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REVIEW

Imminent fracture risk

C. Roux[1,2,3] · K. Briot[2,3]

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Abstract The clinical significance of osteoporosis is in the occurrence of fractures and re-fractures. The main risk factor of sustaining a fracture is a previous one, but a recent fracture is a better fracture risk factor than fracture history. The role of the recency of fracture has been shown for both vertebral and non-vertebral fracture risk. This imminent risk is explained by both bone-related factors (underlying osteoporosis) and fall-related factors (including those related to postfracture care). Such a short-term increased risk has been shown also in patients initiating corticosteroids and in frail osteoporotic subjects with central nervous system (CNS) diseases or drugs targeting CNS, and thus a high risk of falls. Patients with an imminent (i.e. 2 years) risk of fracture or refracture should be identified in priority in order to receive an immediate treatment and a program of fall prevention.

Learning objectives
On completion of this article, you should be able to recognize the following:
1. A recent fracture is a better fracture risk factor than fracture history.
2. The risk of falls must be assessed in osteoporotic patients with or without a recent fracture.
3. Frail elderly patients with osteoporosis and a high risk of falls can have an imminent risk of fracture.
4. Patients with an imminent (i.e. 2 years) fracture risk can be identified and should receive the highest priority for treatment and fall prevention.

✉ C. Roux
christian.roux@aphp.fr

[1] Paris Descartes University, Paris, France

[2] Epidemiology and Biostatistics Sorbonne Paris Cité Research Center, UMR U1153, Paris, France

[3] Department of Rheumatology, Cochin Hospital, Assistance-Publique-Hôpitaux de Paris, Paris, France

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The clinical significance of osteoporosis is in the occurrence of fractures and re-fractures. The number of frail elderly people at high risk for falls and recurrent fractures is increasing due to the ageing of the population. Fractures and re-fractures can have severe consequences in morbidity and can increase mortality, especially within the 5 years after the fracture [1]. Randomized clinical trials with optimal methodology have shown that anti-osteoporotic treatments are able to decrease the risk of fractures. Thus, guidelines are available worldwide to identify patients with a high risk of fracture who should receive an anti-osteoporotic treatment. Despite all these efforts, many patients are not being prescribed treatment. Moreover, some patients with an increased fracture risk refuse to take treatment when prescribed.

Is "increased fracture risk" understandable for a patient?

Recent studies show that most of the patients perceive their own risk as low, even if they have been diagnosed as having osteoporosis, and even if they receive an anti-osteoporotic treatment [2]. Fractures are perceived as random events, and patients believe that high risk has little relevance to their personal circumstances [3]. In patients' mind, the fractures are related to hazard in environment, accidental falls or unsafe behaviour and not to the underlying osteoporosis, with the perception that careful attention against falls is enough to prevent fractures, and thus that taking a drug for years is unnecessary [4]. Moreover, the level of risk at which a treatment is necessary is dramatically different for patients and their physicians [5]. Finally, the 10-year risk is a misnomer for some patients as they consider that

other health problems that they perceive as more important than osteoporosis can occur within this long period of time. Indeed, awareness of complications of other chronic diseases is dramatically higher than awareness about the devastating consequences of osteoporosis [4]. Nevertheless, physicians perceive for some patients that not only the risk of fracture is high but also that this event may occur soon.

Is there a rationale to consider an "imminent fracture risk" for some individuals?

A key example is fracture risk associated with glucocorticoid (GC) treatment. The incidence of fractures increases at the time of initiation of GCs: the incidence of non-vertebral fractures increases from 1.6 per 100 person-years in the year before beginning of oral GCs, to 2.0 over the first 3 months of treatment [6]. The annual rate of having at least one vertebral fracture is higher in patients who initiate GCs treatment, as compared to chronic users [7]. There may be different reasons for such results, including characteristics of the patients and higher doses of GCs at the beginning of treatment, which can have an immediate deleterious effect on patients with underlying osteoporosis. Patients receiving high-dose GCs represent typically a vulnerable population for whom prevention of fractures must be implemented given this imminent fracture risk.

In postmenopausal osteoporosis, the main risk factor of sustaining a fracture is a previous one. On average, the risk is doubled in the presence of a prior fracture. But the risk is not constant and fluctuates overtime, as the subsequent fracture occurs shortly after the first one. In a large community-dwelling population, 41 and 52% of subsequent fractures in women and men respectively occurred within 2 years after initial fracture [8]. Subsequent fractures cluster in time after the first fracture [9]. This has been shown in a population-based study of 4140 postmenopausal women aged between 50 and 90 years; 22% had a first fracture and 26% had a subsequent one; 23% of all subsequent fractures occurred within 1 year (and 54% within 5 years) [9]. Thus, the relative risk is not constant overtime: it reaches 5.3 1 year after the fracture and declines thereafter: 2.8 within 2–5 years and 1.4 within the 6–10 years. The 1-year absolute risk for subsequent fracture was 6.1%. This study, analysing in details the time-dependent effect, shows that there is a 65% higher risk of subsequent fracture in women with a recent one as compared to patients with a prior fracture more than 5 years before. Such results were confirmed in a large population-based cohort of 18,872 men and women: 1 year after the first major osteoporotic fracture, the risk of a second one was 2.7 (2.4–3.0) fold higher than the population risk [10]. The decline of the relative risk by the end of very long follow-up periods may reflect a selection of healthier subjects [8, 9], and/or exclusion of patients with incident fractures. This methodological issue does not wane the message of an imminent risk after a fracture in some individuals.

