Suggested Guidelines for Evaluation and Treatment of Glucocorticoid-Induced Osteoporosis for the Department of Veterans Affairs

Robert A. Adler, MD; Marc C. Hochberg, MD, MPH

Background: Glucocorticoid-induced osteoporosis is an important disorder in the predominantly male US veteran population. Department of Veterans Affairs facilities vary considerably in evaluation and management of glucocorticoid-induced osteoporosis.

Methods: We suggest how evaluation and management can take place in medical centers with and without bone mineral density measurements by dual energy x-ray absorptiometry (DXA). The proposed guidelines can be applied to other health care systems.

Results: Use of DXA can help determine fracture risk for patients taking glucocorticoid therapy and for those starting therapy for at least 3 months. Patients with low bone mineral density should be treated with a bisphosphonate as should all patients about to start prednisone treatment at a dose of 7.5 mg/d or more. In facilities without DXA, most patients should be treated with bisphosphonates, the cost of which is about $30 to $35 per month. In addition, the use of urinary calcium measurements is encouraged to determine which patients might benefit from augmented vitamin D and calcium supplementation.

Conclusion: Attention to fracture risk assessment in patients undergoing glucocorticoid therapy and timely bisphosphonate treatment should lead to fewer fractures.

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Glucocorticoids are commonly prescribed for inflammatory diseases such as rheumatoid arthritis and asthma, and for decreasing the inflammatory component of chronic obstructive pulmonary disease. Although glucocorticoid therapy saves lives, important side effects are frequent, particularly with extended treatment. One important adverse effect is bone loss, which significantly increases fracture risk. Fracture of the spine may further worsen respiratory function, and hip fracture is associated with strikingly increased mortality and morbidity, particularly in men.

Studies have shown that there is great variability in providers’ knowledge about glucocorticoid-induced osteoporosis (GIOP), and many physicians, including those at Veterans Affairs Medical Centers (VAMCs) do not routinely administer agents that may prevent the bone loss complication of glucocorticoid therapy. Osteoporosis is often thought to be a disorder of women; and in the predominantly male population of the typical VAMC, osteoporosis may not be considered a common problem. The fact is that men and African Americans, not usually thought at high risk for osteoporosis, may experience the consequences of GIOP. Moreover, men have worse outcomes after hip fracture, including increased risk of death.

Much has been learned from an analysis of the General Practice Research Database in the United Kingdom. About 40% of those receiving glucocorticoids had respiratory disorders, and about 40% of the corticosteroid users were men. With increasing daily dosage, there was an increased risk of hip fracture, increasing to a relative risk of 2.27 for doses greater than 7.5 mg/d of prednisolone equivalent. Similar doses of prednisolone were associated with a relative risk of 5.18 for vertebral fracture. Interestingly, the risk of fracture increased soon after starting therapy and decreased toward baseline soon after stopping therapy. This implies that even the patient receiving intermittent glucocorticoid therapy may be at risk for GIOP. It is also clear that patients receiving glucocorticoids via alternate routes, such as patients with chronic obstructive pulmonary disease using inhaled triamcinolone, will have lower bone mineral...
density (BMD) than those not exposed to inhaled glucocorticoids.

PATHOGENESIS OF GIOP

A complete discussion of the pathogenesis of GIOP is beyond the scope of this article, and the reader is directed to comprehensive reviews. However, several aspects of GIOP are important to mention because they help explain the severity of GIOP and the rationale for various preventive and therapeutic maneuvers. Bone undergoes a remodeling cycle in which osteoclasts first resorb bone over a period of about 2 weeks. Thereafter osteoblasts appear and fill in the resorbed area over a 3- to 4-month period. In postmenopausal osteoporosis, both bone resorption and formation are increased, but formation is unable to match resorption. In GIOP, while resorption may or may not be increased, bone formation is greatly diminished. This particular mechanism may be the reason that GIOP can lead so rapidly to bone loss and increased fracture risk. Other mechanisms are also important. Glucocorticoids cause increased urinary calcium excretion and decreased intestinal absorption of calcium, possibly leading to secondary hyperparathyroidism. This results in loss of bone mineral. In addition, the general catabolic effects of glucocorticoids cause decreases of bone matrix and muscle. Glucocorticoid therapy may affect pituitary gonadotropin secretion, causing a functional hypogonadism in women and men. In addition, suppression of the adrenal gland by exogenous glucocorticoids decreases adrenal androgen secretion (such as dehydroepiandrosterone), which may also be related to bone loss. A summary of GIOP mechanisms is provided in Table 1.

