Screening for Reversible Osteoporosis: Is Cortisol a Culprit?

In this issue, Chiodini and colleagues (1) measured the prevalence of subclinical hypercortisolism in 219 consecutive patients 44 to 72 years of age with suspected idiopathic osteoporosis. These individuals had no known secondary cause of osteoporosis, had not received drugs known to influence bone or cortisol, and had no apparent signs or symptoms of cortisol excess (including moon facies, red striae, skin atrophy, or buffalo hump). The investigators screened each patient for hypercortisolism with a 1-mg dexamethasone suppression test and required an abnormal response to the 2-mg, 2-day dexamethasone test, in addition to abnormal urine cortisol levels and midnight cortisol values to establish the diagnosis. Overall, 3.3% of the patients had abnormal responses to these tests. Because the patients did not have clinically recognized hypercortisolism, the authors used the term subclinical hypercortisolism to describe the disorder. The study suggests that hypercortisolism may contribute to few cases of osteoporosis, at least in a restricted subpopulation that is older and has experienced fractures. This editorial addresses several questions raised by this unexpectedly high rate of hypercortisolism.

First, are these results believable, given the rarity of the Cushing syndrome? The 3.3% prevalence of subclinical hypercortisolism in patients with suspected idiopathic osteoporosis is surprisingly high. Clinically apparent Cushing syndrome is rare, being diagnosed in 0.7 to 2.4 per 1 million persons annually (2). As a result, until recently, clinically inapparent hypercortisolism has not been considered as an important—and potentially reversible—cause of disorders associated with hypercortisolism. However, studies of patients with diabetes, hypertension, and hirsutism showed a prevalence of the Cushing syndrome of 2% to 4%, 1%, and 0.25%, respectively. In light of these relatively high prevalences and the findings reported by Chiodini and colleagues, it seems reasonable to screen patients with these disorders for hypercortisolism and perhaps even investigate the prevalence of pathogenic Cushing syndrome in patients with other signs of the syndrome, such as osteoporosis (3–5).

Subclinical hypercortisolism refers to the dysregulation of the hypothalamic–pituitary–adrenal axis along with clinical characteristics compatible with the Cushing syndrome but not sufficiently suggestive to raise a diagnostic red flag. Usually the patients are middle-age or older and have disorders common in that age group, such as obesity, diabetes, hypertension, and depression. Often these features appeared insidiously, and the physician has not considered hypercortisolism as an etiologic factor.

One problem in Chiodini and colleagues’ study stems from the difficulty in validating the diagnosis of subclinical Cushing syndrome. We do not know the best tests for subclinical hypercortisolism. Chiodini and colleagues used abnormal responses to dexamethasone and increased midnight serum or urinary free cortisol levels to identify subclinical hypercortisolism. These abnormalities are present in clear-cut Cushing syndrome, and they therefore indicate cortisol dysregulation. However, people who have non-specific clinical features but do not have overt Cushing syndrome sometimes have similar abnormalities (6). To measure the sensitivity and specificity of these tests, a gold standard is needed for the diagnosis of subclinical Cushing syndrome. Until one is agreed on, we will have difficulty confirming the diagnosis and should rely on several abnormal tests of adrenal function. Meanwhile, some investigators have relied on post–adrenal surgery hypocortisolism or improvement in clinical features to validate the diagnosis retrospectively (7–10). Unfortunately, not all patients who are obese, have hypertension, or have diabetes improve after surgery, and it is not possible to predict beforehand who will benefit from surgery.

Second, do these results suggest a causal relationship between hypercortisolism and reduced bone density? Florid glucocorticoid excess is toxic to bone health. Children can stop growing, and patients can have bone demineralization and necrosis (11). The clinical scenario is usually straightforward: The patient has an unmistakable clinical phenotype of the Cushing syndrome, with recent weight gain, abnormal fat distribution, diabetes, hypertension, hirsutism, depression, stretch marks, and weakness. In these cases, a return to normal glucocorticoid levels allows growth and remineralization of bone (12). The length of time that glucocorticoid levels need to be at a high level in order to cause a toxic effect of cortisol is not known, although recent publications suggest that subtle hypercortisolism may account for osteopenia in both depression and subclinical Cushing syndrome (7, 13).

