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Osteoporosis in men: Suspect secondary disease first

ABSTRACT

Since osteoporosis in men is more often secondary rather than primary (idiopathic), we need to seek the underlying cause through the history and laboratory testing. Treatment options are similar to those for women, although data are limited about their efficacy in men.

KEY POINTS

Prevention is the best approach to treatment of osteoporosis in men, given the limited options at the moment.

Glucocorticoids top the list of drugs that can cause osteoporosis. Prescribe a bisphosphonate prophylactically when starting long-term glucocorticoid therapy.

Bone densitometry can be problematic in men, as the T score is often indexed to a reference database in young women. Men are currently not covered for reimbursement under the Bone Mass Measurement Act, but they should undergo densitometry as women do.

The biochemical evaluation tends to be more extensive in men with osteoporosis because the bone loss is usually secondary to another condition. The younger the male patient, the more important the laboratory evaluation.

Alendronate has been shown to increase skeletal density in men comparably to levels seen in women. It is now approved for use in men. Teriparatide, a parathyroid hormone preparation, is now approved to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.

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CONTRARY TO POPULAR NOTIONS, osteoporosis is a disease not only of women. In fact, men account for about 20% of cases of osteoporosis and 25% of hip fractures.

But there are differences. The consequences are worse for men than for women. Compared with women, men with hip fractures have higher rates of mortality and morbidity.[1,2] More are institutionalized, and 30% to 50% die within a year of fracture vs about 20% of women.

Another difference of note: from 50% to 70% of cases of osteoporosis in men are secondary to another condition, whereas osteoporosis in women is usually primary (idiopathic). Hence, in assessing a man, we should think of secondary osteoporosis first and primary second.

Many advances have occurred in the past decade, including increased awareness of osteoporosis, the technology to diagnose it in its early, asymptomatic stage, and many new treatments. Osteoporosis is now viewed as a treatable disease, rather than as an inevitable consequence of aging. Unfortunately, awareness of osteoporosis in men lags behind that in women, as do research and rates of detection and treatment.

This article outlines the unique features of osteoporosis in men, including its pathophysiology, causes, diagnosis, and treatment.

BIMODAL PREVALENCE BY AGE

The prevalence of osteoporosis by age in men and in women is quite different (FIGURE 1). Whereas in women the distribution of osteoporosis with age is skewed toward the later years, in men many cases occur before age 50,

Distribution of osteoporosis cases by age in men and women

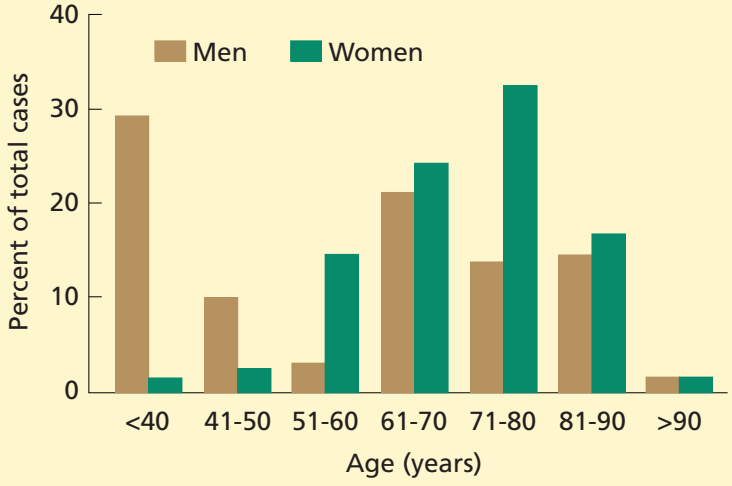

FIGURE 1. In women most cases of osteoporosis occur in the later years; in men the distribution is bimodal. The early peak is mostly due to secondary osteoporosis, while the later peak mostly represents primary osteoporosis.

Glucocorticoids attack the skeleton on two fronts

with a second peak in the later years. The cases early in life in men tend to be secondary osteoporosis and the later cases tend to be primary, although this is not always true.

WHY FEWER MEN GET OSTEOPOROSIS

Although men do get osteoporosis, they have a lower prevalence than women, for several reasons:

Men accumulate more bone mass during the peak growth years, making the adult male skeleton generally stronger. They also accumulate more muscle mass during puberty, which contributes to skeletal strength.

Men do not go through menopause. Male hormone production does not abruptly cease. Instead, testosterone levels decline slowly throughout life unless there is an abrupt change (eg, due to surgical or chemical orchiectomy).

