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Review

Laboratory testing for secondary osteoporosis evaluation

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ABSTRACT

Osteoporosis has been classified into primary and secondary forms. All patients with osteoporosis should have measurements of 25-hydroxyvitamin D, serum and urine calcium, and some estimation of renal function. There are a wide variety of disorders that lead to secondary osteoporosis, and the tests that confirm these diagnoses are described herein. Making the specific diagnosis is important because treatment of the underlying condition may be sufficient to lessen fracture risk, although some patients may also need usual treatment for osteoporosis. Laboratory testing in addition to a careful history and physical examination will often lead to diagnoses of treatable conditions.

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Introduction

Over 25 years ago, Riggs and Melton established a classification of osteoporosis into primary and secondary forms [1]. Primary osteoporosis was further divided into Type 1, which occurred in patients between 50 and 70 years old, and Type 2, for patients over 70. The former was mostly women with postmenopausal osteoporosis, clearly related to the loss of estrogen with menopause. In Type 1 osteoporosis, trabecular bone was more affected than cortical bone, leading to fractures in regions high in trabecular bone content, the spine and distal forearm. A small proportion of men have this earlier type of osteoporosis, and several potential mechanisms have been proposed to explain the vertebral fractures found in such men [2]. The value of laboratory testing in Type 1 osteoporosis will be discussed briefly below, as well as the more common age-related Type 2. Indeed, in past years, laboratory testing in Type 2 primary osteoporosis was minimal. As knowledge of the pathophysiology of osteoporosis has increased, laboratory evaluation has become more important. Type 2 primary osteoporosis affects both trabecular and cortical bone, leading to hip fractures in addition to spine, forearm, rib, and humerus fractures. According to the Riggs and Melton classification [1], patients with osteoporosis clearly associated with a particular medical condition were labeled as having secondary osteoporosis. Laboratory testing to identify these disorders is the focus of this review. Treatment of an underlying condition may improve bone quantity and/or quality and decrease fracture risk. Some younger women with unexplained osteoporosis [3] undergo laboratory testing to eliminate known secondary causes rather than to diagnose a specific abnormality. For younger men with osteoporosis [4], some potential pathogenic mechanisms have led to laboratory testing, which will be discussed below.

General testing for osteoporosis

Primary osteoporosis Type 1 and idiopathic osteoporosis in younger adults

The younger patient with osteoporosis (defined here as 45 to 70 years old, although sometimes younger) presents with a painful compression fracture of the spine, an asymptomatic spine fracture found incidentally on an X-ray image, or as a distal forearm fracture (usually Colles' fracture of the distal radius). Most patients are women over 50 years old who have undergone menopause. While not measured routinely, laboratory testing reveals low levels of serum estradiol and elevation of serum gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Instead, laboratory testing may be done to rule out secondary causes (see Section 4) as well as a few basic laboratory tests (Table 1). The serum level of the major circulating vitamin D molecule, 25-hydroxyvitamin D, is considered an important part of the evaluation because of the finding in many diverse populations that serum levels are sub-optimal [5,6]. There is considerable controversy as to the ideal serum level. The Institute of Medicine (IOM) [7] concluded that for population bone health a serum level of 20 ng/mL (50 nmol/L) was adequate; others [8] have argued that for the patient with osteoporosis 30 ng/mL (75 nmol/L) was a better target. Reasons for aiming for the higher level include reports of poor adherence to vitamin D supplementation [9], overestimation of levels by some assays [10], increased volume of distribution due to obesity [11]; and in one study [12] a level of 30 ng/mL was necessary to eliminate all histologic evidence of osteomalacia. Indeed, the IOM report [7] concluded that while most adults need 600–800 IU of vitamin D daily, doses of up to 4000 IU daily were probably safe. In practice each additional 100 IU of daily cholecalciferol supplementation raises the serum 25-hydroxyvitamin D level by about 1 ng/mL. Other laboratory tests are done to rule out secondary causes (see Section 4 below) and for medication safety purposes. Some osteoporosis medications, such as bisphosphonates, are potentially toxic to the kidneys. Thus, serum creatinine and estimates of glomerular filtration rate are routinely measured in patients with osteoporosis. In addition, patients with severely decreased renal function (end stage renal disease {ESRD} or chronic kidney disease 5 {CKD 5}) may have increased fracture risk based on abnormalities in addition to osteoporosis, including adynamic bone disease, and secondary hyperparathyroidism [13].

