Journal of Clinical Densitometry, vol. 9, no. 1, 47–57, 2006

1094-6950/06/9:47–57/$32.00
DOI: 10.1016/j.jocd.2006.01.001

ISCD Canadian Standards

Standards for Performing DXA in Individuals With Secondary Causes of Osteoporosis

Aliya A. Khan,[*,1] *David A. Hanley,*[2] *John P. Bilezikian,*[3] *Neil Binkley,*[4] *Jacques P. Brown,*[5] *Anthony B. Hodsman,*[6] *Robert G. Josse,*[7] *David L. Kendler,*[8] *E. Michael Lewiecki,*[9] *Paul D. Miller,*[10] *Wojciech P. Olszynski,*[11] *Steven M. Petak,*[12] *Zeba A. Syed,*[13] *Diane Theriault,*[14] *and Nelson B. Watts*[15]

[1]*Divisions of Endocrinology and Geriatrics, McMaster University, Hamilton, Ontario, Canada;* [2]*Department of Medicine, University of Calgary, Calgary, Alberta, Canada;* [3]*College of Physicians and Surgeons, Columbia University, New York, New York;* [4]*University of Wisconsin, Madison, Wisconsin;* [5]*CHUR Research Centre, Laval University, Quebec City, Quebec, Canada;* [6]*University of Western Ontario, London, Ontario, Canada;* [7]*University of Toronto, Toronto, Ontario, Canada;* [8]*University of British Columbia, Vancouver, British Columbia, Canada;* [9]*New Mexico Clinical Research and Osteoporosis Center, Albuquerque, NM;* [10]*Colorado Center for Bone Research, Lakewood, CO;* [11]*University of Saskatchewan, Saskatoon, Saskatchewan, Canada;* [12]*Texas Institute for Reproductive Medicine, Houston, TX;* [13]*Muscoloskeletal Radiologist, Hanover General Hospital, Hanover, PA;* [14]*Dartmouth, Nova Scotia, Canada;*
and [15]*University of Cinncinnati, Cinncinnati, OH*

Abstract

This document addresses skeletal health assessment in individuals with secondary causes of osteoporosis. Recommendations are based on consensus of the Canadian Panel of the International Society for Clinical Densitometry and invited international experts. Bone mineral density (BMD) testing in these populations is performed in conjunction with careful evaluation of the disease state contributing to bone loss and increased fragility fracture risk, as well as assessment of other contributing risk factors for fracture. The presence of secondary causes of bone loss may further increase the risk of fracture independently of BMD and may necessitate earlier pharmacologic intervention. Dual-energy X-ray absorptiometry is indicated in the initial workup of secondary causes of osteoporosis. The BMD fracture risk relationship is not known for individuals with chronic renal failure (CRF). The BMD testing in this population may be normal in the presence of skeletal fragility, and quantitative bone histomorphometry is better at evaluating skeletal status than BMD in CRF. Dual-energy X-ray absorptiometry is a valuable tool in assessing skeletal health in individuals with secondary causes of osteoporosis.

Key Words: Absorptiometry; dual-energy X-ray absorptiometry; DXA; osteoporosis; secondary causes of osteoporosis; standards for performing DXA.

This document was created by the ISCD Canadian Regional Panel. The ISCD has approved this document as being relevant to local or regional needs and does not necessarily represent official ISCD positions or ISCD positions as they relate to this specific jurisdiction.

*Address correspondence to: Aliya A. Khan, MD, FRCPC, FACP, Associate Clinical Professor of Medicine, Divisions Endocrinology and Geriatrics, McMaster University, 331-209 Sheddon Avenue, Oakville, ON L6J 1X8, Canada. E-mail: avkhan@aol.com

Introduction

Recently the Canadian Panel of the International Society for Clinical Densitometry (ISCD) developed standards of care to establish a minimum level of acceptable performance with respect to the practice of bone densitometry in Canada. The Canadian Panel previously published standards I *(1)* and II *(2)* that addressed the performance of dual-energy X-ray absorptiometry (DXA) in pre- and postmenopausal women,

as well as in men and children. The current document addresses the assessment of skeletal health in individuals with secondary causes of osteoporosis. As with the previously published standards and guidelines, the most recent recommendations were developed by the Canadian Panel of the ISCD and invited international experts in conjunction with the 2005 ISCD Position Development Conference. The primary goal of these standards of care is to optimize the evaluation and management of patients with secondary causes of osteoporosis.

Utilization of DXA in Glucocorticoid-Induced Osteoporosis

Glucocorticoids (GCs) are of value in the management of a wide range of autoimmune diseases including pulmonary, rheumatologic, bowel, and skin disorders as well as being an important component of standard protocols in preventing graft rejection post-organ transplantation *(3–5)*. Approximately 0.5% to 3.2% of the population has received or is currently receiving GCs *(6,7)*. GC use ranks third in importance as a risk factor for osteoporosis; only preceded by postmenopausal bone loss and age-related bone loss. GC use is the leading cause of drug-induced osteoporosis. One recent study *(8)* estimated that 1 in 6 vertebral fractures and 1 in 13 nonvertebral fractures are attributed to oral GC use. Glucocorticoid use is associated with rapid losses in bone mineral density (BMD), with as much as 6.4% within the first 6 months *(9,10)*. Losses are greatest at sites rich in cancellous bone, such as the spine *(10)*. Calcium and vitamin D do not prevent these losses *(10)*. Aggressive preventive therapy is necessary to preserve bone mass when GC therapy is initiated. Thirty to fifty percent of individuals treated chronically with GC experience a fracture *(11–13)*. This document identifies individuals on GC at increased fracture risk, enabling institution of appropriate therapy.

The increased risk of fracture on GC therapy is due to several factors including the dose and duration of GC therapy; the underlying disease process being treated with GC; as well as other risk factors for fracture which may be present (*see* Table 1).

Table 1
Glucocorticoid-Related and Patient-Related Risks for Fractures

Drug related risk factors	Patient related risk factors
Dose	Age
Mode of administration	Gender
Duration	Fragility fracture after age 40
	Menopausal status
	Underlying illness
	Baseline bone mineral density
	Other risks

Fracture Risk and Dose of Oral GC

Fracture risk increases with GC use. Doses as low as 2.5–7.5 mg/day of prednisone are associated with a relative risk (RR) for hip fracture of 1.77 and for vertebral fracture of 2.59 *(3)*. Doses greater than 7.5 mg/day are associated with even higher fracture risks (RR: 2.27 for hip fractures and 5.18 for vertebral fractures). The increased risk of fracture is seen as early as 3 months after GC therapy is initiated. Fracture risk is more related to current daily dose than to cumulative dose *(14,15)*. A history of prior GC therapy use is also associated with an increased risk of fracture in comparison to those with no history of GC use, as confirmed in a recent meta-analysis *(16)*. Discontinuation of GC therapy is associated with reductions in fracture risk *(3)*.