Life expectancy for men has been shorter than for women, so that primary osteoporosis had less time to develop and cause fragility fractures. However, more men are now living long enough to develop primary osteoporosis.

Ascertainment bias. Fewer men than women undergo bone density measurement, leading to the incorrect conclusion that men do not get osteoporosis. However, the third National Health and Nutrition Examination Survey,[3] using T-score criteria, found that 28% to 47% of men over age 50 have osteopenia at the femoral neck, and 36% have osteoporosis. For a 50-year-old man, the lifetime risk for any fracture of the femur, vertebrae, or distal forearm ranges from 13% to 50%.[3]

PRIMARY OSTEOPOROSIS MAY BE DIFFERENT IN MEN

Primary osteoporosis is often ascribed to aging. Some believe that in men it results from trabecular thinning rather than from trabecular destruction, as seen in women.[4]

With age, a variety of metabolic and endocrine changes combine to weaken the skeleton.[5–10] Production of testosterone and growth hormone decreases, and muscles deteriorate. Calcium absorption becomes inefficient. Secondary hyperparathyroidism arises. Ambient parathyroid hormone levels are higher in older than in younger patients. Varying degrees of vitamin D dysfunction may be seen, from ineffective function to deficiency.

CAUSES OF SECONDARY OSTEOPOROSIS

Many diseases and drugs can cause secondary osteoporosis (TABLE 1).

Drug-induced bone loss

Glucocorticoids top the list of drugs that can cause osteoporosis. Although oral glucocorticoids are the major culprits, potent inhaled glucocorticoids may also have systemic effects on the skeleton.[11]

Excessive doses of glucocorticoids have many bad effects on calcium and bone metabolism.[12] They blunt intestinal calcium absorption directly, even with adequate serum levels of vitamin D, and secondary hyperparathyroidism develops. Osteoclasts increase their activity, and skeletal turnover increases. The drugs also directly blunt osteoblastic activity, thus attacking skeletal integrity on two fronts.

Renal tubulopathy and calciuria develop (a direct effect of the steroids), drawing calcium from the body and exaggerating the hyperparathyroid state. Sex steroid production declines by suppression of gonadal function and pituitary gonadotropin secretion.

However, many other drugs can cause osteopenia, osteoporosis, and osteomalacia,[13] including:

- **Anticonvulsants,** which enhance vitamin D metabolism and cause calcium malabsorption and secondary hyperparathyroidism
- **Antigonadotropic drugs** used in treating prostate cancer are known to cause osteopenia, but the true incidence of clinical osteoporosis and fracture rates is not known.

Tobacco and alcohol are both directly toxic to the skeleton. Alcohol use is an independent risk factor for osteoporosis.[14] It suppresses osteoblast activity: intake of as little as 50 g (four standard drinks) per day causes a dose-dependent decrease in osteocalcin, a marker of osteoblastic activity. Higher intakes (>100 g/day) used for years cause decreased skeletal mass.[15] However, moderate drinking is not deleterious.

Gastrointestinal diseases

Gastrointestinal diseases such as primary liver disease (with or without cirrhosis), ulcers requiring gastrectomy, inflammatory bowel disease, pancreatic insufficiency, and malabsorptive problems cause osteoporosis and, at times, osteomalacia.[16–19] Alcoholic cirrhosis, primary biliary cirrhosis, and steroid-treated autoimmune hepatitis lead more to osteoporosis than to osteomalacia.

Hypercalciuria: Hyperabsorptive or renal tubular?

Hypercalciuria, with or without stone disease, is found in 20% of men with osteoporosis evaluated in our clinic. Often, it is occult and is not associated with overt stone disease. In my experience, patients with latent calciuria may have normal calcium excretion because their calcium intake is low, but if you give them a calcium supplement for a week and remeasure their calcium excretion, it will be high.

Both hyperabsorptive hypercalciuria and renal tubular hypercalciuria (renal leak) are associated with osteopenia and osteoporosis.