Type 1 osteoporosis in younger men: is it idiopathic?

Osteoporosis in middle aged men has been called idiopathic, but many have specific causes found upon laboratory examination [2].

Table 1
Laboratory testing in some forms of osteoporosis.

For all types of osteoporosis
Serum calcium (usually corrected with serum albumin)
Serum 25-hydroxyvitamin D
Urinary calcium and creatinine (preferably a 24 hour specimen)
Complete blood count
For selected secondary causes of osteoporosis
Hypogonadism
LH, FSH, estradiol or testosterone, sometimes prolactin
Hyperthyroidism
TSH, Free T4, sometimes total T3
Cushing's syndrome
24 hour urinary free cortisol, dexamethasone suppression test
Hyperparathyroidism
Parathyroid hormone
Celiac disease
Endomysial IgA antibodies, anti-tissue transglutaminase, IgA and IgG antibodies to synthetic deamidated gliadin peptide
Hemochromatosis
Serum total iron binding capacity, transferrin, plasma ferritin
Multiple myeloma
Serum and/or urine protein electrophoresis, serum light chain assay
Mastocytosis
Serum tryptase

Thus, there is blurring of the classification of primary and secondary osteoporosis. For such younger men, a 24 hour urine collection may yield evidence of hypercalciuria [14], probably the most common specific cause of osteoporosis in younger men. In one report [15], hypercalciuric men with nephrolithiasis were more likely to have osteoporosis than those who did not have kidney stones. Two studies have demonstrated unusual laboratory abnormalities in small populations of men with so-called idiopathic osteoporosis. One group has low serum levels of insulin-like growth factor I (IGF-I) [4,16]. Circulating IGF-I levels are usually strongly correlated with secretion of and measurements of serum growth hormone (GH) levels, but interestingly in this syndrome, the serum GH concentrations are normal. A variable region of the IGF-I gene appears to be responsible for this syndrome [4]. In a second group of male family members with low bone mass, serum concentrations of bioavailable estradiol appear to be the causative factor [17]. Measurements of IGF-I and bioavailable estradiol have not been established as the standard of care in the man with early osteoporosis. However, the 24 hour urine calcium should be obtained in all such men.

Idiopathic osteoporosis in young women

Recent studies [3] of idiopathic osteoporosis in premenopausal women reveal normal laboratory studies, including serum levels of 25-hydroxyvitamin D, urinary calcium excretion, and bone turnover markers. By bone histomorphometry, some of the women were found to have high bone turnover, compared to control women. The high bone turnover women had increased levels of 1,25-dihydroxyvitamin D and a trend to higher urinary calcium excretion, as well as slightly higher levels of parathyroid hormone (PTH). Although women with clear hypercalciuria (>300 mg/24 h) were excluded from this study, it is possible that some of the high turnover women had a milder degree of hypercalciuria as the cause of their low bone mass.

Primary osteoporosis Type 2

General laboratory testing in patients over 70 years old

Primary osteoporosis Type 2 presents in women and men over age 70 with low trauma fractures of the spine, hip, forearm, humerus, or ribs. However, many other patients will be diagnosed because of an asymptomatic compression spine fracture found on X-ray or a low bone mineral density measured by dual energy X-ray absorptiometry (DXA). Indeed, the American Association of Clinical Endocrinologists [18] and the United States Preventive Services Task Force (USPSTF) recommend that all women have a DXA test for osteoporosis at age 65 [19]. While the USPSTF believes that screening older men is not yet indicated, other organizations such as the American College of Preventive Medicine [20] and the National Osteoporosis Foundation [21] recommend screening many men with DXA at age 70. Women and men require the same laboratory evaluation to rule out secondary causes (see Section 4 below) but also require measurement of 25-hydroxyvitamin D levels. Measurement of renal function as a safety test is more important because the glomerular filtration rate decreases with aging. A major question to be answered is whether the declining kidney function in the older adult makes the bone disease (i.e. increased fracture risk) something more than just osteoporosis. In other words, when does osteoporosis with the age-related diminution of renal function become the multi-factorial bone disorder of chronic kidney disease [13]?

