Vitamin D Deficiency (VDD): Research Experience in Pakistan

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Outline

- Salient features of Vitamin D Deficiency
- Evolution of research
- Research findings
- Future directions
Causes of vitamin D deficiency

- Primary 25OHD Deficiency:
  - Inadequate sunlight exposure
  - Low dietary intake
- Secondary 25OHD Deficiency
  - Fat malabsorption
  - Liver diseases
  - Kidney disease
- Inherited conditions
  - Type 1: Abnormal or absent 1-hydroxylase enzyme
  - Type II: End-organ resistance
Vitamin D deficiency (25OHD)

- Decreased 1,25(OH)$_2$D
  - Decreased absorption of intestinal calcium
    - Increase Parathyroid Hormone
      - Increase 1-hydroxylase - increase 1,25(OH)$_2$D
      - Increase mobilization of bone calcium
      - Increase excretion of phosphates - hypophosphatemia
  - Increases bioavailability of calcium
Vitamin D deficiency osteomalacia

- Osteomalacia means “soft bones”
- Failure of mineralization of remodeled bone
- Bone pains in arms, legs, spine, and pelvis, with actual tenderness of the bones
- Progressive weakness
- Muscle weakness
- Waddling gait & muscle cramps
- High incidence of fracture than expected for age
Bone & Mineral Research Experience: Background

Year 2002 – 2004
Evolution of Research
Clinical Observation

- Patients at endocrine clinic of AKUH
- Mostly post pubertal females
- Presented with bone pains, muscles aches and proximal myopathy
- Hypophosphatemia
- Most of these were treated with high doses of calcitriol
Review of Literature

1970’s:

- High incidence of VDD in Asians in UK
- Dietary vitamin D deficiency?
  - Various causes were postulated (low exposure, life style)
  - Several questions remain unanswered
Pakistanis’s living elsewhere

- Indian and Pakistani women had lower BMD then their western counterparts
- Lower 25 vitamin D
  - Caucasian
  - Other ethnic groups

Osteoporosis International 1999;9(4):327-38
Local Data

- Maternal D deficiency noted in 48% mothers and 52% infants in Pakistan.

- 35% of women in Pakistan have low D levels

# Clinical Laboratory Data at AKUH (2002 – 2004) N=3099

<table>
<thead>
<tr>
<th>Serum levels of 25 OHD</th>
<th>No of cases N=3099 (%)</th>
<th>Mean levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Deficiency</td>
<td>2107 (72)</td>
<td>8.04</td>
</tr>
<tr>
<td>Vitamin D Insufficiency</td>
<td>572 (18)</td>
<td>27.6</td>
</tr>
<tr>
<td>Optimal</td>
<td>280 (9)</td>
<td>61.0</td>
</tr>
<tr>
<td>Toxic</td>
<td>37 (0.1)</td>
<td>107.9</td>
</tr>
</tbody>
</table>

Note: 618 (20.8) cases had levels below 1.5
Vitamin D deficiency osteomalacia: the continuing challenge

- Immediate action
- Early identification
- Public awareness
- Education of primary care physician
- Nutritional causes and inadequate exposure to sunlight
- Physicians in Pakistan give 1,25 (OH)₂ to patients
- There is likely to be significant under diagnosis of Vitamin D deficiency
Is it Vitamin D deficiency?

- Paucity of data
- Need to exclude Vitamin D deficiency by testing
- Lack of funding/resources
- Management strategies needs to be reviewed
Research Questions

What is the status in:
- out-patient?
- healthy population?
- in our community?
High Prevalence of Vitamin D Deficiency in Out-Patients

- 95% had D deficiency
- A low serum calcium and elevated alkaline phosphatase were reflective of severe deficiency
- Elevated iPTH correlated with mild to moderate deficiency
- Serum calcium, phosphate and alkaline phosphatase are poor markers of moderate to mild deficiency, and cannot be relied upon as a screening tool
- A serum 25 vitamin D level and an iPTH are better biofunctional markers of this deficiency.

Lubna M Z, Aysha HK: Vitamin D Deficiency in Ambulatory Patients: JPMA, 2008
Healthy Volunteers (n=123, 43% females; 57% males)

- Thirty eight participants (30.89%), have raised PTH (mean 107 ±18.04 pg/ml).
- Negative correlation between serum iPTH and Vitamin D levels (P=<0.001, r=0.3).


