

# Unrecognized and Unappreciated Secondary Causes of Osteoporosis

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## KEYWORDS

- Bone • Cause • Secondary osteoporosis

## KEY POINTS

- Renal tubular acidosis is a chronic form of metabolic acidosis that is caused by either the reduced capacity of the proximal tubule of the kidney to reabsorb the filtered bicarbonate load (proximal) or the reduced capacity of the distal renal tubule to maximally acidify the urine.<sup>1-3</sup>
- The bone is an reservoir for buffering hydrogen ions.
- The carbonate ion (from the splitting of calcium from calcium carbonate) buffers hydrogen ions.
- The focus for secondary causes of osteoporosis is separated into 5 systems: renal, hematological, gastrointestinal, endocrine and drugs associated with osteoporosis.
- There are many secondary causes of osteoporosis, including celiac disease, MGUS (monoclonal antibody of undetermined significance), impaired renal function, diabetes mellitus, and renal tubular acidosis.
- Through targeted laboratory tests, many secondary causes of osteoporosis can be identified.

## INTRODUCTION

There are many secondary causes of osteoporosis.<sup>1-6</sup> However, before this article discusses specific secondary osteoporosis, it is important to define osteoporosis in the clinical sense.

The National Institutes of Health (NIH) consensus statement on how osteoporosis is defined is correct and scientific.<sup>7</sup> However, the NIH definition is not applicable in clinical practice, because bone quality, an important component of the definition and contributor to bone strength, cannot be measured in clinical practice at this time. After 1994, the World Health Organization (WHO) diagnostic criteria for postmenopausal osteoporosis was based on a bone mineral density (BMD) and a T score of  $-2.5$  or lower,<sup>8</sup> but the diagnosis of osteoporosis could, and still can, be made after a low-trauma fragility fracture in women or men 50 years of age and older.<sup>7</sup> The classic fractures identified as being osteoporotic-type fractures are fractures of the hip and vertebrae, although

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low-trauma fractures of the humerus, forearm, femur shaft, tibia, and/or fibula are also associated with a high risk for future fractures in untreated population studies. Even fragility fractures (or low dual-energy x-ray absorptiometry values) may be caused by metabolic bone diseases that are not osteoporosis (**Box 1**).<sup>9,10</sup>

Once a clinician is confident that a patient has osteoporosis, then the question is whether the diagnosis is postmenopausal osteoporosis, or osteoporosis of aging (the most common forms of osteoporosis) or some other form of osteoporosis. In men, the osteoporosis that develops in the elderly is usually related to hypogonadism.

Although estrogen deficiency is the most common cause of osteoporosis in postmenopausal women, there are many other conditions that may accompany estrogen deficiency and contribute to the impairment of bone strength in this population. Laboratory evaluation to detect any secondary mechanisms leading to derangements in bone metabolism in postmenopausal patients includes tests that may be ordered as a standard of care at the primary care level, and more in-depth tests that are considered in complex patients.<sup>11-13</sup> The basic primary, as opposed to secondary and more complex, laboratory assessment for causes of osteoporosis is listed in **Boxes 2 and 3**. This article also focuses on clinical issues related to targeted laboratory tests (see **Box 2**). Although 24-hour urine calcium and creatinine clearance are often considered to be a component of a basic evaluation for osteoporosis, this article classifies this important test as targeted because it is inconsistently performed and commonly misinterpreted at the primary care level. However, a 24-hour urine is strongly advised.

In this article, the focus for secondary causes of osteoporosis is separated into 5 systems: renal, hematological, gastrointestinal, endocrine, and drugs associated with osteoporosis.