Bone turnover markers

Serum and urine bone turnover markers reflect the activity of osteoclasts and osteoblasts and in cohort studies predict fracture risk, independent of BMD. The place of such markers in clinical practice is debated [22,23]. Markers are used more to monitor therapeutic response rather than to diagnose a specific kind of secondary osteoporosis. Variability in the assays and in the day-to-day levels in a given patient has decreased usefulness [24], but a recent consensus statement [25] proposes that two markers be chosen as international standards. The osteoclast activity marker proposed is serum c-terminal telopeptide of type I collagen, s-CTX; and the osteoblast activity marker proposed is serum procollagen type I N propeptide, s-PINP. Whether these or other potential markers, such as sex hormone binding globulin [26] can be used to monitor therapy, predict fracture risk, or identify a specific type of osteoporosis remains to be proven.

Secondary osteoporosis

Endocrine causes of secondary osteoporosis

Some secondary causes of osteoporosis, such as medications, will sometimes not require laboratory testing because the history and the physical examination will lead to a diagnosis. For example, glucocorticoid-induced osteoporosis is more likely due to oral glucocorticoid therapy (e.g. prednisone) rather than endogenous Cushing's syndrome, but the testing for Cushing's syndrome is described below (Section 4.1.3). History and physical examination will often reveal clues to which potential secondary causes require laboratory investigation (Table 1).

Gonadal disorders

Hypogonadism can decrease attainment of peak bone mass and/or increase loss of bone with aging. Sometimes the clinical diagnosis is adequate, and laboratory testing will not be needed. For example, young women with anorexia nervosa or with the combination of excess exercise/decreased nutrition leading to amenorrhea are at risk for not attaining genetically determined peak bone mass and later risk for osteoporosis. Laboratory determinations may help with the diagnosis or with assessing the level of estrogen insufficiency, but for the bone complications, laboratory examination is usually not needed. Surgical menopause also will need no specific laboratory testing.

Nonetheless, the patient with unexplained hypogonadism needs evaluation. For women, measurement of estradiol and gonadotropins LH and FSH will make the diagnosis definitive and determine whether the hypogonadism is primary or secondary. For example, autoimmune premature ovarian failure is characterized by low serum estradiol and elevated LH and FSH. Similarly, a man with primary testicular failure will have a low serum testosterone concentration with increased LH and FSH. In an individual with a pituitary tumor, the low sex steroid level will be accompanied by normal or low LH and FSH levels. In general, these tests are done early in the morning. Testosterone in particular has a diurnal variation, so samples should be obtained before 10 AM. New studies suggest that testosterone should be measured in the fasting state because high serum glucose may decrease testosterone [27]. Accurate measure of serum testosterone has been challenging. While isotopic dialysis methods have clear advantages in accuracy, expense and technical difficulties have led to the use of physical methods such as liquid chromatography/tandem mass spectrophotometry. A consortium [28] has been formed to establish optimization and standardization of testosterone assessment. In addition there are new studies [29] to establish reference ranges. Measurement of sex hormone binding globulin (SHBG) and albumin can be used with the total sex steroid hormone level to calculate bioavailable hormone levels using a calculator provided on an accessible website (www.issam.ch/freetesto.htm). An alternative method using spreadsheet calculations has also been reported [30]. The most common hypersecretory pituitary tumor is the prolactinoma. Thus for some patients with osteoporosis from secondary hypogonadism,

measurement of serum prolactin is indicated. For those in whom a pituitary tumor is diagnosed, testing of other pituitary function is necessary.

