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Original article

Serum calcium, vitamin D and parathyroid hormone relationship among diabetic and non-diabetic pregnant women and their neonates

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ABSTRACT

Aims: The purpose of the study was to determine the prevalence of osteomalacia and hypovitaminosis D among diabetic and non-diabetic pregnant women and in their neonates.
Methods: Serum calcium, phosphorus, heat labile alkaline phosphatase, 25(OH) vitamin D and PTH were measured in 32 non-diabetic, 16 gestational diabetic and 8 Type 1 diabetic pregnant women and in cord blood of their newborn.
Results: Among 32 non-diabetic subjects, 4 subjects (12.5%) had biochemical osteomalacia. 4 out of 16 gestational diabetic subjects (25%) had biochemical osteomalacia whereas 5 out of 8 Type 1 diabetic subjects (62.5%) had biochemical osteomalacia. Mean concentration of 25(OH) vitamin D in the non-diabetic group was 17.18 ± 9.88 ng/ml. Mean concentration of 25(OH) vitamin D in the Gestational diabetic group was 14.75 ± 6.90 ng/ml, while in Type 1 diabetic group, it was 7.81 ± 3.79 ng/ml. 50% of neonates of normal pregnant women had vitamin D deficiency whereas, 50% had vitamin D insufficiency. 40% of neonates of Gestational diabetic pregnant women had vitamin D deficiency whereas, 40% had vitamin D insufficiency.
Conclusion: Vitamin D deficiency and biochemical osteomalacia was present in significant percentage of normal pregnant women and their neonates. Gestational diabetes and Type 1 diabetic women were more prone to develop vitamin D deficiency and biochemical osteomalacia.

1. Introduction

Significant changes in maternal calcium and vitamin D metabolism occur during pregnancy to provide the calcium needed for fetal bone mineral accretion. By the end of pregnancy, approximately 30 g of calcium is transferred to the fetal skeleton, most of it during the last trimester. Several studies have reported vitamin D deficiency in pregnancy [1–3].

Vitamin D deficiency during pregnancy has important consequences for the newborn, including fetal hypovitaminosis D, neonatal rickets and tetany, and infantile rickets [4,5]. Rickets during infancy is associated with high prevalence of lower respiratory tract infections [6], which is the largest cause of infant mortality in India.

Though studies from different parts of country have shown widespread vitamin D deficiency in all age groups [7–10], there are few data on serum 25(OH) vitamin D concentration and the prevalence of osteomalacia among pregnant women from India [11,12]. Many studies have shown that, in diabetic pregnancy and especially in insulin dependent diabetic pregnant women, the concentration of 25(OH) vitamin D and PTH remains low in late pregnancy compared to normal pregnant women [13–15]. The present study was undertaken to determine the prevalence of clinical or biochemical osteomalacia and among diabetic and non-diabetic pregnant women and in their neonates.

2. Subjects and methods

2.1. Study population

The present study was conducted on pregnant women and their neonates at the Centre for Diabetes and Endocrinology, Department of Medicine and Department of Obstetrics and Gynecology, Aligarh Muslim University. Women with full-term live pregnancy and their neonates who presented to the hospital in a 16 month period from October 2007 to January 2009 were recruited for the study which was carried out in winter season to eliminate the effects of seasonal variation and to reduce the effect of individual variation in exposure to sunlight. The study group consisted of 24 diabetic women and 32 non-diabetic women. Of diabetic subjects 8 were having Type 1 diabetes while 16 had gestational diabetes. All mothers were healthy; had singleton pregnancies without

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complications and all delivered vaginally full term normal-weight infants. All the subjects gave informed consent and those with renal disease, chronic liver disease, treatment with ATT or antiepileptic drugs in previous 3 months and pregnancy induced hypertension are excluded from the study.

Detailed history and examination of the subjects were performed as per a pre-designed proforma with special regard to current and past pregnancies and labor and clinical features suggestive of osteomalacia (proximal muscle weakness, bone pain, tenderness and fractures) or past rickets. Daily intake of dietary calcium was calculated from a food frequency questionnaire. Any supplemental calcium intake in the current pregnancy was noted. Daily sun exposure was calculated by taking detailed history of daily routine and of the type of clothing worn. Sunshine exposure was calculated as hours of sun exposure per day × percentage of body surface area exposed.

