECTS AND METHODS

Participants

This randomized, double-blind, placebo-controlled clinical trial was conducted in Kashan, Iran, during January 2013 to April 2013. On the basis of the sample size formula suggested for randomized clinical trials, considering a type I error of 5% (a = 0.05) and type II error of 20% (β = 0.20, power = 80%) and serum vitamin D concentration as a key variable (21), we determined a sample size of 24 persons for each group. Pregnant women aged 18–40 y diagnosed with GDM by a 100-g oral-glucose-tolerance test at 24–28 wk gestation were recruited into this study. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment (22). Pregnant women without a previous diagnosis of glucose intolerance were screened for GDM by 2 procedures. First, a 50-g glucose challenge test was used as preliminary screening. Individuals with 1-h plasma glucose concentrations >140 mg/dL were then asked to participate in a 100-g oral-glucose-tolerance test. Diagnosis of GDM was based on the criteria set by the American Diabetes Association (23): those individuals whose plasma glucose met ≥2 of the following criteria were considered to have GDM: fasting, >95 mg/dL; 1 h, ≥180 mg/dL; 2 h, ≥155 mg/dL; and 3 h, ≥140 mg/dL. A total of 960 pregnant women attending maternity clinics affiliated with Kashan University of Medical Sciences, Kashan, Iran, were screened for GDM. A total of 54 pregnant women met the inclusion criteria (896 women were excluded because of not meeting GDM class A2, which required insulin therapy). We found that the amount of cholecalciferol in the prescribed capsules was in the range of 47,500–52,500 IU/capsule. Participants were asked not to alter their routine physical activity or usual dietary intakes throughout the study and not to consume any supplements other than the one provided to them by the investigators. All subjects also consumed 400 µg folic acid/d from the beginning of pregnancy and 60 mg ferrous sulfate/d from the second trimester. Dietary intakes of participants throughout intervention were assessed by means of 3-d dietary records. The dietary records were based on estimated values in household measurements. To obtain nutrient intakes of participants on the basis of these 3-d food diaries, we used Nutritionist IV software (First Databank) modified for Iranian foods.

Assessment of variables

Data on prepregnancy weight and height (measured values) were taken from the clinic records of the pregnant women. A trained midwife at the maternity clinic performed anthropometric measurements at study baseline and at 6 wk after the intervention. Body weight was measured to the nearest 0.1 kg after overnight fasting, without shoes and wearing minimal clothing, by the use of a digital scale (Seca). Height was measured to the nearest 0.1 cm by using a nonstretched tape measure (Seca). BMI was calculated as weight in kilograms divided by height in meters squared. Blood samples (10 mL) were collected at baseline and after the 6-wk intervention in the early morning after an overnight fast. Blood samples were immediately centrifuged (Hettich D-78532; Hettich GmbH) at 3500 rpm for 10 min to separate serum. Samples were then stored at −70°C before analysis at the Kashan University of Medical Sciences reference laboratory. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were assayed by using a commercial ELISA kit (Immuno Diagnostic Systems). The inter- and intraassay CVs for serum 25(OH)D assays ranged from 5% to 7.5%. Commercial kits
were used to measure fasting plasma glucose (FPG), serum calcium, cholesterol, triglyceride, and LDL- and HDL-cholesterol concentrations (Pars Azmun). The intra- and interassay CVs for FPG were 2.0% and 3.5%, respectively. All inter- and intraassay CVs for lipid profile measurements were <5%. Serum insulin was assayed by using an ELISA kit (DiaMetra). The intra- and interassay CVs for serum insulin were 2.9% and 5.9%, respectively. HOMA-IR and β cell function (HOMA-B) and quantitative insulin sensitivity check index (QUICKI) were calculated on the basis of suggested formulas (24). Serum high-sensitivity C-reactive protein (hs-CRP) was quantified by using an ELISA kit (Labor Diagnostika Nord) with intra- and interassay CVs of 2.5% and 3.8%, respectively. Plasma total antioxidant capacity (TAC) was assessed by the use of the ferric reducing antioxidant power method developed by Benzie and Strain (25). The plasma total glutathione (GSH) was measured by the method of Beutler and Gelbart (26). Measurements of vitamin D, glucose, lipids, insulin, hs-CRP, TAC, GSH, and calcium were performed in a blinded fashion in duplicate, in pairs (before and after the intervention) at the same time, in the same analytic run, and in random order to reduce systematic error and interassay variability.