TABLE 1

Causes of secondary osteoporosis

Drugs
- Alcohol
- Anticonvulsants
- Antigonadotropins
- Glucocorticoids (oral, inhaled)
- Nonsteroidal anti-inflammatory drugs
- Thyroxine
- Tobacco

Endocrine
- Acromegaly
- Hypercortisolism
- Hyperparathyroidism
- Hyperprolactinemia
- Hyperthyroidism
- Hypogonadism

Gastrointestinal
- Cirrhosis
- Inflammatory bowel disease
- Malabsorption

Genetic and metabolic
- Homocystinuria
- Hypophosphatasia
- Marfan syndrome
- Osteogenesis imperfecta

Neoplastic
- Anemia (vitamin B_{12} deficiency, thalassemia)
- Leukemia
- Myeloma, benign gammopathies

Neurologic
- Disuse syndrome
- Glucocorticoid, adrenocorticotropin therapy for myasthenia gravis, multiple sclerosis
- Immobilization
- Muscle atrophy
- Paralysis

Pulmonary
- Cystic fibrosis
- Drug therapy for asthma, chronic obstructive pulmonary disease
- Idiopathic pulmonary fibrosis

Renal
- Chronic renal failure, dialysis
- Mineral-losing tubulopathies
- Stone disease

Transplantation bone disease
- Lung, liver, heart, kidney

The hyperabsorptive problem is associated with increased or high-normal levels of 1,25 dihydroxyvitamin D. This above-normal level increases bone metabolism and, consequently, skeletal loss.[20–24]

In renal tubular hypercalciuria, initially there is a failure to reclaim urinary calcium, and serum levels decline. A sustained compensatory rise in serum parathyroid hormone corrects this drop in calcium at the expense of increased bone turnover.

Renal tubular acidosis is another entity to be mindful of.[25]

Endocrine disorders

Several endocrine disorders are well-known causes of osteoporosis. The clinical challenge is when they occur in an atypical or occult fashion.

Hypogonadism during puberty is an established cause of adult skeletal deficiency, primarily as it inhibits the development of peak bone mass.[26–28] In a young patient, replacement of sex steroids may reverse the problem.

Abrupt hypogonadism in adult men following chemical or surgical orchiectomy (eg, for the treatment of prostate cancer)[29] is comparable to menopause in women and is equally destructive to the skeleton. On the other hand, the milder forms of hypogonadism of aging have not been shown to cause bone loss.

Fracture may be the only presenting feature in some men with occult endocrine disorders

Hyperparathyroidism causes bone destruction, although skeletal problems such as osteitis fibrosis cystica are rare nowadays because this disorder is usually discovered early in routine health care evaluations and laboratory testing. More than 80% of patients with hyperparathyroidism have no symptoms, however. Secondary and tertiary hyperparathyroidism of renal disease is not a diagnostic challenge, but it is often overlooked, even in patients on renal dialysis.

Endogenous hypercortisolism can present atypically. About 5% of patients present with osteoporosis and never show the typical features of cortisol excess, such as centripetal obesity, aberrant deposition of fat, diabetes mellitus, or hypertension. Fractures may be the only presenting characteristic.

Hyperprolactinemia in men is insidious. Unrecognized, it decreases testosterone production and libido and in theory can cause osteoporosis. Whether fractures develop, however, depends on other issues, such as chronicity of the disorder, initial peak bone mass, and traumatic events.

Primary hyperthyroidism is an unlikely cause of osteoporosis because it is usually diagnosed long before it can destroy the skeleton. The real concern is exogenous hyperthyroidism caused by thyroxine supplementation that suppresses thyroid-stimulating hormone. However, this should not be a clinically significant issue now that we have sensitive assays for thyroid-stimulating hormone, bone densitometry, and therapy to counteract bone loss.

Acromegaly can lead to osteoporosis paradoxically, apparently when a growing pituitary tumor produces less gonadotropin, thus suppressing testosterone synthesis.

Other causes

Plasma cell dyscrasias cause osteoporosis or osteopenia.

Multiple myeloma and even benign monoclonal gammopathy increase bone turnover.[30] This skeletal effect arises from increased osteoclastic activity due to the elaboration of cytokines within the bone marrow. The degree to which these disorders are occult and go undiagnosed determines the extent of skeletal destruction.

Leukemia may also be associated with bone destruction if sufficiently occult and chronic.[31]

Benign hematologic disorders such as thalassemia and vitamin B_{12} deficiency also contribute to bone loss.[32,33]

Focal metastatic disease causes local bone destruction, not systemic osteoporosis.

Humoral hypercalcemia of malignancy is not a clinically significant cause of osteoporosis, since it portends a short prognosis.

Genetic or metabolic disorders known to cause osteoporosis or osteopenia include homocystinuria, Marfan syndrome, hypophosphatasia, and osteogenesis imperfecta.[34–37] A family history of any skeletal disorder should raise our suspicion, although the rarity of many of these disorders makes them less likely considerations in general medical practice.

BONE DENSITOMETRY AND T SCORES

Bone densitometry is the greatest single advance that has made possible the awareness, diagnosis, and early treatment of osteoporosis. Dual energy x-ray absorptiometry of the spine

and hip can detect osteoporosis in women and men quite early in its course.