2.2. Blood sample collection

Maternal blood sample was collected from antecubital vein into a plain vacuum tube in third trimester or just before labor. A mixed cord blood sample was collected from clamped cord of newborn immediately following delivery in subjects who delivered at hospital. For the analysis of serum calcium, phosphorus, albumin, alkaline phosphatase, serum 25(OH) vitamin D and PTH, the blood sample in vacuum tube was centrifuged and sera frozen at −20 °C. Cord blood samples were similarly processed.

2.3. Biochemical analyses

Serum total calcium, albumin and inorganic phosphorus were analysed with a Technicon SMA Analyzer (Tarrytown, N.Y., USA) according to the instruction manual. Serum alkaline phosphatase was measured spectrophotometrically (Boehringer Mannheim, Mannheim, Germany). Heat-labile alkaline phosphatase (HLAP) was analysed to exclude placental isoenzyme [16]. 25(OH) vitamin D estimation was carried out quantitatively by LIAISON 25 OH Vitamin D TOTAL Assay which utilizes chemiluminescent immunoassay (CLIA) technology. Intact PTH estimation was carried out quantitatively by LIAISON N-tact PTH Assay which utilizes chemiluminescent immunoassay (CLIA) technology.

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 10.0 Statistical package for windows (SPSS, Chicago, IL). Continuous variables were expressed as mean ± standard deviation (Gaussian distribution) or range. Unpaired tests for independent samples were used in comparing continuous data between two groups. ANOVA with Bonferroni's post hoc analysis was used to compare continuous data between three groups. Proportions were compared with chi-square test. Correlations were studied by using Pearson's correlation coefficient.

3. Observations and results

3.1. Distribution of study subjects according to presence of osteomalacia

The baseline clinical characteristics and glycemic parameters are shown in Table 1. Clinical evidence of osteomalacia was not seen in any subject, as defined by proximal muscle weakness and bony pains or tenderness. However, biochemical osteomalacia was observed in significant number of patients. Biochemical osteomalacia was defined as Heat-labile Alkaline phosphatase (HLAP) level above 125 U/l. Subjects in all three groups were further divided into two groups based on serum alkaline phosphatase values, Group A-without biochemical osteomalacia and Group B-with biochemical osteomalacia (Table 2). The statistical analysis revealed that Type 1 diabetic and Gestational diabetic group had significantly higher percentage of subjects with biochemical osteomalacia compared to non-diabetic group ($p < 0.01$).

Serum corrected calcium levels were in lower side of normal range in all study subjects. When compared with non-diabetic group by applying ANOVA analysis, the mean value of HLAP was significantly higher in both Gestational diabetic group ($p < 0.01$) and Type 1 diabetic group ($p < 0.01$). Whereas, there was no significant difference between later two groups. When compared with non-diabetic group and Gestational diabetic group by applying one way ANOVA analysis, the mean value of 25(OH) vitamin D was significantly lower in Type 1 diabetic group ($p < 0.05$) (Table 3). Though the level was lower in Gestational diabetic group than non-diabetic group, it was not found to be statistically significant.

3.2. Groups of subjects according to vitamin D status

Study subjects were further divided on the basis of serum 25(OH) vitamin D concentrations into three groups:

(a) Vitamin D deficiency: serum 25(OH)D below 10 ng/ml.
(b) Vitamin D insufficiency: serum 25(OH)D between 10 and 30 ng/ml.
(c) Vitamin D sufficiency: serum 25(OH)D between 30 and 100 ng/ml.

The distribution of study subjects into categories according to vitamin D concentration is shown in Fig. 1. PTH levels were higher

Table 1
Baseline clinical characteristics of study subjects[a,b,c].

