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Bone Fragility Fractures in Hemodialysis Patients: Croatian Surveys

Iva Šimunović[1], Draško Pavlović[1], Boris Kudumija[2], Dubravka Mihaljević[3], Vesna Lovčić[4] and Marko Jakić[3]

[1] University of Zagreb, University Hospital Center »Sestre Milosrdnice«, Zagreb, Croatia
[2] Dialysis Center Avitum, Zagreb, Croatia
[3] »J. J. Strossmayer« University, University Hospital Center Osijek, Osijek, Croatia
[4] General Hospital Bjelovar, Bjelovar, Croatia

ABSTRACT

Disturbances of bone mineral metabolism are common complications of chronic kidney disease with bone fractures as one of the most important consequences. The aim of this study was to estimate prevalence of bone fractures among Croatian hemodialysis patients and to determine the possible fracture risk. The study was carried out in 767 hemodialysis patients from nine Croatian hemodialysis centers. Demographic, laboratory and bone fracture data were collected from medical records as well as therapy with vitamin D analogs. Fragility fractures were defined according to the World Health Organization definition. In 31 patient a total of 36 fractures were recorded. The prevalence of patients with bone fractures was 4.0%. The mean age of patients with fractures was 68.6 years. There were 9 male and 22 female patients with fractures. The mean hemodialysis duration was 63.3 months. Among all fractures the most common were hip fractures (39%) followed by forearm fractures (22%). This is the first study regarding epidemiology of bone fractures in Croatian hemodialysis patients. The prevalence of patients with bone fractures in our group of hemodialysis patients is high. Fractures were more frequent among women and older patients, patients who have been longer on dialysis and in patients with higher concentration of PTH.

Key words: *hemodialysis, secondary hyperparathyroidism, fragility fractures, epidemiology, Croatia*

Introduction

More than 60 years ago the term »renal osteodystrophy« was used to describe bone disease associated with chronic renal failure[1,2]. Since then, prevention and treatment of bone disease in chronic kidney disease (CKD) is a great challenge for many nephrologists[3]. At the same time due to broad basic and clinical research it was recognized that bone disease is only one consequence of disturbed mineral metabolism. In 2006, a new definition was established »Chronic Kidney Disease – Mineral and Bone Disorder« (CKD-MBD). It describes a very broad clinical syndrome, i.e. a systemic disorder of mineral and bone metabolism due to chronic kidney disease manifested by abnormalities of calcium, phosphorous, PTH and vitamin D; abnormalities in bone turnover, mineralization, volume, strength or linear growth and soft tissue and vascular calcification[4,5]. Renal osteodystrophy, as a part of CKD-MBD, is a multifactorial disorder of bone metabolism. One of the most important clinical consequences of renal osteodystrophy is bone fracture[6]. Several studies have shown that there is an increased risk, incidence and prevalence of bone fractures, particularly hip fractures among hemodialysis patients[7–10].

It is well known that age is one of greatest risks of fragility bone fractures in general population[11]. The worldwide population is aging and dialysis patients are also increasingly older[12]. In the general population osteoporosis, a common disorder of aging is the main cause of fragility bone fractures[13]. Renal osteodystrophy and superimposed age-related bone changes, i.e. osteoporosis, put CKD patients in a very high risk group.

Interestingly, only in the last 10 years has the nephrology community had sufficient data on risk factors for bone fractures in hemodialysis patients. During the last 10 years, there were several studies, particularly in the United States regarding incidence, prevalence and risk factors of bone fractures among hemodialysis patients[7–10,14]. The primary objective of this multicentric cross-sectional

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study was to investigate the prevalence of patients with skeletal fractures among Croatian hemodialysis patients and to investigate the biochemical markers related to bone fractures and try to determine the possible fracture risk among hemodialysis patients.

