

# Potential significance of Vitamin D deficiency in apparently healthy subjects in Delhi

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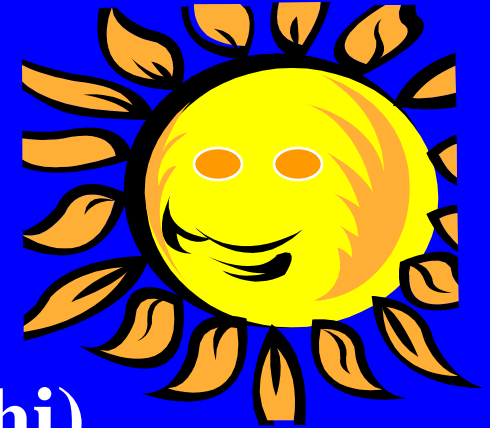
# Sunshine in India

Delhi latitude & longitude: 28.35°N & 77.12° E

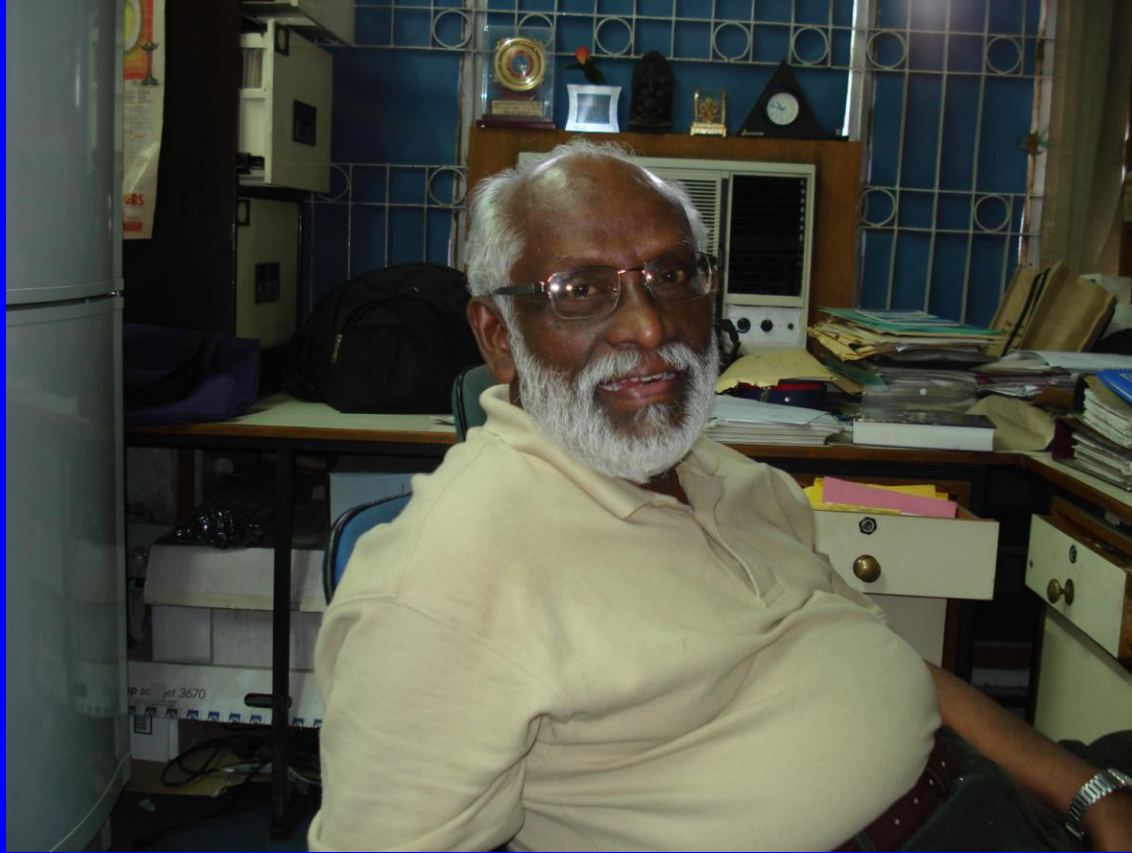
**Cloud free sunshine**

**7 hrs/summer &**

**3.1 hrs/winter (Meteorology, Delhi)**



**Vitamin D deficiency does not exist in India  
(Hodgkin Lancet 1978)**



Harinarayan CV & Kochupilai N  
Clin Endocrinol 1995 (AIIMS)

Goswami R & Kochupillai N  
Am J Clin Nutr 2000 (AIIMS)

# Vitamin D deficiency in India in 2000-06

Harinarayan et al, Clin Endocrinol 1995, AIIMS

Goswami et al; Adults, Am J Clin Nutr 2000 (AIIMS)

