Original Article

# Vitamin D Effects on GH, IGF-1, Glycemic Control Indicators, and Lipid Profile in Gestational Diabetes Mellitus

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## Abstract

Gestational diabetes mellitus is an unfavorable outcome in some pregnancies, which its prevalence has increased in the world in recent years. The present study is designed and performed to evaluate the effects of oral supplementation of vitamin D on the metabolic condition of expectant women suffering from gestational diabetes. In the present double-blind randomized clinical trial study, 36 women suffering from gestational diabetes in the range of 18-40 years were randomly divided into two groups. People in the vitamin D group (n=15) got a single dose of 2000 IU/d vitamin D during six weeks of intervention, and the people in the control group (n=15) similarly got placebo. Blood specimens of the persons were taken as fasting once at the research beginning and once at the termination of the sixth week of intermediation. In total, 30 participants were entered into the final analysis. In the vitamin D group, it was found a significant decrease in FPG (-0.4±10 vs -14.8±14.4, $p$=0.004), insulin (-0.2±1 vs -0.7±1.2, $p$=0.03) and HOMA-IR (-0.4±0.3 vs 0.1±0.4, $p$=0.001) and a significant enhancement in HOMA_B (184.5±120 vs -4.2±105, $p$<0.001) and QUICKI (0.009±0.008 vs -0.003±0.008, $p$<0.001) in comparison to the control group. Vitamin D3 supplementation had no significant impact on serum contents of total cholesterol, triglyceride, LDL, HDL, IGF-1, and growth hormone levels. Supplementation with 2000 IU vitamin D3 for six weeks has positive effects on glycemic condition control in expectant women suffering from GDM but does not affect the lipid profile, growth hormone, and IGF-1 levels, in them.

**Keywords:** Vitamin-D, Gestational diabetes, IGF-1, Lipid profile

## Introduction

Gestational Diabetes Mellitus (GDM) includes any glucose intolerance or defect in insulin metabolism that is started in pregnancy for the first time or diagnosed during 24-28th weeks of gestation period [1]. In recent years, due to the changes in the living standards of the human population and also advances in medical diagnosis technology, the prevalence of GDM has increased in the world [2, 3]. In addition, in Iran, the prevalence of GDM is growing, as the prevalence has been estimated at 5.88% in 2014 [4].

Obesity, family history of diabetes, old age of mother at pregnancy, sedentary lifestyle and low physical activity, and receiving energy-rich foods, are some of the factors that can increase the risk of GDM [5, 6]. GDM may have serious adverse effects on maternal and fetal health and can cause long-term and short-term side effects such as pre-eclampsia, increased cesarean section, metabolic syndrome, and enhanced risk of developing type II diabetes in the future [6, 7].

Recently, there have been many efforts to identify the factors that can delay the development of GDM. In this field, there is a great interest to evaluate vitamin D [8]. Recent studies indicate that vitamin D is involved in cardiovascular diseases, cancer, immune-related diseases, and also diabetes due to the wide distribution of vitamin D receptors [9]. Vitamin D receptors are present in beta cells of the Islets of Langerhans, and vitamin D affects insulin secretion and insulin function by affecting its receptors on these cells [10]. On the other hand, insulin resistance can cause dyslipidemia; and situations like hypertriglyceridemia are also linked to the incidence of insulin resistance [11, 12].

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**How to cite this article:** Mohammadi F, Bahadori F, Khalkhali H, Ghavamzadeh S. Vitamin D Effects on GH, IGF-1, Glycemic Control Indicators, and Lipid Profile in Gestational Diabetes Mellitus. Arch Pharm Pract. 2021;12(1):118-25. https://doi.org/10.51847/lEjOtr8bg2

Vitamin D deficiency has been reported in 80% of Iranian pregnant women and is more likely to occur in women with GDM in comparison to women with standard carbohydrate tolerance [13, 14]. This situation may happen due to inadequate intake of vitamin D, which in turn affects maternal physiology, fetal and placental growth at the cellular level, and GDM progression [15, 16]. Along with vitamin D, other endocrine factors involved in insulin homeostasis include growth hormone (GH), which in combination with prolactin and placental lactogen, stimulates beta-cell proliferation, insulin gene expression, biosynthesis, and insulin secretion [17]. GH in combination with Insulin-like Growth Factor-1 (IGF-1) and insulin increases nitrogen storage during the body's surplus energy conditions, and when food intake is low, shifts the energy source from carbohydrate and protein fuels to fat and maintains vital protein reserves [18]. IGF-1 is a polypeptide that has a similar structure to insulin, and researches indicate that its injection causes hypoglycemia in experimental animals as a result of peripheral glucose uptake [19]. IGF-1 also reduces blood glucose and improves insulin activity in insulin-resistant patients [20]. Although some studies have shown that vitamin D affects circulating IGF-1 levels and may also influence its synthesis or activity, the interaction between vitamin D and the GH/IGF-1 system is very complicated and has not been fully identified yet [21].

