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A cross-sectional comparative study: To evaluate the relationship between low maternal serum vitamin D levels and gestational diabetes mellitus in a tertiary centre

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Abstract
Background: Maternal vitamin D status has been associated with gestational diabetes mellitus (GDM) however, the evidence is inconsistent. During pregnancy, this deficiency is even more critical. The objective of this study was to evaluate the relationship between low maternal serum vitamin d levels and gestational diabetes mellitus in tertiary
Methods: This cross-sectional study included 140 pregnant women. 70 women already diagnosed with GDM were taken as cases and 70 normal pregnant women were taken as control. All the patients included were subjected to detailed history taking. BMI matched in cases and controls. Blood sample were taken from both cases and control ant sent for Vitamin-D level, HbA1c, Fasting blood glucose and 2hrs postprandial glucose test.
Results: In this study an attempt has been made to assess the association of maternal serum vitamin D with Gestational diabetes mellitus and also to see its relation with glycemic control in patients with GDM. Overall 71% Indian women are vitamin D deficient in our study. The mean maternal serum vitamin D levels were 8.83 ± 5.77ng/ml in Group A and 17.04 ± 8.67ng/ml in group B. The difference was statistically significant reflecting that the mean serum vitamin D was decreased in women with GDM. (P value=0.001). The correlation coefficient (r) between HbA1c levels and Vitamin D level was -0.570 with a P value <0.0001. Similar associations were also found with the fasting blood sugar levels (r = - 0.549) Vitamin D levels correlated significantly with the fasting blood glucose, the fasting serum insulin and the HbA1c levels, the P value in all these correlations were <0.0001.
Conclusions: Low maternal serum vitamin d levels were associated with gestational diabetes mellitus. There is a statistically significant negative correlation between the glycemic control and vitamin D levels in serum in the whole study population. The effect of adequate vitamin D replacement on glycemic control was not studied in our work correlation. We suggest larger scale studies addressing this issue.

Keywords: Cross-sectional comparative, vitamin D levels, gestational diabetes mellitus

Introduction
Rising economic prospects bring a change in lifestyle, standard of living and in turn dietary changes as well as patterns of disease they experience. With increasing obesity, insulin resistance and better Screening protocols, GDM is increasingly being diagnosed in Indian women. Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1]. Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. The disease has important health implications for mother and child. Early diagnosis and treatment of GDM can reduce adverse pregnancy outcomes, including stillbirth, neonatal macrosomia, neonatal hypoglycaemia, birth trauma and neonatal respiratory distress syndrome as well as decrease the risk of preeclampsia in the mother [2].
Vitamin D deficiency is closely associated with Gestational Diabetes Mellitus (GDM). Vitamin D induces insulin receptor expression through Vitamin D receptor (VDR), enhancing insulin-dependent glucose transport. Vitamin D is also a potential immunosuppressant, which down-regulates the expression of pro-inflammation markers, such as TNF-α and IL-2, among pregnant women with GDM [3].
In recent years, vitamin D deficiency has been increasingly recognized as one potential contributor [4]. While epidemiologic studies have shown a fairly consistent link between vitamin D deficiency and a higher risk of type 2 diabetes [5, 6], and obesity is strongly associated with

both GDM [7, 8] and vitamin D deficiency [9, 10, 11], it remains unclear whether vitamin D deficiency contributes to a mother's risk of developing GDM. Compelling evidence suggests a role of vitamin D deficiency in the pathogenesis of insulin resistance and insulin secretion derangements. The coexistence of insulin resistance and vitamin D deficiency has generated several hypotheses as worsening insulin resistance [12]. Immense interest persists in vitamin D and its potential effects on several pregnancy outcomes including fetal growth, hypertensive disorders and gestational diabetes mellitus (GDM) [13]. Two factors make vitamin D intriguing to perinatal investigators studying GDM. First, vitamin D has been shown to improve pancreatic exocrine function and insulin sensitivity in animal models. Second, vitamin D status, like most micronutrients, is easily modified by dietary supplementation [13].

Aims

- To determine the relation between low maternal serum vitamin D levels and gestational diabetes mellitus (GDM).
- To study relation between vitamin D and the glycemic control in-patient with GDM assessed by HbA1c and blood glucose levels.