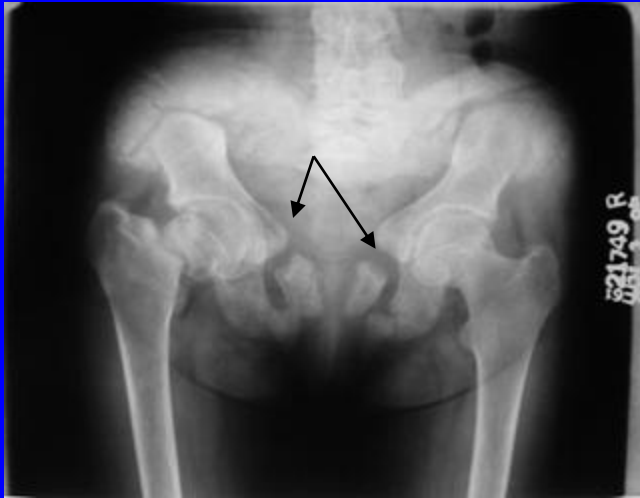
Marwaha et al; Children, Am J Clin Nutr 2005 (INMAS)

Sachan & Bhatia et al ; Pregnancy, Am J Clin Nutr 2005 (SGPGI)

Vupputuri & Goswami et al, Am J Clin Nutr 2006

Harinarayan et al, South Indians, AJCN 2006

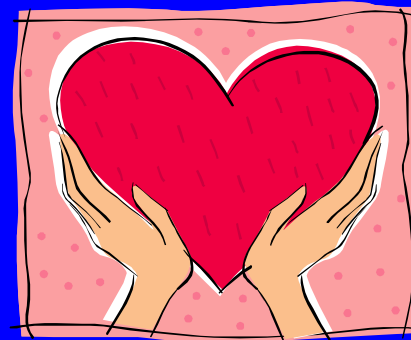




# Functional significance of vitamin D deficiency

## Bone Health

Implications of vitamin D deficiency in India  
other than bone health: Yes ?



# Functional significance of vitamin D deficiency **Bone Health**

## Overt MBD

Osteomalacia and rickets are common in India

On an average 100 OSM/ Rickets: in 2 years at AIIMS

110 patients with sporadic idiopathic hypoparathyroidism a reflection of unmasking of hypocalcemia due to background vitamin deficiency.

Goswami et al , JCEM, 2006

# Functional significance of vitamin D deficiency **Bone Health**

In-utero and infancy

School children

Adults

# Functional significance of vitamin D deficiency **Bone Health**

## In-utero

84% VDD prevalence in Pregnancy

(Sacchan & Bhatia et al, AJCN, 2005, (Lucknow))

VD supplementation in pregnancy

Higher body weight,

Head circumference,

Midarm circumference

Longer knee heel length.(up to 4.3 cm>)

Maraya IJMR 1988 (Rohtak)

Potential for catch-up growth is less because VD continues



# Functional significance of vitamin D deficiency Bone Health

## School-Children

Lower 25(OH)D and forearm BMD in Delhi school children (Marwaha et al , AJCN, 2005)

14 months of supplementaion with VD containing micronutrients or placebo to school children of 6-16 years of age at Hyderabad

Significant increment in height, weight, bone mineral content, BMD at femur neck in micronutrients supplemented group

Shatrugna et al : Nutrition, 2006,(Hyderabad)

# Functional significance of vitamin D deficiency Bone Health

## School-Children

**VDD MAY BE ONE OF THE CAUSE OF  
SHORT STATURE IN INDIAN CHILDREN**

# Functional significance of vitamin D deficiency Bone Health

## ADULTS

Up to 90% Prevalence of VDD in Adults  
(25(OH)D <32 ng/ml)

# Hypovitaminosis D in apparently healthy subjects in terms of bone health

1: Higher PTH

2: Calcium deficiency



3: Lower Bone density



4. Medication precipitating OSM/Rickets

5. Environmental factors: Fluorosis

6. VDD and Genetics of Osteoporosis

**significance of low Serum 25(OH)D in terms of  
PTH**

# Prevalence and significance of low 25(OH)D in normal subjects in Delhi (PTH)

Four groups of subjects were recruited based on different characteristics relevant to bone mineral homeostasis

Physicians and nurses (Summer & winter)

Soldiers (winter)

Pregnant women and their newborns (Summer)

