DOI: 10.1111/j.1464-5491.2011.03473.x

Article: Treatment

Effects of a single post-partum injection of a high dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus

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Accepted 29 September 2011

Abstract

Aim This study was performed to determine the effect of a single, large, intramuscular injection of vitamin D post-partum on glucose tolerance and insulin resistance in women with gestational diabetes.

Methods Forty-five participants in a randomized controlled trial on gestational diabetes mellitus were divided into an intervention group and a control group. Only subjects in the intervention group received one intramuscular injection of 300 000 IU of vitamin D3. HbA_{1c}, serum 25-hydroxyvitamin D3, fasting insulin and blood glucose, C-peptide, homeostasis model assessment insulin resistance index (HOMA-IR), β-cell function, insulin sensitivity and the Quantitative Insulin Sensitivity Check Index (QUICKI) were measured at baseline and after 3 months of intervention.

Results Approximately 80% of the mothers had a degree of vitamin D deficiency. Post-intervention, this was found in 4.2 and 71.4% in the intervention and control groups, respectively. The medians of HOMA-IR indices before and after intervention were 0.6 and 0.5 ($P = 0.7$), respectively, in subjects in the intervention group, and 0.5 and 0.9 ($P = 0.01$) in subjects in the control group. The mean of the QUICKI fell only in the control group ($P = 0.008$). In the control group, β-cell function increased by ~8% ($P = 0.01$) and insulin sensitivity decreased after 3 months ($P = 0.002$). Post-intervention, the median C-peptide decreased in the intervention group and increased in the control group, but the change was significant only in the control group ($P = 0.03$).

Conclusions A single injection of 300 000 IU of vitamin D3 achieves a 3-month serum 25-hydroxyvitamin D range of 50–80 nmol/l and is an efficient, effective and safe procedure for improving the vitamin status and indices of insulin resistance in mothers with gestational diabetes after delivery.

Diabet. Med. 29, 36–42 (2012)

Keywords diabetes, insulin resistance

Abbreviations HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index

Introduction

Unlike earlier work concentrating mainly on the role of vitamin D in calcium and phosphorus homeostasis and the prevention and treatment of rickets, publications over the last 20 years—since vitamin D receptors were found in many tissues—have reported several other physiologic roles for this vitamin, with strong inverse correlations between depletion and risk for diseases such as cancer, and infectious, neurologic and endocrine diseases, including different types of diabetes [1]. Mechanisms have been identified explaining the impact of this vitamin on the tissues; for example, by increasing intracytoplasmic calcium or releasing calcium from intracellular organelles, in addition to genomic effects [2,3].

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Evidence suggests that reduced vitamin D availability (lower serum 25-hydroxyvitamin D concentration in serum) is associated with impairment in glucose tolerance and increased risks of incident Type 2 diabetes [4]. There are also reports of negative relationships between baseline serum concentration of 25-hydroxyvitamin D and subsequent risks of increased insulin resistance [5]. Vitamin D supplementation in hyperglycaemia and in individuals with vitamin D deficiency has increased insulin secretion [6,7]. There are, however, other studies on the supplementary role of vitamin D and glucose tolerance, indicating no positive role of the vitamin in this process [6,8,9]. These disparities may be explained by factors such as the dose of vitamin D given (D2 or D3), the duration of supplementation and the vitamin D status in subjects before supplementation, in addition to the route of administration and variation in compliance amongst participants.

Today, there is still controversy in the scientific world over the ideal dosages or route of administration for vitamin D supplementation in glucose tolerance. However, researchers consider that a dose of > 50 μg (2000 IU) daily, which maintains serum 25-hydroxyvitamin D3 concentrations at ~80 nmol/l, to be appropriate [10].

Serum 25-hydroxyvitamin D concentrations at 24–28 weeks of pregnancy, or when gestational diabetes mellitus is diagnosed, have been remarkably low in pregnant women with gestational diabetes, compared with values in pregnancies in women with normal glucose tolerance [11,12]. Vitamin D deficiency and gestational diabetes are both important disorders, but vitamin D status has not often been assessed in gestational diabetes. In Iran, vitamin D deficiency has ranged from 18 to 84% using various definitions (usually 25-hydroxyvitamin D < 35 nmol/l). This deficiency, however, is more severe in women with gestational diabetes compared with healthy individuals [11,12]. Gestational diabetes, where diabetes first develops in pregnancy or is diagnosed in pregnancy, is seen in 3–8% of pregnancies [13]. In Tehran, the overall prevalence of gestational diabetes is reported as ~7% [11].

