

## NON-HIP PERIPHERAL OSTEOPOROTIC FRACTURES: EPIDEMIOLOGY AND SIGNIFICANCE

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Fractures are the most serious consequence of osteoporosis. Non-vertebral and non-hip fractures are seldom recognised as important, even though they account for the majority of all fractures. The most prevalent localisations are distal radius, proximal humerus, ribs, clavicle, and the pelvis. According to the results from large phase III clinical trials for placebo groups, their incidence ranges from 4.9 % to 12.0 %. Hospital morbidity data in Croatia in 2006 show that peripheral non-hip fractures ranked among the leading fifteen injuries, accounting for 23.7 % of all injuries in patients aged 60 years and above. Risk factors for non-hip and non-vertebral fractures are similar to other osteoporotic fractures, and the main are low bone mineral density and earlier fractures. Quality of life is considerably affected by these fractures, and medical costs are very high, soaring as high as 36.9 % of all national medical costs in the USA. Non-vertebral non-hip fractures need more attention, which was also recognised by the European regulatory bodies that approve use of anti-osteoporotic drugs.

**KEY WORDS:** *bone mineral density, medical costs, non-vertebral fractures, osteoporosis, quality of life*

Osteoporosis is a metabolic bone disease and one of the most serious public health problems. It is estimated that around 43 million women in Europe have osteoporosis and that in the year 2000, women aged over 50 years had 2.8 million fractures (1). The lifetime risk for any osteoporotic fracture in 50-year-old women is 46 % in Sweden and 53 % in Great Britain (2).

Main attention in osteoporosis is focused on the spine and hip fractures. However, there are insufficient data on the epidemiology and consequences of other osteoporotic fractures.

For 45-year-old people the lifetime risks of shoulder and forearm fractures are 13.3 % and 21.5 % in women and 4.4 % and 5.2 % in men, respectively (3). Ten-year and 15-year risks for all fractures increase until the age of 80. After that, due to the competitive risk of fracture and death, they approach the lifetime risk of fracture. Peripheral non-hip fractures account

for 90 % of all fractures until the age of 80 and for 59 % after that age (4).

Data from placebo groups included in large phase III clinical trials are very useful in analysing the incidence of peripheral fractures. The incidences range between 4.9 % and 12 %, and more often refer to all peripheral fractures, rather than for specific sites (5-8).

In a large population-based three-year study in England, the annual fracture incidence was 19 per 100,000 people for metacarpal bones and 243 per 100,000 for distal forearm, with significant differences in men-to-women ratios between metacarpal bones (0.16) and distal radius (1.33) (Table 1) (9). Until the age of 55 years, fractures were more often in men and after that age in women (9).

Similar data were found in a ten-year trial in England and Wales (10). The most frequent fracture sites were distal radius in women (30.2 per 10,000

**Table 1** Annual incidence of non-hip peripheral fractures (adapted from reference 9)\*

Fracture site	Incidence per 100,000		
	Men (M)	Women (W)	Ratio W/M
Distal radius and ulna	182	243	1.33
Ankle	87	65	0.75
Humerus	58	76	1.31
Clavicle	67	32	0.47
Metacarpal bones	117	19	0.16
Tarsal and metatarsal bones	73	52	0.71

\*Leicestershire (UK) – N=23,276 (12,771 men and 10,566 women); fractures in 3 years.

a year) and carpal bones in men (26.2 per 10,000 a year). Fractures of carpal bones, feet, tibia and fibula are more frequent in childhood and in young people, while fractures of the spine, distal radius, hip, proximal humerus, ribs, clavicle and pelvis are more frequent in the older age, although the clavicle has two incidence peaks (11).

There are significant demographic differences in the incidence of fractures in general, as well as of the fracture of distal radius, which is a typical peripheral fracture. The range of incidences is wide and reflects racial differences. For example, in Nigeria, the incidence of fractures is 3 per 100,000 women and 4 per 100,000 men, while the incidence in Norway is 767 per 100,000 women and 202 per 100,000 men (11). Similar to spine and hip fractures, an increase in the incidence of osteoporotic fractures of other sites has been noticed over the past decades, which has been evidenced for proximal humerus fractures (12, 13).

