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Relation of Age, Gender and Bone Mineral Density to Vitamin D Levels in Osteoporosis in the Central Indian Population- A Retrospective Prevalence Study

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Abstract

Background: The function of vitamin D is to maintain serum calcium and phosphate concentrations, which are important for many physiological functions. Osteoporosis or bone loss is a disease characterized by the decrease of bone density and the tendency of bones to fracture easily.

Objectives: To investigate the relation of vitamin D levels to osteoporosis in adults of Central Indian Population.

Methods: This retrospective cross-sectional study comprised of 400 female and 400 male patient aged 20-70 years who were randomly sampled as three age groups as 20-35 years, 36-50 years and 51-70 years. Bone marrow density at the lumbar spine and femoral neck was measured by Bone density scan, serum concentrations of 25(OH)D and parathyroid hormone (PTH) levels were assessed.

Results: The mean age of participants was 47.39 ± 19.32 years. Serum 25(OH)D levels were significantly lower in women than men (25.35 ± 6.59 ng/mL vs 27.25 ± 7.94 ng/mL, $P < 0.05$). The prevalence of 25(OH)D severe deficiency (<10 ng/mL) was 1.6% in men, zero in women; 25(OH)D deficiency (10-20 ng/mL) was 22.9% in women and 20.5% in men; and 25(OH)D insufficiency (20-30 ng/mL) was 73.4% in women and 65.6% in men. An inverse relationship between serum 25(OH)D levels and age was observed in men, but no correlation was found in women. Serum 25(OH)D levels were positively associated with lumbar spine and femoral neck BMD in elderly women and in young men.

Conclusion: A high prevalence of hypovitaminosis D and low BMD were observed in the 50-70 year age group of studied population.

Keywords: Bone mineral density; Bone turnover markers, Osteoporosis, 25(OH)D, parathyroid hormone (PTH).

Introduction

Vitamin D is known for its role in calcium homeostasis for optimal skeletal health. It was previously believed that only elderly or hospitalized patients were at risk for vitamin D insufficiency, but many people in the Indian population have insufficient levels of 25-hydroxyvitamin D (25[OH]D).[1-5]

Vitamin D's classic role is to increase the intestinal efficacy of calcium absorption, but other nonclassic roles for vitamin D have been investigated over the past several decades. The function of vitamin D is to maintain serum calcium and phosphate concentrations, which are important for many physiological functions.10 These include normal mineralization of bone, muscle contraction, nerve conduction and prevention of

hypocalcemic tetany.[6-8] Sniadecki argued that inadequate exposure to sunlight in childhood causes devastating bone deformities known as rickets.8 Exposing children to UVB radiation (290–315 nm) using a mercury arc lamp or sunlight was shown to be an effective treatment for this condition, and even prevented it from occurring.[9,10] Calcium is actively absorbed from the small intestine in the presence of vitamin D. Calcium and phosphorus form hydroxyapatite crystals to mineralize and strengthen bones. Thus, a diet containing both optimal vitamin D and calcium is important for proper mineralization of bone.[11,12] Recent studies have demonstrated that a minimum 25(OH)D level of 32 ng/mL is necessary for optimal protection from fracture and intestinal absorption of calcium. Recently, vitamin D has been recognized as important for extraskeletal functions such as immune function, cancer prevention, and hypertension prevention.[9-12]

Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult.[4,5] Osteoporosis or bone loss is a disease characterized by the decrease of bone density and the tendency of bones to fracture easily. It manifests itself when the ratio of bone synthesis to resorption is shifted towards resorption, when bone formation slows down, for example, and therefore bone destruction becomes more prevalent. Both processes are part of regular bone remodeling, in which old bone tissue is continuously broken down and rebuilt. As a result of this, every seven to ten years the entire skeleton of a person is rebuilt. The hormones estrogen and androgen protect bones from increased mineral loss. With menopause, however, women's estrogen level decreases – making older women especially more prone to osteoporosis, contrary to men of the same age. About 95% of cases are primary osteoporosis. On the other hand, diabetic patients are especially affected by secondary osteoporosis, which occurs as a consequence of other diseases and also patients who have taken medications containing cortisone or those suffering from hyperthyroidism are affected.[12,13] Osteoporosis especially affects the vertebral bodies and the femoral neck because first of all, they are quite fragile and secondly, they have to carry a lot of weight. The other bones of the skeleton are also more prone to fractures. This is typically measured by dual-energy X-ray absorptiometry (DEXA).[13]

