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Original Article

Biochemistry Section

Vitamin D Levels in Gestational Diabetes Mellitus and its Influence on Future Type 2 Diabetes Mellitus- An Observational Study

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) and persistent hyperglycaemia postpartum is a rising health challenge. Multiple researches have contributed to the understanding of the magnitude of the causal factors involved. One such factor is Vitamin D deficiency though, widely studied exact role in development of Diabetes Mellitus (DM) is not investigated.

Aim: To predict the risk of pre-diabetes and DM in GDM patients with Vitamin D deficiency.

Materials and Methods: Hundred pregnant women were recruited-50 study group, 50 control group; based on WHO criteria for GDM diagnosis at 24-28 weeks of gestation. Study parameters in antepartum period were maternal age, Body Mass Index (BMI), Vitamin D, Fasting blood glucose, 2 hour Oral Glucose Tolerance Test (OGTT). Study parameters in postpartum follow-up were fasting blood glucose, postprandial blood glucose, vitamin D. Mann-Whitney U-test and Binary Logistic regression analysis were the statistical tools used to predict the risk.

Results: Antepartum Vitamin D deficiency (<20 ng/mL) showed 2.2 fold significantly increased risk for developing pre-diabetes and DM. High frequency of pre-diabetes (52% of cases) post-delivery (6 weeks) was proved. Maternal age, BMI and OGTT values had direct relationship in predicting risk of DM which was proved with postpartum follow-up.

Conclusion: Vitamin D deficiency has a significant role in development of pre-diabetes and DM in GDM patients.

Keywords: Biomarker, Glucose intolerance, Pre-diabetes, Risk prediction, Vitamin D deficiency

INTRODUCTION

The GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. GDM has potential risk of developing perinatal and neonatal complications like high rate of caesarean section, large for gestational age babies, intrauterine foetal death, pre-eclampsia and neonatal hypoglycaemia, hyperbilirubinemia, polycythemia, calcium deficiency etc., respectively. Both mother and baby are more likely to develop Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT) or overt type 2 DM [2].

The prevalence of gestational diabetes is rising in India. [3]. Therefore risk assessment and evaluation for GDM should be made mandatory at the first prenatal visit. Already known high risk factors for developing GDM are race/ethnicity, obesity, history of GDM, large for gestational age baby, bad obstetric history, excessive glycosuria and a strong family history of diabetes [4,5]. All these factors if effectively assessed, evaluated and managed can go a long way in prevention or better outcome in patients since, it has become a vastly growing public health concern. Multiple studies [6-9] have been conducted with this concept in view to find ways through which future DM can be predicted in pre/antenatal period. These studies have found factors, like insulin use, gestational age, BMI, HbA1c [8], insulin sensitivity [9], inflammatory markers [10], Vitamin D deficiency etc., showing biomarker potential in predicting DM.

Vitamin D is well known as a regulator of homeostasis of bone and mineral metabolism, but its varied actions owing to the presence of Vitamin D Receptors (VDR) in brain, breast, colon, pancreas, prostate and immune cells are little known. The role of vitamin 25 (OH) D3 deficiency in insulin resistance has been proposed to be associated with inherited gene polymorphisms including vitamin D-Binding Protein (DBP), vitamin D receptor [11-13], CYP1 alpha gene polymorphism [14] and disruption of normal Vitamin D synthesis, transport and action process. Other modes of action on insulin resistance include activation of innate and acquired immunity [15], increasing T cell proliferation, dendritic cell maturation [16], macrophage differentiation, release of Interleukin (IL)-12, IL-2, Interferon gamma (IFN-γ), and Tumor Necrosis Factor alpha (TNF-α) which contributes to destruction of β-cell. Inflammatory actions include increase regulation of Nuclear Factor kappa B (NF-κB) and induction of pro inflammatory action of TNFα, decreasing mRNA stability and increasing IκB-α phosphorylation thereby down regulating IκB-α [17], augmenting the Toll Like Receptor 2 (TLR2), TLR4 protein and mRNA expression in human monocytes [18] and also lowering cytokine release. Finally, molecular actions that contribute to alteration of glucose homeostasis [19,20] includes lowering calcium status which in turn lowers glucose stimulated insulin secretion in β-cell [21], reducing liver, muscle and adipose tissue uptake of glucose by elevating Parathyroid Hormone (PTH) levels [22] and Vitamin D deficiency itself induces adiposity and enhanced sequestration of Vitamin D in adipose tissue [23].