Statistical analysis

We used the Kolmogrov-Smirnov test to examine the normal distribution of variables. Log transformation was conducted for nonnormally distributed variables. The analyses were performed on the basis of an intention-to-treat approach. Missing values were treated according to the last-observation-carried-forward method. Independent-samples Student’s t test was used to detect differences in general characteristics and dietary intakes between the 2 groups. To determine the effects of vitamin D supplementation on glucose metabolism, lipid profiles, serum hs-CRP, and biomarkers of oxidative stress, we used 1-factor repeated-measures ANOVA. In this analysis, the treatment (vitamin D compared with placebo) was regarded as the between-subjects factor and time with 2 time points (baseline and week 6 of the intervention) was considered as the within-subjects factor. To assess if the magnitude of the change depended on the baseline value, we conditioned all analyses on baseline values to avoid the potential bias that might have resulted. These adjustments were performed by using ANCOVA. P < 0.05 was considered significant. All statistical analyses were conducted by using the SPSS, version 17 (SPSS Inc).

RESULTS

Three women in the vitamin D group were excluded due to intrauterine fetal death (n = 1), placenta abruption (n = 1), and hospitalization (n = 1). Three women in the placebo group were also excluded for the following reasons: hospitalization (n = 1), insulin therapy (n = 1), and severe preeclampsia (n = 1). A total of 48 participants [vitamin D (n = 24) and placebo (n = 24)] completed the trial (Figure 1). However, the statistical analyses were performed on the original 54 participants on the basis of an intention-to-treat approach, and missing values for these 6 excluded participants were determined on the basis of the last-observation-carried-forward method. On average, the rate of compliance in our study was high, such that 100% of capsules were taken throughout the study in both groups.

Mean (±SD) age, prepregnancy weight, and BMI of study participants were 31.5 ± 6.1 y, 70.6 ± 10.7 kg, and 27.7 ± 4.1, respectively. Baseline and end-of-trial means of weight and BMI were not significantly different between vitamin D and placebo groups (Table 1).

On the basis of the 3-d dietary records obtained throughout the intervention, no significant differences were seen between

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**FIGURE 1.** Summary of patient flow. Individuals in the vitamin D group received capsules containing 50,000 IU vitamin D₃ 2 times during the study at baseline and at day 21 of the intervention; those in the placebo group received 2 placebo capsules at the same times. IUFD, intrauterine fetal death.
DISCUSSION

The 2 groups in terms of dietary intakes of energy, carbohydrate, protein, fat, SFAs, PUFAs, MUFAs, cholesterol, dietary fiber, magnesium, calcium, vitamin D, vitamin C, or selenium (Table 2).

Baseline values of calcium, FPG, HOMA-IR, QUICKI, TAC, and GSH were significantly different between the 2 groups. Cholecalciferol supplementation resulted in increased serum 25(OH)D concentrations compared with placebo (+18.5 ± 20.4 compared with +0.5 ± 6.1 ng/mL; P < 0.001; Table 3). Furthermore, intake of vitamin D supplements led to a significant decrease in FPG (−17.1 ± 14.8 compared with −0.9 ± 16.6 mg/dL; P < 0.001), serum insulin concentration (−3.08 ± 6.62 compared with +1.34 ± 6.51 μIU/mL; P = 0.01), and HOMA-IR (−1.28 ± 1.41 compared with +0.34 ± 1.79; P < 0.001) and a significant increase in QUICKI (+0.03 ± 0.03 compared with −0.001 ± 0.02; P = 0.003) compared with placebo. A significant reduction in concentrations of total (−11.0 ± 23.5 compared with +9.5 ± 36.5 mg/dL; P = 0.01) and LDL (−10.8 ± 22.4 compared with +10.4 ± 28.0 mg/dL; P = 0.003) cholesterol was also seen after vitamin D supplementation. We did not find any significant effect of vitamin D supplementation on serum calcium, triglycerides, HDL cholesterol, hs-CRP, plasma TAC, and total GSH. When the analyses were adjusted for baseline values, no significant changes in our findings were observed, except for FPG (P = 0.09) and serum calcium (P = 0.03) concentrations (Table 4).