The results of the GDM studies are not consistent; for example, in Yazdchi *et al.*'s (2016) research on 76 patients with GDM, intervention with 50,000 IU vitamin D supplement per week for two months, showed a significant change in fasting glucose, total cholesterol and LDL-cholesterol in the supplemented group, but no significant changes in fasting insulin and hemostasis model evaluation index of insulin-resistance (HOMA-IR) were seen in either group and also measured improvement in lipid profile was not statistically significant [22]. Moreover, in Aasemi *et al.*'s (2013) study with 50,000 IU vitamin D supplement once every three weeks for six weeks, the results showed positive impacts on glycemic status control, total cholesterol, and LDL-cholesterol in GDM patients, while other components of lipid profile were not affected [10]. According to our knowledge, among the studies that have been done on GDM patients, none have directly assessed the GH and IGF-1. This research is designed and performed aiming at evaluating the impacts of oral supplementation of vitamin D on the metabolic condition of expectant ladies suffering from gestational diabetes and also to evaluate interactions between vitamin D and GH/IGF-1 system.

## Materials and Methods

### *Participants*

The present random, double-blind, placebo-controlled intervention was performed between September 2018 and March 2019 in Urmia. The proposed formula for clinical trials was used to estimate the sample volume. Error type I ($\alpha$) and error type II ($\beta$) (80% power) were considered 0.05 and 0.2, respectively, and FPG was considered as a key variable [10]. By applying average values and standard deviation of change in FPG after intervention in formula (-17.12±14.84 in the vitamin D group and -0.96±16.64 in the placebo group), 15 individuals were obtained for each group. Considering a 20% dropout rate, the total number of individuals considered for each group is 18. Study participants were pregnant women aged 18-40 years with GDM diagnosed using the OGTT test with 75 g glucose during 24-28 weeks of pregnancy [23]. Pregnancy age was calculated from the date of the last menstruation using clinical assessments [24]. Diagnostic criteria of the International Diabetes and Gestation Society were used to diagnose GDM; as having one of the following conditions confirms the diagnosis of GDM: FBS≥92 mg/dl, GTT1h>180 mg/dl, and GTT2h>153 mg/dl [25]. Among the 550 pregnant women screened at the Midwifery Clinic of Urmia University of Medical Sciences for diagnosis of GDM, 36 were eligible for entering the study. 500 patients were excluded from the study due to not having GDM, and 14 were omitted due to having at least one exclusion criterion **(Figure 1)**. Exclusion criteria included chronic hypertension or gestational hypertension, history of liver or gastrointestinal diseases, smoking or using alcohol, twin or multiple pregnancies, receiving vitamin D supplements or hypoglycemic drugs, and body mass index was over 40. Finally, 36 participants were randomly assigned to supplement (n=18) and placebo (n=18) groups and were interventions and followed up for six weeks. Random assignment was carried out by sealed envelopes designed by a person other than the researcher. Informed written agreement was completed for all pregnant women taking part in the study. The present study is confirmed by the Ethics Committee of Research in Urmia University of Medical Sciences and is registered at the Iranian Clinical Trial Study Database with the code IRCT20130616013678N29. In addition, the grants of this research are funded by the Urmia University of Medical Sciences.