In children, oral GC therapy has been associated with a modest increase in fracture risk (adjusted odds ratio: 1.32). This increased fracture risk may be the result of the underlying disease process in addition to GC therapy *(17)*.

Inhaled GCs and Fractures

A systematic review of 4 randomized controlled trials (RCTs) *(18)* and a large population based cohort-control study *(19)* suggest that inhaled steroid use contribute to increased fracture risk. The literature however is not able to clearly define the relationship between inhaled GC dose and fracture risk *(20,21)*. The impact of the underlying disease on fracture risk also needs to be further evaluated. In children with asthma, the risk of fracture on inhaled GC was no different than the fracture risk seen with bronchodilator use *(22)*.

Pulse Steroids

Data is limited regarding administration of pulse steroids and fracture risk. In a small study in individuals with multiple sclerosis treated with intravenous pulsed therapy, BMD losses appear to be related to limited ambulatory ability to a greater degree than to GC use *(23)*. A short term study evaluating intermittent methylprednisolone pulsed therapy over a median of 5.7 months revealed modest BMD losses of 2.2% at the femoral neck and 1% at the spine *(24)*. Published data on the use of intravenous pulsed steroids and fracture incidence is limited. Intramuscular pulsed depomedrone in individuals with rheumatoid arthritis has been associated with an increased risk of vertebral fractures in comparison with placebo in a 2-year randomized controlled trial *(25)*.

Coexisting Risk Factors for Fracture

Fracture risk is clearly affected by other important risk factors that may also be present in addition to GC use.

GC are extensively utilized in significant doses and duration in the older population *(3,4,7,26)*. Age and menopausal status independently impact fracture risk *(27–29)*. In three randomized controlled trials evaluating the protective skeletal effects of bisphosphonates with GC use, vertebral fractures occurred in 7.6–21.9% of the postmenopausal study population treated with calcium and vitamin D alone *(27–29)*. No fractures were seen in the 97 premenopausal women enrolled in the placebo arms.

A large retrospective cohort study (n = 280,645) reported that the rate of vertebral and nonvertebral fractures in women exposed to GCs was greater than the fracture rate seen in men on GC, at any age group *(8)*. Among women in all age groups >30 years, vertebral and nonvertebral fracture rates were higher among those on GCs than among those not exposed to GCs. In men administered GC, there was no significant increase in the rate of nonvertebral fractures compared with nonexposed controls. Vertebral fracture rates were increased however in GC-exposed men after age 50. Kanis et al *(16)* evaluated fracture risk with GC use in a meta-analysis of data from 7 cohort studies totaling approximately 42,000 men and women. Current and past use of GCs were determined to be an important predictor of fracture risk both in men and women, independent of BMD and history of prior fractures.

Van Staa et al *(15)* examined the relationship between baseline BMD and the risk of incident vertebral fractures at 12 months in 111 patients enrolled in the placebo groups of 2 RCTs investigating glucocorticoid-induced osteoporosis (GC-IO). Baseline BMD was a strong predictor of incident fracture; for each standard deviation decrease in T-score, the relative risk for fracture increased by 1.85. For those with a baseline lumbar BMD < -2.5, the risk of vertebral fracture at 12 months was 34.5%, whereas it was 5.9% for individuals with a baseline BMD T-score of ≥ -2.5. Van Staa et al *(15)* further compared the postmenopausal women (n = 56) in these placebo groups to 1,899 women in the placebo groups of trials evaluating risedronate. Women on GC therapy had more fractures than the postmenopausal osteoporotic women even though they were younger (mean age: 64.7 years old vs. 74.1 years old), had higher baseline BMD (T-score: −1.8 vs. −2.6), and had a lower percentage of baseline fractures (42.9% vs. 58.3%). The postmenopausal GC users however had a much higher incidence of fractures at 12 months than nonusers of GCs (16.7% vs. 7.0%). Finally, although baseline BMD predicted vertebral fracture risk in GC users, fracture risk was significantly increased at any given level of BMD compared with the postmenopausal osteoporosis group. This finding is supported by the results of the recent meta-analysis of 7 cohorts followed prospectively demonstrating a greater fracture risk in GC-IO than in postmenopausal osteoporosis for the same level of BMD *(16)*.

These findings suggest that non-BMD factors may contribute to the increased fracture risk seen with GC therapy. Such factors include the impact of GC on bone microarchitecture, osteocyte and osteoblast lifespan and function. Effect of GC on muscle strength and risk of falls may also impact future risk. Comorbidity such as the presence of rheumatoid arthritis also has an impact on skeletal fragility. Thus the risk of fracture is significantly greater in GC-IO in comparison to postmenopausal osteoporosis with higher fracture risk given the same level of BMD. Pharmacologic intervention is recommended in GC-IO at higher BMD values than advised for postmenopausal osteoporosis.

Although there is a significant correlation between fracture risk and baseline BMD in individuals receiving GC therapy, one should not assume that a normal baseline BMD is protective against incident fractures in the presence of GC therapy. In certain situations, such as transplantation, the risk of fracture is markedly enhanced despite normal baseline BMD.

Recommendations:

1. The lowest effective dose of GC should be used, and for the shortest duration possible. Inhaled GCs are preferable to oral GCs. When medically indicated, alternative therapies that may minimize GC exposure should be considered.
2. Prior to initiation of GC, other important risk factors for fracture should be evaluated including age, prevalent vertebral fractures and BMD.
3. Lifestyle changes to ensure maintenance of skeletal health (i.e., smoking cessation, adequate calcium and vitamin D, active lifestyle, etc.) should be emphasized.
4. Baseline BMD measurements are indicated for men and women taking oral GC for >3 months. Baseline BMD measurements should also be obtained in individuals who receive GC by intravenous pulsed therapy. In those on long-term, high-dose inhaled GC therapy, BMD might be considered. In geographic areas with limited access to BMD, appropriate therapy should be initiated in adults in the absence of a BMD test. The BMD measurements (at baseline and follow-up) are helpful in clinical decision making, but are not the only factors determining appropriate prevention and treatment strategies.
5. Serial BMD measurements should be obtained every 6 to 12 months and should be considered in conjunction with other risk factors for fracture.
6. Baseline evaluation and monitoring of height by a calibrated stadiometer are recommended. Vertebral fracture assessment is recommended in patients expected to receive GCs in daily doses of $\geq$7.5 mg for more than 3 months. Spine x-rays are recommended in patients with clinical vertebral fractures or in the presence of height loss.
7. Treatment to prevent osteoporosis should be initiated in the following circumstances: (a) BMD T-scores of ≤ -1.5 at the hip, spine, or 1.3 radius sites; or (b) doses of prednisone $\geq$7.5 mg daily for a duration of 3 months or longer; or (c) presence of fragility fractures.

Utilization of DXA in Vitamin D Deficiency/ Insufficiency States

Given its high prevalence in the general population *(30)*, vitamin D inadequacy is commonly identified when testing for secondary causes of osteoporosis. In the vitamin D literature, the terms vitamin D ''deficiency'' and ''insufficiency'' reflect different degrees of the same problem (i.e., inadequate body supply or stores of vitamin D). Inadequate vitamin D is deleterious to bone health, with the more severe deficiency state resulting in rickets or osteomalacia. In this section, we will use the term inadequacy to encompass both insufficiency and deficiency.