Mothers with gestational diabetes often exhibit continued glucose intolerance post-partum, with the metabolic syndrome with increased insulin resistance 3 days after delivery, in relation to that of comparable women without gestational diabetes [14]. Increased insulin resistance likely increases the risk of the metabolic syndrome and Type 2 diabetes in subsequent years, as long-term follow-up shows that gestational diabetes is followed by the development of Type 2 diabetes in up to 50% of all affected pregnancies [15,16]. With regard to the role of vitamin D in glucose tolerance and insulin resistance, the possibility that administration of vitamin D supplements to women with gestational diabetes and avoidance of possible deficiency may improve indices of insulin resistance and other markers of glucose intolerance. Therefore, as the effect of a single, large, intramuscular injection of vitamin D on post-partum glucose tolerance and insulin resistance indices in gestational diabetes has not been studied, we have investigated the effects of a single, intramuscular injection of vitamin D3 (300 000 IU) on indices of insulin resistance and insulin secretion over 3 months.

Material and methods

Design and population

This was a randomized, controlled trial study with a 3-month follow-up of 45 women with gestational diabetes with and without post-partum vitamin D supplementation. Gestational diabetes was diagnosed at 24–28 weeks of gestation on the basis of Carpenter and Coustan criteria [17].

Participants were selected from pregnant women who developed gestational diabetes for the first time during their recent pregnancy. Criteria for inclusion included lack of thyroid, renal and hepatic diseases and absence of malabsorption. They were randomly assigned into an intervention group and a control group. Women in the intervention group, but not those in the control group, received one intramuscular injection of 300 000 IU of vitamin D3.

Participants were invited to return to the Diabetes Research Centre in Shahid Sadoughi University of Medical Sciences 3–10 days after delivery, so that details such as anthropometric measurements of both the mothers and their infants could be recorded and the trial started. The participants' weight was measured through a Seca scale with an accuracy of 0.1 kg. In addition, a questionnaire including questions on age, literacy level, occupation, type of treatment for gestational diabetes, type of delivery and infant feeding method, was completed with information taken from medical history files, as well as by interview. The participants were asked not to change their normal diet. Infant anthropometric measurements, including birthweight and height, were recorded using the infant growth monitoring card. These measurements were recorded monthly at the healthcare centre and the infant's growth status was determined using the World Health Organization anthropometric variables percentile.

Experiments

A total of 6 ml of peripheral blood was taken from each of the mothers after 8 h or more of fasting and before 10 days post-delivery.

For HbA_{1c} assays, 2 ml of blood was collected into tubes containing EDTA; plasma and serum were separated and stored at –20 °Ċ until assay. The immunoassay method (NycoCard; Nyco Corporation, Oslo, Norway) was used for serum 25-hydroxyvitamin D; other tests were carried out on serum stored at –80 °Ċ in 1.5-ml vials. Post-intervention, patients gave further blood samples after 8 h or more of fasting. Aliquots of pre- and post-intervention serum samples were defrosted and immunoassay of serum 25-hydroxyvitamin D3 was carried out using ELISA and an Immunodiagnostic Systems Ltd kit (IDS Ltd, Boldon, UK) with a sensitivity of 2 nmol/ml. Fasting serum insulin concentrations were also assessed using ELISA kits

(Diametra Corporation, Milan, Italy) with a sensitivity of 2 μIU/ml. Serum concentration of C-peptide, using an ELISA kit (Diametra Corporation) and with a sensitivity of 0.1 ng/ml, was measured; an oral 75-g glucose tolerance test was accomplished before and after the intervention. Glucose concentration of serum (fasting and after 2 h) was also assessed using an enzymatic (glucose oxidize–peroxides) *in vitro* test (Autoanalyser; Echo Plus Corporation, Roma, Italy).