Profile	Non-diabetic ($n = 32$)	Gestational diabetic ($n = 16$)	Type 1 diabetic ($n = 08$)
Age (years)	25.62 ± 4.75	26.56 ± 3.57	25.87 ± 4.15
Parity	1.59 ± 1.01	1.81 ± 0.83	1.62 ± 1.06
Calcium intake (mg/day)	859.12 ± 178.16	852.68 ± 191.54	840.37 ± 164.5
Sun exposure (h/day)	4.53 ± 1.084	4.34 ± 1.60	4.56 ± 1.42
Percentage of body exposed (%)	31.56 ± 5.88	30.00 ± 4.08	29.37 ± 4.95
Sunshine index[d]	1.46 ± 0.46	1.36 ± 0.55	1.35 ± 0.54
BS (F)[e] (mg/dl)	96.4 ± 9.8	116.3 ± 24.2	124 ± 30.2
BS (pp)[f] (mg/dl)	124.2 ± 8.65	166.8 ± 28.5	161.5 ± 26.4
HbA1c (%)	5.12 ± 0.25	7.06 ± 0.28	7.15 ± 0.22

[a] Compared by ANOVA with Bonferroni's post hoc analysis.
[b] Values are mean ± S.D., p-value indicates difference. NS = not significant.
[c] N D: non-diabetic group, G D: gestational diabetic group, T 1 D: Type 1 diabetic group.
[d] Sunshine index = sun exposure (h/day) × percentage of body exposed.
[e] BS (F): blood sugar fasting.
[f] BS (pp): blood sugar post-prandial.

Table 2
Distribution of study subjects according to presence of osteomalacia.

Groups ($n=56$)	Without osteomalacia		With osteomalacia		Total	Significance (p) by chi-square
	No. of subjects	Percentage (%)	No. of subjects	Percentage (%)		
All subjects	43	76.79	13	23.21	56	
Non-diabetic group	28	87.50	04	12.50	32	0.011
Gestational diabetic group	12	75.00	04	25.00	16	
Type 1 diabetic group	03	37.50	05	62.50	08	

Table 3
Biochemical parameters in study subjects[a,b].

Parameter	N D[d] ($n=32$)	G D[d] ($n=16$)	T 1 D[d] ($n=08$)	Difference (p)		
				N D vs. G D	N D vs. T 1 D	G D vs. T 1 D
Serum corrected calcium (mg/dl)	8.93 ± 0.68	9.03 ± 0.40	8.76 ± 0.26	NS	NS	NS
Serum phosphorus (mg/dl)	3.82 ± 0.44	3.89 ± 0.32	3.71 ± 0.53	NS	NS	NS
Serum HLAP[c] (U/l)	80.93 ± 26.80	111.68 ± 25.07	120.12 ± 19.61	<0.01	<0.01	NS
Serum 25(OH) vit D (ng/ml)	17.18 ± 9.88	14.75 ± 6.90	7.81 ± 3.79	NS	<0.05	NS
Serum PTH (pg/ml)	71.87 ± 33.17	55.87 ± 14.21	48.50 ± 18.04	NS	NS	NS

[a] Values are mean ± S.D.
[b] ANOVA with Bonferroni's post hoc analysis. p-value indicate difference. NS = not significant.
[c] HLAP = heat labile alkaline phosphatase.
[d] N D: non-diabetic group, G D: gestational diabetic group, T 1 D: Type 1 diabetic group.

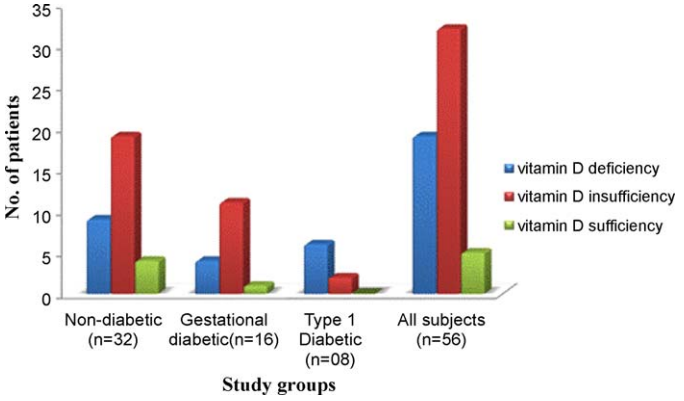

Fig. 1. Vitamin D status of study subjects.

in non-diabetic group as compared to other two groups. However, the difference was not statistically significant ($p > 0.05$).

