

## ISCD Canadian Standards

# Standards for Performing DXA in Individuals With Secondary Causes of Osteoporosis

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## 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.

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## 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  $\geq -2.5$ . 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  $\leq -1.5$  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 anti-convulsants, or carbamazepine, 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 PHPT (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  $\leq -2.5$  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 <sup>a</sup>	Chronic heparin use
	Chronic metabolic acidosis

<sup>a</sup>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.

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