Many studies have proven the influence of low Vitamin D levels in development of type 2 DM [24] and GDM [25-27] by altering insulin sensitivity, calcium metabolism and evidence also shows placental secretion of Vitamin D attributing to possible autocrine or paracrine functions [28] but the influence on development and progression of GDM and hyperglycaemia persistenceis are still under conflict [29] due to multiple confounding factors contributing to Vitamin D metabolism like seasonal variation, ethnicity, diet, physical activity, exposure to sunlight, maternal obesity, etc.

At present there are very few studies exploring the relationship of postpartum persistence of glucose intolerance in Vitamin D deficient GDM patients. Hence, in this study the levels of Vitamin D during and after pregnancy in women of South Indian ethnicity were focused on to see how the levels get altered as the pregnancy progresses and to evaluate their correlation to predict the risk of persistence of glucose intolerance or development of type 2 DM within six weeks of postpartum follow-up in patients pre-diagnosed with Vitamin D deficiency in antenatal period.

MATERIALS AND METHODS

This was an observational prospective cross-sectional study performed, during the period of July 2017 to July 2018, in a private Medical College and hospital, Chennai Tamil Nadu. The study was started after obtaining clearance from Institutional ethical committee (Ref no.002/SBMC/IHEC/2017/984) and was conducted in accordance with the Institutional policy for Biomedical research in human beings.

After getting due informed consent, 100 pregnant women with singleton pregnancy from age group 20-35 years with no other known acute or chronic diseases who had come to Department of Obstetrics and Gynaecology were evaluated. Out of them, 50 were selected as study group and 50 were established as control group based on their Fasting and OGTT values with 82.5G glucose monohydrate load at 24-28 weeks of gestation with WHO diagnostic criteria [30]. In terms of physical activity all women in both study and control group were predominantly of sedentary lifestyle involving only indoor work. Pre-gestational and mid trimester BMI was calculated using kilograms/meter^2 for all women in the study.

Study group: (if one or more of the following cut-off value was fulfilled) Fasting >92 mg/dL, OGTT 1 hr >180 mg/dL and/or 2 hour OGTT >153 mg/dL,

Control group: Normoglycaemic women with all values within limits of criteria.

Cases with multiple pregnancy, family history of DM, known case of any type of DM [31], history of GDM, pre-eclampsia, polycystic ovarian disease, thyroid, parathyroid, metabolic bone, kidney and liver disorders and also drug history related to Calcium and Vitamin D metabolism were all excluded.

Methodology

For all the women in the study and control group plasma glucose was estimated using Hexokinase method in a fully automated analyser and serum 25-hydroxy Vitamin D levels using High performance Liquid chromatography method at 24-28 weeks of gestation. Values <20 ng/mL were set as deficiency criteria [32].

At six weeks follow-up post-delivery [31] the study group were tested for fasting blood glucose, postprandial blood glucose and Vitamin D. Their antenatal management was according to general outlined protocol of the Department of Obstetrics and Gynaecology, which included management with Insulin, dietary modifications and physical exercise. Study participants who showed compliance with treatment were only selected.

STATISTICAL ANALYSIS

The parameters defining cohort characteristics which were continuous variables were expressed as mean±SD. The study group and control groups were compared using Mann-Whitney U-test for non-parametric tests with skewed distribution to establish significant relationship and then they were also analysed using Binary Logistic Regression analysis to predict the risk contributed by each of the antepartum study parameters in development of prediabetes or DM. Then analysis of postpartum blood glucose and vitamin D levels was done using Binary Logistic Regression analysis to determine whether levels of Vitamin D in postpartum period have a significant predictive risk on development of DM. The confidence level of significance was set at 95% p<0.05. Data were analysed using SPSS software.

RESULTS

A total of 100 pregnant women who fulfilled the above criteria were recruited for the study out of them 50 were study group with GDM and 50 were control group with no GDM as diagnosed at 24-28 weeks of gestation.