Bones that commonly break include the vertebrae in the spine, the bones of the forearm, and the hip.[8] Until a broken bone occurs there are typically no symptoms.[3] Bones may weaken to such a degree that a break may occur with minor stress or spontaneously.[14] Chronic pain and a decreased ability to carry out normal activities may occur following a broken bone.[11,15] Prevention of osteoporosis includes a proper diet during childhood and efforts to avoid medications that increase the rate of bone loss.[12] Efforts to prevent broken bones in those with osteoporosis include a good diet, exercise, and fall prevention.[14,15] Chronic use of medications like Steroid-induced osteoporosis (SIOP) like barbiturates, phenytoin and some other enzyme-inducing antiepileptics, L-Thyroxine, Several drugs induce hypogonadism, for example aromatase inhibitors used in breast cancer, methotrexateand other antimetabolite drugs, depot progesterone and gonadotropin-releasing hormone agonists, Anticoagulants etc induces osteoporosis.[16,18]

Diagnosis

The diagnosis of osteoporosis can be made using conventional radiography and by measuring the bone mineral density (BMD). The most popular method of measuring BMD is dual-energy X-ray absorptiometry. In addition to the detection of abnormal BMD, the diagnosis

of osteoporosis requires investigations into potentially modifiable underlying causes; this may be done with blood tests. [15,16,18]

Conventional radiography: Conventional radiography is useful, both by itself and in conjunction with CT or MRI, for detecting complications of osteopenia (reduced bone mass; pre-osteoporosis). The main radiographic features of generalized osteoporosis are cortical thinning and increased radiolucency. Frequent complications of osteoporosis are vertebral fractures for which spinal radiography can help considerably in diagnosis and follow-up.[15]

Dual-energy X-ray: Dual-energy X-ray absorptiometry (DEXA scan) is considered the gold standard for the diagnosis of osteoporosis. Osteoporosis is diagnosed when the bone mineral density is less than or equal to 2.5 standard deviations below that of a young (30–40-year-old)[16,17] healthy adult women reference population. This is translated as a T-score. But because bone density decreases with age, more people become osteoporotic with increasing age.[18]

Table 1: The World Health Organization has established the following diagnostic guidelines.[5,8]

Category	T-score range	% young women
Normal	T-score ≥ −1.0	85%
Osteopenia	−2.5 < T-score < −1.0	14%
Osteoporosis	T-score ≤ −2.5	0.6%
Severe osteoporosis	T-score ≤ −2.5 with fragility fracture[20]	

Material and Methods

A cross-sectional study was conducted on 400 men and 400 women aged 20–70 years in the Department of Orthopedics, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh, over a period of 2 years from October 2016 to October 2018. An ethical clearance was obtained from the institutional committee prior the study. The hospital is situated in the Central India which was established to provide multispeciality care services. 800 patients were randomly sampled as three age groups as 20-35 years, 36-50 years and 51-70 years.

Case history

Demographic data such as age, gender, Body mass index (BMI), menopausal age, present illness, medication, vitamin and calcium supplements, alcohol, tobacco and smoking habits were obtained through case history.

Biochemical measurement

Urine analysis: Fasting blood samples of urine were drawn in the morning to analyze Serum calcium, creatinine, inorganic phosphorus, total alkaline phosphatase and urinary calcium.

Blood investigation: Serum 25-hydroxyvitamin D [25(OH)D] was measured by radioimmunoassay, Plasma intact para- thyroid hormone (PTH) level.

Radiological investigation

Bone mineral density (BMD): BMD of lumbar spine at L2-4 and femoral neck was measured by dual-energy X-ray absorptiometry (DEXA). Subjects were classified as having osteoporosis if the BMD T-score was -2.5, or as having osteopenia if the BMD T-score was > −2.5 and < −1.0, or as normal BMD if the BMD T-score was ≥ -1.0, according to the World Health Organization (WHO) criteria.[5,8] (Table1)

Statistical analysis: Descriptive results were presented as mean ± SD or median and 95% confidence interval of median. The chi-square test was used to compare proportions between groups. A pairwise correlation was assessed using Pearson correlation coefficient. Stepwise multiple linear regression was applied by fitting BMD on

significant variables (i.e. years since menopause, chronic disease, serum calcium, serum phosphatase and urinary calcium/urinary creatinine) suggested by the univariate analysis.