#### **RENAL-RELATED ASSOCIATIONS BETWEEN LOW BMD AND/OR FRACTURES, EXCLUDING PATIENTS ON DIALYSIS AND POSTTRANSPLANTATION BONE DISEASE** *Hypercalciuria*

The upper limit of normal for a 24-hour urine calcium has been identified as 4.0 mg/kg/d for women and 4.5 mg/kg/d for men.<sup>14,15</sup> The upper limit of the normal laboratory reference range was established in population studies showing that patients exceeding this level were often excreting more calcium than any specific reference range established by any particular study. There was also evidence that those who formed hypercalciuric calcium renal stone were at a higher risk for fractures and/or loss of BMD than is seen in hypercalciuric individuals who do not form stones.<sup>16-21</sup> Because of the difference in skeletal-related outcomes of hypercalciuric patients who form stones and those who do not form stones, it may be helpful to obtain a noncontrast computed tomography scan of the kidneys in some hypercalciuric patients with no history of a clinical renal

##### **Box 1**

##### **Example of nonosteoporotic causes of low BMD or fractures**

Osteomalacia

Genetic disorders (eg, osteogenesis imperfecta)

Renal bone disease

Bone marrow disorders (eg, multiple myeloma, mastocytosis, monoclonal gammopathy of undetermined significance [MGUS])

Paget disease, fibrous dysplasia

Metastatic cancer to bone

**Box 2****Evaluation of secondary causes of osteoporosis: basic work-up**

Careful history and physical examination

Basic laboratory tests:

Complete blood count

Biochemical profile (to include serum calcium, phosphorus, electrolytes, alkaline phosphatase, and creatinine)

Thyroid-stimulating hormone

25-Hydroxyvitamin D level

Serum protein electrophoresis

stone event; the finding of a silent radiographic stone may change clinical strategy toward consideration of intervention with a thiazide diuretic. What is the origin of high urinary calcium? Although it has been suggested that there are 3 possible sources of increased urinary calcium excretion (bone, renal, or gut),<sup>22</sup> it is difficult to discriminate among these sources in clinical practice. Although increased intact parathyroid hormone (PTH) or 1,25-dihydroxyvitamin D levels may suggest a renal leak or hyperabsorption from the gastrointestinal tract, clinical management may not differ as long as the clinician is certain that the patient does not have primary hyperparathyroidism as a cause of an increased PTH. Several normal serum calcium concentrations (rather than a single isolated normal value) may be necessary to exclude primary hyperparathyroidism. Restriction of calcium intake has been suggested in patients with gastrointestinal hyperabsorption as the mechanism for hypercalciuria.

**Box 3****Evaluation of secondary causes of osteoporosis: comprehensive work-up**

Serum parathyroid hormone

Bone-specific alkaline phosphatase (BSAP)

Serum immunoelectrophoresis and serum free light chains

Celiac disease testing

Biochemical bone turnover markers (BTM: c-telopeptide and propeptide type I collagen)

Serum free T<sup>4</sup> and fasting plasma cortisol

(May prefer 24-hour urinary free cortisol and midnight salivary cortisol)

1,25-Dihydroxyvitamin D

24-Hour urine for calcium, phosphorus, protein, and creatinine clearance

Small bowel biopsy (for celiac disease)

Serum prolactin

Serum insulinlike growth factor 1 (in anorexia, diabetes)

Fibroblastic growth factor 23<sup>a</sup>

Bone biopsy

<sup>a</sup> Chronic kidney disease (CKD), hypophosphatemia, osteomalacia, normal 25-hydroxyvitamin D and low 1,25-dihydroxyvitamin D, unexplained increase of BSAP, after tumor removal in oncogenic osteomalacia to monitor adequacy of tissue ablation.

However, without strong evidence that this dietary calcium restriction consistently reduces the risk of renal stone formation, there is the potential negative trade-off of reducing bone mass in others whose source of hypercalciuria is renal or bone. When should a clinician treat hypercalciuria? Should everyone identified with hypercalciuria be treated with agents, such as thiazide diuretics, that reduce urinary calcium excretion? In this author's opinion, no. Some patients may have low BMD and hypercalciuria without a causal relationship. Patients with hypercalciuria and no renal stones may never have a clinical event associated with their hypercalciuria and, in that regard, could be considered to have healthy hypercalciuria. Interventions to lower urinary calcium should treat those patients who have a negative clinical consequence, such as a renal stone or unexplained fracture, associated with the hypercalciuria.

