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Review Article

Vitamin D and Gestational Diabetes

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Abstract

Aim: To investigate the relationship between maternal vitamin D status with glucose intolerance and its consequences in pregnant women with (GDM): Gestational Diabetes.

Methods: One hundred and twenty middle-aged pregnant women, in their third trimester, with and without GDM, were consecutively enrolled from the Obstetrics and Gynaecology Department at King Abdulaziz University Hospital. They were matched for age and gestational age in a case-control study design. All participants were subjected to medical history taking, clinical examination and laboratory investigations.

Results: Obesity and vitamin D severe deficiency were highly prevalent among the study participants. Significantly higher alkaline phosphatase activity, C-reactive protein and haemoglobin A1c values were found among GDM patients than their control counterparts ($p<0.05$). Serum 25-OH vitamin D levels were inversely correlated with bone-specific ALP activity ($r= - 0.232$, $p<0.05$) and with the current body mass index classes ($r = -0.246$, $p<0.01$).

Conclusion: Although vitamin D status was not associated with the risk of developing GDM, hypovitaminosis D and obesity were highly prevalent among our study population of Saudi pregnant women with and without GDM. The effect of vitamin D deficiency on maternal health and foetal development requires conducting more clinical studies to clarify the exact implication of vitamin D in inducing adverse maternal and neonatal effects.

Keywords: BMI; CRP; Hba1c

Introduction

Vitamin D deficiency and insufficiency have been associated with a variety of adverse maternal and foetal outcomes, ranging from preeclampsia, gestational diabetes, preterm delivery, intrauterine growth restriction, spontaneous abortion, and cesarean section [1-4]. Certain high risk groups for vitamin D deficiency in pregnancy have been identified, including vegetarians, women with limited sun exposure, ethnic minorities, especially those with darker skin and also among heavier women than leaner individuals [5-6]. GDM: Gestational Diabetes Mellitus: is a state of hyperglycaemia or glucose intolerance with first recognition during pregnancy that affects maternal, fetal and neonatal well-being [7]. The causes of GDM are an active area of investigation, with growing interest in vitamin D deficiency as a potential cause [8]. GDM and maternal obesity are independently associated with several adverse complications [9]. The HAPO: Hyperglycemia and Adverse Pregnancy Outcome; study demonstrated a positive linear relationship between fasting and post-load glucose concentrations and adverse perinatal outcomes including fetal size, adiposity and hyperinsulinism [10]. Although obesity is associated strongly with both GDM [11] and vitamin D deficiency [12], it remains unclear whether vitamin D status affects a mother's risk of experiencing GDM. Therefore, this study aimed to investigate the relationship between maternal vitamin D status with glucose intolerance and its consequences in pregnant women with GDM.

Methods

Sixty pregnant consecutive women with established diagnosis of GDM were matched for age and gestational age with 60 pregnant women without GDM in a case-control study design. Study subjects were consecutively enrolled from the Obstetrics and Gynaecology Department at King Abdulaziz University Hospital (KAUH). GDM diagnosis was depicted by estimating the fasting and 2-hours post-prandial blood glucose levels in previous antenatal care visit and they were receiving treatment through a collaborative approach with the GDM clinics at the Internal Medicine Department at KAUH. Control subjects were recruited during their routine antenatal care visits and they had normal fasting and 2-hours post-prandial blood glucose levels blood glucose levels. All participants provided informed consent. The study was approved by the ethical committee of KAUH, King Abdulaziz University, Jeddah, Saudi Arabia. Eligibility criteria included women aged between 16 and 45 years, and gestational age >24 weeks pregnant without a history of type 1 or 2 diabetes mellitus, thyroid or parathyroid disorders, renal or hepatic diseases, as well as any cardiovascular diseases (such as hypertension or cardiac disease). Those receiving anticonvulsant drugs, chemotherapy, psychotropic drugs, or calcium and vitamin D supplements or medical complications related to pregnancy were excluded from the study. Gestational ages were confirmed with Doppler ultrasound early in pregnancy. All participants were subjected to detailed history taking with special focus on sociodemographic characteristics, parity, preterm delivery, spontaneous abortion, previous history of a child with macrosomia, gestational age at diagnosis of gestational diabetes, family history of diabetes and history of gestational diabetes in previous pregnancies and lifestyle habits. Maternal height was measured at first prenatal

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Table 1: Clinical characteristics the study population (N=200).