**TABLE 2**

| General characteristics of pregnant women with GDM who received either vitamin D supplements or placebo1 |
|---------------------|---------------------|---------------------|
| Maternal age (y)    | 31.8 ± 6.6          | 31.7 ± 5.6          | 0.96 |
| Height (cm)         | 159.4 ± 4.2         | 160.7 ± 6.8         | 0.41 |
| Prepregnancy weight (kg)2 | 70.3 ± 11.8         | 70.6 ± 8.7          | 0.89 |
| Weight at study baseline (kg) | 78.3 ± 13.4 | 79.3 ± 9.5 | 0.74 |
| Weight at end of trial (kg) | 80.2 ± 13.1         | 80.8 ± 9.6          | 0.84 |
| Prepregnancy BMI (kg/m²)2 | 27.6 ± 4.1          | 27.5 ± 4.0          | 0.92 |
| BMI at study baseline (kg/m²) | 30.7 ± 4.5          | 30.9 ± 4.5          | 0.89 |
| BMI at end-of-trial (kg/m²) | 31.5 ± 4.5          | 31.4 ± 4.6          | 0.99 |

1 All values are means ± SDs. GDM, gestational diabetes mellitus.
2 Received placebo 2 times during the study: at baseline and at day 21 of the intervention.
3 Received 50,000 IU vitamin D3 2 times during the study: at baseline and at day 21 of the intervention.
4 Obtained from independent-samples t test.
5 Based on participants’ measured weight and height from maternity clinic records.

**TABLE 3**

| Dietary intake of pregnant women with GDM who received either vitamin D supplements or placebo throughout the study1 |
|---------------------|---------------------|---------------------|
| Placebo group2 (n = 27) | Vitamin D group2 (n = 27) | P value4 |
| Energy (kcal/d)      | 2409 ± 188          | 2384 ± 322          | 0.72 |
| Carbohydrate (g/d)   | 335.1 ± 38.1        | 337.0 ± 60.3        | 0.88 |
| Protein (g/d)        | 89.3 ± 14.2         | 85.0 ± 13.5         | 0.24 |
| Fat (g/d)            | 86.2 ± 11.7         | 80.8 ± 14.8         | 0.13 |
| SFAs (g/d)           | 25.7 ± 4.9          | 25.7 ± 6.0          | 0.97 |
| PUFAs (g/d)          | 26.1 ± 7.2          | 24.6 ± 5.8          | 0.37 |
| MUFAs (g/d)          | 24.2 ± 5.9          | 23.4 ± 7.0          | 0.65 |
| Cholesterol (mg/d)   | 216.5 ± 116.6       | 181.4 ± 63.3        | 0.17 |
| Dietary fiber (g/d)  | 18.9 ± 4.5          | 20.5 ± 5.0          | 0.20 |
| Magnesium (mg/d)     | 293.8 ± 66.0        | 289.9 ± 68.9        | 0.83 |
| Calcium (mg/d)       | 1153.4 ± 198.5      | 1152.8 ± 198.8      | 0.97 |
| Vitamin D (μg/d)     | 3.0 ± 1.0           | 2.7 ± 0.7           | 0.30 |
| Vitamin C (mg/d)     | 175.6 ± 97.7        | 203.9 ± 80.5        | 0.24 |
| Selenium (μg/d)      | 121.2 ± 32.1        | 112.3 ± 31.8        | 0.30 |

