Pregnancy / Lactation / Infancy And Childhood *Indian Perspective*

Dr Nikhil Tandon
Professor, Department of Endocrinology
All India Institute of Medical Sciences, New Delhi
Secretary, Indian Society for Bone and Mineral Research

Childhood

Bone Health in Children
Community Based Studies

Author	Nature of pediatric population studied	Prevalence of rickets
Shrivastav et al, 1970	Pre-school	11.4% active; 15.2% healed
Gupta and Bhandari, 1973	Pre-school	1.5% tribal; 2.7% non-tribal
Mankhodi et al, 1974	Lower SE class, pre-school	5.2% urban; 4.7% rural
Dwivedi et al, 1992	Urban slum, pre-school	9.4%
Chainani et al, 1994	Pre-school	2% normal children 12% malnourished
Awate et al, 1996	Primary school	0.2%

Bone Health in Children
Immigrant Studies

- Dunnigan et al, 1962: clinical evidence of Vitamin D deficiency in 13.2% Pakistani children
- Holmes et al, 1973: clinical evidence of rickets was 30%, biochemical evidence was 74%
- Ford et al, 1973: biochemical evidence of rickets in 45% Asian children
- Goel et al, 1976: 2% Asian children had florid rickets, 7.5% sub-clinical rickets >> other ethnic groups
- Dunnigan et al, 1981: 14% had radiological evidence of active rickets, 40% had biochemical evidence; 44% had 25(OH)D < 5 ng/ml
- **Later studies: declining prevalence**

Bone Health in Children
25(OH)D Measurements in Indian Children

- Raghuramulu and Reddy, 1980:
  - Mean 25(OH)D in rachitic children 7.1 ng/ml <<< non-rachetic children (lean and normal BMI)

- Raghuramulu, 1987: 25(OH)D in children with rickets (6.5 ng/ml) << healthy children (35.2 ng/ml)

Role of vitamin D deficiency in the etiology of rickets: Young Children vs. Adolescents

- 24 children, 16 adolescents with rickets / osteomalacia
- Young children cf. controls:
  - Lower calcium intake
  - Similar 25(OH)D levels: 49 ± 38 vs. 61 ± 36 nmol/l
  - 16 children had 25(OH)D levels > 25 nmol/L (rachitic range)
  - Showed healing when given calcium (± vitamin D)
- Adolescents cf. controls:
  - Lower calcium intake
  - Lower 25(OH)D levels: 12.6 ± 7.1 vs. 46 ± 45.4 nmol/l
  - Showed healing only when given Ca + vitamin D

Balasubramanian et al, 2003

Vitamin D Status in School Children in Delhi

- 5137 school children
- Socioeconomic stratification:
  - 3089 - LSES
  - 2048 - USES
- 760 children selected by cluster randomization for detailed biochemical / hormonal work up

Am J Clin Nutr, 82: 477

Vitamin D Status in School Children in Delhi

- Two definitions of hypovitaminosis D:
  - 25(OH): 9.0-37.6 ng/ml
  - 25(OH)D < 20 ng/ml [Lips classification]

Am J Clin Nutr, 82: 477

Serum Alkaline Phosphatase

- Adjusted mean ± SE values for LSES and USES: 387.1 ± 8.9 IU/L vs. 299.2 ± 10.3 IU/L (P < 0.01)
- Significant positive correlation between SAP and iPTH (r=0.330; P < 0.01)

Am J Clin Nutr, 82: 477

Serum iPTH

PTH (pg/mL)[4]	LSES Males	USES Males	LSES Females	USES Females
10-12 yrs	35.4 ± 19.8 (n=42)	24.4 ± 13.6 (n=33)	44.3 ± 37.1 (n=78)	25.8 ± 12.0 (n=47)
13-15 yrs	42.3 ± 33.2 (n=85)	28.6 ± 15.5 (n=70)	46.7 ± 51.8 (n=123)	26.2 ± 18.4 (n=62)
16-18 yrs	37.9 ± 35.8 (n=40)	24.2 ± 14.4 (n=55)	32.1 ± 23.6 (n=62)	22.2 ± 10.4 (n=63)