Table 2
Clinical States Associated With Inadequate Vitamin D

- Low Vitamin D Intake
- Malabsorption
  Celiac disease
  Inflammatory bowel disease
  Gastrectomy
  Bariatric surgery (intestinal bypass)
  Pancreatic insufficiency
  Cystic fibrosis
- Anticonvulsant therapy (particularly phenytoin and barbiturate derivatives, carbamazepine)
- Low levels of sunlight exposure
  Living at high latitude
  Use of topical sunblock
  Institutionalization
  Voluntary sun avoidance
  Any chronic disease restricting outdoor activity

Apart from being a risk factor for low-bone density, there is nothing distinctive or diagnostic about DXA measurements in the setting of vitamin D inadequacy. Disorders and conditions commonly associated with vitamin D inadequacy are listed in Table 2 *(31–45)*.

The adequacy of vitamin D status is best assessed by a reliable assay of serum 25-OH vitamin D (25-OHD) *(30,46)*. A very low level of serum 25-OHD ($<$20 nmol/L) is associated with impaired skeletal mineralization, causing rickets and osteomalacia. A much higher level (probably in the range of 70–150 nmol/L) is optimal for skeletal health. This recommendation for optimal levels is much higher than what was formerly recommended *(47–49)*. With serum levels $>$70–80 nmol/L, there probably is an optimal vitamin D level for the regulation of calcium absorption, and maximum vitamin D-related suppression of serum parathyroid hormone (PTH). Excessively high levels of vitamin D, although unusual, may be associated with hypercalcemia and renal stones.

Some clinicians rely on an elevated serum PTH as an indicator of vitamin D insufficiency or deficiency, as the serum PTH rises in response to decreased levels of this vitamin (i.e., an insufficiency) or to the chronically low calcium absorption (resulting from a deficiency). Unfortunately, this intuitively-logical approach does not produce reliable results in individual patients. Calcium intake can suppress PTH, despite low vitamin D levels *(50)*, and many individuals will have normal PTH levels despite low vitamin D status *(47–49,51,52)*. In addition, a rise in PTH within the normal reference range may occur with vitamin D inadequacy, and this may be misinterpreted in the absence of a baseline 25-OHD level. Thus PTH levels should not be used to assess or to document vitamin D inadequacy. Measurement of serum 25-OHD remains the laboratory procedure necessary for assessment of vitamin D status, despite lingering problems with the performance of some assays *(53,54)*.

Due to its high prevalence, one of the first considerations in any person failing to respond to osteoporosis treatment should be the possibility of vitamin D inadequacy. If the individual is already taking calcium and vitamin D supplementation, a serum 25-hydroxyvitamin D measurement should be obtained. A poor BMD response to bisphosphonate therapy for osteoporosis (i.e., significant BMD loss after 1–2 yr of therapy) should definitely trigger a search for secondary causes of osteoporosis as well. Similarly, because it is possible that vitamin D deficiency could develop with time, even among those who initially test normal for vitamin D, we would recommend retesting among those on osteoporosis therapy who fail to respond during the 1–2 years. A serum 25-OHD measurement is the best way to assess vitamin D status. It is generally believed that the response to bisphosphonate therapy is attenuated by inadequate vitamin D, although this has only been documented in one small study of cyclical etidronate therapy *(55)*. However, it is appropriate to correct vitamin D inadequacy, if found, in a patient who is not responding to bisphosphonates.

Once vitamin D inadequacy is recognized and treated, the response may be monitored by DXA, preferably 1 year after effective therapy has been instituted. Dramatic increases in BMD have been documented in the treatment of vitamin D deficiency *(56–58)*, as lack of mineralization of existing bone matrix has caused the BMD to be low.

Recommendations:

The Canadian Panel of the ISCD recommends:

1. Patients at high risk for vitamin D deficiency because of low vitamin D intake or inadequate sunlight exposure such as the institutionalized elderly should have serum 25-OHD measured.
2. Individuals taking phenytoin or barbiturate-derived anticonvulsants, or carbamazepene, or with disorders associated with malabsorption (*see* Table 2), should receive further skeletal evaluation, including BMD assessment and serum 25-OHD measurement.
3. After intervention with appropriate vitamin D replacement, BMD measurement should be repeated at 1 year with the expectation that improvement in bone mineralization will result in an increase in, or in milder cases, at least a stabilization of BMD.

Utilization of DXA in Hypogonadal States in Males and in Females Early Post-Menopause

Normal circulating levels of sex steroids are required for optimal calcium homeostasis and skeletal health *(59)*. Estradiol plays a key role in the attainment and maintenance of peak bone mass in women. Estrogen is also produced both in men and women from the aromatization of androgens in peripheral tissues. In both sexes it has an anti-resorptive effect, contributing to the attainment of peak bone mass and maintenance of skeletal health in the adult. Conversely, estradiol deficiency results in increased bone turnover and a negative remodeling balance.

In men, testosterone levels decline gradually with age, especially after middle age. Morning serum levels of total

testosterone (T) and sex hormone binding globulin should be measured in symptomatic men. If the T level is borderline low, free testosterone should be measured by equilibrium dialysis *(60)*. To distinguish between primary (testicular) and secondary (pituitary/hypothalamic) hypogonadism, gonadotropin levels should be evaluated. Measurement of serum levels of prolactin and other pituitary hormones is completed if secondary hypogonadism is suspected *(60)*. Testosterone is not routinely measured in healthy men; however, testing should be completed in men who are at risk for hypogonadism, including men with symptoms, with known prior pituitary, or testicular disease, or with low bone mass.

Circulating testosterone plays a vital role in maintaining sexual function, body composition, and cognitive function. Hypogonadal men may present with a variety of symptoms, signs, and laboratory findings, somewhat dependent on age, which include: absence or regression of secondary sex characteristics, sexual dysfunction, infertility anemia, muscle wasting, decreased bone mass and bone density, increased body fat (in particular, abdominal adiposity), decreased serum high-density lipoprotein cholesterol levels, depressed mood, increased irritability, difficulty concentrating and, less frequently, hot flashes *(61)*. In men presenting with both a clinical picture suggestive of testosterone deficiency and laboratory evidence of testosterone deficiency, testosterone replacement is clearly warranted. Moreover, BMD should be performed in order to identify whether specific musculoskeletal intervention is indicated, and to determine how aggressive that intervention should be. In younger men, preferential early loss of trabecular bone may lead to lower spine BMD than hip BMD. In older men, age-related degenerative changes and osteophytes in the spine may result in falsely-elevated BMD readings, making the hip site generally a more accurate measure of bone status and/or requiring forearm measurement.