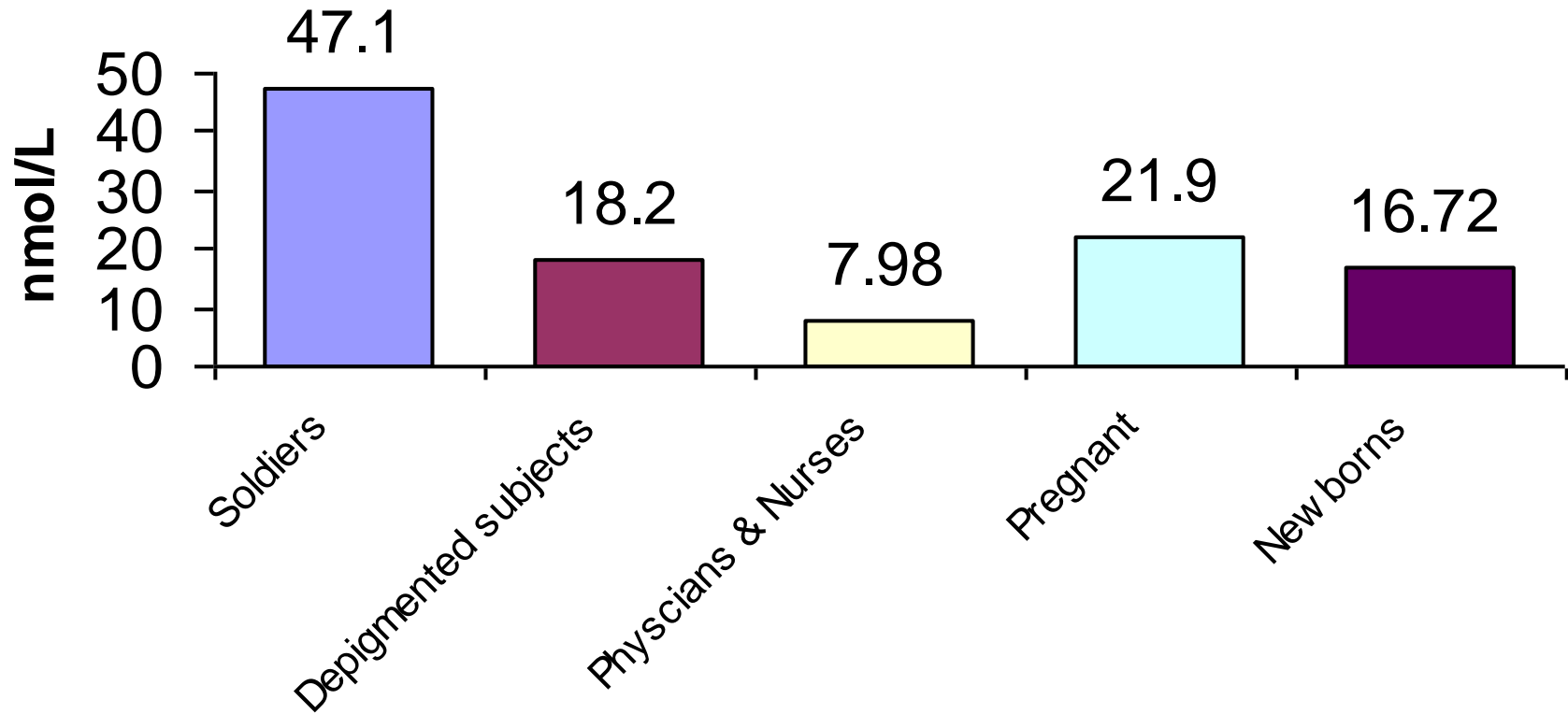
Depigmented subjects (winter)

