Sometimes surrogate markers useful in clinical trials also translate into effective clinical measures.

Take serum glucose levels in patients with diabetes. On page 477 of this issue, Dr. Byron J. Hoogwerf describes two new drugs recently approved as adjunctive therapies based on the results of a surrogate marker—the ability to improve blood sugar control in patients with diabetes.

For years it was debated whether hypoglycemia should be avoided at all costs, and fluctuations in glucose levels were an acceptable tradeoff to avoid the sequelae of overly low blood glucose levels. But after several trials showed that tight control decreases the vascular complications of diabetes, most clinicians now accept that it is good patient care, and serum glucose levels (and the hemoglobin A1c) are well accepted as powerful surrogate markers for improved outcome.

Bone densitometry is another story. For years we ignored osteoporosis and consequent fractures. We had no therapy, so we needed no practical diagnostic tests for early detection. Then the bisphosphonates appeared. Since dual-energy x-ray absorptiometry was used in clinical trials to document efficacy, the medical community rapidly embraced it as a diagnostic test for osteoporosis. The T score became a surrogate marker for fracture risk and response to therapy. But there were paradoxes. Fluoride treatment produced dense bone, but bone that fractured. Patients on corticosteroids seem to suffer fractures at higher-than-expected T scores.

Most patients with lower-than-normal T scores do not sustain fractures. Perhaps we have overcompensated, from ordering too few bone density studies and ignoring osteoporosis to treating too many people. Analysis of patient subsets using the concept of number needed to treat may be helpful to add perspective.

On page 473, Dr. Angelo A. Licata cautions against overreliance on bone densitometry to diagnose osteoporosis. Not every low T score reflects osteoporosis. Bone architecture is a truer predictor of fracture, but is not measurable. Furthermore, causes of secondary bone loss need to be considered. Osteomalacia is often unrecognized. We are beginning to look more frequently for vitamin D deficiency, a mini-epidemic in some populations, and this is an important step forward.

The T score may soon be routinely supplemented or even replaced by specific blood and urine markers of bone metabolism. But that will take significant education of clinicians; the T score was easy. For the present, Dr. Licata appropriately emphasizes that we need to be aware of the limitations of this test, which, like many other tests, needs to be evaluated in the clinical context. It is not a surrogate for physician assessment.

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