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Testosterone and Vitamin D Deficiency as Risk Factors for Hip Fracture Elderly Male Patients: Time for Vitamin D and Testosterone Replacement

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The results were analyzed using T-test for paired data and Chi-square test for the dichotomous data when applicable. The levels of free and total testosterone (<0.001), LH (<0.001), total protein (<0.001), albumin (<0.001), PTH (<0.001), and free estradilol levels (<0.04) were significantly low in patients with hip fracture compared to controls.

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Conclusions: testosterone and vitamin D deficiency are potentially preventable risk factors in elderly male patients with non-pathological hip fracture. Vitamin D deficiency might also be implicated for the rise in PTH levels, secondary hyperparathyroidism and bone mineral disorders. Hormonal treatment may be potential option to prevent osteoporosis and decrease the risk of hip fracture in elderly male patients.

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I. Introduction

Vitamin D and hormonal deficiency are well recognized disorders in elderly women. However, there has been insufficient awareness in the medical profession or the public arena that these disorders are leading secondary causes for osteoporosis in elderly males. Osteoporotic fractures are public health problems and any measures to curtail their frequency will have a great impact on the health delivery and expenditure. Trauma in the form of falls, reduced bone density and impaired bone quality all contribute to fracture risks. The incidence of hip fracture increases sharply after 75 years of age. It is also greater at higher latitude. There is encouraging data from Canada and elsewhere that the age-standard rate decline in hip fracture in both females and males is occurring (1). However, the one year mortality and the need for institutional care after hip fracture are higher in men than women. On the other hand, men are less likely to be investigated and treated for secondary causes of osteoporosis excluding age (2). How common is osteoporosis in men? Has not unfortunately, been answered clearly and sufficiently as the case in women. Even though, the definition of osteoporosis in men is ambiguous (-2.5 T-score below the normal young males), It is estimated that 3-6% of males >50 years of age are osteoporotic, compared to 22% in women (3).

Between 28-60% of fractures in elderly females >80 yrs are attributed to osteoporosis (3, 4). Bone quantity and quality as well as the extent of trauma are important determinants of hip fracture in this age group (5-7).

Androgen deficiency and advanced age have been associated with increased parathyroid hormone (PTH) level (8,9). Reduced levels of 25-hydroxycholecalciferol [25(OH)D] and 1,25-dihydroxycholecalciferol [1,25(OH)2D] (10-13) may have contributed to the frequent occurrence of hip fracture in elderly male patients.

II. Participants and Methods

This study included 28 elderly male patients with fracture neck of femur who were admitted to the orthopedic ward for surgery. The age range of these patients was 61-89 years, mean age 74.4 years. A 28 age and sex matched elderly male patients (age range 60-85 years, mean age 72.4 years) admitted to the medical ward for various medical problems, including chest pain, gastroenteritis, or upper respiratory tract infection were included. Informed consent was obtained from each participant in the study and the study is

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approved by the local IRB. The 2 groups are well balanced as far as age, weight and height, tobacco and alcohol consumption.

The eligibility criteria are age >60 years, participants should have no previous fracture, no use of steroids or vitamin D supplements. Patients had to be ambulatory and have suffered a fracture neck of femur due to minor trauma (fall). All blood samples were taken from the patients within 24 hours to minimize the effect of trauma on the biochemical parameters.

The exclusion criteria include: i) pathological fracture ii)previous fracture or fractures of femurs secondary to trauma other than falls iii) thyroid diseases iv) alcohol abuse v) use of calcium or vitamin D supplements vi) use of thiazide, bisphosphonate, calcitonin or corticosteroids medications for more than 3 months.

Blood was drawn from each participant including the control group for estimations of parathyroid hormone (PTH), vitamin D levels, CBC, complete metabolic panel, luteinizing hormone (LH), testosterone, and estradiol levels. Bone mineral density scan were done within one week from the patients and controls using dual-energy X-ray absorptiometry (DXA). Area bone mineral density (BMD) was used measured using Lunar DPX-L scanner (Lunar Corp., Madison, WI, USA) according to the manufacture specification.

a) Statistical analysis

All statistical analysis was done using the SAS (Statistical analysis systems Inc. NC, USA). P value of 0.05 or less is taken as significant results. Student T-test is used for continuous data and all p value is reported as two-sided. Dichotomous data are analyzed using the chi-square test whenever applicable.

III. Results

Serum vitamin D levels below the reference range were found in 19/28(68%) of patients with hip fracture compared to 3/28(10.7%) in control subjects. Both 25(OH)D 23/28(82%) Vs 4/28(14.3%) and 1, $25(OH)_2$ D levels were significantly lower in patients compared to controls. This may explain the significant higher levels of PTH and evidence of compensatory secondary hyperparathyroidism in patients compared to control subjects. The PTH levels were higher in patients compared to control 16/28(57.1%) vs 2/28(7.1%).

Total protein and albumin levels were significantly lower in patients compared to control subjects. The trauma incurred during fall with fractures could have been contributing factors to low levels of proteins and albumin in patients compared to control subjects.