Is the imminent risk observed whatever the location of the previous fracture?

The highest level of evidence on the role of a recent fracture has been shown for vertebral fractures (VFs). Yearly systematic X-rays of the spine are available in clinical trials, and placebo groups are convenient for analysing the natural history of VFs in osteoporotic patients. Among 2725 postmenopausal women, with a mean age of 74 years, with a lumbar spine T-score of 2.6 ± 1.3, and a 58% prevalence of at least one VF, receiving only calcium and vitamin D, 381 participants developed an incident VF over the follow-up. In these untreated patients, the incidence of a new VF in the subsequent year was 19.2% [11]. This incidence is thus 4-fold higher than the 4.6% incidence in the presence of a radiographic VF at baseline but of unknown timing [11]. In a 4-year follow-up of 3358 postmenopausal women, 74 years on average, with an average T-score at the lumbar spine of 3.0 ± 1.5, receiving placebo in another trial, the risk of sustaining a VF during the third and fourth years of follow-up was higher in patients who had an incident fracture during the first 2 years of the study than in patients without [12]. During the first 2 years, 156 patients had only mild incident VFs, and 173 other patients had at least one incident moderate or severe VF. As compared to patients without incident VFs, the RR of sustaining a new VF over the 2 subsequent years was 1.7 (1.1–1.6) and 1.9 (1.3–2.6), respectively. Moreover, in patients having at least one incident moderate or severe VF during the first 2 years, the RR of having a non-vertebral fracture during the 2 subsequent years was increased (RR = 1.68 (1.36–2.09)) [12].

The clustering in time after clinical fractures has been shown also after non-vertebral fractures. In 1921, patients presenting with a non-vertebral fracture, the absolute 5-year risk of a subsequent one is 17.6% (with a 5-year risk of mortality of 32.3%); this risk actually changes with time, being higher in the first year and progressively decreasing; one third of the patients sustained a subsequent non-vertebral fracture within the first year after the baseline one [13].

Wrist and humerus fractures are well-known risk factors for hip fracture, but the risk is mainly driven by recent fractures. Among 10,874 patients (aged more than 40 years) hospitalized for a non-trauma humerus fracture, 6588 were rehospitalized within 2 years, 7.5% of them because of a hip fracture, occurring in a median of 353 days; these patients were older and had more comorbidities than patients without hip fracture [14]. In the SOF study, following 8049 postmenopausal women, 321 patients sustained a proximal humeral fracture, and 44 of them sustained a subsequent hip fracture; the risk was higher within 1 year after the humeral fracture

(hazard ratio 5.68), and the association actually was no more significant after the first year [15]. The relationship between a prior wrist fracture and incident hip fracture is driven mainly by bone mineral density (i.e. underlying osteoporosis), but also by the time interval since the prior wrist fracture: wrist fracture is no more a significant hip fracture risk in analyses restricted to hip fractures that occurred 7 or more years after the examination in the follow-up [16].

Is age a determinant of imminent fracture risk?

The clustering in time of fractures is observed also in elderly populations.

In 184 long-term care residents (mean age of 89 years) who had a hip fracture, 6% experienced a subsequent fracture within 6 months, and 12% within 1 year [17]. Among elderly residents in aged care facilities, those with a non hip fracture in the first 2 years had an increased risk of subsequent hip fracture for about 2.5 years [18]. In a cohort of 169,145 patients with a first hip fracture, a total of 27,834 had a second hip fracture, and the cumulative incidence was 9% after 1 year, with an increased subsequent mortality [19].

In a population-based cohort [10], the imminent risk of refracture measured as early as 6 months is similar across all age groups, i.e. 60 years, or older than 80. In the elderly, age and comorbidities have strong effect on the short-term risk of second fracture, more that the location of the index fracture [20].

What are the reasons for an imminent fracture risk?

The imminent risk of refracture can be related to different factors. The treatment of the fracture and postfracture care can, paradoxically, increase the risk, through an increasing risk of falls during rehabilitation, because of walking aids and plastering, and impaired coordination. The immobility may increase cortical and trabecular bone loss. The perioperative period can increase the frailty of some patients, with acute changes of cognitive functions. Moreover, the underlying conditions may not be appropriately managed: in a total of 168,133 patients with a fragility fracture, mean age 80 years, roughly 70% of patients were exposed to at least one drug associated with increased fracture risk, and this proportion was unchanged at the time of discharge [21]. Thus, the fracture was a missed opportunity for secondary prevention.

Is imminent fracture risk amenable to therapeutic intervention?