I believe that bone density evaluation should be mandatory for men after age 60 or 65 if there is no specific history of unexplained fracture, and certainly before this age in any man with a history of low trauma fracture. Guidelines for its use are likely to be the same for men as for women, although this has not been clearly delineated.

Unfortunately, although the federal Bone Mass Measurement Act requires Medicare to pay for bone density measurements for women within certain guidelines, men have not yet been included. One hopes that Congress will rectify this omission.

Caveats about T scores

The T score, used to determine the risk for fracture in women, is also used in men, but with a caveat: a male data base must be used for deriving the score.

Recall that the T score is the number of standard deviations (SD) below or above the mean value in a reference population. If a female data base is used, only 3% to 5% of men have osteoporosis, whereas 30% of men over age 50 have osteopenia or osteoporosis when a male data base is used. Hence, a male data base is mandatory for accurate diagnosis of osteoporosis in men.

The definitions of disease by T scores are the same for men as for women. A T score of 2.5 or more standard deviations (SD) below the mean (ie, < –2.5 SD) is classified as osteoporosis. (Remember that these are negative numbers, so –3.5 is *less* than –2.5.) A T score of –1.5 to –2.5 is classified as osteopenia, and a T score of –1.5 or higher is normal.

But T scores should only be considered as guidelines for detection of osteoporosis. Treatment should not be withheld until a patient's T score reaches a specific level. Rather, the diagnosis and decision to treat should be based on clinical criteria. Sometimes, treatment should be started before the T score declines to –2.5, for example, in patients taking glucocorticosteroids.

Moreover, there is no "safe" T score, ie, no discrete cutoff for "osteoporosis" or "no osteoporosis." The scores are a continuum of fracture risk. People with lower scores (more standard deviations below the mean) are at greater risk than people with higher scores, but the score alone does not diagnose osteoporosis: the clinician diagnoses osteoporosis on the basis of the personal and family history, physical examination, laboratory values, and bone densitometry.

TABLE 2

Diagnostic evaluation of osteoporosis in men

History
- Family history
- Past medical history (secondary causes identifiable)
- Health habits (use of alcohol or tobacco, lack of exercise)
- Drug use (bone-toxic agents)

Physical examination
- Signs of specific diseases

Initial laboratory evaluation
- Complete blood cell count
- Complete chemical profile
- Parathyroid hormone
- 25 vitamin D
- 24-hour urinary calcium

Follow-up laboratory evaluation
- Urine cortisol
- Serum testosterone
- Protein electrophoresis of serum
- Serum growth hormone
- Insulin-like growth factor 1
- Prolactin

Do not withhold treatment until the T score reaches an arbitrary number

CLINICAL AND LABORATORY DIAGNOSIS OF OSTEOPOROSIS IN MEN

In men, we should consider primary osteoporosis only after ruling out a specific cause. In women, too, we should never assume that osteoporosis is primary: the high incidence of primary disease in women often obscures consideration of secondary causes, but secondary causes do exist and need to be considered.

History and physical examination

In most men with osteoporosis, the history raises the suspicion of a possible cause, which is then pursued with appropriate laboratory and radiologic testing (TABLE 2).

A family history of osteoporosis is as important a consideration in men as it is in women. Osteoporosis in family members is a risk factor, especially in families with a tendency toward small, thin stature. In addition, pediatric data show similarities in bone density of parents and their children.[38,39]

The physical examination may reveal cushingoid features, acromegaly, or hypogonadism, or evidence of blood dyscrasias or cancer, liver disease, or pathognomonic skeletal abnormalities.

Laboratory testing more extensive in men

The biochemical evaluation tends to be more extensive in men with osteoporosis because the bone loss is usually secondary to another condition. The younger the male patient, the more important the laboratory evaluation.

A tiered evaluation is recommended, proceeding from routine to more exotic metabolic and endocrine tests.

Routine biochemical profiles and a complete blood cell count may reveal suspicious findings that should be evaluated further, such as abnormalities in calcium, phosphorus, other electrolytes, alkaline phosphatase, liver or kidney function, and blood counts.

Measure 24-hour calcium excretion in all men with osteoporosis

Routine urine testing for 24-hour excretion of calcium is suggested initially in all men because hypercalciuria is common. Levels of urinary phosphorus and other substances, such as amino acids or sugars, may be evaluated later if there is suspicion of renal tubulopathy and associated bone disease.

Measurement of parathyroid hormone and 25-hydroxyvitamin D may uncover subtle secondary hyperparathyroidism or vitamin D deficiency.