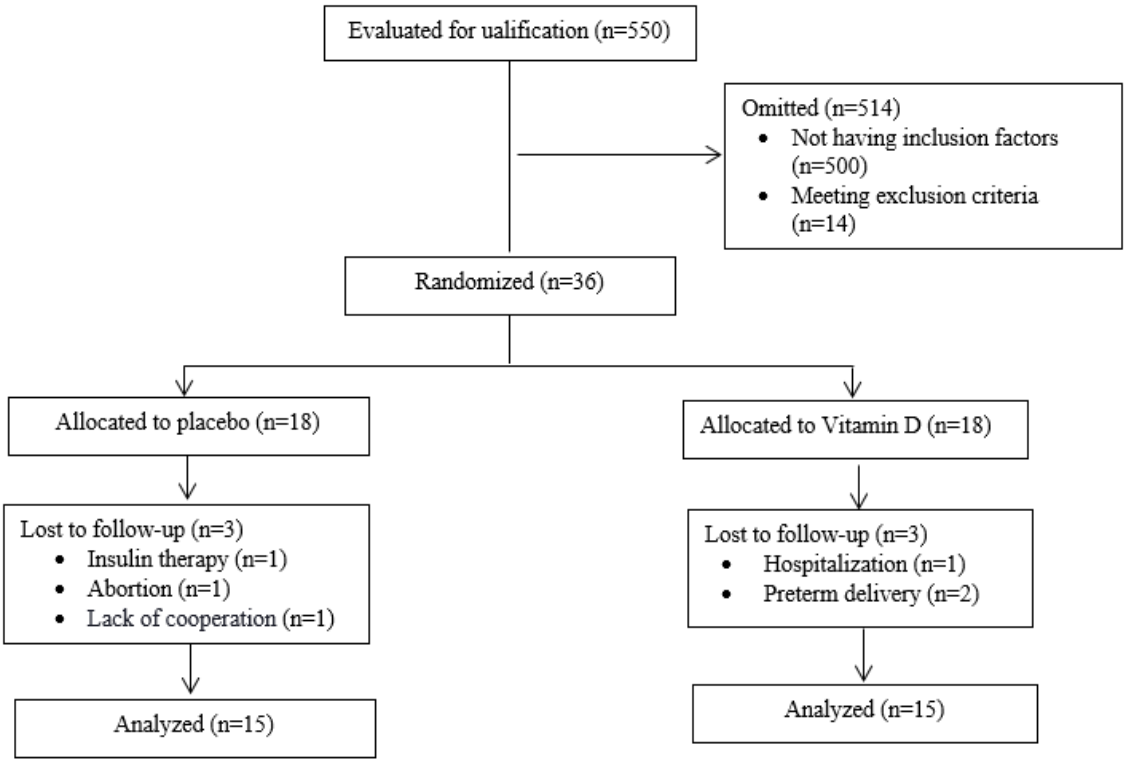


**Figure 1.** Summary of Patient Flow. Individuals in the Vitamin D Group Received Perls Containing 2000 IU Vitamin D3 Daily During the Study; Participants in the Control Group Received Placebo Daily at the Same Times.

### *Study Design*

Participants (randomly placed in one of the experimental and control groups) in the vitamin D group received a daily oral dose of 2000 IU vitamin D3. The placebo group was also given one placebo pill daily. The main supplements and placebo, made by Zahravi Pharmaceutical Company, looked completely the same. Supplement and placebo packages were coded A and B by a person other than the researcher beforehand, and the researcher was unaware of the nature of the cans until the end of the data analysis. The intervention lasted for six weeks. All participants received 400 µg/day folic acid three months before gestation and 60 mg/day ferrous sulfate since week 16 of pregnancy according to national guidelines. Compliance with vitamin D supplementation was assessed by measuring vitamin D serum levels.

### *Evaluating the Variables*

Demographic data of the participants, including age, education level, smoking and alcohol using status, place of residence, history of illness, and medicines and supplements intake, were completed through a general information questionnaire. Anthropometric data including weight (measured without shoes, with the lowest possible clothes using SECA scale (made in Germany) with the precision of 100 g), height (assessed without shoes, using a tape measure installed on the wall with the precision of 0.5 cm), BMI (weight in kg divided by height in meters to the power of 2), and blood pressure (in the sitting position using Riester barometer (made in Germany)) were obtained at the beginning of the research and the end of the intermediation. Dietary intakes of the participants were assessed for measuring vitamin D, the amount of energy, carbohydrate, protein, fat, and fiber intake using a 24-hour recall questionnaire at the beginning of the research and the end of the intermediation. The information was collected in two three-day intervals (three times in the first week and three times in the last week of the intervention) and two normal days and one day off from participants. The first and the final evaluation were done in person and the other four times by telephone. Nutrition intake data were analyzed by Nutritionist IV (modified for Iranian foods). The patients' physical activity and exposure to sunlight were also assessed by the related questionnaire. At the beginning of the research and end of the sixth week of the intermediation, after at least 12 hours of fasting, 5 ml of venous blood was collected by a laboratory technician at the laboratory of Medical Diagnosis and Pathology of Shahid Motahari Educational and Medical Center. For serum separation, blood specimens were quickly centrifuged at 3000 rpm for 10 minutes, and the serums were frozen at -80° until final analysis time.

