Vitamin D deficiency from childhood through to elderly: Indian Scenario

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Vitamin D is an important hormone necessary not only for maintaining calcium balance and safeguarding skeletal integrity but also essential for overall health and well being.

It is primarily acquired by exposure to sunlight and food articles commonly consumed by Indians do not provide adequate vitamin D.

No food articles are adequately fortified in India.

Nutritional rickets and vitamin D deficiency continues to exist as a major health problem in India.
The most sensitive index in assessing vitamin D status is 25(OH)D

(Hollis BW Calcif Tissue Int; 1996; 58; 4-5).

Age, sex, pubertal status, latitude, season, race, pollution and ethnicity influence 25(OH)D levels.

Approximately 40-50% of total skeletal mass at maturity is accumulated during childhood and adolescence.

(Mora et al, 1999; Cadogan et al, 1998)

Life style determinants - exercise, body composition, nutrition, calcium and Vitamin D intake affect bone development.

Peak bone density is attained by 3rd decade.
Role of Vitamin-D in our health

- It maintains blood calcium level in normal range which is vital for normal functioning of nervous system, bone growth and achieving peak bone density.

- It is a potent immune system modulator and prevents development of respiratory infections like influenza virus and autoimmune disorders.

- It inhibits uncontrolled proliferation and stimulates differentiation of cells thereby preventing common cancers.

- Plays a role in insulin secretion under conditions of increased insulin demand.

Whiting J S and Calvo S M American Society of Nutritional Sciences, 2005
Why Sound Bone Health?

- Poor bone health is responsible for causation of 8.9 million Fractures annually worldwide.

- Life time risk for hip, vertebral and wrist fracture is 30-40%.

- High morbidity and mortality associated with osteoporotic fractures.
Projected Number of Osteoporotic Hip Fractures Worldwide

Estimated number of hip fractures: (1000s)

Projected to reach 3.250 million in Asia by 2050

Total number of hip fractures:
1950 = 1.66 million
2050 = 6.26 million

Adapted from C. Cooper et al, Osteoporos Int. 1992; 2:285-9
All Fractures are Associated with Morbidity

One year after a hip fracture:

- Death within one year: 20%
- Permanent disability: 30%
- Unable to walk independently: 40%
- Unable to carry out at least one independent activity of daily living: 80%
Functions of the Skeleton

- Supports the body
- Protects internal organs
- Muscles attached for movement
- Cavities for blood formation
- Reservoir for minerals
Calcium and Vitamin D Insufficiency and Bone Loss

- Dietary calcium intake
  - Calcium absorption
    - Plasma calcium
      - Bone turnover and resorption
        - BONE LOSS
  - Vitamin D intake and synthesis
    - Estrogen deficiency
      - PTH secretion
Determinants of Peak Bone Mass

- Genetics
- Nutrition
- PEAK BONE MASS
  20-22 years of age
- Hormones
- Lifestyle
Can we Quantify Fracture Benefits in Old Age from BMD improvements in Peak bone mass?

- Hernandez et al using computer simulation study showed that a 10% increase in peak bone mass would delay onset of osteoporosis by 13 yrs.

(Hernandez CJ et al, Osteoporosis Int (2003))
A 10% increase in peak BMD translates to one SD higher BMD at the Lumbar Spine from the age of 60 yrs.

For one SD decrease in LS BMD, there is a 60% increase in hip fracture risk (Cummings SR et al, *lancet*; 1999)

This suggests that the long benefits of improving peak bone mass in childhood could be very substantial in old age.
• Exact cut-offs for “deficiency” and “insufficiency” remain controversial

• **Several classifications exist e.g. Lips P:**
  
  <5 ng/mL - severe hypovitaminosis D
  
  5-10 ng/mL - moderate hypovitaminosis D
  
  10-20 ng/mL - mild hypovitaminosis D
Functional indicators for defining 25(OH)D adequacy (80 nmol/L, 32ng/ml) as the “cut-off”

- Parathyroid hormone (PTH) (Vieth R et al JCEM 2003)
Recommendations for Vitamin-D intake levels

- Infants: 400 IU/day
- Children & Adults: 800-1000 IU/day.

Rx of vitamin D deficiency in adults:
60,000 IU/wk for 8 wks followed by 60,000 IU/month as maintenance dose

VITAMIN D TOXICITY
Vitamin D toxicity is rare in healthy people with intake levels lower than 10,000 IU/day
WHY SHOULD WE BOTHER ABOUT VITAMIN D LEVELS?
Vitamin D deficiency/insufficiency in Pregnancy & Lactation:

- Adverse maternal outcomes like Osteomalacia and Preeclampsia
- Lower birth weight
- Lower crown heel length, head circumference and mild arm circumference
- Low bone mass
- Poor/ delayed Growth
- Ricket in utero/ at birth
- Tetany
- Neonatal hypocalcemic seizures
- Abnormal enamel formation and dental caries
ADVERSE EFFECTS OF VITAMIN D DEFICIENCY

*Children and adolescents:*
- Poor growth velocity
- Rickets
- Short stature
- Low bone mass
- Genu Varum (Bow legs)
- Genu Valgum (Knock knees)
- Respiratory viral infections (including swine flu)

*Adult & old age:*
- Muscle pain & fatigue
- Osteomalacia
- Osteoporosis
- Hip, Spine, Forearm and other fractures.
- Increase prevalence of autoimmune disorders, cardiovascular diseases, common cancers and infections.
Caution

- Drugs such as Phenytoin (Dilantin), Phenobarbital (Luminal), Carbamazepine (Tegretol) and Rifampicin increase the metabolism and decrease serum vitamin D levels.
Status of Vitamin D Deficiency in Indians
Nutritional Rickets

- MAJOR PUBLIC HEALTH PROBLEM
- It is primarily due to deficiency of calcium and vitamin D deficiency as shown in several studies.