### ***Renal Tubular Acidosis***

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Renal tubular acidosis (RTA) is a chronic form of metabolic acidosis that is either caused by the reduced capacity of the proximal tubule of the kidney to reabsorb the filtered bicarbonate load (proximal), or the reduced capacity of the distal renal tubule to maximally acidify the urine.<sup>1-3</sup> The bone is a large reservoir for buffering hydrogen ions. The carbonate ion (from the splitting of calcium from calcium carbonate) buffers hydrogen ions. When this hydrogen ion load is greater than the normal daily acid load, the bone becomes the buffer. This may result in a spectrum of metabolic bone disorders from osteomalacia (with proximal RTA) to osteoporosis (with distal RTA), both of which can result in low BMD and/or fractures. However, in clinical practice, suspicion for RTA is best screened with serum electrolytes. The finding of an increased chloride (>110 mEq/L) and an low carbon dioxide (<18 meq/L) should lead to more sophisticated investigations into the possibility of an RTA, the most important of which is an arterial blood gas and a urine pH (best measured with a pH meter). An increased chloride and low serum CO<sub>2</sub> could also be caused by a respiratory alkalosis.<sup>23</sup>

### ***Chronic Kidney Disease***

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The National Kidney Foundation classifies the severity of chronic kidney disease (CKD) from the glomerular filtration rate (GFR), as measured by 24-hour urine for creatinine clearance, or as estimated by the Cockcroft-Gault equation or, preferably, the Modification of Diet in Renal Disease (MDRD) equation (calculators are available at [www.kidney.org/professionals/kdoqi/gfr\\_calculator.cfm](http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm)):

- Stage 1: GFR 90 mL/min/1.73 m<sup>2</sup> or higher with urine abnormalities (hematuria, proteinuria)
- Stage 2: GFR 60 to 89 mL/min with urine abnormalities
- Stage 3: GFR 30 to 59 mL/min without urine abnormalities
- Stage 4: GFR 15 to 29 mL/min without urine abnormalities
- Stage 5: GFR lower than 15, or if the patient is on dialysis. (Another stage, called 5D, was added to the list to denote patients on dialysis, because the metabolic derangements in bone and systemic biology may differ between patients on dialysis and those not on dialysis.)<sup>24</sup>

This staging system is relevant to the discussion of bone fragility that follows.

The diagnosis of osteoporosis in these patients has no universally accepted criteria, except for agreement that the diagnosis of osteoporosis can be made in stage 1 to 3 CKD on the basis of the WHO BMD criteria or a fragility fracture, if there are no concomitant metabolic abnormalities that could suggest the presence of CKD-mineral and bone disorders (CKD-MBD).<sup>25</sup> CKD-MBD is a term used to encompass

the systemic derangements in bone (mineralization, turnover, volume) that are linked to the systemic vascular calcification of severe CKD.

The diagnosis of osteoporosis in stage 4 to 5 and 5D CKD is best suggested by excluding other forms of renal osteodystrophy by quantitative histomorphometry or by attempting to classify the form of renal osteodystrophy by noninvasive means of assessing bone turnover, mineralization, and volume (CKD-MBD).<sup>25</sup> However, there are no clinical tools to make these distinctions between renal osteodystrophy and CKD-MBD in individual patients. Although many promising radiologic techniques that examine bone microarchitecture offer hope of being able to define turnover, mineralization, and volume noninvasively in severe CKD, they are investigational and unproven at this time in discriminating between renal osteodystrophy and osteoporosis.<sup>26</sup> As understanding of the relationships between turnover, mineralization, volume, and bone strength increase, these noninvasive imaging technologies may become the means to correlate turnover, mineralization, and volume with bone strength and open up a new way to classify skeletal strength. Because fracture risk is approximately doubled in patients even at stage 3 CKD compared with age-matched, body mass index (BMI)-matched, and BMD-matched persons without CKD, understanding the mechanisms that lead to the greater risk for fracture in these populations is important.<sup>26</sup> In the meantime, the clinician is left with quantitative bone histomorphometry (which requires biopsy) and biochemical markers of bone turnover to characterize the bone disease that may be responsible for low-trauma fractures in stage 5 CKD.<sup>27,28</sup> The clinician should use biochemical markers before bone biopsy to distinguish the form of renal osteodystrophy, because this distinction may prevent an unnecessary biopsy.

