Seminars in Dialysis

A Rational Guide to Reducing Fracture Risk in Dialysis Patients

Nigel D. Toussaint,* Grahame J. Elder,† and Peter G. Kerr*
*Department of Nephrology, Monash Medical Centre and Monash University, Clayton, Vic., Australia, and †Centre for Transplant and Renal Research, Westmead Millennium Institute and Bone and Mineral Program, Garvan Institute of Medical Research, Sydney, NSW, Australia

ABSTRACT

Extrapolation of evidence-based management of disorders in the general population to patients with chronic kidney disease (CKD) is not always appropriate, and the prevention of bone fracture and reduction of fracture risk in CKD stages 3–5 is one example. Compared to the general population, fracture risk is greater in CKD patients, especially those on dialysis (CKD-5D). Fractures in CKD-5D are associated with a marked increase in morbidity and mortality and with an aging dialysis population the burden of disease caused by fracture is likely to increase. Patients with CKD-5D have distinct risks for fracture, as well as sharing risks identified in the general population. The development of the CKD mineral and bone disorder constitutes a significant cause for these differences. Literature addressing the determination of fracture risk and the efficacy of treatments to reduce fracture in patients on dialysis is limited. While some tools used for the diagnosis and monitoring of osteoporosis are applicable to patients on dialysis, bone mineral density measurement by dual-energy X-ray absorptiometry is generally not helpful and therapeutic interventions that reduce fracture risk in the nonuremic population cannot be generalized to patients on dialysis. This review outlines available evidence on the incidence, risk factors, and management of fractures in CKD-5D with recommendations for strategies to reduce fracture risk.

Chronic kidney disease (CKD) affects all age groups but is frequently a disease of aging. The development of renal osteodystrophy (ROD) that is characterized by abnormalities of bone turnover, mineralisation, and volume frequently accompanies reductions in glomerular filtration rate (GFR) and in the elderly may be superimposed on age-related bone mineral density (BMD) loss and degenerative changes.

The histomorphometry of ROD is often complex. Bone turnover can range from adynamic to dramatically increased, may coexist with changes of osteomalacia, and structural changes may differ between trabecular and cortical bone. Bone turnover markers and dual-energy X-ray absorptiometry (DEXA), used in age-related osteoporosis diagnosis and monitoring, are often unreliable in predicting the histomorphometric changes of CKD. A confident diagnosis of the underlying bone histology can only be made by bone biopsy.

The changes associated with ROD influence bone's material and mechanical characteristics and bone architecture, which contribute to "bone quality." In combination with bone mass, these factors determine the strength of bone and its resistance to fracture. So not surprisingly, rates of fracture are high in patients on dialysis, particularly at nonvertebral sites (1–3).

Cardiovascular disease represents the leading cause of mortality for patients with CKD stage 5 on dialysis (CKD-5D), but interventions to modify risk factors such as lipid levels have been disappointing (4,5). Clinical and laboratory studies support an important role for nontraditional risk factors, particularly abnormal levels of serum calcium and phosphate. Both are influenced by suppression of bone turnover or, when turnover is increased, with uncoupling of bone formation from resorption. Interestingly, an inverse relationship between BMD and cardiovascular disease, including vascular calcification, has been reported in both the general population (6–9) and in patients with CKD-5D (10–12). Recently, the term "Chronic Kidney Disease-Mineral and Bone Disorder" (CKD-MBD) has been applied to these disturbances of mineral metabolism, ROD, and vascular calcification in CKD 3-5D, together with patient-level outcomes of fracture, cardiovascular disease, and mortality (13).

The medical and economic burden of fracture in CKD is substantial and with an aging dialysis population this burden is likely to increase. Fracture prediction and prevention are difficult in CKD patients and there are limited data on management. This review highlights the complexity of extrapolating evidence relating to fracture risk from the general population to aid decision

Address correspondence to: Dr. Nigel Toussaint, Department of Nephrology, Monash Medical Centre, 246 Clayton Road, Clayton, Vic. 3168, Australia, or e-mail: nigel.toussaint@med.monash.edu.au.

Seminars in Dialysis—Vol 23, No 1 (January–February) 2010 pp. 43–54
DOI: 10.1111/j.1525-139X.2009.00650.x

making in CKD-5D, but also presents strategies that may reduce fracture rates in these patients.

Epidemiology of Fractures in CKD 3-5D

Fracture rates in patients with CKD-5D are reported to be similar to or greater than that of people 10 or 20 years older in the general population (14). In a study using data from the U.S. Renal Data System (USRDS) Registry, hip fractures were increased fourfold in Caucasian dialysis patients compared to a matched sample from the general population (2). Although the fracture risk was higher for all age groups of CKD-5D in this study, for those less than 65 years old the relative risk (RR) ranged between 10- and 100-fold higher, most likely due to the low incidence of hip fracture in the general population in this age range. The incidence of hip fracture was 7.5 per 1000 patient-years for males and 13.6 per 1000 patient-years for females and the RR increased with time on dialysis.

