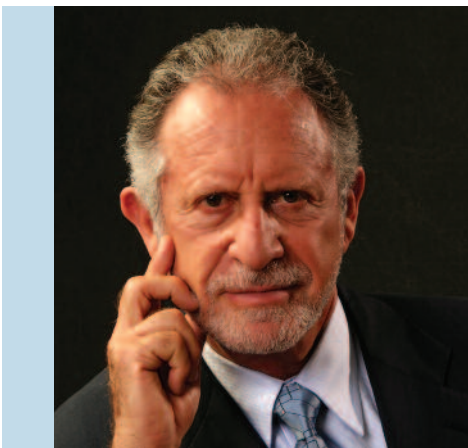


From the EDITOR



Dr. Wulf H. Utian, consultant in women's health and reproductive endocrinology, has served as Editor-in-Chief of *Menopause Management* since its inception in 1988. The Arthur H. Bill Professor Emeritus of Reproductive Biology and Obstetrics and Gynecology, Case Western Reserve University School of Medicine, he is also Consultant, Obstetrics, Gynecology and Women's Health Institute at the Cleveland Clinic, and Executive Director of The North American Menopause Society (NAMS). He is Chairman of the Advisory Board of Rapid Medical Research, Cleveland. He received his medical degree from the University of Witwatersrand, Johannesburg, South Africa, and his PhD from the University of Cape Town, South Africa, and is a Fellow of the Royal and American Colleges of Obstetricians and Gynecologists, as well as the International College of Surgeons. In 2007 he earned the DSc(Med) degree from the University of Cape Town, its highest degree and only awarded 11 times in over 100 years.

A pioneer in Women's Health issues and menopause research, in 1967 he established the Groote Schuur Menopause Research Clinic in Cape Town, the world's first such clinic. He was one of the three original founders of the International Menopause Society in 1976, of which he is Honorary Past President, and founded the North American Menopause Society in 1989.

He is the recipient of numerous national and international awards and research grants, and is still an active investigator with multiple grants. Dr. Utian has written over 200 papers related to the reproductive system in women and has authored five books on menopause and its effects on women. He is editor of *Menopause: The Journal of The North American Menopause Society*.

Bisphosphonates and Unusual Fractures: Red Herring or Tip of the Iceberg?

Is everyone on bisphosphonates?

As a lead investigator at a clinical research center I have been impressed in recent times with how difficult it has become to find postmenopausal women who are bisphosphonate (BP) virgins! As a clinician over that same period of time I had become concerned about the use of BP in many women who most likely did not have justifiable indications for therapy. In many instances the latter had occurred because of misinterpretation or inappropriate utilization of bone densitometry.¹ Now, it seems another concern has reared its head—unusual fractures in otherwise healthy women on long-term BP therapy. The question of the moment is whether this is a real problem, a direct relationship between long-term BP use and fractures, or another misdirection in science and only a coincidence.

The Nature of the Problem

There have been historic concerns about over-suppression of bone turnover with long-term BP use leading to so-called “frozen bone,” but until fairly recently there was little substantial clinical reporting. The current literature consists largely of individual or small-number case reports of unusual, spontaneous, non-spiral fractures of the femoral diaphysis in women on BP therapy (largely alendronate) for 3–8 years.²⁻³ Although most of the fractures have involved the upper half of the femur, other sites, such as the pubis and ileum, have also been reported.⁴

In most of these cases, bone biopsy has revealed reduced bone turnover. Indeed, it has been suggested that osteoclast tolerance for pharmacologic suppression may vary between individuals, so that anti-remodeling therapy may, in some cases, result in skeletal harm.⁵ In other words, long-term BP use—usually alendronate because it has been around the longest and is the most widely

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used BP—may overly suppress bone metabolism. In turn, low-energy femoral shaft fractures with a simple transverse pattern and hypertrophy of the diaphyseal cortex may result. It is speculated that this is a result of propagation of stress fractures, the repair of which were retarded by prolonged BP use, which had diminished osteoclast activity and microdamage repair.^{6,7}

Are There Warning Signs or Early Diagnostic Tests?

There have been other interesting observations and suggestions. Up to 65% of patients with such a fracture may demonstrate stress fractures on the opposite femur.⁸ Warning prodromal symptoms include thigh pain, vague discomfort or subjective weakness, often dismissed or treated as symptoms of spinal stenosis. Any patient on BP with these complaints should undergo radiographic examination of the symptomatic femur. Bone scanning and magnetic resonance imaging also should be considered; both have greater sensitivity for incipient fracture. Any patient with one of these unusual fractures of the femur should have the opposite femur screened as well.

Is the Case Against Long-Term BP Use Proven?

The evidence at this time is really narrative in nature (mostly individual case reports) and no long-term, large-study outcome data are available. So, the question of whether the unusual fractures are directly related to prolonged BP use or happen to have been coincidental in a population overexposed to BP remains one for speculation. But the concern, nonetheless, is there.

It must be stated that these femoral insufficiency fractures are associated with increased mortality and may represent markers of ill health with multifactorial causes.⁹ It would, therefore, be injudicious and premature to ascribe atypical fractures only to BP-induced over-suppression of bone. Secondary factors should always be given consideration.

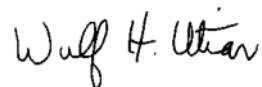
What Should Clinicians Do in the Interim?

So, what should we advise our patients in the absence of evidence? It is my considered opin-

ion, given the evidence for and against all bone-sparing drugs, that the early postmenopausal woman with reduced bone mass who is a “virgin” to any therapy should be placed on hormone therapy for 5 to 10 years, provided she has no contraindications and is followed according to current clinical recommendations. If follow-up therapy for reduced bone mass is justified beyond that time, according to current clinical guidelines and risk assessment, conversion to BP for 5 years would be the next appropriate step. In this way, the maximum benefit and minimum harm could be derived from both these families of drugs.

What about the woman already on long-term BP therapy? Schneider has recommended that “it is reasonable to suggest that patients consider stopping the BP drug after several years, continue weight bearing exercise and calcium, and wait to see what the next scheduled DEXA examination shows.”³ I can do no better than to concur, perhaps adding only that vitamin D intake or supplementation should be adequate, and that all patients should be subject to careful follow-up.

There have been many red herrings in the history of medicine. Whether this situation is just another, or is the real thing, will be proven with time and further study. Until then, keep an open mind, but stay alert!



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References

1. Utian WH. Bone mineral density testing: storm clouds rising. *Menopause Management* 2002;11:6-7.
2. Odvina CV, Zerwekh JE, Rao DS, et al. A potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005;90:1294-1301.
3. Schneider J. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long term alendronate. *Geriatrics* 2006;61:31-3.
4. Kazuhiro I, Yamamoto S, Anamizu Y, Horiuchi T. Pelvic insufficiency fracture associated with severe suppression of bone turnover by alendronate therapy. *J Bone Miner Metab* 2007;25:333-6.
5. Visekruna M, Wilson M, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 2008;93:2948-52.
6. Neviasser AS, Lane JM, Lenart BA, et al. Low energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 2008;22:346-50.
7. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 2008;358:1304-06.
8. Kwek EB, Koh JSB, Howe TS. More on atypical fractures of the femoral diaphysis. *N Engl J Med* 2008;359:316-17.
9. Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density; multiple insufficiency fractures in a woman with postmenopausal osteoporosis on alendronate therapy. *J Endocrinol Invest* 2007;30:590-7.