Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2017; 2(1): 117-125 Website: jnfs.ssu.ac.ir

The Effect of a Single Mega dose Injection of Vitamin D on Blood Pressure in Mothers at First Gestational Diabetes Mellitus: A Randomized Controlled Clinical Trial

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ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 10 May 2016
Revised: 11 Jun 2016
Accepted: 4 Aug 2016

IRCT code:
138902113840N1

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ABSTRACT

Background: Health benefits of vitamin D has been proved by a large number of studies, however, to the best of our knowledge there has been no study investigating the effect of mega dose of vitamin D on gestational diabetes mellitus (GDM). This study was the first to assess the effect of postpartum injection of mega dose of vitamin D on blood pressure (BP) in GDM. **Methods:** This is a randomized controlled clinical trial conducted on 58 pregnant women suffering from GDM who were randomly assigned into control (CG, n = 24) and intervention group (IG, n = 24). Patients in intervention group (IG) received an intramuscular injection of 300,000 IU of vitamin D. BP, Serum concentration of 25 (OH) D3, parathyroid hormone (PTH), calcium, phosphor, diastolic (DBP) and systolic blood pressure (SBP) were measured at the baseline and after 3 months. **Results:** Mega dose supplementation resulted in increased serum 25-hydroxy vitamin D concentrations in IG compared with the CG (62.10 nmol/l compared with 24.10 nmol/l, $P < 0.001$). Additionally, injection of vitamin D significantly reduced SBP (98.1 ± 9.0 mmHg compared with 106.9 ± 15.9 mmHg, $P = 0.02$) and slightly decreased DBP but it was not statistically significant (63.3 ± 1.5 mmHg compared with 73.6 ± 10.3 mmHg, $P = 0.13$). Serum PTH significantly decrease after intervention in IG compared with CG (2.88 ± 1.60 pmol/l compared with 4.78 ± 2.4 pmol/l $P = 0.003$). **Conclusions:** This study strongly improved vitamin D status in women with GDM and consequently confirmed the efficacy of a mega dose of vitamin D injection on decreasing of BP.

Keywords: *Gestational Diabetes Mellitus; Blood Pressure; Vitamin D*

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic problem in pregnant women and is defined as any abnormal glucose tolerance for the first recognition during pregnancy. 1-14% of all pregnant women suffer from GDM and its incidence increases in pregnancy (American Diabetes Association, 2009, 2009, Carpenter and Coustan, 1982, Sibai and Ross, 2010). The prevalence of vitamin D deficiency was about 82% in women with GDM in

This paper should be cited as: Hosseinzadeh M, Mozaffari-Khosravi H, Shareghfarid E. ***The Effect of a Single Mega dose Injection of Vitamin D on Blood Pressure in Mothers at First Gestational Diabetes Mellitus: A Randomized Controlled Clinical Trial.*** *Journal Of Nutrition And Food Security (JNFS)*, 2017; 2 (1): 117-125.

[DOR: 20.1001.1.24767417.2017.2.1.2.6]

India as a large population country of Asia (Sachan et al., 2005).

Vitamin D in the body is derived from dietary intake and endogenous production in the skin under the sunlight (Holick, 2004, Lips, 2001). It has become deeply entrenched to improved bone health and calcification in literature, but recent studies have shown that vitamin D receptors exist on a very wide range of tissues, including the endothelium and the myocardium (Yuan et al., 2007). So, it was demonstrated that vitamin D has many endocrine and physiological roles other than bone health.

Prevalence of this vitamin in Iran was 86% among pregnant women independent of their clothing type or exposure to the sunlight which is maybe because of low intake of vitamin D sources in their diet (Hashemipour et al., 2004, Kazemi et al., 2009). Maternal serum of 25-(OH) D correlated positively with cord blood 25-(OH)D (Sachan et al., 2005) that has been represented as 75% among the newborns (Kazemi et al., 2009). Another study even reported that each 5 ng/ml decrease in 25-(OH)D concentrations is associated with a 1.29-fold increase in GDM risk (Zhang et al., 2008).

Researchers showed that the relation between GDM and high blood pressure (BP) is a two way relationship (Conen et al., 2007, Lauenborg et al., 2005). The association between poor vitamin D status and hypertension could potentially be mediated by elevated parathyroid hormone (PTH) levels. Elevated PTH levels were associated with high BP and hypertension in several studies (Brickman *et al.*, 1990, Jorde *et al.*, 2000, Jorde *et al.*, 2005, Morfis *et al.*, 1997, Resnick *et al.*, 1986, Young *et al.*, 1990).