**Goswami et al, Am J of Clin Nutr, 2000;72: 472-75**

# Baseline Characteristics of the study subjects,

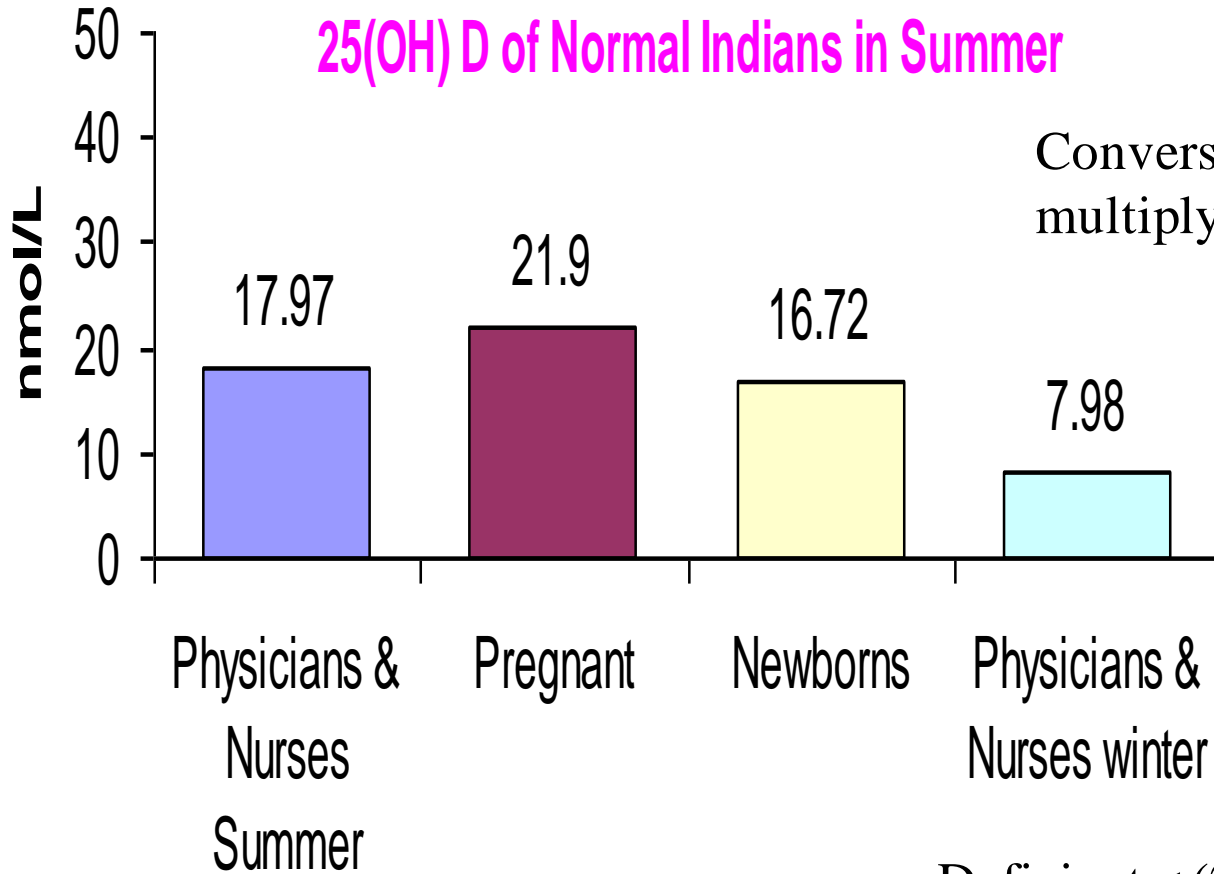
Variable	Soldiers (Winter) N=31	Physicians (Winter) N=19	Vitiligo (Winter) N=15	Physicians (Summer) N=19	Pregnant (Summer) N=29
Age(y)	25 ± 5 <sup>b</sup>	23 ± 5 <sup>b</sup>	43 ± 16 <sup>a</sup>	24 ± 4 <sup>b</sup>	23 ± 3
Diet Ca (g/day)	1.1 ± 0.6	0.88 ± 0.16	0.98 ± 0.3	0.88 ± 0.16	0.34 ± 0.08 <sup>a</sup>
Phytate: Calcium Ratio	0.96 ± 0.4	0.74 ± 0.42	0.82 ± 0.5	0.74 ± 0.42	1.69 ± 1.1 <sup>a</sup>
Sunshine exposure (min/day)	370 ± 30 <sup>b</sup>	25 ± 5	5 ± 5 <sup>a</sup>	25 ± 5	25 ± 5

## 25(OH) D status of Normal Indians





## 25(OH) D of Normal Indians in Summer



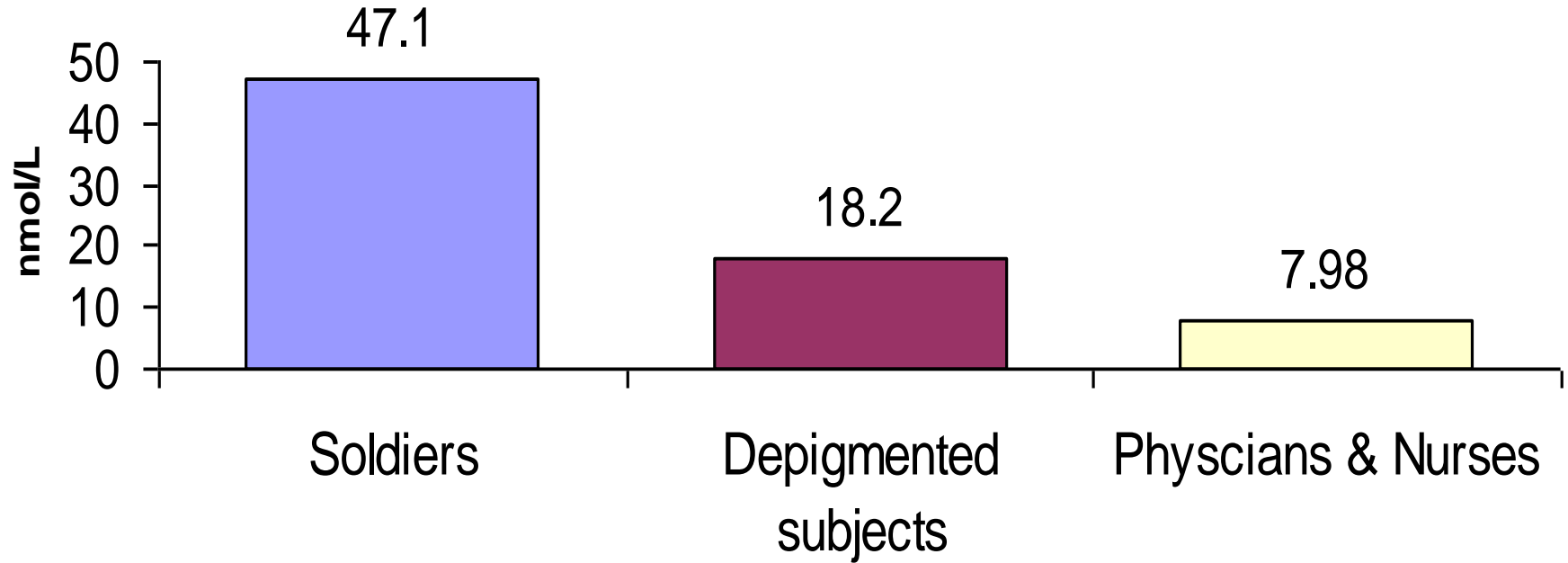
Conversion from ng/ml to nmol/l  
multiply by 2.496