	Whole population	Control subjects (n=60)	GDM patients (n=60)	*p*
Parity				
None	37 (31)	20 (33)	17 (28)	
1 – 2	41 (34)	23 (38)	18 (30)	NS
3 – 4	33 (28)	15 (25)	18 (30)	
5 or more	9 (8)	2 (3)	7 (12)	
Previous abortions				
0	88 (73)	47 (78)	41 (68)	
1	23 (19)	10 (17)	13 (22)	
2	4 (3)	1 (2)	3 (5)	NS
3	5 (4)	2 (3)	3 (5)	
GDM history in previous pregnancies	23 (19)	6 (10)	17 (28)	<0.01
History of macrosomic babies	14 (12)	6 (10)	9 (15)	NS
Family History of GDM	32 (27)	14 (23)	18 (30)	NS
Family History of DM	74 (62)	30 (50)	44 (73)	<0.01
Family History of HTN	54 (45)	24 (40)	40 (50)	NS
Family History of CHD	19 (16)	6 (10)	13 (22)	NS
Body height (cm)	156.7±5.7	157.6±5.7	155.8±5.7	NS
Pre-pregnancy weight (Kg)	66.8±14.9	66.6±15.7	67.1±14.1	NS
Current weight (Kg)	78.6±17.5	76.6±18.2	80.5±16.9	NS
Pre-pregnancy BMI (Kg/m^2)	43.1±9.2	42.9±9.5	43.4±8.9	NS
Current BMI (kg/m^2)	50.5±10.8	49.1±10.7	51.9±10.8	NS
SBP (mmHg)	117.8±11.7	117.2±12.4	118.3±11.2	NS
DBP (mmHg)	69.1±8.1	70.8 ±7.4	67.7±8.4	<0.05

Numeric data are presented as mean ± SD and categoric data as number (percentage). Continuous variables are compared by Mann-Whitney test. Categorical variables are compared by χ^2 test. BMI: Body Mass Index, DBP: Diastolic Blood Pressure; GDM: Gestational Diabetes; NS: Not Significant; SBP: Systolic Blood Pressure

visit using a wall-mounted stadiometer (Seca 217 Mobile Stadiometer, UK) to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg using a portable digital scales (TANITA ultimate scale 2000 scales, Tanita Corporation, Tokyo, Japan). Blood pressure was measured while the participant was sitting quietly for at least 10minutes by auscultation using aneroid sphygmomanometer instruments, and an average of two measurements was used in the analysis (OMRON 705IT; Omron Healthcare Co, Kyoto, Japan). Samples of peripheral EDTA-blood were taken after at least 8hr fasting in the third trimester of pregnancy since the diagnosis of GDM is usually made after the 24th week of gestation. Plasma was separated by centrifugation at 1500xg at 4°C and stored at -80°C until analysis. FBG: Fasting Blood Glucose: CMF: Calcium Magnesium Phosphorus; ALP: Alkaline Phosphatase; PTH: Parathyroid Hormone; Hb a1c: Haemoglobin A1c; CRP: C-Reactive Protein; 25-OH Vitamin D: 25-Hydroxyvitamin D; serum levels were evaluated for all study participants. Parameters of bone function profile were determined by standard laboratory procedures using an auto analyzer (Cobase 601, Roche, Switzerland). Participants underwent a 2hr oral glucose tolerance test and blood samples were collected at time 60 and 120 min to measure plasma glucose levels. Gestational diabetes was diagnosed based on the criteria of the American Diabetes Association, using the "Two-step" approach with a 50g (non-fasting) screen followed by a 100g oral glucose tolerance test (OGTT) for those who screen positive [13]. If the glucose level was ≥7.8mmol/L, 1 hour after a non-fasting 50g oral glucose load, the participant was referred for a 100g fasting glucose 3-hour tolerance tests. Normal results were a fasting blood glucose level of <5.3mmol/L at baseline, <10mmol/L at 1 hours, <8.6mmol/L at 2 hours, and <7.8mmol/L at 3 hours. Serum 25-OH vitamin D was measured by chemiluminescent immunoassay according to the manufacturer's instructions (DiaSorin LIAISON1, MN, USA). Vitamin D status was categorized according to serum 25-OH vitamin D concentrations as follows: severe deficiency (<25nmol/L); deficiency (25-50nmol/L); insufficiency (51–74 nmol/L); and sufficiency (≥75nmol/L) [14]. HbA1c was measured by radioimmunoassay to assess the glycemic control. Ideally HbA1c <6.5% (48mmol/mol) is recommended to reduce the risk of congenital anomalies [15]. Data were described in terms of mean ± SD or frequencies (percentages) as appropriate. Normality of quantitative data was evaluated using the Kolmogorov–Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square test was performed. Fisher's exact test (two-tailed) replaced the chi-squared test in cases of small sample size and where the expected frequency was less than five in

Table 2: Biochemical characteristics of the study population (N=200).