A p-value less than 0.05, considered as statistically significant. All statistical analyses were performed using the SPSS version 22.0 (INOVA).

Results

400 male and 400 female patients aged between 20-70 years were included in the study. The age and genderwise distribution of three age groups of patients are shown in table 2.

Demographic and Biochemical Variables of the Subjects explained in the table 3. All participants in this study were non-smoking and non-alcohol drinking with the mean age of 41.2 ± 6.0. Among 800 participants, only 76% of subjects were directly exposed to more than 2 hours of sunlight per day. 232 (29%) and 76 (9.7%) of subjects received elemental calcium 240 mg/day and/or alfacalcidol 0.25 mg/day for less than 3 months. Only 52 women (6.5%) received both calcium and vitamin D supplementation. The purpose of these supplements was to prevent osteoporosis. However, serum 25(OH)D level was not different between women who were taking vitamin D supplement and those who were not (68.6 ± 14.6 vs. 64.1 ± 14.9 nmol/l). The frequency distribution of 25(OH)D concentration of the subjects is shown in Table 3. The distribution was approximately normal with a minimum value of 26.8 nmol/l. The prevalence of vitamin D insufficiency was 61.3% (95% CI: 50.6%, 71.2%). Only one fifty-two women (38.7%) had 25(OH)D levels > 70 nmol/l. However, when using the threshold as defined by 25(OH)D levels less than 50 [15] and 75 nmol/L [16], the prevalence of vitamin D insufficiency was 21.5% and 77.4%, respectively.

The mean BMD of lumbar spine and/or femoral neck were categorized in the osteopenia or osteoporosis with a prevalence of 41 (44.1%, 95% CI: 33.8, 54.8%) and 44 (47.3%, 95% CI: 36.9%, 57.9%), respectively (Table 2). The prevalence of osteoporosis or osteopenia at the femoral neck was significantly higher than the prevalence at the lumbar spine (89.2% vs. 73.1%, p= 0.019).

Pearson correlation was applied to explore the correlation between variables and markers. Serum 25(OH)D level did not correlate with age ($r = -0.11$, $p = 0.3$) and none of the other variables. Energy expenditure and serum calcium correlated significantly with both lumbar spine (energy ex- penditure, $r = 0.022$, $p = 0.02$; serum calcium, $r = -0.26$, $p = 0.01$) and femoral neck BMD (energy expenditure, $r = 0.024$, $p = 0.03$; serum calcium, $r = -0.25$, $p = 0.02$), whereas urinary calcium and urinary creatinine ratio correlated significantly with lumbar BMD ($r = -0.017$, $p = 0.008$). In addition, serum calcium correlated with serum PTH levels. Factors that correlated significantly with BMD in the univariate analysis were simultaneously entered in a linear regression model to identify the determinants of BMD by stepwise selection procedure. We found that serum calcium concentration was the major determinant of both lumbar spine and femoral neck BMD, i.e., every 1 unit of calcium increased, lumbar and femoral BMD decreased 0.226 and 0.121 g/cm^2 (Table 3).

Discussion

Researchers have linked vitamin D deficiency to muscle pain and muscle weakness. [16,18] In severe scenarios, researchers have found that muscle atrophy is related to secondary hyperparathyroidism, resulting in hypophosphatemia.[8,9] A recent meta-analysis of elderly people showed that taking supplemental and active forms

of vitamin D daily reduced the incidence of falls by 19% and 23%, respectively.[17] In addition, a number of investigators have shown that the incidence of certain types of cancer was higher among populations in higher latitudes, who experienced reduced sun exposure.[10,18] However, a double-blind, randomized clinical trial evaluating the effectiveness of high doses of vitamin D in improving the lower extremity activities and reducing the risks of falls showed that high doses of up to 60,000 IU neither significantly improved body functions nor reduced the incidence of falls despite adjusting the level of vitamin D in blood levels to 30 ng/mL.[19] Previous studies have shed light on the connection between vitamin D deficiency and cardiovascular diseases.[20–22] In the prospective Intermountain Heart Collaborative Study, which had more than 40,000 participants, the researchers showed that participants with levels of 1,25(OH)2D less than 15 ng/mL were more likely to suffer from hypertension, hyperlipidemia, peripheral vascular disease, coronary artery disease, myocardial infarction, heart failure, and stroke compared with healthy controls.[23] In 2012, a meta-analysis evaluation through two prospective clinical trials revealed that a U-shaped relationship exists between vitamin D deficiency and the occurrence of cardiac problems. This confirms the increased susceptibility of individuals with low levels of vitamin D to the development of cardiovascular disease.[24] There was significant seasonal variation in the vitamin D levels; the lowest levels were measured in winter and the highest in summer which was in accordance with the study conducted by H. P. Bhattoa et al.[27]