3.3. Differences in non-diabetic subjects with and without biochemical osteomalacia

Non-diabetic subjects were divided into two groups:

(1) Group A: subjects without biochemical osteomalacia ($n = 28$).
(2) Group B: subjects with biochemical osteomalacia ($n = 04$).

Various clinical and biochemical parameters were compared between group A and group B as shown in Table 4. The sunshine index was significantly low in subjects with biochemical osteomalacia with mean value of 0.96 ± 0.25 as compared to 1.53 ± 0.44 in subjects without biochemical osteomalacia ($p < 0.05$).

There was no significant difference in serum calcium and serum 25(OH) vit D levels between two groups. Serum PTH levels were higher in subjects with biochemical osteomalacia with mean value of 101.42 ± 48.37 pg/ml as compared to 67.65 ± 29.25 pg/ml in subjects without biochemical osteomalacia. However the difference was not statistically significant ($p > 0.05$). Pearson's correlation coefficient showed that maternal serum 25(OH) vit D had moderate negative correlation with maternal serum PTH ($r = -0.435$; $p < 0.05$); moderate negative correlation with sun index ($r = -0.416$; $p < 0.05$); moderate positive correlation with serum calcium concentration ($r = 0.552$; $p < 0.01$). Maternal serum HLAP had weak negative correlation with sun index ($r = 0.376$; $p = 0.07$).

Because of loss of follow up, we were able to collect cord blood samples from 30 women who delivered at our hospital. 20 of them were non-diabetic women, whereas 10 were from Gestational diabetic group.

In non-diabetic group, the mean cord blood level of calcium was 8.83 ± 1.13 mg/dl (range 7.2–10.4 mg/dl), while it was significantly lower i.e. 7.88 ± 0.46 mg/dl (range 7.1–8.4 mg/dl) in diabetic group ($p < 0.05$). Serum concentration of PTH was 15.55 ± 10.57 pg/ml

Table 4
Differences in subjects in non-diabetic group with and without biochemical osteomalacia[a,b].

Parameters	Without biochemical osteomalacia ($n=28$)	With biochemical osteomalacia ($n=4$)	p
Age (years)	25.78 ± 4.87	24.50 ± 4.20	NS
Parity	1.64 ± 1.02	1.25 ± 0.95	NS
Calcium intake (mg/day)	856.50 ± 187.52	877.50 ± 104.94	NS
Sunshine index	1.53 ± 0.44	0.96 ± 0.25	<0.05
Serum calcium (mg/dl)	8.92 ± 0.66	9.05 ± 0.86	NS
Serum Phosphorus (mg/dl)	3.81 ± 0.46	3.95 ± 0.23	NS
Serum HLAP (U/l)	73.10 ± 17.72	135.75 ± 4.34	<0.01
Serum 25(OH) vit D (ng/ml)	17.57 ± 9.43	14.39 ± 14.00	NS
Serum PTH (pg/ml)	67.65 ± 29.25	101.42 ± 48.37	NS

[a] Compared by independent samples t-test.
[b] Values are mean ± S.D., p-value indicate difference. NS = not significant.

Table 5
Comparison of various biochemical parameters in cord blood analysis[a,b].

Profile	Non-diabetic ($n = 20$)	Gestational diabetic ($n = 10$)	Difference (p)
Serum calcium (m/dl)	8.83 ± 1.13	7.88 ± 0.46	<0.05
Serum phosphorus (m/dl)	3.78 ± 0.50	3.80 ± 0.46	NS
Serum HLAP (U/l)	95.50 ± 44.55	113.40 ± 41.64	NS
Serum 25(OH) vitamin D (ng/ml)	12.06 ± 5.99	15 ± 10.06	NS
Serum PTH (pg/ml)	15.55 ± 10.57	17.90 ± 11.61	NS

[a] Independent samples t-test.
[b] Values are mean ± S.D., p-value indicates difference. NS = not significant.

