eISSN 2255-0569

ORIGINAL

Effect of vitamin D supplement on glycemic control in gestational diabetes

Efecto del suplemento de vitamina D sobre el control glucémico en diabetes gestacional

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Received: 10 - VII - 2021
Accepted: 15 - VIII - 2021

doi: 10.3306/AJHS.2021.36.04.81

Abstract

Introduction: Gestational diabetes mellitus (GDM) is a pregnancy complication characterized by intolerance to carbohydrates and metabolic diseases. Vitamin D supplement prescription has been shown to be effective on glycemic control and other pregnancy outcomes. Therefore, this study aimed to investigate the effect of high dose of vitamin D supplement on glycemic control in pregnancy and its effect on reducing other adverse outcomes of pregnancy.

Methods: The study was conducted on 40 pregnant women in the first trimester who had impaired glucose tolerance test by the randomized clinical trial method. Subjects were divided into two groups. Simultaneously with the regimen, the intervention group was given a higher dose of vitamin D and the control group received vitamin D routinely. Then, HbA1c level, fasting blood sugar, fasting serum insulin, and insulin resistance were measured at the beginning and 6 weeks later. Patients were followed up for pregnancy complications until the end of pregnancy.

Results: Fasting blood sugar, HbA1C, serum insulin level, and HOMA-IR level after receiving vitamin D in the case group were less than the control group, which were significantly different (p.v <0.001). Cases that required insulin therapy and preterm labor were higher in the control group, but it was not significant. There were no significant differences in other outcomes of pregnancy. The level of vitamin D in umbilical cord blood was higher and significant in the case group (p.v <0.001) but there was no significant difference with pregnancy complications in the two groups.

Conclusion: Our study showed that administering a dose higher than the current vitamin D recommendation in pregnancy can help prevent gestational diabetes and its adverse outcomes.

Keywords: Gestational diabetes, vitamin D, supplement, pregnancy outcomes, glucose.

Resumen

Introducción: La diabetes mellitus gestacional (DMG) es una complicación del embarazo caracterizada por la intolerancia a los hidratos de carbono y las enfermedades metabólicas. Se ha demostrado que la prescripción de suplementos de vitamina D es eficaz para el control glucémico y otros resultados del embarazo. Por lo tanto, este estudio tenía como objetivo investigar el efecto de una dosis alta de suplemento de vitamina D en el control glucémico en el embarazo y su efecto en la reducción de otros resultados adversos del embarazo.

Métodos: El estudio se llevó a cabo en 40 mujeres embarazadas en el primer trimestre que tenían una prueba de tolerancia a la glucosa alterada por el método de ensayo clínico aleatorio. Los sujetos se dividieron en dos grupos. Al grupo de intervención se le administró una dosis más alta de vitamina D y el grupo de control recibió vitamina D de forma rutinaria. A continuación, se midieron el nivel de HbA1c, la glucemia en ayunas, la insulina sérica en ayunas y la resistencia a la insulina al principio y 6 semanas después. Se realizó un seguimiento de las pacientes para detectar complicaciones del embarazo hasta el final del mismo.

Resultados: La glucemia en ayunas, la HbA1C, el nivel de insulina sérica y el nivel HOMA-IR después de recibir vitamina D en el grupo de casos fueron menores que en el grupo de control, que fueron significativamente diferentes (p.v <0,001). Los casos que requirieron terapia de insulina y parto prematuro fueron mayores en el grupo de control, pero no fue significativo. No hubo diferencias significativas en otros resultados del embarazo. El nivel de vitamina D en la sangre del cordón umbilical fue mayor y significativo en el grupo de casos (p.v <0,001), pero no hubo diferencias significativas con las complicaciones del embarazo en los dos grupos.

Conclusión: Nuestro estudio demostró que la administración de una dosis superior a la recomendación actual de vitamina D en el embarazo puede ayudar a prevenir la diabetes gestacional y sus resultados adversos.

Palabras clave: Diabetes gestacional, vitamina D, suplemento, resultados del embarazo, glucosa.