Certain studies have revealed an inverse correlation between serum PTH levels and BMD values, particularly at the femoral neck, pointing out the catabolic role of PTH on corti-cal bones.[28,29] These studies have also shown that decreased levels of serum calcium are associated with defects in min-eralization and consequently low BMD.[13] In line with these studies, Hosseinpanah et al. reported a negative correlation between PTH levels and BMD values at femoral neck in the absence of similar correlations between serum 25(OH)D and BMD of other sites.[30] Sadat Ali et al.[31] showed that vitamin D levels significantly influence BMD reading among Saudi indi-viduals, pointing out a significant positive correlation between 25OHD level and BMD and significant negative correlation with parathyroid hormone in the studied groups. The present study, on the contrary, reported PTH to be inversely correlated with BMD values at all sites rather than spine. The correlation, however, was reported to be significant only at the femoral trochanters. The present study was conducted on healthy individ-uals based on their self-reported history; a potential bias of undiagnosed underlying diseases, therefore, is probable. Additionally, the cross-sectional nature of the present study is an important limitation of this study. Moreover, this study only measured five biochemical markers, namely PTH and 25(OH)D, while more recent studies have linked markers such as intact osteocalcin (OC) to BMD values and fracture risk.[32,33] In addition, 25(OH)D measurements were performed in winter, when its levels are believed to be at the lowest level com-pared to other months of the year.

Conclusion

It should be noted that the present study was an observational study in which the effect of important factors such as population differences (gender, age, ethnic, sex, extent of sun exposure, and vitamin D intake) was not assessed. Large prospective studies, therefore, are needed to better evaluate the correlation between biochemical mark-ers and BMD values in different populations.

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Tables

Table 2: age and gender distribution in three groups of patients.

Variables		Male		Female		Total	
	Groups	**No**	**%**	**No**	**%**	**No**	**%**
Age (years)	**20-35**	128	32	104	26	232	29
	36-50	132	33	124	31	256	32
	51-70	140	35	172	43	312	39
	Total	400	100	400	100	800	100

Table 3. Demographic and Biochemical Variables of the Subjects (N =800)

Characteristics	Mean ± SD	Reference range
Age (years)	41.2 ± 6.0	**20-70 years**
Weight (kilograms)	56.5 ± 8.0	
Height (centimeters)	147.7 ± 6.1	
BMI (kg/m^2)	24.1 ± 3.6	
Years since menopause in women (years)	8.9 ± 8.0	
Energy expenditure (kcal/day)	1,590.4 ± 205.4	
Dietary calcium intake (mg/day)	305.8 ± 158.4	
Caloric intake (kcal/day)	901.4 ± 291.2	
Serum calcium (mmol/L)	2.44 ± 0.08	2.2 -2.62
Serum creatinine (µmol/l)	680 (47–150)*	53 - 88
Inorganic phosphorus (mmol/L)	1.27 ± 0.13	0.81 – 1.58
Alkaline phosphatase (U/l)	82.5 ± 24.9	50 - 136
Serum 25(OH)D (nmol/L)	68.6 ± 14.6	> 70
Plasma intact PTH (pmol/L)	4.2 ± 1.5	1.6 – 6.9
Urinary calcium (mmol)	0.48 ± 0.29	0.104 – 1.008

Table 4. Variables and Independent determinant of BMD by sites.

Variables	Lumbar spine at L2-L4 BMD (g/cm^2)			Femoral neck BMD (g/cm^2)		
	Coefficients	SE	P-value	Coefficients	SE	P-value
Intercept	1.076	0.051	<0.001	0.598	0.041	<0.001
Urinary calcium/ creatinine (mmol)	−0.169	0.065	0.011	Exclude	-	-
Year since menopause	Exclude	-	-	−0.003	0.001	0.047
Energy expenditure (kcal/day)	Exclude	-	-	Exclude	-	-