Adjusted mean ± SE values for LSES and USES:

42.8 ± 1.6 mg/dl vs. 23.5 ± 1.9 mg/dl (P < 0.01)

Sig. neg. correlation between iPTH and 25(OH)D: r = -0.202; P < 0.01

Serum 25 Hydroxy Vitamin D

25(OH)D (ng/mL)	LSES Males	USES Males	LSES Females	USES Females
10-12 yrs	12.4 ± 5.5 (n=42)	19.3 ± 8.8 (n=33)	11.2 ± 6.5 (n=78)	12.5 ± 8.9 (n=47)
13-15 yrs	11.3 ± 5.8 (n=85)	13.1 ± 7.0 (n=70)	9.9 ± 6.2 (n=123)	10.2 ± 5.7 (n=62)
16-18 yrs	11.3 ± 5.3 (n=40)	13.5 ± 7.0 (n=55)	10.5 ± 5.7 (n=62)	12.9 ± 10.5 (n=63)

Unadjusted mean serum 25(OH)D: 11.8 ± 7.2ng/ml

Adjusted mean ± SE values for LSES and USES were:
10.4 ± 0.4 ng/dl vs. 13.7 ± 0.4 ng/dl (P < 0.01)

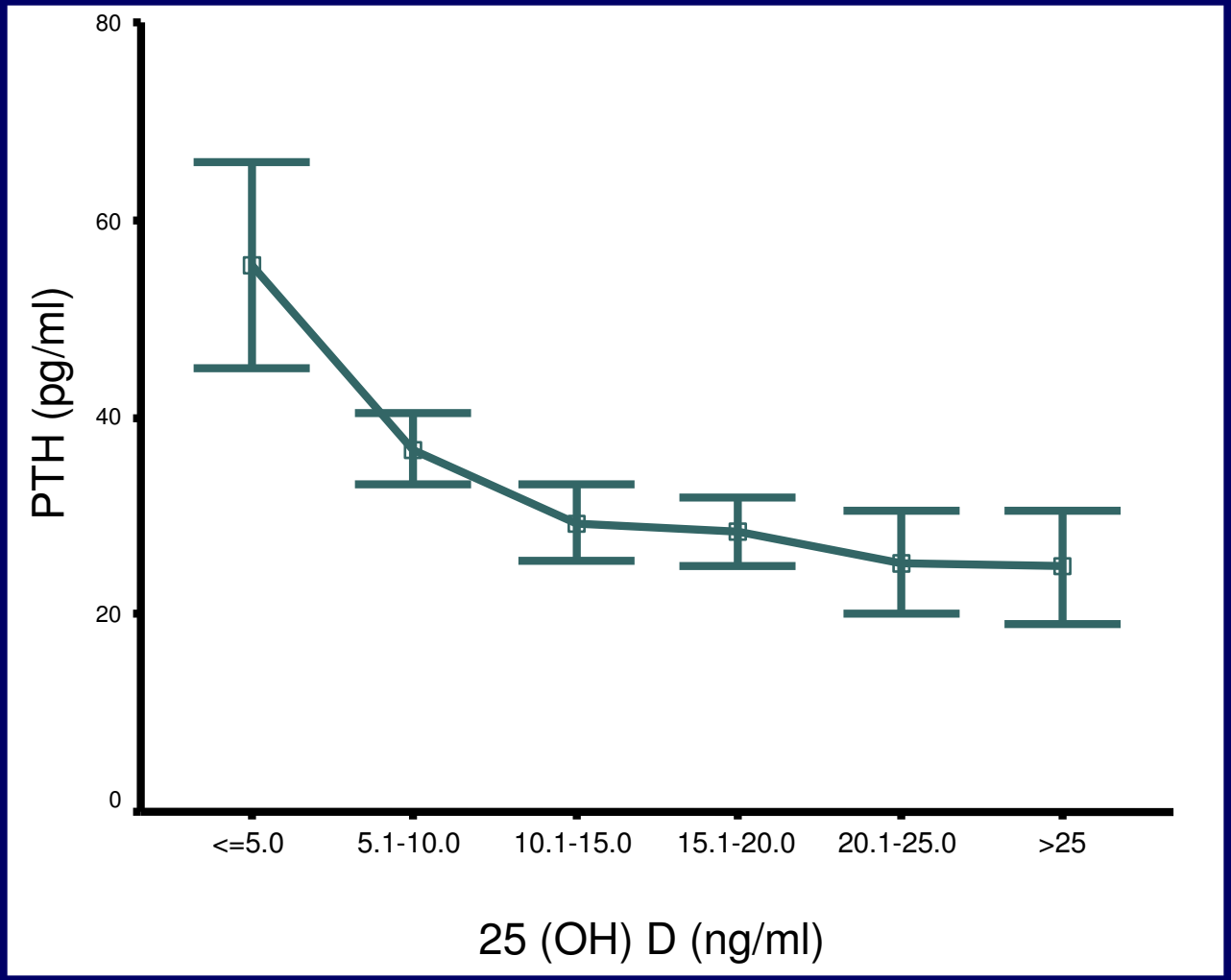
Am J Clin Nutr, 82: 477

Serum 25 Hydroxy Vitamin D

- **35.7%** children had 25(OH)D values < 9 ng/ml
  - Only 10.3% of these had iPTH levels above normal
- Males had a higher serum 25(OH)D cf. females in both SES
- As per Lips classification, hypovitaminosis D seen in:
  - 92.6% LSES (11.2% severe, 39.5% moderate, 42.1% mild)
  - 84.9% USES (4.9% severe, 25.5% moderate, 57.6% mild)

Am J Clin Nutr, 82: 477

Vitamin D and PTH



PTH levels start to rise at vitamin D levels below 25 ng/ml

Am J Clin Nutr, 82: 477

Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi

Relation to nutrition and lifestyle

- Healthy schoolgirls (6-18 years): LSES =1477; USES=1650
- 404 randomly selected girls (LSES =193, USES =211) underwent detailed dietary, biochemical and hormonal assessment.

Br J Nutr 2008; 99:876

Baseline characteristics, lifestyle and biochemical parameters

Variables	LSES (n=193)		USES (n=211)		
	Mean	SD	Mean	SD	P value
Age (years)	12.4	3.2	12.3	3.0	0.704
S.Ca (mmol/l)	2.22	0.2	2.30	0.1	0.000
S. P (mmol/l)	1.48	0.25	1.35	0.22	0.000
ALP (IU/L)	484.5	257.5	330.6	170.3	0.000
PTH (pg/ml)	32.4	20.8	33.4	19.7	0.615
25(OH)D (nmol/l)	34.61	17.43	29.38	12.69	0.001

- **25(OH) D < 9ng/ml - 30% subjects**
- **Hypovitaminosis D (<20 ng/ml): 90.8% of the population**

Br J Nutr 2008 ;99(4):876

Intake of nutrients

Diet Variables	SI / RDA	LSES (n=193)		USES (n=211)		
		Mean	SD	Mean	SD	P value*
Energy (kJ)	8151-8611	5542.3	716.4	5849.1	677.1	0.000
Protein (g)	41-65	37.4	7.0	43.8	7.1	0.000
Carbohydrate (g)	-	202.8	31.6	194.6	30.2	0.009
Fat (g)	22	39.5	7.7	49.2	7.4	0.000
Dietary Fibre (g)	-	13.9	7.5	9.7	6.2	0.000
Phytate (mg)		105.3	53.3	85.6	53.6	0.000
Calcium (mg)	400-600	454.2	187.4	685.5	184.8	0.000