Methods

This study was a hospital based case control comparative analytical type of observational study conducted in Dept. of Obstetrics & Gynaecology, SMS Medical College, Jaipur from February 2016 to February 2017. We approached the pregnant women, in the third trimester, attending the antenatal care clinic; the target age group was between 20-40 years. Exclusion Criteria are H/O type 1 or 2 diabetes mellitus antedating pregnancy, medical disorders (HTN, Cardiac diseases etc.) and medical complications related to pregnancy. 70 pregnant women in their 3rd trimester with established diagnosis of GDM as per DIPSI guidelines and randomly selected 70 pregnant women with normal blood sugar attending ANC was enrolled and taken as cases and control after written and informed consent. They were subjected to detailed history taking with special focus on maternal age, parity, gestational age at diagnosis of gestational diabetes, previous history or family history of diabetes, history of gestational diabetes in previous pregnancies. Data concerning insulin regimens, insulin types and doses were also noted. Complete general physical examination, systemic examination and obstetric examination. Body Mass Index (BMI) was calculated for all subjects and matched in cases and controls.Blood sample was collected from both cases and control and sent for laboratory investigations. Assessment of serum 25(OH) Vitamin D was done by using CLIA method. The Biochemistry Department SMS Medical College Jaipur carried out chemiluminescence immunoassay. CLIA is a quantitative immunoassay method used for the determination of total 25 (OH) D in serum or plasma on a fully automated platform. It is a highly sensitive technology in which a specific antibody to vitamin D is used for coating magnetic particles (solid phase) and vitamin D is linked to an isoluminol derivative. Result of both groups was compared to evaluate association in maternal plasma 25- Hydroxyvitamin D level and GDM. Reference value of maternal plasma 25-Hydroxyvitamin-D level-Deficiency <20ng/ml; Insufficiency 20-30ng/ml; Sufficiency>30ng/ml. Glycosylated hemoglobin is a blood glucose control marker in diabetic patients. HbA1c results from post-translation changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. HbA1c was measured by chemiluminescence to assess the glycemic control. Data collected and statistical analysis was done.

Statistics

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference

Results

140 women in their third trimester were enrolled in the study.70 women with already diagnosed GDM were taken as cases and 70 normal pregnant women as cases. The mean age of cases and controls were 27.75±3.85 and 25.25 ± 3.87. It was not statistically significant. Majority of the women belonged to Hindu religion. GDM patients were mostly from urban area. Most of the women were housewives. In Group A, 81.4% women were literate and in Group B 60% women were literate. This wide gap in the study population may be because of increase awareness and better use of health care facilities amongst the literate.

The upper middle class made the majority of the study population in group A and in group B majority i.e. 31.4% belonged to lower middle class. In our study out of 140 subjects, 115(82.14%) subjects were vegetarian and 25 (17.8%) subjects were non-vegetarian. In group A 92.8% were vegetarian and 7.2% were non-vegetarian. Whereas in group B 71.4% were vegetarian and 7.2% were non-vegetarian. GDM were mostly vegetarian (P value = 0.010) and had low physical activity in sun (P value= 0.005). Past h/o GDM is an important risk factor for GDM (P value=0.013). No correlation was found with family history of Diabetes mellitus (P= 0.301). Calcium intake and periconceptional multivitamin (P value = 0.275) intake had no association with GDM.

In our study vitamin deficiency was seen in 71% of the study population out of 140 subjects. The mean level of Vitamin D is 8.83 ± 5.77 in GDM cases and in the controls the mean is 17.04 ± 8.67. Thus low level of Vitamin D was seen in patients with GDM (P value= 0.001). A significant inverse correlation was found between the HbA1C levels and Vitamin D levels (correlation coefficient r = -0.549, P value <0.05), where the higher the

