COMMENTARIES

Are Wrist Fractures a Good Predictor of Future Fractures, and What Are the Implications for FRAX®?

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One of the strongest indicators that a skeleton will fail in the future is the fact that it has failed in the past – fractures beget fractures. Many cohort, case-control and cross-sectional studies have established that a prior osteoporotic fracture increases the risk of future fractures (1-11). This consistent observation, and its independence from the association of other risk variables such as age and BMD, has resulted in the inclusion of prior fracture within the majority of published fracture prediction tools, including the FRAX® tool (12-16) and clinical guidelines (17-20).

It would perhaps be surprising if a prior fracture at one site had similar predictive value for fractures, irrespective of the site of the subsequent fracture. Indeed, it might be expected that a prior fracture at one site had greater predictive value for a further fracture at the same site than at other sites. The empirical data would support this view. The risk of another vertebral fracture is particularly high after a spine fracture, an observation that has also been found in the setting of randomized clinical trials where in the placebo arm, the risk of vertebral deformities is approximately 5-fold higher in patients with a prior vertebral deformity than in those without (5;21;22). This strong association between existing and future vertebral fractures was also reported in a meta-analysis (23). The same analysis also reported that a prior forearm fracture was particularly predictive of a forearm fracture (RR = 3.0; 95% CI, 2.0-5.3) compared to the risk of fracture at other sites.

Consistent with the notion of a heterogeneity of predictive value, a paper based on the Manitoba Bone Density Cohort reported that a prior wrist fracture was associated with a significantly lower hazard ratio (HR) for recurrent osteoporotic fracture than prior clinical fractures of the spine, humerus or hip (24). The HR for recurrent fracture was only 1.58 (95% CI, 1.29-1.93) compared to 2.66 (2.30-3.08) for the other fracture sites combined. Contrary to expectation, primary wrist fractures were not significantly associated with subsequent hip fractures (adjusted HR, 1.29; 95% CI, 0.88-1.89), unlike other primary fracture sites (HRs ranging from 1.52 for clinical spine to 2.06 for humeral fractures). The absence of any significant predictive value of a forearm fracture for hip fracture contrasts with the meta-analysis of Klotzbuecher et al. (RR 1.9; 95% CI, 1.6-2.2) (23). A lower incidence of fracture at specific skeletal sites following a primary wrist fracture has been reported previously; in a study based on the UK General Practice Research Database, 222, 369 subjects (119,317 women and 103,052 men) who had sustained at least one fracture during a 10-year period were identified. For any subsequent fracture, the standardized incidence ratios (SIRs) were similar for wrist fracture, vertebral fracture and hip fracture (3.0, 2.9 and 2.6, respectively) (8). In both men and women, however, a prior wrist fracture had a lower SIR for a subsequent hip fracture than a prior vertebral fracture (e.g., in women, SIR of 3.3, 95% CI, 2.8-3.9 vs. 5.8, 4.1-8.1 for prior wrist and vertebral fracture, respectively). All observations support the view that a prior fracture has a somewhat different significance for subsequent fractures that depends crucially on the primary site of fracture and the site of the subsequent fracture.

The question arises about the implications of these observations for risk assessment
tools. On the face of it, the inclusion of information about the site of prior fracture should lead to an enhanced performance of the assessment tool. Certainly, enhanced performance could be easily predicted if the site of prior fracture was the only factor used in estimating risk. However, prior fracture is combined with many other factors in the assessment of fracture risk and it is important to consider the impact in terms of the overall risk score calculated by the tool. This would require an in-depth analysis of how each independent site of prior fracture interacted with other important variables such as age, BMD, BMI and dichotomous risk variables such as prior parental hip fracture, smoking and alcohol exposure. The impact of the site of fracture may be somewhat less once these variables are taken into account. For example, the Manitoba data illustrate very clearly that the addition of BMD will have a greater effect in someone with a prior wrist fracture compared to that of BMD in the presence of a prior vertebral, humeral or hip fracture. These interactions would tend to lessen the differences in the gradient of risk for the overall risk score and diminish the impact of site of prior fracture on the performance of the tool.

Secondly, in assessment tools such as FRAX®, the relationship between the risk variable and mortality is also taken into account and this would need to be examined for the various sites of prior fracture. Smoking is perhaps the best example of this. Many population cohort studies have suggested that smoking is associated with a decreased risk of hip fracture, but this is an artefact caused by the simultaneous interaction between smoking and mortality. Smoking does actually increase the incidence of hip fracture. While perhaps not causative, there are disparate relationships between sites of fracture and mortality. Hip fractures and vertebral fractures have been consistently shown to be associated with increased mortality, as have other fracture sites (9;25-32). In contrast, forearm fractures have not usually been associated with excess mortality.

In addition to the site of prior fracture, similar arguments could be made for other potential enhancements for risk prediction, such as including the dose of glucocorticoids, the number of prior fractures, the actual alcohol intake or a more detailed smoking history. FRAX® uses only “yes” or “no” responses, and so does not take account of dose-responses for several risk factors including the number of previous fractures, the dose and duration of glucocorticoid therapy and tobacco exposure. Furthermore, the propensity to fall is not included. Thus health care professionals will need to take such factors into account when interpreting fracture probabilities. These and other topics will be addressed at a joint ISCD/IOF meeting in November 2010 devoted to FRAX®.

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References


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