These mechanisms are complicated by the reasons for which patients are prescribed glucocorticoids: conditions such as chronic obstructive pulmonary disease and inflammatory arthritides that decrease one’s ability to exercise (and therefore decrease bone mass) can be associated with bone loss even when glucocorticoids are not used as therapy. In summary, the patient receiving glucocorticoids has many reasons to be at risk of fracture.

ASSESSING FRACTURE RISK

Not all patients receiving glucocorticoid therapy have fractures, and stratification of risk would target therapy to those at highest risk. From the study of Van Staa et al, it is clear that all doses of glucocorticoids increase fracture risk and the risk increases with higher doses. In other types of osteoporosis, measurements of bone mass predict fracture risk. Patients with GIOP appear to fracture at the same BMD as patients with other forms of osteoporosis, although some studies suggest that fracture can occur at higher bone density. History of fragility fracture and age are also important risk factors for future fracture. A new study suggests that patients older than 70 years treated with glucocorticoids are at such higher risk for vertebral fracture that treatment can be started without measurement of BMD.

The standard method for assessing bone mass is dual energy x-ray absorptiometry (DXA) of the spine and hip. This essentially risk-free measurement of central bone density is available in many VAMCs and many other clinical settings. While there are other methods to measure bone density (quantitative computed tomography) and bone quality (quantitative ultrasound of bone), the most widely used and accepted method is DXA of the spine and hip. DXA measurements are also needed to assess the response to therapy. New methods to use these measurements in determining 5- or 10-year fracture risk are being developed.

SERUM AND URINE TESTS

Osteoporosis cannot be diagnosed by blood or urine tests, but there are a few tests to help in management of patients treated with glucocorticoids. Urinary calcium excretion, as measured in a 24-hour urine sample or estimated from a spot or 2-hour timed urinary calcium-to-creatinine ratio may be helpful in following patients’ response to calcium and vitamin D supplementation. Some authorities have suggested measurements of the major circulating vitamin D metabolite, 25-hydroxyvitamin D, to decide which patients need additional vitamin D treatment beyond usual doses (400-800 IU/d). Patients with low urinary calcium excretion may have malabsorption, the evaluation of which should include 25-hydroxyvitamin D levels. High levels of urinary calcium excretion may be seen in some patients with osteoporosis and in patients who have excessive calcium and/or vitamin D intake. Serum markers of bone formation, such as osteocalcin, may be lowered by even the first dose of prednisone therapy, but there is little clinical use of such markers. Measurements of serum and urinary markers of bone resorption are also of little clinical usefulness at this time. Assessment of gonadal status by measurement of serum testosterone or estradiol levels plus the pituitary gonadotropins luteinizing hormone and follicle-stimulating hormone, may help decide which patients will likely improve from hormone replacement therapy. Many VAMCs can measure testosterone, luteinizing hormone, and follicle-stimulating hormone by automated testing that costs approximately $6 per test. In the community, these tests cost much more. Serum estradiol levels are usually measured by commercial laboratories, and the cost per test is approximately $75. For most men taking long-term glucocorticoid therapy, sex hormone testing is indicated for men who are candidates for testosterone replacement (eg, those without prostate hyperplasia or carcinoma). For pre-

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**Table 1. Mechanisms of Glucocorticoid-Induced Osteoporosis**

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tr>
<td>Rapid decrease in bone formation</td>
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<tr>
<td>Possible increase in bone resorption</td>
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<tr>
<td>Decreased gut absorption of calcium</td>
</tr>
<tr>
<td>Increased urinary excretion of calcium</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Decreased muscle mass</td>
</tr>
<tr>
<td>Decreased bone matrix</td>
</tr>
<tr>
<td>Suppression of gonadal function</td>
</tr>
<tr>
<td>Suppression of adrenal androgen secretion</td>
</tr>
<tr>
<td>Patient inactivity from underlying disorder</td>
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<td>Possible effects of inflammatory conditions</td>
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menopausal women, clinical assessment of estrogen status may be adequate.

