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Maternal Vitamin D Status in Gestational Diabetes Mellitus Women

Zainedeen Nassar[1] and Mazen Alzaharna[1*]

[1]*Department of Medical Laboratory Sciences, Faculty of Health Sciences, Islamic University of Gaza, Gaza Strip, Palestine.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To assess vitamin D status among Gestational Diabetes Mellitus pregnant women in Gaza Strip.
Study Design: Case control study.
Place and Duration of Study: Samples were collected from pregnant women attending primary health care centers, Gaza, Gaza Strip.
Methodology: The study comprised 90 participants, 45 GDM pregnant women and 45 apparently healthy pregnant women. Serum vitamin D and insulin levels were measured by ELISA, fasting blood glucose (FBG), 2 h oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), triglycerides (TG), cholesterol, high-density lipoprotein (HDL), phosphorus and calcium were determined chemically. Blood pressure was measured. Body mass index (BMI) and low-density lipoprotein (LDL) were calculated. Ethical approval was acquired from Helsinki committee. All data was analyzed using the SPSS program.
Results: The average vitamin D in GDM cases was lower than that in controls (P=0.031). There was an increase in the average of FBG, OGTT, HbA1c and insulin levels in GDM cases versus controls (P<0.001). The average levels of serum cholesterol, TG and LDL were significantly higher in cases as compared to controls. The average systolic and diastolic blood pressure levels were higher in GDM cases in relation to controls. Pearson correlation test showed a significant negative

Corresponding author: E-mail: mzaharna@iugaza.edu.ps;

correlation between vitamin D and the parameters: BMI, glucose, OGTT, HbA1c and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).
Conclusion: Vitamin D was lower in GDM women compared to controls. Low vitamin D status may be associated with insulin resistance and act as a risk factor for GDM.

Keywords: Vitamin D; gestational diabetes mellitus; oral glucose tolerance test; insulin resistance.

ABBREVIATIONS

1,25-(OH)$_2$D: 1,25-Dihydroxyvitamin D; 1º: Primary; 2º: Secondary; BG: Blood glucose; BMI: body mass index; Ca: Calcium; DBP: Diastolic blood pressure; DM: diabetes mellitus; FBG: fasting blood glucose; GDM: Gestational diabetes mellitus; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL-C: Low-density lipoprotein; OGTT: Oral glucose tolerance test; P: Phosphorus; Prep.: Preparatory; SPB: Systolic blood pressure; t: Student t-test; T2DM: Type 2 diabetes mellitus; TG: Triglyceride; USD: United States Dollar; VDRs: Vitamin D receptors; χ^2: Chi-square test.

1. INTRODUCTION

Gestational diabetes mellitus is defined as glucose intolerance of various degrees of severity, which appears or recognized during pregnancy [1]. The global prevalence of GDM is 4.1% to 27.5% based on the ethnical mix of the people and tests administered for the diagnosis [2]. A study of prevalence and demographic characteristics of GDM in 2014 revealed that GDM prevalence among Gaza refugee women was 1.8% [3]. Gestational diabetes mellitus is related to increased risk of numerous complications among pregnant women and fetus during birth and in later life. The complications associated with GDM include preeclampsia, cesarean section and increase risk of getting type 2 diabetes mellitus (T2DM) later in life. Infant's complications include macrosomia, congenital abnormality, birth trauma, respiratory difficulty, hypoglycemia and jaundice [2].

Vitamin D, known also as calciferol, is a prohormone that has an important role in homeostasis of calcium and phosphorus and supports protection of bone's health. Humans gain vitamin D either from the diet directly or by direct exposure to sun light, ultraviolet-B (UV-B) radiation. Vitamin D has also a significant role in neuromuscular functions [4]. Functionally, vitamin D includes two major forms, vitamin D2 (ergocalciferol) and vitaminD3 (cholecalciferol) [4]. The pleiotropic actions of vitamin D and their clinical significance are becoming more apparent now, the human genome contains 2776 vitamin D receptor binding sites [5].

Different researchers have found an association between vitamin D insufficiency and various pathological conditions, including cardiovascular diseases, cancer, neurocognitive disorders, adverse pregnancy, GDM or birth defects, and less common immunological dysfunctions [6,7]. Epidemiological studies have also shown complete proper association between deficiency of vitamin D and elevated risk of T2DM [2].