Deficient < (20 ng/ml) = 50 nmol

Insufficient 20-32 ng/ml

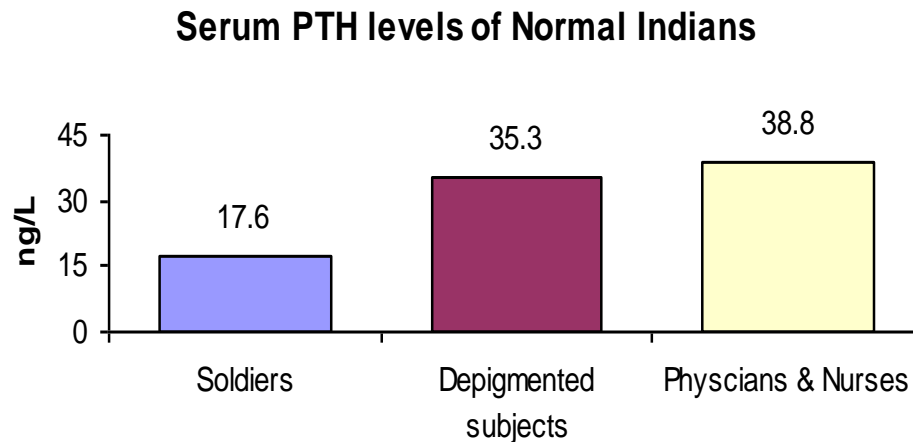
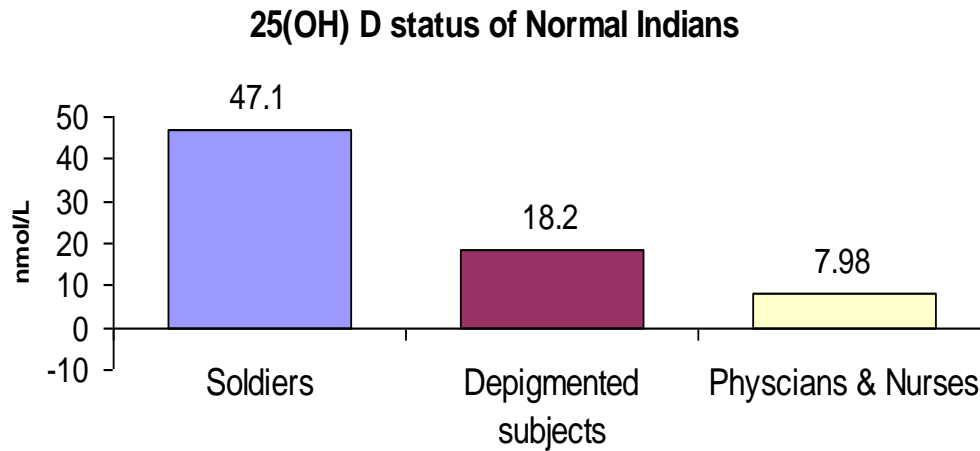
Sufficient > 32ng/ml