Introduction

Gestational diabetes mellitus (GDM) is a common medical complication of pregnancy that is defined as "diabetes diagnosed in the second or third trimester of pregnancy where diabetes is not overt"[1,2]. It is estimated that approximately 7% of all pregnant women in the United States have GDM, but its prevalence is between 1% and 4% of all pregnancies worldwide, depending on the study population and diagnostic criteria[3,4]. Various factors such as old age during the first pregnancy, stressful living conditions, a sedentary lifestyle with low physical activity, and poor diet affect the incidence of this complication and lead to an increased risk of GDM [5]. Recent studies have shown that calcium and vitamin D supplements for patients with GDM may affect pregnancy outcomes[6,7].

Vitamin D has been one of the most important topics in the medical world for the last decade due to its numerous effects on human health[8-10]. This vitamin has important and multifaceted effects beyond the effects of the skeletal system. Some of the activities of this vitamin during pregnancy are the effect on fetal skeletal growth and development, regulating calcium transfer from the placenta, modulating immune reactions during placental implantation and its effect on fetal development and brain development[11,12]. Several studies have shown that the 25-hydroxyvitamin D level is significantly lower in patients with diabetes than in healthy individuals[13-15]. Many studies show that pregnant women are at higher risk for vitamin D deficiency due to the increased need of the fetus due to rapid growth and calcification of bones in the third trimester[16-18]. Also, according to studies, there is a high prevalence of vitamin D deficiency in newborns and their mothers in Iran[19].

The appropriate dose of vitamin D during pregnancy is unknown, although it appears to be greater than the current dietary reference intake of 200–400 IU/d. In 2010, the FDA estimated the appropriate amount of vitamin D during pregnancy at 600 IU/d[20,21]. Several studies have shown that more than 1000IU of vitamin D is required to reach the normal level of 25OHD[22,23]. The Endocrine Society has recommended daily intake of vitamin D at a dose of 1500-2000 IU to reach the level of 30 ng/ml from 25OHD[24]. However, one study found that with a daily intake of 4,000 IU, approximately 83% of women reached a minimum serum level of 32 ng/ml at the time of delivery and suggested that 4,000 IU was the appropriate dose for pregnant women[25,26].

There are few studies on the effect of vitamin D supplement on maternal and fetal pregnancy outcomes. A number of observational studies have been conducted, but there are few interventional studies to evaluate the effect of vitamin D supplement on blood glucose metabolism, gestational diabetes, preeclampsia, intrauterine growth retardation, intrauterine fetal death, and macrosomia. Therefore, the present study aimed to investigate the effect of high dose of vitamin D supplement (50,000 oral units) on blood sugar control in pregnant women and also its effect on outcomes such as preeclampsia, intrauterine growth retardation, intrauterine fetal death, and macrosomia.

Materials and methods

Selection of patients

In this randomized clinical trial study, 40 pregnant women with impaired glucose tolerance test in the first trimester of pregnancy during 2014-2015 in the city of Kerman were investigated.

Inclusion criteria were women over 18 years of age, gestational age of 8 to 13 weeks, and exclusion criteria were patients with renal or hepatic insufficiency, alcoholism, malabsorption, hypo or hyperparathyroidism, malignancies, use of effective drugs on vitamin D metabolism, previous use of vitamin D supplements, and a history of previous diabetes.

This study was presented in the Ethics Committee of Kerman University of Medical Sciences and was approved with the number 1394.203. Also, it was registered in IRCT with the code N12015122725725. Therefore, at first, the objectives, nature, and the research process were explained to the sample and their consent to participate in the research was obtained. The sample was assured that their information would be kept confidential and reminded that the results of the research would be made available to them if they wished. The sample was also reassured that they could leave the research at any stage of the research if they did not wish to continue and be referred to a psychiatrist if they needed medical treatment.

Method of implementation

The diagnosis of gestational diabetes was made according to the criteria of the American Diabetes Association (ADA) [25]. A two-hour diabetes screening test (GTT) was performed by prescribing 75 grams of glucose 75 g of glucose. First, fasting blood sugar was measured and after consuming 75 grams of glucose, 4 cc of blood was taken from each patient twice one and two hours later, and blood glucose was measured one and two hours later.

Values of FBS<92 /BS1hpp <180 / BS2hpp <153 were considered normal. Patients who had an abnormal test in the above three cases were considered to have an impaired test, which HbA1C and serum insulin were measured immediately from the stored serum of them. HbA1C level <6 normal and fasting serum insulin level less than 5 µU/ml were considered normal. Sampling continued until reaching the sample size of 40 people (impaired test).

