Bone Density and Markers of Bone Turnover in Predicting Fracture Risk and How Changes in These Measures Predict Fracture Risk Reduction

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While this paper will examine these two issues in depth, the fundamental point must be made that were it not for serial measurements of bone mineral density (BMD) and bone turnover markers (BTM), the clinical practice of osteoporosis would be relegated to guess-work.

Surrogate Markers

There are many chronic diseases where surrogate markers are used to assess the efficacy of therapy, even though the most important endpoint for treatment is the reduction in the risk for the specific clinical event. For example, the reduction in the risk for myocardial infarction is the most important outcome for the use of therapies designed to lower serum cholesterol concentrations. However, if clinicians waited for a myocardial infarction as the endpoint to assess therapeutic efficacy of pharmacologic agents designed to reduce the level of elevated serum cholesterol, one of the major risk factors for heart attacks, without measuring the reduction in the surrogate endpoint (serum cholesterol), no patient would take the medication, no health care plan would pay for the medication, and no physician would prescribe the medication. The trust in the surrogate marker as providing evidence for modifying the clinical outcome depends on the strength (power) of the pharmacologically-induced change in the surrogate marker as reflecting the change in the risk for the clinical event. In this regard, the field of osteoporosis therapies is rich in the accumulation of data that have examined the utility of two surrogate markers: BMD and BTM.

Surrogate markers in clinical medicine provide a useful means to assess therapeutic response to pharmacologic therapy in a wide range of chronic disease states. In the area of osteoporosis, the surrogate markers of change in bone mineral density (BMD) and bone turnover markers (BTM) provide the clinician with a means of assessing the biologic response to osteoporosis-specific pharmacologic agents. Increases in BMD and/or reductions in BTM can independently be correlated to reductions in vertebral and nonvertebral fracture risk. In managing osteoporosis patients, the BTM change at an earlier point of time after initiation of therapy and a change in BTM can provide earlier feedback to the patient and clinician regarding issues such as compliance and a bone biologic response. An increase in BMD at 12 or 24 months after initiation of therapy is also evidence of an improvement in bone strength though with antiresorptive agents no change in BMD may also be associated with risk reduction within clinical trial sets. In this regard, changes in BMD and BTM are complementary in their application to patient management.

Introduction

Over the past several years in the field of osteoporosis clinical management, no area has been more hotly debated than the following controversial issues—To what degree adding bone mineral to an osteoporotic skeleton with pharmacologic agents used to treat osteoporosis increases bone strength and reduces the risk for fracture?; To what degree reducing bone turnover by pharmacologic agents used to treat osteoporosis increases bone strength and reduces the risk for fracture independent of adding bone mineral?
Within the bisphosphonate class [8,9,10], markers as providing evidence for fracture risk reduction of the trust that exists for accepting these two surrogate evidence of surrogate marker data, not fracture data, because the treatment of postmenopausal osteoporosis on the evidences of many clinical trials) and statistical analysis of any using statistical analysis (meta-analysis—summary statistics of many clinical trials) and statistical analysis of any methodology comparing changes in BMD and bone strength in non–head-to-head clinical trials has been the explosion of scientific debate and scientific development that tries to explain why bone strength improves with the use of antiresorptive agents independent of adding bone mineral. There has been improvement in the science that has helped to explain how bisphosphonates improve bone strength independent of adding bone mineral [19••,20–23]. In addition, changes in crystal size and collagen orientation also independently contribute to bone strength (Table 3) [24–29]. Yet, we have no clinical tools available to measure these other contributions to bone strength and, therefore, must rely on the surrogate markers of BMD and BTM to assess the skeletal response to osteoporosis treatments.

Without head-to-head fracture endpoints, we will never know for certain if small differences in BMD achieved between different bisphosphonates translate into differences in fracture reduction.

The best we can achieve is using different statistical analysis to explain these relationships between the magnitude of change in BMD and the magnitude of fracture risk reduction; or to use comparison of surrogate markers within head-to-head clinical trials to provide insight into potential differences between agents. Both approaches are imperfect and have some degree of scientific merit along with some scientific flaws [30–34].

Analysis

Using statistical analysis (meta-analysis—summary statistics of many clinical trials) and statistical analysis of any given clinical trial (eg, Freedman’s analysis) have provided evidence that there is a relationship between measurable increases in axial or appendicular (eg, hip) BMD measured by dual-energy x-ray absorptiometry (DXA) and the prediction of fracture risk reduction in groups of patients [2••,3, 11, 30–32].