The study parameters were maternal age, prepregnancy BMI, 24-28 weeks of gestation BMI, fasting blood glucose, OGTT 1 hour, OGTT 2 hours and 25-OH Vitamin D and their mean and SD is shown in [Table/Fig-1].

Parameters	Control group (no GDM) Mean (SD)	Study group (with GDM) Mean (SD)	Mann-Whitney U-test
Age (years)	29.2 (2.542)	30.2 (2.0)	0.148
Prepregnancy BMI (kg/m^2)	22.258 (1.369)	27.622 (1.6605)	<0.001*
BMI at 24-28 weeks (kg/m^2)	26.348 (1.505)	30.586 (1.8014)	<0.001*
FBS (mg/dL)	85.340 (4.397)	104.8 (6.0609)	<0.001*
OGTT 1 hr (mg/dL)	167.280 (5.334)	182.36 (4.6369)	<0.001*
OGTT 2 hr (mg/dL)	142.680 (5.995)	170.62 (7.7457)	<0.001*
25-OH Vitamin D (ng/mL)	30.298 (4.038)	21.088 (3.3321)	<0.001*

[Table/Fig-1]: Study parameters.
*Significance 95% CI; OGTT: Oral glucose tolerance test; FBS: Fasting blood sugar

[Table/Fig-1] also shows the Mann-Whitney U-test results showing significance at 95% CI (p<0.05) proving that significant statistical difference was present between the two groups in terms of FBS, OGTT 1 hour, OGTT 2 hour, Prepregnancy BMI, BMI at 24-28 weeks and especially Vitamin D levels.

[Table/Fig-2] Binary Logistic regression findings show the risk for developing DM in future based on prepartum and antepartum (24-28 weeks) levels of the study parameters. The findings observed were: increased maternal age (OR=1.2), prepregnancy BMI (OR=26.6), BMI during second trimester (OR=5.8), OGTT 1 hour (OR=2) values in the antenatal period directly contribute to statistically significant increased risk for developing DM.

Parameters	Odds ratio	Lower limit	Upper limit	p-value
Age	1.216	1.009	1.465	0.04*
Prepregnancy BMI	26.569	1.795	393.191	0.017*
BMI at 24-28 weeks	5.826	2.619	12.961	<0.001**
OGTT 1 hr	2.001	1.421	2.817	<0.001**
25-OH Vitamin D#	2.217	1.580	3.106	<0.001**

[Table/Fig-2]: Risk prediction for development of DM prepartum and antepartum factors.
*Significance at 95% CI; **Significance at 99% CI; #Predicts risk as value decreases

Vitamin D deficiency during the antepartum period is shown to be associated with 2.2 fold statistically significant increased risk for developing DM in the future.

[Table/Fig-3] gives details of risk prediction for developing Diabetes and pre-diabetes based on their postpartum FBS, PPBS and Vitamin D levels and maternal age based on binary logistic regression analysis. Postpartum levels of FBS and PPBS are only statistically significant to predict the risk for DM or pre-diabetes.

Parameters	Odds ratio	Lower limit	Upper limit	p-value
Age	1.256	0.924	1.708	0.145
FBS	1.96	1.273	3.016	0.002*
PPBS	1.116	1.009	1.235	0.032*
Vitamin D	1.076	0.951	1.218	0.248

[Table/Fig-3]: Risk prediction for DM and pre diabetes -postpartum 6 weeks factors.
*significance at 95% CL; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar

Postpartum Vitamin D deficiency has been shown to have no statistically significant risk in development of DM or pre-diabetes. Hence, showing the importance of antepartum Vitamin D deficiency.

The frequency of GDM patients who had persistent pre-diabetes and DM based on their fasting and 2 hour postprandial glucose values after delivery is shown in [Table/Fig-4].

Though DM frequency was low (4%) in the early (6 weeks) postpartum follow-up may result in more DM conversions. But more than half i.e. 52% of GDM patients in the study group with Vitamin D deficiency in their gestational period had developed persistent hyperglycaemia

Parameter	N (50)	Frequency
Diabetes mellitus	2	4%
Normoglycemia	22	44%
Pre diabetes -Impaired fasting glucose -Impaired glucose tolerance -Both	26	52%
	15	30%
	1	2%
	10	20%

[Table/Fig-4]: Frequency of DM and Pre-diabetes in study group in postpartum.

in the form of pre-diabetes in early postpartum period itself. These patients have 2.2 times higher risk for developing DM compared to women who were normoglycemic after GDM and also control group women with Vitamin D deficiency. Hence antepartum Vitamin D deficiency appears to be a modifiable risk factor contributing to pre-diabetes in early postpartum period.