## 25(OH) D status of Normal Indians in winter



# What is the significance of low Serum 25(OH)D?

## Effect on PTH



# **What is the significance of low Serum 25(OH)D? Effect on PTH of Asian Indians**

**Up to 25% of apparently healthy Asian Indians have high PTH**

**Whether by Diasorin RIA kits or Electrochemiluminiscence assays**

**What is the significance of low Serum 25(OH)D?**

**In terms of serum calcium in Asian Indians**

# Serum 25(OH)D vs. Serum Calcium

1,25(OH)D  VDR



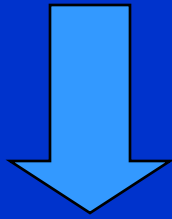
up-regulate transcription of

Intestinal Calcium transporters luminal surface

Cytosolic Calbindin-9k protein

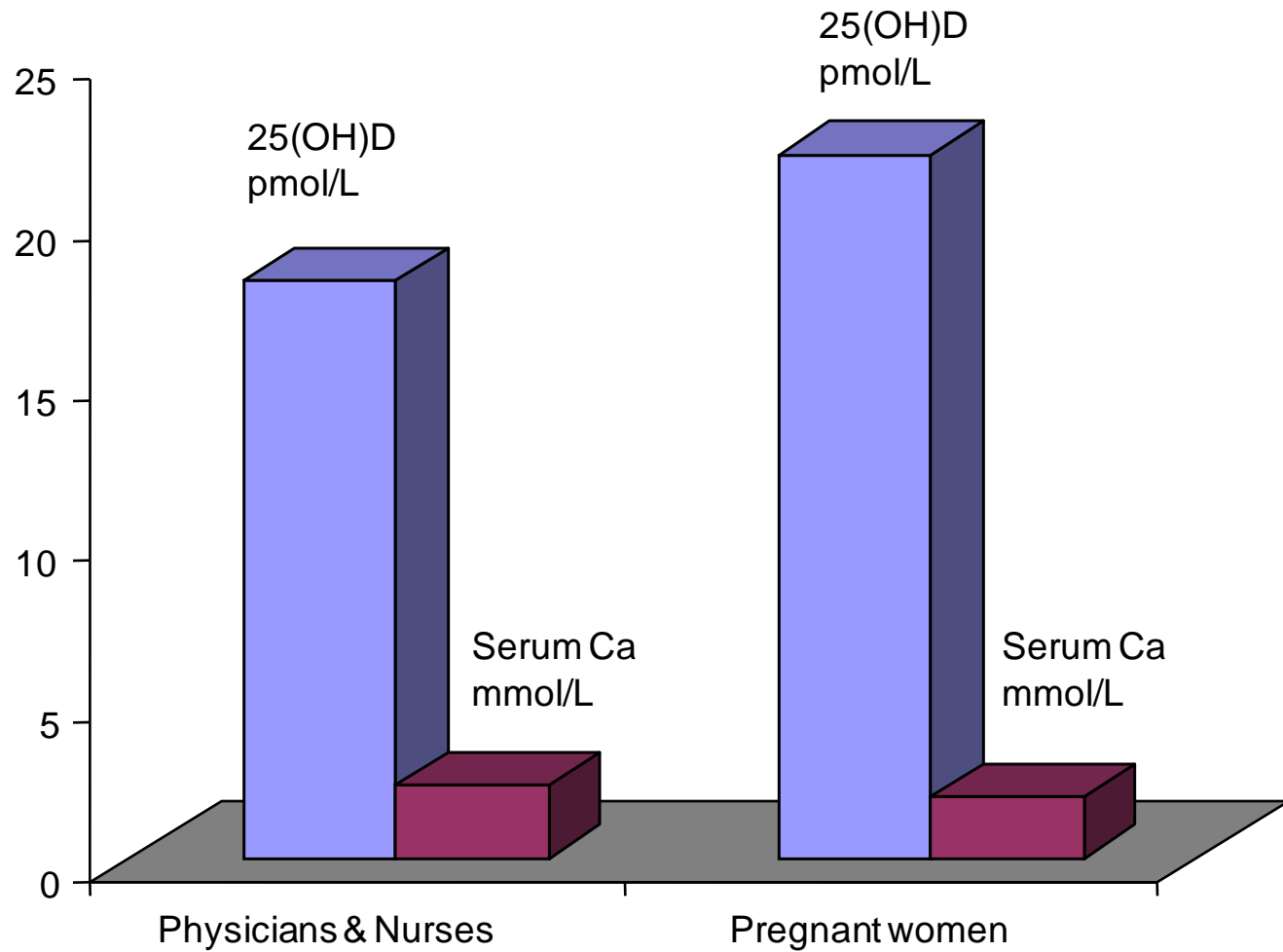
Plasma Calcium ATPase on the basal side

# Serum 25(OH)D vs. dietary Calcium



VDD dietary calcium absorption would be reduced from 60% to 15%

# Serum 25(OH)D vs. serum total Calcium





**What is the significance of low Serum 25(OH)D?  
In terms of serum calcium in Asian Indians**

**Up to 30% have serum total calcium in the low normal range**

# Hypovitaminosis D in apparently healthy subjects in terms of bone health

1: Higher PTH

2: Calcium deficiency



3: Lower Bone density



# What is the significance of low Serum 25(OH)D? Effect on Bone Density

29% prevalence of osteoporosis in rural Indians

- **Dietary calcium intake correlates with Hip BMD**
- **But not with Forearm and Spine BMD**
- **Shatrugna et al; Osteoporosis International, 2005**

## What is the significance of low Serum 25(OH)D? Effect on Bone Density

Significant correlation between serum 25(OH)D and hip BMD in 92 healthy hospital staff at SGPGI (Lucknow)

Arya and Mittal et al Osteoporos Int (2004)

**Presence of low serum 25-hydroxyvitamin D and single nucleotide polymorphisms of the vitamin D receptor and PTH genes and their relationship with variation in bone mineral density in north Asian Indians (AIIMS)**

Madhav & Goswami et al; Am J Clin Nutr (2006)

## Mean (SD) of BMD parameters in Indian subjects with different serum 25(OH)D levels

Site	BMD (gm/cm <sup>2</sup> ) 25(OH)D ≤9 ng/ml	BMD (gm/cm <sup>2</sup> ) 25(OH)D >9.0 ng/ml	* <i>p-value</i>
AP spine (L1-L4)	0.930 ± 0.132	0.954 ± 0.119	0.12
Femoral neck	0.727 ± 0.109	0.779 ± 0.105	0.002
Trochanter	0.609 ± 0.084	0.666 ± 0.101	<0.001
Inter-trochanter	1.006 ± 0.141	1.072 ± 0.142	0.003
Total Hip	0.839 ± 0.112	0.893 ± 0.114	0.001
Ultradistal forearm	0.391 ± 0.064	0.402 ± 0.062	0.36
Mid forearm	0.544 ± 0.058	0.565 ± 0.063	0.119
Proximal forearm	0.632 ± 0.064	0.652 ± 0.075	0.37
Total forearm	0.525 ± 0.058	0.541 ± 0.062	0.20