No standard guidelines regarding dose, duration and route of administration of vitamin D in treatment of rickets with different regimes recommended by different authorities

Vitamin D deficiency despite adequate sunlight, is probably due to likely to be due to:

- Increased skin pigmentation
- Insufficient exposure to sunlight
- Atmospheric pollution
- Use of sunscreen
- Absence of food fortification program.
Prevalence of Vitamin-D insufficiency in children

- **Community-based studies** - the prevalence of clinical rickets in preschool children in India
  - **1.5% to 11.4% - 1970’s**
  - **2% to 9.4% - 1990’s**

- However, hypovitaminosis D was not documented in apparently normal children.

- **Hospital based studies** - a prevalence of 0.2% to 5.3%.
Vitamin D status in Asian immigrants

- In Asian migrants in the United Kingdom - prevalence in children and adolescents –
  5% to 30%

- Immigrant studies using biochemical and radiological parameters –
  12.5% to 66%

- In children of Indian origin residing in South Africa, the prevalence of knock knees and bow legs –
  6.1 - 19.4%
  (Richardson BD Postgrad Med. J 1975)

- Incidence of rickets had come down in the immigrant population
  (Goel et al. Lancet 1981)
Vitamin D and bone mineral density status of healthy schoolchildren in northern India¹,²,³

Raman K Marwaha, Nikhil Tandon, Devi Reddy HK Reddy, Rashmi Aggarwal, Rajvir Singh, Ramesh C Sawhney, Bobbin Saluja, M Ashraf Ganie and Satveer Singh

ORIGINAL RESEARCH COMMUNICATION
**Background:** Current data on the prevalence of vitamin D deficiency in India are scarce.

**Objective:** We assessed the calcium-vitamin D-parathyroid hormone axis in apparently healthy children from 2 different socioeconomic backgrounds in New Delhi, India.

**Design:** Clinical evaluation for evidence of vitamin D deficiency was carried out in 5137 apparently healthy schoolchildren, aged 10-18 y, attending lower (LSES) and upper (USES) socioeconomic status schools. Serum calcium, inorganic phosphorus, alkaline phosphatase, 25-hydroxyvitamin D [25(OH)D], and immunoreactive parathyroid hormone were measured in 760 children randomly selected from the larger cohort. Bone mineral density of the forearm and the calcaneum was measured in 555 children by using peripheral dual-energy X-ray absorptiometry.
Clinical vitamin D deficiency in 556/5137 (10.82%) subjects [LSES – 11.6%, USES – 9.7% (P = 0.07)]

Genu Varum in 7.5% [B=8%, G=7.2% (P=0.39)],
Genu Valgum in 3.3% [B=2.4%, G=3.9% (P< 0.01)]

Low 25(OH)D levels according to Lips criteria seen in 92% of LSES and 84% of USES

25(OH)D higher in boys than girls in both the groups (P = 0.030 in LSES; P = 0.015 in USES).

Mean 25(OH)D values were 11.8±7.2 ng/ml and 12.74±6.17ng/ml respectively.
• Prevalence of biochemical hypovitaminosis D (serum 25-hydroxyvitamin D < 50 nmol/l) was seen in 90.8 % of girls (89.6 % LSES, 91.9 % USES, NS).

• Mean intake of energy, protein, fat, Ca, vitamin D and milk/milk products was significantly higher in USES than LSES girls. Conversely, carbohydrate, fibre, phytate and cereal intakes were higher in LSES than USES girls. Daily intake of Vitamin D through meals was 2-2.5 ug/day (80-100 IU/day)

• Significant correlation between serum 25-hydroxyvitamin D and estimated sun exposure (r 0.185, P = 0.001) and percentage body surface area exposed (r 0.146, P = 0.004) suggests that these lifestyle-related factors may contribute significantly to the vitamin D status of the apparently healthy schoolgirls.
Conclusion

- In the absence of vitamin D fortification of foods, diet alone appears to have an insignificant role.

- Physical activity, optimal nutrition and adequate sun exposure are vital for attaining peak bone mass.
ADVERSE EFFECTS OF VITAMIN D DEFICIENCY
Hypovitaminosis D and hypocalcemic seizures in infancy


BACKGROUND:
Hypocalcaemia accounts for a majority of seizures in infants reporting to the emergency ward of our hospital.

OBJECTIVE:
To evaluate the role of Vitamin D deficiency in the etiology of hypocalcemic seizures in infancy.

DESIGN AND SETTING:
Cross sectional hospital based study, from April 2006-March 2007.

SUBJECTS:
60 infants with hypocalcemic seizures and their mothers (study group) and 60 healthy breastfed infants with their lactating mothers (control group).

MEASUREMENTS:
Vitamin D [25(OH) D] and intact para-thormone levels.
Conclusion

- Infants born to vitamin deficient mothers are at a significantly higher risk of developing hypocalcemic seizures.
Peripheral bone mineral density and its predictors in healthy school girls from two different socioeconomic groups in Delhi.

RESULTS:
Girls belonging to the USES were significantly taller (149.7 +/- 12.3 cm vs 144.4 +/- 11.9 cm; P < 0.001) and weighed more (44.3 +/- 12.9 kg vs 35.9 +/- 10.0 kg; P < 0.001) than girls from the LSES. USES girls had a significantly higher mean serum calcium (9.3 +/- 0.7 mg/dl vs 9.2 +/- 0.8 mg/dl; P < 0.05) and significantly lower alkaline phosphatase (316 +/- 166 IU/l vs 423 +/- 228 IU/l; P < 0.01) and iPTH (29.9 +/- 18.4 pg/ml vs 45.7 +/- 64.6 pg/ml; P < 0.01).

• There was no significant difference in mean serum phosphorus and 25-OHD levels between the two groups.

• USES subjects had higher BMD at both sites than LSES subjects. BMDdf and BMDca increased with age and tended to plateau by 16 years and 12 years of age respectively in both the groups.

• Age, height and weight explained approximately 50% of the variability, while biochemical parameters explained approximately 30% of variability in BMD at both the sites.