At the current time, the most useful of the biochemical profiling methods to discriminate among the major renal bone diseases in which an antiresorptive agent may not be desirable (adynamic bone disease) are bone-specific alkaline phosphatase and intact PTH. If a patient's bone-specific alkaline phosphatase level is increased, adynamic bone disease is highly unlikely. Assuming that other causes of this increased level (eg, Paget disease of bone, metastatic cancer) have already been excluded, the increased level could represent either osteomalacia or hyperparathyroid bone disease. However, a normal bone-specific alkaline phosphatase level does not exclude adynamic bone disease, whereas a low level is more often associated with low bone turnover. An increased PTH level does not exclude adynamic renal bone disease, but a low level (<150 pg/mL) suggests a low-bone-turnover state. A level 6 times or more greater than the upper limit of normal is more likely to be associated with high bone turnover. Thus, in clinical practice, patients with stage 4 or 5 CKD who have increased bone-specific alkaline phosphatase or very high (>6× the upper limit of the reference range) PTH values do not have adynamic bone disease.<sup>27</sup> Furthermore, once other causes of these aberrant biochemical abnormalities have been defined, then high-bone-turnover osteoporosis may be a consideration. In my opinion, if bone turnover markers suggest low bone turnover, bone biopsy is necessary before starting an antiresorptive agent.<sup>5</sup> The clinician should refer patients with suspected renal osteodystrophy or fracture with stage 4 to 5 CKD to a specialist dealing with such diseases because the other metabolic disturbances, such as an increased phosphate, low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and anemia, all need to be dealt with in such a complex disease.

## HEMATOLOGICAL DISEASES

Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) are 2 of the most common secondary causes of osteoporosis or fragility fractures.

MGUS is the most common plasma cell disorder; with an overall prevalence in the United States population of 3% in those 50 years of age and older, and nearly 7% of the population 80 years of age and older.<sup>29</sup> MGUS is defined as the detection of a monoclonal protein but with either no M protein, or a serum M protein value of 3 gm/dL or less, small amounts of light chains in the urine, and a proportion of plasma cells in the bone marrow of 10% or less in the absence of bone lesions, anemia, hypercalcemia, or renal failure related to the MGUS.<sup>29</sup> MGUS may be a precursor of more serious diseases, including MM, Waldenstrom macroglobulinemia, or primary amyloidosis. In the evaluation of patients, especially elderly patients with unexplained fractures, routine serum protein electrophoresis misses ~50% of patients with an M spike, and hence a more sensitive screening test using a combination of serum immunofixation and serum free light chains detects more than 95% of MM and/or MGUS.<sup>30</sup> The serum free  $\kappa/\lambda$  light chain ratio is a sensitive discriminator and also has prognostic value in helping to stratify risk for progression from MGUS to MM.<sup>31</sup> If there is doubt about the correct diagnosis or progression of disease, referral to an experienced hematologist/oncologist for bone marrow aspirations should be considered. It is important to know that, although bone lytic lesions are rare in MGUS, they still have a higher risk for osteoporotic fragility fractures that may be either related to an increase in marrow-derived receptor activator of nuclear factor  $\kappa$ -B ligand or to a decrease in osteoblast activity caused by plasma cell production of an osteoblast inhibitor, Dickkopf-1.<sup>32</sup>

### ***Mastocytosis***

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Mastocytosis as the mechanism for fragility fractures is a difficult disease to diagnose without bone marrow. Mastocytosis, if systemic, especially involving the skin, becomes an easier diagnosis if a skin biopsy shows the mast cells in the lesion. The proximity of the mast cell to bone remodeling surfaces and the production by this cell of a large number of chemical mediators and cytokines capable of modulating bone turnover (especially heparin) translates to skeletal involvement, ranging from severe osteolysis to significant osteosclerosis, with osteoporosis being the most frequently observed disorder.<sup>33-38</sup> Increased 24-hour urine excretion of *N*-methylhistamine may be valuable if there is suspicion of mastocytosis. However, the diagnosis requires a histologic confirmation.