	Whole population	Control subjects (n=60)	GDM patients (n=60)	*P*
Vitamin D (nmol/L)	27.9 ± 14.5	30.0 ± 15.8	25.71 ± 12.8	NS
Vitamin D categories Severe deficiency (<25nmol/L) Deficiency (25-50.9nmol/L) Insufficiency (51–74.9nmol/L) Optimal (≥75nmol/L)	 59 (49) 47 (39) 14 (12) 0 (0)	 29 (48) 21 (35) 10 (17) 0 (0)	 30 (50) 26 (43) 4 (7) 0 (0)	 NS
PTH (pmol/L)	4.29 ± 2.5	4.21 ± 2.3	4.37 ± 2.7	NS
ALP (U/L)	105.6 ± 44.5	92.02 ± 35.9	118.4 ± 48.2	<0.01
Magnesium (nmol/L)	0.82 ± 0.49	0.90 ± 0.69	0.12 ± 0.09	NS
Calcium (nmol/L)	2.14 ± 0.29	2.08 ± 0.39	2.19 ± 0.10	NS
Phosphate (mmol/L)	1.06 ± 0.20	1.09 ± 0.26	1.03 ± 0.14	NS
CRP (mg/L)	4.65 ± 2.4	4.28 ± 2.1	5.02 ± 2.6	<0.05
HbA1c (%)	5.28 ± 1.3	4.88 ± 1.5	5.69 ± 0.8	<0.01

Numeric data are presented as mean±SD and categoric data as number (percentage). Continuous variables are compared by Mann-Whitney test. Categorical variables are compared by χ^2 test. ALP: Alkaline Phosphatase; HbA1c: Haemoglobin A1c; CRP: C Reactive Protein; NS: Not Significant; PTH: Para Thyroid Hormone

any of the cells. Pearson's correlation coefficient was used for the calculation of associations between variables. P values <0.05 was considered statistically significant. All statistical calculations were done using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

One hundred and twenty middle-aged pregnant women, in their third trimester, with and without GDM, were matched for age and gestational age. Summarizes clinical characteristics of the study population. About one third of the overall sample was nulliparous. History of macrosomic babies was reported by one tenth of the study subjects and approximately 70% had no previous abortions. Positive history of previous GDM seemed more likely in GDM group when compared to controls (p<0.01). Family history of chronic disease were consistently more frequent among GDM patients as compared to their age-matched controls, but statistical significant difference was only reported for family history of DM (p<0.05). The average age and gestational age of the whole population were 31.1 ± 4.7 years and 30.9 ± 4.2 weeks respectively, with no significant difference in between the study groups (p>0.05). Likewise, no statistical difference was observed between pregnant women with and without GDM in terms of BMI values before and during pregnancy (Table 1). Noteworthy, 25% of controls and 40% of GDM patients were of normal weight according to their pre-pregnancy BMI <25Kg/m^2. However, as shown in Figure 1, more women in both groups became obese after their current pregnancy (90% vs. 73% of controls, 97% vs. 58% of GDM cases) with BMI values ≥30Kg/m^2. Apart from slightly higher DBP readings in the control subjects than the GDM subjects (p<0.05), no statistically significant differences were observed in the remaining anthropometric characteristics presented in table 1. Of the 60 cases with GDM, 53% were on the diet only whereas 47% were using metformin and only 7% of the cases were on insulin therapy. Figure 2 depicts the results of OGTT in both groups (p<0.0001). Moreover, Table (2) shows that both study groups had comparable serum levels of bone function variables except for slightly higher ALP activity, CRP and HbA1c values among GDM patients than their control counterparts (p<0.05). As regards vitamin D levels, low mean serum levels were found in both groups, with no statistical difference (25.71 ± 12.8nmol/L in GDM patients vs. 30.0 ± 15.8nmol/L in controls). Furthermore, Table (2) demonstrates that almost half of the study