Subjects with impaired tests were divided into intervention and control groups by simple randomized method. In both groups, the amount of insulin resistance was calculated by homeostasis model assessment (HOMA-IR). Both groups were on a diet. Simultaneously with the diet, the intervention group received 50,000 IU of oral vitamin D (one pearl) up to three doses once every two weeks, and the control group routinely received up to 28,000 IU of vitamin D during the same period. 2 weeks after the last dose of vitamin D, serum HbA1c, fasting serum insulin, fasting blood sugar were measured and HOMA-IR was calculated. Then patients were followed up until the end of pregnancy in terms of pregnancy complications including intrauterine fetal demise (IUFD), intrauterine growth restriction (IUGR), large for gestational age (LGA) infant, preeclampsia (BP>=140/90 and proteinuria), preterm delivery less than 37 weeks of gestation, and the need for insulin regimen therapy. After delivery, 5 cc blood of umbilical cord was taken to check the level of vitamin D, and the relationship between the level of vitamin D in the umbilical cord blood and pregnancy complications such as preeclampsia, intrauterine fetal demise, intrauterine growth retardation was investigated.

Data analysis

Data were analyzed by SPSS software version 25 (version 25, SPSS Inc., Chicago, IL). Frequency, relative frequency and central tendency of mean were used for descriptive statistics and chi-square and t-tests were used to compare quantitative and qualitative variables in the two groups. Finally, P less than 0.05 was considered statistically significant.

Results

In this study, 254 pregnant women underwent diabetes screening. Of these, 40 had impaired glucose tolerance test that were divided into case and control groups.

The mean serum level of fasting blood sugar in the case group was significantly lower than the control group. The level of fasting serum insulin and hemoglobin A1C in the case group was much lower than the control group. The level of HOMA-IR in the case group was clearly different and lower than the control group. These findings confirm the statistically significant difference between the two groups (p <0.001) (**Table I**).

Also, the mean level of vitamin D in umbilical cord blood at delivery in the case group was clearly higher than the control group, which was a statistically significant difference (p <0.001).

The frequency of need for insulin regimen therapy was investigated in the two groups. 3 patients (15%) in the case group and 7 patients (35%) in the control group needed insulin regimen due to lack of blood sugar control or diet and vitamin D supplement. There was no statistically significant difference between the two groups in the frequency of need for insulin regimen.

In terms of delivery status, our results showed that 19 term deliveries (95%) were performed in the case group and 15 term deliveries (75%) were performed in the control group, resulting in 1 preterm delivery (5%) in the case group and 5 preterm deliveries (25%) in the control group. There was no significant difference between the two groups in terms of delivery status (**Figure 1**).

Pregnancy complications between the two groups also showed that no intrauterine fetal death (IUFD) was seen in the case group but one case was observed in the control group. Preterm labor pain (PLP) was reported in two patients in the case group and six patients in the control group. Intrauterine growth restriction (IUGR) was not seen in the case group but one case was observed in the control group. Large for gestational age (LGA) infants were seen in one case in the case group and in four cases in the control group. Preeclampsia (PIH) was not seen in the case group but was reported in three subjects in the control group. There was no significant difference between the two groups in terms of pregnancy complications (**Figure 2**).

Table I: Comparison of serum levels of serum insulin, hemoglobin A1C, fasting blood sugar, and HOMA-IR.

	Groups		
	Case	Control	p.v*
Fasting blood sugar before regimen	107.50±11.85	107.75 ± 15.19	0.254
Fasting blood sugar after regimen	93.40±6.47	76.65±7.74	0.001>
HOMA-IR before regimen	7.04 ±1.82	6.14 ±2.35	0.187
HOMA-IR after regimen	6.39±1.76	2.94 ±1.35	0.001>
Hemoglobin A1C levels before regimen	6.68±1.01	5.92±1.12	0.038
Hemoglobin A1C levels after regimen	6.43±0.92	5.02±0.83	0.001>
Insulin levels before regimen	26.34±5.33	23.17±8.52	0.166
Insulin levels after regimen	26.90±5.65	15.68±7.36	0.001>
Vitamin D levels in umbilical cord blood	13.33±4.60	21.35±15.39	0.001>

Figure 1: Comparison of the frequency of delivery status in the case and control groups.