\*The *p*-value for BMD parameters are age & BMI adjusted  
 Madhav & Goswami et al; Am J Clin Nutr (2006)

# Hypovitaminosis D in apparently healthy subjects in terms of bone health

ATT, Steroid therapy, anticonvulsant therapy

Bisphosphonate therapy would easily precipitate OSM

1/3 of our patients with OSM/Rickets have prior history of intake of these drugs

**Skeletal fluorosis predominantly manifests in children with dietary calcium intake <**

**300mg/day**

Teotia M et al, Indian J Pediatr 1998

# Bone health of Indians: Genetic factors

## Data From the West

- 1 Monozygotic twins > dizygotic twins.
- 2 Decreased BMD daughters of osteoporotic women
- 3 >70% of variation in BMD: genetic factors

Pocock et al J Clin Invest 80: 706-10.

Seeman et al N Engl J Med 320: 554-8.

Evans et al Ann Intern Med 109: 870-3.

Genetic factors largely unknown

Candidate genes being investigated

Vitamin D receptor gene, PTH,

Estrogen receptor and

Collagen, CaSR

Genetic factors would have little influence on

BMD in hypovitaminotic D population

Genetic factors and Bone health

Limited data available for Indians



# Bone health of Indians: Genetic factors

**Presence of low serum 25-hydroxyvitamin D and single nucleotide polymorphisms of the vitamin D receptor and PTH genes and their relationship with variation in bone mineral density in north Asian Indians**

**Madhav & Goswami Am J Clin Nutr (2006)**

# Mean (SD) of bone mineral density parameters in subjects with different VDR genotype groups

Parameters	VDR <i>TaqI</i>		<i>*p</i> -value	<b>** <i>p</i>-value</b>
	TT	tt/Tt		
AP spine (L1-4)	1.037 0.125	0.914 0.126	0.013	0.052**
Femoral neck	0.820 0.087	0.734 0.115	0.027	0.108**
Trochanter	0.679 0.060	0.620 0.101	0.078	
Inter-trochanter	1.100 0.100	1.017 0.152	0.046	0.172**
Total Hip	0.927 0.078	0.839 0.122	0.019	0.076**
Ultradistal forearm	0.471 0.051	0.383 0.056	0.001	0.004**
Mid forearm	0.625 0.050	0.543 0.059	0.015	0.060**
Proximal forearm	0.728 0.059	0.633 0.067	0.011	0.044**
Total forearm	0.599 0.058	0.517 0.056	0.001	0.004**

\*The *p*-value for BMD parameters are age & BMI adjusted for the spine and hip and age, BMI & gender adjusted for the forearm region.

\*\*The *p*-value corrected for the number of VDR SNPs tested

# Bone health of Indians: Genetic factors

The genetic factors also influence BMD as reflected by significantly lower forearm BMD in subjects with Tt/tt genotype related to *TaqI* SNP of the VDR gene

Such genetic Effects on BMD are apparent even in presence of hypovitaminotic D state as seen in Indians

# Other factors affecting bone mineral health in presence of VDD

Low BMI

Early menopausal age of Asian Women

Cataract

Easy fall

# Other factors associated with Bone mineral health in Indians

Body mass index good predictor of BMD at Hip and Spine in Indians

Shatrugna et al; Osteoporosis International, 2005 (NIN)

Goswami Am J Clin Nutr 2006 (AIIMS)

It is important to maintain normal BMI  
Body weight of <55 kg in females is associated with rise in prevalence of osteoporosis

# Potential significance of VDD other than Bone

VDR is expressed in more than 30 tissues

Has role in transcription of several genes concerned with tissue differentiation and apoptosis

Various diseases have been associated with VDD

Limited data from India

# Potential significance of VDD other than Bone

Type 2- DIABETES MELLITUS

TUBERCULOSIS

CARDIOVASCULAR DISEASE

MALIGNANCY

OSTEOARTHRITIS

# Potential significance of VDD other than Bone

## Type 2- DIABETES MELLITUS and VDD

Winters Blood glucose values are worse

6288 non diabetic Americans:

inverse correlation between 25(OH)D and fasting and post glucose load blood values

Meta analysis: Odds ratio for presence of diabetes = 0.54 (0.23-1.27) in subjects with sufficient 25(OH)D (25-38 vs. 10-23 ng/ml)

Pittas et al, JCEM: Clinical review, 2007



# Potential significance of VDD other than Bone

## Type 2- DIABETES MELLITUS

Interventional trials assessing effect of Vit D on glycemic improvement are limited