Additionally, a relation was suggested between vitamin D deficiency and hypertension as one of the metabolic syndrome components (Boucher, 1998). Much evidence from epidemiological and clinical studies in the last decades has suggested a connection between vitamin D and BP. Some descriptive studies showed that low concentration of 25-(OH)D is related with higher BP with a greater chance of developing hypertension in the future (Forman et al., 2008, Scragg et al., 2007) , increased mortality, and higher rates of cardiovascular events (Wang et al., 2008b). Also, vitamin D and calcium supplementation have been shown to decrease BP (Pfeifer et al., 2001). Seasonal variations in BP have been reported in temperate climates, with higher BP in winter (low UV irradiation) than in summer (high UV irradiation) (Li et al., 2004). Results of the association between vitamin D status and BP, however, may have been inconsistent due to study design and type of vitamin D supplementation. For instance, a study of elderly women showed no significant relationship between vitamin D and BP. Also a systematic review of clinical trials showed no relation between this vitamin and BP in normal dose (Beveridge et al., 2015, Pfeifer et al., 2001).

To our knowledge there is not any data about the effect of mega dose of vitamin D supplementation on BP in women with GDM. These patients have their own problems such as high blood glucose which is significantly and inversely associated with serum 25-(OH)D concentration (Clifton Bligh et al., 2008). Thus, this study was undertaken to investigate the effect of the injection of a mega dose of vitamin D on BP among GDM.

Materials and Methods

Design and Population: This is a randomized clinical trial with a 3-month follow-up of GDM patients post-partum vitamin D supplementation (n = 45) GDM was diagnosed in 24-28 weeks of gestation on the basis of Carpenter and Coustan criteria (Carpenter and Coustan, 1982). Patients were selected among pregnant women affected by GDM for the first time during their recent pregnancy. Inclusion criteria were lack of thyroid, renal and hepatic diseases, and absence of mal absorption. They were randomly assigned into intervention (IG) and control group (CG). IG patients received one intramuscular injection of 300,000 IU of vitamin D.

Participants were asked to refer to the Yazd Diabetes Research Centre in Shahid Sadoughi University of Medical Sciences (SSUMS). Mothers and infants visited the center 3-10 days after the child delivery for recording anthropometric measurements and the project started.

[DOR: 20.1001.1.24767417.2017.2.1.2.6]

Measurements: The patients' weight was measured by Seca scale (Germany Seca) with the accuracy of 0.1 kg. In addition, we interviewed mothers asking about information such as age, literacy level, occupation, type of GDM treatment, type of delivery, and type of feeding, then their information were recorded in some questionnaires for further analysis. BP was measured twice in left arm by Mercury sphygmomanometers (Japan; Panasonic) and the mean value of the two readings was calculated while patients were in relaxing position. Moreover, patients were asked not to change their normal diet.

According to American Heart Association's criteria normal BP for systolic blood pressure (SBP) was less than 120 mmHg and less than 80 mmHg for diastolic blood pressure (DBP). While, prehypertension was defined as 120–139 mmHg for SBP and/or 80–89 mmHg for DBP, and at least 140 mmHg for SBP or 90 mmHg for DBP was called hypertension (Li et al., 2002).

The serum 25-(OH)D3 was measured by ELISA and kit of immunodiagnostic systems Ltd Nyco card equipment (Nyco corporation, Norway) and with the sensitivity of 2 nmol/ml. PTH was also measured by ELISA and immunodiagnostic systems Ltd (Italy; IDS Ltd) as well as sensitivity of 0.6 picomol/l. The serum calcium and phosphor were measured by colorimetric method by AutoAnalyzer (Echoplus Corporation, Italy) and Biosystems kit (Spain; Barcelona; Biosystems).

Administration dose and Follow-up: Vitamin D supplements injection was made by Iran Hormon Corp (Iran, Tehran). Ampoules were kept away from light or frost at 15-30 °C. 12 weeks after vitamin D injection, blood sampling was repeated and the same variables were examined in the same way as for the baseline samples.

Ethical Considerations: The patients freely volunteered to participate in this study and could withdraw from the study whenever they wished. Written informed consent was obtained from each subject before and after the study, after the study proposal had been approved and confirmed by Ethics-in-Research Commission in SSUMS. Also this work was registered in Iranian randomized clinical trial (www.irct.ir). RCT registration code was: IRCT 138902113840N1.

