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Original Article

Studying the relation between vitamin D deficiency and glycemic state among pregnant women with gestational diabetes

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ABSTRACT

Aim: This study was conducted to illustrate the relation between vitamin D deficiency and glycemic parameters.

Materials and methods: The study was carried out on 80 pregnant females who were attending obstetrics and gynecology out-patient clinic in el-Shatby hospital in Alexandria university, Egypt. They were divided into 2 groups: group 1 (n = 40) pregnant females diagnosed with gestational diabetes de novo at week 24–28 and group 2 (n = 40) pregnant females of the same age group who were not suffering from any glucose intolerance (control group). Each patient was subjected to detailed history taking, complete physical examination, One step 75 gm Oral glucose tolerance test, insulin, glycated hemoglobin(HbA1c),homeostatic model assessment of insulin resistance(HOMA-IR), 25 hydroxy-vitamin D, serum calcium, phosphorous and parathormone were assessed.

Results: A statistically significant higher fasting blood glucose (FBG), HbA1c%, fasting insulin and HOMA-IR was observed in patients with Gestational diabetes mellitus (GDM) versus control ($p < 0.001$). However, no significant difference was observed as regards Vitamin D levels in patients with GDM and control group. Among patients with GDM, vitamin D was found to correlate negatively with HbA1c ($p < 0.001$), insulin($p = 0.019$) and HOMA-IR($p = 0.034$).

Conclusion: No definite causal relationship was observed between low vitamin D and subsequent occurrence of GDM.however, a significant correlation was found between the degree of vitamin D deficiency and the insulin resistance in patients with GDM.

1. Introduction

Vitamin D is one of the steroid hormones which is synthesized in the skin under the effect of sun rays and then metabolized in liver and kidneys in humans [1].

It increases the gut uptake of dietary calcium and phosphorus and improves the kidney ability to reabsorb calcium so its role is crucial in regulation of bone homeostasis [2].

Vitamin D also has several non-classical roles, including its relation to cardiovascular system, skeletal muscles and immune system functions [3].

Many evidences were found regarding vitamin D role in maintaining normal glucose homeostasis. For instance, in many studies vitamin D deficiency was significantly related to insulin resistance and insulin secretion. Also, a strong association was observed between β-cell dysfunction and vitamin D deficiency in non-diabetic and diabetic populations [4].

Although there is no definite data on the ideal levels of vitamin D in blood, vitamin D deficiency was defined in most studies as a 25-hydroxyvitamin D level of <20 ng/ml [5,6], while the level of 20–32 ng/ml can be considered as relative insufficiency [7]. Using such definitions, it has been estimated that around 1 billion people worldwide have vitamin D deficiency or insufficiency [8].

Pregnancy is an insulin-resistant state during which B-cell proliferate to secrete more insulin to meet the increased demands related to this period [9].

GDM is a state of glucose intolerance which is diagnosed for the first time during pregnancy. It affects approximately 4% of all American females [10]. As obesity rate increases, the rate of

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developing gestational diabetes is also increasing [11].

Women who are diagnosed with GDM carry higher risk for developing diabetes mellitus later on and are more likely to have babies with large birth weight than others with normal blood glucose mothers which increase the risk for shoulder dystocia and birth injuries such as nerve palsies and bone fractures [12]. In addition, these babies are more likely to be overweight and glucose intolerant [13].

In pregnancy the fetus grows rapidly specially at the end where calcium requirements increase for adequate bone development [14]. And hence vitamin D deficiency is common at that time estimated to be from 18% to 84%, depending on the place and type of clothes [15].

Many researchers found high prevalence of vitamin D deficiency in pregnant females specially at the time of expected high glucose intolerance (24–29-week gestation) [16].Others studied the effect of vitamin D supplements on improving metabolic profiles and glycemic state in patients with and without GDM [17].

Gestational diabetes and vitamin D link was widely studied however, no definite relationship was clearly concluded hence we conducted our study to determine the relation between vitamin D deficiency and gestational diabetes.

1.1. Subjects

This is a prospective study which was held on 80 subjects who were attending El-Shatby hospital obstetrics and gynecology outpatient clinic in Alexandria, Egypt. They were subdivided into 2 groups; **Group 1:** included 40 pregnant females with GDM diagnosed denovo at week 24–28 with no treatment given and **Group 2:** included 40 pregnant females of the same age group who were not suffering any disorder of glucose metabolism (control group).