In rare cases, evaluation for hypophosphatasia, homocystinuria, or osteogenesis imperfecta might be needed. Evaluate for hypophosphatasia in patients with fracture and low serum alkaline phosphatase. Evaluate for homocystinuria in those with physical features and a history of fracture. Evaluate for osteogenesis imperfecta in those with a family history, fracture as a child, and physical features.

Skeletal biopsy

If no abnormality is found on laboratory testing, tetracycline-labeled biopsy of the skeleton might be helpful. Histologic study may show unexpected findings, such as hematologic disease or osteomalacia. In our clinical experience, however, biopsy has not proven as helpful as laboratory or clinical data. Nonetheless, it should be kept in mind, such as in a patient with a continuing history of fractures or bone pain and no obviously abnormal laboratory tests.

TREATING SECONDARY OSTEOPOROSIS IN MEN

Treating osteoporosis in men usually implies treating the underlying cause. The reversibility of osteoporosis after the underlying cause is controlled or eliminated depends on the degree of bone damage. Treatment of hypercortisolism, hyperparathyroidism, acromegaly, or hyperprolactinemia can reverse bone loss to varying degrees. Resolution of a deficiency, such as hypogonadism or vitamin D deficiency, may be all that is needed.

Skeletal disease due to intestinal or drug-induced malabsorption often responds well to calcium and vitamin D supplementation.

Drug-related bone loss should, in theory, respond to stopping the drug, but this may not be easy. For example, the therapeutic need for glucocorticoids may preclude stopping them. Fortunately, the bisphosphonates alendronate (Fosamax) and risedronate (Actonel) are available for patients using glucocorticoids, and these two drugs should be prescribed prophylactically when chronic steroid treatment is started.

Thiazide diuretics can stop renal calcium loss and reverse skeletal deficiency to varying degrees.

Treatment of various neoplastic diseases may control the skeletal disease and fractures attending these illnesses, but additional bone-specific therapies are often needed.

TREATING IDIOPATHIC OSTEOPOROSIS IN MEN

Idiopathic osteoporosis in men was not satisfactorily treated until the recent approval of alendronate for use in men.

Nonpharmacologic measures

Nonpharmacologic measures alone are not sufficient. Nevertheless, calcium and vitamin D supplementation and exercise should be part of any treatment program for men. A healthy lifestyle with smoking cessation and limited use of alcohol is as important in men as it is in women.

Hormonal therapy

Testosterone therapy is marginally effective in the hypogonadism of aging but is more effective in hypogonadism of younger men.[40,41]

Estradiol has been found, in a few rare cases, to have a positive effect on the male skeleton, although the true clinical significance of this is not yet known.[42,43]

Calcitonin has not undergone any large studies in men with primary osteoporosis, although small increases in bone density and a reduction in vertebral fractures were seen in major studies in women.[44]

Parathyroid hormone increases skeletal density in men,[45] but its full potential has not been explored. A commercial product, teriparatide (Forteo), has received FDA approval for use in men and women.[46]

Growth hormone increases bone density in patients with adult growth hormone deficiency.[47] Since growth hormone secretion decreases with aging, its use has theoretical merit in the treatment of osteoporosis.[48,49] Its high cost and parenteral route of administration are limitations to its widespread use, however.

Sodium fluoride

Sodium fluoride has long been used in women as an osteoblastic stimulator, and most studies of its efficacy have been in women. Its use in men has not been fully evaluated, but there are limited studies.[50] Unfortunately, the safety margin is narrow.[51] In women, excessive doses produce dense but poor-quality bone that is prone to fracture.

Bisphosphonates

Alendronate is the first drug to show efficacy in men in a well-controlled trial, increasing skeletal density comparably to levels seen in women. Its effects do not appear to depend on testosterone levels. The study was not statistically powered to evaluate the efficacy of fracture reduction, but a tendency in that direction was noted.[52]

Etidronate in cyclical regimens is used in women and, theoretically, should help men. Risedronate should also be beneficial.[53–55]

PREVENTION IS BEST TREATMENT

The take-home message is essentially the same as that for women: prevention is better than treatment, given the limited treatment options at the moment.