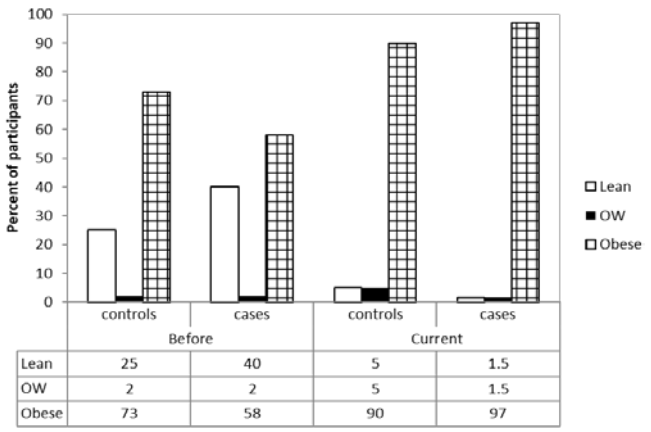

Figure 1: Distribution of subjects in GDM group (n=60) and the control group (n=60) according to BMI classes before and during pregnancy. Normal is (18.5-24.9Kg/m^2), Overweight is (25-29.9Kg/m^2) and Obese is (≥30Kg/m^2).

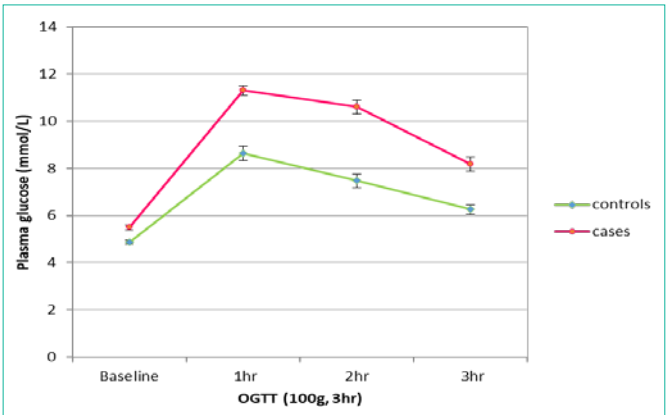

Figure 2: Mean ± SEM of 100g OGTT results in 60 GDM group and 60 control group (p<0.0001). Normal results were a fasting blood glucose level of <5.3mmol/L at baseline, <10mmol/L at 1 hours, <8.6mmol/L at 2 hours, and <7.8mmol/L at 3 hours.

sample had <25nmol/L of serum 25-OH vitamin D levels (i.e., severe deficiency). In the whole group, there was no correlation between 25-OH vitamin D levels and biochemical variables except for an inverse correlation with bone-specific ALP activity (r= - 0.232, p<0.05) as well as a negative association was found with the current BMI classes (r= -0.246, p<0.01).