2. Materials and Methods

Each patient was subjected to full history taking stressing upon on symptoms of diabetes mellitus, complete physical examination. Diagnosis of gestational diabetes depended upon the one-step strategy [18] using 75-g Oral glucose tolerance test (OGTT), with fasting plasma glucose measurement (after 8 h fasting) and at 1 h and 2 h after glucose intake. The diagnosis of GDM was confirmed when any of the following plasma glucose values were met or exceeded; fasting: 92 mg/dL (5.1 mmol/L), 1 h: 180 mg/dL (10.0 mmol/L), and 2 h: 153 mg/dL (8.5 mmol/L). Glycated hemoglobin (HbA1c) was done to exclude patients with diabetes prior pregnancy. Fasting insulin level and HOMA-IR were done for all subjects to determine the presence of insulin resistance.

Serum 25 hydroxy vitamin D (using ELISA technique), serum parathormone (using ELISA technique), Serum calcium and serum phosphorous were done for all subjects.

Exclusion criteria included patients previously diagnosed with diabetes mellitus prior to conception, those with any renal disease, anemia or taking corticosteroids.

2.1. Statistical analysis of the data [19]

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) [20]. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level ($p < 0.05$). The used tests were:

1 -**Chi-square test:** for categorical variables, to compare between different groups.
2 -**Fisher's Exact or Monte Carlo correction:** correction for chi-square when more than 20% of the cells have expected count less than 5.
3 -**Student t-test:** for normally distributed quantitative variables, to compare between two studied groups.
4 -**Pearson coefficient:** to correlate between two normally distributed quantitative variables.
5 -**Mann Whitney test:** for abnormally distributed quantitative variables, to compare between two studied groups.

3. Results

(see Tables 1–3, Figs. 1–3).

4. Discussion

Vitamin D deficiency was found to be highly prevalent in many studies among different age groups with special predilection to the young age and pregnant females [21].Also gestational diabetes mellitus prevalence is increasing worldwide.

The link between vitamin D and Gestational diabetes was widely mentioned however, no definite relation was concluded. Therefore, this study was held to present the relationship between vitamin D status and gestational diabetes.

In our study fasting blood glucose, fasting serum insulin and HOMA-IR were statistically significantly higher in cases versus control which is in concordance with the results of Smirnakis et al. that reported fasting glucose, fasting insulin and the HOMA index were significantly higher in women who developed GDM later on as compared with control subjects. They also concluded that higher insulin resistance is a predisposing factor for development of GDM later on [22].

Similar results were declared by Clark et al. who measured the glycemic parameters (insulin and HOMA-IR) among GDM patients versus no GDM and concluded that insulin resistance is a predicted risk for development of GDM [23]. This is consistent with our results where fasting blood glucose, HbA1c, insulin and HOMA-IR were found statistically significant higher in GDM female versus

Table 1
Comparison between patients with GDM and the control group as regards FBG, HbA1c, insulin and HOMA-IR.

	Cases (n = 40)	Control (n = 40)	T	P
FBG (mg/dl)				
Min. – Max.	93.0–201.0	48.0–90.0	10.444*	<0.001*
Mean ± SD.	133.4 ± 33.4	74.68 ± 12.24		
Median	120.0	72.50		
HbA1C (%)				
Min. – Max.	4.70–6.40	4.30–6.40	4.231*	<0.001*
Mean ± SD.	5.84 ± 0.44	5.36 ± 0.56		
Median	6.0	5.20		
Insulin (μ unit/ml)				
Min. – Max.	0.92–88.20	0.72–24.90	U = 304.50*	<0.001*
Mean ± SD.	19.20 ± 15.89	7.33 ± 6.46		
Median	13.95	5.64		
HOMA-IR				
Min. – Max.	0.20–35.50	0.11–4.85	U = 178.00*	<0.001*
Mean ± SD.	7.06 ± 7.35	1.34 ± 1.27		
Median	4.26	1.02		

t, p: t and p values for **Student t-test** for comparing between the two groups.
*: Statistically significant at $p \leq 0.05$.
χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups.
U, p: U and p values for **Mann Whitney test** for comparing between the two groups.
❖ There were statistical significant differences in FBS, HbA1C, insulin and HOMA-IR between patient with GDM and control group.

Table 2
Comparison between both groups (GDM versus controls) as regards serum 25OH vitamin D levels.

25 OH vitamin D (ng/ml)	Cases (n = 40)		Control (n = 40)		Test of Sig.	P
	No.	%	No.	%		
Deficiency (<20)	34	85.0	31	77.5	$\chi^2 = 0.781$	$^{FE}p = 0.703$
Relative insufficiency (20–30)	3	7.5	4	10.0		
Normal (>30)	3	7.5	5	12.5		
Min. – Max.	5.38–34.0		5.22–36.50		t = 1.219	0.227
Mean ± SD.	14.01 ± 7.01		16.14 ± 8.57			
Median	12.35		13.70			

χ^2: Chi square test for comparing between the two groups.
^{FE}p: p value for Fisher Exact for Chi square test for comparing between the two groups.
t, p: t and p values for Student t-test for comparing between the two groups.
Cases: Gestational DM.
Control: No Gestational DM.
❖ In group I, 85% of females were found to have vitamin D deficiency while 7.5% had relative insufficiency and 7.5% had normal vitamin D level. In group II, 77.5% were having vitamin D deficiency while 10% had relative insufficiency and 12.5% with normal vitamin D level.
❖ No significant difference was noted among both groups as regards vitamin D level.