## **GASTROINTESTINAL DISEASES**

### ***Celiac Disease***

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Celiac disease is a prevalent disorder and is one of the most common secondary causes of osteoporosis. The loss of small intestinal villi and accompanying pathophysiology leads to selective malabsorption of calcium (and iron) with a progressive negative calcium balance. Celiac disease laboratory detection is best accomplished by measuring serum antibodies to gluten, both the tissue transglutaminase (TT-IgA) antibody and the endomesial antibody (EmA). The sensitivity/specificity of these antibodies in patients with gastrointestinal symptoms is high: 87%/99% for TT-IgA and 87%/97% for EmA.<sup>39</sup> However, the sensitivity/specificity of these antibodies in asymptomatic celiac disease is less clear, because there have been few robust studies of small bowel biopsies, the gold standard for diagnosis, in asymptomatic patients. The sensitivity/specificity of the antibodies are correlated with the severity of the histologic findings; those with partial villous atrophy often have normal antibodies. From clinical experience, patients with osteoporosis who have no gastrointestinal symptoms and normal serum antibody levels should be considered for small bowel biopsies when there is a very low 24-hour urine calcium (<50 mg/d), unexplained secondary

hyperparathyroidism, 25-hydroxyvitamin D deficiency, unexplained iron deficiency, or higher-than-expected bone turnover marker levels despite compliance with oral anti-resorptive therapy.

### ***Crohn Disease and Other Inflammatory Bowel Diseases***

In Crohn disease, the pathophysiology of osteoporosis is multifactorial, including the effect of inflammatory cytokines mediating disease activity (interleukin [IL]-6, IL-1, tumor necrosis factor  $\alpha$ ), intestinal malabsorption caused by disease activity or intestinal resection, the use of glucocorticoids, malnutrition, immobilization, and, often, a low BMI.<sup>40,41</sup> Ileum resection has been identified as the single most significant risk factor for osteoporosis.<sup>42</sup> Patients with Crohn disease are young, and the relationship between the host of factors potentially deleterious to the skeleton and increased risk for osteoporosis and fractures remains unclear. Because fat-soluble vitamins (including vitamin D) are absorbed in the terminal ileum where Crohn disease is most prevalent, these patients often have exceptionally low 24-hydroxyvitamin D serum levels.

### ***Bariatric Surgery***

Obesity is a serious public health issue that has reached pandemic proportions, and has been ranked the number 1 threat to American health by the Centers for Disease Control and Prevention since 2004. Results from the 2003 to 2005 National Health and Nutrition Examination Survey (NHANES) estimated that 33.8% of US adults were obese (BMI  $\geq 30$ ), and the prevalence of overweight and obesity combined (BMI  $\geq 25$ ) is 68% of the population.<sup>43,44</sup> Bariatric (weight loss) surgery is the only effective therapy for morbid obesity; it has been performed since the 1940s but has undergone a resurgence in the last 2 decades in response to the obesity pandemic and the need to address the myriad comorbidities for which obesity is directly responsible. Recent data indicate that the number of bariatric surgeries performed in the United States increased from 13,365 in 1998 to an estimated 200,000 in 2007.<sup>45</sup>