Br J Nutr 2008; 99:876

Vitamin D levels in slum children

Time of sampling	Area studied	No. sampled	Mean 25(OH) D level (SD)	% with 25(OH)D levels < 35 nmol/L
January	Sundernagari	47	96.3 n mol/L (25.7)	2.0
February	Rajiv Colony	49	23.76 n mol/L (27.03)	82.9
August	Rajiv Colony	48	17.8 n mol/L (22.4)	84.0
August	Gurgaon	52	19.2 n mol/L (20.2)	82.0

Tiwari & Puliyel, 2004

The impact of atmospheric pollution on vitamin D status of infants and toddlers

Table 1 Age, gender, haze score, and biochemical parameters of subjects from the Mori Gate and Gurgaon areas

	Mori Gate High pollution area n=26	Gurgaon Low pollution area n=31
Age (months)	16 (4.1)	15.9 (3.8)
Haze score	2.1 (0.5)	2.7 (0.4)*
Gender	15 males, 11 females	15 males, 16 females
Ca (mg %)	9.7 (0.9)	9.6 (0.8)
ALP (IU/l), median (range)	498 (116–3739)	398* (196–780)
$25(OH)D_3$ (ng/ml)	11.7 (7)	27.1 (7)***
$25(OH)D_2$ (ng/ml)	2.4 (0.6) (n=5)	0
Total 25(OH)D (ng/ml)	12.4 (7)	27.1 (7)***
$1,25(OH)_2D$ (pg/ml)	73.7 (30)	65 (19)
PTH (pg/ml), median (range)	25 (5–284)	13.1** (1.6–37)

Except for ALP and PTH, all data are presented as mean (1 SD). Serum $25(OH)D_2$ was only detected in five children from the Mori Gate area and none from the Gurgaon area; it is presented as range only for the subjects from the Mori Gate area.
Thirty four subjects aged 9–24 months were recruited from each of the study areas; however, data are not provided for eight subjects from the Mori Gate area and three subjects from the Gurgaon area due to failed venepunctures.
*p<0.05, **p< 0.01, ***p<0.001.

Agarwal et al, 2002

Rural Data

- 121 adolescent girls; 139 pregnant women (2nd trimester); 28 adolescent girls vs 34 male siblings
- Hypovitaminosis D [25(OH)D < 50 nmol/l]: 88.6% adolescent girls; 74% pregnant women
- 25(OH)D levels in summer [55.5 ± 19.8 nmol/l] > winter levels [27.3 ± 12.3 nmol/l]
- Winter 25(OH)D levels in boys [67.5 ± 29.0 nmol/l] > female siblings [31.3 ± 13.5 nmol/l]

Sahu et al, 2009

Impact on the clinical manifestation of environmental fluoride excess

- Case control study: high fluoride vs. control village
- Skeletal deformities: 20% (HFV) vs 0%(CV)
- Mean serum 25 (OH)D levels were significantly lower among the children with deformities as compared to those without deformities

Calcif Tissue Int. 2005;76:412

Pregnant Women

Pregnant Women and their Newborn

- 207 urban and rural pregnant women at full term; cord blood from 117 newborns
- Maternal 25(OH)D = 14 ng/ml; cord blood 25(OH)D = 8.4 ng/ml

Clinical characteristics and biochemical indexes of urban and rural women[7]

	Urban women	Rural women
Daily vitamin D intake (IU/d)	16.4 ± 7.4	16.5 ± 7.7
HLAP (U/L)[8]	87 ± 60	73 ± 31
Elevated HLAP [*n* (%)][9]	24 (17)	5 (7)
Serum 25(OH)D (ng/mL)[10]	14.0 ± 9.5	14.1 ± 8.9
Maternal hypovitaminosis D [*n* (%)][11]	118 (84)	56 (84)
Maternal PTH (pg/mL)[12]	94 ± 127	57 ± 49