Dialab kits (Austria, Dialab) and a BT 1500 device (made in Italy) were used to measure FPG, cholesterol, TG, LDL, and HDL factors. The intra-assay and inter-assay CVs FPG were 1.29% and 1.50%, respectively. For lipid profiles, the inter-assay and inter-assay CVs were less than 5%. Serum contents of 25(OH)D were assessed by the Roche

Electrochemiluminescence kit (Germany, Mannheim, Roche) and a Cobas e 411 device (made in Germany). The intra-assay and inter-assay CVs for 25(OH)D were 5.16 and 3.44%, respectively. Serum levels of insulin and GH were assessed by ELISA kit (USA, Monobind) and Stat Fax 4200 (USA) device. The intra-assay and inter-assay CVs for insulin and GH were 4.36% and 6.15%, respectively. Serum levels of IGF-1 were also measured using the ELISA kit (Germany, Nordhorn, LDN). The intra-assay and inter-assay CVs for IGF-1 were 12.60% and 6.90%, respectively. HOMA-IR, HOMA-B, and QUICKI indexes were assessed based on the proposed formulas. Measurements of vitamin D, glucose, insulin, lipid profile, GH, and IGF-1 of a placenta were performed (before and after the intervention) in a blind procedure and with the same analysis.

### *Statistical Analysis*

In this study, data analysis was conducted using SPSS v.16 software. Kolmogorov-Smirnov test was applied to evaluate the normality of the distribution of variables. Logarithmic transforms were applied for variables with an abnormal distribution. ANOVA and analysis of variance tests were applied to specify and compare diversities in the general specification, blood factors, and dietary intakes. To compare participants in terms of physical activity and sunlight exposure time, we used the Chi-squared method. In all statistical tests, a significance level of less than 0.05 was considered statistically significant.

## Results and Discussion

Among the participants, three of the experimental group were omitted because of preterm labor (n=2) and hospitalization (n=1). Additionally, three participants in the control group were omitted because of insulin therapy (n=1), abortion (n=1), and lack of cooperation (n=1 due to the distance). Finally, 30 participants (15 in the vitamin D group and 15 in the placebo group) completed the intervention.

The average weight and BMI at the beginning of the research and after ending the intervention, and the average age and height were not significantly different between the participants of the two groups. Blood pressure and maternal weight gain at the beginning of the study and after six weeks of intermediation with 2000 IU vitamin D3 were not significantly different between control and experimental groups **(Table 1)**. Participants' dietary intakes, according to three-day dietary records during the intermediation, showed no significant difference between the two groups concerning receiving energy, carbohydrate, protein, fat, saturated fatty acids, cholesterol, total dietary fiber, and vitamin D **(Table 2)**.

**Table 1.** General Characteristics of GDM Patients Who Received Vitamin D Supplements or Placebo 1

| | Placebo group 2 (n=15) | Vitamin D group 3 (n=15) | *P*-value 4 |
|---|---|---|---|
| Maternal age (y) | 30.4±7.8 | 33.3±5.8 | 0.26 |
| Gestatitonal age (w) | 29.6±2.3 | 29±2.1 | 0.52 |
| Height (cm) | 157.6±7.2 | 154±5.6 | 0.13 |
| Weight at the beginning of the study (kg) | 70.2±12 | 73.6±7.2 | 0.35 |
| Weight at end-of-test (kg) | 72.4±12.5 | 75.1±7.6 | 0.48 |
| Weight changes (kg) | 2.2±1.5 | 1.5±1.5 | 0.21 |
| BMI at the beginning of the study (kg/m²) | 28.4±5.8 | 31±2.6 | 0.13 |
| BMI at end-of-test (kg/m²) | 29.4±6 | 31.6±2.7 | 0.19 |
| BMI changes (kg/m²) | 0.9±0.6 | 0.6±0.6 | 0.25 |
| SBP at the beginning of the study (mmHg) | 105.3±6.3 | 108±9.4 | 0.37 |
| DBP at end-of-test (mmHg) | 109.3±9.6 | 113.3±10.2 | 0.75 |
| SBP at the beginning of the study (mmHg) | 70.3±5.4 | 69.6±6.1 | 0.28 |
| DBP at end-of-test (mmHg) | 74.3±7.2 | 74.3±8.2 | 1.0 |
| Weight gain during of intervention (gr) | 2286.6±1547 | 1520±1493 | 0.18 |

GDM= Gestational Diabetes Mellitus; BMI= Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure
1 Data are means ± standard deviations.
2 Received one placebo pill daily during the study.
3 Received 2000 IU vitamin D3 daily during the study.
4 Obtained from analysis of variance test.