Bone loss caused by weight reduction is multifactorial and correlates strongly with the velocity at which the weight is lost. Decreased calcium, vitamin D, and protein intake during periods of caloric restriction result in decreased calcium absorption, a subsequent increase in PTH, and increased bone resorption. Proposed mechanisms include effects caused by increased levels of circulating cortisol, and decreased levels of circulating estrogen, insulinlike growth factor (IGF) 1, leptin, ghrelin, and glucagon-like peptide 2, particularly in patients who have undergone bariatric surgery.<sup>45-51</sup> Rapid weight loss of 45 kg to greater than 90 kg is common among patients who have had successful bariatric surgery. Combined with severely restricted oral intake, this decreased calcium absorption, and vitamin D deficiency, places these patients at high risk for rapid bone loss. Bone loss can affect more than 70% of patients who have undergone a malabsorptive procedure, and this may be associated with increased markers of bone resorption as soon as 8 weeks after bariatric surgery, regardless of whether the patient underwent a malabsorptive or restrictive bariatric procedure. In these patients, as soon as 12 months after undergoing gastric banding 48% may have a statistically significant bone mineral reduction of greater than 3%. These patients require a higher vitamin D and calcium intake following surgery, and careful monitoring of the BMD and biochemical markers of bone turnover (at least annually). However, there are no data on whether these patients fracture more frequently. Bariatric surgery is also being performed in obese diabetics and has been shown to have a beneficial effect on glucose and insulin homeostasis, but this may also add to the complexity of the clinical picture of weight loss in diabetic patients who may have a predisposition to bone disease.

### ***Osteoporosis Associated with Eating Disorders***

Since the recognition of the importance of estrogen production and nutrition in the maintenance of skeletal health, clinical syndromes have been identified that include the development of bone mass loss and fractures in young women with the eating disorders anorexia nervosa and bulimia.<sup>52,53</sup>

The associations between eating disorders and skeletal fragility are systemic syndromes that involve psychological, nutritional, hypothalamic, ovarian, and bone-muscle-fat interrelationships.<sup>54-60</sup>

These patients often present to the osteoporosis clinic with low-trauma, nonvertebral fractures. They have low BMI, usually less than 17 kg/m<sup>2</sup>, and have a unique biochemical profile including a low plasma estradiol without an increase of their follicle-stimulating hormone, consistent with the hypothalamic disorder that accompanies this syndrome. Other biochemical and hormonal abnormalities include increased cortisol, low IGF-1, and increased growth hormone. In this author's experience, quantitative bone histomorphometry shows low bone turnover, suggesting that the skeletal fragility that may be seen even with normal BMD (eg, T scores) is a low-bone-turnover disease.

### **ENDOCRINE**

Although many endocrine diseases may be associated with osteoporosis, the 3 most commonly seen in a primary care clinical practice are diabetes mellitus, primary hyperparathyroidism, and hyperthyroidism. Other less common endocrine associations with osteoporosis include Cushing disease and prolactinomas.

### **OSTEOPOROSIS ASSOCIATED WITH DIABETES MELLITUS**

The deleterious effects of diabetes mellitus (DM) on the skeleton are multifactorial and both types 1 and 2 DM are associated with increased fracture risk.<sup>61-65</sup> Data from the Iowa Women's Health Study suggest that women with type 1 DM are 12 times more likely to sustain hip fractures than women without DM, and that women with type 2 DM have a 1.7-fold increased risk of sustaining hip fractures despite maintaining a normal bone mass.<sup>65</sup> Diabetes is associated with a reduction in BMD compared with age-matched and BMI-matched controls. However it is common to find an increased BMD in the obese. Low bone turnover is seen in patients with DM. The high prevalence of fractures in type 2 DM is likely to also be influenced by a greater risk of falls related to retinopathy-induced visual impairment, neuropathy-induced decreased balance, and sarcopenia.<sup>61,62</sup> The osteoporosis of DM is one of low bone turnover, with the main mechanism of bone loss being decreased bone formation. Insulin and amylin have an anabolic effect on bone, and their decrease in type 1 DM may lead to impaired bone formation, primarily because of a decrease in IGF-1 concentrations.<sup>66</sup> In vitro studies also show that sustained exposure to high glucose concentrations results in osteoblast dysfunction, and poor metabolic control has a clear negative impact on bone mass. In DM, there is increased bone marrow adiposity, which has also been linked with the osteoporosis of aging, glucocorticoid use, and immobility.<sup>55,59</sup> Several members of the nuclear hormone receptor family specifically control the critical adipogenic and osteogenic steps, and evidence has been mounting for an interdependence of adipogenesis and osteogenesis.<sup>55,59,64</sup> In the bone marrow microenvironment, the inverse relationship between adipogenic and osteogenic differentiation was shown to be mediated, at least in part, through crosstalk between pathways activated by steroid receptors (estrogen, thyroid,



