Osteoporosis, an Underdiagnosed Disease

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THE RESULTS FROM THE NATIONAL OSTEOPOROSIS RISK Assessment (NORA), the largest study of osteoporosis conducted to date in the United States, have been eagerly awaited by osteoporosis researchers and clinicians. NORA, which commenced in 1997, is a longitudinal observational study involving more than 200 000 postmenopausal women. The study was initially designed to assess the association between osteoporosis risk factors and low bone mineral density (BMD) and to examine the relationship between BMD and other risk factors and short-term (1-year) fracture incidence.[1]

In this issue of THE JOURNAL, Siris et al[2] report the study's initial findings of an unexpectedly high prevalence of unsuspected osteopenia and osteoporosis (as determined by BMD) among generally healthy postmenopausal women followed up in primary care practices. The study also confirms the utility of measurement of BMD at peripheral bone sites using several devices to predict short-term fracture risk. The importance of such findings, indicating a need for greater attention to the identification and management of osteoporotic risk, should not be underestimated.

In NORA, 200 160 postmenopausal women underwent peripheral bone densitometry or ultrasonography of heel, finger, or forearm in their physicians' offices. They also completed questionnaires assessing risk factors and, approximately 1 year later, new skeletal fractures. Participants did not have a previous history of osteoporosis and were not currently treated with US Food and Drug Administration (FDA)–approved osteoporosis therapies except for estrogen replacement. Overall, approximately 40% of tested women had a peripheral BMD measurement denoting osteopenia (T score of –1 to –2.49), and approximately 7% had BMD in the osteoporotic range (T score ≤–2.5) according to the World Health Organization classification for significant bone loss.[3] At baseline, 11% of women reported at least 1 fracture after age 45 years.

Among the 163 979 participants with follow-up information, a BMD classification of osteoporosis was associated with a fracture rate approximately 4 times that of a normal BMD. Moreover, osteoporosis (defined by baseline BMD) increased the risk of incident fracture within 1 year by 2.7 times, and osteopenia increased the risk of incident fracture by 1.7 times.

This study also confirms previously noted risk factors for osteoporosis, including age, history of previous fracture, smoking, and glucocorticoid use. Estrogen replacement, diuretic use, exercise, a high body mass index, and, interestingly, alcohol consumption decreased the likelihood of osteoporosis. In an assessment of race/ethnicity as a risk factor, Asian or Hispanic heritage was associated with an increased risk of osteoporosis, and African American heritage decreased the risk. However, as determined by BMD, 32% of African American women were osteopenic and 4% were osteoporotic, indicating a substantial absolute risk of osteoporotic fracture and suggesting that African American heritage may not confer full protection against osteoporosis.

Assets of NORA include enrollment of a large number of geographically and ethnically diverse women; also, the women were primarily enrolled from clinical practice, providing a realistic cross-sectional and longitudinal assessment of osteoporosis risk in primary care practices in the United States. In addition, this study provides a stringent and scientifically rigorous evaluation of the utility of the peripheral densitometry/ultrasonography technologies for screening large groups of women for bone loss, and generally supports the validity of these modes in screening of large populations for osteoporotic risk. Given the current attention to other predictors and mediators of fracture risk (eg, bone quality and turnover),[4,5] reinforcement of the parameter of bone quantity (BMD) as a clinical mode for defining fracture risk is appropriate.

A number of limitations of the study are addressed by the authors, including a potential underestimation of the true prevalence of osteoporosis in the study cohort by (1) exclusion of women with previous diagnosis or treatment of osteoporosis (except for hormone replacement therapy); (2) recording of risk factors and, particularly, fracture prevalence and incidence by self-report and recall without medical record or x-ray corroboration; and (3) the inability of the study to assess nonclinical (ie, asymptomatic) spine fracture.[6] The latter criticisms are of concern because while self-reporting of fractures has been generally accurate,[7,8] many osteoporotic spine fractures are unrecognized by both patient and practitioner. However, the lack of full documentation of skeletal fracture in the study is balanced and necessitated by the robustness of the study size and the desired use of a clinical prac-

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tice environment. This study would have been logistically difficult to provide in a cost-efficient manner if radiographs and medical record retrieval were required for all patients.