Table 1: Clinical and biochemical demographic data of the studied groups

	Group-A (n=70, cases)	Group-B (n=70, controls)	P-Value
Maternal age	27.75±3.85	25.25 ± 3.87	0.99(NS)
Parity	1.79 ± 1.06	1.81 ± 2.95	0.665(NS)
Diet(vegetarian)	92.8%	71.4%	0.010(S)
H/O GDM	10%	0%	0.013(S)
Family h/o type 2DM	8.6%	4.3%	0.301(NS)
Calcium intake	64.3%	72.9%	0.275(NS)
Periconceptional multivitamin	27.1%	35.7%	0.275(NS)
Physical activity in the sun (>3hrs)	10%	30%	0.005(S)
Smoking	4.3%	8.6%	0.493(NS)
Fasting blood sugar	93.18 ± 8.05	78.70 ± 4.54	
HbA1c	6.62 ± 1.29	4.8 ± 0.28	
Vitamin D	8.83 ± 5.77	17.04 ± 8.67	0.001(S)

DM: diabetes mellitus, GDM: gestational diabetes mellitus, NS: not significant, S: significant

Levels of Vitamin D, the lower the HbA1c levels indicating a good glycemic control in women with gestational diabetes. An inverse association was also found with the fasting blood sugar levels which was statistically significant (the correlation coefficient r = - 0.570)

As regards the Vitamin D levels, Table shows that they negatively correlated with the fasting blood glucose levels (Figure 1) and the HbA1c levels, in the whole study population including both groups; women with GDM and controls. The P value in all these correlations were <0.05.

Table 2: The correlation between the Vitamin D levels and the various maternal biochemical variables in women included in the study

Variable	Correlation coefficient (r value)	P value	Significance
Fasting blood sugar	-0.570	<0.0001	S
HbA1c	-0.549	<0.0001	S

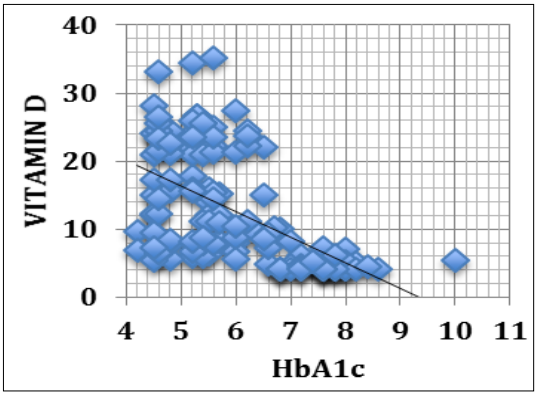

Fig 1: The scatter plot shows negative linear correlation between HbA1c and Vitamin D level (r = - 0.549)

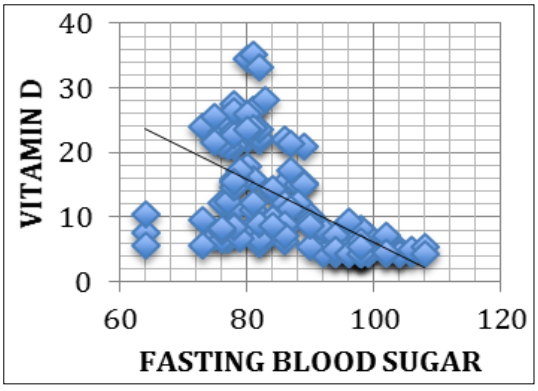

Fig 2: The scatter plot shows negative linear correlation between fasting blood glucose and Vitamin D level (r = - 0.570)

Discussion

Vitamin D seems to have several extra skeletal functions including regulation of glucose metabolism through influencing insulin sensitivity, although the mechanisms are not fully understood. In our study we have found high prevalence of deficiency in overall study sample. This may be explained by poor sun exposure, poor dietary intake, and lack of physical activity. In our study we also tried to find a correlation between Vitamin D and Gestational diabetes mellitus in pregnant women in their third trimester already diagnosed to have GDM at previous ANC visits, and we included normal pregnant population as control. Vitamin D deficiency was the salient feature in both groups.

The mean age of group A was 27.75±3.85 and for group B was 25.25 ± 3.87. The majority of the GDM subjects came from urban population (81.4%). Upper middle class patients constituted the major part of the GDM population (40%) whereas, in the control group majority belonged to lower middle class (31.4%). Janani Shishu Suraksha Karyakram offering free treatment (surgery plus drugs) attracted the mass of the study population from lower and middle class.