Turner's syndrome and Klinefelter's syndrome are relatively common genetic disorders leading to primary hypogonadism and decreased attainment of peak adult bone mass. In both cases, the sex steroid levels will be low with elevation of serum LH and FSH. Chromosomal analysis may be necessary to solidify the clinical diagnosis.

Thyroid disorders

Hyperthyroidism increases bone turnover, and there are several studies demonstrating low bone mass in patients with hyperthyroidism [31,32]. While serum thyrotropin (TSH) is considered the best thyroid function screening test, measurement of free thyroxine (free T4) or total thyroxine plus a measure of thyroid binding proteins (usually the T3 resin uptake test) is necessary to establish the diagnosis of hyperthyroidism. In some cases it will also be necessary to measure the total triiodothyronine in addition to free thyroxine. In most cases, automated free T4 analog assays are adequate.

Adrenal disorders

Cushing's syndrome, defined as glucocorticoid excess, leads to profound bone loss and muscle loss, resulting in greatly increased fracture risk. In the large majority of patients, the cause is exogenous oral glucocorticoid therapy for inflammatory diseases [33,34], but a small number of hypercortisolism cases may be due to adrenal adenoma or carcinoma, pituitary tumors hypersecreting ACTH, carcinoid tumors secreting ACTH, or ACTH-producing carcinomas, usually of lung or pancreas. The full differential diagnosis of such abnormalities is beyond the scope of this article, but glucocorticoid excess (i.e. Cushing's syndrome) can be defined by an elevated 24 hour urinary free cortisol or lack of suppression of the 8 AM serum cortisol by dexamethasone (1 to 2 mg, depending on body weight) taken at 11 PM the night before. The patient with Cushing's syndrome then needs further evaluation to determine the site of the problem.

Parathyroid disorders

Patients with primary hyperparathyroidism are identified much earlier in the course of the disease because widely used screening tests include serum calcium levels, whereas in the past, patients presented with a variety of bone abnormalities that mimicked osteoporosis. Nonetheless, low bone mass is an indication for surgical management of hyperparathyroidism [35]. The diagnosis is made by measuring serum calcium and serum levels of parathyroid hormone (PTH). Because calcium circulates bound to albumin, a corrected serum calcium must be calculated if the serum albumin is low. The serum calcium is raised 0.8 mg/dL for every 1 g/dL decrease in the serum albumin. Although ionized calcium avoids this problem, specimen handling and other technical problems make corrected total serum calcium the preferred test in hyperparathyroidism. Serum parathyroid hormone assays have undergone revision because fragments of the 1–84 amino acid PTH have interacted with some antibodies used in the various assays. For most patients, however, standard PTH assays are adequate. A newer assay that does not measure a 7–84 PTH fragment [36] has potential advantages. Patients may also have a component of secondary hyperparathyroidism if the 25-hydroxyvitamin D level is markedly decreased. Thus, PTH and concomitant serum calcium should be measured after vitamin D is replenished.

Diabetes mellitus and osteoporosis

Both Type 1 and Type 2 diabetes mellitus have been associated with increased fracture risk [37]. The mechanisms for this are not well understood. For now, no specific laboratory testing is done for such patients, although fasting and postprandial glucose levels and glycated hemoglobin are standard tests for the diagnosis and management of diabetes mellitus.

Gastrointestinal causes of secondary osteoporosis

A recent review [38] highlights the increased fracture risk of patients with several gastrointestinal disorders. In this large population study, chronic pancreatitis, gastrectomy, celiac disease, and cirrhosis increased fracture risk to 2.5 times that of control patients, and Crohn's disease caused slightly less increased risk.

Gastrectomy

Prior to the development of better medical treatment, severe peptic ulcer disease was often treated with gastrectomy, usually partial gastrectomy to decrease acid production. Consequent poor absorption of calcium and vitamin D may be manifested by decreased serum levels and by decreased urinary calcium excretion (in a 24 hour sample). Interestingly, drugs for peptic ulcer disease, particularly proton pump inhibitors [39], are also associated with increased fracture risk but no specific laboratory test can predict bone loss associated with this medication class. Hypomagnesemia [40] is considered a common complication of proton pump therapy, but its potential role in osteoporosis is not established.