Calcium, vitamin D, exercise are part of any treatment plan in men

REFERENCES

1. **Diamond TH, Thornley SW, Sekel R, Smerdely P.** Hip fracture in elderly men; prognostic factors and outcomes. Med J Aust 1997; 167:412–415.
2. **Center JN, Nguyen TV, Schneider D, Sambrook PN, Eisman JA.** Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999; 353:878–882.
3. **Looker AC, Orwoll ES, Johnston CC, et al.** Prevalence of low femoral bone density in older US adults from the NHANES III. J Bone Miner Res 1997; 12:1761–1783.
4. **Jaron JJ, Makins NB, Sagreiya K.** The microanatomy of trabecular bone loss in normal aging men and women. Clin Orthop 1987; 215:260–271.
5. **Portale AA, Lonergan ET, Tanney D, Halloran BP.** Aging alters calcium regulation of serum concentration of parathyroid hormone in healthy men. Am J Physiol 1997; 272:139–146.
6. **Cahaupey MC, Durr F, Chapui P.** Age-related changes in parathyroid hormone and 25 hydroxy cholecalciferol levels. J Gerontol 1983; 38: 19–22.
7. **Haden ST, Brown VM, Hurwitz S, Scott J, El-Elajj FG.** The effects of Asian gender on parathyroid hormone dynamics. Clin Endocrinol 2000; 52:329–338.
8. **Gallagher JC, Kinyamu HK, Fowler SE, Dawson-Hughes B, Dalsky GP, Sherman SS.** Calciotropic hormones in bone markers in the elderly. J Bone Miner Res 1998; 13:475–482.
9. **Lau KH, Baylink DJ.** Vitamin D therapy of osteoporosis: plain vitamin D therapy vs active vitamin D analog (D-hormone) therapy. Calcif Tissue Int 1999; 65:296–306.
10. **Orwoll ES, Meier DE.** Alterations in calcium, vitamin D in parathyroid hormone physiology in normal men with aging: relationship to the development of senile osteopenia. J Clin Endocrinol Metab 1986; 63:1262–1269.
11. **Lipworth BJ.** Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta analysis. Arch Intern Med 1999; 159:941–955.
12. **Zaqqa D, Jackson R.** Diagnosis and treatment of glucocorticoid-induced osteoporosis. Cleve Clin J Med 1999; 63:221–230.
13. **Tannirandom P, Epstein S.** Drug-induced bone loss. Osteoporos Int 2000; 11:637–659.
14. **Turner RT.** Skeletal response to alcohol. Alcohol Clin Exp Res 2000; 24:1693–1701.
15. **Diamond T, Stiel D, Lunzer ML, et al.** Ethanol reduces bone formation and may cause osteoporosis. Am J Med 1989; 86:282–288.

