INVITED COMMENTARY

Incidentaloma, glucocorticoid excess and low bone mineral density: a coincidence?

Jean-Pierre Devogelaer
Rheumatology Unit, St-Luc University Hospital, Université catholique de Louvain, avenue Hippocrate 10, B-1200 Brussels, Belgium

The paper by L Tauchmanova et al. published in this issue of the Journal leads to the discussion of several aspects of the management of patients suspected of being exposed to glucocorticoid excess (1). The first point to be considered is that there is no doubt, nowadays, that glucocorticoid (GC) excess, whether endogenous or exogenous, leads to rapid bone loss early after the start of GC therapy and, by extrapolation, presumably early in the course of excessive adrenal secretion. It increases dramatically the risk of fragility fractures (2). Osteoporosis (OP) had already been observed by H Cushing in his princeps description of the syndrome which, since then, bears his name. The mechanisms of glucocorticoid-induced osteoporosis (GC-OP) are multiple, but not yet fully understood. Grossly, GC-OP is the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3). Both act synergistically to provoke bone fragility. Increased bone resorption may be the consequence of decreased bone formation and increased bone resorption, the former being more marked than the latter (3).
to some confusion among users. Their attractive value is that they do not use ionizing radiation, and are cheaper and more portable than conventional bone densitometers using DXA that scan the spine and the femur, two sites central to fragility fractures. Whether peripheral ultrasonography can predict fracture risk as accurately as DXA has been suggested in studies on senile and postmenopausal osteoporosis, at least for the measurement of the heel in a water bath (14). So far, it has not been demonstrated that this will also be the case in GC-OP for both calcaneus and finger ultrasonography, the latter elegant technique of measurement having been used by L Tauchmanová et al. (1). According to their results, ultrasonography might at least be useful to preselect patients in whom more cumbersome axial and femoral DXA is indicated to confirm/exclude osteoporosis at the spine or hip, when there remains some doubt about a correct diagnosis.

A third point is to determine whether patients with adrenal incidentaloma (AI) are at significant increased risk of osteoporosis. Since the introduction in clinical practice of performant diagnostic tools such as ultrasound, computed tomography (CT scan) and magnetic resonance imaging (MRI), AI is more and more frequently observed. Quite a few studies have approached this question, but they seemingly yield different responses. Only small cross-sectional studies are currently available. Torlontano et al. (15) studied BMD in 32 female patients suffering from AI by two different techniques: by single energy quantitative computed tomography (L1-L4) (QCT), a technique which is able to measure pure trabecular BMD, and by DXA of the spine (L2-L4) and of the hip. A significant bone loss was observed in the small subgroup with subclinical hypercortisolism only, as compared with values of the reference population at their center. Their 64 controls tested were in the normal range. In another study, Rossi et al. (16) from the same group as Tauchmanová (1) evaluated BMD in 18 patients by DXA of the lumbar spine in patients under 65 years (n = not given) and of the left femoral neck in those older than 65 years (n = not given). They were compared with the international pooled sample provided as reference value by the densitometer’s manufacturer. No local control group was available. The BMD data looked consistent with the lack of significant bone loss in patients with adrenal adenoma, even when associated with subclinical Cushing’s syndrome. More recently, Osella et al. (17) have measured BMD also by DXA at the lumbar spine and at the hip in 27 patients with AI, with reference to the manufacturer’s normative data. A local control group (n = 54) had their lumbar spine measured, but unfortunately not the hip because of ‘budgetary restrictions’. Lumbar BMD values in patients with AI were not significantly different from those in control subjects which, however, had BMD values a little lower (but not significantly) than the manufacturer’s reference group. Nevertheless, the ranges of the Z-scores (numbers of standard deviations from the mean BMD of the age- and sex-matched manufacturer’s controls) were quite large: −3.86 to +1.79 versus −2.96 to +2.67 s.d. in the studied group and the control group respectively, underlying the large variation of BMD values in the studied population. Forty-eight percent of the patients were in the osteopenia and osteoporosis ranges according to the WHO rules (13). The authors also observed a good correlation between BMD values and serum PTH levels, and, as mentioned above, secondary hyperparathyroidism has been implicated in the pathogenesis of GC-OP. In the present study (1), 34 patients were studied both by DXA at the lumbar spine and at the hip, and by ultrasonography (US) of the proximal phalanges; reference values were those provided by the manufacturers. All patients had significantly lower BMD and US values as compared with controls. Bone loss was consistently more marked in patients with overt Cushing’s syndrome as compared with patients with subclinical Cushing’s syndrome. How can the apparent discrepancies between studies performed in the same country and even in the same center be explained? First, the numbers of studied patients are quite low. Secondly, the criteria to define subclinical Cushing’s syndrome may differ from one study to the other. They were less stringent in one study (15), but look similar in others (1, 16, 17). Thirdly, the techniques of BMD measurements also differed, from ultrasonography of the phalanges, DXA of the lumbar spine and/or the hip, to QCT of the spine, and by comparison to local controls or to the manufacturers’ reference values.

What approach should the clinician adopt in the near future when dealing with a patient suffering from AI? The first step should be to rule out the hypothesis of a primary or a secondary metastatic lesion. If the tumor proves to be benign, how does one determine which small tumor will deserve a surgical removal? Besides the lack of knowledge of the natural history of patients with an apparently silent AI, there remains some uncertainty about the long-term safety of subclinical Cushing’s syndrome. In the presence of excessive glucocorticoid secretion, the search for any complication like hypertension, diabetes, obesity and dyslipidemia seems advisable. BMD and bone metabolism assessment should also be reasonably added to the decision tree for a therapeutic intervention. A low BMD should help to decide in favor of a surgical operation, somewhat in a similar manner that low BMD is thought to have a role in the indication for parathyroid surgery in asymptomatic hyperparathyroidism (18). Long-term longitudinal studies of bone metabolism and BMD in patients with asymptomatic AI are urgently needed to help to understand better the clinical implication of subclinical Cushing’s syndrome in a complicated pathological issue such as GC-OP.
References


Received 12 April 2001
Accepted 25 May 2001