Bariatric surgery

Several forms of gastrointestinal surgery are performed to induce weight loss. Some provide a smaller stomach, and others have diversion of part of the small intestine limiting absorption of nutrients. Calcium and vitamin D malabsorption occurs frequently, as measured by low 25-hydroxyvitamin D levels and low urinary calcium excretion. Other potential micronutrients may be affected by the altered anatomy, but at this time, corrected serum calcium and 25-hydroxyvitamin D are the only tests done routinely in this increasing population of patients [41].

Inflammatory bowel disease

There may be profound malabsorption in Crohn's disease, leading to osteoporosis and sometimes osteomalacia. Again, measurement of corrected serum calcium, 25-hydroxyvitamin D, and urinary calcium excretion may be helpful. Improvement in the underlying disorder often leads to marked improvement in bone mineral density and normalization of laboratory values. However, patients may need much larger doses of vitamin D. The role of serum markers of inflammation in the prediction of fracture risk has not been established.

Exocrine pancreatic insufficiency

Patients with chronic pancreatitis or after pancreatectomy may have steatorrhea and/or malabsorption of vitamin D and calcium, and the risk of osteoporotic fracture is elevated [38]. The diagnosis of pancreatitis can be made with measurements of serum amylase and lipase levels. Improvement of pancreatitis and/or use of pancreatic enzyme therapy to improve gut absorption will help to normalize vitamin D and calcium status. While corrected serum calcium may be normal, urinary calcium excretion may be low, and 25-hydroxyvitamin D levels may also be decreased. Improvement in pancreatitis with cessation of steatorrhea should improve absorption of calcium and vitamin D, but depending on the length and severity of the illness (plus concomitant risk factors such as alcohol abuse), low urinary calcium and low 25-hydroxyvitamin D levels may persist.

Hepatic disorders and osteoporosis

Biliary cirrhosis is the classic hepatic disorder associated with osteoporosis. Although the pathogenesis is still not established, low bone formation is considered important. There are no specific tests for the osteoporosis with biliary cirrhosis. The usual laboratory tests for the condition [42], such as elevations of serum alkaline

phosphatase with mild or no elevation of aminotransferases and the presence of anti-mitochondrial and anti-nuclear antibodies, are important for the diagnosis and for following liver disease; but they do not provide specific information about the associated osteoporosis. Chronic active hepatitis and cirrhosis may also be associated with low bone mass. Thus, in addition to clinical history and examination, hepatic function tests may be helpful in making these diagnoses.

Alcohol abuse and osteoporosis

The patient with alcoholism is at risk for fracture based on many potential mechanisms, some of which may be reflected in laboratory tests. Alcoholics may have hypogonadism, mediated by effects at all levels of the hypothalamo–pituitary–gonadal axis. This has been studied more in men than in women, and while low serum testosterone levels are likely, levels of gonadotropins (LH and FSH) are variable. Low serum 25-hydroxyvitamin D levels may be due to poor dietary intake, lack of sunlight exposure, and use of enzyme-inducing anti-convulsant medications for alcohol-related seizures. Evidence of pancreatitis and/or alcoholic liver disease may be reflected in standard laboratory tests for these disorders. Serum calcium may appear to be low if albumin is decreased due to poor hepatic synthetic function. Corrected serum calcium is usually normal.

Celiac disease

An under-appreciated cause of secondary osteoporosis is non-tropical sprue, known more commonly as celiac disease or gluten-sensitive enteropathy. This disorder, which can affect both children and adults, has a wide variety of clinical manifestations, from very mild/absent gastrointestinal symptoms to full blown malabsorption with severe steatorrhea [43]. In children, there may be growth delay and delayed puberty as consequences of the malabsorption caused by villous atrophy in response to dietary gluten, resulting in delayed bone growth, Vitamin D deficiency, and even fracture. Adults may also present with fracture or low bone mineral density and few gastrointestinal symptoms. While small bowel biopsy provides a definitive diagnosis, serological testing has improved. The standard tests have been endomysial IgA antibodies and anti-human tissue transglutaminase [44]. More recently, IgA and IgG antibodies to a synthetic deamidated gliadin peptide have also been found to predict the presence of this disorder [45]. For the patient with evidence of malabsorption, marked vitamin D deficiency, and evidence of low bone mass, screening with celiac antibodies may well signal a diagnosis.