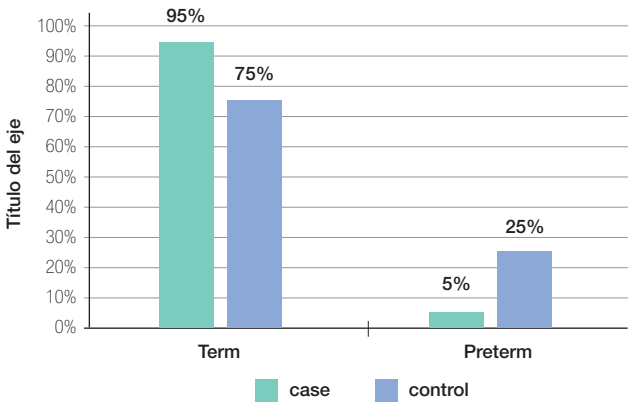
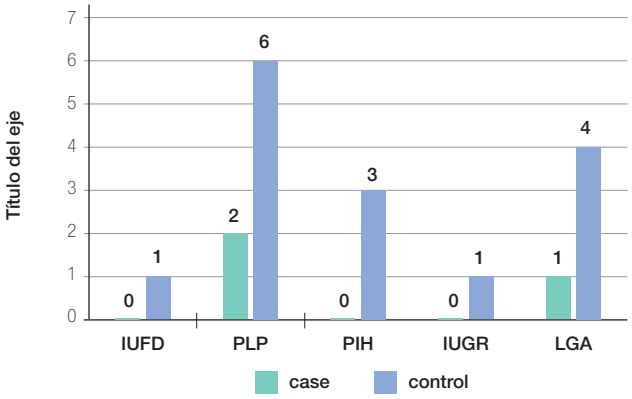


Figure 2: Comparison of pregnancy complications in the case and control groups.



The level of vitamin D in umbilical cord blood was not significantly different in any of the groups based on pregnancy complications (**Tables II** and **III**).

Table II: Comparison of vitamin D levels in umbilical cord blood and pregnancy complications in the case group.

	No	Yes	p.v*
Intrauterine fetal death	30.05±2.67	26.11±5.97	30.05±2.67
Preterm delivery	16.19± 30.77	21.12 ± 35.50	0.692
Preeclampsia	13.42 ±4.71	11.06±0	0.710
Intrauterine growth restriction	13.42 ±4.71	11.06±0	0.710
Large for gestational age infant	14.97± 32.35	0± 10.20	0.166

Table III: Comparison of vitamin D levels in umbilical cord blood and pregnancy complications in the control group.

	No	Yes	p.v*
Intrauterine fetal death	13.42±4.71	11.06±0	0.710
Preterm delivery	13.60±4.08	12.70±6.04	0.698
Preeclampsia	13.74±4.83	11±2.17	0.354
Intrauterine growth restriction	13.53±4.63	9.5±0	0.407
Large for gestational age infant	4.97± 13.08	2.94 ±14.35	0.635

Discussion

It has been shown that the need for vitamin D and calcium during pregnancy and lack of proper nutrition at this important time in life may increase the risk of GDM[27]. The results of several meta-analyses have shown that there is a significant inverse relationship between serum 25-(OH) D concentration and GDM risk[28,29]. Several mechanisms have been proposed for the association between vitamin D and type II diabetes. These mechanisms are associated with diabetes and vitamin D in three ways and affect insulin secretion, peripheral tissue resistance to insulin, and inflammation[30]. Therefore, the present study aimed to investigate the effect of vitamin D supplement on glycemic control in GDM.

The results of the present study showed that the level of fasting serum insulin, hemoglobin A1C and HOMA-IR levels in the case group were lower than the control group. Meanwhile, the mean level of vitamin D in umbilical cord blood at delivery was higher in the case group than the control group, but there was no significant difference with pregnancy complications in the two groups. Also, in statistical studies, there was no significant difference between the two groups in terms of pregnancy complications.

Cross-sectional studies have shown an association between maternal vitamin D levels and impaired glucose metabolism in pregnant women[31-33]. Wang et al. also reported that vitamin D supplement in women with GDM may improve glycemic control and reduce adverse outcomes for mother and infant[34]. Ojo et al. also reported in a systematic review study that vitamin D supplement has the potential to increase blood sugar control in women with GDM. However, they reported that due to the limited number of studies in meta-analysis, the conclusion should be interpreted with caution and further studies are required to fully understand the exact mechanism of the effect of vitamin D on glucose metabolism[35]. However, no such association was found in the study of Pleskacovu[36]. The results of our study showed the effect of vitamin D on decreasing fasting blood sugar and hemoglobin A1C, but the need for insulin therapy did not differ significantly between the two groups. It has been shown that normal pregnancy requires increased insulin secretion due to increased insulin resistance, and women with impaired insulin secretion are at risk for developing gestational diabetes[37].