Subjects and Methods

The study was carried out in prevalent hemodialysis patients from nine Croatian hemodialysis centres from September 2009 to January 2010. The data about bone fragility fractures was collected from the medical records or by patient interviews by facility physicians. The fractures occurred after the onset of hemodialysis were taken into consideration. Low-trauma, i.e. fragility fractures were defined according to the World Health Organization definition: fractures that were caused by minor trauma or by fall from a maximum height equal to or below the upright position of the patient. Demographic parameters which included gender, age, presence of diabetes mellitus and date of hemodialysis onset were collected from medical records. Laboratory data included serum levels of PTH (pg/ml, normal range 6–64 pg/ml), calcium (mmol/L), phosphate (mmol/L) as well as alkaline phosphathase (U/L) taken from a patient not more than two months before the occurrence of the bone fracture were also collected as well as bone fracture data: the date of occurrence of the fracture and the location of fracture (hip, forearm, upper arm, rib, vertebrae, lower leg, femur or hand). Data about therapy with vitamin D (calcitriol per os) or analogs of vitamin D (paricalcitol i.v.) was also collected. All patients were on hemodialysis four hours three times per week. Standard dialyzate calcium concentration in Croatian dialysis centres is 1.5 mmol/l. Aluminium hydroxide has not been used as phosphate binder in Croatia for more than 20 years. Calcium carbonate or sevelamer hydrochloride is used as phosphate a binder (Table 1).

All data management and analyses were conducted using Microsoft Excel. Results are given as the means and standard deviations (SD) or percentages. Results are considered to be significant at the 5% critical level ($p<0.05$). The prevalence of patients with fractures is calculated as the percentage of patients with fractures of a total number of hemodialysis patients. We used bivariate analyses (t-test, Fisher's test) to examine differences between PTH values among forearm and hip fractures, fractures of the predominantly spongious bones (fractures of vertebra and hip) and predominantly compact bones (fractures of ribs, upper arm, forearm, femur and lower leg). We defined PTH values <180 pg/ml as relative hypoparathyroidism, and PTH values >300 pg/ml as secondary hyperparathyroidism.

TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS WITH BONE FRACTURES

Age (years)	68.6±10.8
Gender (female/male)	2/9
HD vintage (months)	63.3±54.8
Diabetes mellitus (%)	19
Vitamin D therapy (%)	52
Sevelamer hydrochloride (%)	29
Ca (mmol/L)	2.25±0.23
P (mmol/L)	1.57±0.55
Ca x P ($mmol^2/L^2$)	3.13±3.28
PTH (pg/ml)	376.97±446.07
tAP (U/L)	172.89±170.91

Data are $\overline{X}$±SD or number (%)

Results

767 hemodialysis patients were included in this study. In 31 patients a total of 36 fractures were recorded. 26 patients suffered one and five patients suffered two fractures. The prevalence of patients with bone fractures was 4.0%. The mean age of patients with fractures was 68.6±9.1 years (range 46–87). In patients less than 40 years of age no bone fractures were observed. 8 bone fractures (22%) were recorded in patients aged between 41 and 60 as well as 28 bone fractures (78%) in patients older than 60 years. (Figure 1) There were 9 (29%) male and 22 (71%) female patients. Only 6 (19%) patients were diabetics. The mean hemodialysis duration was 63.3±37.2 months (range 0–265). Fractures were more often observed in patients on hemodialysis for more than five years, i.e. 50% of all bone fractures were observed in patients on hemodialysis for more than 60 months (Figure 2). Among all fractures there were 14 hip fractures (39%), eight forearm fractures (22%), five upper arm fractures (14%), four femur fractures (11%), two lower leg fractures

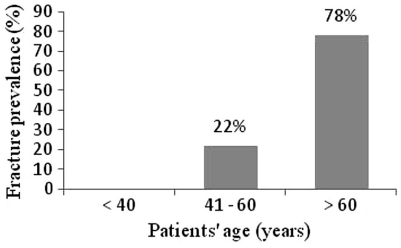

Fig. 1. Prevalence of fractures depending on age of hemodialysis patients.

