Bone 45 (2009) 154–157

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Perspective

The importance and applications of absolute fracture risk estimation in clinical practice and research

Keywords: Absolute risk, Bone fractures, Dual-energy X-ray absorptiometry, Epidemiology, Fracture risk Assessment, Osteoporosis, Quantitative ultrasound

Introduction

Currently we are facing a universal shift towards the use of absolute fracture risk estimation in the field of osteoporosis research and clinical practice guidelines. Recent attempts by the World Health Organization Scientific Group for assessment of osteoporosis at the primary health care level have resulted in a clinical tool for the estimation of a 10-year absolute risk of fracture in different populations [1,2]. This online tool, namely FRAX™, aims to shift the previous clinical practice (which was mainly based on defining osteoporosis using a single bone density assessment) to a more clinically relevant practice which combines information gained from clinical risk factors and bone mineral density (BMD) measurement to an estimate of absolute fracture risk and categorizes patients using this measure. The field is open now to medical researchers working on osteoporosis assessment and diagnosis who can either try to estimate and validate the 10-year absolute risk figures in their populations (using various epidemiological study designs and biostatistical approaches) or try to calculate country-specific risk thresholds for patient categorization (using principles of health economics and mathematical modeling). Clinicians also need to familiarize themselves with the concept and try to utilize the upcoming results in their clinical practice.

The 10-year absolute risk of fracture is an easily understood measure for most clinicians and patients as it is a direct assessment of the main clinical event at which preventive interventions are aimed. This measure may lie somewhere between about 0–5% for young healthy men and women without fracture risk factors and up to about 50–80% for older women with established osteoporosis. Unlike traditional classification of patients for osteoporosis which only considers BMD testing results, absolute risk charts (like the ones produced by FRAX team) can take into account other clinical risk factors known to influence risk of osteoporotic fractures (such as age, sex, past or parental history of fracture, body mass index, smoking, alcohol consumption, medications and comorbidities) [3]. These values can be measured for populations with different characteristics (sex, age, ethnicity, etc). Conventional statistical models such as Poisson or Cox regression (available via most of statistical packages) or other mathematical modeling approaches have been shown to be efficient tools for pulling together all the available and relevant information for prediction of 10-year absolute risks of fracture [4–8]. Thresholds for categorization of patients using absolute risk measures may well differ in different countries taking into account cost-effectiveness and affordability of different drug regimens and competing health priorities.

Although the main idea behind absolute risk estimation approach is more systematic management of patients with the use of derived estimates, the value of this approach in clinical practice and research is by no means restricted to this subject. In this issue of the Journal, we are reporting a new application for absolute risk measures based on the European Prospective Investigation into Cancer (EPIC)-Norfolk study [9]. EPIC-Norfolk is an ongoing prospective study started at 1993 in the county of Norfolk, United Kingdom [10]. In the original cohort, more than 25,000 men and women aged 40–79 years at baseline underwent a health examination including extensive demographic, anthropometric, and lifestyle assessment and a subset of them were assessed by dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS). All participants have been followed for an average of 11.3 years. We calculated a 10-year absolute risk of fracture for all participants using Cox proportional-hazard regression models. With reference to some of the results of this study, I will review a number of the new applications for and opportunities created by absolute risk measures from an epidemiological perspective.

Introducing new risk factors

There is a critical distinction in epidemiology between an 'associated factor' and a 'risk factor'. In the osteoporosis literature, there are numerous factors suggested to be associated with the disease (as determined by BMD testing) or osteoporotic fractures and the number of these factors (including biochemical variables, lifestyle factors, anthropometrical or structural characteristics of bone, etc.) is increasing. Some of these observed associations are perceived to be etiologically linked with fractures (presumably due to a biological background). However, when assessed in an epidemiological framework, any association, even an etiologic one, should satisfy certain criteria to be accepted as an independent 'risk factor' [11]. The main principles are persistence of the association after adjustment for other known risk factors as well as an increase in our predictive power for the outcome by adding the 'new' risk factor to our set of risk factors. While the first principle is usually taken into account with the use of a multivariable regression analysis, the second principle (increase in the predictive power) is generally neglected. Again, use of absolute fracture risks can help researchers with this issue.

This topic is of vital importance especially for introducing new techniques into clinical practice for assessment of osteoporosis. All the

8756-3282/$ – see front matter
doi:10.1016/j.bone.2009.03.666

new radiological techniques or biochemical assays need to demonstrate that they add some useful information to the current practice of BMD testing using DXA assessment. In other words, they can predict fractures independently from BMD. We have examined this for quantitative ultrasound (QUS) measurement in the EPIC-Norfolk study. The results are published in this issue of the Journal [9]. In summary, two models were constructed for prediction of fractures. One model only used BMD measures and the other used both BMD and QUS measures. After calculation of a 10-year absolute risk of fracture using each of these models, participants were categorized into three groups of low-, intermediate-, and high-risk. Groupings based on two models were then compared. The figure presented in that article [9] shows that, while most of participants were categorized into the same risk groups using both models, there was a considerable amount of discordance between the results of two models. About 17% of total participants were reclassified to other categories using the model including QUS measure. Comparison of the predicted risks and observed risks further revealed that the predicted values using the model including both BMD and QUS measures were more accurate. Therefore, we were able to confirm that BUA adds useful information to our predictive power.