The maximum numbers of subjects were Hindus (72.1%). There was no significant difference in distribution of study population according to religion. Maximum no. of the study population were literate (75%).Majority (82.14%) of the subjects were vegetarian (P-value is 0.010). Study population consisted mostly of primigravida. Majority of the subjects were diagnosed at 26 weeks of gestation i.e. 44.3%. Past H/O GDM is an important risk factor for GDM. In group A 10% had history of GDM (P value 0.013). Calcium and periconceptional multivitamin intake in both groups did not show statistical significance. Jain madhu *et al.* [16] also had similar finding in their study. Majority of the study population were non-smokers.

In group A 90% had low sun exposure (physical activity in the sun <3hrs) and in group B 70% had low sun exposure, (P value= 0.005). This paradox of majority of the study population having low sun exposure, in a tropical country like India in spite of abundant sunlight for most of the year, can be explained due to many prevalent social and cultural practices e.g. increased urbanisation, poor outdoor activity, greater pollution that preclude exposure of women to sunlight. The mean HbA1c in group A is 6.62 ± 1.29 and in group B the mean is 4.8 ± 0.28.

Overall 71% 0f the study population are vitamin D deficient. Sahu M *et al.*, showed a prevalence of 74.1% from north-eastern part of India [14]. Sachan A *et al.*, reported a prevalence of 84.3% urban and 83.6% in rural area [15]. The mean maternal serum vitamin D levels were 8.83 ± 5.77ng/ml in Group A and 17.04 ± 8.67ng/ml in group B. The difference was statistically

significant reflecting that the mean serum vitamin D was decreased in women with GDM. (P value 0.001). Similarly zhang C *et al*. [17], Muthukrishnan Jayaraman *et al*. [18], Debnath arijit *et al*. [19] and PleskaIová Anna *et al*. [20] also found similar association between Vitamin D levels and GDM.

Poel *et al*. in a meta-analysis of four out of seven observational studies have reported a high incidence of Vitamin D deficiency (>50%, 25 (OH)<50 nmol/L) in pregnant women with the risk of GDM with an Odds ratio of 1.61 [21].

Contrary to our study, Farrant *et al*. found no association between maternal Vitamin D status and risk of GDM in a cross sectional study of 559 women from south India at gestational age of thirty weeks. However, he found negative correlation between 25(OH) D and 30 minutes blood sugar level, after adjustment of age and BMI [22].

There is a negative correlation between the Vitamin D levels and fasting blood sugar, higher levels of fasting blood sugar were found in women with lower Vitamin D levels (r=-0.570). Negative correlation also seen between the Vitamin D levels and HbA1c, thus indicating poor glycemic control, this inverse relation was found to be statistically significant (r=-0.549). Similar observation were made by El Lithy *et al*. [23] (correlation coefficient(r = -0.492, P value <0.05) and Debnath arijit *et al*. (r-value=0.571; Spearman correlation) [18].

Thus the low serum Vitamin D levels were associated with Gestational diabetes mellitus (GDM). So finally we concluded that the maternal serum Vitamin D level could be done as a routine investigation in pregnancy and Vitamin D deficiency should be treated to avoid risk of GDM. The strength of present study was its good sample size, meticulous data collection, analysis and interpretation of the results.

However, there are limitations. India is a country with high predisposition for insulin resistance leading to Vitamin D deficiency. Genetic factors in Asian women and majority of the population being vegetarian further adds to it. Therefore large randomized trials are needed to confirm our results and to find if Vitamin D supplementation could improve glycemic control in women with GDM and reduce the adverse outcome in mother and fetus.

Conclusion

We conclude that there is high prevalence of Vitamin D deficiency in our study population. Low serum Vitamin D levels were associated with Gestational diabetes mellitus (GDM). Maternal serum Vitamin D level can be done as a routine investigation in pregnancy and Vitamin D deficiency should be treated to avoid risk of GDM. We also found a negative correlation between Vitamin D levels and blood sugar levels and also a negative correlation was seen between Vitamin D levels and HbA1c. Thus, low Vitamin D levels are associated with poor glycemic control.

The strength of present study was its good sample size, meticulous data collection, analysis and interpretation of the results. To avoid complications as a result of Vitamin D deficiency in the mother and foetus, antenatal counselling regarding diet, personal habits, regular ANC visit and follow up is necessary to improve the feto-maternal outcome as limited similar studies are available.

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