IBMS BoneKEy. 2010 July;7(7):254-258
http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/7/254
doi: 10.1138/20100455

COMMENTARIES

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

Eugene McCloskey

WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, United Kingdom

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®.

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

References

1. Gunnes M, Mellström D, Johnell O. How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women. *Acta Orthop Scand*. 1998 Oct;69(5):508-12.

2. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1999 May;14(5):821-8.

3. Nevitt MC, Ross PD, Palermo L, Musliner T, Genant HK, Thompson DE. Association of prevalent vertebral fractures, bone density, and alendronate treatment with incident vertebral fractures: effect of number and spinal location of fractures. The Fracture Intervention Trial Research Group. *Bone*. 1999 Nov;25(5):613-9.

4. Johnell O, Oden A, Caulin F, Kanis JA. Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. *Osteoporos Int*. 2001;12(3):207-14.

5. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E. Risk of new vertebral fracture in the year following a fracture. *JAMA*. 2001 Jan 17;285(3):320-3.

6. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002 May 18;359(9319):1761-7.

7. Robinson CM, Royds M, Abraham A, McQueen MM, Court-Brown CM, Christie J. Refractures in patients at least forty-five years old: a prospective analysis of twenty-two thousand and sixty patients. *J Bone Joint Surg Am*. 2002 Sep;84-A(9):1528-33.

8. van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int*. 2002 Aug;13(8):624-9.

9. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O; European Vertebral Osteoporosis Study. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. *Osteoporos Int*. 2003 Jan;14(1):61-8.

10. Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, De Laet C, Jönsson B. Fracture risk following an osteoporotic fracture. *Osteoporos Int*. 2004 Mar;15(3):175-9.

11. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004 Aug;35(2):375-82.

12. Black DM, Steinbuch M, Palermo L, Dargent-Molina P, Lindsay R, Hoseyni MS, Johnell O. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int*. 2001;12(7):519-28.

13. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. *QJM*. 2005 Mar;98(3):191-8.

14. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ 3rd, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int*. 2007 Aug;18(8):1033-46.

15. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. *Osteoporos Int*. 2007 Aug;18(8):1109-17.

16. Kanis JA, on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK; 2008.

17. Royal College of Physicians. Osteoporosis: clinical guidelines for prevention and treatment. London: Royal College of Physicians; 1999.

18. Royal College of Physicians. Glucocorticoid-induced osteoporosis. Guidelines for prevention and treatment. Bone and Tooth Society of Great Britain, National Osteoporosis Society and

Royal College of Physicians. London: Royal College of Physicians; 2002.

19. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2008.

20. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2008 Apr;19(4):399-428.

21. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996 Dec 7;348(9041):1535-41.

22. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998 Dec 23-30;280(24):2077-82.

23. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000 Apr;15(4):721-39.

24. Hodsman AB, Leslie WD, Tsang JF, Gamble GD. 10-year probability of recurrent fractures following wrist and other osteoporotic fractures in a large clinical cohort: an analysis from the Manitoba Bone Density Program. *Arch Intern Med*. 2008 Nov 10;168(20):2261-7.

25. Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, Delmas P, Falch JA, Felsch B, Hoszowski K, Johnell O, Diaz-Lopez JB, Lopez Vaz A, Marchand F, Raspe H, Reid DM, Todd C, Weber K, Woolf A, Reeve J, Silman AJ. Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int*. 1998;8(3):291-7.

26. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int*. 2000;11(7):556-61.

27. Ensrud KE, Thompson DE, Cauley JA, Nevitt MC, Kado DM, Hochberg MC, Santora AC 2nd, Black DM. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. Fracture Intervention Trial Research Group. *J Am Geriatr Soc*. 2000 Mar;48(3):241-9.

28. Jalava T, Sarna S, Pylkkänen L, Mawer B, Kanis JA, Selby P, Davies M, Adams J, Francis RM, Robinson J, McCloskey E. Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res*. 2003 Jul;18(7):1254-60.

29. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone*. 2003 May;32(5):468-73.

30. Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, De Laet C, Jönsson B. Mortality after osteoporotic fractures. *Osteoporos Int*. 2004 Jan;15(1):38-42.

31. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int*. 2004 Feb;15(2):108-12.

32. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk

associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA*. 2009 Feb 4;301(5):513-21.