Data from epidemiological studies for non-hip non-vertebral osteoporotic fractures in Croatia are lacking. The Croatian Health Service Yearbook is an up-to date source where data are gathered from hospital discharge documentation. Among fifteen leading injuries in hospitalised patients aged 60 years and above in 2006, fractures of the lower leg, including the ankle, accounted for 11.5 %, and together with other peripheral non-hip fractures for 23.7 % of all injuries (14).

#### Risk factors

It seems that non-hip peripheral fractures are related to low bone mineral density (BMD) and to other standard risk factors, especially to age. A study of Becker et al. (15) showed a significant heterogeneity in risk factors for falls and osteoporosis in old people hospitalised due to osteoporotic fractures. Those

differences included sex, ethnicity and the type of fracture, but not BMD, which was low in all patients, save for the total hip region. Ten-year probability of osteoporotic fractures increases with age and lower T-score, with the exception of fractures of distal radius in men (16). BMD value better predicts the incidence of proximal femur fracture than of peripheral and spinal fracture (17). Other studies showed several independent risk factors for different fractures: low hip BMD in both sexes and low body weight in women for humerus fracture; low hip BMD, low body height, and history of falls in women (and low calcium intake in men for radius fracture (18). The Epidemiology of Osteoporosis Study (EPIDOS), which included 7,598 French women aged over 74 years, showed the importance of low BMD and falls for proximal humerus fractures in women (19). However, the National Study for Osteoporosis Risk Assessment (NORA), which was based on a cohort of approximately 150,000 postmenopausal Caucasian women in the USA, found that as many as 82 % of women with peripheral fracture had T-score better than -2.5 (20). The same study showed for the first time, that fracture risk in younger postmenopausal women (aged 50 to 64 years) with low BMD was similar to the risk in women aged 65 or over. In a prospective, population-based, cohort Rotterdam Study, which investigated factors that determine the occurrence of many chronic diseases in elderly people, only 44 % of all non-vertebral fractures in women and 21 % of all non-vertebral fractures in men occurred at T-scores lower than -2.5 (21). Gallagher et al. noticed that vitamin D deficiency in older people with osteoporotic fractures had greater influence on hip fracture than on other fractures (22).

Studies in peri- and postmenopausal women showed that the risk of new fracture was twice as great in women with previous fracture as in women who had

no fracture (23). The results of Multiple Outcomes of Raloxifene Evaluation (MORE) study in placebo controls showed that severity was a better predictor of new non-vertebral fractures than the number of previous fractures (24). Previous fractures of distal forearm can also be a predictor of new osteoporotic fractures. Overall ten-year cumulative incidence for any fracture was 55 %: for the hip fracture if the distal forearm fracture has occurred after 70 years of life, and for the spinal fracture independently of the age of occurrence (25). This was confirmed in by recently published data from the NORA study. Prior wrist fracture was a good predictor of the three-year risk of any future osteoporotic fracture in older and younger postmenopausal women, independent of the baseline BMD and common osteoporosis risk factors (26). Rib fractures can also predict future, mainly humerus and hip fractures in women (27).

For non-hip and non-vertebral fractures in Croatia the only relevant study is the one by Matković et al., who evaluated bone status and fracture rates in two populations with very different dietary habits. Although there was a higher rate of proximal femur fracture in the district with lower calcium intake, no difference was found for the forearm fracture rates between the two regions (28).

#### *Mortality, health-related quality of life, and economic burden*

Johnell et al. (29) explored epidemiological characteristics of mortality after fractures. In a sample of nearly 3,000 inhabitants of Malmö (Sweden), they found the highest mortality in the first year after fracture, and it was greater in men than in women. The one-year survival after fracture was higher for forearm and shoulder fractures (94 % and 87 %, respectively) than for spine and hip fractures (72 % and 78 %, respectively). Similar was found five years later, when the survival rate for forearm fracture was 74 %, for shoulder fracture 64 %, for hip fracture 41 %, and for spine fracture 28 %. A significant increase in mortality risk after clinical osteoporotic fractures was found in the Fracture Intervention Trial (FIT) study, a randomized, placebo-controlled trial designed to test the hypothesis that alendronate reduced the rate of fractures in 6,457 women aged 55 to 80 years with low hip BMD (30). The overall age-adjusted relative risk of death following a clinical fracture was 2.15 (95 % CI = 1.36 to 3.42). The greatest risk was shown for spine fracture (8.64 times) and hip fracture (6.68 times), while it did not increase for forearm fracture. Results

were similar after adjusting for assigned treatment, health status and specific common co-morbidities.

