LETTERS TO THE EDITOR

Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes*  
To the editor:

We have read the interesting paper “Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes” by Umpierrez et al. (1), which is one of the few studies on this issue conducted on a satisfactory number of patients. However, in our opinion, to conclude that newly diagnosed hyperglycemia is a “marker” for in-hospital mortality when compared with known diabetes and normoglycemia, a more homogenous patient group had to be evaluated. Comparison of admissions of the patient groups showed that distribution of patients among services on admission were different between the three groups. Although there was no significant difference of admission rates for medical and surgical departments, Intensive Care Unit (ICU) admission was 29% in new hyperglycemia (P < 0.01 vs. normoglycemic, and P < 0.001 vs. known diabetic patients), 14% in known diabetes (P < 0.01 vs. normoglycemic patients), and 9% in normoglycemia groups. Patients with newly diagnosed hyperglycemia were more likely to be admitted to the ICU, which may explain the higher rate of in-hospital mortality noted in these patients. Hyperglycemia on admission without known diabetes has been investigated as a risk factor for increased mortality in specific patient groups before, and the results were controversial (2–4). As a result, it may be inappropriate to suggest hyperglycemia as a marker in “all” patient groups with this heterogenous patient population.

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References

doi: 10.1210/jc.2002-020995

Authors’ Response: Hyperglycemia—An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetesb
To the editor:

We appreciate the interest of Dr. Cakir and colleagues in our recent publication regarding in-patient hyperglycemia. Several observational studies have shown that admission hyperglycemia in patients without diabetes is associated with increased morbidity and mortality during critical illnesses (1–5). Similarly, several intervention studies in acutely ill patients have shown that control of hyperglycemia significantly reduces the rate of complications and risk of death (6–8). This evidence strongly suggests that hyperglycemia was associated with adverse outcomes for hospitalized patients with and without diabetes and that improvement in outcome can be achieved with improved glycemic control (9). The major findings of our study are that hyperglycemia was present in 38% of patients admitted to the hospital, of whom one third had no history of diabetes before the admission, and that newly discovered hyperglycemia was associated with higher in-hospital mortality rate and lower functional outcome not only in critically ill patients admitted to the Intensive Care Unit (ICU) but also in patients admitted to general medicine or surgical wards. We agree with Dr. Cakir’s comments that a number of features suggest that patients with new hyperglycemia are under more severe stress and had a more severe illness as indicated by a higher rate of ICU admission, a longer length of hospital stay, and the increased referral rate to an extended care facility after discharge. Further research should focus on the optimal management of hyperglycemia in patients admitted to both the ICU and the general medicine and surgical wards.

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References

doi: 10.1210/jc.2002-021718

Efficacy of Teriparatide and Alendronate on Nonvertebral Fractures
To the editor:

I applaud Body et al. (1) on their recent study, but I am writing to clarify what I believe to be an important point: the statement in the

Received November 4, 2002. Address correspondence to: Nelson Watts, M.D., University of Cincinnati, Bone Health and Osteoporosis Center, 222 Piedmont Avenue, Suite 4300, Cincinnati, Ohio 45219. E-mail: nelson.watts@uc.edu.
abstract that “nonvertebral fracture incidence was significantly lower in the teriparatide group than in the alendronate group.” That is technically true, but it is misleading.

It is generally accepted that fractures of the toes and feet are not related to osteoporosis, and fractures of the ribs and ankles are usually not included in clinical trials to evaluate the effect of medications on osteoporotic fractures. The authors point out in the Subjects and Methods section that fractures were recorded without regard to trauma; however, information regarding the contribution of trauma to these fractures is not provided in the paper. The discussion simply states that “fracture incidence was not a primary outcome of this study and should be confirmed in a larger study.”

Because this is a study “in postmenopausal women with osteoporosis,” the natural response of a casual reader would be to assume that the study showed a greater effect of teriparatide compared with alendronate on osteoporosis-related fractures. This is not the case. Table 2 shows that of the small number of fractures, only three radial fractures might be related to osteoporosis.

I am concerned that the statement referenced above will be taken out of context, leading to the erroneous conclusion that teriparatide has been shown to reduce the incidence of nonvertebral osteoporotic fractures to a greater degree than alendronate, a conclusion that I do not believe can be supported by their data.