Data analysis: Kolmogorov–Smirnov test was conducted to illustrate normal distribution of the quantitative data. Paired *t*-test was used for comparing means of variables with normal distribution at the beginning and end of the study for each group. Then, Student *t*-test was applied for comparing the means of the variables between the two groups. In addition, Wilcoxon test was carried out to compare the variables with no normal distribution in each group before and after the intervention. Mann–Whitney U test was also used for comparing data from the two groups. Chi-square and Fisher's exact test were conducted to compare qualitative variables between the two groups. The results of the quantitative data with normal distribution were reported as mean ± SD. The significance level was set at P-value equal or less than 0.05.

Results

The statistical analysis were performed totally for 45 patients, 24 of them with the age average of 30.7 ± 6.2 year in the IG and the other 21 with the age average of 29.5 ± 4.0 year in the CG. Just three women were excluded from the CG (**Figure 1**). **Table 1** demonstrates the mean ± SD of the age, pregnancy month for diagnosing GDM, literacy level, type of treatment, type of delivery, and body mass index (BMI) of participants before the intervention. As it is shown, the BMI for the participants in the IG and CG were 28.9±4.8 and 27.9 ± 3.6 kg/m^2, respectively with a non- significance difference at the beginning of the study. Also, based on the BMI classification of World Health Organization, BMI stood at 25-30 kg/m^2 (58.3% in the IG and 57.1% in the CG), and the frequency of the patients between the two groups at the beginning of the intervention was not significant.

Table 2, shows the mean or median for quantitative variables under the study in the two groups before and after the intervention. The mean concentration of serum 25-(OH)D3 in the IG reached

[DOR: 20.1001.1.24767417.2017.2.1.2.6]

from 24.25 to 62.10 nmol/l after the intervention, showing an increase of around 156%, whereas this rate decreased for the CG at around 4.7%. Serum PTH significantly decreased after intervention in IG compared with CG (2.88 ± 106 compared with 4.78 ± 2.4 pmol/l, P = 0.003). In contrast, there were not any evidence of changes in calcium and phosphor of serum at the end of the study.

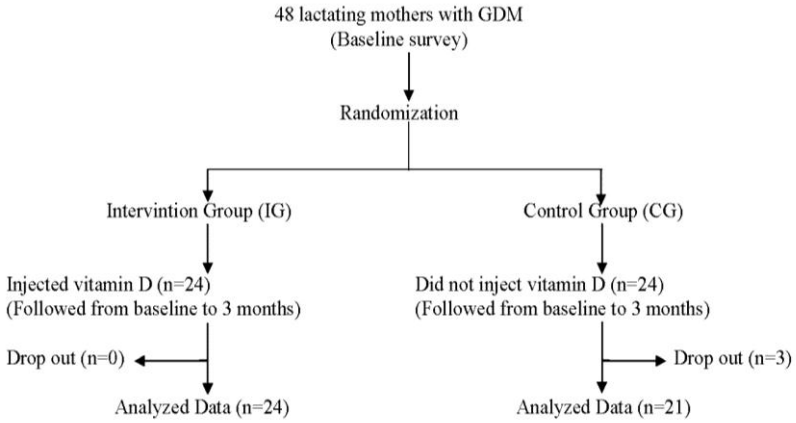

Figure 1. Sampling scheme for the trial

Table 1. Comparing mean ± SD and percentage of variables in control and intervention groups

Variables/groups	Intervention group (n = 24)	Control group (n = 21)	P-value
Age (y)	30.7 ± 6.2	29.5 ± 4.0	0.4[a]
Pregnancy month for diagnosing GDM	5.1 ± 2.3	4.7 ± 2.2	0.6 [a]
Weight (kg)	70.2 ± 12.5	69.9 ± 11.0	0.9 [a]
Height (cm)	155.6 ± 5.0	157.9 ± 4.4	0.4 [a]
Body mass index (kg /m^2)	28.9 ± 4.8	27.9 ± 3.6	0.4 [a]
Literacy Level	n (%)	n (%)	
Illiterate	2(8.3)	3(14.4)	0.3[b]
Guidance school graduate	10(41.7)	11(52.4)	
High school graduate	7(29.2)	3(14.3)	
University graduate	5(20.8)	4(19.0)	
Type of treatment			
Insulin	11(45.8)	9(42.9)	0.9[b]
Diet therapy	10(41.7)	10(47.6)	
Insulin and diet therapy	2(9.5)	3(12.5)	
Type of delivery			
Natural	12(50.0)	14(66.7)	0.2 [b]
Cesarean section	12(50.0)	7(33.3)	
Body mass index categorization(kg/m2)			
18.5-24.9	4(16.7)	4(19.0)	0.9 [b]
25-29.9	14(58.3)	12(57.1)	
30 <	6(25.0)	5(23.8)	