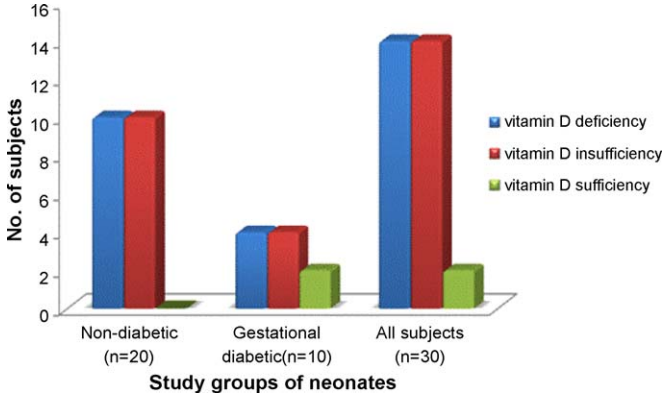

Fig. 2. Vitamin D status of neonates.

(range 2.5–30 pg/ml) and 17.90 ± 11.61 pg/ml (range 2.5–37 pg/ml) in non-diabetic group and diabetic group respectively. These levels are significantly low in both the groups compared to maternal levels at delivery ($p < 0.01$) (Table 5). The mean cord blood level of 25(OH) vitamin D was quite low in both groups. However, there was no significant difference between the two groups.

Out of all 30 neonates studied, 10 subjects (33.33%) had biochemical osteomalacia. Among 20 neonates from non-diabetic group, 6 subjects (30%) had biochemical osteomalacia. 4 out of 10 neonates from Gestational diabetic group (40%) had biochemical osteomalacia. A large proportion of neonates had hypovitaminosis D. The distribution of neonates into categories according to vitamin D concentration is shown in Fig. 2.

Maternal serum 25(OH) vit D had strong positive correlation with cord blood 25(OH) vit D ($r = 0.716$; $p < 0.001$) and cord blood calcium concentration ($r = 0.880$; $p < 0.001$). Cord blood 25(OH) vit D also had weak positive correlation with maternal sunshine index ($r = 0.538$; $p < 0.05$) and weak negative correlation with maternal PTH concentration ($r = -0.515$; $p < 0.05$). Maternal HLAP had strong positive correlation with cord blood HLAP ($r = 0.771$; $p < 0.001$).

4. Discussion

The finding of low mean daily calcium intake in our study subjects is consistent with other studies which also observed low calcium intake, notable being the study by Mohapatra et al. which reported mean daily calcium intake of 250 mg/day in antenatal women in rural India [17]. The finding of biochemical osteomalacia in significant percentage of normal pregnant women is consistent with observations in recent studies on pregnant women. Sachan et al. reported biochemical osteomalacia in 14% of healthy pregnant women in northern India [18]. Rab and Baseer from Pakistan and Marya et al. from India reported elevated total alkaline phosphatase in pregnant women [19,11]. We also found significantly higher levels of HLAP and larger percentage of subjects with osteomalacia in both Gestational diabetic group and Type 1 diabetic group compared to non-diabetic group. Kuoppala et al. showed that serum alkaline phosphatase was higher in Type 1 diabetic pregnant women than in normal pregnant women [13].

We found mean serum corrected calcium levels in normal range in all subjects. Early studies of human pregnancy found a significant decrease in the total serum calcium as pregnancy progressed, with a nadir at 28–32 weeks [20]. The serum concentration of 25(OH)D is the most sensitive clinical marker of subject's vitamin D status [21]. Vitamin D deficiency was previously considered to be rare in India because of ample sunshine in most of the parts [22]. Our study demonstrated high prevalence of hypovitaminosis D among pregnant women by measurement of 25(OH)D. This finding is consistent with recent studies in northern India by various researchers such as Sachan et al. and Goswami et al. [18,12]. Hypovitaminosis D and osteomalacia among pregnant South Asian women have been widely reported [19,23,24]. Similarly, there are various reports of Hypovitaminosis D in Asian women residing in other parts of world [25–27]. When compared with non-diabetic group and Gestational diabetic group, the mean value of 25(OH) vitamin D was significantly lower in Type 1 diabetic group. All subjects with Type 1 diabetes and 93.75% of Gestational diabetic group exhibited Hypovitaminosis D. This finding agrees with previous reports in pregnant [28,13] and non-pregnant subjects [29]. Fleischman et al. suggested that increased levels of glucocorticoids in pregnancy can induce hepatic microsomal enzymes and thus increase the degradation of 25(OH) vitamin D to more polar, inactive metabolites [28].