Alternatively, a man may present with osteoporosis, either because of a fracture or because a BMD measurement has been performed for some other reason. In these men, even in those whose history and physical examination may not suggest it, hypogonadism is an important cause of male osteoporosis that must be excluded.

It is important to consider skeletal health in the male with prostate cancer who is receiving androgen deprivation therapy as these men are at risk for osteoporosis. It also is important to consider the possibility of vertebral compression fractures as a cause for back pain in these individuals, in the differential in addition to other potential causes for back pain such as a blastic lesion, and monitor and/or manage osteoporosis accordingly.

Treatment of hypogonadal men with alendronate yields gains in BMD that are similar to those achieved in eugonadal men and in women with postmenopausal osteoporosis *(62)*. The anabolic agent, teriparatide (PTH 1-34), also leads to BMD gains among hypogonadal men that are similar to those observed in eugonadal men and postmenopausal women *(63)*. If medically indicated, hypogonadal men should receive T supplementation. Possible issues with regard to T replacement, such as prostate health, sleep apnea, and effect on low-density lipoprotein levels should be considered. The response to T varies among hypogonadal men, due in part to the relative degree of hypogonadism, the extent of bone loss at the time therapy is started, and the form of androgen replacement therapy instituted *(64)*. There is no evidence that T use in eugonadal men improves skeletal health.

Subclinical estrogen deficiency may occur during the perimenopausal period. Premature loss of ovarian function may be due to premature ovarian failure, autoimmune disease, ovarian surgery, chemotherapy, radiation therapy, and genetic syndromes such as Turner's syndrome. Hypogonadism may also result from pituitary or hypothalamic disease, as well as from gonadotropin-releasing hormone agonist therapy (e.g., treatment for endometriosis). Anorexia may induce hypogonadism in the presence of significant weight loss. Also, among female athletes who over-exercise, estrogen deficiency can occur due to a combination of the exercise itself and becoming underweight. Progestational agents used for contraception in young women potentially cause bone loss due to the associated estrogen deficiency. Recovery of BMD may occur when depot medroxyprogesterone acetate (DMPA) is stopped *(65)*. Significant gains in BMD were seen in adolescent women discontinuing DMPA therapy in a prospective cohort study demonstrating that the loss of bone can be reversed *(65)*.

Estrogen therapy, in combination with a progestin if the uterus is present, should be considered in hypogonadal women with significant vasomotor symptoms. Therapy with estrogen in women with anorexia is often not adequate to benefit bone in the absence of weight gain from increased calorie and nutrient intake *(66)*. Estrogen therapy in asymptomatic postmenopausal women is no longer recommended for prevention or therapy of osteoporosis because of findings from the Women's Health Initiative that suggests that the use of estrogen and progestin in healthy asymptomatic postmenopausal women may result in risks that exceed the benefits of therapy *(67)*.

Recommendations:

The Canadian Panel of the ISCD recommends *(68–71)*:

1. All men, certainly age 70 years and younger, who present with clinical hypogonadism or BMD evidence of osteoporosis should be tested for hypogonadism by measurement of total and free testosterone levels.
2. All hypogonadal men should undergo baseline BMD to assess bone density and then again at 12–24 mo to detect accelerated bone loss.
3. Hypogonadal men who are found to have osteoporosis should receive BMD testing at baseline and at 12–24 mo post-intervention to assess for clinical response.
4. Premenopausal women with amenorrhea that has persisted for more than 6–12 mo should undergo BMD testing, and then again at 12 months to detect accelerated bone loss. Women on long-term depot medroxyprogesterone acetate for more than 2 yr may be at risk for significant bone loss, and BMD testing may be considered in the presence of other risk factors for fracture.

5. Subclinical or clinical estrogen deficiency in women younger than age 50 who are found to have osteoporosis should have a repeat BMD 12–24 mo after estrogen replacement has been initiated to assess for clinical response.

Utilization of DXA in Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is associated with a reduction in BMD, particularly at sites rich in cortical bone, such as the distal third of the radius (mid radius). At cancellous sites, such as the lumbar spine, BMD can be relatively well preserved *(72)*. However, bone loss in the lumbar spine can occur in PHPT *(73)*. Currently, fracture risk in individuals with asymptomatic PHPT is not well defined due to the lack of prospective, longitudinal fracture data. Asymptomatic PHPT may be associated with an increased risk of fracture at cortical skeletal sites. It is not known whether the lumbar spine is protected by virtue of relatively well preserved bone density in many patients with PHTP *(74)*. Data obtained from geometric and histomorphometric studies in PHPT suggest that features protective against fracture may, in fact, be present *(75)*.

The results of the National Institutes of Health workshop on asymptomatic PHPT led to a revision in recommendations regarding the assessment of skeletal status in PHPT *(76)*. These recommendations now include measurement of all 3 sites: (1) the lumbar spine, (2) the hip, and (3) the mid-radius, both at baseline and annually thereafter *(74)*. Reductions in BMD to a T-score ≤ -2.5 at any of these 3 skeletal sites serves as an indication for parathyroidectomy *(76)*. The Canadian consensus document on PHPT endorses this position *(77)*.

After parathyroidectomy, lumbar spine and hip BMD generally increase markedly *(78)*. The mid radius tends to be stable. In the absence of surgery, improvements in BMD have been observed in randomized, placebo-controlled clinical trials using antiresorptive agents *(79–83)*. Antiresorptive agents lower markers of bone turnover in PHPT in pre- and postmenopausal women and in men *(84)*. Antiresorptive agents appear to protect the skeleton in PHPT by improving BMD and reducing bone turnover. However, there are no prospective data documenting reduction in fractures with antiresorptive intervention in PHPT.

Recommendations:

The Canadian Panel recommends:

1. Skeletal status should be evaluated in PHPT, with assessment of BMD at the lumbar spine, hip, and one-third radius at the time of diagnosis and on an annual basis thereafter.
2. Parathyroidectomy, as well as antiresorptive therapies, has been accompanied by an improvement in BMD and a reduction in markers of bone turnover. However, measurement of bone markers is currently useful in selected patients and not recommended for routine clinical practice.

Table 3
Metabolic Bone Diseases Associated With Severe Renal Disease

Osteitis fibrosa
Osteomalacia
Vitamin D related
Nonvitamin D dependent
Aluminum toxicity
Chronic metabolic acidosis
Phosphate depletion
Adynamic bone disease
Mixed uremic osteodystrophy
Amyloid bone disease
Osteoporosis

Utilization of DXA in Patients With Renal Insufficiency

Renal osteodystrophy is the end result of a complex interaction comprising several pathophysiological disorders, which are summarized in Table 3. In the great majority of patients, secondary hyperparathyroidism dominates the picture. In its severest form, peri-trabecular fibrosis (''osteitis fibrosa'') may occur, associated with woven, poorly mineralized bone *(88)*. At the opposite end of this spectrum, extremely low bone turnover is seen in adynamic bone disease (ABD) *(88,89)*. The prevalence of the latter condition is variable, but it has become more common as a consequence of using calcium-based phosphate binders, instead of aluminum-based agents. Parfitt *(90)* has argued cogently that the prevalence of ABD has been exaggerated by an imperfect understanding of quantitative bone histomorphometry, and is largely the result of overtreatment of the underlying hyperparathyroidism. Parfitt *(90)* also argues that the suppressed bone turnover, characteristic of ABD, does not necessarily lead to the development of bone that is qualitatively more ''brittle'' or fracture-prone than the normal bone of nonuremic subjects. However, dialysis patients do suffer from fractures, which often raises the issue of whether they have ''osteoporosis'' *(85)*.