No significant difference was seen between control and experimental groups concerning physical activity and sunlight exposure time. There was no significant difference between the two groups in the initial values (except the ratio of total cholesterol to HDL). Supplementation with 2000 IU vitamin D3 in comparison to placebo led to a remarkable enhancement in serum contents of 25(OH)D (10.7±6.8 vs 1.7±6, $p$=0.001). Besides, vitamin D3 supplementation significantly reduced FPG (-14.8±14.4 vs -0.4±10, $p$=0.004), insulin (-0.2±1 vs -0.7±1.2, $p$=0.03) and HOMA-IR (-0.4±0.3 vs 0.1±0.4, $p$=0.001) and significantly increased HOMA-B (184.5±120 vs -4.2±105, $p$<0.001) and QUICKI

(0.009±0.008 vs -0.003±0.008, $p<0.001$) compare to placebo. In addition, no significant impact of vitamin D3 supplementation on serum total cholesterol, triglyceride, LDL, HDL, total cholesterol to HDL ratio, IGF-1, and GH was observed **(Table 3)**.

**Table 2.** Dietary Intakes of GDM Patients Who Received Vitamin D Supplements or Placebo during the Research 1

| | Placebo group 2 (n=15) | Vitamin D group 3 (n=15) | *P*-value 4 |
|---|---|---|---|
| Energy (kcal/day) | 1600±444.5 | 1401.7±645.6 | 0.33 |
| Carbohydrate (g/day) | 196.6±72.7 | 185.3±104.8 | 0.73 |
| Protein (g/day) | 63.7±28.2 | 52.3±25.2 | 0.25 |
| Fat (g/day) | 62.7±16.6 | 51.6±21.9 | 0.13 |
| Saturated fatty acids (g/day) | 12.4±3.4 | 11±5.4 | 0.39 |
| Cholesterol (g/day) | 96.7±99.7 | 140.3±119.8 | 0.28 |
| Fiber (g/day) | 25.4±13.3 | 21.2±18.1 | 0.48 |
| Vitamin D (µg/day) | 1.7±0.3 | 1.7±0.5 | 0.79 |

GDM= Gestational Diabetes Mellitus;
1 Data are means ± standard deviations.
2 Received one placebo pill daily during the study.
3 Received 2000 IU vitamin D3 daily during the study.
4 Obtained from analysis of variance test.
Normalization using Logarithmic transforms.¶

**Table 3.** Metabolic Profiles, GH and IGF-1 at the Beginning of the Study and 6 Weeks after the Intermediation in GDM Patients Who Received Vitamin D Supplements or Placebo 1