Osteoporotic fractures are associated with increased direct and indirect costs. According to the US data, the highest costs in the first year are associated with the fracture of distal and proximal femur (median US\$ 11,756 and 11,241, respectively), and then with the lower leg fracture (US\$ 2,967), while the lowest costs are associated with rib fracture (US\$ 213) (31). Although there is a linear relationship between cost and post-fracture disability, relative costs associated with humerus fracture are somewhat higher (US\$ 2.317) than the relative disability cost that ensued. According to the National Committee of Health, costs associated with non-vertebral fractures in Sweden range between Euro 1,955 for hand fractures and Euro 3,745 for leg fractures, ankle included (32). The number of visits and time in the hospital also depend on the site of fracture. The average number of hospital admissions is lower for distal forearm fractures than for spine, shoulder and especially for hip fractures (33). Patients with hip and shoulder fractures most often visit the physiotherapist, and patients with spine and forearm fractures most often visit the hospital and family physicians. In the United States, medical costs of non-hip fractures are huge, accounting for no less than 36.9 % of all national medical costs (34).

#### *Regulatory changes in Europe*

The importance of non-hip peripheral fractures has been acknowledged through amendments to the "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis" (35). Until recently, the EU Guideline was focused on hip fractures, among non-vertebral fractures. Now, to confirm drug anti-fracture efficacy, it is necessary to study parameters for both vertebral (clinical and morphometric) and all non-vertebral fractures, including the hip (35).

To conclude, peripheral non-hip fractures are frequent and easy to diagnose. They are neglected and less studied than fractures at other sites. Although no increased mortality risk is associated with peripheral fractures except for the hip and radiocarpal joint, they considerably affect the quality of life and burden economy. Fractures caused by low-energy trauma, save for the fractures of the skull, cervical spine, arm and foot fingers, require further testing for osteoporosis, especially in people older than 50 years.

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**Sažetak**

## PERIFERNE OSTEOPOROTSKE FRAKTURE OSIM KUKA - EPIDEMIOLOGIJA I ZNAČENJE

Prijelomi su najozbiljnija posljedica osteoporoze. Iako čine većinu svih fraktura, nevertebralne frakture osim kuka rijetko se prepoznaju kao značajne. Najčešće lokalizacije tih prijeloma su: distalni dio radijusa, proksimalni dio humerusa, rebra, klavikula i zdjelica. Prema rezultatima iz placebo-grupa III. faze velikih kliničkih ispitivanja raspon njihove incidencije iznosi između 4,9 % i 12,0 %. Prema podacima bolničkog pobolijevanja za 2006. g. u Hrvatskoj, među 15 vodećih ozljeda u dobnoj grupi 60 i više godina 23,7 % bile su periferne frakture osim kuka. Čimbenici rizika za nevertebralne frakture osim onih kuka slični su kao i za druge osteoporotske frakture gdje središnje mjesto imaju niska mineralna gustoća kosti i prethodne frakture. Ove frakture imaju velik utjecaj na kvalitetu života, a njihovi su troškovi vrlo visoki, tako da u SAD-u iznose čak 36.9 % svih nacionalnih medicinskih troškova. Nevertebralne frakture osim kuka zahtijevaju veću pozornost, što su i prepoznala europska regulatorna tijela koja odobravaju upotrebu antiosteoporotskih lijekova.

**KLJUČNE RIJEČI:** *kvaliteta života, mineralna gustoća kosti, nevertebralne frakture, osteoporoza, troškovi liječenja*

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