Table 4
Osteoporosis in Dialysis Patients

Risk factors antecedent to dialysis	Risk factors during dialysis
Age >60 years	Poor nutrition
Postmenopausal	Vitamin D deficiency
Prolonged glucocorticoid therapy	Hyperparathyroidism
Diabetes mellitus	Hypogonadism
Other established major or minor risk factors[a]	Chronic heparin use
	Chronic metabolic acidosis

[a]Clinical Practice Guidelines, Canada. 2002 CMAJ 167:S1–S34.

Despite the practical difficulties associated with defining ''osteoporosis'' in uremic patients, dialysis patients have many reasons for developing deterioration in bone microarchitecture, some of which are common to nonuremic patients with osteoporosis (*see* Table 4). Most women on dialysis are already postmenopausal or will become amenorrheic as they become dependent on dialysis. Many patients receive high doses of GC during the pre-dialysis course of their disease, particularly those with vasculitis. Diabetic patients constitute approximately 30% of the dialysis population. During dialysis, patients may experience severe secondary hyperparathyroidism, chronic metabolic acidosis, poor nutrition, and nutritional vitamin D deficiency, together with repeated heparin exposure. If undergoing renal transplantation, the majority of patients are exposed to high doses of GC and calcineurin inhibitors. The precise interrelationship of these many factors has not been defined; however, age, menopausal status, and the presence of diabetes are 3 of the risk factors most clearly associated with an increased risk for fracture. Dialysis patients are at an apparently increased risk both for vertebral and hip fractures *(86,87,91)*. This risk has been better defined for patients following renal transplantation, who are exposed both to high doses of GC and to calcineurin inhibitors during their first year following transplantation *(91–94)*.

In general, dialysis patients have lower BMD measurements than expected, significantly lower than age-matched reference values, with a somewhat disproportionate but consistent reduction in femoral neck Z-score *(95–104)*. The lower values seen at the femoral neck may reflect the well-established finding of cortical bone loss in patients with PHPT. However, both lumbar spine (a primarily trabecular site) and mid-radius (a primarily cortical site) BMD measurements are poor predictors of fracture in hemodialysis patients *(99)*.

During the first year following renal transplantation, bone loss, as assessed by DXA, is rapid and averages 4–9% in the lumbar spine and in the hip *(85,91–93)*. Histomorphometric studies of bone biopsies that were obtained, both at the time of transplantation and 6 months later, demonstrate a rapid decline in bone formation rates consistent with the known effects of high-dose GC therapy. In the early posttransplantation period, patients may be particularly susceptible to the adverse skeletal effects of high-dose GC therapy, especially if high bone turnover persists *(92,105)*. Other immunosuppressive agents may also contribute to this rapid bone loss *(106)*. After the first year, the rate of bone loss diminishes greatly, and bone density may even improve *(92)*. Although low BMD predicts fractures during the posttransplant period, many patients experience fractures at normal BMD values *(107)*. This is due both to the rapidity of bone loss and the fact that GC-associated fractures typically occur at higher BMDs *(108)*.

In contrast to the pivotal role of BMD in establishing the diagnosis of osteoporosis in postmenopausal women, the heterogeneous nature of renal osteodystrophy makes a precise diagnosis of the underlying skeletal status possible only by proper quantitative examination of an iliac crest bone biopsy. Biochemical profiling can be used with some confidence to determine the likelihood that secondary hyperparathyroidism is present, and can be used to exclude nutritional vitamin D deficiency and aluminum accumulation. The kidney disease outcomes quality initiative (K-DOQI) clinical guidelines for the management of metabolic bone disease in uremic patients clearly set out the therapy to manage uremic secondary hyperparathyroidism, but as yet there are no guidelines for the management of fractures in dialysis or renal transplant patients *(90)*.

The best role for DXA in this patient population is in determining the response to therapy with antiresorptive agents in postmenopausal osteoporosis (PMO). Numerous RCTs have estimated the increments of improvement in BMD measurement (both by DXA and quantitative computerized tomography) that are expected in response to estrogens, selective estrogen receptive modulators (raloxifene), and bisphosphonates in PMO *(109,110)*. Serial BMD measurements have been helpful in identifying ''response'' to therapy, when repeated at appropriate intervals to detect significant changes. Small, but significant gains in BMD at both the lumbar spine and femoral neck have been reported in dialysis patients treated with estrogen *(96)*. Smaller increments have been observed in the lumbar spine, but not at the femoral neck, following the use of raloxifene in dialysis patients *(111)*. Clear safety and efficacy data are not available for bisphosphonates in dialysis patients, although their use is plausible for patients expected to have high bone turnover and in whom underlying osteomalacia has been excluded.

In the early posttransplant period, RCTs have been carried out with bisphosphonates given either intravenously *(92,112–116)* or orally *(92,117–120)*. Control patients invariably lost bone at both the lumbar spine and hip sites, while bisphosphonate-treated patients either maintained or gained BMD, particularly in the lumbar spine. These short-term studies with bisphosphonates typically have been limited to 1 yr or less. A longer, 3-year study involving 2 postoperative doses of intravenous zoledronate, administered within the first 3 months after transplantation, demonstrated no persistent differences between the treated group and the placebo group *(120)*. In only one study with intravenous ibandronate was some evidence provided for reduced vertebral fracture incidence *(115)*. Nonetheless, the use of DXA has proven helpful in defining a response to therapy with bisphosphonates in the transplanted patient.

In summary, DXA cannot be used to make a diagnosis of osteoporosis or any other variant of metabolic bone disease in patients with advanced or end-stage renal failure. Although DXA measurements may be lower than average in uremic patients, there are no prospective data to link BMD values with fracture risk. Indeed, it is well documented that both dialysis *(99)* and transplanted patients *(107)* are prone to fragility fractures, even when BMD values are ''normal.'' To date, the only role for DXA in this patient population may lie in detecting response to therapy.

Recommendations:

The Canadian Panel of the ISCD recommends:

1. DXA should not be used to make a diagnosis of osteoporosis or to assess fracture risk in dialysis or renal transplant patients.

2. DXA measurements should be used in the context of prevalent fractures in either dialysis or renal transplant patients for whom the risk of future fractures is expected to be very high, and in whom treatment to prevent future fractures is planned.
3. Baseline and follow-up DXA measurements (obtained at 12–24 mo) may be used to detect changes following treatment.