Vitamin D plays an important role in glucose homeostasis. The doubled roles of vitamin D involve the presence of specific vitamin D receptors (VDRs) on pancreatic β-cells, the expression of 1-α- hydroxylase enzyme in pancreatic β-cells which catalyzes transformation of 25-(OH)D to 1, 25-(OH)2D [8]. Presence of a vitamin D response element in human insulin gene promoter, and the existence of VDR in skeletal muscle. 1,25-(OH)$_2$D immediately provides transcription activation of the human insulin receptor gene [9], provides peroxisome proliferators activator receptor-δ, which stimulates the expression of insulin receptor, and stimulates insulin-mediated glucose transport in vitro [9].

In Gaza Strip, no previous studies have investigated the association between vitamin D and GDM. Therefore, the present study aimed to assess serum vitamin D level in GDM patients from Gaza Strip.

2. MATERIALS AND METHODS

2.1 Study Design & Population

The present study is a case control one. The study was conducted on 45 women with GDM cases and 45 apparently healthy pregnant controls aged 25 to 37 years old.

2.2 Data and Samples Collection

A questionnaire was designed to match the study need for both cases and controls. The samples were collected from women with GDM and healthy pregnant women from Ministry of Health Clinics in Gaza Strip. GDM women were diagnosed by a 2-h 75-g OGTT at 24 - 28 weeks of gestation, the cut-off values being > 92 mg/dl FBG level, and >140 mg/dl at 2 h 75-g OGTT [10].

2.3 Samples Processing & Analysis

Venous blood samples (5ml) were drawn from the participants. About 2 ml were placed into EDTA tube to determine HbA1c. The remaining quantity of blood was placed into the plain tube to allow blood to clot and serum was separated by centrifugation. Serum was used for analysis of FBG, cholesterol, HDL, LDL, calcium, phosphorus, vitamin D, and insulin. Another blood sample (3ml) was drawn after 2h for OGTT. All samples were preserved on ice and directly analyzed. 1 ml of the serum was aliquoted and stored at -20°C for analysis of insulin and vitamin D using ELISA kits. For all biochemical tests normal and abnormal controls were used (QCA seriscan, Spain).

2.4 Inclusion Criteria

Inclusion criteria includes pregnant women on second trimester gestation (24-28) weeks, with mild hyperglycemia (92-126 mg/dl), aged 25-37 years old.

2.5 Exclusion Criteria

Women with the following criteria were excluded: cases and controls aged under 25 and above 37 years old. Women with different chronic diseases. Women who take hormone replacement therapy or corticosteroid therapy and women on vitamin D supplements.

2.6 Statistical Analysis

Data was analyzed using IBM SPSS/PC (Statistical Package for the Social Science Inc. Chicago, Illinois USA, version 22) statistical package. Simple distribution of the study variables and the cross tabulation was used. Chi-square (χ^2) was applied to identify the significance of the associations, relations, and interactions between different variables. The independent sample t-test procedure was used to compare means of quantitative variables by the separated cases into two qualitative groups such as the relationship between cases and controls vitamin D. Pearson correlation test was applied. The results were considered as statistically significant when the P-value< 5%.

3. RESULTS

3.1 General Characteristics of the Study Population

As shown in (Table 1), The BMI in cases was significantly higher compared to controls (P<0.001). The number of cases with family history of DM was 26 women (57.8%) in contrast to 12 women in controls (26.7%), while those without family history of DM were 19 women in cases (42.2%) in contrast to 33 women in controls (73.3%), the difference was statistically significant (P=0.003). On the other hand, regarding the family history of GDM, 10 (22.2%) of cases have family history in contrast to none in controls. The difference was statistically significant (P=0.001). GDM cases who have physical activity were 12 (26.7%) in contrast to 17 (37.8%) in controls, the difference was not statistically significant (P=0.259).

3.1.1 Vitamin D, insulin, HbA1c and glucose levels among the study population

Table 2 shows that the average concentration of vitamin D in GDM cases was (29.6±10.6 ng/ml) which is lower than that that in controls (34.5±10.6 ng/ml), the difference was statistically significant (P=0.031). The FBG results were higher in GDM cases (105.8±15.8 mg/dl) compared to the controls (66.5±8.1 mg/dl), the difference was also statistically significant (P<0.001). On the other hand, the average OGTT in GDM cases was (187±25.5 mg/dl) in contrast to that in controls (85.8±8 mg/dl), the difference was statistically significant (P<0.001). While, the average percentage of HbA1c was higher in GDM cases (7.1±0.4%) in contrast to controls (4.4±0.4%), the difference was also statistically significant (P<0.001). On the other hand, serum insulin level was higher in GDM cases (20.4±8.4 µIU/ml) compared to controls with average insulin level (6.2±1.7 µIU/ml), the difference was statistically significant (P<0.001). The HOMA-IR was higher in cases (5.2±2.2) compared to controls (1.0 ±0.3) and the difference was also statistically significant (P<0.001).