PREVENTION AND TREATMENT OF GIOP

Adjustment of Glucocorticoid Therapy

Using shorter-acting glucocorticoids (eg, prednisone instead of dexamethasone) and alternate-day therapy help to minimize adverse effects in general, and use of topical or inhaled glucocorticoids may help prevent osteoporosis. Nonetheless, application of glucocorticoids to the skin (particularly with occlusive dressings) and normal doses of inhaled steroids can have a deleterious effect on BMD.9

Calcium and Vitamin D

There is evidence that oral calcium and vitamin D supplementation can prevent bone loss in patients receiving lower doses (<20 mg/d of prednisone) of glucocorticoid therapy. In controlled trials of other agents,26 “placebo” groups receiving calcium at 800 to 1000 mg/d (elemental calcium) as well as vitamin D (doses of 250-400 IU/d) did not lose bone from the spine or certain sites in the hip, despite taking up to 15 mg of prednisone per day. These data corroborate those of a 2-year study27 of patients with rheumatoid arthritis receiving an average prednisone dose of about 6 mg/d. Thus, for patients receiving low-dose prednisone therapy, calcium and vitamin D supplementation appears to be a cost-effective way to prevent GIOP. In the VAMC, the monthly cost for daily supplementation with 1 g of elemental calcium in the form of calcium carbonate and 400 U of vitamin D in the form of a multivitamin tablet is $3.16. This cost is considerably less than other treatments, as shown in Table 2.

Calcitonin

Although some small studies have shown that subcutaneous29 or intranasal30 calcitonin can be used in the management of GIOP, larger blinded studies31,32 have not shown much effect of calcitonin beyond that from the calcium and vitamin D used for both placebo and active drug groups. While calcitonin has been found to have an analgesic effect33 that may be helpful in patients with painful fracture, it is not approved by the Food and Drug Administration (FDA) for GIOP.

Bisphosphonates

There are now several excellent studies demonstrating the effectiveness of bisphosphonate therapy in preventing or treating GIOP in both men and women. Two randomized studies34,35 showed that etidronate disodium given in cyclic fashion (400 mg orally daily for 2 weeks every 3 months) could prevent bone loss and vertebral fracture in patients just starting glucocorticoids at doses of 7.5 mg of prednisone or more. In more recent studies of newer bisphosphonates, alendronate sodium36,37 and risedronate sodium38,39 have been shown to successfully prevent and treat GIOP. In the alendronate study,36 the relative risk of spine fracture defined by morphometric analysis of x-ray films was 0.6 in the men and women taking alendronate. In the 2-year blinded extension,37 continued alendronate therapy was shown to dramatically decrease the incidence of morphometric vertebral fractures. In a study of risedronate in patients receiving long-term glucocorticoid therapy,39 the vertebral fracture rate was decreased by 70% in 1 year in men and women who received risedronate. This was confirmed by another randomized, controlled, double-blinded study39 of risedronate in patients beginning glucocorticoid therapy.

Bisphosphonate therapy can decrease fracture risk and increase bone density in patients about to start glucocorticoid therapy and in patients already taking prednisone or its equivalents. The FDA has approved alendronate for treatment of GIOP. The approved dose is 5 mg/d, except for postmenopausal women not receiving hormone replacement therapy, for whom the approved dose is 10 mg/d. Risedronate sodium at 5 mg/d is FDA approved for both prevention and treatment of GIOP. Trials of alendronate sodium, 70 mg once weekly, and risedronate sodium, 35 mg once weekly, in GIOP are currently in progress. A recent study40 suggests that intravenous pamidronate disodium may be used as an alternative to oral bisphosphonates to prevent GIOP, but this is not FDA-approved therapy. A summary of bisphosphonate treatment regimens that have not yet received FDA approval is listed below.