Hemochromatosis

This relatively common genetic disorder leads to iron deposition in the liver and the pancreas, but the anterior pituitary can also be affected by iron overload, leading to secondary hypogonadism. The standard screening tests for hemochromatosis are the serum or plasma total iron binding capacity or transferrin and the plasma ferritin levels [46]. Some patients will need confirmatory testing with a liver biopsy stained for the presence of iron.

Miscellaneous secondary causes of osteoporosis

Rheumatoid arthritis

Rheumatoid arthritis can lead to periarticular bone loss as well as systemic skeletal deficiency. Treatment with glucocorticoids increases the incidence of clinically significant low bone mass and fracture risk. Although there are many clues to the diagnosis from history and physical examination, serological testing includes measurement of rheumatoid factor and anti-citrullinated protein antibodies [47]. Acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are used to assess activity of the disease. While these factors are helpful for the diagnosis and management of rheumatoid arthritis, they do not have any direct impact on osteoporosis risk. However, those patients with the most severe disease and requiring prednisone treatment will more likely have secondary osteoporosis.

Chronic Obstructive Pulmonary Disease (COPD)

Particularly in men, COPD is strongly associated with osteoporosis [48], presumably due to decreased physical activity and the consequences of smoking, the usual cause of COPD. Emphysema has catabolic effects, leading to weight and muscle loss, which can be magnified by prednisone use. There are no specific laboratory tests for COPD, but blood gas measurements will reflect the severity of the disorder, and measurement of the pCO_2 will usually help differentiate whether the patient has mostly chronic bronchitis or emphysema. Other pulmonary disease, such as sarcoidosis [49], can also lead to osteoporosis via decreased physical activity, chronic inflammation, and/or use of oral glucocorticoid therapy. Active sarcoidosis and other granulomatous diseases may produce hypervitaminosis D because of unregulated 1α-hydroxylase levels in the granulomas. Thus, calcium and vitamin D supplements given to most patients with osteoporosis can increase the potential for hypercalciuria and hypercalcemia. To confirm that hypercalciuria and/or hypercalcemia is due to the patient's sarcoidosis, it is necessary to measure 1,25-dihydroxyvitamin D.

Mobility disorders

Many disorders of mobility are associated with osteoporosis. Presumably the decreased muscle activity, lack of loading the skeleton, and general debilitation play a role in the pathogenesis of this secondary osteoporosis. However, there may be evidence of denervation, particularly in spinal cord injury [50]. Other disorders such as stroke (cerebrovascular accident, CVA), Parkinson's disease [51], and multiple sclerosis are also causes of osteoporosis, but their diagnoses are mostly clinical. If patients with multiple sclerosis are treated with oral glucocorticoids, the bone loss may be accelerated. No specific laboratory test will determine the extent of osteoporosis in these disorders.

Multiple myeloma

This cancer of bone may look like osteoporosis on X-ray with compression fractures of the spine which are difficult to differentiate from those of osteoporosis. This is an important differential to make when first evaluating a patient. A hint to the diagnosis may be provided by the hemoglobin or hematocrit level because these levels should be normal in most patients with osteoporosis. Measurement of serum and/or urine protein electrophoresis [52] is the standard method to make the diagnosis, although bone marrow biopsy and measurement of serum light chains [53] may be necessary in some cases.

Mastocytosis

Systemic mastocytosis has always been in the differential diagnosis of osteoporosis. The patients usually present with urticaria pigmentosa and pruritis. In addition to skin biopsy, laboratory testing includes a complete blood count, liver function testing, and serum tryptase levels [54]. Most patients will need a bone marrow aspiration biopsy to confirm the diagnosis. These tests establish the diagnosis of mastocytosis, but they do not determine the severity of osteoporosis that is associated with this disorder.