- Mean age $29.06\pm6.89$ (18 – 48 years)
- Mean BMI $23.12\pm4.58$ (13.84 – 41.2) kg/m²
- 92.8% of the females were identified as D deficient,
- 6.1% had insufficient levels
- 1.1% had optimal levels.
- Secondary hyperparathyroidism was present in 25.9% volunteers
Clinical and subclinical vitamin D deficiency…. It’s the tip of the iceberg

Rickets & Clinical Osteomalacia

Asymptomatic Osteomalacia

- Cancers
- Diabetes
- CVS
- Osteoporosis
- Tuberculosis
Causes of Vitamin D deficiency

• Two main determinants:
  • nutrient intake
  • sunlight exposure

• Issues:
  • Lack of tools for assessment of nutrient intake and sunlight exposure
Development and validation of a food frequency questionnaire for assessing macronutrient and calcium intake in women residing in Karachi, Pakistan

Romaina I, et al
### Mean daily nutrient intakes estimated by the FFQ and 24 h recalls

<table>
<thead>
<tr>
<th>Variables</th>
<th>FFQ</th>
<th>Mean of 4 24h recalls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>1643.5</td>
<td>703.2</td>
</tr>
<tr>
<td>Calcium</td>
<td>610.7</td>
<td>306.4</td>
</tr>
</tbody>
</table>

- All of the correlations between mean of 24 hr recalls estimates and FFQ were significant.
Development and Validation of Sunlight Exposure Measurement Questionnaire (SEM-Q) for use in adult population residing in Pakistan

Quratulain Humayun, Romaina Iqbal et al
25OHD status in premenopausal women from Community in Karachi, Pakistan n=200

<table>
<thead>
<tr>
<th>Biochemical Parameters</th>
<th>Mean ± SD</th>
<th>Saddar</th>
<th>Gulshan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D (ng/ml)</td>
<td>8.5 ± 8.4</td>
<td>6.2 ± 5.4</td>
<td>10.8 ± 10.4</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>92.19 ± 72.53</td>
<td>111.8 ± 90.5</td>
<td>72.5 ± 40</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.98 ± 0.49</td>
<td>9.0 ± 0.5</td>
<td>8.9 ± 0.4</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.05 ± 2.29</td>
<td>4.2 ± 3.2</td>
<td>3.9 ± 0.3</td>
</tr>
</tbody>
</table>

AH. Khan, G. Naureen, F. Dar, R. Iqbal
Prevalence of vitamin D deficiency in Saddar & Gulshan Town in Karachi

n=200

- Deficient < 20 ng/ml: 91%
- Insufficient 20-30 ng/ml: 3%
- Sufficient > 30 ng/ml: 6%

Legend:
- Blue: Deficient < 20 ng/ml
- Red: Insufficient 20-30 ng/ml
- Green: Sufficient > 30 ng/ml
iPTH status of study participants

- Normal 16-87pg/ml: 59%
- High > 87pg/ml: 1%
- Low <16 pg/ml: 40%

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<thead>
<tr>
<th>iPTH Status</th>
<th>Mean Vit. D ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal iPTH</td>
<td>9.5 ± 8.1</td>
</tr>
<tr>
<td>High iPTH</td>
<td>6.2 ± 6.2</td>
</tr>
</tbody>
</table>
Relationship of housing structure with vitamin D and iPTH

<table>
<thead>
<tr>
<th>Apartments</th>
<th>Town House</th>
<th>Small Bungalows</th>
<th>Large Bungalows</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit. D (ng/ml)</td>
<td>7.46</td>
<td>5.5</td>
<td>10.8</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>104.62</td>
<td>102.5</td>
<td>75.55</td>
</tr>
</tbody>
</table>

P-value < 0.001
Nutrient intake of study participants

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Mean/Day ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Energy (kcal)</td>
<td>1870.2 ± 695.7</td>
</tr>
<tr>
<td>Total Fat (g)</td>
<td>55 ± 21g</td>
</tr>
<tr>
<td>Total Protein (g)</td>
<td>58 ± 20g</td>
</tr>
<tr>
<td>Total Calcium (mg)</td>
<td>686.2 ± 271.4</td>
</tr>
</tbody>
</table>
Highlights of the Research

- Vitamin D deficiency with sHPTH is highly prevalent among females
- Important to address life style variables
- Need to explore other factors such as genetics (Wang et al. 2010)
- Measures for improving the status of vitamin D
- Public Awareness
Year 2010 Onwards

Future Directions
Why is D deficiency so extensive?

1. Genetics
2. What is the optimum level for our population?
3. Are we unable to manufacture D efficiently from sunlight?
4. Are we breaking down active D more rapidly?
5. Is it a difference in expression of Vitamin D receptor and its signaling pathways?