Calcitonin nasal spray 200 U/d 38.40
Calcium carbonate 1 g/d elemental calcium 2.03
Calcium citrate 1 g/d elemental calcium 3.04
Multivitamin 1 tablet/d (400 U) 1.13
Calcitonin nasal spray 200 U/d 38.40
Etidronate disodium 400 mg/d × 14 every mo 11.05
Alendronate sodium 10 mg/d 34.57
Alendronate sodium 70 mg/ wk 34.47
Risedronate sodium 5 mg/d 32.07
Risedronate sodium 35 mg/ wk 34.02
Pamidronate disodium 30 mg intravenously every 3 mo 46.53

Table 2. Monthly Costs of Therapy for Glucocorticoid-Induced Osteoporosis at a Veterans Affairs Medical Center

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Monthly Cost, $</th>
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<tbody>
<tr>
<td>Calcium carbonate 1 g/d elemental calcium</td>
<td>2.03</td>
<td></td>
</tr>
<tr>
<td>Calcium citrate 1 g/d elemental calcium</td>
<td>3.04</td>
<td></td>
</tr>
<tr>
<td>Multivitamin 1 tablet/d (400 U)</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>Calcitonin nasal spray 200 U/d</td>
<td>38.40</td>
<td></td>
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<tr>
<td>Etidronate disodium 400 mg/d × 14 every mo</td>
<td>11.05</td>
<td></td>
</tr>
<tr>
<td>Alendronate sodium 10 mg/d</td>
<td>34.57</td>
<td></td>
</tr>
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<td>Alendronate sodium 70 mg/ wk</td>
<td>34.47</td>
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</tr>
<tr>
<td>Risedronate sodium 5 mg/d</td>
<td>32.07</td>
<td></td>
</tr>
<tr>
<td>Risedronate sodium 35 mg/ wk</td>
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<td></td>
</tr>
<tr>
<td>Pamidronate disodium 30 mg intravenously every 3 mo</td>
<td>46.53</td>
<td></td>
</tr>
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</table>

Off-Label Bisphosphonate Therapy

Etidronate disodium, 400 mg orally every day for 2 weeks every 3 months
Alendronate sodium, 70 mg/ wk orally
Risedronate sodium, 35 mg/ wk orally
Pamidronate disodium, 30 mg intravenously every 3 months

There is evidence that these regimens will increase BMD in postmenopausal osteoporosis, and there are ongoing studies to determine if these regimens are applicable to GIOP. Patients prefer the weekly regimens, and compliance may be better. In addition, for patients unable to tolerate oral bisphosphonates, intravenous pamidronate has been widely used off label, despite lack of fracture efficacy data. Nonetheless, there is reason to believe that these alternatives may be of benefit to many patients. Etidronate is widely used for GIOP in other countries. As discussed below, teriparatide, an active frag-
ment of parathyroid hormone (PTH), has been approved for postmenopausal osteoporosis and for primary or hypogonadal osteoporosis in men. It is likely to be useful in GIOP.

Anabolic Agents

The antiresorptive agents, such as bisphosphonates, fill in the remodeling space, but drugs that actually increase bone formation would make great sense in a disorder marked by decreased bone formation. Fluoride has anabolic effects in bone. Even though it increased BMD in patients with GIOP, fracture rate was not decreased. More recently, intermittent PTH1-34 fragment has been used in postmenopausal women with osteoporosis and GIOP as an anabolic agent. This seemingly contradictory effect of PTH is well demonstrated by a study, in which postmenopausal women taking glucocorticoids and with history of fracture were given a fragment of PTH (containing amino acids 1-34) as a daily injection. Women who received the PTH fragment had a dramatic increase in BMD, as measured by DXA and by quantitative computed tomography. Although there are no fracture data from the study of PTH in patients with GIOP, a different preparation of the same fragment (teriparatide) decreased vertebral fracture risk in women with postmenopausal osteoporosis. Parathyroid hormone fragment (teriparatide) has also been shown to markedly increase BMD in men with idiopathic osteoporosis. Finally, in one recent study of postmenopausal osteoporosis, patients received 1 year of PTH therapy followed by 1 year of alendronate therapy, resulting in dramatic increases in BMD. It is likely that various types of combination therapy will be successfully tested in GIOP. Teriparatide, the PTH fragment used in some of the studies described above, has now been approved for postmenopausal osteoporosis and for men with primary or hypogonadal osteoporosis.