Maternal 25(OH)D showed:

- Strong positive correlation with cord blood 25(OH)D: r = 0.79; P < 0.001
- Moderate negative correlation with maternal PTH: r = -0.35; P < 0.001

Sachan et al, 2005

Breast Fed Infants and Lactating Mothers

Vitamin D Nutrition status of exclusively breast fed infants and their mothers

- 180 healthy lactating mothers and exclusively breast fed infants, 2-24 weeks old
- 82% infants had normal nutrition
- Mother-infant pairs underwent concurrent clinical, biochemical and hormonal evaluation for Calcium-Vitamin D-PTH axis

JPEM 2009

Vitamin D Nutrition Status of Exclusively Breast Fed Infants

- 180 exclusively breast-fed infants (2-24 weeks) and their mothers
- 25(OH)D levels of mothers: **47.8% < 10 ng/ml; 94% < 20 ng/ml**
- 25(OH)D levels of infants: 43.2% < 10 ng/ml; 91% < 20 ng/ml

Serum Conc.	Mothers (Mean ± SD)	Infants (Mean ± SD)
Total Ca (mg/dl)	9.8 ± 0.89	10.01 ± 1.2
Ionized Ca (mg/dl)	4.6 ± 0.40	4.6 ± 0.47
PTH (pg/ml)	52.6 ± 52.6	57.0 ± 61.0
25(OH)D (ng/ml)	10.9 ± 5.8	11.6 ± 8.3
Phosphorus (mg/dl)	4.4 ± 1.1	5.3 ± 1.40
ALP (IU/L)	337 ± 172	655 ± 311

JPEM, 2009

Vitamin D status in mothers and infants

Parameter	Mothers (%)	Infants (%)
25(OH)D: < 20 ng/ml	93.8	91.1
- 25(OH)D: 10-20 ng/ml	46.1	47.2
- 25(OH)D: 5-10 ng/ml	33.9	22.8
- 25(OH)D: < 5 ng/ml	13.8	21.1
% Elevated PTH if 25(OH)D < 10 ng/ml	59.3	69.6
% Elevated PTH if 25(OH)D ≥ 10 ng/ml	4.3	3.1
Correlation between 25(OH)D and PTH	-0.597	-0.431
25(OH)D level below which PTH rose above normal	10.7 ng/ml	11.7 ng/ml