Animal studies have shown that vitamin D deficiency impairs the function of pancreatic B cells[38]. The effect of vitamin D on pancreatic B cell function and insulin resistance has also been shown in human studies[39]. In some studies, vitamin D deficiency has been reported to be more common in pregnant women with gestational diabetes than in normal individuals[40,41]. In the of study Lau, vitamin D deficiency was indirectly associated with poor glycemic control and recommended measuring vitamin D levels before or during pregnancy and recommending treatment with vitamin D[42]. The study of Alzaim had similar results and recommended the prescription of vitamin D supplement[43]. Zhang et al. also reported that women with vitamin D deficiency during early pregnancy had a 3.7-fold increased risk of developing GDM compared with those who were vitamin D replete[44]. In these studies, which showed negative results of vitamin D deficiency and gestational diabetes, none of them investigated the results of prescribing vitamin D supplement on developing and controlling glucose.

There are several studies on non-pregnant patients that have investigated the effect of vitamin D supplement on the incidence of diabetes[45]. However, few studies have investigated the effect of vitamin D supplement on glucose metabolism in pregnancy. In the study of Rodniki on 12 pregnant women with GDM, administration of 1,25 dihydroxyvitamin calciferol reduced fasting blood sugar[46]. In the study of Soheilikhah, pregnant women

were treated with three doses of vitamin D (200 IU daily, 50,000 IU monthly, and 50,000 IU every two weeks) from the beginning of pregnancy to delivery. There was a significant improvement in the HOMA-IR index at the end of pregnancy compared to the beginning of pregnancy in the group receiving 50,000 IU of vitamin D every two weeks, which was consistent with our study. However, in the study of Soheilikhah, vitamin D supplement had no effect on fasting blood sugar[47]. But in our study, fasting blood sugar and hemoglobin A1C were significantly reduced in people who took vitamin D supplement. In another study by Asemi et al., vitamin D supplement with a dose of 50,000 IU every 21 days was administered in GDM that improved fasting blood sugar and HOMA-IR index[48], which was consistent with our study. Vitamin D in umbilical cord was not investigated in these studies. In the study of Yap et al., pregnant women with GDM received vitamin D supplement at a dose of 5,000 IU or 400 IU per day. In this study, taking the supplement in the two groups had no effect on fasting blood sugar HOMA - IR, and pregnancy complications such as gestational hypertension, preeclampsia and preterm delivery were not different in the two groups, which was consistent with our study. Furthermore, vitamin D levels in umbilical cord were higher in those who received higher doses of the vitamin, and in our study, vitamin D levels in umbilical cord were higher in those who received vitamin D supplement, although it had no association with obstetric complications[49]. In the study of Mojibian et al. patients were treated with vitamin D 5000 IU daily and a group with 50,000 IU every two weeks, obstetric complications such as preeclampsia, gestational hypertension, preterm delivery, and low birth weight did not differ between the two groups, which was consistent with our study. Also, in their study, those who received higher doses of vitamin D were less likely to develop gestational diabetes[50,51].

However, vitamin D can reach to the body using diverse food sources, but the risk of foodborne diseases is another important issue[52-55]. According to the results of this study and previous studies, it can be concluded that vitamin D deficiency in pregnancy is one of the factors affecting gestational diabetes in addition to other known factors such as race, age, BMI, family history of diabetes, and etc. Also, prescribing vitamin D with a high dose in pregnancy can help better control blood sugar and possibly reduce the need for insulin therapy. However, studies with a larger sample size in which the type of treatment has also been investigated are recommended for better conclusions.

Conclusion

In our study, those who received higher doses of vitamin D were less likely to need insulin therapy than those who received vitamin D routinely. However, there was no statistically significant difference that had not been investigated in other studies.

Acknowledgments

Acknowledgments to all the individuals, institutions, and organizations that have helped us in some way, both in the project process and financially, but this cooperation has not been enough to be mentioned as authors.

Interests conflict

The researchers declare that they have no conflict of interest.

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