1 All values are means ± SDs. GDM, gestational diabetes mellitus.
2 Received placebo 2 times during the study: at baseline and at day 21 of the intervention.
3 Received 50,000 IU vitamin D3 2 times during the study: at baseline and at day 21 of the intervention.
4 Obtained from independent-samples t test.
TABLE 3
Metabolic profiles, hs-CRP, and biomarkers of oxidative stress at study baseline and 6 wk after the intervention in pregnant women with GDM who received either vitamin D supplements or placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 27)</th>
<th>Vitamin D group (n = 27)</th>
<th>Change</th>
<th>Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 6</td>
<td></td>
<td>Week 0</td>
<td>Week 6</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>20.41 ± 13.43</td>
<td>20.92 ± 13.79</td>
<td>0.51 ± 6.16</td>
<td>20.44 ± 14.31</td>
<td>38.95 ± 24.72*</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.90 ± 1.32</td>
<td>7.82 ± 1.61</td>
<td>−0.08 ± 1.34</td>
<td>8.65 ± 1.02</td>
<td>8.97 ± 0.88</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>71.70 ± 17.09</td>
<td>70.74 ± 21.53</td>
<td>−0.96 ± 16.64</td>
<td>95.49 ± 13.71</td>
<td>78.37 ± 15.27*</td>
</tr>
<tr>
<td>Insulin (µIU/mL)</td>
<td>14.68 ± 8.60</td>
<td>16.02 ± 11.11</td>
<td>1.34 ± 6.51</td>
<td>15.90 ± 8.41</td>
<td>12.82 ± 8.54*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.58 ± 1.58</td>
<td>2.92 ± 2.61</td>
<td>0.34 ± 1.79</td>
<td>3.76 ± 2.04</td>
<td>2.48 ± 1.75*</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>73.83 ± 46.77</td>
<td>83.18 ± 62.17</td>
<td>9.35 ± 44.95</td>
<td>57.06 ± 32.07</td>
<td>57.30 ± 40.33</td>
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<tr>
<td>QUICKI</td>
<td>0.34 ± 0.03</td>
<td>0.34 ± 0.05</td>
<td>0.001 ± 0.02</td>
<td>0.32 ± 0.02</td>
<td>0.35 ± 0.04*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>194.23 ± 49.18</td>
<td>203.73 ± 60.24</td>
<td>9.50 ± 36.55</td>
<td>211.35 ± 43.22</td>
<td>200.31 ± 41.63*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>182.26 ± 60.94</td>
<td>179.82 ± 61.67</td>
<td>−2.44 ± 55.82</td>
<td>187.59 ± 66.26</td>
<td>178.81 ± 64.86</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>105.78 ± 33.01</td>
<td>116.23 ± 41.83</td>
<td>10.45 ± 28.01</td>
<td>121.84 ± 36.37</td>
<td>111.00 ± 38.54*</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>51.99 ± 19.35</td>
<td>51.52 ± 19.35</td>
<td>−0.47 ± 9.33</td>
<td>51.99 ± 10.38</td>
<td>53.54 ± 11.21</td>
</tr>
<tr>
<td>Total:HDL-cholesterol ratio</td>
<td>3.88 ± 0.78</td>
<td>4.06 ± 0.69</td>
<td>0.18 ± 0.35</td>
<td>4.24 ± 1.07</td>
<td>4.08 ± 1.79</td>
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<tr>
<td>hs-CRP (ng/mL)</td>
<td>6017.53 ± 3727.98</td>
<td>5901.63 ± 4125.42</td>
<td>−115.90 ± 4068.72</td>
<td>8695.43 ± 5118.56</td>
<td>7420.61 ± 3906.69</td>
</tr>
<tr>
<td>TAC (mmol/L)</td>
<td>741.17 ± 208.66</td>
<td>803.94 ± 204.20</td>
<td>62.77 ± 126.33</td>
<td>871.80 ± 255.42</td>
<td>883.88 ± 349.06</td>
</tr>
<tr>
<td>GSH (µmol/L)</td>
<td>765.82 ± 401.27</td>
<td>733.25 ± 382.26</td>
<td>−32.57 ± 212.57</td>
<td>576.19 ± 218.27</td>
<td>610.25 ± 283.79</td>
</tr>
</tbody>
</table>

1 All values are means ± SDs. Baseline values of calcium, FPG, HOMA-IR, QUICKI, TAC, and GSH were significantly different between the 2 groups. *Different from week 0, P < 0.05. FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; GSH, total glutathione; HOMA-B, homeostatic model assessment–β cell function; hs-CRP, high-sensitivity C-reactive protein; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity.

2 Received placebo 2 times during the study: at baseline and at day 21 of the intervention.

3 Received 50,000 IU vitamin D3 2 times during the study: at baseline and at day 21 of the intervention.

4 Obtained from repeated-measures ANOVA.
that 1,25-dihydroxyvitamin D3 increases transcription of insulin vitamin D receptors in skeletal muscle (37) along with the fact its effect on calcium and phosphorus metabolism and through supplements along with the study duration might provide some characteristics of study participants as well as the dosage of vitamin D in vitamin D–deficient obese adults (20). The baseline contained with supplementation of 7,000 IU vitamin D/d for 26 wk supplementation with 1,000 IU vitamin D/d for 12 wk did not pregnancy until delivery (34). In contrast to our findings, some were taking 50,000 IU vitamin D3/wk for 8 wk (19) as well as in pregnant women who indicated in diabetic patients who were orally taking 50,000 IU reductions in serum total and LDL-cholesterol concentrations compared with placebo but did not influence serum triglyceride and HDL-cholesterol concentrations. Consistent with our study, a significant reduction in serum total cholesterol concentrations was seen with the intake of 4000 IU vitamin D supplements/d for 12 wk in vitamin D–deficient, HIV-infected patients (38). Vitamin D3 supplementation for 18 mo in patients with diabetes has also led to improved lipid profiles (39). However, some investigations did not find any significant effect of vitamin D supplementation on serum lipid profiles (40, 41). Improved insulin sensitivity and parathyroid hormone reduction after vitamin D intake might result in decreased lipid profiles (40). Insulin decreases biosynthesis of cholesterol via increased β-hydroxy-β-methylglutaryl coenzyme A reductase activity (42).