Pregnancy and lactation

During pregnancy, the need for fetal calcium is compensated by increased maternal gut calcium absorption. During lactation, up to 400 mg of calcium may be transferred to milk [55], and most women have no clinical consequences. Thus, osteoporosis during pregnancy or lactation is rare but presents with vertebral fractures. Although there are no specific laboratory abnormalities have been described, in reported cases there have been interesting findings. For example, a 27 year old woman developed vertebral fractures during

lactation [56]. She had become hypoparathyroid because of surgery for papillary thyroid carcinoma. Her replacement regimen included 2000 mg of elemental calcium, 2 μg of alpha-calcidiol daily, and 1.9 mg of L-thyroxine weekly. The thyroid replacement suppressed her thyrotropin (TSH) level to <0.01 mIU/mL despite a normal free T4. She had normal serum and urinary calcium concentrations. After 3 months of breastfeeding twins, she developed 10 vertebral compression fractures. Surprisingly serum calcium concentration and urinary calcium excretion became elevated despite a mildly low 25-hydroxyvitamin D level. The level of parathyroid hormone-related peptide (PTHrP) became detectable, and serum bone turnover markers were elevated. With cessation of lactation, lowering of the calcidiol dose, and estrogen/progestin replacement, serum calcium and bone turnover markers returned to normal. PTHrp became undetectable. This is obviously an unusual case, but it illustrates the dramatic presentation and the need for thorough laboratory evaluation in such patients.

Medications that lead to secondary osteoporosis

Medications that affect laboratory tests

There are a few medications that increase osteoporosis risk and clearly affect laboratory testing. Anti-seizure medications that increase the catabolism of vitamin D will lead to lower serum concentrations of 25-hydroxyvitamin D [57], increasing the chance to develop osteoporosis and/or osteomalacia. The list of such anticonvulsants includes phenytoin, phenobarbital, carbamazepine, and primidone. High doses of L-thyroxine will suppress levels of TSH and increase levels of free thyroxine in the serum. Any cause of hyperthyroidism, including from exogenous L-thyroxine leads to increased bone turnover and loss. Drugs that raise the serum prolactin, such as the major neuroleptic drugs (phenothiazines, haloperidol, thiothixene) may cause osteoporosis [58]. At least some of the osteoporosis is mediated by the hypogonadal effect of elevated prolactin secretion. Some of the newer drugs for psychiatric conditions, such as risperidone, also raise the serum prolactin and can theoretically lead to hypogonadism and loss of bone.

There are two classes of drugs that may cause profound loss of bone. While laboratory measurements will confirm the effects of these drugs, such tests are often unnecessary. Aromatase inhibitors prevent conversion of androgens to estrogens, so that measurement of serum estradiol would be low in a woman with breast cancer taking an aromatase inhibitor. Markedly low levels of LH, FSH, testosterone, and estradiol will occur some days after a patient with prostate cancer starts androgen deprivation therapy with an analog of gonadotropin releasing hormone [59]. It is interesting that after early stimulation of LH and FSH, these analogs cause decreased pituitary gonadotropin secretion.

As mentioned above, oral glucocorticoids such as prednisone are common causes of secondary osteoporosis. Many of this drug class will cross-react in cortisol assays. Dexamethasone is a helpful glucocorticoid because its potency is so high that it does not interfere with the serum measurement, although it will be sensed by the anterior pituitary as a glucocorticoid, leading to decreased ACTH and endogenous cortisol production.

Conclusion

It is obvious that the differential diagnosis of secondary osteoporosis is quite long. The illustrations provided here are not comprehensive, although the great majority of patients with secondary osteoporosis can have a diagnosis made from a thorough history, physical examination, and a carefully chosen short list of laboratory tests. Most tests will establish the diagnosis of the disorder but will not necessarily reflect the severity of the impact on bone. In both women [60] and men [61], laboratory assessment plays an important role in the evaluation of osteoporosis.

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