JPEM 2009

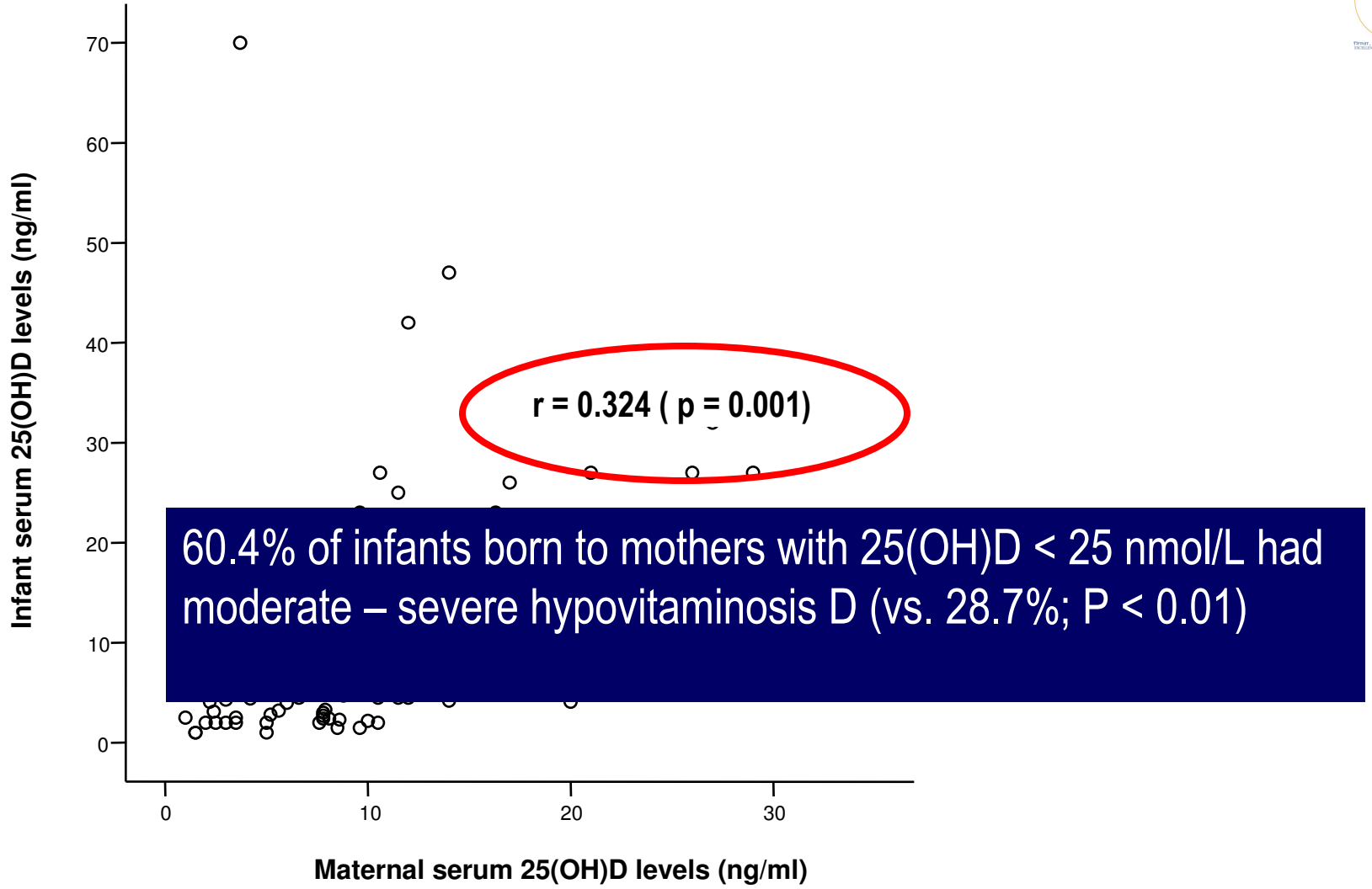


Figure 1: Relationship between serum 25(OH)D levels of mother-infant pairs

JPEM 2009

Hypovitaminosis D and hypocalcemic seizures in infancy

- Hypocalcemia is an important cause for seizures in infants
- 60 infants with hypocalcemic seizures (serum Ca < 8 mg/dl) and their mothers (study group)
- 60 healthy breast-fed infants with their lactating mothers (control group)
- Concurrent evaluation to assess the calcium-vitamin D-PTH axis

Indian Pediatrics, 2009

Hypovitaminosis D and hypocalcemic seizures in infancy

- Wide anterior fontanelle and craniotabes: 13% study infants; no control infant
- Radiological evidence of rickets: 30% study infants
- Mothers of study infants had significantly lower BMI, calorie and calcium intake and sun exposure compared with mothers of control infants

Indian Pediatrics, 2009

Serum Calcium and Phosphorus levels in control and study infant-mother groups

Parameter	Mothers			Infants		
	Controls Mean ± SD	Study Mean ± SD	P value	Controls Mean ± SD	Study Mean ± SD	P value
Serum tCa (mg/dl)	9.83 ± 0.67	9.57 ± 0.48	0.014	9.79 ± 0.78	7.11 ± 0.46	0.0001
Serum Ca^{2+} (mg/dl)	4.70 ± 0.27	4.42 ± 0.34	0.0001	4.54 ± 0.28	3.30 ± 0.26	0.0001
Serum IP (mg/dl)	3.84 ± 0.73	4.16 ± 0.89	0.087	4.37 ± 0.83	3.33 ± 1.35	0.005

