Bone may have the reputation of being a staid and somewhat passive tissue but, at least in growing children, a lot of exciting action is going on in the skeleton. To grow in length, growth plate cartilage needs to be converted into bone tissue. To maintain stability, children’s bones keep getting wider and are ceaselessly reshaped and renewed. Two cell types are mainly responsible for this bone turnover, the bone-forming osteoblasts and the bone-resorbing osteoclasts.

To meet the needs of the skeleton, osteoblasts and osteoclasts can work in 2 different modes, remodeling and modeling. In remodeling, we find a few osteoclasts drilling trenches or tunnels through the bone, followed by a team of osteoblasts that refill those trenches or tunnels. Osteoclast and osteoblast actions thus cancel each other out, which makes remodeling look like a rather pointless exercise. However, the net effect is to repair the little defects that arise from the wear and tear of daily use. The remodeling process is the focus of intense research activity, because it is disturbed in some common bone disorders affecting adults. In postmenopausal osteoporosis, for example, osteoblasts fail to replace completely the bone that was previously removed by the osteoclasts, and bone is lost as a consequence.

Continuous maintenance through remodeling may be all that is needed in adult bone. Growth, however, calls for more vigorous action. Increasing bone length, body weight, and muscle force impose rapidly rising requirements on bone strength. This is where modeling comes in. In modeling, osteoblasts and osteoclasts are not tightly linked to each other like in remodeling, but act independently. The growth in width of a long bone shaft is an example of this. Osteoblasts continually add new material on the outer bone surface. At the same time, the bone marrow cavity is getting bigger because osteoclasts remove material from the inner surface of the bone’s cortex. Modeling allows for much faster changes in the amount and distribution of bone than could possibly be achieved by remodeling.

Whether engaged in modeling or remodeling, osteoblasts and osteoclasts shed by-products that can be quantified in serum or urine and are used clinically as biochemical “bone markers.” Bone-specific alkaline phosphatase (BSAP), a membrane-bound osteoblast enzyme, is a widely used bone formation marker that can be measured in serum. Deoxypyridinoline (DPD) is a bone resorption maker that is released into the circulation when osteoclasts degrade bone matrix. It is excreted unchanged via the kidneys and is usually quantified in urine samples.

In adults, bone markers can be used to evaluate bone-remodeling activity and to monitor the effect of treatments that interfere with bone remodeling. Because bone metabolism is far more complex in children than in adults, bone marker results are much harder to interpret. To help with this task, it would be useful to tease out individual factors that determine bone marker levels in children. This is what Tuchman et al set out to do in a study that is published in this issue of The Journal. They determined BSAP and DPD in a group of 202 healthy subjects from 5 to 21 years of age. The levels of these bone markers were compared with a number of clinical characteristics and to whole-body bone mineral content (ie, the total amount of mineral in the body). The main finding was that sex, Tanner stage, baseline whole-body bone mineral content, height velocity, and whole-body bone mineral content accrual in the 6 months after the bone marker test were significantly and independently associated with BSAP and DPD levels, explaining 77% to 80% of the variability of these bone markers.

What sets this work apart from earlier pediatric bone marker studies is that the independent contribution of each factor was evaluated in a carefully assembled multivariate model. The final multivariate model does not contain major surprises. Earlier studies consistently found a profound influence of sex and pubertal stage on bone markers. It is also well known that the rate of bone growth in length (and thereby height velocity) is an important determinant of bone marker levels. DPD has long been used as an indicator of the growth response to growth hormone therapy in children who have a growth hormone deficiency.

The importance of bone mass for bone marker levels is also quite obvious. Everything else being equal, a skeleton that weighs 2 kg should produce twice as many bone marker molecules as a skeleton that weighs 1 kg. Maybe the least expected finding is the correlation between bone markers and bone mass accrual. Theoretically, bone mass accrual should depend on the difference between the amounts of bone formed and resorbed rather than on the absolute bone formation or bone resorption activity. The results of this study therefore indicate that as the amounts of bone formed and resorbed increase so does the difference in the 2.

Tuchman et al then went on to assess bone metabolism in children and adolescents with Crohn’s dis-

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ease. Compared with healthy control subjects, these patients had pubertal delay, were short, had low bone mass, grew more slowly, and accrued less bone mass during the 6-month follow-up interval. This is a long list of things that all influence bone marker results. Armed with their earlier established multivariate model, the authors addressed the question of whether Crohn’s disease influences bone marker levels in ways other than by causing pubertal delay, short stature, low bone mass, slow growth, and sluggish bone mass accrual. Their answer is yes. Even after adjusting for all of these confounders, patients with Crohn’s disease had lower BSAP levels, but higher DPD levels than control subjects.

The interpretation of these results is not exactly straightforward. For example, the pathophysiological correlate of the statistical construct “low serum levels of BSAP adjusted for pubertal status, height, whole-body bone mass, height velocity, and whole-body bone mass accrual rate” is not immediately obvious. However, the authors take their results to mean that Crohn’s disease probably has some direct effect on bone cells. This seems plausible, with the little caveat that most of the patients in this study had already received treatment with glucocorticoids or Infliximab. In a cross-sectional study such as this, it is hard to distinguish between the skeletal effects of the disease and the effects of the treatment.

Despite this limitation, the study by Tuchman et al raises the bar for future bone marker studies in pediatric populations. To make the most of such bone marker results, you should know about pubertal stage, height velocity, total body bone mineral content, and the speed of total body bone mineral content accrual.

But even when you have all this additional data at your disposal, the information gleaned from bone marker data takes you only that far. Blood and urine simply are not the best places to look when you want to know what is going wrong with bone. Because many processes occur simultaneously in the growing skeleton, you need to look at the bone itself if you really want to investigate bone metabolism. The only way to do this at present is to take a bone biopsy, preferably after tetracycline labeling, and measure bone cell activity directly in the tissue. With bone biopsy information, it would be possible to make statements about the presence of mineralization defects, the remodeling activity of trabecular and cortical bone, and the modeling activity in cortical bone.

Studies into the pathophysiology of skeletal involvement in Crohn’s disease are certainly very useful. However, the question foremost on a clinician’s mind is, “Are these things relevant to my patients?” As so often happens, the answer is a somewhat evasive: “They might, but more data are needed.” Although there is no shortage of studies showing that bone density tends to be low in pediatric Crohn’s disease, surprisingly little is known on the clinical impact of such skeletal involvement. Adults with Crohn’s disease may have a higher risk of vertebral fractures, but this appears to be independent of bone density. In the pediatric literature there are scattered case reports of teenagers with Crohn’s disease who sustained vertebral fractures. Only 1 study counted the number of fractures in pediatric patients with Crohn’s disease, and it found that fracture rates were similar to those of the patients’ siblings. Next to nothing is known about other skeletal outcomes in pediatric Crohn’s disease, such as the amount of bone pain, mobility limitation, or whether skeletal problems impact the quality of life of such patients.

Thus, clinical researchers in the pediatric field of “Crohn’s and bones” have their work cut out. To move ahead on the pathophysiology level, direct information is needed about what is going on in the bone tissue. The clinical importance of the problem needs to be delineated more carefully. Whatever the clinical severity of the problem, adequate disease control, physical activity, and nutrition should help keep bones strong in children with Crohn’s disease.

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REFERENCES