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Reference

doi: 10.1210/jc.2002-021727

Author’s Response: Efficacy of Teriparatide and Alendronate on Nonvertebral Fractures

To the editor:

We appreciate Dr. Watts’ interest in our paper. We think that we have been quite cautious in this comparison between fracture incidence in both groups. As Dr. Watts described, we provided all relevant facts for the reader. Even among published large fracture treatment studies, there is little consensus in the definition of “osteoporotic fracture,” with some studies defining osteoporotic fractures by site without regard to trauma (1); others excluding facial, skull, pathological, and traumatic fractures (2); and still others reporting all nonvertebral fractures (3). In this small study, it was possible to enumerate all nonvertebral fractures without imposing our own biases regarding the relevance of site or trauma. It is interesting, however, that all three fractures of the radius highlighted by Dr. Watts occurred in the alendronate group and none in the teriparatide group. It is evident that the study was not powered for detecting a difference in antifracture efficacy between both groups, and this was not the primary objective of this trial. Nevertheless, we think the data are interesting, provocative, and worthwhile to be reported, but we agree with Dr. Watts that they would have to be confirmed in a larger trial.

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References

1. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut 3rd CH, Brown J, Eriksen EF, Housey MS, Axelrod DW, Miller PD 1999 Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Ver-
To the editor:

Based on a retrospective charts review, Tannenbaum et al. (1) propose groups of tests to identify secondary contributors to osteoporosis in otherwise healthy women. Having essentially the same objective in mind, we examined prospectively 272 patients who were referred to this University Hospital for evaluation of osteoporosis (2). Our patients' age was 71.8 ± 11.9 yr (mean ± sd). Ninety-six percent of them were women. We carefully reviewed the medical history of each patient, paying special attention to history of thyroid disease, anticoagulant therapy, glucocorticoid therapy, heparin therapy, kidney stones, and fractures. Each patient was subjected to an in-depth laboratory evaluation designed to identify the following conditions: osteomalacia, hyperparathyroidism, hypercalcemia, hyperthyroidism, hyperadrenocorticism, prolactinoma, anemia, and liver disease.

Our findings were that 17.9% of the patients had vitamin D deficiency, defined by us as 25-hydroxyvitamin D (25OHD) blood level less than 16 ng/ml. In this group, intact PTH blood level was 78.1 ± 16.4 pg/ml, compared with a level of 45.0 ± 35.0 pg/ml (P = 0.001) in the patient group with no underlying disease (75.4% of the total group). The elevation of PTH indicates that the low 25OHD was physiologically significant. Despite the limitation of 24-h urine collection (2, 3), we found that 6.3% of the patients had hypercalcemia, defined as urinary calcium excretion greater than 250 mg/24 h, ranging from 260–380 mg/24 h. The hypercalcicuric patients were not significantly different from those without underlying disease in terms of age, T-score of the spine or the femur, serum calcium, 25OHD, or PTH. Two of our patients (0.7%) were found to have hyperparathyroidism. One patient on heparin therapy had had actively progressive osteoporosis with multiple fractures. Thyroid disease was not a significant contributor to the osteoporosis, and occult prolactinoma, occult hyperadrenocorticism, anemia, and liver disease were not found in our cohort.

We agree with Tannenbaum et al. that there is no way of identifying hypercalcemic patients other than by an adequate 24-h urine collection. The main difference between our prospective study and the retrospective study of Tannenbaum et al. is in the number of patients with low 25OHD. Having excluded patients with osteomalacia from their study, they identified only 4.6% of their subjects as having low 25OHD. This is much lower than the prevalence of vitamin D deficiency observed by us (17.9%) and that reported from the Midwest (4) and Boston (5, 6).

The conclusions of our study were therefore slightly different from those of Tannenbaum et al. We concluded that, at the minimum, patients with low bone density should have simultaneous determinations of blood calcium, 25OHD level, and 24-h urinary calcium excretion. [We have previously described the importance of thyroid function screening in the elderly (7).]

There is a tendency among primary physicians to assume that all patients with low bone density have osteoporosis and to treat them with antiresorptives or with selective estrogen receptor modulators, without subjecting them to any additional diagnostic workup. Our observation is that this is clearly inappropriate in approximately 25% of patients. In summary, it should be recognized that densitometry identifies subjects with low bone density but does not provide the diagnostic information needed for the optimal treatment of each individual patient.