Administration dose and follow-up

Vitamin D supplements for injection were made by the Iran Hormone Corp. (Tehran, Iran). in the form of 1-ml ampoules (each containing 300 000 IU cholecalciferol). Ampoules were kept away from light or frost at temperatures of 15–30 °C. Twelve weeks after vitamin D injection, blood sampling was repeated and the same variables examined in the same way as for baseline samples. Serum calcium was measured by calorimetric method using an Autoanalyser (Echo Plus Corporation) and a Biosystems' kit (Biosystems, Barcelona, Spain).

Ethical considerations

The participants freely volunteered to participate in this study and could withdraw from the study whenever they wished. The study proposal was approved and confirmed by the Ethics-in-Research Commission of Shahid Sadoughi University of Medical Sciences and written informed consent was obtained from each subject.

Statistical analysis

Insulin resistance status was assessed using the following indices: homeostasis model assessment of insulin resistance (HOMA-IR), level of β-cell function (B%), insulin sensitivity (S%), as well as Quantitative Insulin Sensitivity Check Index (QUICKI). HOMA-IR, β-cell function and insulin sensitivity were assessed using a software calculation, HOMA (HOMA calculator, version 2.2.2; Diabetes Trial Unit, University of Oxford, www.dtu.ox.ac.uk) and the QUICKI calculated using the logarithmic transformation: 1/[log fasting insulin (U/ml) + log fasting glucose (mg/dl)] [9]. SPSS software version 11 (SPSS Inc., Chicago, IL, USA) was used to analyse the data and the following tests were used: the Kolmogorov–Smirnov test to illustrate normal distribution of the quantitative data; the paired *t*-test for comparing means of variables with normal distribution at the beginning and the end of the study for each group; the Student *t*-test for comparing the mean of the variables between the two groups; the Wilcoxon test to compare the variables not normally distributed in each group before and after the intervention; the Mann–Whitney *U*-test for comparing data from the two groups; and the χ^2-test and Fisher's exact test for comparing qualitative variables between the two groups. The results of the quantitative data with normal distribution were reported as mean ± SD, but quantitative data not normally distributed was reported using percentiles 25, 50 (median) and 75. The significance level was set at a *P*-value equal or less than 0.05.

Results

In this study, 24 women in the intervention group and 21 in the control group, with an average age of 30.7 ± 6.2 and 29.5 ± 4.0 years, respectively, completed the study. Table 1 demonstrates the baseline characteristics of the participants before the intervention. As shown, no significant differences were found for quantitative variables such as BMI, month of diagnosing gestational diabetes and HbA_{1c}, or for qualitative variables such as literacy level, type of gestational diabetes therapy and type of delivery between the groups. The means and medians (percentile 50) for quantitative variables under study in the two groups, before and after the intervention, are shown in Table 2. Median concentrations of serum 25-hydroxyvitamin D3 in the intervention group before and after the intervention were 24.25 and 62.1 nmol/l, respectively ($P < 0.001$), whereas in the control group the concentrations were 25.3 and 24.1 nmol/l, respectively ($P = 0.02$). As shown in Table 2, median concentration of this vitamin D metabolite did not differ in these groups. If vitamin D deficiency is defined as a serum concentration of 25-hydroxyvitamin D3 < 35 nmol/l [18], approximately 80% of mothers had a degree of vitamin D deficiency. Post-intervention, these figures were 4.2% in the intervention group and 71.4% in the control group.

Throughout the intervention, 23 (95.8%) babies in the intervention group and 20 (95.2%) in the control group were breastfed exclusively, with no evidence of growth abnormalities during the intervention period. The median baseline HOMA-IR index did not differ in the two groups (Table 2). However, post-intervention median of this index was significantly higher in the control group than in the intervention group ($P = 0.004$). In contrast, only in the control group did the median of this index rise significantly after the supplementation ($P = 0.01$), whereas in the intervention group it did not show a significant difference ($P = 0.70$).

The mean QUICKI did not show a significant difference between the study groups at baseline (Table 2), whereas the mean in the control group decreased significantly ($P = 0.006$) after the intervention. Also, the mean of this index did not change after supplementation in the intervention group, although this index increased in the control group ($P = 0.008$).