Table 1. General characteristics of the study population

General characteristics		Controls (n=45)	Cases (n=45)	P-value
Age (years)	**Mean±SD**	29.3±3.2 (25-36)	30.3±3.5 (25-36)	0.151
Weight (Kg)	(Min-max)	70.5±9.2(57-97)	89.2±10.9 (62.5-113)	0.013*
Height (cm)		157.8±6.8(133.4-170)	161.2±5.8 (150-172.5)	<0.001*
BMI (Kg/m^2)		22.4±3(18.0-30.4)	27.9±3.6 (18.9-36.6)	<0.001*
Education	**n (%)**			0.006*
University		15(33.3)	3(6.7)	
2º school		18(40.0)	27(60.0)	
Prep. & 1º school		12 (26.7)	15(33.3)	
Employment				0.557
Yes		1(2.2)	2(4.4)	
No		44(97.8)	43(95.6)	
Income (USD/month)				0.528
<285		19(42.2)	24(53.3)	
285-570		24(53.3)	20(44.5)	
>570		2(4.4)	1(2.2)	
Family history of DM				0.003*
Yes		12(26.7)	26(57.8)	
No		33(73.3)	19(42.2)	
Family history of GDM				0.001*
Yes		0(0.0)	10(22.2)	
No		45(100)	35(77.8)	
Physical activity				0.259
Yes		17(37.8)	12(26.7)	
No		28(62.2)	33(73.3)	

*BMI: body mass index; DM: diabetes mellitus; GDM: Gestational diabetes mellitus; n: number of the subjects; Prep.: Preparatory; t: student t-test; USD: United states Dollar; χ^2: chi-square test, 1º: Primary; 2º: Secondary. *P-value significant at p≤0.05*

Table 2. Vitamin D, insulin, HbA1c and glucose levels among the study population

Parameters	**Controls (n=45)** Mean ± SD	**Cases (n=45)** Mean ± SD	P-value
Vitamin D (ng/ml) (Min - max)	34.5±10.6 (7-59)	29.6±10.6 (8-56)	0.031*
FBG (mg/dl) (Min - max)	66.5±8.1 (52-84)	105.8±15.8 (89-171)	<0.001*
OGTT (mg/dl) (Min - max)	85.8±8.0 (72-99)	187.0±25.5 (146-294)	<0.001*
HbA1c (%) (Min - max)	4.4±0.4 (3.8-5.2)	7.1±0.4 (6.3-8.1)	<0.001*
Insulin (uIU/ml) (Min - max)	6.2±1.7 (3.4-9)	20.4±8.4 (6.3-41.2)	<0.001*
HOMA-IR (Min - max)	1.0±0.3 (0.5-1.8)	5.2±2.2 (1.9-12.1)	< 0.001*

FBG: fasting blood glucose; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; OGTT: oral glucose tolerance test; n: number of the subjects; SD: standard deviation. P-value significant at P≤0.05

3.1.2 Lipid profile of the study participants

As shown in Table 3, the average serum TG level in GDM cases was higher (150.6±40.3 mg/dl) compared to controls (114.7±40 mg/dl), the difference was statistically significant (P<0.001). The average serum total cholesterol level among GDM cases was higher (198.7±55.3 mg/dl) in contrast to controls (162.4±46.1 mg/dl), the difference was also statistically significant (P=0.001). Moreover, the average serum LDL cholesterol level in GDM women was higher

(121.9±53.5 mg/dl), in contrast to controls (94.6±44.8 mg/dl), the difference was statistically significant (P=0.010). On the other hand, there was almost no difference in HDL between cases and controls.

3.1.3 The levels of calcium, phosphorus, Systolic & Diastolic blood pressure among the study population

As shown in Table 4, the difference between the serum total calcium and phosphorus levels in GDM cases and controls were not statistically significant.

On the other hand, the average systolic blood pressure (SBP) level in GDM cases was higher (116.3±10.3 mmHg), compared to controls (107±8.1 mmHg), the difference was statistically significant (P< 0.001). Moreover, the average diastolic blood pressure (DBP) in GDM cases was higher (74.8±9 mmHg), in contrast to controls (68.7±7.5 mmHg), the difference was also statistically significant (P=0.001) (Table 4).