Determination of blood calcium, 25OHD level, and 24-h urinary calcium excretion are, in our opinion, the minimum workup required in such cases.

Received October 24, 2002. Address correspondence to: Uriel S. Barzel, M.D., Montefiore Medical Center, Montefiore Medical Group, Department of Medicine, 3400 Bainbridge Avenue, Bronx, New York 10467-2490. E-mail: ubarzel@montefiore.org.

References


2. Recommended Testing in Patients with Low Bone Density

To the editor:


References


Received November 25, 2002. Address correspondence to: A. Elisabeth Hak, M.D., Erasmus Medical Center, Department of Internal Medicine, Room D429, P. O. Box 2040, Rotterdam, 3000 CA, The Netherlands. E-mail: pols@inw3.azr.nl.
were no patient exclusion criteria reported by Freitag and Barzel (1). In addition, the mean age of their population was 6.3 yr older, which may also have resulted in a higher prevalence of vitamin D deficiency.

Dr. Barzel suggests that measurement of 25(OH) vitamin D be included in the evaluation of patients with osteoporosis, a recommendation with which we strongly agree. The costs and benefits of potential screening strategies are highly dependent on the diagnostic criteria used to define a clinically significant disorder. When this study was originally designed, the generally accepted value for vitamin D deficiency was a 25(OH) vitamin D level of less than 12.5 ng/liter (30 nmol/liter), based on its association with rickets and osteomalacia. Parfitt (3), however, has pointed out that mild to moderate degrees of vitamin D insufficiency produce osteoporosis, not osteomalacia. There is now evidence that vitamin D sufficiency requires levels ranging from approximately 33–50 ng/ml (80–120 nmol/liter), with lower levels associated with reduced calcium absorption, higher concentrations of PTH, and increased rates of bone resorption (4–6). On the basis of these studies, it is generally accepted that a 25(OH) vitamin D values below 20 ng/ml indicate significant vitamin D deficiency. Whereas values between 20 and 32 ng/ml (48–80 nmol/liter) can be associated with metabolic consequences such as suboptimal calcium absorption and increased PTH secretion. If we apply these newer diagnostic criteria to our data, 21% of our 173 subjects were vitamin D deficient, whereas an additional 34% had vitamin D insufficiency. At this diagnostic yield, the cost-effectiveness of 25(OH) vitamin D measurements is very high. In addition, there are important therapeutic implications to diagnosing vitamin D deficiency because currently recommended vitamin D supplementation may not produce adequate vitamin D levels in patients with vitamin D sufficiency (9–10). Thus, 25(OH) vitamin D measurements should be included in the evaluation of osteoporotic patients to identify a correctable secondary cause of bone loss and to help to optimize therapy.

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References


doi: 10.1210/jc.2002-021660

Authors’ Response: Recommended Testing in Patients with Low Bone Density

To the editor:

Dr. Barzel refers in his letter to his recently published study in Gerontology (1) that also identified a high prevalence of “significant underlying conditions” in patients referred to their university-based osteoporosis center. The prevalence of newly identified abnormalities was similar in our study (32%; Ref. 2) and theirs (25%), with a slightly higher prevalence perhaps due to the identification of low urinary calcium excretion and calcium malabsorption, which were not addressed in their study.

Dr. Barzel points out in his letter that the prevalence of vitamin D deficiency in their study (17.9%) is significantly greater than the 4.6% prevalence reported by us, despite the fact that both populations are from the New York City area. It is important to note, however, that the diagnostic cut-off used to define vitamin D deficiency differed in the two studies (25 OH vitamin D concentration of <16 ng/ml in his study; <12.5 ng/ml in ours). If we reanalyze our data using the less than 16 ng/ml criterion, 10% of our subjects had vitamin D deficiency.

Several important population differences could explain the remaining discrepancy in the incidence of vitamin D deficiency between these two studies. Subjects with diseases or taking medications known to impair absorption or metabolism of vitamin D (such as inflammatory bowel disease, malabsorption, hepatic dysfunction, and anticonvulsant use) were specifically excluded from our study. Also excluded were all patients referred to us for known osteomalacia or for abnormal laboratory results suggestive of vitamin D deficiency, which undoubtedly lowered the incidence of vitamin D deficiency in our population. There were no patient exclusion criteria reported by Freitag and Barzel (1). In

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doi: 10.1210/jc.2002-021996