Table 2 shows mean β-cell function and insulin sensitivity for the two study groups. Mean β-cell function did not differ after intervention ($P = 0.4$); but increased by ∼8% in the control group after supplementation ($P = 0.01$). There was no significant difference in insulin sensitivity between the study groups at baseline; after supplementation, insulin sensitivity was lower by ∼58% in the control group ($P = 0.002$), whilst insulin sensitivity did not change over the 3-month follow-up in participants in the intervention group.

As shown in Table 2, C-peptide was not significantly different between the two study groups at baseline, whereas after the

Table 1 The comparison of baseline findings for the variables under the study in the intervention group with those in the control group

Variables	Intervention group (n = 24)*	Control group (n = 21)	P-value
Age (year)	30.7 ± 6.2	29.5 ± 4	0.4
Month of pregnancy for diagnosing gestational diabetes	5.1 ± 2.3	4.7 ± 2.2	0.6
Weight (kg)	70.2 ± 12.5	69.9 ± 11	0.9
Height (cm)	155.6 ± 5	157.9 ± 4.4	0.4
Weight before pregnancy (kg)	69.58 ± 13.57	67.23 ± 13.06	0.5
Waist circumference (cm)	90.0 ± 8.7	107.8 ± 8.8	0.9
Hip circumference (cm)	110.3 ± 10.3	107.8 ± 8.8	0.5
BMI (kg/m^2)	28.9 ± 4.8	27.9 ± 3.6	0.4
HbA_{1c} (mmol/mol)	36 ± 7	33 ± 7	0.2
HbA_{1c} (%)	5.48 ± 0.69	5.20 ± 0.73	0.1
Systolic blood pressure (mmHg)	101.0 ± 10.5	107.1 ± 15.6	0.1
Diastolic blood pressure (mmHg)	67.7 ± 8.0	74.8 ± 23.2	0.1
Literacy level	n (%)	n (%)	
Illiterate	2 (8.3)	3 (14.4)	0.6
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)	
Type of treatment			
Insulin	11 (45.8)	9 (42.9)	0.9
Diet therapy	10 (41.7)	10 (47.6)	
Insulin and diet therapy	2 (9.5)	3 (12.5)	
Type of delivery			
Natural	12 (50)	14 (66.7)	0.2
Caesarean section	12 (50)	7 (33.3)	
BMI (kg/m^2)			
18.5–24.9	4 (16.7)	4 (19)	0.9
25–29.9	14 (58.3)	12 (57.1)	
≥ 30	6 (25)	5 (23.8)	
Serum 25-hydroxyvitamin D, nmol/l)			
< 35	19 (79.2)	16 (76.2)	0.6
> 35	5 (20.8)	5 (23.8)	

intervention it was significantly higher in participants in the control group (P = 0.05) because of non-significant decreases in C-peptide after supplementation and increases in C-peptide in participants in the control group (P = 0.03).

Mean fasting blood glucose did not differ between the study groups, either at baseline or after the intervention (see Table 2), nor did it change with supplementation in participants in the intervention group, although in the participants in the control group it increased significantly (P = 0.05). Mean 2-h blood glucose at 75-g oral glucose tolerance test did not differ at baseline or at 3-month follow-up between the intervention and control study groups, although it was increased at follow-up in both groups.

Mean HbA_{1c} did not differ between the two groups either before or after intervention, nor did pre- or post-intervention means differ in either group (see Table 2).

The means of serum calcium concentration compared before and after the intervention between the two groups were not statistically significant. Only the mean of the intervention group increased significantly after the supplementation. The ranges of this element at the end of the supplementation in the intervention group and the control group were 8.6–10.3 and 8.7–10.3 mg/dl, respectively.

Discussion

The present study found that a single large supplementary dose of vitamin D3 (300 000 IU) by intramuscular injection in women with gestational diabetes immediately after delivery not only improved vitamin D status but also inhibited the significant increases in HOMA-IR index and reductions in the QUICKI and insulin sensitivity that were seen in the control subjects at 3-month follow-up who had not been given a supplement.

. In mothers, there was no incident of hypercalcaemia or of undue increase in serum 25-hydroxyvitamin D, suggesting that this is a safe procedure for mothers; normal infant growth and well-being after supplementation suggest that this method is also safe for breastfed infants.