3.1.4 Correlation between vitamin D and the studied parameters

As shown in Table 5, vitamin D shows a negative correlation which is statistically significant with BMI (r = -0.223, P=0.035). The results also show that there is a negative correlation which is statistically significant between vitamin D and FBG (r = -0.235, P=0.026), OGTT (r = -0.249, P=0.018)), HbA1c (r = -0.232, P=0.028), and HOMA-IR (r = -0.215, P=0.042).

4. DISCUSSION

Vitamin D deficiency impairs insulin secretion and stimulates glucose intolerance. Supplementation of vitamin D has shown to decrease the risk of developing T1DM, T2DM and GDM. Vitamin D has also been shown to decrease the risk of diabetes associated complications [1]. Many studies have shown that the problem of vitamin D deficiency is not limited to low sun areas of the world but also is common in sunny regions such as Middle Eastern countries like Jordan [11].

4.1 General Characteristics of the Study Population

The results of the present study show that BMI was significantly higher in cases compared to controls. Therefore, high BMI may be considered as a risk factor in pregnant women for GDM. Our results are compatible with different studies which agree that the main associated factors with GDM are obesity and increased BMI [1,12]. Recently, in Gaza Strip the increase in obesity prevalence has also increased the prevalence of GDM [3]. Obesity and subsequently GDM rise the risk of adverse pregnancy and infant's health outcomes and also a higher risk of developing T2DM later in life in both the mother and child [2].

On the other hand, the results of the current study show that there is a statistically significant difference between cases and controls regarding family history of DM, cases have higher family history of DM in relation to controls. The results agree with those of Tomedi et al. (2013) who indicated pregnant women with family history of DM is linked to elevated incidence of different degree of glucose intolerance and DM particularly at environmental trigger acting on an underlying genetic susceptibility [13].

4.1.1 Vitamin D, insulin, HbA1c and glucose profile among the study population

The average level vitamin D in GDM cases was lower compared to that of controls and the difference was statistically significant. These results agree with the results of different studies which showed that low vitamin D levels are associated with higher risk of developing GDM [14,15]. In contrast, different studies have shown that there is no association between the low levels of vitamin D and the risk of developing GDM [16,17]. There are conflicting results regarding maternal vitamin D status and risk of GDM. The reason may be due to differences in population characteristics including ethnicity, geographic location, gestational age at sampling and diagnostic criteria for GDM.

Regarding the results of FBG, OGTT and HbA1c, the levels were higher in GDM cases compared to controls. The higher levels of HbA1c in cases approve that there was a poor glycemic control in cases for at least the past 2 months. These results agree with those of others including Maghbooli et al. and Wang et al., [18,19].

Serum insulin mean level in GDM cases was higher in contrast to controls with statistical significance difference. These results are linked to insulin resistance in GDM cases. This can be confirmed from the HOMA-IR results which showed that GDM cases have higher values compared to controls. During pregnancy,

Table 3. Lipid profile among the study population

Parameters	Controls (n=45) Mean ± SD	Cases (n=45) Mean ± SD	P-value
Cholesterol (mg/dl) (Min - max)	162.4±46.1 (81-272)	198.7±55.3 (100-290)	0.001*
TG (mg/dl) (Min - max)	114.7±40 (41-208)	150.6±40.3 (38-215)	<0.001*
HDL (mg/dl) (Min - max)	45.0±7.8 (33-63)	45.6±10.7 (29-69)	0.763
LDL (mg/dl) (Min - max)	94.6±44.8 (20-206)	121.9±53.5 (25-206)	0.010*

*HDL: high-density lipoprotein; LDL: low-density lipoprotein; n: number of the subjects; SD: standard deviation; TG: Triglycerides. *P-value significant at P≤0.05*

Table 4. Calcium, phosphorus, SBP & DBP among the study population

Parameters	Controls (n=45) Mean±SD	Cases (n=45) Mean±SD	P-value
Ca (mg/dl)(Min - max)	8.9±0.4 (7.9-9.5)	8.7±0.5 (7.3-9.7)	0.296
P (mg/dl) (Min - max)	4.0±0.6 (3.1-6.0)	4.1±0.8 (2.4-5.7)	0.343
SBP (mmHg) (Min - max)	107±8.1 (95-125)	116.3±10.3 (100-140)	<0.001*
DBP (mmHg) (Min - max)	68.7±7.5 (55-85)	74.8±9.0 (60-95)	0.001*

