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Lubna M Zuberi  
*Aga Khan University*

Aysha Habib  
*Aga Khan University*

Naeemul Haque  
*Aga Khan University*

Abdul Jabbar  
*Aga Khan University*

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### **Vitamin D Deficiency in Ambulatory patients**

Lubna M. Zuberi<sup>1</sup>, Aysha Habib<sup>2</sup>, Naeemul Haque<sup>3</sup>, Abdul Jabbar<sup>4</sup>

Department of Medicine<sup>1,3,4</sup>, Department of Chemical Pathology<sup>2</sup>, Aga Khan University Hospital, Karachi.

#### **Abstract**

**Objective:** To determine the frequency of subclinical vitamin D deficiency in an ambulatory care setting.

**Methods:** This was an observational study which measured 25 vitamin D levels in medical clinic patients. Patients with chronic renal failure, known osteomalacia and rickets were excluded. A total of 119 patients were evaluated. They were divided in three diagnostic categories based on their serum 25 vitamin D levels. Those with levels below 8 ng/ml were categorized to have severe deficiency, levels between 8 - 20 ng/ml as moderate deficiency and levels of 21 - 35 mg/ml as mild deficiency.

**Results:** Of 119 patients, 92% had vitamin D deficiency. Their mean age was  $44.3 \pm 18.3$  years, with female to male ratio of 5:1. Sixty two percent (62%) had severe, 24% moderate and 8% had mild deficiency. Nearly half of all these patients (including those with severe deficiency) were asymptomatic. Whereas a low serum calcium, elevated phosphate and elevated alkaline phosphatase were reflective of severe deficiency. It was only an elevated iPTH that correlated with mild to moderate deficiency.

**Conclusion:** Subclinical vitamin D deficiency is extensive in the adult ambulatory care patients. Serum calcium, phosphate and alkaline phosphatase are poor markers of moderate to mild deficiency. A serum 25 vitamin D level and an iPTH are better biofunctional markers of this deficiency (JPMA 58:482;2008).

#### **Introduction**

The nutritional importance of vitamin D in maintaining bone health is undebatable as is the development of rickets and osteomalacia caused by its deficiency. Over the past decade, the importance of 25-hydroxyvitamin D in maintaining the health and the function of the immune, reproductive, muscular, skeletal, and integumentary system of people of all ages and races have come to the forefront<sup>1</sup>. Evidence supported strong association between vitamin D status and risk of chronic disease that can now be linked to vitamin D intake and reduced sun exposure<sup>2</sup>.

Surprisingly several recent studies have identified a high prevalence of vitamin D deficiency and insufficiency in otherwise healthy adults and children living in North America and Europe. There are reports of extensive vitamin D deficiency in nursing home patients<sup>3</sup>, seasonal variation in vitamin D levels related to sun exposure<sup>4</sup> and the benefits that post menopausal women get from its replacement<sup>5</sup>. Osteomalacia in Pakistani women has been well documented in literature<sup>6,7</sup>, but scant evidence exists regarding prevalence of vitamin D status in asymptomatic patient population.

The aim of this study was to determine the frequency of vitamin D deficiency in an ambulatory care setting in Pakistan.

#### **Methods**

A review of cases presenting to the endocrine and medicine clinics at Aga Khan University Hospital, Karachi

was done. A total of 224 patients referred for measurement of vitamin D levels were enrolled, between May 2002 and December 2004. Patients under the age of 16 years, those with chronic renal failure, primary hyperparathyroidism, those with established diagnosis of rickets and osteomalacia, those taking phenytoin or glucocorticoids were excluded from the final analysis. Majority of these patients were being followed at the endocrine clinic for diabetes, obesity, hypertension or hyperlipidemia. Others were seen in general medicine clinic for various nonspecific symptoms. Recorded variables included biochemical measurements of serum calcium, phosphorus, albumin, alkaline phosphate and intact parathyroid hormone. The measurement of 25 hydroxyvitamin D was performed in the hospital laboratory with a radioimmunoassay kit from DiaSorinR, using I125 for quantitative determination.

For the purpose of this study, patients were divided into three diagnostic categories based on their serum 25 vitamin D levels. Those with levels below 8 ng/ml were categorized to have severe deficiency, levels between 8 - 20 ng/ml as moderate deficiency and levels of 21 - 35 mg/ml as mild deficiency.

The Statistical Package for Social Sciences SPSS (Release 13.5, standard version) was used for data analysis. Descriptive analysis was done for demographic and clinical variables. Results are expressed as mean  $\pm$  standard deviation for quantitative variables and number

(percentage) are reported for qualitative variables. Chi square test or Fisher exact test was used to assess the differences in proportion, p-value less than 0.05 was considered statistically significant.

### Results

A total of 119 patients were selected for final analysis. Their mean age was  $44.3 \pm 18.32$  years, majority were females, in the ratio of 5:1. The most common reason for requesting vitamin D level included generalized myalgias and bone pains (51%). Other reasons included presence of proximal myopathy on physical exam (9%), underlying osteoporosis (9%) or fractures (6%). Symptom complex of chronic fatigue, leg pains and low grade fever were present in some patients. Twenty one percent (21 %) of the group had diabetes and 27% had hypertension. The mean serum albumin was  $3.5 \pm 1.9$  mg/dl, and the mean haemoglobin level was  $11.36 \pm 1.8$  gm/dl.