• The only biochemical parameter which had a significant association with BMD was ALP at the distal forearm.

CONCLUSION:
In conclusion, age, nutrition, height and weight are significantly associated with BMD at peripheral sites.
Comparison of unadjusted means of bone mineral density (BMD) in the two socioeconomic groups

Marwaha RK et al Am Jour Clin Nutr 2005

<table>
<thead>
<tr>
<th>Variable and age category</th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LSES Group</td>
<td>USES Group</td>
</tr>
<tr>
<td>Forearm BMD (gm/cm²) (p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-12 yrs</td>
<td>0.313± 0.044</td>
<td>0.387 ±0.146</td>
</tr>
<tr>
<td>13-15 yrs</td>
<td>0.359± 0.067</td>
<td>0.397± 0.064</td>
</tr>
<tr>
<td>16-18 yrs</td>
<td>0.414± 0.059</td>
<td>0.408 ±0.049</td>
</tr>
<tr>
<td>Calcaneum BMD (gm/cm²) (P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-12 yrs</td>
<td>0.424± 0.088</td>
<td>0.501± 0.073</td>
</tr>
<tr>
<td>13-15 yrs</td>
<td>0.464± 0.074</td>
<td>0.557± 0.095</td>
</tr>
<tr>
<td>16-18 yrs</td>
<td>0.505 ±0.073</td>
<td>0.592± 0.089</td>
</tr>
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</table>
## VITAMIN D STATUS IN INDIAN ADULTS

### Delhi:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Soldiers Winter</th>
<th>Physicians &amp; Nurses Winter</th>
<th>Physicians &amp; Nurses Summer</th>
<th>Pregnant Women Summer</th>
<th>New Borns Summer</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (pg/ml)</td>
<td>17.6 4.8</td>
<td>38.8 18.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>


### Lucknow:

67% of the subjects had serum 25(OH)D levels < 15 ng/ml

### Kashmir Valley:

Vitamin D deficiency (25 (OH)D<20ng/ml) reported in 83%.

- Mild hypovitaminosis D – 25%
- Moderate hypovitaminosis D – 33%
- Severe hypovitaminosis D – 25%

*Zargar et al Postgraduate Medical Journal 2007*
Tirupati:
- **Mean 25(OH)D values in Males:**
  Urban-18.54±0.8 ng/ml, Rural-23.73±0.8 ng/ml.
- **Mean 25(OH)D values in Females:**
  Urban- 15.5±0.3 ng/ml, Rural- 19±0.89 ng/ml.
  *Harinarayan CV et al: AmJClinNutr 2007*

Delhi Rural:
- Mean vitamin D levels in Females – 10.7 ± 6.3 ng/ml
- Mean Vitamin D levels in Males – 17.68±9.6 ng/ml
  *Goswami R et al JAPI 2008*
VITAMIN D STATUS IN HEALTHY INDIANS AGED 50 YEARS AND ABOVE

Marwaha RK et al JAPI 2011

- Methods:
- Total no. of subjects evaluated: 1346 (Male: 643, Females: 703)
- Mean age: 58.95 years (range 50 – 84 years)
- Mean 25(OH)D levels: Males- 9.7±6.8 ng/ml, Females- 9.6±7.51 ng/ml
- Prevalence of Vit D def was noted in 92% subjects.
Bone health in healthy Indian population aged 50 years and above.

Osteoporos Int. 2011 Jan 27.


Department of Endocrinology and Thyroid Research Centre, Institute of Nuclear Medicine and Allied Sciences, Delhi, 110054, India, marwaha_ramank@hotmail.com.
Establishment of Age-Specified Bone Mineral Density Reference Range for Indian Females Using Dual-Energy X-Ray Absorptiometry

Raman K. Marwaha,* 1 Nikhil Tandon, 2 Parjeet Kaur, 2 Aparna Sastry, 1 Kuntal Bhadra, 1 Archna Narang, 1 Saurav Arora, 1 and Kalaivani Mani 3

1 Department of Endocrinology and Thyroid Research Centre, Institute of Nuclear Medicine and Allied Sciences, New Delhi, India; 2 Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India; and 3 Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India
RESULTS

- **Prevalence of Osteoporosis:**
  562 subjects (35.1%) [M-24.8%; F-42.5%]

- **Prevalence of Osteopenia:**
  792 subjects (49.5%) [M-54.3%; F-44.9%]

Prevalence of osteoporosis increased significantly with age.
The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS)

Raman K. Marwaha • Nikhil Tandon • Yashdeep Gupta • Kuntal Bhadra • Archana Narang • Kalaivani Mani • Ambrish Mithal • Subhash Kukreja

Received: 9 March 2012 / Accepted: 9 August 2012
© International Osteoporosis Foundation and National Osteoporosis Foundation 2012
Fig. 1 Prevalence of vertebral fractures in males and females according to age strata

<table>
<thead>
<tr>
<th>Age groups in years</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>21.6</td>
<td>14.7</td>
</tr>
<tr>
<td>60-69</td>
<td>17.2</td>
<td>17.3</td>
</tr>
<tr>
<td>≥70</td>
<td>20.3</td>
<td>22.4</td>
</tr>
</tbody>
</table>
Incidence of Hip Fractures in India

- Incidence in elderly Indians >55Yrs old
- Male - 121/100,000
- Females – 163/100,000
- *Dinesh Dhanwal et al Osteoporos Int. Supplement 2, Dec 2010*

- Strong association of vitamin D deficiency with Hip Fractures have been reported by
- *Ghadgawat R et al in Osteoporos Int. 2012*
Hip fracture rates in Indian men and women

Dinesh Danwal et al 2010
High prevalence of vitamin D deficiency in Indians of all age and sex groups is a major public health problem which needs urgent attention.

Calcium and Vitamin D are critical for achieving maximum peak bone mass and maintenance of sound bone health in all ages.