Calcium, phosphorus, and creatinine levels are similar in the 2 groups.

No significant difference observed between the 2 groups as far as age, height, tobacco habits, and alcohol consumption. However, the BMI was significantly lower in patients compared to control subjects' table-1.

Serum total and free testosterone levels less than the reference value were found in 24/28(85.7%) and 26/28(92.9%) of patients compared to 5/28(17.9%) and 3/28(10.7%) in controls, respectively. As a results of low androgen levels secondary to primary gonad insufficiency the LH is significantly higher in patients compared to controls.

Bone mineral density were lower in patients compared to controls, denoting evidence of osteoporosis probably secondary to testosterone and vitamin D deficiencies in patients compared to controls table-1.

IV. Discussion

Low vitamin D with secondary hyperparathyroidism (SHPT) and decreased radial bone density in elderly men was illustrated in Baltimore Longitudinal Study of aging and others (14,15). In a study involving 133 community based elderly men the inverse relationship between high level of PTH after adjusting for BMI and low level of BMD of multiple femoral sites have supporting the notion that SHPT may contribute to bone loss in elderly men with increased incidence of hip fracture. The high levels of PTH coupled with low levels of 25(OH)D in patients with hip fracture is in agreement with our study (16-18). Even after adjusting for protein binding, the low level s of 25(OH) D in patient s with hip fracture is well demonstrated. These findings are concurring with our results (18). The levels of 1,25(OH)2D showed no difference between the patients and the controls denoting that the activity of 1 α-hydroxylase enzyme is sensitive to PTH levels even in elderly men (19). The normal levels of 1,25(OH)D in patients with hip fracture may explain the low incidence of osteomalacia in cases of hip fracture (20,21). Moreover, the increased activity of 1α-hydroxylase brings about normalization of 1,25(OH)D at the expense of low levels of 25(OH)D3. This effect is mediated by high levels of PTH.

The androgen deficiencies in hip fracture patients along with high levels of LH are consistent with primary gonadal failure (22). Androgens are indeed essential for the maintenance of bone mass; especially if we believe that hypogonadism in adult men is associated with osteopenia (23-25). There have been reports that treatment with testosterone in hypogonadal adults could result in high BMD with reversal of bone loss (26,27). Androgen and vitamin D deficiencies in elderly men with hip fracture have additive but not synergistic effect.

This study and others have shed light on how common androgen and vitamin D deficiencies in elderly male patients with osteoporotic hip fractures. This study

also showed that (68% and 92.9%) of elderly male patients with hip fracture had vitamin D and testosterone deficiencies, respectively, while 57.1% had increased levels of PTH as a compensatory SHPT from low 25(OH)D levels. These staggering numbers call for further studies to evaluate the importance of vitamin D and testosterone supplementation to prevent osteoporotic hip fractures in this section of population.

The limitation of this study is that markers of bone resorption were not done. The small sample size and effects of other cofounders like trauma on the levels of protein, albumin, and testosterone in these patients could not be entirely dismissed. A cross-sectional study like this can not suggest cause and effect relationships between androgen and vitamin D and bone resorption. Our study also was not design to study the effects of hormone replacement therapy on the quality and quantities of underlying bone fracture.

V. Conclusion

Testosterone and vitamin D deficiency are potentially preventable risk factors in elderly male patients with non-pathological hip fracture. Vitamin D deficiency might also be implicated for the rise in PTH levels, secondary hyperparathyroidism and bone mineral disorders. Hormonal treatment may be potential option to prevent osteoporosis and decrease the risk of hip fracture in elderly male patients.

Table-1 : Clinical and biochemical data for fracture neck of femur patients and controls.

	Controls (n = 28)		Patients (n = 28)		(p value)
	Mean	SD	Mean	SD	
Age (years)	74.4	4.3	72.4	4.7	0.12
BMI (kg/m2)	27.3	2.8	24.9	5.1	0.005
Phosphorus (mg/dl)	3.1	0.6	3.0	0.7	0.87
Calcium (mg/dl)	9.5	0.4	9.3	0.5	0.10
Total Protein (g/dl)	7.3	0.3	6.2	0.2	0.001
Albumin (g/dl)	4.3	0.4	3.5	0.3	0.001
Creatinine (mg/dl)	1.05	0.14	1.08	0.18	0.18
Total 25(OH)D (ng/ml)	18.9	7.3	11.2	8.5	<0.001
Total 1,25(OH)$_2$D pg/ml)	47.9	8.9	35.6	14.9	<0.001
PTH (pg/ml)	15.3	7.2	44.5	26.8	<0.001
LH μIU/ml)	7.0	4.6	13.8	8.7	<0.001
Total testosterone (ng/dl)	435.8	178.4	169.3	81.3	<0.001
Total estradiol (pg/ml)	25.7	6.4	23.2	14.6	0.21
Free testosterone index	8.3	2.8	3.2	1.3	<0.001
Free estradiol index	1.6	0.3	1.2	0.7	0.04
Femoral neck BMD (g/cm2)	0.952	0.128	0.615	0.103	<0.001

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