Sex Hormone Replacement Therapy

In men made hypogonadal by glucocorticoid therapy it makes intuitive sense to replace androgens. In a study by Reid et al, men with GIOP due to lung diseases were found to have low serum testosterone levels. Replacement of testosterone resulted in increased BMD. In postmenopausal women with rheumatoid arthritis, hormone replacement therapy increases BMD. Thus, at this stage in our knowledge, hormone replacement therapy (testosterone or estrogen with or without progestin) is indicated for many patients with GIOP. However, the sorts of cautions in using such agents (eg, increase in hormone-sensitive tumors) apply to patients with GIOP. An alternative to hormone replacement therapy for women is the selective estrogen receptor modulator raloxifene, which has been demonstrated to be an effective treatment for postmenopausal osteoporosis. There are no data available on the use of raloxifene in postmenopausal women with GIOP.

**STRATEGY FOR VETERANS WITH OR AT RISK FOR GIOP**

In an ideal world, all patients receiving glucocorticoid treatment or about to start should be assessed by DXA. However, not all VAMCs have densitometers. An overall management strategy is shown in Table 3.

<table>
<thead>
<tr>
<th>Table 3. General Strategy for Glucocorticoid-Induced Osteoporosis</th>
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<tbody>
<tr>
<td>For all patients, encourage exercise, especially weight-bearing exercise; prevent falls</td>
</tr>
<tr>
<td>For postmenopausal women, consider hormone therapy or selective estrogen receptor modulators such as raloxifene</td>
</tr>
<tr>
<td>For premenopausal women and men, assess gonadal status and consider estrogen or testosterone replacement</td>
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</table>

**Patients Already Taking Glucocorticoids for More Than 3 Months**

In VAMCs with densitometers, bone density of the spine and hip should be measured. For patients with bone density–defined osteoporosis or marked osteopenia, treatment is listed below. For VAMCs without a densitometer, there are at least 2 alternatives: (1) It may be possible to send the patient to another VAMC with a densitometer. Each VISN (Veterans Integrated Service Network, a group of hospitals and clinics with centralized management) is likely to have at least 1 densitometer. In some cases, DXA at a community medical facility may be available. (2) For patients taking glucocorticoids for more than 3 months and without other risk factors for osteoporosis, conservative therapy (1000 mg/d of calcium and 400-800 U of vitamin D per day) can be considered. Note that patients taking more than 7.5 mg of prednisone equivalent per day are at much higher risk for bone loss than patients taking lower doses. Patients with risk factors other than glucocorticoid therapy (eg, older age, history of fracture, postmenopausal or low testosterone level, current cigarette smoking, low calcium intake) should be considered for pharmacologic therapy with a nitrogen-containing bisphosphonate. The problem with the latter approach is that some patients who do not have GIOP will be treated, and it will be impossible to determine the response to therapy. As can be seen from Table 2, the cost of pharmacologic therapy with either alendronate or risedronate is about $33 per month, in addition to the cost of calcium and vitamin D.

In many VAMCs, the Pharmacy Database can be used to identify patients taking long-term glucocorticoid therapy. Clinical reminders can be added to electroni-
sary ordered prescriptions to ask the practitioner if preventive measures have been instituted for each patient.

Patients Starting Glucocorticoid Therapy

All patients starting use of glucocorticoids (and expected to need them for at least 3 months) should be offered calcium supplementation (1 g/d elemental calcium) and vitamin D (400-800 IU/d), with monitoring of 24-hour urinary calcium or urinary calcium-creatinine ratio (when measured in milligrams per deciliter divided by milligrams per deciliter, the ratio should be between 0.05 and 0.16). Patients receiving lower-dose glucocorticoid therapy (≤5 mg/d prednisone equivalent) will likely maintain bone on this regimen. For patients starting moderate-dose glucocorticoid therapy (5-7.5 mg/d prednisone) bone densitometry should be performed to determine which patients need bisphosphonate therapy. In VAMCs without DXA testing, a case can be made to treat all patients who will need more than 3 months of prednisone at doses of 5 mg/d or more. From the studies of van Staa et al, the daily dose of glucocorticoid was more important than the cumulative dose. Increased fracture risk was seen in the medium-dose range (2.5-7.5 mg/d of prednisolone, approximately 3-9 mg/d of prednisone). For patients who will need more than 7.5 mg of prednisone daily, bisphosphonate therapy with alendronate or risedronate is clearly indicated. The study of Naganathan et al suggests that all glucocorticoid-treated patients older than 70 years should receive bisphosphonate therapy, but it will be necessary to have other studies support their conclusion.