Table 3
Comparison between both groups as regards to serum calcium level, phosphorous and PTH.

	Cases (n = 40)		Control (n = 40)		Test of Sig.	P
	No.	%	No.	%		
Serum calcium (mg/dl)						
Min. – Max.	7.60–10.10		7.50–10.10		t = 0.088	0.930
Mean ± SD.	8.85 ± 0.66		8.84 ± 0.61			
Median	8.95		8.95			
Serum Phosphorous (mg/dl)						
Min-Max	2.30–4.60		2.70–4.30		t = 0.113	0.910
Mean ± SD	3.44 ± 0.61		3.43 ± 0.34			
Median	3.50		3.40			
PTH (pg/ml)						
Min. – Max.	1.20–66.70		1.13–64.70		U = 649.50	0.148
Mean ± SD.	25.34 ± 18.93		19.12 ± 13.47			
Median	23.50		16.80			

*: Statistically significant at $p \leq 0.05$.
❖ There is no significant difference among both groups as regards serum calcium, serum phosphorus and serum PTH.

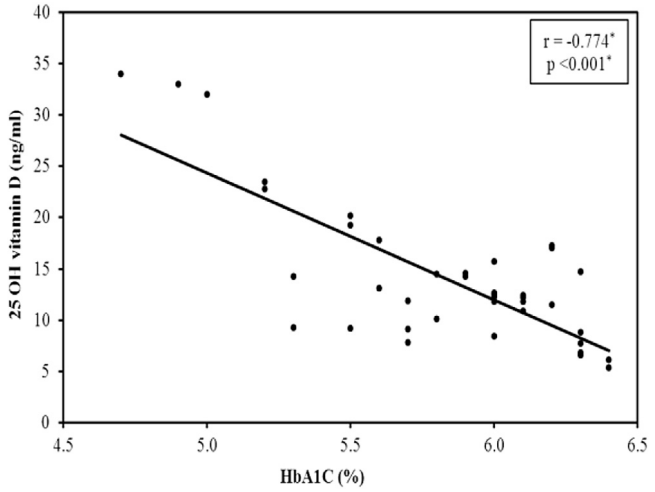

Fig. 1. Correlation between 25 OH Vit D and HbA1C among patients with GDM.
❖ A statistically significant negative correlation was observed between serum 25 OH vit D and HbA1c among group I patients.

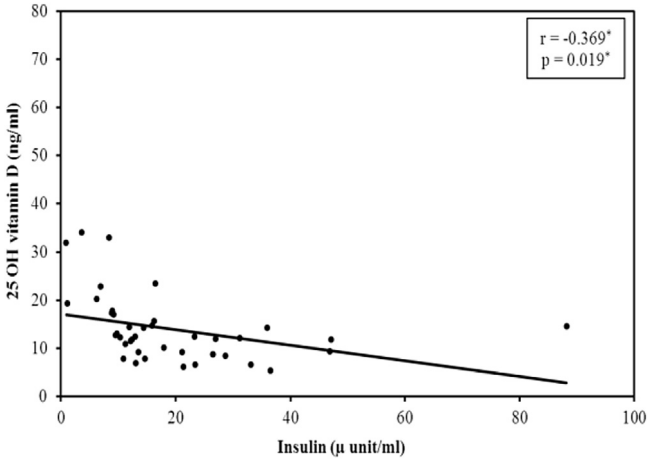

Fig. 2. Correlation between serum 25 OH Vit D and serum insulin among patients with GDM
❖ A statistically significant negative correlation was observed between serum 25 OH vit D and serum insulin among patients with GDM.

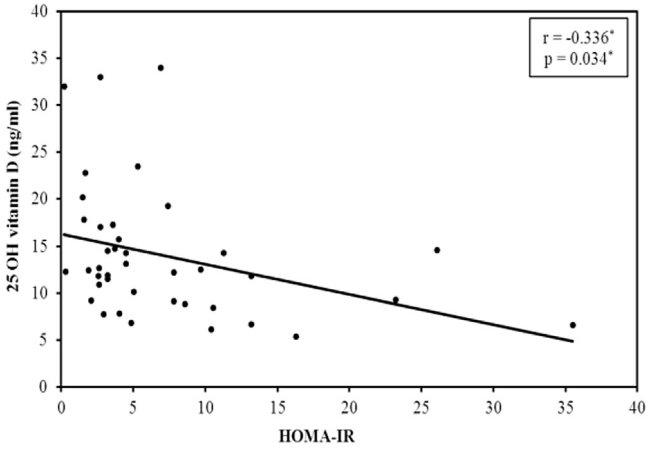

Fig. 3. Correlation between serum 25 OH Vit D and HOMA-IR among patients with GDM
❖ A statistically significant negative correlation was observed between serum 25 OH vit D and HOMA-1R among patients with GDM.

eu-glycemic females.