[a]: Mann Whitney test; [b]: Chi square test

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Table 2. The comparison of means or median of the variables between and within the two groups

Variables/groups	Intervention group (n = 24)	Control group (n = 21)	P-value[b]
25-(OH)D3 (nmol/l)			
Before	24.25(13.3-202.4)[a]	25.30(12.8-137.2)	0.440
After	62.10(31.7-278.9)	24.10(18.0-191.7)	< 0.001
P-value [c]	< 0.001	0.020	
Parathyroid hormone (pmol/l)			
Before	3.42 ± 1.8	3.60 ± 1.5	0.600
After	2.88 ± 1.6	4.78 ± 2.4	0.003
P-value	0.06	0.04	
Serum Calcium (mg/dl)			
Before	9.01 ± 0.20	8.90 ± 0.10	0.100
After	9.17 ± 0.35	9.12 ± 0.45	0.700
P-value	0.070	0.013	
Serum Phosphor (mg/dl)			
Before	3.37 ± 0.45	3.61 ± 0.39	0.070
After	3.25 ± 0.30	3.41 ± 0.36	0.300
P-value	0.500	0.500	
Body mass index (kg/m^2)			
Before	29.1 ± 5.0	27.9 ± 3.6	0.400
After	29.0 ± 5.6	27.4 ± 3.7	0.100
P-value	0.350	0.250	

[a]: Median (Min-Max); [b]: Mann- Whitney U test has been used for 25-$(OH)D_3$ and Student *t*-test for others; [c]: Wilcoxon test has been used for 25-$(OH)D_3$ and Paired *t*-test for other cases.

As it is tabulated in **Table 3**, no significant differences were found between CG and IG for both SBP and DBP before intervention. In contrast after intervention, the SBP decreased in IG which was statistically significant (98.1 ± 9.0 compared with 101.0 ± 10.5, $P = 0.05$), however this was not significant in CG.

DBP decreased between two groups after intervention but it was not statistically significant (63.3 ± 14.5 compared with 67.7 ± 8.0, $P = 0.13$).

Discussion

In our study the mega doses supplemented with vitamin D presented higher plasma 25-(OH) D after 3 months. After the intervention with a single dose of 300,000 IU of vitamin D and after 12 weeks of incubation, these figures reached to 4.2% and 71.4% for the IG. There was a statistically significant reduction in the SBP of participants, while there was no significant reduction in the DBP. To our knowledge, this study is the first one to link mega dose of vitamin D injection and BP in GDM. The safety of this dose was published elsewhere (Hosseinzadeh-Shamsi-Anar et al., 2012).

There were some results in line with our study, for example a study in African-Caribbean youths found that supplementing with 2000IU/d vitamin D may be effective at optimizing vitamin D status and reducing aortic stiffness (Dong et al., 2010). Results achieved by a randomized control trial study also said that for every 1-ng/mL 25-(OH) D that was increased in plasma, a significant 0.2-mmHg reduction in SBP was indicated (Forman et al., 2013). A meta-analysis of four RCT with large population suggested that oral vitamin D supplementation may cause a reduction in SBP but not DBP (Wu et al., 2010). Another study that aimed to investigate the effect of vitamin D supplementation on flow mediated vasodilatation in

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diabetic patients also concluded that vitamin D supplementation decreased SBP and improved flow-mediated vasodilatation (Sugden et al., 2008). Third national health and nutrition examination survey (NHANES III) also revealed that high sun exposure of vitamin D supplementation, was inversely associated with BP in a large sample representative (Scragg et al., 2007).

Table 3. The comparison mean ± SD of systolic and diastolic blood pressure within and between two groups

Variables/groups	Intervention group (n = 24)	Control group (n = 21)	P-value[a]
Systolic blood pressure (mmHg)			
Before	101.0 ± 10.5	107.1 ± 15.6	0.10
After	98.1 ± 9.0	106.0. ± 15.9	0.20
P-value[b]	0.05	0.94	
Diastolic blood pressure (mmHg)			
Before	67.7 ± 8.0	74.8 ± 23.2	0.10
After	63.3 ± 14.5	73.6 ± 10.3	0.01
P-value	0.13	0.80	