Although there are no studies large enough to determine whether sex hormone replacement therapy lowers fracture risk in GIOP, the data suggest that the addition of estrogen, a selective estrogen receptor modulator, or testosterone replacement will have a salutary effect on BMD in patients with GIOP. New treatments from anabolic agents such as PTH hold promise for even greater prevention of fracture.

Other Measures

For all patients at risk for osteoporosis, preventing falls is of great importance. A recent study suggests that the use of hip protectors for frail elders with osteoporosis is very effective in preventing hip fracture.

Patients With Sarcoidosis

Patients with sarcoidosis may be treated with glucocorticoids and may be at risk for osteoporosis. Most of the studies of this disorder have been in African American patients and may be at somewhat lower risk for GIOP. However, sarcoidosis can cause a vitamin D excess syndrome due to activation of vitamin D in the sarcoid granulomas. This can lead to hypercalciuria and hypercalcemia, which could be exacerbated by standard therapy for GIOP, supplementary calcium and vitamin D. In a retrospective analysis of patients with sarcoidosis at a VAMC, hypercalciuria was found to be uncommon and no patients had hypercalcemia, despite some patients having been treated with supplements. In all patients with GIOP, it is prudent to measure serum calcium and urinary calcium (with creatinine) levels in a spot or 24-hour urine sample before and 4 to 8 weeks after starting calcium and vitamin D supplementation. These same tests should be done periodically thereafter.

Patients Undergoing Organ Transplantation

In several VAMCs, patients may undergo transplantation of the kidney, lung, liver, bone marrow, or heart. Patients receive antirejection medications that include glucocorticoids and other drugs such as cyclosporine that may be toxic to bone. These patients are at very high risk for bone loss and fracture, and they require careful, individualized therapy. A full discussion of this topic is beyond these guidelines, but all transplant patients should be referred to a physician specializing in osteoporosis for management of their bone loss.

OTHER GUIDELINES AND CLINICAL SETTINGS

The reader is directed to guidelines for GIOP issued by a United Kingdom Consensus Group and to the recently revised guidelines for GIOP issued by the American College of Rheumatology. The strategy for veterans with GIOP can be applied to other managed care settings and to patients in general. The costs of tests, availability of BMD testing, and costs of therapy will vary with the clinical setting.

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From the Endocrinology Section, McGuire Veterans Affairs Medical Center, and Departments of Internal Medicine and Preventive Medicine and Community Health, Medical College of Virginia of Virginia Commonwealth University, Richmond (Dr Adler); and Departments of Medicine and Epidemiology and Preventive Medicine, University of Maryland School of Medicine, and Department of Medicine, Maryland Veterans Affairs Health Care System, Baltimore (Dr Hochberg). Dr Adler has served on the speakers bureau of or received honoraria from Merck & Co, Procter & Gamble, and Eli Lilly Inc. Dr Hochberg has served as consultant to Aai Laboratories, Abbott Laboratories, Aventis Pharmaceutical Co Inc, Bristol Myers Squibb, Eli Lilly Inc, Genzyme Corporation, La Jolla Pharmaceutical Co, Laboratories NEGMA, Merck & Co, Novartis, Sanoﬁ-Synthelabo, Scios Inc, and Wyeth Ayerst, and is a stock shareholder in Johnson & Johnson, Eli Lilly Inc, Merck & Co, Procter & Gamble, and Schering Plough.

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Corresponding author and reprints: Robert A. Adler, MD, Endocrinology Section (111-P), McGuire Veterans Affairs Medical Center, Richmond, VA 23249 (e-mail: robert.adler@med.va.gov).

REFERENCES