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Frequency of Osteomalacia in Elderly Patients With Hip Fracture

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Abstract

Background: Osteomalacia represents a risk factor for hip fracture (HF), which is one of the most common and costly injuries in elderly.
Objectives: This study was performed to determine the frequency of histopathologic and laboratory osteomalacia in elderly patients with HF.
Patients and Methods: Totally, 87 patients with HF, admitted to Imam Khomeini hospital, Tehran, Iran, from 2005 to 2006, were studied. Laboratory investigations included serum calcium, phosphorus, alkaline phosphatase (ALP), albumin and 25-hydroxy vitamin D_3 [25 (OH) D_3]. Open biopsy from ipsilateral iliac crest was performed during the same surgery.
Results: The average age was 78.06 ± 8.4 years. Bone biopsy showed osteomalacia in eight patients (9.2%), hypocalcaemia in 42.5%, hypophosphatemia in 17.2%, hypoalbuminemia in 66.6% and 25 (OH) D_3 deficiencies in 66.6%. Concomitant hypophosphatemia and hypovitaminosis [25 (OH) D_3 <10 ng/mL] was detected in 13 patients (14.6%). An increased level of serum ALP was found in 52.8%. Five (38.5%) patients had only laboratory osteomalacia, when histopathological findings were negative.
Conclusions: Elderly patients with femoral neck or intertrochanteric fractures may have osteomalacia, as a treatable cause for osteopenia, and laboratory tests may not be precise criteria for diagnosis in HF patients.

Keywords: Alkaline Phosphatase, Hip Fractures, Hypophosphatemia, Osteomalacia, Osteopenia, Vitamin D

1. Background

Hip fracture (HF) is a common injury in elderly, which affects several aspects of health, such as functional and psychological states. It could lead to long duration of rehabilitation and also impose a remarkable functional burden. Despite the advances in surgical techniques and technology, HF has been one of the financial black holes for the health system of developed and developing countries. In 1995, the incidence of HF in fifteen European countries was 382,000, with estimated expenses of about 9 billion Euros (1). About 250,000 HF occur in the United States annually, number which is estimated to duplicate among older people up to 2050 (2). Annual medical expenses of HF were calculated at about 14 billion dollars. Also, mortality rate, one year after fracture, had ranged between 14% - 36%, when the maximum was during the first 6 months (2). Only 40% and 25% of patients restored prefracture mobility and functional state, one year after fracture, respectively (3). Osteomalacia occurs when there is a defect of mineralization of the organic matrix of the skeleton. The process of mineralization is controlled by vitamin D and, therefore, deficiency of vitamin D or its metabolites leads to accumulation of osteoid in the skeleton, resulting in osteomalacia (4). Osteomalacia has been associated with increased risk of HF (5). When histopathologic examination represents the gold standard for osteomalacia (6), the diagnosis of this risk factor, by laboratory tests, seems challenging. A study performed on Asian immigrants in the United Kingdom showed that titration of serum level of calcium, phosphate and alkaline phosphatase (ALP) only, led to 20% rate of missed diagnosis of osteomalacia (7). To make the problem even more confusing, several other studies proved that the serum level of vitamin D may not be reliable to screen osteomalacia in patients with HF (8). Also, it was reported that the level of 1, 25 (OH) VitD was similarly low, in osteomalacic and nonosteomalacic elderly patients with HF (9). The prevalence of osteomalacia among elderly of different countries was reported at a range of 0% - 24% (6, 10, 11). However, there have been no statistics in Iran about the osteomalacia among elderly affected by HF.

2. Objectives

This study was planned to evaluate the prevalence of

histopathologic and laboratory osteomalacia in HF of elderly patients.