corticosteroid, and growth hormone receptors), the peroxisome proliferator activator receptors (PPARs), and other cytokine and paracrine factors. PPARs play a central role in initiating adipogenesis in bone marrow and other stromal-like cells in vitro and in vivo,<sup>67</sup> and their ligands (rosiglitazone and pioglitazone) play a prominent role in directing mesenchymal cell precursors toward adipocyte and away from osteoblast differentiation.<sup>68</sup> Other potential harmful metabolic abnormalities include accumulation of advanced glycosylation end products; acidosis; vitamin D deficiency, particularly in the obese diabetic, and renal impairment.

### ***Primary Hyperparathyroidism and Osteoporosis***

There is a gradient of skeletal health in primary hyperparathyroidism, from a clear link to fragility fractures in severe primary hyperparathyroidism to scant evidence for an increase in fracture risk in asymptomatic primary hyperparathyroidism.<sup>69-71</sup> There are conflicting studies relating the fracture risk in untreated primary hyperparathyroidism or the benefit/lack of benefit of parathyroid surgery on the modification of risk.<sup>72,73</sup> Given the complexity of skeletal effects of chronic exposure to increased PTH levels, the uncertain relationship between BMD and fracture risk with primary hyperparathyroidism, discordant findings on fracture risk at different skeletal sites before and after surgery, and limitations of study design, severity of disease, and patient selection in many reports, further study is indicated.<sup>74,75</sup> The NIH has held 3 separate consensus conferences on when surgery should be considered in asymptomatic primary hyperparathyroidism.<sup>76</sup> There is a role for medical monitoring of these patients whose average blood calcium is less than 11.0 mg/dL; who are not forming kidney stones; who are not fracturing or losing BMD because of the primary hyperparathyroidism (and not because of other causes of bone loss such as estrogen deficiency)<sup>77</sup>; and who do not have unexplained, sustained increases of bone-specific alkaline phosphatase. Although there may be a forme fruste of normocalcemic primary hyperparathyroidism, whose serum calcium concentration repeatedly remains within the laboratory-defined normal reference range despite an increased PTH, and in which causes of secondary hyperparathyroidism have been excluded, surgery in this type of patient should only be considered after consultation with a parathyroid expert.<sup>78</sup>

One other important point concerning the diagnosis of primary hyperparathyroidism is that, although the combination of an increased serum calcium and PTH is most often caused by primary hyperparathyroidism, another parathyroid condition in which no parathyroid adenoma or hyperplasia is found is familial hypercalcemia hypocalciuria (FHH).<sup>79</sup> The diagnosis is established by the calculation of the ratio of the clearance of calcium to the clearance of creatinine (<0.01), and now with genetic testing of the inactivating calcium-sensing receptor gene mutation. This differential is important because parathyroid surgery is not indicated in most cases of FHH.

### **DRUGS ASSOCIATED WITH LOW BMD AND/OR FRACTURES**

**Box 4** provides a list of medications that can be associated with the loss of BMD and/or an increased risk of fractures.<sup>80</sup> This list is not complete, and this article focuses on a few of the more commonly encountered drugs that are seen in clinical practice: Depo-Provera, aromatase inhibitors, and protein pump inhibitors (PPIs).