Findings from the current study showed that the administration of vitamin D supplements did not affect serum hs-CRP concentrations in GDM patients. In line with our study, supplementation with high doses of vitamin D (20,000–40,000 IU/wk) after 6–12 mo had no significant effect on serum hs-CRP concentrations in subjects without vitamin D deficiency (43). Similar findings have also been shown with intakes of 2500 IU vitamin D/d for 4 mo in postmenopausal women with serum 25(OH)D concentrations of >10 and <60 ng/mL (44) as well as with intakes of 4000 IU vitamin D/d for 12 wk in healthy overweight adults (45). These findings are in contrast to observational studies, in which the association between vitamin D and inflammation is well established. For instance, in a study by Eleftheriadis et al (46), an inverse association between serum 25(OH)D concentrations and concentrations of serum hs-CRP and IL-6 was reported. The same findings were observed in diabetic patients undergoing coronary angiography (47) as well

### TABLE 4

| Metabolic Variable | Placebo group ($n = 27$) | Vitamin D group ($n = 27$) | $P$ value
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>0.51 ± 2.93</td>
<td>18.50 ± 2.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>−0.19 ± 0.20</td>
<td>0.44 ± 0.20</td>
<td>0.03</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>−4.45 ± 3.45</td>
<td>−13.66 ± 3.45</td>
<td>0.09</td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>1.26 ± 1.26</td>
<td>−3.00 ± 1.26</td>
<td>0.02</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.24 ± 0.31</td>
<td>−1.19 ± 0.31</td>
<td>0.003</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>10.43 ± 7.67</td>
<td>−0.83 ± 7.67</td>
<td>0.31</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.001 ± 0.006</td>
<td>0.02 ± 0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>8.68 ± 5.96</td>
<td>−10.22 ± 5.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>−3.43 ± 5.55</td>
<td>−7.78 ± 5.55</td>
<td>0.74</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>9.67 ± 4.96</td>
<td>−10.06 ± 4.96</td>
<td>0.008</td>
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<td>HDL cholesterol (mg/dL)</td>
<td>−0.46 ± 1.81</td>
<td>1.55 ± 1.81</td>
<td>0.43</td>
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<tr>
<td>Total-HDL cholesterol ratio</td>
<td>0.16 ± 0.25</td>
<td>−0.14 ± 0.21</td>
<td>0.35</td>
</tr>
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<td>hs-CRP (ng/mL)</td>
<td>−70.12 ± 651.41</td>
<td>−689.20 ± 651.41</td>
<td>0.98</td>
</tr>
<tr>
<td>TAC (mmol/L)</td>
<td>55.13 ± 39.32</td>
<td>24.22 ± 39.32</td>
<td>0.58</td>
</tr>
<tr>
<td>GSH (μmol/L)</td>
<td>−17.47 ± 39.51</td>
<td>18.96 ± 39.51</td>
<td>0.52</td>
</tr>
</tbody>
</table>

All values are means ± SEs adjusted for baseline values. FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; GSH, total glutathione; HOMA-B, homeostatic model assessment–β cell function; hs-CRP, high-sensitivity C-reactive protein; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity.

- Received placebo 2 times during the study: at baseline and at day 21 of the intervention.
- Received 50,000 IU vitamin D3 2 times during the study: at baseline and at day 21 of the intervention.
- Obtained from ANCOVA.

gestation (<26 or ≥26 wk) and by the use of computer-generated random numbers. Therefore, the difference in FPG between the 2 groups occurred by chance. In addition, when we adjusted the analyses for baseline values, no significant changes in our findings were observed.