Attaining high peak bone density is important for prevention of osteoporosis and fractures.

Not enough attention has been paid to bone health in our country.

- Screening of susceptible groups like pregnant and lactating mothers, infants and school children and post-menopausal women should be carried out.

- Physical activity at all ages, particularly weight bearing is important for bone health.
TAKE HOME MESSAGES

- Not enough attention has been paid to bone health.

- Attaining high peak bone density is important for prevention of fractures.

- Physical activity at all ages, particularly weight bearing is important for bone health.

- Calcium and Vitamin D are critical for sound bone health.
Schools should promote physical activity and emphasize during educational programs, the importance of calcium and vitamin D. Role of teachers in this endeavor is particularly important.

School dresses should be designed in a manner that expose legs and arms to sunshine and outdoor physical activity should be undertaken during 9AM to 4PM.
Families should educate themselves on the importance of bone health and recognize the need for good nutrition, exposure to sunlight and physical activity.

Research Institutions should generate the relevant information in non-technical language.

Anganwadi and primary health workers should be given additional training to enable them to give attention to bone health among children and women.
Framework for Action: National Plan for Bone Health...Cont...

- Food processing Industry should fortify foods with vitamin D

- Pharma Industry should develop and promote appropriate supplements to make up for calcium and vitamin D deficiencies.

- The central govt should fund research organisations to undertake national survey on bone health and related issues

- The ministry of health should initiate a public health awareness program through media conveying key messages.
Thank You!
Nutritional Rickets

- **MAJOR PUBLIC HEALTH PROBLEM**
- It is primarily due to deficiency of calcium and vitamin D deficiency as shown in several studies.

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IJMR 2008;127(3):239
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No standard guidelines regarding dose, duration and route of administration of vitamin D in treatment of rickets with different regimes recommended by different authorities

Vitamin D deficiency despite adequate sunlight, is probably due to likely to be due to:
- Increased skin pigmentation
- Insufficient exposure to sunlight
- Atmospheric pollution
- Use of sunscreen
- Absence of food fortification program.
Studies in South Africa and Nigeria suggest that a dietary deficiency of calcium may cause rickets.

In both regions, calcium supplementation alone resulted in healing of the rickets comparable to a combination of calcium and vitamin D.

Metabolism 1991;40:209
Ambulatory Child Health 1997;3:56
Lancet 1999;353:296
What plays a more important role in the management of nutritional rickets in India??

- Vitamin D deficiency
- Calcium deficiency
A Randomized Controlled Trial of Calcium, Vitamin D or Both in Management of Nutritional Rickets

Varun Aggarwal, Anju Seth & R K Marwaha
JCEM 2013
Objectives

- Evaluate the dietary intake of calcium and serum 25 (OH)D levels in children with rickets

- Compare the three therapeutic options in the treatment of nutritional rickets:
  - Vitamin D alone (6 Lakh IU single i.m)
  - Calcium alone (75 mg/kg/day for 12 weeks)
  - Combination of the two
Methods

Cases

- 100 children with clinical and radiological features of rickets screened
- 6 months to 5 years
- From the OPD of KSCH
- Dec’07 – Jan’09
Methodology

Exclusion Criteria

- Non-nutritional etiology (renal or hepatic disease, antiepileptic drug intake or any chronic illness)
- Cases presenting with hypocalcemic seizures
- History of consuming calcium or vitamin D supplements in the preceding six months
Methods.

- **Biochemical Measurements**
  - S. Calcium (total and ionic) [Colorimetric method]
  - S. Phosphate (iP) [Ion exchange method]
  - S. Alkaline phosphatase (ALP) [Photometric analysis]
  - S. iPTH [Electro-chemiluminescence assay]
  - S. $25$($OH)$VitD$_3$ [Electro-chemiluminescence assay]

- **Radiographs of left wrist and knee**
  - Evaluated by a separate observer blinded to treatment protocol and scored on a 0 – 10 point scale.
  - A Score of > 1.5 indicated rickets

Randomization

The cases were randomized to one of the three treatment arms:

- **Group 1**: 6 lakh IU Vitamin D single i/m injection.

- **Group 2**: 6 lakh IU Vitamin D single i/m injection and 75 mg/kg elemental calcium in three divided doses per day for 12 weeks.

- **Group 3**: 75 mg/kg elemental calcium in three divided doses per day for 12 weeks.
Re-evaluation at 12 weeks

- **X-ray Lt. wrist & knee**: radiological score

- **Biochemical Parameters**
  - S. Calcium (total and ionic)
  - S. Phosphate (iP)
  - S. Alkaline phosphatase (ALP)
  - S. Parathyroid Hormone (PTH)
  - S. 25(OH) Vitamin D₃ (25(OH) D₃)
100 Cases screened

Cases Enrolled - 67

Group 1 (Vitamin D) (n = 23)
19 – Final Evaluation

Group 2 (Vitamin D + Calcium) (n = 22)
20 – Final Evaluation

Group 3 (Calcium) (n = 22)
17 – Final Evaluation

Excluded 33

Taken supplements: 18
Chronic diseases: 5
Outside age range: 7
Refused consent: 3
Serum Vitamin D levels

29.8% < 11 ng/ml

Only 4 subjects had >30 ng/ml
Dietary Calcium intake was much lower than the RDA (500 mg/day) in all the three groups.