16. **Valentine F, Snisky CA.** Prevention and treatment of osteoporosis in patients with inflammatory bowel disease. Am J Gastroenterol 1999; 94:878–883.
17. **Vasquez H, Mazure R, Gonzalez D, et al.** Risk of fractures in celiac disease patients: a cross-sectional, case control study. Am J Gastroenterol 2000; 95:183–189.
18. **Vleggaar FP, VanBuuren HR, Wolfhagen FH, Schalm SW, Pols HA.** Prevention and treatment of osteoporosis in primary biliary cirrhosis. Eur J Gastroenterol Hepatol 1999; 11:617–621.
19. **McCaughan W, Feller RB.** Osteoporosis in chronic liver disease: pathogenesis, risk factors and management. Dig Dis 1994; 12:223–231.
20. **Borghi L, Meschi T, Guerra A, et al.** Vertebral mineral content in diet-dependent and diet-independent hypercalciuria. J Urol 1991; 146:1334–1338.
21. **Bataille P, Achard JM, Fournier A, et al.** Diet, vitamin D, and vertebral mineral density in hypercalciuric calcium stone formers. Kidney Int 1991; 39:1193–1205.
22. **Ghazali A, Fuentes V, Desanaint C, et al.** Low bone marrow density and peripheral blood monocyte activation profile in calcium stone formers with idiopathic hypercalciuria. J Clin Endocrinol Metab 1997; 82:32–38.
23. **Audran M, Legrand E.** Hypercalciuria. Joint Bone Spine 2000; 67:509–515.
24. **Pietschrnann F, Bleslau NA, Pak CY.** Reduced vertebral bone density in hypercalciuric nephrolithiasis. J Bone Miner Res 1992; 7:1383–1388.
25. **Domrongkitchaiporn S, Pongsakul C, Stitchantrakul W, et al.** Bone mineral density and histology in distal renal tubular acidosis. Kidney Int 2001; 59:1086–1093.
26. **Finkelstein JS, Neer RM, Biller B, et al.** Osteopenia in men with a history of delayed puberty. N Engl J Med 1992; 226:600–604.
27. **Finkelstein JS, Klibanski A, Neer RM.** A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. J Clin Endocrinol Metab 1996; 81:1152–1155.
28. **Berteloni S, Baroncelli G, Battini R, et al.** Short-term effective testosterone treatment from reduced bone density in boys with constitutional delay of puberty. J Bone Miner Res 1995; 10:140–148.
29. **Daniell HW.** Osteoporosis after orchiectomy for prostate cancer. J Urol 1997; 157:439–444.
30. **Pecherstorfer M, Seibel MJ, Woitge HW, et al.** Bone resorption in multiple myeloma and in monoclonal gamrnopathy of undetermined significance: quantification by urinary pyridinium links of collagen. Blood 1997; 103:743–750.
31. **Hoorweg-Numan J, Kardos G, Roos JC, et al.** Bone mineral density and markers of bone turnover in young adult survivors of childhood lymphoblastic leukemia. Clin Endocrinol 1999; 50:227–244.
32. **Wonke B, Jensen C, Hanslip JJ, et al.** Genetic and acquired predisposing factors in treatment of osteoporosis and thalassemia major. J Pediatr Endocrinol Metab 1998; 11:795–801.
33. **Goerss JB, Kim CH, Atkinson EJ, et al.** Risk of fractures in patients with pernicious anemia. J Bone Miner Res 1992; 7:573–579.
34. **Brenton DP, Dow CJ.** Homocystinuria and Marfan syndrome: a comparison. J Bone Joint Surg 1972; 54:277–298.
35. **Magid D, Pyeritz R, Fishman EK.** Musculoskeletal manifestations of the Marfan syndrome. Am J Roentgenol 1990; 155:99–104.
36. **Weinstein RS, Whyte MP.** Management of adult hypophosphatasia: report of severe and mild cases. Arch Intern Med 1981; 141:727–731.
37. **Bischoff H, Freitag P, Jundt G, Steinmann B, Tyndall A, Theiler R.** Type 1 osteogenesis imperfecta: diagnostic difficulties. Clin Rheumatol 1999; 18:48–51.
38. **Ferrari S, Rizzoli R, Slosman D, Bonjour TP.** Familial resemblance for bone mineral mass is expressed before puberty. J Clin Endocrinol Metab 1998; 83:358–361.
39. **Lonzer MD, Imrie R, Rogers D, Worley D, Licata A.** Effects of heredity, age, weight, puberty, activity, and calcium intake on bone mineral density in children. Clin Pediatr 1996; 35:185–189.
40. **Finkelstein JS, Klibanski A, Neer RM, et al.** Increase in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1999; 84:1966–1975.
41. **Snyder PJ, Peachey H, Hannoush P, et al.** Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999; 84:1966–1972.
42. **Slemenda CW, Longcope C, Zhou L, et al.** Sex steroids and bone mass in older men; positive associations with serum estrogens and negative associations with androgens. J Clin Invest 1997; 100:1755–1759.
43. **Smith EP, Boyd J, Frank GR, et al.** Estrogen resistance caused by a mutation in the estrogen receptor gene in a man. N Engl J Med 1994; 331:1059–1061.
44. **Chesnut CH 3rd, Silverman S, Andriano K, et al.** A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis. PROOF Study Group. Am J Med 2000; 109:267–276.
45. **Slovik DM, Rosenthal DI, Doppelt SH, et al.** Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxyvitamin D. J Bone Miner Res 1986; 1:377–381.
46. **Neer RM, Arnaud CD, Zanchetta JR, et al.** Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women osteoporosis. N Engl J Med 2001; 19:1434–1441.
47. **Ho KK, Hoffman DM.** Aging and growth hormone. Horm Res 1993; 40:80–86.
48. **Lissett CA, Shalet SM.** Effects of growth hormone on bone and muscle. Growth Horm IGF Res 2000; 10(suppl B):95–101.
49. **Baurn BM, Biller BMK, Finkelstein JS, et al.** Effect of physiological growth hormone therapy on bone density and body composition in patients with adult onset growth hormone deficiency: a randomized placebo-controlled trial. Ann Intern Med 1996; 125:883–890.
50. **Ringe JD, Rovaati LC.** Treatment of osteoporosis in men with fluoride alone or in combination with bisphosphonates. Calcif Tissue Int 2001; 69:252–255.
51. **Ringe JD, Rovati LC.** Treatment of osteoporosis in men with fluoride alone or in combination with bisphosphonates. Calcif Tissue Int 2001; 69:252–255.
52. **Orwoll E, Ettinger M, Weiss S, et al.** Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000; 343: 604–610.
53. **Haguenauer D, Welch V, Shea B, Tugwell P, Adachi JD, Wells G.** Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. Osteoporos Int 2000; 11:727–738.
54. **Cortet B, Vasseur J, Grardel B, et al.** Management of male osteoporosis. Joint Bone Spine 2001; 68:252–256.
55. **Miller PD, Watts NB, Licata AA, et al.** Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. Am J Med 1997; 103:468–476.