Ninety five percent of the patients had deficient vitamin D levels. Of the total, 62% had severe, 24% had moderate and 8% had mild deficiency. Table shows the demographic and laboratory characteristics of these three groups. Of all those with low vitamin D levels, more women had severe deficiency (68% in women and 37% in men), whereas moderate to severe deficiency was equally prevalent in both sexes. Surprisingly 40 %

of the patients did not have symptoms suggestive of or attributable to hypovitaminosis D. The three groups were matched in terms of Body Mass Index (BMI). Symptoms of bone pains were not predictive of underlying D deficiency, and did not indicate the severity of this deficiency. As expected those with severe deficiency were more likely to have lower serum calcium ( $P < 0.001$ ), lower serum phosphate ( $P < 0.004$ ) and higher parathyroid hormone levels ( $P < 0.01$ ). Serum alkaline phosphate levels did not show statistical difference between the three groups. Of note is that in those with moderate and mild deficiency serum calcium, phosphate and alkaline phosphate remained normal. The only biochemical abnormality relating to D deficiency in these two groups was an elevated parathyroid hormone level.

Presence of other comorbid conditions such as diabetes, hypertension, coronary artery disease and obesity did not influence severity of D deficiency.

### Discussion

A widespread deficiency of vitamin D levels in ambulatory general medicine clinic patients was observed in this study. What was more of a surprise was their mean age. As a cohort this group was much younger than any previously reported in populations at risk of vitamin D deficiency.

**Table: Demographic, clinical and laboratory features of patients with Vitamin D deficiency.**

Features	Vitamin D Level			P-value
	$\leq 8$ IU (n=74)	9 - 20 IU (n=29)	$\geq 21$ IU (n=15)	
Age (in years)	$41.1 \pm 18.9$	$47.5 \pm 14.1$	$53.3 \pm 20.6$	0.041
Gender				
Male	7 (37%)	7 (37%)	5 (26%)	0.035
Female	67 (68%)	22 (22%)	10 (10%)	
Bone pains				
Yes	39 (65%)	12 (20%)	9 (15%)	0.439
No	35 (60%)	17 (29%)	6 (11%)	
Body mass index (kg/m <sup>2</sup> )	$25.3 \pm 7.8$	$29.0 \pm 6.3$	$27.5 \pm 7.1$	0.079
Serum Calcium	$8.0 \pm 1.5$	$9.1 \pm 0.7$	$9.8 \pm 1.7$	$< 0.001$
Serum Phosphate	$2.9 \pm 1.2$	$3.9 \pm 1.2$	$3.5 \pm 1.2$	0.004
Alkaline Phosphate	$272.2 \pm 338.6$	$122.9 \pm 98.0$	$85.5 \pm 63.7$	0.070
Parathyroid Homon	$317.7 \pm 280.1$	$99.5 \pm 88.4$	$95.9 \pm 151.4$	0.010

Results are presented as mean  $\pm$  standard deviation, and number (percentages).

There are sporadic reports of vitamin D deficiency and subclinical osteomalacia in pregnant and lactating women from Pakistan. The first report of the presence of "occult osteomalacia" was published in *Lancet* in 1976<sup>8</sup>. This showed that 12.6% of healthy and 33% of pregnant women attending a government hospital's out patient clinic had biochemical abnormalities in their serum calcium, phosphorus and alkaline phosphatase levels, which were consistent with osteomalacia. Low vitamin D levels have been reported by M Atiq et al in 48% of healthy Pakistani nursing mothers<sup>8</sup>. Their group also showed that higher prevalence was found in mothers belonging to the upper socioeconomic class. Clearly these reports are in high risk populations, such as nursing mothers and patients belonging to a lower socioeconomic background, unlike our study population.

More recently population based studies from Norway, in immigrant Pakistanis have shown that serious vitamin D deficiency and secondary hyperparathyroidism is four times as prevalent in Pakistani women than Norwegian women. Similarly Pakistani men had five times as much vitamin D deficiency and secondary hyperparathyroidism, as Norwegian men<sup>10</sup>. In another report, in five different immigrant groups living in Oslo, Pakistani women had the highest prevalence of vitamin D deficiency<sup>11</sup>.

The reasons behind such a high prevalence of vitamin D deficiency in our population are unclear, but most likely multiple. It could be ascribed to the lack of fortification of vitamin D in our diets or consumption of low vitamin D containing foods. An alteration in the vitamin D metabolism has been postulated after finding in increased 24 hydroxylase activity in skin fibroblasts of South Asians<sup>12</sup>. Environmental agents such as betel nut chewing has been shown to be an independent determinant of increased 24 hydroxylase expression and of decreased serum calcitriol levels<sup>13</sup>.

A lot has been written in the literature with regards to vitamin D deficiency in the elderly, the institutionalized and the nursing home patients, and recently in hospitalized patients<sup>14,15</sup>. The present study showed the severity of this problem is in the outpatient setting. Though subclinical in nearly half of the patients, levels below 35 ug/dl have clearly been shown to decrease calcium absorption,

stimulate iPTH production and lower bone mineral density<sup>16</sup>. Recent investigations by Heaney et al have shown that iPTH can serve as a functional biomarker of vitamin D deficiency<sup>17</sup>.

Vitamin D deficiency is prevalent in the outpatient clinic setting. In those suspected to have vitamin D deficiency serum 25 hydroxyvitamin D and Parathyroid hormone levels should be requested, as serum calcium, phosphorous and alkaline phosphate levels remain normal in those with mild to moderate deficiency.

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