The method described above can be extended for direct comparison of known risk factors (e.g. can we use BUA in place of BMD for fracture prediction?) or use of surrogate markers (e.g. can we use magnetic resonance imaging [MRI] in place of bone biopsy for the assessment of bone quality?). Statistical methodology supporting the use of absolute risk categorization is progressing fast and we are now able to compare the predictive power of models with different sets of risk factors. Conventional methods such as sensitivity/specificity and receiver operating characteristics (ROC) curves have proved to be incompetent for comparison of discriminative power of models introducing new variables to pre-defined sets of risk factors [12]. Pepe et al. [13] have shown the statistical privileges of an absolute risk-derived curve (named as 'predictiveness curve'). This method increases our power for comparison of two risk factors inside a set of fixed risk factors and needs to be considered more in osteoporosis research.

Distributions of fracture risk

Having estimated a 10-year probability of fracture for all participants in a prospective study, researchers would be able to look at the distribution of the risk in the populations from different aspects. Careful inspection of the risk scattering in different subpopulations and comparison of risk estimates at different levels of known risk factors would help in acquisition of better understanding of the exposure–outcome relationships. We know that different risk factors may interact with each other in predicting risk of fractures among individuals. The term interaction (or effect modification) in epidemiology describes a situation in which two or more risk factors modify the effect of each other with regard to the occurrence or level of a given outcome [14]. Although these interactions are usually identified using the incidence rates of outcome in different levels of exposures (to estimate attributable risk or relative risk models), distribution of absolute risks at different levels of exposure can provide better alternative to this method as it provides multivariate-adjusted estimates for comparison.

Fig. 1 shows an example of interaction observed between age and sex for the prediction of a 10-year absolute risk of fracture among EPIC-Norfolk participants. The effect of age on fracture risk is modified by different handling of sex in the multivariate-adjusted proportional-hazard models. In the pooled analysis, in which men and women both entered into the same model, a 10-year probability of fracture showed a greater proportional increase among men (from 0.6% to 4.4%) and less among women (from 1.2% to 9.5%) in different age groups. However, when estimates where based on two different models for

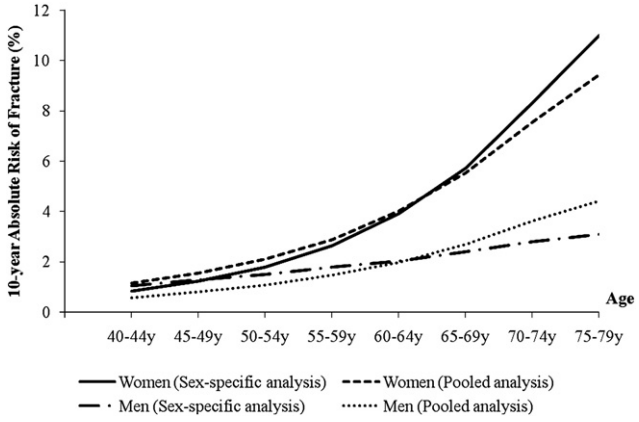

Fig. 1. 10-year absolute risks of fracture based on sex-specific and pooled Cox proportional-hazard regression models among 25,472 men and women in the EPIC-Norfolk study.

men and women, the increase in fracture risk was steeper among women (from 0.9% to 11%) compared with men (from 1.1% to 3.1%). This shows that the association between age and fracture risk is not identical in different genders. Alongside the biological implications of these sorts of findings, they would be of great importance for the field of risk assessment since generalization of risk estimates at one level of a contributory variable to other levels would not be justified anymore.

An important point is that, while because of limited data researchers may derive absolute risks for a particular population (e.g., women at age 70 years) and then estimate the absolute risks for other groups (e.g., men at age 60 years) based on the relative risks observed in other studies, these assumptions do not necessarily hold. Therefore, we need more directly observed estimates of absolute risk from real data on populations. This is the rationale for conducting studies in different populations in different countries, and different age and sex groups rather than assuming that the absolute risk estimates derived from a particular population can be modeled appropriately for other populations.

Public health perspective

Attention to the risk distributions can also help public health agencies consider other aspects of disease burden for estimation of appropriate thresholds. The impact of a health program to prevent fractures in the next 10 years is obviously linked to the risk distribution in the target population. Fig. 2 presents this distribution for women of different ages in the EPIC-Norfolk study. In this figure, percentiles of a 10-year absolute risk (derived from sex-specific proportional-hazards model with adjustment for all known confounders) have been estimated for women in different age groups. Inspection of both horizontal and vertical axes can provide useful information for economic analysis in order to inform choice of risk thresholds. For instance, a reference line on the horizontal axis marks the absolute risk cut points to identify 5% of women with the highest risk of fracture in each age group (these cut points go up from 1.6% in women aged 40–49 years to 15.7% in women aged 70–79 years).

The usual question of 'at what absolute risk should patients (of a particular group) be treated?' could be replaced with 'what is the absolute risk level if we choose to treat a certain fraction of high-risk population (in a particular group)?' For instance, health economic studies may suggest that we can only afford to treat 20% of highest-risk women in East Anglia. EPIC-Norfolk study suggests that the 10-year absolute fracture risk corresponding to this number for the whole population of women is about 5%. Fig. 2 shows that none of women in the 40–49 year age group and almost all of the women in 70–79 years would be eligible for treatment in this case. About 2% of women aged 50–59 years and 35% of women aged 60–69 years would also be