**Parameter** | **Group 1** (Vitamin D, n=23) | **Group 2** (Vit D+Calcium, n=22) | **Group 3** (Calcium, n=22) |
---|---|---|---|
**Total Ca (mg/day)** | 204.0±182.67 | 202.25±91.66 | 207.4±100.2 |

All p values >0.05
A significant increase was also seen in Serum Calcium (both ionic and total), serum iP, and vitamin D levels in the three groups when compared to baseline.
## Percentage change in various parameters at 12 weeks as compared to baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Vitamin D (n=19)</th>
<th>Group 2 Vitamin D+Calcium (n=20)</th>
<th>Group 3 Calcium (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. ALP (↓)</td>
<td>55.37 ± 0.15%</td>
<td>74.02 ± 8.0%</td>
<td>56.05 ± 11.0%</td>
</tr>
<tr>
<td>S. PTH (↓)</td>
<td>69.03 ± 18.1%</td>
<td>65.57 ± 28.8%</td>
<td>49.66 ± 46.01%</td>
</tr>
<tr>
<td>S. 25(OH)D$_3$ (↑)</td>
<td>258.74 ± 329.05%</td>
<td>92.17 ± 189.34%</td>
<td>86.20 ± 179.7%</td>
</tr>
<tr>
<td>S. Ca (total) (↑)</td>
<td>11.19 ± 11.0%</td>
<td>23.94 ± 14.5%</td>
<td>8.85 ± 7.7%</td>
</tr>
<tr>
<td>S. Ca (ionic) (↑)</td>
<td>21.19 ± 16.4%</td>
<td>37.82 ± 17.3%</td>
<td>13.19 ± 10.8%</td>
</tr>
<tr>
<td>S. iP (↑)</td>
<td>64.87 ± 32.3%</td>
<td>110.2 ± 66.0%</td>
<td>54.37 ± 47%</td>
</tr>
<tr>
<td>Rad. Score (↓)</td>
<td>70.35 ± 9.33%</td>
<td>82.22 ± 5.75%</td>
<td>59.56 ± 15.8%</td>
</tr>
</tbody>
</table>

* p value <0.05 group 2 vs group 1 and group 3, No significant difference in parameters between groups 1 & 3 except radiological score
Combined end point of normal serum ALP (<420 IU/L) and radiological score <1.5 was seen in 50% of group 2, 15.7% of group 1 & 11.7% of group 3
## Serum 25(OH)D₃ level pre & post treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group1 Vitamin D (n=23)</th>
<th>Group 2 Vit D+Calcium (n=22)</th>
<th>Group 3 Calcium (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D₃ (ng/ml) Baseline</td>
<td>12.4(7.2,16.6)</td>
<td>13.9(11.4,22)</td>
<td>14.9(11.38,17.9)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>22.9(16.5,49.1)</td>
<td>29.4(15.4,45.2)</td>
<td>16.2(13.1,20.5)</td>
</tr>
</tbody>
</table>

- Even with 6L IU vitamin D, the mean serum 25(OH)D₃ in groups 1 and 2 still had levels in insufficiency range
- 15 children in group 1 and 11 children in group 2 still had serum 25(OH) D₃ level in the deficiency range
Present study in comparison to other relevant publications

- Kutlek et al (Turkey)
  - Best response was observed with combination therapy as compared to either modality alone
    
    J Trop Ped 2002;48:351

- Thacher et al (Nigeria)
  - Combined end point of normal ALP and radiological healing at 24 weeks
    - 61% with Calcium alone
    - 58% with combination
    - 19% Vitamin-D alone
    
    NEJM 1999;341:563
How does this study compare with other related works?

- Balasubramaniam et al (India)
  - 24 children with nutritional rickets
    - Mean S. Vitamin-D: 20 + 15.5 ng/ml
    - Mean dietary Ca intake: 285 ± 113 mg/day
  - Randomized to receive calcium with and without Vitamin D
    - Patients in both groups had comparable biochemical and radiological healing at the end of three months

A randomized controlled trial on safety and efficacy of single intramuscular v/s staggered oral dose of 600,000 iu vitamin D in treatment of nutritional rickets”

K. Mondal, A. Seth & R. K. Marwaha
Route of administration of vitamin D
oral/parenteral- which is better?

- Lubani et al, An Trop peds, 1989-
  Oral group (2000 IU/day for 4 weeks)- 40 % children did not respond to treatment after 12 weeks
  I/M group (600,000 IU single dose)- Evidence of healing in all at 12 weeks

- Billo et al, J Col Phy Surg, 2003- One time administration of both oral and intramuscular Vit D 200,000 iu - safe and effective in nutritional rickets
Randomization and treatment group allocation

- The cases were randomized to receive one of the following treatment protocols:
  
  a. 600,000 iu vitamin D as a single intramuscular dose  
  b. 60,000 iu vitamin D orally once a week for 10 weeks  

- Inj Vit D was given in the hospital, oral vit D was given under direct supervision to the extent possible  

- All cases received oral calcium (dose 50 mg/kg/day) during the study  

- All children were followed up for 12 weeks
Results

Study flow chart

Cases screened
76

Excluded -5
(non nutritional=2, received vitamin D=3)

Included-71

37 i/m 600,000 IU vitamin D and calcium orally 50 mg/kg/day

Lost-6
Completed 12 weeks follow up-31

34 Oral vitamin D 60,000 IU/wk for 10 weeks and oral calcium 50 mg/kg/day

Lost-4
Completed 12 weeks follow up-30
Mean serum 25(OH)D before and after treatment

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Serum 25(OH)D (mean ± SD) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.51± 10.79</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>38.09± 28.44</td>
</tr>
</tbody>
</table>

- P >0.05 on comparing vit D level in 2 treatment groups at 12 weeks
- Significant rise (P < 0.001) after treatment in both groups as compared to pre-treatment level
Percentage of children with biochemical pointer of rickets at baseline and follow up in 2 groups

<table>
<thead>
<tr>
<th>parameters</th>
<th>% of subjects</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oral group</td>
<td>I/M group</td>
<td>Oral group</td>
</tr>
<tr>
<td>Oral group</td>
<td>83.33%</td>
<td>90.32%</td>
<td>33.33%</td>
<td>25.80%</td>
</tr>
<tr>
<td>Serum ALP &gt;420 IU/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia (serum ionic calcium &lt;4.48 mg/dl)</td>
<td>43.33%</td>
<td>35.48%</td>
<td>16.67%</td>
<td>3.23%</td>
</tr>
<tr>
<td>Hypophosphatemia (serum phosphate &lt;3.8 mg/dl)</td>
<td>83.33%</td>
<td>74.49%</td>
<td>23.33%</td>
<td>22.58%</td>
</tr>
<tr>
<td>Serum 25(OH)D &lt;20 ng/ml</td>
<td>96.67%</td>
<td>93.55%</td>
<td>30%</td>
<td>29.03%</td>
</tr>
</tbody>
</table>
Radiological score of two groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Radiological score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.116± 2.07</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4.36± 1.766</td>
</tr>
<tr>
<td>12 weeks</td>
<td>0.583± 0.63</td>
</tr>
</tbody>
</table>