Another concern in NORA is the use of multiple peripheral densitometric/ultrasonographic devices at multiple skeletal sites, yielding discordant estimates of the prevalence of osteopenia and osteoporosis across the cohort. Such discrepancies, possibly due to differing referent populations for each manufacturer's device, have been noted previously.[9] However, BMD was measured with single-energy x-ray absorptiometry (SXA) at the heel in more than half of the women and with 1 of 2 devices (heel SXA or wrist DXA) in 83% of women. Thus, it is unlikely that the use of different BMD devices or measurement of differing skeletal sites significantly affected the study conclusions. Reports from other NORA studies have shown comparable predictive ability for overall fracture risk for BMD measured at all peripheral sites, using receiver operating characteristic curve analysis.[10,11]

Industry sponsorship and management of the study warrants mention. A potential for bias might be proposed for the NORA trial because documentation of an increased number of women at risk for osteoporosis and, consequently, an increased number of women to be considered for therapeutic intervention with an osteoporosis therapeutic agent would be to the sponsor's advantage. However, full access to all the data and data assessment by independent investigator-authors, quality assurance of the BMD measurements in the study by an independent group, and full disclosure of the study funding source and the authors' financial interests argue against any such bias.

In summary, NORA confirms what many clinicians and osteoporosis researchers have long suspected, ie, that a significant number of postmenopausal women in primary care practices have clinically significant low BMD and that such women have an increased risk of incident fracture within 1 year. Such underidentification of osteoporosis risk implies undertreatment of osteoporosis. Given the current availability of 5 FDA-approved therapies for prevention and treatment of osteoporosis, such underidentification is unfortunate. Based on the current study, strategies to identify, manage, and treat osteoporosis in primary care need to be established and implemented—hopefully, sooner rather than later.

REFERENCES

1. Siris E, Miller P, Barrett-Connor E, Abbot T, Sherwood L, Berger M. Design of NORA, the National Osteoporosis Risk Assessment Program. *Osteoporos Int.* 1998; 8(suppl 1):S62-S69.
2. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA*. 2001;286:2815-2822.
3. *Assessment of Fracture Risk and Application to Screening for Postmenopausal Osteoporosis.* Geneva, Switzerland: World Health Organization; 1994.
4. Chesnut CH, Rosen CJ. Reconsidering the effects of antiresorptive therapies in reducing osteoporotic fracture. *J Bone Miner Res*. In press.
5. Delmas PD. How does antiresorptive therapy decrease the risk of fracture in women with osteoporosis? *Bone*. 2000;27:1-3.
6. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ. The incidence of clinically diagnosed vertebral fractures. *J Bone Miner Res.* 1992;7:221-227.
7. Ismail AA, O'Neill TW, Cockerill W, et al. Validity of self-report of fractures. *Osteoporos Int*. 2000;11:248-254.
8. Nevitt MC, Cummings SR, Browner WS, et al The accuracy of self-report of fractures in elderly women. *Am J Epidemiol.* 1992;135:490-499.
9. Grampp S, Genant HK, Mathur A, et al. Comparisons of noninvasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. *J Bone Miner Res.* 1997;12:687-711.
10. Miller P, Abbott T, Wehren L, et al. Fracture risk assessment across peripheral sites: results from the NORA study. Presented at: International Society for Clinical Densitometry Annual Scientific Meeting; March 14-17, 2001; Dallas, Tex.
11. Miller P, Siris E, Abbott T, et al. Prediction of fracture risk in postmenopausal Caucasian women with peripheral bone densitometry: evidence from National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res.* 2001;16:S193.

Improving Drug Use in Elderly Patients
Getting to the Next Level

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THE SENSATION OF DEJA VU IS ALWAYS UNSETTLING, more so if the event reexperienced is an unpleasant one. In this issue of THE JOURNAL, Zhan and colleagues[1] provide a reprise of a now-classic tale in geriatric pharmacology and remind physicians of a persistent and troublesome issue in the care of the elderly population. The authors adapted a well-known list of drugs to be avoided in elderly patients[2-4] and apply it to data describing medication use among a nationally representative sample of older Americans, collected in 1996. Their study represents an update of studies based on data from 1987[5] and 1992.[6] Extrapolating from their sample to the United States as a whole, Zhan et al[1] estimate that 2.6% of the US population older than 65 years took 1 or more of 11 drugs that should never be used in this age group.

Zhan et al[1] also report that an additional 9.1% of patients were using drugs judged to be rarely appropriate in elderly patients. By far the largest proportion of these pa-

See also p 2823.

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