Quantitative Radionuclide Studies of Bone

In the current issue of *The Journal of Nuclear Medicine,* Uchida et al. present results from a prospective study using ^{18}F-fluoride PET to assess the effects of bisphosphonate treatment on bone metabolism in patients with glucocorticoid-induced osteoporosis (*1*). By quantifying localized bone turnover in terms of ^{18}F-fluoride standardized uptake value (SUV) measured at the lumbar spine and femoral neck, the authors report a statistically significant decrease in SUV that parallels changes in biochemical markers of bone formation and bone resorption.

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Quantitative measurements of bone remodeling have an important role in research studies examining the pathophysiology of metabolic bone diseases and the response of patients to treatment (*2–6*). The most accurate method is bone histomorphometry performed by taking a bone biopsy from the iliac crest (*7,8*), and for the most detailed information the process of double tetracycline labeling is used (*7*). The limitation of bone biopsies is that they are a relatively invasive procedure that requires sedation of the patient. Also, the measurement site is restricted to the iliac crest, and when bone biopsy is used to assess response to treatment

the patient is required to undergo serial biopsies.

In practice, the most widely used technique for studying bone remodeling is the measurement of biochemical markers of bone resorption and bone formation in serum or urine (*9,10*). A variety of different markers has been studied, with bone resorption markers being the by-products of collagen breakdown and formation markers being chemicals released by osteoblasts during bone formation. Biochemical markers have the advantage of showing a rapid response in patients commencing treatment, and in postmenopausal women with osteoporosis treated with an antiresorptive agent such as a bisphosphonate, bone resorption markers decline rapidly to reach a new lower plateau within 4 wk of the start of therapy (*11*). Consistent with the remodeling cycle, bone formation markers show no response at 4 wk but subsequently decline to reach a new plateau around 3 mo after the start of therapy. Rigorous quality control is required to achieve the best results when biochemical markers are used in research studies, with all the samples from a single study stored at $-70°C$ until they can be assayed together. A limitation of biochemical markers for monitoring individual patients is that any changes may be masked by the relatively large day-to-day variation in the measurements, including the presence of a significant diurnal rhythm for some markers (*12,13*). Another major limitation is that measurements in serum or urine reflect processes occurring throughout the entire skeleton. Although constituting only 20% of the whole skeleton, trabecular bone is considerably more responsive to treatment than is cortical bone. It would be useful to have ways of selecting for measurement clinically important sites such as the spine

and hip that have high trabecular bone content.

Bone densitometry using dual-energy x-ray absorptiometry is another method for monitoring changes in bone remodeling (*14,15*). In patients starting treatment for osteoporosis, an increase in bone mineral density is observed at trabecular bone sites such as the spine and hip because of infilling of remodeling space (*16*). However, even at the most favorable measurement site, the lumbar spine, the changes are small and several years may be required before a statistically significant effect can be measured in an individual patient. Moreover, other factors, including the development of degenerative disease with aging, can complicate the interpretation of bone mineral density changes. In patients treated with a bisphosphonate, part of the bone mineral density increase is caused by the increased secondary mineralization of newly formed bone tissue associated with the longer remodeling cycle (*17*). For patients treated with strontium ranelate, exceptionally large bone mineral density changes are measured using dual-energy x-ray absorptiometry, but these are caused by the replacement of some of the calcium atoms in bone by strontium, which attenuates x-rays more strongly than does calcium (*18*).

Quantitative radionuclide studies of bone are of interest because they provide an alternative method for studying bone remodeling that avoids some of the limitations of the techniques described above (*19*). Studies using ^{18}F-fluoride (*20*) or ^{99m}Tc-methylene diphosphonate (MDP) (*21*) reflect the combined effects of bone blood flow and osteoblastic activity on bone tracer kinetics (*19*). The advantage of an imaging technique such as PET is that quantitative studies of bone tracer kinetics can be performed directly at

the spine or hip (*22–34*). The technique has been validated by comparison with bone histomorphometric indices, with significant correlations observed between regional skeletal kinetic parameters using ^{18}F-fluoride PET and the bone formation and mineral apposition rate (*23,27*). ^{18}F-fluoride PET has been used to investigate regional bone metabolism in patients with metabolic bone disease (*23,24,28,31,33*) and to evaluate therapies for these diseases (*30,33*). In addition, important differences in remodeling activity between cortical and trabecula-rich sites can be investigated (*26*). ^{18}F-fluoride PET may also have an important role in the investigation of neovascularization after allogenic bone grafting, periprosthetic bone formation after joint replacement (*35–37*), and fracture healing (*38*).