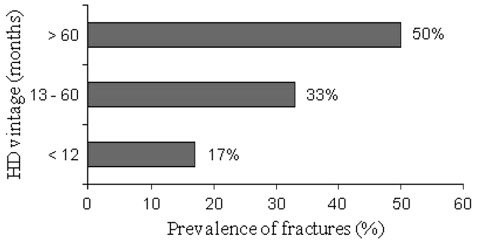

Fig. 2. Prevalence of fractures depending on HD vintage.

(5%) and one rib, vertebrae and hand fracture each (3%) (Figure 3). Ten bone fractures (28%) were associated with PTH levels <180 pg/ml and 12 bone fractures (33%) with PTH between 181 and 300 pg/ml; 14 (39%) with PTH > 300 pg/ml (Figure 4). Patients with hip fractures had the highest level of PTH – 541.4 (range 23–1790) pg/ml. The lowest PTH was in patients with forearm fractures 198.5 (range 57.3–310.9) pg/ml. The mean level of PTH among fractures of predominantly spongious bones, e.g. ribs, vertebre was 517.7 (range 23–2017) pg/ml and among fractures of predominantly compact bones (forearm and hip) 276.4 (range 30.4–726.1) pg/ml. The differences were not statistically significant due to very low PTH levels in two patients with hip fractures. Sixteen patients (52%) with bone fractures were on therapy with calcitriol or paricalcitrol at the time of the fractures.

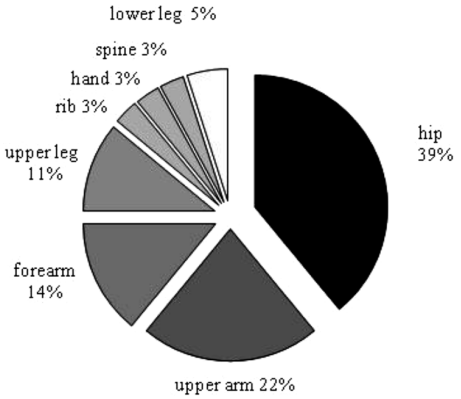

Fig. 3. Localization of bone fractures among hemodialysis patients.

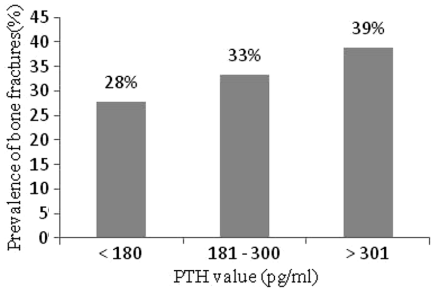

Fig. 4. Prevalence of bone fractures depending on PTH values.

Discussion

There is no doubt that incidence and prevalence of fragility bone fractures in hemodialysis patients is high and much higher than in general population[7,9].

This is first study regarding epidemiology of bone fractures in Croatian hemodialysis patients. Croatia, a small country with slightly less than 4.5 million inhabitants[15] has a relatively high incidence and prevalence of patients on renal replacement therapy. In 2008, there were 2743 patients on hemodialysis (prevalence 618 pmp) and 244 on peritoneal dialysis (prevalence 55 pmp). The median age of patients starting hemodialysis in 2008 was 67 years[16]. There were 767 patients from 9 dialysis centres in our study group – approximately 28% of hemodialysis patients in Croatia. We think that the number of patients is representative enough to estimate the prevalence of fragility bone fractures in Croatian hemodialysis patients. The prevalence is large, i.e. 4.0%. Since the total number of patients and fractures was nevertheless small, we did not particularly examine the prevalence of individual fractures. However, the most frequent type of fracture was a fracture of the hip, followed, interestingly, by fractures of the upper extremities. The average age of patients with bone fractures (68.6 years) is somewhat greater than the median of patients who started dialysis in 2008, 67 years[16]. As was expected, fractures were more frequent among women and among older patients. Patients who have been longer on dialysis and, in our investigation, patients with a higher concentration of PTH (secondary hyperparathyroidism) are especially threatened.