- P >0.05 on comparing 2 treatment groups at all points of time
- Fall in radiological score was significant at 4 weeks compared to baseline and at 12 weeks compared to 4 weeks in both groups (p<0.001)

All children had a radiological score >1.5 at baseline.
At 12 weeks all but 1 child in each group had achieved a score <1.5 indicating complete healing
Comparison of efficacy of the two regimes

- Rise in serum calcium, phosphate & 25 OHD and fall in serum ALP level & radiological score was similar in two groups, both demonstrating a good evidence of healing.

- Combined end point of ALP <420 IU/L and radiological score <1.5 at 12 weeks was achieved in 28/30 (93.33%) subjects in oral group and 28/31 (90.32%) subjects in i/m group.
Families should educate themselves on the importance of bone health and recognize the need for good nutrition, exposure to sunlight and physical activity.

Research Institutions should generate the relevant information in non-technical language.

Anganwadi and primary health workers should be given additional training to enable them to give attention to bone health among children and women.
Steps to deal with the problem

- Increase exposure to sunlight
- Decrease atmospheric pollution
- Advise against usage of sunscreen
- Supplementation of vitamin D
- Introduction of food fortification program in India
Vitamin D status at different stages of life

**Vitamin D status in last trimester of pregnancy:**

- **Prevalence:** 74-98% [25(OH)D < 20 ng/ml]
- The mean 25(OH)D values varied from 8.7±4.3 to 14±9.3 ng/ml.

(Sachan A et al; AJCN 2005, Sahu M et al; Clin Endocrinol 2009 (Lucknow), Goswami R, Marwaha RK et al; AJCN 2000).
The present cross-sectional study was conducted to determine the vitamin D status of pregnant Indian women and their breast-fed infants. Subjects were recruited from the Department of Obstetrics, Armed Forces Clinic and Army Hospital (Research and Referral), Delhi. A total of 541 apparently healthy women with uncomplicated, single, intra-uterine gestation reporting in any trimester were consecutively recruited.

Of these 541 women, 299 (first trimester, ninety-seven; second trimester, 125; third trimester, seventy-seven) were recruited in summer (April-October) and 242 (first trimester, fifty-nine, second trimester, ninety-three; third trimester, ninety) were recruited in winter (November-March) to study seasonal variations in vitamin D status.

Clinical, dietary, biochemical and hormonal evaluations for the Ca-vitamin D-parathormone axis were performed. A subset of 342 mother-infant pairs was re-evaluated 6 weeks postpartum.


Vitamin D Status in three trimesters of pregnancy

Marwaha RK et al BJN 2011.

- Mean serum \([25(OH)D]\): 9.32±4.89ng/ml

- Hypovitaminosis D: 96.3% subjects (36.8% mild, 41.8% moderate 17.7% severe).

- The prevalence of maternal hypovitaminosis D was not different in the three trimesters whether studied in summers (96.9% vs. 92% vs. 98.7%) or winters (100% vs. 97.9% vs. 95.6%) in 1st, 2nd and 3rd trimesters, respectively.

- A strong positive correlation was noted in 25(OH)D levels in mother infant pairs \((r=0.324, p=0.001)\)
Vitamin D nutritional status of exclusively breast fed infants and their mothers


BACKGROUND:
Vitamin D nutrition has a profound effect on the development of an infant. Vitamin D status of mothers and their infants are closely correlated. While hypovitaminosis D has emerged as a significant public health problem across all age groups, there is limited information of this condition in lactating mothers and their breast fed infants.

AIM:
To evaluate the vitamin D status of lactating mothers and their breast fed infants.

SUBJECTS AND METHODS:
180 healthy lactating mothers and exclusively breast fed infants, 2-24 weeks old, were recruited for the study. The mother-infant pairs underwent concurrent clinical, biochemical and hormonal evaluation for calcium-vitamin D-PTH axis.
Vitamin-D status in lactating mothers and their exclusively breast fed infants

Vitamin D status of Lactating mothers:
- 180 mother-infant pairs from Kalavati hospital were undertaken for the study
- Prevalence of hypovitaminosis D was seen in S: 93.8% [25(OH)D < 20 ng/ml]
- Mean serum 25(OH)D: 10.9 5.8 ng/ml

Seth A and Marwaha RK et al;JPEM 2009

Vitamin D status of Neonates and Infants:
- Clinical features of vitamin D deficiency: 3.9% (7/180)
- High prevalence of low serum 25(OH)D levels in 80-91% infants 2-24 weeks old.
- Mean 25 (OH)D=11.55±8.3 ng/ml.
- Infants born to mothers with 25(OH)D< 10ng/ml had four times higher risk of developing moderate to severe hypovitaminosis D when compared those with 25(OH)D levels > 10 ng/ml

(Seth A & Marwaha RK et al;JPEM 2009,Bhalala et al;Indian Pediatrics)
SUMMARY

• High prevalence of low 25(OH)D levels in Indians of all age and sex groups is a major public health problem which needs urgent attention.

• Screening of susceptible groups like pregnant and lactating mothers, infants and school children should be made mandatory.

• Absence of raised PTH observed in more than 50 -70 % individuals with Vit D deficiency, merits further evaluation.