| | Placebo group 2 (n=15) | | | Vitamin D group 3 (n=15) | | | *P*-value |
|---|---|---|---|---|---|---|---|
| | Week 0 | Week 6 | Change | Week 0 | Week 6 | Change | |
| Vitamin D (ng/mL) | 19.1±8.3 | 20.9±8.3 | 1.7±6 | 19.5±9.4 | 30.2±7.4 | 10.7±6.8 | 0.001 |
| FPG (mg/dL) | 87.2±17.8 | 86.8±11.9 | -0.4±10 | 91.5±14.6 | 76.7±3.4 | -14.8±14.4 | 0.004 |
| Insulin (µIU/mL) | 10.5±1.3 | 11.2±1.3 | 0.7±1.2 | 11.1±1.3 | 10.3±0.9 | -0.2±1 | 0.03 |
| HOMA-IR | 2.2±0.5 | 2.3±0.3 | 0.1±0.4 | 2.5±0.4 | 1.9±0.2 | -0.4±0.3 | 0.001 |
| HOMA-B | 217.1±102 | 212.9±110 | -4.2±105 | 162.1±51.8 | 330.3±131 | 184.5±120 | < 0.001 |
| QUICKI | 0.3±0.01 | 0.33±0.006 | -0.003±0.008 | 0.33±0.009 | 0.34±0.007 | 0.009±0.008 | < 0.001 |
| Total cholesterol (mg/dL) | 233.8±51.9 | 249.4±54.5 | 15.6±42.5 | 227.2±39.3 | 234.8±42.2 | 7.5±20.4 | 0.51 |
| Triglycerides (mg/dL) | 202.6±54.9 | 252.5±57.2 | 49.9±75.5 | 208.1±52.6 | 234.6±48.6 | 26.5±40.4 | 0.29 |
| LDL-cholesterol (mg/dL) | 127±32.6 | 131±34.9 | 3.9±28.4 | 117.1±27.4 | 118.9±28.7 | 1.8±14.3 | 0.80 |
| HDL-cholesterol (mg/dL) | 54.6±11 | 52.2±10.6 | -2.4±9.7 | 60.4±5.1 | 60±7 | -0.33±5.8 | 0.47 |
| Total:HDL-cholesterol ratio | 4.3±0.8 | 4.8±1.2 | 0.56±1.3 | 3.7±0.5 | 3.9±0.7 | 0.1±0.5 | 0.32 |
| GH (ng/mL) | 5.3±1.5 | 5.1±1.6 | -0.2±1.1 | 5±1.4 | 5.6±1.9 | 0.6±2.1 | 0.19 |
| IGF-1 (ng/mL) | 347.6±105 | 366.6±98.1 | -9.5±41.3 | 338±93.7 | 386±97 | 19.4±51.5 | 0.10 |

GDM= Gestational Diabetes Mellitus; FPG= Fasting Plasma Glucose; HOMA-IR= Homeostasis Model of Assessment Insulin Resistance; HOMA-B= Homeostatic Model Assessment-Beta Cell Function ; QUICKI= Quantitative Insulin Sensitivity Check Index; LDL-Cholesterol= Low-Density Lipoprotein Cholesterol; HDL Cholesterol= High-Density Lipoprotein Cholesterol; GH= Growth Hormone; IGF-1= Insulin-like Growth Factor-1.
1 Data are means ± standard deviations.
2 Received one placebo pill daily during the study.
3 Received 2000 IU vitamin D3 daily within the research.
4 Obtained from analysis of variance test.
5 Data adjusted for baseline values.

## Conclusion

According to our findings, supplementation with 2000 IU daily vitamin D for six weeks led to a significant reduction in FPG, insulin, and HOMA-IR, and a significant enhancement in HOMA-B and QUICKI in patients with GDM. However, no significant impact of vitamin D supplementation on serum levels of total cholesterol, triglyceride, LDL, HDL, total cholesterol to HDL ratio, IGF-1, and GH was observed in these patients. GDM includes various severities of carbohydrate intolerance with onset during the pregnancy or diagnosis in 24-28th weeks of gestation [26]. Poor control of maternal glycemic status can lead to complications such as