#### ***Depo-Provera***

Depo-Provera (medroxyprogesterone) is the most widely used contraceptive worldwide. Because of its wide use in younger women and the documentation that administration of Depo-Provera may be associated with a loss of BMD, the US Food and

**Box 4****Drugs associated with low BMD or fractures<sup>a</sup>**

Glucocorticoids  
 Unfractionated heparin  
 Aromatase inhibitors  
 Gonadotrophin-releasing hormone agonists  
 Medroxyprogesterone  
 Excessive thyroid replacement  
 Thiazolidinediones  
 PPIs  
 Selective serotonin reuptake inhibitors  
 Antiseizure medications  
 Calcineurin inhibitors (eg, cyclosporine)

<sup>a</sup> This list is not complete.

Drug Administration has attached a black-box warning to its label, which has been controversial because of the lack of reliable evidence of any negative short-term or long-term outcomes.<sup>81-84</sup> In longitudinal observations, the loss of BMD with use of depomedroxyprogesterone acetate rapidly returns to baseline after discontinuation.<sup>85</sup> Because the risk of fracture is small (if any), and the benefit of affordable and widely available parenteral contraception is great, the use of medroxyprogesterone acetate should not be limited by its effect on the skeleton, although the association with loss of BMD should be discussed with the patient.

### ***Aromatase Inhibitors***

The aromatase inhibitors are highly effective at reducing the reoccurrence of breast cancer. Aromatase inhibitors are now regarded as front-line adjuvant therapy in women with estrogen receptor-positive breast cancer.<sup>86</sup> They reduce endogenous estrogen production by 80% to 90% by blocking the peripheral conversion of androgens to estrogen, and have largely replaced the selective estrogen receptor modulator, tamoxifen, as the preferred treatment option for postmenopausal women. The existing biomarker data indicate that all 3 aromatase inhibitors increase bone turnover, although some studies indicate a proportionately greater effect of exemestane on formation than resorption. Increased rates of bone loss have also been reported; for example, in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, median rates of bone loss at the spine and hip were 4.1% and 3.9%, respectively, over 2 years.<sup>87,88</sup> Data on fractures are confounded by prior or concomitant use of tamoxifen, which is not associated with bone loss or fractures. In the ATAC study, there was a greater risk for fractures after 5 years in subjects on this aromatase inhibitor.<sup>87</sup> Prevention of bone loss associated with aromatase inhibitor therapy has been shown with intravenous zoledronic acid, 4 mg every 6 months, oral risedronate 35 mg once weekly, and denosumab 60 mg subcutaneously every 6 months, although data on fracture reduction are lacking.<sup>89-93</sup> Management decisions on whether or not to intervene with antiresorptive agents for aromatase inhibitors are lacking but should follow those decisions for management of postmenopausal osteoporosis: monitoring BMD and bone turnover markers at intervals dictated by individual patient considerations.

### PPIs

PPIs have received a great deal of attention since the initial claims from database retrospective analysis suggesting that a small increase in the risk of hip fractures is associated with long-term use of PPIs.<sup>94–97</sup> Because of their widespread use (7 registered PPIs available and more than US\$14 billion annual sales), a common question from patients and physicians alike is related to their effects on bone. Data support an acid-suppressive association.

Data support an association between acid-suppressive medication, duration of use, and increased fracture risk. The limitations of observational studies (particularly the effects of potential but unmeasured confounding factors), have to be recognized. Furthermore, a mechanism of action whereby PPIs might be associated with an increased fracture risk is not known, with theories ranging from effects on gastrointestinal acid production and calcium absorption to effects on bone cell activity or BMD. It is reasonable to maintain PPIs in patients who need them, advise optimum calcium and vitamin D intake, and focus on other means to reduce their fracture risk, including reducing the risk for falls.

### SUMMARY

There are many secondary causes of osteoporosis, besides those mentioned earlier, that also need to be recognized; for example, human immunodeficiency virus and the drugs used to treat the disease; stroke and immobilization; chronic heart, liver, and lung disease; and autoimmune diseases. As patients who present with osteoporosis are studied, many unrecognized causes begin to appear. Albert Einstein once stated that “Everything should be made as simple as possible but not simpler.” This is also true of the many findings of secondary contributors to low BMD or fractures in these patients; in this sense, osteoporosis becomes a kaleidoscope of general medicine. Keep looking and keep finding.

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