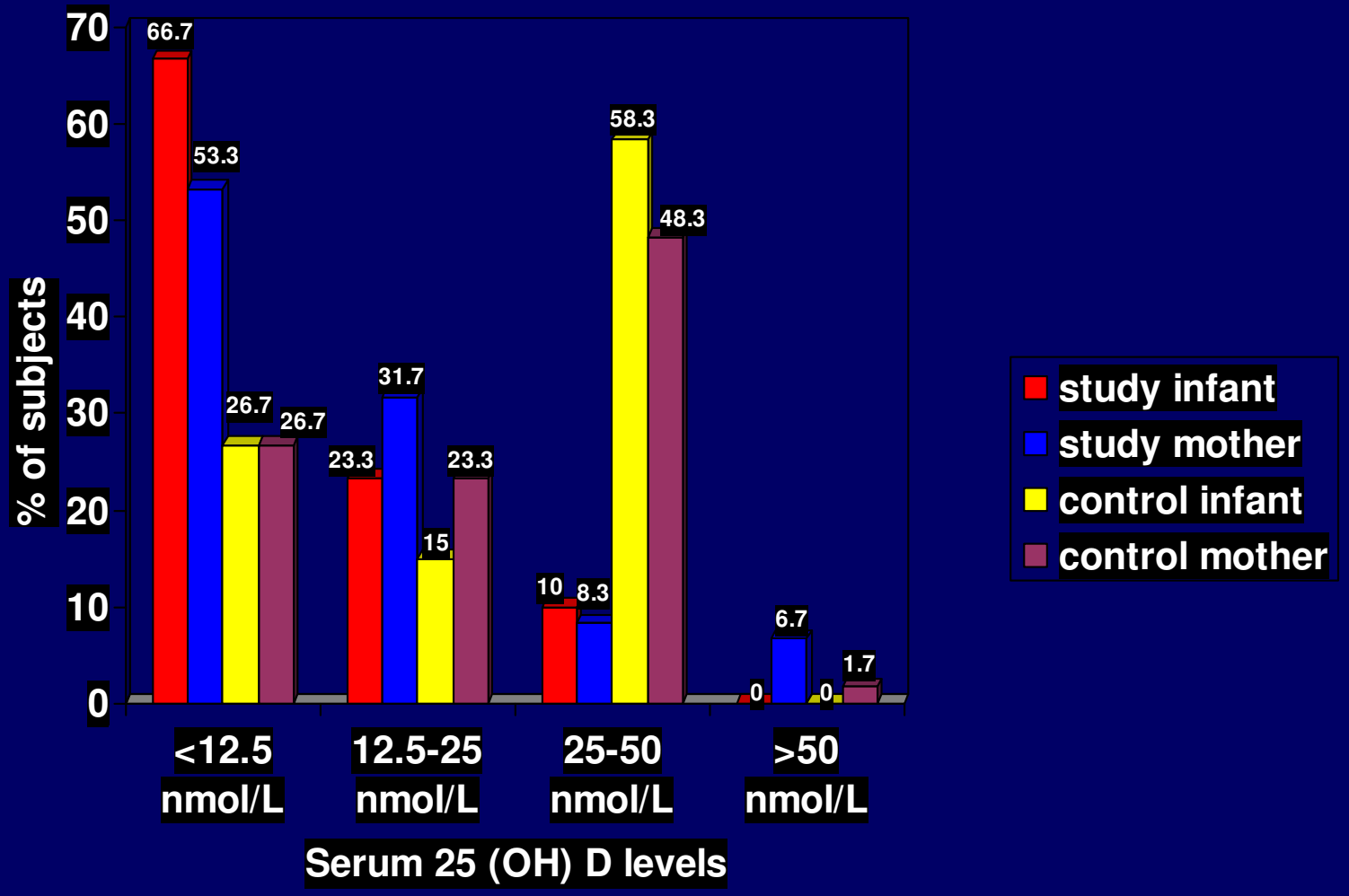
Indian Pediatrics, 2009

Median serum alkaline phosphatase, 25 (OH)D and PTH levels in infant-mother groups