Discussion

In summary, these standards address the assessment of skeletal health in individuals with secondary causes of osteoporosis, including GC-IO, vitamin D deficiency, hypogonadism, PHPT, and renal osteodystrophy. Patients presenting with osteoporosis, as well as those for whom antiresorptive therapy has failed, should be evaluated for underlying conditions. DXA is indicated in the initial workup of all of these secondary causes of osteoporosis, with the exception of renal disease, for which quantitative bone histomorphometry is better at defining the underlying skeletal status than BMD.

In most circumstances, DXA of the hip and lumbar spine are sufficient, although one-third radius measurements are warranted in PHPT. Moreover, especially in elderly patients in whom spinal degenerative changes may exist, BMD of the spine may be falsely elevated, so that DXA of the hip may be a more accurate indication of bone status.

Treatment should be considered both for the osteoporosis itself and for the secondary cause. In general, follow-up DXA is indicated once a diagnosis of osteoporosis has been made, and in general 12–24 mo after therapy for osteoporosis has been initiated. More aggressive monitoring is warranted in patients on GCs, possibly as early as 6 mo after treatment has begun. In certain circumstances, in particular in patients with GC-IO, repeat DXA is warranted, even in the absence of treatment, to reevaluate BMD for evidence of potential progressive bone loss. Bone densitometry is a valuable tool in the management of conditions associated with skeletal fragility.

Acknowledgments

We would like to thank Professor John Kanis for his review of the manuscript and his valuable suggestions and comments.

References

1. Khan AA, Brown J, Faulkner K, et al. 2002 Standards and guidelines for performing central dual x-ray densitometry from the Canadian Panel of International Society for Clinical Densitometry. J Clinic Densitom 5:435–445.
2. Khan AA, Bachrach L, Brown JP, et al. 2004 Standards and guidelines for performing central dual x-ray densitometry in premenopausal women, men, and children from the Canadian Panel of the International Society of Clinical Densitometry. J Clin Densitom 7:51–63.
3. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. 2000 Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15(6):993–1000.
4. Gudbjornsson B, Juliusson UI, Gudjonsson FV. 2002 Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. Ann Rheum Dis 61(1):32–36.
5. Mudano A, Allison J, Hill J, Rothermel T, Saag K. 2001 Variations in glucocorticoid induced osteoporosis prevention in a managed care cohort. J Rheumatol 28(6):1298–1305.
6. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. 1996 Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 313(7053):344–346.
7. Van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. 2000 Use of oral corticosteroids in the United Kingdom. QJM 93(2):105–111.
8. Donnan PT, Libby G, Boyter AC, Thompson P. 2005 The population risk of fractures attributable to oral corticosteroids. Pharmacoepidemiol Drug Saf 14(3):177–186.
9. LoCascio V, Bonucci E, Imbimbo B, Ballanti P, Tartarotti D, Galvanini G, et al. 1984 Bone loss after glucocorticoid therapy. Calcif Tissue Int 36(4):435–438.
10. Adachi JD, Bensen WG, Bianchi F, RJ, et al. 1996 Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year follow-up. J Rheumatol 23(6):995–1000.
11. Adinoff AD, Hollister JR. 1983 Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 309(5):265–268.
12. Michel BA, Bloch DA, Fries JF. 1991 Predictors of fractures in early rheumatoid arthritis. J Rheumatol 18(6):804–808.
13. Dykman TR, Gluck OS, Murphy WA, Hahn TJ, Hahn BH. 1985 Evaluation of factors associated with glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 28(4):361–368.
14. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. 2000 Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford) 39(12): 1383–1389.
15. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. 2003 Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 48(11):3224–3229.
16. Kanis JA, Johansson H, Oden A, et al. 2004 A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19(6):893–899.
17. Van Staa TP, Cooper C, Leufkens HG, Bishop N. 2003 Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 18(5):913–918.
18. Richy F, Bousquet J, Ehrlich GE, et al. 2003 Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. Osteoporos Int 14(3):179–190.
19. Hubbard RB, Smith CJ, Smeeth L, Harrison TW, Tattersfield AE. 2002 Inhaled corticosteroids and hip fracture: a population-based case-control study. Am J Respir Crit Care Med 166(12 Pt 1):1563–1566.
20. Suissa S, Ernst P. 2004 Inhaled corticosteroids and fracture risk in COPD. Am J Respir Crit Care Med 170(1):94–95.
21. Lee TA, Weiss KB. 2004 Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169(7):855–859.
22. Van Staa TP, Bishop N, Leufkens HG, Cooper C. 2004 Are inhaled corticosteroids associated with an increased risk of fracture in children? Osteoporos Int 15(10):785–791.
23. Schwid SR, Goodman AD, Puzas JE, McDermott MP, Mattson DH. 1996 Sporadic corticosteroid pulses and osteoporosis in multiple sclerosis. Arch Neurol 53(8):753–757.
24. Haugeberg G, Griffiths B, Sokoll KB, Emery P. 2004 Bone loss in patients treated with pulses of methylprednisolone is not