3. Patients and Methods

Between October 2007 and October 2008, all patients older than 45 years with proximal femoral fracture (femoral neck, intertrochanteric fracture), due to low energy trauma, admitted in the orthopedics ward of Imam Khomeini hospital complex of Tehran University of Medical Sciences, Tehran, Iran, were included in this study. Exclusion criteria included high energy trauma (like fall from height and motor vehicle accident), pathologic fracture due to local pathology (tumor) or non-osteoporotic osteopathies, history or laboratory finding of major renal, hepatic or endocrine known diseases, gastrectomy or history of taking diphenylhydantoin. After approval of the study protocol by ethics committee of Tehran University of Medical Sciences, Tehran, Iran, the informed consent was taken from each patient. During the surgery for fracture fixation, open biopsy was performed from ipsilateral iliac crest. The samples were sent for frozen section study. Histopathologic diagnosis of osteomalacia was made on the basis of mineralization level < 60%, osteoid level > 24%, and thickness of osteoid > 24% (12, 13). Also, plasma level of total calcium, ALP, albumin and vitamin D_3 25 (OH) D_3 was measured. Corrected total level of serum calcium was calculated in based on serum albumin, meaning that for each 1 mg/dL of decrease in albumin, 0.8 mg/dL was added to measured total calcium. In this study, a simultaneous phosphate level < 3 mg/dL and 25 (OH) D_3 < 10 ng/mL was considered as laboratory criteria of osteomalacia (14-16). All histopathologic examination of biopsies and laboratory measurements were done in the pathologic laboratory of Imam Khomeini hospital, Tehran, Iran. Collected data were analyzed by SPSS version 19 (SPSS Inc., Chicago, IL, USA). Comparison between variables to find correlations was performed by t-test, χ^2 test and Pearson test. A $P < 0.05$ accounted for significance of comparisons.

4. Results

For 87 proximal femoral fractures in 87 patients, laboratory and histopathologic examination for osteomalacia was performed. The average age of 60 women and 27 men was 78.1 (± 8.4; range: 63 - 94) years. Eighteen (20.7%) and 69 (79.3%) had femoral neck and intertrochanteric fracture, respectively. Histopathologic osteomalacia was detected in eight (9.2%) patients (three men and five women). There was no significant association between age and histopathologic osteomalacia. Table 1 demonstrates the frequency of laboratory data and histopathologic osteomalacia.

The mean of 25 (OH) D_3 was 18.3 ng/mL (± 6.8). Fifty eight patients (66.6%) had hypoalbuminemia (serum albumin < 3 g/dL). Mean of albumin was 3.2 g/dL (± 1.2). Table 2 depicts the frequency of osteomalacia in relation to type of fracture ($P > 0.05$). Five (38.5%) patients had only laboratory osteomalacia, when histopathological findings were negative (accounted as false positive).

Table 1. Absolute and Relative Frequency of Laboratory Markers and Histopathologic Studies Related to Osteomalacia[a]

Parameter	Number of patients
Hypocalcaemia, serum Ca < 9 mg/dL	37 (42.5)
Corrected hypocalcaemia, for 1 mg/dL decrease of albumin, 0.8 mg/dL was added to measured total Ca	25 (28.7)
Serum 25 (OH) D_3 < 10 ng/mL	58 (66.7)
Hypophosphatemia, Serum P < 3 mg/dL	15 (17.2)
Laboratory osteomalaci simultaneous phosphate level of < 3 mg/dL and 25 (OH) D_3 < 10 ng/mL	13 (14.6)
Histopathologic osteomalacia	8 (9.1)
ALP, > 116 IU/L	46 (52.8)
Serum albumin, < 3 g/dL	58 (66.6)
Total	87 (100)

Abbreviations: ALP, alkaline phosphatase; Ca, calcium; P, phosphorus; 25 (OH) D3, vitamin D3.[a]Values are expressed as No. (%).

Table 2. Frequency of Laboratory and Histopathologic Osteomalacia in Femoral Neck and Intertrochanteric Fracture Patients[a]

	Femoral Neck Fracture	Intertrochanteric Fracture	Total (n = 87)	P Value
Histopathologic osteomalacia	2 (11.1)	6 (10)	8 (9.2)	> 0.05
Laboratory osteomalacia	2 (11.1)	11 (15.9)	13 (14.9)	> 0.05

[a]Values are expressed as No. (%).