*Ca: Calcium; DBP: diastolic blood pressure; n: number of the subjects; P: phosphorus; SD: standard deviation; SPB: systolic blood pressure. *P-value is significant at P ≤ 0.05.*

Table 5. Correlation between vitamin D and the studied parameters

Parameters	Vitamin D (ng/ml)	
	Pearson correlation (r)	P-value
BMI (Kg/m^2)	-0.223	0.035*
FBG (mg/dl)	-0.235	0.026*
OGTT (mg/dl)	-0.249	0.018*
HbA1c (%)	-0.232	0.028*
Insulin (uIU/ml)	-0.191	0.071
HOMA-IR	-0.215	*0.042
Cholesterol (mg/dl)	-0.088	0.409
TG (mg/dl)	-0.188	0.076
HDL (mg/dl)	0.100	0.347
LDL (mg/dl)	-0.073	0.495
SBP (mmHg)	-0.099	0.352
DBP (mmHg)	-0.101	0.343

*BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HbA1c: Hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; OGTT: oral glucose tolerance test; SPB: systolic blood pressure; TG: Triglycerides; r: Pearson correlation. *P-value is significant at P ≤ 0.05.*

different factors can bind to the insulin receptor including hormones and can cause interference with the action of insulin. The pancreas needs to secrete more insulin to control this resistance; where 1.5–2.5 times more insulin is produced than in a normal pregnancy [20]. The association between low vitamin D levels and insulin resistance was demonstrated in different studies [15,21,22].

4.1.2 Serum lipid profile of the study participants

The average levels of serum cholesterol, TG and LDL were higher in GDM cases in contrast to controls and the difference was statistically significant. The results are congruent with those of different studies [21,23-26]. One reason of hypercholesterolemia during pregnancy is due to an increase in production of sex steroids. Another reason may be due to the insulin resistance which causes changes in hepatic and adipose tissue metabolism. On the other hand, the increased progesterone concentration contributes to the rise in LDL levels [26,27]. The consistent increase in the levels of TG during the course of pregnancy in GDM women in relation to those without insulin resistance is important as hypertriglyceridemia is thought to be one of the key drivers of fetal macrosomia [28]. On the other hand, the average serum level of HDL in GDM cases was approximately similar to the level in controls (P = 0.763) results are in agreement with Al-Musharaf, (2017) [29]. Insulin resistance was linked to high plasma TG and low plasma HDL cholesterol levels [30].

4.1.3 The levels of SBP and DBP among the study population

The present study shows that the average levels of SBP and DBP were higher in GDM cases in contrast to that of controls, the difference was statistically significance. The development of high blood pressure during pregnancy is known as preeclampsia; preeclampsia and GDM also affect the women’s babies. Women with preeclampsia were more likely to give birth to underweight babies and deliver prematurely. Women with GDM were more likely to deliver overweight babies. These results are congruent with those of Rutkowska et al. (2016) [31].

4.1.4 Correlation between Vitamin D and the studied parameters

The results show that vitamin D has a statistically significant negative correlations with FBG (r = -0.235), HbA1c (r = -0.232) and OGTT (r = -0.249). The results agree with those of Pleskacova et al. (2015) and Ghasemi et al. (2016). This again shows the inverse relationship between vitamin D and the different glucose parameters [32,33]. Low levels of vitamin D affects the levels of insulin negatively and therefore affects the levels of FBG, OGTT and HbA1c positively.

Many studies have determined the association between vitamin D and insulin in GDM females but the present study proved a correlation between vitamin D deficiency and impaired insulin sensitivity in GDM cases (HOMA-IR results) that confirm the previous studies [14,34,35].

5. CONCLUSIONS

The mean level of vitamin D was significantly lower in cases as compared to controls. Moreover, the average levels of serum FBG, OGTT, HbA1c, insulin and HOMA-IR were significantly higher in cases as compared to controls. The results also show that vitamin D has a significant negative correlation with BMI, FBG, OGTT, HbA1c and HOMA-IR. The results also show that serum vitamin D level has a relationship with GDM among pregnant women. Vitamin D supplementation to pregnant women may be helpful in the prevention strategy of GDM and the serious complications which can affect both the mother and the fetus during pregnancy and after birth.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed consent was taken from all women who accepted to participate in the study after well explanation of the procedures and objectives and considerations beyond the study.

ETHICAL APPROVAL

An approval to perform the study was taken from the Palestinian Ethical Committee (Helsinki Ethics Committee) (PHRC/HC/88/16).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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