Recent studies of supplementary vitamin D on glucose homeostasis have been contradictory. Oral doses of 100 000 IU twice a week for 2 weeks made no difference to mean serum insulin or blood pressure in participants (n = 33) with vitamin D deficiency but free of diabetes [9]. No reported changes in insulin secretion or sensitivity were reported with three doses of vitamin D (each of 120 000 IU) in apparently healthy but centrally obese men over 6 weeks [19]. In another

Table 2 The comparison of quantitative variables between the control group and the intervention group before and after the 3-month follow-up period

	Intervention group		Control group		
Groups Variables	Mean ± SD	*P*-value	Mean ± SD	*P*-value*	Between group *P*-value‡
QUICKI					
Baseline	0.37 ± 0.23	0.09	0.38 ± 0.29	0.008	0.80
End	0.38 ± 0.02		0.36 ± 0.02		0.006
β-cell function (%B)					
Baseline	76.27 ± 35.33	0.40	69.01 ± 28.82	0.01	0.40
End	69.97 ± 28.13		77.68 ± 34.44		0.40
Insulin sensitivity (%S)					
Baseline	164.36 ± 51.28	0.70	175.26 ± 61.16	0.001	0.50
End	169.68 ± 53.48		122.84 ± 41.15		0.002
Fasting blood glucose (mg/dl)					
Baseline	91.8 ± 17.3	0.76	98.3 ± 30.7	0.05	0.41
End	92.9 ± 10.6		104.7 ± 33.5		0.11
Glucose tolerance test (mg/dl)					
Baseline	114 ± 45.5	0.6	107 ± 65.5	0.06	0.1
End	123 ± 69.04		117 ± 56.3		0.8
HbA_{1c} (mmol/mol)					
Baseline	36 ± 7	0.63	33 ± 7	0.77	0.20
End	37 ± 13		34 ± 6		0.22
HbA_{1c} (%)					
Baseline	5.48 ± 0.6	0.73	5.20 ± 0.73	0.67	0.1
End	5.58 ± 1.2		5.21 ± 0.52		0.2
BMI (kg/m^2)					
Baseline	29.15 ± 5	0.35	27.9 ± 3.6	0.25	0.4
End	29.8 ± 5.6		27.4 ± 3.7		0.1
Calcium (mg/dl)					
Baseline	9.01 ± 0.2	0.07	8.9 ± 0.10	0.01	0.1
End	9.17 ± 0.35		9.12 ± 0.45		0.7
Percentiles	25th, 50th, 75th	*P*-value	25th, 50th, 75th	*P*-value†	*P*-value§
HOMA-IR					
Baseline	0.5, 0.6, 0.8	0.7	0.5, 0.5, 0.8	0.01	0.50
End	0.4, 0.5, 0.8		0.7, 0.9, 1.0		0.004
C-peptide (ng/ml)					
Baseline	0.9, 1.3, 1.80	0.36	0.7, 1.1, 1.95	0.03	0.34
End	0.65, 1.20, 1.67		0.75, 1.90, 2.50		0.05
25-hydroxyvitamin D (nmol/l)					
Baseline	17.05, 24.25, 28.2	< 0.001	20.00, 25.30, 32.35	0.02	0.44
End	55.47, 62.10, 71.70		21.70, 24.10, 48.60		< 0.001

*Paired *t*-test.
†Wilcoxon test.
‡Student *t*-test.
§Mann–Whitney *U*-test.
HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index.

study [20], where 61 patients with diabetes were randomly assigned into three groups to receive 100 000 and 200 000 IU doses of vitamin D or placebo, no differences were observed in HbA_{1c} after 16 weeks; however, mean HOMA-IR was significantly reduced in the group receiving 200 000 IU vs. placebo. In a study of women with vitamin D deficiency that examined insulin resistance [21], participants were given vitamin D (4000 IU/day) for 6 months and indices of insulin sensitivity were improved after 3 months. After 6 months, however, no significant differences were detected, but this was attributed to non-compliance with supplementation. In the present study, injected supplements avoided non-compliance, which may explain the fact that we found improvement in HOMA and QUICKI in participants who had been given the supplements. In addition, there was no hypervitaminosis, hypercalcaemia or other complications in the intervention group.