[a]: Student *t*-test; [b] Paired *t*-test

The effect of vitamin D on BP is an issue of controversy. A systematic review and meta-analysis of 46 clinical trials study in contrast with ours showed no significant relationship between vitamin D supplementation and DBP or SBP. This may be because of various doses applied in different studies i.e., from 1600 to more than 5000 IU/d (Beveridge et al., 2015). Since most doses were in low ranges, so it could have different effects in comparison with mega doses of this study. Another research investigating supplementation with calcium and vitamin D could slightly decrease BP in elderly women but it didn't show any significant relationship (Pfeifer et al., 2001), which could be because of different factors such as the low skin synthesis of vitamin D in elderly, short term of supplementation, or insufficient doses of vitamin. Furthermore, a cohort study found that low intake of vitamin D or calcium food sources was positively associated with hypertension and supplementation with calcium or vitamin D improved it (Wang et al., 2008a). Additionally, 11 weeks of supplementing with 5 micrograms vitamin D had no significant effect on BP in elderly (Pan et al., 1992).

We hypothesized that the effect of vitamin D on BP is most likely due to the restoration of parathyroid gland functions to normal status particularly in GDM. This makes a defective cycle between incidence of GDM and vitamin D deficiency and hypertension.

There are some potential mechanisms for relation between vitamin D deficiency and hypertension. Some studies suggested that this effects may be mediated via renin-angiotensin aldosterone-system (RAAS) or endothelial or vascular smooth muscle (VSM) function directly. Hypertension is may be a kind of hyper parathyroidism that happens in vitamin D and calcium deficiency (Langford et al., 1980). Parathyroidectomy after primary hyper parathyroidism showed clearly that this effect of PTH decreases blood pressure and improves arterial smooth muscle (Bertorini, 1989, Stefenelli et al., 1993).It may be because of the effect of PTH up-regulates RAAS activity and promoting renin release (Koiwa et al., 2012, Mizobuchi et al., 2007). The mechanism linking PTH and blood pressure is still unclear and several pathways might be under consideration. PTH also directly promotes aldosterone release from adrenal glands (Tomaschitz et al., 2012). There is an inverse association between vitamin D concentration and plasma rennin and circulating angiotensin II (Hosseinzadeh-Shamsi-Anar et al., 2012, Hosseinzadeh et al., 2016). On the other hand, direct

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effects may include increased occurrence of diabetes mellitus, atherosclerosis, vascular calcification, and, changes in renal structure and function (Rostand, 2014). Results of a human study on hypertensive patient investigated that high doses of vitamin D increases aldosterone response to angiotensin II infusion, and suppresses the effect on renal-vascular tissue- renin–angiotensin system renin–angiotensin system (Carrera et al., 2007).

The outstanding point in our study was the presence of a control group and the administration of blood taking for participants as well as the measurement of calcium and phosphor together with 25-(OH)D of the serum. Lack of calcium and creatinine measures in the urine can be taken as a limitation of this intervention since this could confirm the presence of hypervitaminosis more exactly and confidently. Also, ELISA kit was applied to measure vitamin D, which is of lower accuracy compared with HPLC and RIA methods. Another limitation of the study was its short duration, while if a longer period had been taken it could better control the efficacy of a mega dose of vitamin D. Whilst, its effect on serum concentration of related parameters to vitamin D as well as the likelihood of causing hypervitaminosis could be controlled too.

Further clinical trial studies with different doses of vitamin D have to be conducted to determine the effect of mega doses of vitamin D on other health-related parameters such as the factors related to metabolic syndrome as well as arterial health.

Conclusions

The 300,000 IU single dose of IM injection of vitamin D is regarded as an effective and safe procedure to improve vitamin D status promptly. Also it ameliorates the factors related to the health specially to reduce blood pressure in the regions faced with severe vitamin D deficiency.

Acknowledgments

We would like to first thank the respectful staff in Yazd Diabetes Research Centre particularly Mrs Leila Azodi and Mrs Fateme Zare for their cooperation in blood taking and biochemical tests; lactating 12 mothers who participated in the study; and Shahid Sadoughi University of Medical Sciences for funding the project.

Author contribution s

Mozaffari-Khosravi H participated to conception and design of study, managing the project and drafting the manuscript. Hosseinzadeh M contributed to design of study, acquisition and analysis of data, and drafting the manuscript and Shareghfarid E participated to data analysis and drafting the manuscript. All authors read the paper and verified it.

Conflicts of interest

None of the authors had any conflict of interest.

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[DOR: 20.1001.1.24767417.2017.2.1.2.6]