In our study, no significant difference was noted between mean serum level of vitamin D among the studied groups however, we found that there was a statistically significant negative correlation between vitamin D and serum insulin level ($r = -0.369$) ($p = 0.019$) and also vitamin D level correlate negatively with HOMA-IR among our cases ($r = -0.336$) ($p = 0.034$) which means that despite the inverse relation between serum vitamin D level and insulin resistance, it can't be confirmed as a predisposing factor for development of GDM.

Similar results were declared by Farrant HJ et al., in 2009 where he conducted his study on 559 pregnant females in India to study the effect of low vitamin D on the glycemic parameters and they concluded that the lower the serum level of vitamin D the higher is serum insulin and proinsulin concentrations, however this was not linked to the occurrence of gestational diabetes [24].

Clifton B et al. conducted another study in Australia in 2008 on 307 pregnant lady where he measured serum 25 OH vitamin D in mid gestation period where period of maximum glucose intolerance is expected and he found that there was a negative correlation between vitamin D in pregnant serum and fasting blood glucose, insulin and insulin resistance assessed by HOMA-IR. This results were similar to the results declared by our study however, we didn't find significant correlation between serum vitamin D and fasting blood glucose but this point was mentioned by Clifton study as point of weak significance owing to the presence of other variables affecting fasting blood glucose as age, ethnicity and body mass index [16].

Consistent with our study, baker et al. conducted another study in USA in 2015 on more than 4000 pregnant women where it was concluded that low vitamin D level was not associated with glucose intolerance, this may be attributed to specific patient selection in the first trimester of pregnancy where the prevalence of vitamin D deficiency is lower compared to the second trimester [25].

On contrary, Zhang MX conducted a meta-analysis on more than 9200 Chinese female and it showed that women with vitamin D deficiency are at a risk for developing GDM [26].

In our study 85% of our cases had vitamin D deficiency compared to 66% in the previous study. This large number is attributed to the special socioeconomic class of the females attending El-Shatby hospital where our study was conducted, this socioeconomic class influenced their dietary habits and way of clothing which affect vitamin D level.

The high frequency of lower serum vitamin D among mothers is consistent with findings in other studies (Sachan et al., 2005) [27]. SouthAsians, both in their country of origin and after migration to Europe or the USA, have lower serum 25(OH)D concentrations as compared to white Caucasians (Goswamietal., 2011; Hamsonetal., 2003) due to skin pigmentation, covered-upclothing (especially common In women) and low dietary vitamin D intake [28].

In Spain (Martinez et al., 1991) found low vitamin D in serum of many pregnant females, and fasting hyperglycaemia improved with vitamin D supplements in one small study of women with gestational diabetes (Rudnicki and Molsted Pedersen, 1997) [29]. However, we did not collect data about vitamin D supplement which is usually given in the last 3 months because our study assessed vitamin D status at the time of 24–28 week gestation.

In 2013, Wei el al studied the relation between vitamin D deficiency and different pregnancy outcomes and concluded that maternal hypovitaminosis D in pregnancy may increase risk for preeclampsia, GDM and preterm birth [30].

Maghbooli and his team studied the relation between vitamin D and GDM in a crossectional study conducted on more than 700 pregnant lady in 24–28 week gestation and reported lower levels of maternal serum 25 hydroxy vitamin D compared to euglycemic controls [31], however in our study no statistical significant difference was observed among the studied groups as regards mean serum vitamin D level.This may be attributed to the high prevalence of vitamin D deficiency among both groups (85% in cases versus 77.5% in controls) compared to 70% in this study.

He also concluded that lower vitamin D levels was associated with higher degree of insulin resistance (higher HOMA-IR) which was consistent with our results.

On contrary to our study, Zhang C et al. studied the relationship between maternal vitamin D level and subsequent glucose intolerance in 2008 on 900 pregnant lady and the team declared that vitamin D deficiency in early pregnancy is an established risk factor for the occurrence of gestational diabetes even after other risk factors (maternal age, family history of type 2 diabetes, race, ethnicity, and pre-pregnancy BMI) are controlled [32].

5. Conclusion

Vitamin D deficiency is prevalent among pregnant females and it negatively correlates with insulin resistance, however it can't be considered as a definite contributing factor of gestational diabetes.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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