• A strong positive correlation of 25(OH)D levels exists in mother infant pairs.
Methods

- All cases were re-evaluated at **6 weeks**
  - It was planned that if any of the subject in group 1 or 3 did not show evidence of radiological healing, then the patient in group 1 shall receive calcium supplements and patient in group 3 shall receive vitamin D supplementation.

- **At the end of study period (12 weeks)**
  - Patients in group 3 received calcium supplements and in group 1 received vitamin D i.m.

- Study protocol was approved by:
  - Institutional Ethical Committee

- Informed written consent was taken from the guardians
Biochemical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Vitamin D (n=23)</th>
<th>Group 2 Vit D+Calcium (n=22)</th>
<th>Group 3 Calcium (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Ca total (mg/dL)</td>
<td>8.64±0.91</td>
<td>8.38±0.82</td>
<td>8.71±0.67</td>
</tr>
<tr>
<td>Ionic Ca (mg/dL)</td>
<td>3.95±0.51</td>
<td>3.7±0.34*</td>
<td>4.04±0.58*</td>
</tr>
<tr>
<td>ALP (IU/L)**</td>
<td>1200(980,1424)</td>
<td>1400(1110,1740)</td>
<td>1205(985,1377)</td>
</tr>
<tr>
<td>iP (mg/dL)</td>
<td>2.83±0.75</td>
<td>2.65±0.58</td>
<td>2.88±0.77</td>
</tr>
<tr>
<td>PTH (pg/ml)**</td>
<td>166.6(110.7,234)</td>
<td>132.5(74.2,345.2)</td>
<td>94.8(52.9,230)</td>
</tr>
<tr>
<td>Vit D (ng/ml)**</td>
<td>12.4(7.2,16.6)</td>
<td>13.9(11.4,22)</td>
<td>14.9(11.38,17.9)</td>
</tr>
</tbody>
</table>

P>0.05 for all parameters except Ionized calcium between *group 2 and *group 3. **Median (25th, 75th centiles)
Results: Demographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Vitamin D (n=23)</th>
<th>Group 2 Vit D + Calcium (n=22)</th>
<th>Group 3 Calcium (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>16.48±11.96</td>
<td>17.05±10.67</td>
<td>19.27±13.04</td>
</tr>
<tr>
<td>Gender</td>
<td>M=13, F=10</td>
<td>M=9, F=13</td>
<td>M=13, F=9</td>
</tr>
<tr>
<td>Ht Z score</td>
<td>-1.72±1.00</td>
<td>-1.59±1.06</td>
<td>-1.82±1.17</td>
</tr>
<tr>
<td>Wt z score</td>
<td>-1.39±1.10</td>
<td>-1.77±0.96</td>
<td>-1.34±1.12</td>
</tr>
</tbody>
</table>

All p values >0.05
Correlation of radiological score with calcium intake & S.25OHD₃ levels

Dietary calcium intake correlated with radiological scores

\[ r = -0.279, \ p = 0.0287 \]

No significant correlation between S. 25(OH) D₃ and radiological score
Incidence of hypercalcemia at follow up

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Incidence of hypercalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group n=30</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>At day 3</td>
<td>0</td>
</tr>
<tr>
<td>At day 7</td>
<td>0</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>2 (11.3, 11.5 mg/dl)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>2 (12.1,11.2 mg/dl)</td>
</tr>
</tbody>
</table>

• All the children with hypercalcemia were asymptomatic

• No child among those with hypercalcemia had hypervitaminosis D at any point of study

• No child with hypercalcemia developed hypercalciuria at any point of study
Hypervitaminosis D (>100 ng/ml)

- Found in 2/30 children in oral group (105.4 ng/ml, 103.6 ng/ml) and 1/31 children in i/m group (106.1 ng/ml) at the assessment done at 12 weeks.

- No child with hypervitaminosis D had hypercalcemia at any point of study.

- 2 children with hypervitaminosis D had hypercalciuria but this was present even at the baseline.
Status of single bolus dose of vitamin D in treatment of rickets

- Stoss therapy, administration of vitamin D 600,000 IU parenterally/orally as a bolus dose: Commonly used to treat rickets

- Advantages:
  - Convenient
  - Ensures compliance

- Limitation: concerns regarding safety
  - Some studies have reported hypercalcemia and hypercalciuria on this therapy (Cesur et al, JPEM, 2003, Ozkan et al, Coc Sag Has Der, 2000, Terrence et al, MJA, 2005)
Objectives

- To compare efficacy of two different regimes in treatment of nutritional rickets in children 6 months to 5 years age:
  a. 600,000 iu vitamin D as a single intramuscular dose
  b. 60,000 iu vitamin D orally once a week for 10 weeks

- To compare the safety of above two regimes as measured by incidence of hypercalcemia, hypercalciuria and hyper-vitaminosis D during a 12 weeks follow up
Methodology

**Study design:**
Randomized controlled trial (Rct registration no: REFCTR1/2010/001427)

**Study population:**
Children in the age group of 6 months to 5 years presenting to OPD and in-patient of KSCH for any reason & demonstrating clinical & radiological signs of rickets

**Time period:**
Nov’09 – Mar’11

**Exclusion criteria:**
- Non-nutritional rickets
  - Evidence of renal disease, liver disease, mal-absorption states
  - Suspicion of familial/ metabolic disorder leading to rickets
- Anti-epileptic intake
- H/o receiving vit D in preceding 6 months
- Concomitant chronic medical and surgical illness
Conclusion

- A dose of 600,000 iu of vitamin D is effective in treatment of nutritional rickets.

- A one-time intramuscular injection of vitamin D is equally efficacious in treatment of nutritional rickets as staggered administration of the same dose orally over a period of 10 weeks.

- 600,000 iu vitamin D administered either orally or intramuscularly is safe in the treatment of nutritional rickets.

- Besides low vitamin D status, very low dietary intake of calcium was seen in cases of rickets.