Discussion

In recent years, vitamin D deficiency has increased in reproductive aged women, and the global prevalence has risen 26-98% in pregnancy, bringing concerns about its consequences and need for supplementation [16-18]. To date, the role of vitamin D in glucose homeostasis during pregnancy and the development of GDM remains inconclusive. The purpose of this study was to investigate the relationship between maternal vitamin D status with glucose intolerance and its consequences in pregnant women with GDM. Obesity and vitamin D severe deficiency were highly prevalent among the study participants. Nevertheless, no significant difference was observed in mean values of serum vitamin D and BMI between GDM patients and their matching controls. However, although nonsignificant, there was a tendency for higher prevalence of vitamin D deficiency among GDM patients than the controls (43% vs. 35%) as shown in the risk of vitamin D deficiency increases during pregnancy due to the increase in maternal and fetal demands [19]. Moreover, vitamin D is postulated to have a potential effect on several pregnancy outcomes including GDM, hypertensive disorders and fetal skeletal outcome [20-21]. Our results are in contrast with the findings of some studies, in which maternal serum levels of 25(OH) D during 24-28 weeks of pregnancy were significantly lower in women with GDM compared with controls [22]. Lack of association between maternal serum 25(OH) D levels and subsequent GDM development was reported during the first trimester of pregnancy [23]. Conversely, an inverse association between maternal serum 25(OH) D levels and fasting blood glucose was demonstrated in the absence of any association between 25(OH) D and GDM [1]. Similar to our results, other studies failed to show a relationship between maternal vitamin D status and risk of developing GDM [23-24]. Nevertheless, despite the reported high prevalence of deficiency and the possible consequences, the desired optimal level needed for pregnant women in their body and the amount of vitamin D intake required to maintain adequate levels is not very well documented [14-19]. Although vitamin D status was not associated with the continuous value of BMI, we have observed a negative association between 25-hydroxyvitamin D levels and the categorized BMI values during pregnancy (r= -0.246, p<0.01). Indeed, the aetiology of hypovitaminosis D among pregnant women is multifactorial, but is due in part to increasing BMI and reduced sunlight exposure, coupled with decreased dietary intake of vitamin D, such as milk and other dairy products. Despite abundant sunlight, hypovitaminosis D is highly prevalent among the Saudi population. It is more frequent in the young and middle-aged group of apparently healthy Saudi adults [25] and in females more than males [26]. This has been linked to cultural practice of complete covering of the body, head and even face, in addition to limited outdoors activities, which might counteract this positive effect of the ample sunlight [27-28]. Other factors associated with circulating 25(OH)D concentration were latitude, season, gestational age, maternal age, parity, maternal social class and education level, tobacco smoking and pre-pregnancy BMI [29-30]. Risk factors for GDM also include women older than 25, obesity, history of a large baby or previously affected pregnancy [31]. As shown in Table 1, more cases have had 2 or more previous abortions than the control subjects (10% of GDM patients vs. 5% of controls). Vitamin D may play a potential role in the prevention of miscarriage due to its combined immunomodulatory and anti-inflammatory properties during early pregnancy [32]. Not surprisingly, vitamin D supplementation has been recently reported to be associated with higher maternal and neonatal vitamin D concentrations at delivery [33] and even with lower rates of preeclampsia, GDM and preterm labor [34]. GDM pregnant women showed significantly higher levels of CRP and HbA1c than their control counterparts [Table 2]. In agreement with our results, the prevalence of vitamin D insufficiency and deficiency was indicated in nulliparous women [17]. Vitamin D deficiency also has been shown to increase insulin resistance and reduce insulin secretion, which has shown to be a risk factor for gestational diabetes [3-35]. Maternal vitamin D deficiency may also predispose women to an increased inflammatory response that characterizes preeclampsia, preterm birth and small for gestational age babies [27]. However, whether vitamin D deficiency is a risk factor for gestational diabetes in itself or if vitamin D supplementation can prevent GDM is yet unknown [36]. None of the estimated bone function profile in Table 2 were different in between the study groups except for slightly higher ALP activity value among GDM patients than their control counterparts (p<0.01). Additionally, PTH was slightly, but non-significantly, higher among GDM patients than the controls. Also, 25(OH) D levels was only negatively associated with bone-specific ALP activity (r= - 0.232, p<0.05). Vitamin D deficiency in mothers may not only cause adverse effects in the growing fetus, but could also involves early programming of childhood bone mass during in utero life [8].

Lower 25(OH) D and higher PTH were reported to be associated with greater metabolic risk in women with GDM [37]. Also, raised ALP was found in combination with low vitamin D and high PTH levels among diabetic subjects, which was attributed to bone disease [38]. The discrepancy with previous studies may be the consequence of lower statistical power (i.e. the small number of cases included in the present study), the differences in gestational age at blood sampling, and the use of different diagnostic criteria. Maternal vitamin D levels vary during gestation. Serum 1, 25(OH) D increases normally from the end of the first trimester and reaches its maximum level in the third trimester [39]. Moreover, Vitamin D action is affected by factors like its metabolism and other hormonal and metabolic pathways [40]. These findings highlight the possibility that factors other than vitamin D can determine maternal and neonatal outcomes. This study was not without certain limitations. First the method for screen in GDM is still controversial. With one step approach more women are labelled with GDM and it is uncertain whether there will be any benefit from treating them all, rendering this approach not cost effective. Therefore we preferred to use the two-step approach. Second important data including dietary history and lifestyle habits were not gathered from all participants and thus could not be included in the analysis. Third we did not measure some biochemical variables, like fasting insulin levels, vitamin D–binding protein and serum albumin, which could have provided a more comprehensive evaluation of the relationship between vitamin D and gestational glucose tolerance. Last the case control study design precludes commentary on causality. In

conclusion, we have revealed high prevalence of maternal obesity and vitamin D deficiency in pregnancy. Although vitamin D status was not associated with the risk of developing GDM, hypovitaminosis D and obesity were highly prevalent among our study population of Saudi pregnant women with and without GDM. The effect of vitamin D deficiency on maternal health and foetal development requires conducting more clinical studies to clarify the exact implication of vitamin D in inducing adverse maternal and neonatal effects.

Acknowledgment

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