negligible: a short term prospective observational study. Ann Rheum Dis 63(8):940–944.
25. Choy EH, Kingsley GH, Khoshaba B, Pipitone N, Scott DL. 2005 A 2 year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Ann Rheum Dis 64(9):1288–1293.
26. Chantler IW, Davie MW, Evans SF, Rees JS. 2003 Oral corticosteroid prescribing in women over 50, use of fracture prevention therapy, and bone densitometry service. Ann Rheum Dis 62(4):350–352.
27. Adachi JD, Bensen WG, Brown J, et al. 1997 Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 337(6):382–387.
28. Saag KG, Emkey R, Schnitzer TJ, et al. 1998 Glucocorticoid-Induced Osteoporosis Intervention Study Group. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 339(5):292–299.
29. Wallach S, Cohen S, Reid DM, et al. 2000 Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 67(4): 277–285.
30. Hanley DA, Davison KS. 2005 Vitamin D insufficiency in North America. J Nutr 135:332–337.
31. Rosen CJ, Black DM, Greenspan SL. 2004 Vignettes in osteoporosis: a road map to successful therapeutics. J Bone Miner Res 19:3–10.
32. Segal E, Baruch Y, Kramsky R, Raz B, Tamir A, Ish-Shalom S. 2003 Predominant factors associated with bone loss in liver transplant patients after prolonged post-transplantation period. Clin Transplant 17:13–19.
33. Vage V, Gjesdal CG, Eide GE, Halse JI, Viste A. 2004 Bone mineral density in females after jejunoileal bypass: a 25-year follow-up study. Obes Surg 14:305–312.
34. Haderslev KV, Jeppesen PB, Sorensen HA, Mortensen PB, Staun M. 2003 Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection. Gut 52:653–658.
35. Jahnsen J, Falch JA, Mowinckel P, Aadland E. 2002 Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. Scand J Gastroenterol 37:192–199.
36. Siffledeen JS, Siminoski K, Steinhart H, Greenberg G, Fedorak RN. 2003 The frequency of vitamin D deficiency in adults with Crohn's disease. Can J Gastroenterol 17:473–478.
37. Ghose R. 1999 Post-gastrectomy bone disease undiagnosed for forty years. N Z Med J 112:290–292.
38. Donovan DS Jr, Papadopoulos A, Staron RB, et al. 1998 Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease. Am J Respir Crit Care Med 157: 1892–1899.
39. Valdimarsson T, Lofman O, Toss G, Strom M. 1996 Reversal of osteopenia with diet in adult coeliac disease. Gut 38: 322–327.
40. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. 1994 High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. Neurology 44:1687–1692.
41. Gough H, Goggin T, Bissesar A, Baker M, Crowley M, Callaghan N. 1986 A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. Q J Med 59(230):569–577.
42. Webb AR, Pilbeam C, Hanafin N, Holick MF. 1990 An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. Am J Clin Nutr 51:1075–1081.
43. Webb AR, Kline L, Holick MF. 1988 Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 67:373–378.
44. Matsuoka LY, Wortsman J, Hollis BW. 1990 Use of topical sunscreen for the evaluation of regional synthesis of vitamin D3. J Am Acad Dermatol 22:772–775.
45. Holick MF, Matsuoka LY, Wortsman J. 1995 Regular use of sunscreen on vitamin D levels. Arch Dermatol 131:1337–1339.
46. Food and Nutrition Board, Institute of Medicine. 1997 Dietary reference intakes for calcium, magnesium, phosphorus, vitamin D, and fluoride. National Academy Press, Washington, DC.
47. Rucker D, Allan JA, Fick GH, Hanley DA. 2002 Vitamin D insufficiency in a population of healthy western Canadians. CMAJ 166:1517–1524.
48. Heaney RP. 2004 Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 80(Suppl 6):1706S–1709S.
49. Chapuy MC, Preziosi P, Maamer M, et al. 1997 Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 7:439–443.
50. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd. 1998 Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res 13:168–174.
51. Marcus R, Madvig P, Young G. 1984 Age-related changes in parathyroid hormone and parathyroid hormone action in normal humans. J Clin Endocrinol Metab 58:223–230.
52. Vieth R, Ladak Y, Walfish PG. 2003 Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab 88:185–191.
53. Binkley N, Krueger D, Cowgill CS, et al. 2004 Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab 89:3152–3157.
54. Hollis BW. 2004 Editorial: the determination of circulating 25-hydroxyvitamin D: no easy task. J Clin Endocrinol Metab 89:3149–3151.
55. Koster JC, Hackeng WH, Mulder H. 1996 Diminished effect of etidronate in vitamin D deficient osteopenic postmenopausal women. Eur J Clin Pharmacol 51:145–147.
56. Grados F, Brazier M, Kamel S, et al. 2003 Effects on bone mineral density of calcium and vitamin D supplementation in elderly women with vitamin D deficiency. Joint Bone Spine 70:203–208.
57. Arekat MR, And G, Lemke S, Moses AM. 2002 Dramatic improvement of BMD following vitamin D therapy in a bone marrow transplant recipient. J Clin Densitom 5:267–271.
58. Adams JS, Kantorovich V, Wu C, Javanbakht M, Hollis BW. 1999 Resolution of vitamin D insufficiency in osteopenic patients results in rapid recovery of bone mineral density. J Clin Endocrinol Metab 84:2729–2730.
59. Stedman's Medical Dictionary. 26th ed. 1995 Williams & Wilkins, Baltimore. 836.
60. Petak SM, Nankin HR, Spark RF, et al. 2002 American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. Endocr Pract 8: 440–456.
61. Seftel A. 2005 Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis. Int J Impot Res Aug 11 11 [Epub ahead of print].

62. Orwoll ES, Ettinger M, Weiss S, Miller P, et al. 1999 Alendronate treatment of Osteoporosis in Men. J Bone Miner Res 14: S184.
63. Orwoll ES, Scheele WH, Paul S, et al. 2003 The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17.
64. Snyder PJ, Peachey H, Hannoush P, et al. 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84:1966–1972.
65. Scholes D, Lacroix AZ, Ott SM, et al. 2005 Bone mineral density in women using dept medroxyprogesterone acetate for contraception. Arch Pediatr Adolesc Med 159(2):139–144.
66. Klibanski A, Biller BM, Schoenfeld DA, et al. 1995 The effects of estrogen administration of trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab 80: 898–904.
67. Grimes DA, Lobo RA. 2002 Perspectives on the Women's Health Initiative trial of hormone replacement therapy. Obstet Gynecol 100(6):1344–1353.
68. U.S. Preventive Services Task Force of the U.S. Dept of Health's Agency for Healthcare Research and Quality. September 2002 guidelines. Available at: http://www.ahrg.gov/clinic/uspstf/uspsoste.htm. Accessed December 20, 2005.
69. National Osteoporosis Foundation. NOF guidelines for bone density testing. Available at: http://www.nof.org/osteoporosis/bonemass.htm. Accessed December 20, 2005.
70. Hodgson SF, Watts NB, Bilezikian JP, et al. 2004 for the AACE Osteoporosis Task Force. 2003 American Association of Clinical Endocrinologists medical guidelines for clinical practice and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003 [published correction appears in Endocr Pract 10–90]. Endocr Pract 9(6):544–564.
71. Lewiecki EM, Watts NB, McClung MR, et al. 2004 International Society for Clinical Densitometry. Official positions of the international society for clinical densitometry. J Clin Endocrinol Metab 89:3651–3655.
72. Khan AA, Syed ZA. 2000 Skeletal effects of primary hyperparathyroidism. Endocr Pract 6:385–388.
73. Silverberg SJ, Shane E, Jacobs TP, et al. 1999 A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery [erratum in N Engl J Med 2000; 342:144] N Engl J Med 241:1249–1255.
74. Khosla S, Melton LJ III, Wermers RA, et al. 1999 Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res 14:1700–1707.
75. Dempster DW, Caldwell NJ, Goldstein SA, et al. 2002 Three-dimensional assessment of trabecular architecture in mild primary hyperparathyroidism [abstract]. J Bone Miner Res 17(Suppl):S166.
76. Bilezikian JP, Potts JT Jr, Fuleihan G-H, et al. 2002 Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Bone Miner Res 17(Suppl 2):N2–N11.
77. Miller PD, Bilezikian JP. 2002 Bone densitometry in asymptomatic primary hyperparathyroidism. J Bone Miner Res 17(Suppl 2):N98–N102.
78. Khan AA, Hanley DA, O'Brien CJ, et al. 2003 Position paper: asymptomatic primary hyperparathyroidism - standards and guidelines for diagnosis and management in Canada. Endocr Pract 9:400–405.
79. Nakoaka D, Sugimoto T, Kobayashi T, et al. 2000 Prediction of bone mass change after parathyroidectomy in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 85(5): 1901–1907.
80. Grey AB, Stapleton JP, Evans MC, et al. 1996 Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism: a randomized controlled trial. Ann Intern Med 125: 360–368.
81. Orr-Walker BJ, Evans MC, Clearwater JM, et al. 2000 Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. Arch Intern Med 160(14):2161–2166.
82. Chow CC, Chan WB, Li JK, et al. 2003 Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 88: 581–587.
83. Rubin MR, Lee KH, McMahon DJ, et al. 2003 Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 88:1174–1178.
84. Khan AA, Bilezikian JP, Kung AW, et al. 2004 Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 90: 3319–3325.
85. Kanis JA, Melton LJ III, Christiansen C, Johnston CC, Khaltaev N. 1994 The diagnosis of osteoporosis. J Bone Miner Metab 9:1137–1141.
86. Marshall D, Johnell O, Wedel H. 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Brit Med J 312:1254–1259.
87. Kanis JA, Johnell O, Oden O, Dawson A, De Laet C, Jonsson B. 2001 Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 12:989–995.
88. Massry SG, Coburn JW. 2003 K/DOQI Clinical Guidelines for bone metabolism and disease in chronic renal disease. Am J Kidney Dis 42(Suppl 3):S1–S201.
89. Malluche H, Faugere M-C. 1990 Renal bone disease: an unmet challenge for the nephrologist. Kidney Int 38:193–211.
90. Parfitt AM. 2003 Renal bone disease: a new conceptual framework for the interpretation of bone histomorphometry. Curr Opin Nephrol Hypertension 12:387–403.
91. Sprague SM, Josephson MA. 2004 Bone disease after transplantation. Seminars in Nephrology 24:82–90.
92. Cohen A, Sambrook P, Shane E. 2004 Management of bone loss after organ transplantation. J Bone Min Res 19:1919–1932.
93. Cohen A, Ebeling P, Sprague S, Shane E. 2003 Transplantation osteoporosis. Favus MJ, ed. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. American Society for Bone and Mineral Research, Washington, DC, 370–379.
94. Hodsman AB. 2001 Fragility fractures in dialysis and transplant patients. Is it osteoporosis, and how should it be treated? Perit Dial Int 21(Suppl 3):S247–S255.
95. Piraino B, Chen T, Cooperstein L, Segre G, Puschett J. 1988 Fractures and vertebral bone mineral density in patients with renal osteodystrophy. Clin Nephrol 30:57–62.
96. Erlichman M, Holohan TV. 1996 Bone densitometry: patients with end-stage renal disease. Health Technol Assess 8:1–27.
97. Matuszkiewicz-Rowinska J, Skorzewska K, Radowicki S, et al. 1999 The benefits of hormone replacement therapy in pre-menopausal women with oestrogen deficiency on haemodialysis. Nephrol Dial Transplant 14:1238–1243.
98. Taal MW, Masud T, Green D, Cassidy M. 1999 Risk factors for reduced bone density in haemodialysis patients. Nephrol Dial Transplant 14:1922–1928.