Table 1. Non–head-to-head comparisons between changes in spinal BMD by DXA and 3-year incident fracture reduction between the antiresorptive agents

<table>
<thead>
<tr>
<th>Trial</th>
<th>Increase in spine BMD, %</th>
<th>Decrease in vertebral Fx, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT II</td>
<td>8.3</td>
<td>44</td>
</tr>
<tr>
<td>FIT I</td>
<td>7.9</td>
<td>47</td>
</tr>
<tr>
<td>RVE</td>
<td>7.1</td>
<td>49</td>
</tr>
<tr>
<td>RVN</td>
<td>5.4</td>
<td>41</td>
</tr>
<tr>
<td>MORE</td>
<td>2.6</td>
<td>40</td>
</tr>
<tr>
<td>PROOF</td>
<td>1.2</td>
<td>36</td>
</tr>
</tbody>
</table>

(Adapted from Faulkner [13••].) BMD—bone mineral density; DXA—dual-energy x-ray absorptiometry; FIT—Fracture Intervention Trial; MORE—Multiple Outcomes for Raloxifene Evaluation; PROOF—Prevent Recurrence of Osteoporotic Fractures; RVE—Risedronate Vertebral European; RVN—Risedronate Vertebral North America.

In the pivotal clinical trials that have led to the Food and Drug Administration (FDA) registration of all antiresorptive agents for the treatment of postmenopausal osteoporosis, the primary endpoint has been vertebral fracture risk reduction over 3 years as compared with the placebo group. For the foreseeable future this most important endpoint will continue to be the primary endpoint for osteoporosis-specific pharmacologic registration, especially for agents that have novel mechanisms of action [6]. Alternatively, for agents that have already achieved FDA registration for fracture risk reduction within a class of agents (eg, the bisphosphonates), surrogate markers are accepted by the FDA and The United States Surgeon General’s Office as evidence of improvements in bone strength [6,7]. As a result, weekly alendronate and risedronate along with monthly ibandronate were FDA approved for the treatment of postmenopausal osteoporosis on the evidence of surrogate marker data, not fracture data, because of the trust that exists for accepting these two surrogate markers as providing evidence for fracture risk reduction within the bisphosphonate class [8,9,10••].

Nonacceptance of BMD and BTM as Surrogate Markers

Why have BMD and BTM not been universally endorsed as providing evidence of improvements in bone strength with the use of antiresorptive agents? [11,12].

First, for individual patient management, no surrogate marker change mediated by any therapy for any chronic condition provides the clinician with the perfect ability to predict risk reduction. Therefore, many patients will still suffer a myocardial infarction even though a statin medication has significantly reduced their serum cholesterol concentration.

Second, analysis in non–head-to-head antiresorptive therapeutic studies that analyze the magnitude of change in BMD and the magnitude in fracture risk reduction between antiresorptive agents suggests that some antiresorptive agents reduce vertebral fracture incidence with little or no change in axial BMD (Table 1) [13••,14]. These analyses are non-scientific, since they are non–head-to-head analysis and the populations are not comparable [13••]. The randomization criteria for all of the antiresorptive clinical trials are different (Table 2). In addition, comparing antiresorptive agents to one another that have different mechanisms of action to inhibit bone resorption is irrational. A selective estrogen receptor modulator does not have the same mechanism of action as calcitonin or a bisphosphonate [15,16]. Even within the bisphosphonate class, there may be sufficient differences in their cellular as well as their bone–binding-affinity and pharmacokinetics to create a scenario where the mechanisms whereby bisphosphonates improve bone strength are also dissimilar [17••,18]. The result, however, of this type of inadequate scientific methodology comparing changes in BMD and bone strength in non–head-to-head clinical trials has been the explosion of scientific debate and scientific development that tries to explain why bone strength improves with the use of antiresorptive agents independent of adding bone mineral. There has been improvement in the science that has helped to explain how bisphosphonates improve bone strength independent of adding bone mineral [19••,20–23]. In addition, changes in crystal size and collagen orientation also independently contribute to bone strength (Table 3) [24–29]. Yet, we have no clinical tools available to measure these other contributions to bone strength and, therefore, must rely on the surrogate markers of BMD and BTM to assess the skeletal response to osteoporosis treatments.

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