To determine the effect of oral vitamin D (calcitriol 0.5 mcg per day) over 8 weeks on glycaemic and lipid indices in haemodialysis patients, Bonakdaran *et al.* [22] examined blood glucose, HbA_{1c}, insulin resistance index, total cholesterol and serum triacylglycerol pre- and post-supplementation and all were significantly decreased by this intervention vs. controls. The changes are in line with those found in our study, although we failed to find reductions in HbA_{1c}, likely because our 8-week

study period was too short for changes in HbA_{1c} to be detectable. In addition, all HbA_{1c} values were in the local normal range, which could also account for this discrepancy.

Several other studies have been conducted on the effect of supplementary vitamin D on glucose and insulin metabolism, with non-significant results [6,8,23,24]. In a cohort study carried out by Vilarrasa *et al.* on obesity, no significant relationships were found between plasma or serum 25-hydroxyvitamin D, blood glucose, insulin resistance or lipid profiles [25]. Other such studies have reported increases [26], decreases [8,24,27] or no changes [6,28] in blood insulin or insulin sensitivity. Of importance, however, is that, in some studies [27], a combination of vitamin D and calcium had been given; thus, various changes cannot always be attributed to vitamin D as, giving calcium alone can affect glucose homeostasis favourably, although increased calcium intakes can also be associated with adverse effects on cardiometabolic outcomes [22,29].

There are other studies on patients with diabetes or impaired glucose tolerance where blood glucose concentration was either decreased [7,8] or increased [24] following vitamin D supplementation. In the present study, however, a considerable rise in fasting blood glucose was seen in the control group that had been prevented by supplementation in the intervention group, although non-significant increases were seen in 2-h blood glucose in both groups (see Table 2).

There is also experimental evidence for associations of vitamin D intakes with Type 2 diabetes. In vitamin-D-deficient rats [30], insulin secretion in response to glucose challenge was increased by provision of vitamin D [31], and suggested effects independent from those of calcium administration, as calcium administration did not improve insulin secretary responses in rats with vitamin D deficiency.

The effect of vitamin D on glucose tolerance and insulin sensitivity, including its direct effect on β-cell insulin secretary function, is effected through pancreatic islets, likely attributable to pancreas vitamin D receptors, as well as through the effects on insulin sensitivity as a result of stimulation of insulin receptor signalling pathway activity [32], as *in vitro* studies show that 1.25-$(OH)_2$D can increase insulin receptor gene transcription as well as the up-regulation of insulin-related glucose-transport genes [9]. In addition, direct stimulation of phosphatidyl 3-kinase by 1.25-$(OH)_2$D can also increase glucose oxidation [33]. Vitamin D insufficiency also leads to an increase in parathyroid hormone secretion, which reduces insulin sensitivity in healthy adults [34].

Further indirect effects of vitamin D repletion can result from the anti-inflammatory effects of vitamin D, as, in insulin resistance, there is increased secretion of pro-inflammatory cytokines, whilst vitamin D reduces secretion of inflammatory cytokines such as interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α)—which can themselves increase insulin resistance—whilst also increasing secretion of anti-inflammatory cytokines such as IL-10 [21,35].

The short follow-up period of 3 months and the small sample size are limitations of the present study. Another limitation is lack of determination of calcium status in mothers' milk and calcium and vitamin D status of their infants as well. Longer-term randomized controlled trials of adequate supplementation for beneficial effects on Type 2 diabetes risk and associated risk factors (such as other metabolic syndrome abnormalities and markers of chronic inflammation) are of considerable current interest [36]. Similarly, we suggest that long-term studies of high-dose vitamin D supplementation are required to determine whether this may reduce the risk of eventual Type 2 diabetes in women who have had gestational diabetes.

Conclusions

A single post-partum injection of 300 000 IU of vitamin D3 in women with gestational diabetes provides a satisfactory serum 25-hydroxyvitamin D of 50–80 nmol/l after 3 months and is an efficient, effective and safe procedure for improving vitamin D status and reducing insulin resistance in mothers with gestational diabetes after delivery. Further investigation is needed, however, to determine whether long-term maintenance of adequate vitamin D status may reduce the risk of later Type 2 diabetes in such women.

Competing interests

Nothing to declare.

Acknowledgements

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

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