pregnancy hypertension, pre-eclampsia, cesarean delivery, macrosomia, and birth time defects [27]. Furthermore, abnormalities in lipid profiles in GDM are associated with endothelial vessel dysfunction, atherosclerosis, intrauterine growth retardation, and type II diabetes [28]. Timely and appropriate management of hyperglycemia and dyslipidemia reduces the complexities and complications of GDM [29]. Epidemiologic researches indicate an opposite association between vitamin D and pregnancy complications, and on the other hand, vitamin D deficiency increases the probability of GDM [30, 31]. The presence of vitamin D is essential in many physiological processes, so adequate levels of this vitamin are necessary and beneficial to achieve optimal levels of health [32-34]. Adequate amounts of vitamin D are also needed during pregnancy to meet the fetus's increased need for calcium during growth and evolution [33-35]. In the present study, supplementation with 2000 IU daily vitamin D for six weeks significantly increased serum levels of 25(OH)D. On the other hand, the FPG and insulin levels and HOMA-HOMA-BIR score decreased significantly in the vitamin D group, and HOMA-B and QUICKI scores increased significantly in this group. In line with the results of this research, Aasemi *et al.*'s study showed that 50,000 IU vitamin D every two weeks for six weeks in pregnant women with GDM significantly reduced fasting glucose and HOMA-IR score, and remarkably enhanced QUICKI [10]. In contrast, Zhang *et al.* study showed that supplementation with 50,000 IU vitamin D every two weeks significantly reduced fasting insulin levels and HOMA-IR score in women with GDM, but FPG level, HOMA-B score, and QUICKI were not affected [36]. The production of inflammatory cytokines is considered one of the mechanisms of the vitamin D effects on insulin resistance; it is thought that the association between vitamin D and chronic inflammation with insulin resistance in type II diabetes is mediated by the immune-modulating features of 1,25(OH)2D3 (that is capable of downregulating the formation of pro-inflammatory cytokines [37]. Several cross-sectional researches show a relationship between hypovitaminosis D with higher values of inflammatory biomarkers like IL-6, while there are other studies that do not support these findings [38, 39]. A recent meta-analysis by Ojo *et al.* shows that vitamin D has a significant effect on serum levels of insulin and blood glucose parameters in patients with GDM and vitamin D supplementation improves these conditions, but whether this effect is due to vitamin D or not is still unclear [40]. The present study showed that the effect of six weeks of intervention with 2000 IU daily vitamin D on serum total cholesterol, triglyceride, HDL, LDL, and ratio of total cholesterol to HDL was not statistically significant. Considering our study, the study by Yazdchi *et al.* showed that oral treatment with 5,0000 IU vitamin D every two weeks for two months in persons with GDM had no significant effect on the lipid profile of the intervention group [22]. Despite our findings, Aasemi *et al.* in another study showed that a six-week intervention with a combined supplement of vitamin D and calcium significantly reduced LDL and ratio of total cholesterol to HDL and significantly enhanced HDL in pregnant women with GDM [41]. The results of various studies on the relationship of vitamin D with lipid profiles are different and sometimes contradictory. For example, Ford *et al.* in the NHANES III study found a negative association between serum levels of 25(OH)D with TG in patients with hypertriglyceridemia, whereas no such association was observed with HDL in healthy persons [42]. Although certain researches have suggested the beneficial impacts of vitamin D on lipid profile, it is unclear whether this effect is due to the hormonal properties of vitamin D or its association with the mechanism of calcium [43, 44]. Calcium prevents fat absorption by forming insoluble soaps with the fat in the food, thereby moderates the effect of high amounts of fat on blood lipid accumulation [45]. On the other hand, vitamin D may affect serum lipid profile by affecting insulin resistance reduction [46]. Different study designs and differences in participants' attitudes may be one of the possible reasons for the differences in the results and findings of the above studies.

In the present study, supplementation with 2000 IU vitamin D for six weeks had no significant effect on serum levels of IGF-1 and GH. Some studies have suggested that the GH regulates the renal alpha-hydroxylase activity, and this is possible that IGF-1 mediates the GH act in regulating vitamin D metabolism [47]. The GH/IGF-1 axis can modulate the metabolism of vitamin D, and in contrast, vitamin D also affects IGF-1 levels [48, 49]. Low concentrations of IGF-1 are involved in the pathogenesis of deleterious metabolic processes such as impaired glucose homeostasis. On the other hand, vitamin D deficiency is particularly prevalent in patients with GH deficiency, which are usually identified based on reduced IGF-1 concentrations [50]. Although some studies have shown that vitamin D affects circulating IGF-1 levels and may affect its synthesis or activity, the interaction between vitamin D and the GH/ IGF-1 system is still unknown [21].

Conducting studies with different intervention duration and using vitamin D mega-doses can help to justify the inconsistent results. In the analysis of the findings of the present study, limitations such as small sample size and supplementation dose lower than the maximum recommended in previous studies should be considered. We also could not evaluate the impact of vitamin D supplementation on other biomarkers of glycemic control, including HbA1c, as well as on PGH and IGF-2. The results of this study indicate that supplementation with 2000 IU vitamin D3 for six weeks has positive effects on glycemic control in patients with GDM, but does not affect the lipid profile and the levels of GH and IGF-1 in these persons. We suggest more interventions to evaluate calcium and biomarkers in patients with GDM. In addition, designing studies with larger sample sizes and longer intervention times may help to more clarify the impacts of vitamin D supplementation on metabolic profile and other blood parameters such as GH and IGF-1.

ACKNOWLEDGMENTS: All costs of this research were covered by the research assistant of Urmia University of Medical Sciences. The authors of this article would like to express their gratitude and appreciation to all those who contributed to the present study and especially to the respected families who participated in this study.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: This article was done with the financial support of Urmia University of Medical Sciences

ETHICS STATEMENT: The present study is confirmed by the Ethics Committee of Research in Urmia University of Medical Sciences and is registered at the Iranian Clinical Trial Study Database with the code IRCT20130616013678N29.

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