Low levels of PTH (relative hypoparathyroidism) are in CKD patients connected with low bone turnover i.e., adynamic bone disease and PTH level >300 pg/ml with high turnover. Although it is known that PTH acts more on a compact bone[17,18], we did not prove that the fracture incidence of compact bone is higher in patients with secondary hyperparathyroidism. The cause might be the relatively small number of patients and sometimes, as in our group, two patients with very low values of PTH (i.e. suspected low bone turnover) who had fractures of the forearm.

Unfortunately, there is no accurate data on the incidence and prevalence of bones fractures among the general population in Croatia. Some studies estimate that the incidence of fractures in persons older than 60 years to be <0.1%, which matches the incidence in the developed European countries[19,20]. Therefore, the incidence and prevalence of fractures in Croatian dialysis patients is significantly greater than in the general population. Age, gender, duration of hemodialysis, and an increased concentration of PTH are linked to a higher risk of bone fracture in our patients than the prevalence of bone fractures in the general population.

Our results match the results of other studies until now[7,8,9]. In the majority of studies age, gender, and duration of dialysis are linked to the risk of bone fracture. Although in some studies hyperparathyroidism has been associated with lower bone mass density at all sites[21,22], in other studies both hypo- and hyperparathyroidism were linked to fractures[14,22,23] and in our patients hyperparathyroidism still holds a greater risk for the appearance of fractures.

Our work has several shortcomings. It was an observational study and we obtained data on fractures on the basis of medical history or from medical documentation. In our study we did not examine other factors that are linked to an increased risk of bones fractures among dialysis patients, such as treatments with anti-depressives, low levels of albumin, low levels of vitamin D or meta-

static calcification. Nevertheless, we think that this type of work will be able to contribute to the recognition of the significance of bone fractures in dialysis patients. Our next step, which is in the preparatory phase, is to include a larger number of centers and patients, to carry out a preliminary investigation during at least the next two years and to examine all of the known risk factors: PTH level, Albumin concentration, 25 OHD level, drug treatment etc.

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D. Pavlović

University of Zagreb, University Hospital Center »Sestre Milosrdnice«, Vinogradska 29, 10000 Zagreb, Croatia
e-mail: drasko.pavlovic@kbcsm.hr

UČESTALOST PRIJELOMA KOSTIJU U BOLESNIKA NA HEMODIJALIZI: HRVATSKI REZULTATI

SAŽETAK

Poremećaj mineralnog metabolizma kostiju česta je komplikacija kroničnog bubrežnog zatajenja s povećanim rizikom prijeloma kostiju. Cilj ovog istraživanja je određivanje učestalosti bolesnika s prijelomima kostiju među hrvatskim bolesnicima na hemodijalizi te ispitivanje čimbenika rizika za nastanak prijeloma. Istraživanje je provedno među 797 bolesnika na hemodijalizi u 9 hrvatskih centara za dijalizu. Pregledom medicinske dokumentacije zabilježeni su kliničkom obradom dokazani prijelomi kostiju, demografski podatci, laboratorijski podatci te podatci o terapiji analozima vitamina D. U tridesetjednog bolesnika zabilježeno je tridesetšest prijeloma. Učestalost bolesnika s prijelomima kostiju je 4,0%. Srednja dob bolesnika s prijelomima je 68,6 godina. Prijelomi su zabilježeni u devet muškaraca i dvadesetdvije žene. Srednje trajanje dijalize je 63,3 mjeseca. Najčešće zabilježeni prijelomi su prijelomi kuka (39%) i podlaktice (22%). 16 bolesnika s prijelomima je bilo na terapiji kalcitriolom ili parikalcitriolom u vrijeme nastanka prijeloma. Ovo je prvo istraživanje o prijelomima kod hrvatskih bolesnika na hemodijalizi. Učestalost bolesnika s prijelomima je visoka, prijelomi su učestaliji kod starijih bolesnika, žena, bolesnika koji su duže na dijalizi i bolesnika povišenim vrijednostima PTH.