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institution of interventional measures that have been shown to be effective in reducing proteinuria, retarding the progression of kidney disease, and improving cardiovascular mortality and morbidity, with the consequent improvement of outcomes for all individuals at increased risk.

Sir Robert Hutchison (1871–1960) must have had a premonition of things to come, when at the turn of the past century he noted that; the ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigation. They ask us, why did you not test my urine?

REFERENCES

1. **Keane WF, Eknoyan G.** Proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). A position paper of the National Kidney Foundation. Am J Kidney Dis 1999; 33:1004–1010.
2. **Grimm RH Jr, Sandsen KH, Kasiske B, Keane WM, Wahi M.** Proteinuria is a risk factor for mortality over 10 years of follow up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int 1997; 63(suppl 63):S10–S14.
3. **Peterson JC, Adler S, Burkart JM, et al.** Blood pressure control, proteinuria and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995; 123:754–762.
4. **Mutner P, He J, Hamm L, Loria C, Whelton P.** Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13:745–753.
5. **Gerstein HC, Mann JF, Yi Q, et al.** Albuminuria and risk of cardiovascular events, death and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286:421–426.
6. **SoRelle R.** Increases in urinary albumin excretion predict risk of death from all causes as well as those from cardiovascular disease. Circulation 2002; 106:e9037–e9038.
7. **Leoncini G, Sacchi G, Viazzi F, et al.** Microalbuminuria identifies overall cardiovascular risk in essential hypertension. J Hypertens 2002; 20:1315–1321.
8. **Hillege HL, Fidler V, Diercks GF, et al.** Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. Circulation 2002; 106:1777–1782.
9. **Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigators.** Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. Ann Intern Med 2001; 134:629–636.
10. **Keane WF.** Proteinuria: Its clinical importance and role in progressive renal disease. Am J Kidney Dis 2000; 35:(suppl 1):S97–S105.
11. **Kashif W, Siddiqi N, Dincer AP, Dincer HE, Hirsch S.** Proteinuria: How to evaluate an important finding. Cleve Clin J Med 2003; 70:535–547.
12. **Schwab SL, Christensen RL, Dougherty K, Klahr S.** Quantification of proteinuria by the use of protein-to-creatinine ratios in single urine samples. Arch Intern Med 1987; 147:943–944.
13. **Chitalia VC, Kothari J, Wells EJ, et al.** Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol 2001; 55:436–447.
14. **National Kidney Foundation.** K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39(suppl 1):S25–S27.

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CORRECTIONS

Osteoporosis in men

(MARCH 2003)

"Osteoporosis in men: Suspect secondary disease first," by Angelo Licata, MD, PhD (Cleve Clin J Med 2003; 70:247–254) contained a typographic error. On page 251 the T-score range for osteopenia was listed as between –1.5 and –2.5. The World Health Organization criteria specify –1.0 to –2.5. We would like to thank Dr. Stefan Monev, of Oshkosh, Wis, for pointing this out.

Preventing kidney failure

(APRIL 2003)

TABLE 2 in "Preventing kidney failure: Primary care physicians must intervene earlier" by Christopher J. Hebert, MD (Cleve Clin J Med 2003; 70:337–344) contained a typographic error. The exponent of the serum albumin concentration should be positive, not negative. The corrected table is shown at right. We would like to thank Dr. Robert Misson, of San Luis Obispo, Cal, for pointing this out.

TABLE 2

Three formulas for calculating the glomerular filtration rate (GFR)

MDRD formula (most accurate – calculator at www.kdoqi.org)

$$GFR = 170 \times \text{serum creatinine concentration}^{-0.999} \times \text{age}^{-0.176} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if race is black)} \times \text{blood urea nitrogen concentration}^{-0.17} \times \text{serum albumin concentration}^{0.318}$$

24-hour creatinine clearance
(intermediate accuracy, least convenient)

$$GFR = \frac{\text{urine creatinine concentration} \times \text{volume in mL}}{\text{serum creatinine concentration} \times \text{time in minutes}}$$

Cockroft-Gault formula (least accurate, most convenient)

$$GFR = \frac{(140 - \text{age}) \times \text{weight in kg} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine concentration}}$$