- **Combination therapy** with both vitamin D and calcium produced better healing of rickets than either modality alone in the study group.
Comparison of efficacy of two treatment regimes

Radiological parameters
Radiograph of left wrist and knee - taken at baseline, 4 weeks and 12 weeks
- Scoring done in a 0-10 point scale, score >1.5 indicates rickets
- Evaluation done by radiologist blind to treatment allocation
- Fall in score with treatment noted

Biochemical parameters
Change in the following parameters with treatment:
- Rise in serum calcium
- Rise in serum phosphate
- Rise in serum 25(OH)D level
- Fall in ALP level
Comparison of safety of two regimes

- Measuring incidence of the following parameters on treatment:
  - **Hypercalcemia**: serum total calcium > 11 mg/dl, serum ionic calcium > 5.28 mg/dl
  - **Hypercalciuria**: spot urinary calcium/creatinine ratio
    - Definition: in < 1 yr age group - >0.53 (mg/mg)
    - In 1 to <2 yr age group - >0.437 (mg/mg)
    - In 2 to 5 yrs age group - > 0.35 (mg/mg)


- **Hypervitaminosis D**: serum 25(OH)D >100 ng/ml

In addition, in i/m group, serum calcium and urinary calcium/creatinine ratio were also measured at day 3 after receiving injection.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Baseline</th>
<th>Day 7</th>
<th>4 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Serum ALP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urinary calcium/creatinine ratio</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Serum 25(OH)D</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Radiological score</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Mean serum ionic calcium in two groups

<table>
<thead>
<tr>
<th></th>
<th>Mean ionic calcium mg/dl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group</td>
<td>I/M group</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.22± 0.658</td>
<td>4.39± 0.466</td>
</tr>
<tr>
<td>At day 3</td>
<td>4.38± 0.345</td>
<td></td>
</tr>
<tr>
<td>At day 7</td>
<td>4.49± 0.28</td>
<td>4.53± 0.274</td>
</tr>
<tr>
<td>At 4 weeks</td>
<td>4.55± 0.34</td>
<td>4.71± 0.183</td>
</tr>
<tr>
<td>At 12 weeks</td>
<td>4.77± 0.13</td>
<td>4.76± 0.139</td>
</tr>
</tbody>
</table>
Mean serum phosphate in each group

<table>
<thead>
<tr>
<th>Time</th>
<th>Oral group</th>
<th>I/M group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.89± 0.97</td>
<td>2.99± 0.944</td>
</tr>
<tr>
<td>At day 7</td>
<td>3.97± 1.07</td>
<td>3.91± 0.989</td>
</tr>
<tr>
<td>At 4 weeks</td>
<td>4.59± 0.942</td>
<td>4.56± 0.946</td>
</tr>
<tr>
<td>At 12 weeks</td>
<td>4.82± 0.759</td>
<td>4.97± 0.746</td>
</tr>
</tbody>
</table>

• P >0.05 on comparing 2 treatment groups at all points of time
• Rise in serum phosphate was significant at day 7 compared to baseline in two groups (p<0.001), and continued thereafter in I/m group, but reached a plateau in oral group at 4 weeks
Methods..

- **Demographic parameters**
  - Age, sex, height, weight

- **Dietary evaluation**
  - 24 hour dietary recall
  - Food frequency questionnaire
  To calculate the daily consumption of calcium
Statistical analysis

- Windows SPSS (version 10)
- *t*-test and ANOVA were used for comparison of parametric & Wilcoxon Rank Sum Test and Kruskal-Wallis test were used for comparison of non-parametric data
- Chi square test was used for comparison of proportion
- Pearson coefficient was used to find the correlation between two variables
Follow-up evaluation

- A total of 56 patients were followed up till 12 weeks
  - 19, 20, and 17 respectively in groups 1, 2 and 3

- Irrespective of the treatment arm
  - All cases showed radiological and biochemical evidence of healing of rickets at 12 weeks
  - However, the improvement was to varying degrees
Health benefits of Vitamin-D Supplementation

- Prevention of Rickets in children, osteomalacia in adults and osteoporosis and fracture risk in old age.

- Enhances immunity and inhibits development of autoimmune disorders like Diabetes Mellitus type I, Inflammatory bowel diseases Rheumatoid arthritis, Pysoriasis and Multiple Sclerosis.

- Decreases the risk of colon, colorectal, breast and prostate cancers.

- Decreases risk of hypertension and Diabetes Mellitus type II.
Vitamin D promotes the production of antimicrobial substances that have the ability to neutralize the activity of influenza virus including swine flu (H1N1).

(Journal of Immunology 2009)

Those who had lowest average levels of vitamin D were about 40% more likely to have recent respiratory infection, including flu, compared to those who had higher levels of vitamin D.

(Archives of Internal Medicine 2009)
Bone health in healthy Indian population aged 50 years and above.

One thousand six hundred healthy subjects aged more than 50 years, residing in Delhi, were evaluated for bone mineral metabolic parameters. High prevalence of osteoporosis (35.1% subjects) was observed in this population. Bone mineral density (BMD) correlated positively with body mass index (BMI) and negatively with PTH levels. No correlation was observed with serum 25(OH)D levels.

Introduction:
To assess the bone health status in elderly Indians and compare peripheral DXA (pDXA) with central DXA in evaluation of osteoporosis.

Methods:
The study involved 1,600 healthy subjects more than 50 years of age residing in Delhi, India, who underwent anthropometric, biochemical, and hormonal evaluation. BMD was measured by DXA at lumbar spine, hip, and distal radius; and by pDXA at forearm and calcaneum.
Incidence of Hip Fractures in India

- Incidence in elderly Indians >55Yrs old
  - Male - 121/100,000
  - Females – 163/100,000
- Similar Incidences were reported from countries like Malaysia, Thailand, Iran, Mexico, China and South Korea (164-273/100,000).
- USA, UK, Norway, Sweden, Japan, Honkong had significantly higher incidence rate (342-922/100,000)
- Dinesh Dhanwal et al Osteoporosis Int. Supplement 2, Dec 2010