PTH levels were higher in non-diabetic group as compared to other two groups. However, the difference was not statistically significant. Considering normal range of our study population as 10–55 pg/ml, majority of normal pregnant women exhibited increased levels of PTH in our study. Thus, our study supports the traditional theory of 'physiologic hyperparathyroidism' during pregnancy. Several studies have suggested that, there is hyperplasia of maternal parathyroid glands and increase in parathyroid hormone (PTH) levels during pregnancy [30,31] particularly during last trimester. However, the bulk of published human data on PTH levels in pregnancy was obtained from studies that used early-generation PTH RIAs. In the present study, we found PTH levels in normal range in gestational diabetic group and Type 1 diabetic group. Cruikshank et al. and Tsang et al. also reported that Type 1 diabetic pregnant women did not exhibit the progressive increase in PTH levels which is seen in nondiabetic pregnancy and found lower levels of PTH in diabetic pregnant women [32,33].

We found low mean cord blood levels of 25(OH) vitamin D in both non-diabetic and Gestational diabetic groups. Maternal serum 25(OH) vit D had strong positive correlation with cord blood 25(OH) vit D and maternal HLAP had strong positive correlation with cord blood HLAP. This is in accordance with the fact that, fetal calcium physiology is greatly affected by imbalance in maternal calcium homeostasis and maternal hypovitaminosis D

predisposes to fetal hypovitaminosis D and higher incidence of osteomalacia in child. Goswami et al. also reported that, the vitamin D deficiency in mother correlates significantly with serum 25(OH) vitamin D levels of newborn [10]. We found that there is no significant difference in cord blood 25(OH) vitamin D levels among diabetic and non-diabetic subjects. This may be due to fact that, cord blood 25(OH) vitamin D comparison in our study included non-pregnant and Gestational diabetic groups while maternal 25(OH) vitamin D comparison included both Gestational diabetic and Type 1 diabetic pregnant women and when compared with non-diabetic group and Gestational diabetic group the mean value of 25(OH) vitamin D was significantly lower in Type 1 diabetic group but equal in other two groups i.e. non-diabetic and Gestational diabetic group. This indicates that the perturbations in 25(OH) vitamin D metabolism are more pronounced in Type 1 diabetic pregnancy. Kuoppala also found low levels of 25(OH) vit D and $1,25(OH)_2$ vit D in Type 1 diabetic pregnant women and normal in gestational diabetic pregnancy [13].

We found that cord blood concentration of PTH was significantly low in both the groups, compared to maternal levels at delivery. Reitz et al. also reported very low to undetectable cord blood PTH levels in study of 150 normal pregnant women [34]. Similar findings have been reported by David and Anast [35]. Based on measurements taken only at birth and 24 h of age in humans, the intact PTH level has been found to rise briskly after birth to within or near the normal adult range [36–38]. However, these studies did not determine how soon the PTH level begins to rise after birth and whether the peak level is attained by 24 h or even later. Low PTH in these neonates may be a consequence of maternal hyperparathyroidism. Although the fetal blood calcium is set independently of the maternal level *in utero* and PTH does not cross the placenta, a number of reported cases in humans have shown that maternal hyperparathyroidism adversely affects the neonate [39,40]. We found that, in non-diabetic group the mean cord blood level of corrected calcium was within normal limit in cord blood. Good calcium status despite a low vitamin D concentration probably reflects the fact that the regulation of calcium balance in fetus is multifactorial. This finding is in contradiction with popular hypothesis that, fetal blood calcium is maintained at a higher level than in the maternal circulation [41]. However, most of the studies in support of this theory are from animal models. In the present study, we found that, the mean cord blood level of calcium was significantly lower in diabetic group. In 1988, Kuoppala reported that, 14% infants of diabetic mothers were hypocalcemic [13]. Fleischman et al. also found that, fetal corrected calcium levels were lower in diabetic than in controls [28].

On the basis of our observations, we conclude that adequate outdoor activities and sun exposure should be ensured in young women. We recommend that vitamin D and calcium supplementation should be incorporated in antenatal care programs in India to improve maternal health as well as fetal mineralization and skeletal development.

Conflict of interest

None of the authors have any conflict of interest or relevant financial disclosures to report.

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