The imminent risk of subsequent fracture after the first fracture creates a window of opportunity to prevent new fractures, and this is the rationale for the fracture liaison services (FLS). A non randomized study shows that, as compared to patients receiving standard procedures, those followed in a FLS had a reduction of 35 and 56% in mortality and risk of subsequent non-vertebral fracture over 2 years of follow-up [22]. This is the result of both pharmacological and non-pharmacological approaches.

None of the clinical trials assessing the anti-fracture effect of drugs give the information on the recency of fractures before inclusion. Only one observational study is available in this matter: this study conducted in 31,069 subjects, 50 years and older who sustained a fragility fracture, suggests a 40% decrease in the 3-year risk of subsequent fracture; however, only 10% of patients were treated with anti-osteoporotic therapy; the rates of fracture were 7.5 and 9.7% in treated and non-treated patients, respectively [23]. In clinical trials, the incidences of fractures over 1 or 2 years are very low, as patients are selected on the basis of underlying low bone density, and prevalent vertebral fractures for most of them, but of unknown timing. These studies were not designed and powered to assess the short-term benefit of the treatment, and thus the absolute decreases in fracture incidence, although significant, are very low over 1 or 2 years. Regardless of statistical significativity, divergence of the curves of fracture incidence in treated and placebo groups occurs at month 12 for clinical fractures in most of the studies. The early effect of treatments is mainly driven by the effect on vertebral fractures. In the subset of women in Fracture Intervention Trial who had osteoporosis at baseline, alendronate reduces the risk of clinical vertebral fracture by month 12, and of non-vertebral fracture by month 24; the risk was actually decreased as early as 6 months after initiation of the treatment [24]. A significant reduction in morphometric vertebral fractures has been shown with risedronate after 12 months [25] and with denosumab for new vertebral fractures at 1 year [26]. In a post hoc analysis of the study of zoledronic acid in patients after hip fracture, significant divergence in the fracture-free survival curves between treated and placebo groups for all clinical fractures was seen as early as 12 months [27]. Anabolic agent teriparatide and abaloparatide decrease vertebral and non-vertebral risk over 21 months [28] and 18 months [29], respectively, and less vertebral fractures were observed over 1 year in patients treated with romosozumab as compared to placebo-treated patients [30].

Data from FLS have shown that patients at higher risk of short-term recurrence of fractures are those having both bone and falls risk factors. Among 834 consecutive patients included in a FLS with a recent non-vertebral fracture, 57 (6.8%) had a subsequent non-vertebral fracture over 2 years: the risk of sustaining a subsequent fracture was 2-fold higher in patients having both bone and fall-related risk factors as compared to other patients (but this does not reach significance after adjusting for age and baseline fracture location) [31]. Risk

factors for falls are well known, and several of them are present and interact in most individuals. Prevention of falls is mandatory in frail patients, and data suggest that some structured physical activity and rehabilitation programs may help in this matter [32, 33]. However, the contribution of risk factors is different for each fracture site; past falls are important for all fractures except spine [34], whereas vertebral fractures represent the paradigm for anti-osteoporotic drugs efficacy. To what extent adherence to a program of fall prevention will improve adherence to an anti-osteoporotic treatment is unknown.

Can we extend this "imminent risk" concept to patients with osteoporosis but (not yet) fracture?

There are no data suggesting that bone parameters only can predict a short-term risk, at least with current bone density measurements. Combination of quantitative and micro architecture parameters should be studied with this objective. In daily practice, the perception of the patients on the role of falls [4] must be recognized and could be used as a motivation for appropriate care. A study using US commercial and medicare supplemental insured data for women and men without recent fracture analysed more than 60 patients characteristics and potential risk factors for fracture. These patients were selected with the diagnosis of osteoporosis in the database, but the T-score and bone mineral density data were not available. Of 163,186 subjects, 32,094 had a fracture; the most important 12-month pre index predictor was falls (OR 6.67 (6.03–7.37)). Advancing age, central nervous system (CNS) diseases, concomitant medications (targeting the CNS) and factors decreasing mobility were also significant predictors with ORs between 1 and 2 [35]. In individuals with a history of frequent falls, this highly relevant risk factor should be incorporated in algorithms of short-term fracture risk assessment [36].

Conclusion

Our attention must be paid in the selection of patients who should receive the highest priority for an anti-osteoporotic treatment, i.e. patients with an imminent risk of fracture. Combining epidemiological data and time of onset of effectiveness of pharmacological treatments on vertebral fractures, we suggest to consider the 2-year risk. Patients with an imminent fracture risk are osteoporotic patients initiating high dose of corticosteroids, postmenopausal women with a recent major osteoporotic fractures, and frail elderly patients with history of frequent falls. In daily practice, physicians and patients will easily reach agreement on the decision to decrease such an imminent fracture risk. Studies should be conducted to determine the clinical benefit and cost-effectiveness of early treatments in these populations.

Compliance with ethical standards

Conflict of interest Christian Roux received research grants and/or honoraria from the following: Alexion, Amgen, Lilly, and UCB. Karine Briot received research grants and/or honoraria from the following: Amgen, Lilly, MSD, and PFIZER.

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