Historically, quantitative radionuclide studies of bone have used one of two different approaches, the first being measurement of skeletal uptake defined as percentage of injected dose of tracer in a specified region of interest, and the second being measurement of plasma clearance from the relationship between the time–activity curve in the selected region of interest and the blood input curve. SUV is defined as tissue activity (kBq/mL) × body weight (kg)/injected activity (MBq) and is equivalent to the measurement of tracer uptake per unit volume. Although SUV is frequently used to quantify PET studies, most ^{18}F-fluoride studies have used the alternative plasma clearance technique first described by Hawkins et al. (*22*). That method is technically more demanding than an SUV measurement, requiring a 60-min dynamic PET acquisition together with continuous blood sampling to accurately define the arterial input function. In addition, a compartmental modeling program is required for computation of the results.

A choice between measuring uptake or plasma clearance also exists for studies using the alternative tracer ^{99m}Tc-MDP. Perhaps the best-known technique for quantitative bone radionuclide studies is the 24-h ^{99m}Tc-MDP whole-body retention test first described by Fogelman et al. (*39*). Because whole-body counters are no longer widely available, several authors have described equivalent methods for measuring ^{99m}Tc-MDP retention based on whole-body γ-camera bone scanning (*40–42*). These techniques are all measurements of tracer uptake, like SUV. However, by combining serial γ-camera imaging with blood sampling, one can also measure ^{99m}Tc-MDP plasma clearance both for the whole skeleton and for selected regions of interest (*43,44*).

Although uptake is technically much simpler to measure than plasma clearance, it is important to ask whether the choice of a simpler method entails any loss of information. One advantage of the PET compartmental modeling approach is that several different tracer kinetic parameters are available for study, including bone blood flow and net clearance to the bone mineral compartment (*22*). In contrast, a disadvantage of bone uptake measurements is that the results may be influenced by uncontrolled aspects of tracer kinetics from outside the immediate region of interest under study. These include the patient's renal function and the presence of bone lesions in other areas of the skeleton. An uptake measurement can be compared to dividing up the cake at a birthday party. Because there is only a finite amount of cake to share, if the number of guests is larger than expected each will receive a smaller slice of cake. In a similar way, there is competition for bone tracer from the kidneys and from bone lesions in other parts of the skeleton that may vary substantially from patient to patient. The advantage of plasma clearance measurements is that such effects are allowed for through their effect on the plasma clearance curve. Thus, in a patient with poor renal function, the plasma concentration decreases more slowly with time, making more tracer available for uptake at the bone measurement site. Similarly, in a patient with widespread Paget's disease, there is more competition for tracer, and the plasma concentration decreases more quickly with time, leading to less tracer being available for uptake (*45*).

An important practical consideration when one is designing research studies is the precision of measurements (*34*). For studies in which individual patients serve as their own controls, the number of subjects required to achieve a statistically significant difference between the results of the baseline and follow-up measurements, assuming a *P* value of 0.05 and a power of 90%, is 21 × (precision error/treatment effect)^2. In this equation, the treatment effect is the average difference between the 2 measurements expressed either as percentage change from baseline or in the natural units of the measurement. The precision error is the root mean square precision measured in a group of subjects (*34*) and similarly can be expressed either as a percentage or in natural units. A technique that has a smaller figure for the ratio of precision error to treatment effect will be more cost-effective in research studies because fewer subjects will be required to achieve a statistically significant result. Studies show that precision errors of as low as 12%−14% can be achieved with ^{18}F-fluoride PET using both the SUV and plasma clearance techniques (*34*).

Finally, is there any advantage between ^{18}F-fluoride and ^{99m}Tc-MDP as tracers for studying bone metabolism? Few studies have directly compared the 2 tracers, but results suggest that whole skeleton plasma clearance measured with ^{18}F-fluoride is around twice that measured with ^{99m}Tc-MDP (*46*), probably reflecting the lighter and more diffusible F$^-$ ion. A complication of the use of ^{99m}Tc-MDP is the significant and variable degree of protein binding, requiring ultrafiltration of plasma samples to derive the true input function (*44*), whereas ^{18}F-fluoride has the advantage of not binding to plasma proteins (*47*). However, other aspects of ^{18}F-fluoride kinetics may complicate their evaluation. Although free (e.g., non–protein-bound) ^{99m}Tc-MDP is cleared by

glomerular filtration, ^{18}F-fluoride has a variable renal clearance that is sensitive to urine flow rate and, therefore, the degree of hydration of the patient (*19,48,49*), possibly affecting the interpretation of some types of study.

Quantitative radionuclide studies of bone turnover now have a well-established role in research studies that include investigations of the pathophysiology of metabolic bone diseases and studies of patients' response to pharmaceutical treatments and surgical interventions. At present, we can choose between ^{99m}Tc-MDP and ^{18}F-fluoride as possible tracers, and between straightforward approaches to scan quantification such as SUV or the more complicated plasma clearance techniques. There remains, however, the challenge of developing and validating simpler methods that may have wider clinical use. It is likely that much still remains to be learned in terms of developing the optimum technique.

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