Parameter	Mothers			Infants		
	Controls Mean ± SD Median (range)	Study Mean ± SD Median (range)	P value	Controls Mean ± SD Median (range)	Study Mean ± SD Median (range)	P value
ALP (IU/L)	310.5 ±102.8 283 (172-635)	654.8 ±141.4 646 (410-990)	0.0001	557.2 ±167.4 567 (236-860)	1738.5 ± 499.2 1653(960-3278)	0.0001
25 OH D (ng/ml)	9.1 ± 4.8 10.25 (1-24)	6.5 ±5.3 4.9 (1-21)	0.007 0.0009	9.0 ± 4.6 11 (1-15.4)	4.9 ± 4.6 3.75 (1-18)	0.0001
PTH (pg/ml)	64.4 ± 56.2 45 (10-260)	60.6 ± 37.6 52 (10-160)	0.56	69.1 ± 72.4 35 (17-416)	132.7 ± 91.7 122.5 (13-490)	0.0001

Indian Pediatrics, 2009

Serum 25 (OH) D levels in control and study subjects



Indian Pediatrics, 2009

Vitamin D nutrition in mothers and infants

- Significant inverse correlation between 25 (OH) D and PTH: study ($r = -0.22$, $p<0.04$) and control ($r = -0.72$; $p<0.0001$) mothers
- No significant correlation between PTH and 25(OH)D in study infants; $r = -0.65$; $P < 0.0001$ in control infants
- Among study infants with 25 (OH) D <10ng/ml, 75% had raised PTH in contrast to only 3.1% infants with 25(OH) D>10ng/ml

Vitamin D nutrition: Correlation between mother-infant pairs

- Strong positive correlation between serum 25(OH)D levels of mother-infant pairs

- Infants born to mothers with 25 (OH) D <10 ng/ml had a **40 times increased risk** of hypovitaminosis D when compared to those born to mothers with 25(OH) D levels >10 ng/ml.

Vitamin D status in Pregnancy / Lactation / Infants / Children

Conclusions

- Significant prevalence of biochemical hypovitaminosis D across physiological states
- Socio-economic status, nutrition have an important bearing
- Impact of environment on occurrence of hypovitaminosis D
- Impact of vitamin D status on skeletal disease resulting from environmental toxicity
- Need to discuss potential public health interventions: at least in high risk states (pregnancy / lactation/ growing infant and children)

The Team

AIIMS

- Nikhil Tandon
- D.H.K. Reddy
- M. Ashraf Ganie
- Rajvir Singh
- C Shiva Prasad
- Kalaivani Mani
- Ranabir Salam
- Parjeet Kaur

IHE

- Seema Puri
- Neha Aggarwal
- Bhavana Sharma

DRDO

- R. K. Marwaha
- Rashmi Agarwal
- Khushi Grewal
- Satvir Singh
- R. C. Sawhney
- Aparna Sastry

LHMC

- S Aneja
- Anju Seth
- Preeti Mehrotra
- Bhupesh Singla

THANK YOU


अखिल भारतीय आयुर्विज्ञान संस्थान
ALL INDIA INSTITUTE OF MEDICAL SCIENCES
शरीरमाद्यं खलु धर्मसाधनम्
1956-2005
शिक्षा, उपचार एवं शोध मे उत्कृष्टता
EXCELLENCE IN EDUCATION , PATIENT CARE & RESEARCH