This study suggests a dose-dependent effect of hypercortisolism on bone mineral density, which is an important criterion for a causal relationship. Almost all (about 96%) patients with normal bone density had a normal cortisol response to 1 mg of dexamethasone. In patients with an abnormal response to 1 mg of dexamethasone, the responses to the 2-mg dexamethasone suppression test varied. Patients without suppression after either dose of dexamethasone presumably had more autonomous, abnormal cortisol secretion than those who have suppression after the 2-mg, but not the 1-mg, dexamethasone dose. Within this group, the cortisol responses to the 2-mg dexamethasone test were inversely related to their T-scores, suggesting that more autonomous cortisol secretion was associated with lower bone density. Subclinical hypercortisolism, the most severe abnormality of cortisol dynamics in the study, was found only in patients with the most severe bone disease, as evidenced by osteoporosis and vertebral fracture. These data suggest a graded effect of hypercortisolism on bone density.
Chiodini and colleagues’ study has several shortcomings. It was a cross-sectional evaluation of a referral population. The prevalence of subclinical hypercortisolism may be lower in a community-based population. As a measure of a relationship at 1 point in time (the defining characteristic of a cross-sectional study), the study tells us nothing about the natural history of the disorder. In addition, the authors did not provide key clinical measurements, such as age, menopausal status, and other clinical features that suggest hypercortisolism (for example, obesity, diabetes, and hypertension). Despite these limitations, the study suggests that hypercortisolism may contribute to few cases of unexplained osteoporosis.

Finally, how should physicians incorporate this information into their daily practice? Should they screen osteoporotic patients for hypercortisolism? It is useful to examine these questions in light of the World Health Organization guidelines for implementing a screening program (14). To be appropriate for screening, a disease should be an important health problem. It should have a known natural course that includes an interval during which the patient is asymptomatic, the disease is detectable, and an intervention is available and effective. The screening test must be acceptable to the population. The decision to screen should take into account the harms of false-positive results.

Screening for subclinical hypercortisolism to prevent osteoporosis meets some of these guidelines. Osteoporosis and its morbidity are certainly important public health issues. However, we have not yet defined the natural history of subclinical hypercortisolism or established its diagnostic criteria.

The World Health Organization criteria say that one should screen for a disease only if treatment is effective during the asymptomatic phase of the disease. The evidence that treating subclinical hypercortisolism would prevent fractures is indirect and tenuous. The natural history of osteoporosis includes a window during which bisphosphonates increase bone mineral density and reduce fracture rates. Perhaps treating subclinical hypercortisolism during this window would have the same effect. Chiodini and colleagues’ study and clinical experience hint that the effect of hypercortisolism on bone mineral density depends on dose and duration of exposure. If so, early diagnosis and intervention might prevent osteoporosis, which would support the case for screening. However, the evidence for this hypothesis is weak. Whether metabolic variables and hypertension improve after surgical treatment of adrenal adenomas with subclinical Cushing syndrome is not clear from the conflicting evidence, and no one has published a study on bone mineral density changes after surgery (9, 10).

Overall, Chiodini and colleagues’ findings suggest a wait-and-see approach to screening for subclinical hypercortisolism in patients with osteoporosis. Their study, excellent as it is, leaves many pertinent questions unanswered, especially about natural history of the disease and response to early treatment.

We need more information to decide whether to screen for hypercortisolism in patients with osteoporosis. What would an ideal study look like? It should be prospective, include several tests to confirm a positive screening test, and measure dexamethasone levels to identify false diagnoses of subclinical hypercortisolism (15). Ideally, authors would validate the diagnosis by documenting post-surgical hypocortisolism. Doing all the tests systematically in all patients would allow the authors to develop an empirical diagnostic algorithm. Subsequent studies could then evaluate the natural history of bone density in these patients and establish the prevalence of the disorder in larger populations of patients with osteoporosis. Trials of medical therapy versus surgical tumor resection would evaluate the efficacy of bone-targeted and tumor-targeted treatments in this setting.

While we wait for these studies, physicians should consider the possibility of hypercortisolism in middle-age and older patients with idiopathic osteoporosis and should perform a careful history and physical examination to detect subtle clues of hypercortisolism. Good clinical judgment, with attention to evolution over time from a subtle cushingoid appearance to more overt signs and symptoms, should guide a nuanced, patient-specific decision to screen for hypercortisolism. Meanwhile, we await definitive evidence that screening should be routine practice.

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References