Although limited data are available assessing the effects of vitamin D supplementation on metabolic status in GDM patients, observational cohort studies indicated a significant inverse association of serum 25(OH)D concentrations and incident GDM (4, 31). In nonpregnant women as well as in animal models, the favorable effects of vitamin D supplementation on glucose homeostasis have been shown. In line with our study, von Hurst et al (32) showed that vitamin D supplementation (4000 IU daily) for 6 mo significantly improved insulin sensitivity in healthy women. In our previous study in healthy pregnant women, we also found reduced insulin resistance after consumption of 400 IU vitamin D supplements for 9 wk (33). Similar findings have also been indicated in diabetic patients who were orally taking 50,000 IU vitamin D3/wk for 8 wk (19) as well as in pregnant women who were taking 50,000 IU vitamin D every 2 wk from week 12 of pregnancy until delivery (34). In contrast to our findings, some studies did not find the effect of vitamin D supplementation on glucose metabolism. In healthy overweight or obese women, supplementation with 1000 IU vitamin D/d for 12 wk did not affect insulin resistance (35). The same results were also obtained with supplementation of 7000 IU vitamin D/d for 26 wk in vitamin D–deficient obese adults (20). The baseline characteristics of study participants as well as the dosage of vitamin D supplements along with the study duration might provide some explanations for the conflicting findings. The beneficial effects of vitamin D on improved insulin action might be explained by its effect on calcium and phosphorus metabolism and through upregulation of the insulin receptor genes (36). The presence of vitamin D receptors in skeletal muscle (37) along with the fact that 1,25-dihydroxyvitamin D3 increases transcription of insulin receptor genes (36) might further explain the effects of vitamin D on insulin resistance.

In the current study, vitamin D supplementation in GDM patients led to a significant reduction in serum total and LDL-cholesterol concentrations with placebo but did not influence serum triglyceride and HDL-cholesterol concentrations. Consistent with our study, a significant reduction in serum total cholesterol concentrations was seen with the intake of 4000 IU vitamin D supplements/d for 12 wk in vitamin D–deficient, HIV-infected patients (38). Vitamin D3 supplementation for 18 mo in patients with diabetes has also led to improved lipid profiles (39). However, some investigations did not find any significant effect of vitamin D supplementation on serum lipid profiles (40, 41). Improved insulin sensitivity and parathyroid hormone reduction after vitamin D intake might result in decreased lipid profiles (40). Insulin decreases biosynthesis of cholesterol via increased β-hydroxy-β-methylglutaryl coenzyme A reductase activity (42).
as in asymptomatic adults (48). Conflicting results might be explained by variations in study designs, discrepancies in participants’ conditions, varying dosages of vitamin D supplementation, as well as duration of the study.

We did not find any effect of vitamin D supplementation on biomarkers of oxidative stress in pregnant women with GDM. Supplementation with 5000 IU vitamin D/d in diabetic patients for 12 wk did not affect biomarkers of oxidative stress (49). However, the combination of vitamin D₃ and dehydroascorbic acid administration resulted in increased GSH activity in both the cortex and corpus striatum of rats (50). Decreased oxidative DNA damage in the normal human colorectal mucosa has also been seen after vitamin D and calcium supplementation (51). Further studies are required to examine the effect of different doses of vitamin D supplementation on biomarkers of oxidative stress. It seems that vitamin D supplementation might affect these biomarkers in those with elevated concentrations of biomarkers of oxidative stress at study baseline.

Some limitations of our study need to be taken into account. As a result of limited funding, we could not examine the effect of vitamin D supplementation on other biomarkers of systemic inflammation, including IL-1, IL-6, and TNF-α, as well as on biomarkers of oxidative stress such as catalase and superoxide dismutase. In addition, the effect of this supplementation on pregnancy outcomes needs to be evaluated to see if these favorable changes in metabolic profiles could mediate the effect of vitamin D supplementation on pregnancy outcomes in these patients. Because of the small sample size in this study, we were unable to examine if the favorable effects of vitamin D supplementation is greater among those with baseline vitamin D deficiency than in those without deficiency. Additional studies are required to provide some insight into this question. Furthermore, the appropriate dosage of vitamin D supplementation in patients with GDM cannot be inferred from this study, and additional data are required.

In conclusion, vitamin D supplementation in pregnant women with GDM had beneficial effects on glycemic status and serum total and LDL-cholesterol concentrations; however, it did not affect other lipid profiles, hs-CRP, plasma TAC, or GSH concentrations.

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