5. Discussion

Osteomalacia is defined as deficit of mineralization of osteoid (bone matrix). The main etiologies of this disorder are deficiency of vitamin D because of inadequate sunlight exposure, reduced dietary intake of vitamin D, reduced absorption of vitamin D due to gastrointestinal disorders, renal insufficiency of 1, 25 (OH) 2 D_3 hydroxylase and target cell resistance (17). Other possible etiologies include renal tubular acidosis, hypophosphatemia (nutritional or renal) and toxins or drugs induced osteomalacia (18). Different reports about prevalence of osteomalacia in different populations exist (6, 19, 20). In this study, the frequency of histopathologic osteomalacia (as a gold standard diagnostic tool) in patients with HF was 9.2%. Tucker et al. (13) assessed this frequency among 26 Indian patients with HF (mean age: 47 years) and the rate was 65%. The obvious discrepancy of the results of this study with other similar reports could be explained by the higher rate of malnutrition, as a consequence of the high frequency of vegetarian individuals in India (13). Riaz et al. (12) reported abnormal biopsy of osteomalacia in 7.7% and abnormal levels of all serum calcium, phosphate and ALP in about 25% of patients a cohort 168 Pakistani patients with HF (mean age 61 years). In our study, there was no significant association between age and histopathologic osteomalacia. However, Hordon and Peacock (21) demonstrated an increased frequency of osteomalacia with increasing age, in patients with hip fracture. Vitamin D was lower than normal in 66.6% of patients in this study. Diamond et al. (22) reported subclinical reduction of 25 (OH) D_3 in 63% of HF patients and 25% of subjects in the control group. Laboratory osteomalacia (concomitant reduction 25 (OH) D_3 and reduced phosphate) was found in 14.2% of HF patients in this study, while histopathologic osteomalacia was detected in only 9.2% of cases. Although it seems logiacal that histopathological osteomalacia is more common that laboratory type, our resuults demonstrate a lower rate of histopatholoc detection. The reason could be the inadequacy of laboratory criteria for diagnosis of laboratory osteomalacia in this study. Both laboratory and histopathologic diagnosis showed no significant difference in femoral neck and intertrochanteric fractures, in this study. Although this finding may change with a higher number of patients, it could also show that osteomalacia is a risk factor for HF, of any type. The diagnosis of osteomalacia may be missed clinically, radiologically or even on the basis of laboratory data. Clinical presentation is usually nonspecific (23, 24). Radiologic evaluation is also nonspecific and may reveal the disease by psedofractures in late stages. Although laboratory data, helpful for diagnosis of osteomalacia include serum level of calcium, phosphate, ALP, parathyroid hormone and 25 (OH) D_3, these levels are dependent on the stages of disease(7, 17) In our study, the rates of abnormal serum calcium, corrected calcium, phosphate and ALP were 42.5%, 28.7%, 17.2% and 52.8%. Tucker et al. (13) reported hypocalcaemia, hypophosphatemia and increased ALP in 23.5%, 29.4% and 41.7% of HF patients. Results of Riaz et al. (12) were 39.5%, 19.9% and 14.2% for these levels. The results of our study is similar to these two reports. In our study, the rate of hypocalcaemia decreased from 42.5% to 28.8%, when it was corrected by reduced albumin (0.8 mg/dL was added to measured total calcium, for 1 mg/dL of decrease of albumin). The rate of hypocalcaemia in 58 proximal fractures was 70% in the research of Hoikka et al. (25) Harma et al. (26) demonstrated a rate of hypocalcaemia of 88.8% in 30 women with proximal HF that reduced to 7.7%, when corrected by level of albumin. It is important to know that a de novo HF could change the metabolites of the body, such as serum levels of calcium, phosphate, albumin, parathyroid hormone and ALP. Therefore, the diagnosis of osteomalacia in patients with a fractured hip may be different, on the basis of the serum levels of these serum markers. Peacey (7), in a retrospective study, evaluated a cohort of 84 diagnosed osteomalacia (without fracture) patients, based on the criteria of serum 25 (OH) D_3 level < 10 μg/L and serum parathyroid hormone level < 54 ng/L. They found normal level of serum calcium, phosphate and ALP in 66%, 81% and 29% of patients, respectively. Only 6% of patients had abnormal levels on all three measurements and these values were normal in 20% of cases. These findings are comparable to our result. However, other studies are necessary to compare these laboratory data in osteomalacic patients, with and without HF. In our study, the rate of hypoalbuminemia was 66.6% (3.2 ± 1.2). Thiebaud et al. (27), in their 180 patients with HF, found that serum albumin was lower by 10% and 28% in the control admitted group and healthy individuals, respectively. They concluded that hypoalbuminemia is the most important risk factor associated with HF. Significant prevalence of osteomalacia in our region may mandate a new point of view about the role of this problem, to prevent related HF (28). This study demonstrates the insufficiency of laboratory criteria of low 25 (OH) D_3 and hypophosphatemia for the diagnosis of subclinical osteomalacia. Other studies impose to assess the best laboratory tests to diagnose osteomalacia in HF.

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