99. Yamaguchi T, Kanno E, Tsubota J, Shiomi T, Nakai M, Hattori S. 1996 Retrospective study on the usefulness of radius and lumbar bone density in the separation of hemodialysis patients with fractures from those without fractures. Bone 19:549–555.
100. Lindberg JS, Moe SM. 1999 Osteoporosis in end-stage renal disease. Seminars in Nephrology 19:115–122.
101. Cunningham J, Sprague SM, Cannata-Andia J, et al. 2004 Osteoporosis in chronic kidney disease. Am J Kidney Dis 43: 566–571.
102. Fontaine MA, Albert A, Dubois B, Saint-Remy A, Rorive G. 2000 Fracture and bone mineral density in hemodialysis patients. Clinical Nephrology 54:218–226.
103. Gabay Ruedin, Slosman D, Bonjour J-P, Leski Rizzoli R. 1993 Bone mineral density in patients with end-stage renal failure. Am J Nephrol 13:115–123.
104. Weisinger JR, Gonzalez L, Alvarez H, et al. 2000 Role of persistent amenorrhea in bone mineral metabolism of young hemodialyzed women. Kidney Int 58:331–335.
105. Julian BA, Laskow DA, Dubovsky J, Curtis JJ, Quarles LD. 1991 Rapid loss of vertebral mineral density after renal transplantation. N Engl J Med 325:544–550.
106. ter Meulen CG, van Riemsdijk I, Hene RJ, et al. 2004 No important influence of limited steroid exposure on bone mass during the first year after renal transplant: a prospective, randomized, multicenter study. Transplantation 78:101–106.
107. Grotz WH, Mundinger FA, Gugel B, Exner VM, Kirste G, Schollmeyer PJ. 1994 Bone fracture and osteodensitometry with dual energy x-ray absorptiometry in kidney transplant recipients. Transplantation 58:912–915.
108. Van Staa TP, Leufkens HG, Abenhaim L. 2000 Use of oral corticosteroids and risk factors. J Bone Miner Res 15:993–1000.
109. Brown JP, Josse RG. 2002 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 167:S1–S34.
110. Guyatt GH, Cranney A, Griffith L, et al. 2002 Summary of meta-analyses of therapies for postmenopausal osteoporosis and the relationship between bone density and fracture risk. Endocrinol Metab Clin North Am 31:659–679.
111. Hernandez E, Valera R, Alonzo E, et al. 2003 Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. Kidney Int 63: 2269–2274.
112. Fan SL-S, Almond MK, Ball E, Evans K, Cunningham J. 2000 Pamidronate therapy as prevention of bone loss following renal transplantation. Kidney Int 7:684–690.
113. Fan SL, Kumar S, Cunningham J. 2003 Long-term effects on bone mineral density of pamidronate given at the time of transplantation. Kidney Int 63:2275–2279.
114. Coco M, Glicklich D, Faugere MC, et al. 2003 Prevention of bone loss in renal transplant recepients: A prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol 14: 2669–2676.
115. Grotz W, Nagel C, Poeschel D, et al. 2001 Effect of ibandronate on bone loss and renal function after kidney tansplantation. J Am Soc Nephrol 12:1530–1537.
116. Haas M, Leko-Mohr Z, Roschger P, et al. 2003 Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. Kidney Int 63:1130–1136.
117. Koc M, Tuglular S, Arikan H, Ozener C, Akolglu E. 2002 Alendronate increases bone mineral density in long-term renal transplant recipients. Transplant Proc 34:2111–2113.
118. Giannini S, Dangel A, Carraro G, et al. 2001 Alendronate prevents further bone loss in renal transplant recipients. J Bone Miner Res 16:2111–2117.
119. Jeffery JR, Leslie WD, Karpinski ME, Nickerson PW, Rush DN. 2003 Prevalence and treatment of decreased bone density in renal transplant recipients: a randomized prospective trial of calcitriol versus alendronate. Transplant 76:1498–1502.
120. Schwarz C, Mitterbauer C, Heinze G, Woloszczuk W, Hass M, Oberbauer R. 2004 Nonsustained effect of short-term bisphosphonate therapy on bone turnover three years after renal transplantation. Kidney Int 65:304–309.