Largest placebo controlled randomized trial

92 subjects (>65 yrs) with impaired FG

Daily 700 IU of vitamin D and 500 mg Ca-citrate X 3 yrs

Fasting blood glucose values & serum insulin reduced ( $p < 0.04$ , reduction 6.1 mg/dl)

(Pittas et al Diabetes care 2007)

# Potential significance of VDD other than Bone

## **Type 2- DIABETES MELLITUS**

### **Mechanism of improvement**

intracellular ionized Ca and insulin release

Inhibition of beta cell apoptosis

By 2030, Indians would have large type 2 DM

Studies are required to see if VD supplementation can prevent or delay the onset of type 2 DM

# Potential significance of VDD other than Bone

## CARDIOVASCULAR DISEASE and VDD

↑ **Prevalence of CAD in CRD**

↑ **CAD prevalence and associated mortality in winter**

↑ **CAD in Urban vs. Rural, linked to poor VD status**

Framingham Cohort: inverse correlation between serum 1,25(OH)D and presence of coronary artery calcification in subjects with hypercholesteremia

(Watson et al, Circulation 1997)

# Potential significance of VDD other than Bone

## CARDIOVASCULAR DISEASE and VDD

Inverse relationship between 25(OH)D and HT  
(Higher intake of vitamin D led to 9.3% decrease in  
systolic blood pressure in elderly women)  
(Pfeifer et al, JCEM 2001)

40% fall in CRP and IL-6 in CAD patients on three  
monthly cholecalciferol (1250 $\mu$ g) injections for a years  
Li YC , JCI 2002,

Significant improvement of EF after VD supplementation

# Potential significance of VDD other than Bone

## CARDIOVASCULAR DISEASE and VDD

VD help Gla matrix protein expression which inhibits activation of vascular calcification

Activation of pro-inflammatory cytokines and suppression of IL-10, anti-inflammatory cytokines

Stimulation of Renin Angiotensin system

6-8% prevalence of overt CAD in urban Indians

Earlier presentation

# Potential significance of VDD other than Bone

## **MALIGNANCY**

Prostate, colonic, Breast and pancreatic cancer are associated with VDD which ↑ incidences & mortality.

2.5 times increase in risk of colorectal Ca over a 8 year period in women health initiative study

In urban India Ca Breast is one of the most prevalent

Prevalence is linked to suppressive effect of VD and VDR on P21 and p27 gene important in Carcinogenesis.

# Potential significance of VDD other than Bone

## OSTEOARTHRITIS

OA in West is associated with poor BMD

Two large studies from the West

N = 715 from Framingham group and 277 Boston OA of knee study.

(Felson et al Arthritis Rheum 2007)

No link between baseline 25(OH) and presence of OA

No link between OA progression over 9 years period and serum 25(OH)D at baseline

Baseline Serum 25(OH)D were >20 ng/ml in most

# Potential significance of VDD other than Bone

## OSTEOARTHRITIS

Up to 29% and 33% prevalence of OA of knee joint in elderly Indians of Chandigarh  
(Joshi et al, Int J Epidemiol, 2003)

NEED TO CONDUCT STUDIES IN INDIA  
ASSESSING VDD and OA



# Potential significance of VDD other than Bone

## TUBERCULOSIS

Cod liver oil was used for Rx for TB in 1770

Sanatorium Rx with exposure to sunshine for patients

Seasonal variation of TB

Three randomized trials assessing effect of VD

supplementation on sputum AFB conversion

100% sputum conversion Vs. 76% when

cholecalciferol (0.25 mg/d for six weeks) was used

along with ATT (n=67)

Radiological improvement more with VD

(Nursyam, Acta Med Indones 2006)

# Potential significance of VDD other than Bone

## TUBERCULOSIS

VDR receptor are there in PBMC

In Vitro studies:  $1,25(\text{OH})\text{D}_2$  favors Th2 rather than Th1 Response

How to explain the paradox of improvement with VD in TB which needs enhancement in Th1 response for quick healing?

# Potential significance of VDD other than Bone

## TUBERCULOSIS

**1,25(OH)D itself leads to increased expression of antibacterial peptide Cathelicidin which kills intracellular MTb**

**Liu et al (Science, 2006 )**

# Potential significance of VDD other than Bone

## TUBERCULOSIS

**TB is National Health Problem in India**

**We have began a DBT funded Placebo controlled double blind study**

**To assess Sputum AFB conversion (rapidity and rate) with adjunct VD supplementation.**

**VD 60,000 IU X 8 weeks & 1 gm CaCO<sub>3</sub> X 6 mons**

**Radiological, Relapse & immunological changes**

**Prospective study of three year duration**

# Potential significance of VDD other than Bone

Mental health Schizophrenia

Type I-DM

Multiple Sclerosis

Crohn's disease

Wheezing disorders

# POTENTIAL SIGNIFICANCE OF VDD IN INDIANS

Wide prevalence of functionally significant hypovitaminosis D affecting bone mineral homeostasis of Indians leading to increased PTH and reduced BMD

Its role in disorders other than that of bone need to be investigated in Indians

**Neetaj Tomar**



**Debarti Ray**

**Thank You**