DISCUSSION

Vitamin D influence on glucose metabolism through modulation of calcium metabolism has directly or indirectly influenced the insulin release and sensitivity which has been proved by many studies [4]. Forouhi NG et al., have also shown an alternate link between Vitamin D and Glucose homeostasis through Insulin like growth factor system [5]. Owing to the possible impact of Vitamin D deficiency in GDM patients on maternal and foetal outcomes studies have been conducted to determine the same [25,26,33]. These studies have found that early gestational Vitamin D deficiency may be implicated in the development of GDM [25]. Aghajafari F et al., have shown Vitamin D insufficiency's association with development of GDM, pre-eclampsia and small for gestational age babies [27]. Though these studies have explored the impact of Vitamin D in development of GDM and in maternal and foetal outcomes, there are very few studies [34] that have investigated the long term postpartum maternal effects of Vitamin D deficiency i.e., the progression of GDM into persistent pre-diabetes or DM.

This study compared the control and study groups and have evidenced the high prevalence of Vitamin D deficiency (cut-off 20ng/mL) among pregnant women of South Indian ethnicity and found statistically significant difference between the groups, which is consistent with findings of Sachan A et al., [35]. Decreased mid-Gestational Vitamin D levels have been shown to have a 2.2 fold statistically significant risk in contributing to the progression of GDM into persistent pre-diabetes or DM. Furthermore, the factors like pregestational BMI, mid trimester BMI and maternal age have also been shown to contribute to development of DM in the study group with statistically significant results.

A retrospective cohort study has shown patients with GDM have a 1.7% probability (ranges 3% to 38% due to heterogenous population, varied diagnostic criteria and in long term follow-up) of developing DM at one year postpartum due to cumulative factors [6], whereas the present study's novelty is exploration of the risk at early postpartum period with Vitamin D deficiency as the modifiable risk factor among other known risk factors like insulin use, maternal BMI, fasting blood glucose, ethnicity, OGTT 1 hour values etc.

Early postpartum (6 weeks) analysis of fasting blood glucose and postprandial blood glucose showed that 52% of women with GDM had progressed into pre-diabetes and 4% into DM rest 44% became normoglycaemic. The conversion positively correlated with severity of Vitamin D deficiency in the antenatal period but no statistical significance was noted with postpartum period. A study showed that at 1 year postpartum follow-up 14.9% of GDM women had persistent glucose abnormality but the mid-gestational and postgestational Vitamin D values had no significance, which may be due to high disparity in the numbers in the group (7 and 40), participants ethnicity (caucasians) and cut-off of Vitamin D levels [34]. Since, similar studies exploring Vitamin D pre and postpartum were not found, comparison regarding postpartum findings have a lacunae which may be filled by this present study's novel findings.

Limitation(s)

The study limitations were the lifestyle factors that contribute to Vitamin D deficiency like seasonal variation, physical activity, exposure to sunlight and diet. All the study participants had a sedentary lifestyle with predominant indoor activity but the quantitative estimation of their physical activity was not done and their diet was not fully explored as to its influence on calcium levels and seasonal variation was not taken into account as the climate was predominantly sunny throughout the period of study.

CONCLUSION(S)

Vitamin D deficiency and its severity in the antepartum period seems to have a significant relationship with development of future DM or pre-diabetes in pregnant women with GDM but the exact causal pathway is to be investigated so that prevention of DM in these patients can be made possible. This study has further highlighted the risk in quantifiable terms and proven the definite development of DM in patients with Vitamin D deficiency by following-up the patients in their post-partum period. The high prevalence of pre-diabetes in GDM patients seen in this study reconfirms the rising Public health challenges. This study needs further verification with a larger population and also in terms of effect of intervention with Vitamin D supplementation on the development of DM in the future and also in the outcome of the pregnancy.

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