In the second phase of the Dialysis Outcomes and Practice Patterns Study (DOPPS), which recorded information on 12,782 hemodialysis (HD) patients from 320 dialysis facilities across 12 countries (2002–2004), the incidence of hip fracture was 8.9 per 1000 patient-years and all fractures 25.6 per 1000 patient-years (15). There were no major differences in fracture rates between countries after adjustment for demographics and comorbidities. The incidence of long-bone fractures in over 7000 patients studied over a 5-year period in the Dialysis Morbidity and Mortality Study (DMMS) was 16.9 per 1000 patient-years, with the femoral neck being the most common site (59.8%) (16). One single-center study of Japanese HD patients reported the prevalence of fractures was 15% in men and 30% in women (17) and another Japanese study showed the prevalence of vertebral fractures in diabetic HD patients to be greater compared to nondiabetic dialysis patients (32 vs. 13%) (18).

Few studies have addressed the risk of fracture and its consequences at earlier stages of CKD, but there is increasing evidence to suggest that patients with CKD-3 to 5 are at greater fracture risk than the general population (19,20). One recent study of 13,177 people aged 75 years and over from the United Kingdom reported that levels of estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2 were associated with an almost twofold increase in mortality after hip fracture (21). In a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) III study, moderate to severe CKD was independently associated with a more than twofold increase in hip fracture and this association was stronger than several traditional risk factors including age and gender (22). In another retrospective cohort from Veterans Affairs medical centers in the United States, the RR of hip fracture for men with levels of eGFR between 30–59 and 15–29 ml/min/1.73 m^2 was 1.28 and 3.98, respectively (23). These studies suggest that the risk of hip fracture in patients with advanced renal impairment is similar to that of dialysis patients.

Risk Factors for Fracture

Fragility fractures generally require a bone with reduced strength being exposed to an impact, usually resulting from a fall. Risk factors consistently associated with an increased risk of fracture for patients on dialysis include older age, female gender, previous renal transplant, and duration of dialysis (Table 1) (15,16,24–27), but there is little information on the influence of ROD on fracture risk.

Using USRDS data, a retrospective study by Stehman-Breen et al. identified additional risk factors for hip fracture of Caucasian race, low body mass index (BMI), and peripheral vascular disease (24). In this study, diabetes and serum abnormalities of mineral metabolism were not associated with fractures, although a more recent study reported increased fracture risk with diabetes and higher levels of intact parathyroid hormone (PTH) (16). Risk factors identified from DOPPS include an elevated PTH (>900 pg/mol) and low albumin, in addition to older age, female gender, and previous renal transplant (15). This study also identified an increased hip fracture risk when patients took selective serotonin reuptake inhibitors (SSRIs) and narcotic-based analgesic medications. In summary, patients on dialysis have many risk factors for fracture in common with the general population, but have additional factors relating to their CKD.

Implications of Fracture in Dialysis

Fractures in dialysis patients, similar to the general population, are associated with significant morbidity and mortality (28,29). Mittalhenkle et al. reported an RR of mortality of 1.99 for dialysis patients with hip fractures vs. control patients without fractures (USRDS data) (30) and Coco and Rush reported the 1-year mortality following fractures to be almost 2.5 times greater in dialysis patients than the general population (1). A recent Spanish study of 193 prevalent HD patients reported that in women, vertebral fractures resulted in greater mortality with an RR of 4.8 (27). In that study,

TABLE 1. Risk factors associated with fracture in dialysis patients

Risk factor	References
Older age	(1,2,15,16,18,24–27,69)
Female gender	(2,15,16,18,24–27)
Longer time on dialysis	(15,16,24–27,52,69)
Diabetes	(16,18)
CVD or PVD	(16,24)
Low BMI	(16,18,24)
Psychoactive medications	(15)
Caucasian race	(1,24)
Previous kidney transplant	(15,16,24–27)
History of any fracture/vertebral fracture	(49)
PTH (high or low)	(1,3,15,16,49,54)
ALP (high or low)	(1,3,46)
Low albumin	(15)
Hyperhomocysteinemia	(63)

PTH, parathyroid hormone; ALP, alkaline phosphatase; CVD, cerebrovascular disease; PVD, peripheral vascular disease; BMI, body mass index.

fractures were associated with increased vascular calcification similar to previous reports of progressive vascular calcification associated with BMD loss and increased fractures (31,32).

Danese et al. reported a 2.7 times increased mortality for dialysis patients with a fracture and markedly increased episodic costs of hip, vertebral, and pelvic fractures ($US 20,800, 17,000, and 14,500, respectively, for a HD patient in 2004) (33). In another study to quantify direct medical costs of fractures, as well as cardiovascular disease and other comorbidities among CKD-5D patients, Doan et al. used data on Medicare claims from the USRDS Registry to determine medical costs of acute episodic events (34). In 2006, peripheral vascular disease ($US 358 million) and congestive heart disease ($US 681 million) contributed the greatest economic burdens of conditions analyzed for acute and chronic events, respectively. Hip, pelvic, and vertebral fractures were reported to cost $US 56.5 million, 8.6 million, and 9.1 million, respectively, in this study.

Methods to Evaluate Fracture Risk

Imaging Techniques

Dual Energy X-Ray Absorptiometry (DEXA)

In the general population, significant reductions in BMD measured by DEXA are associated with an increased risk of low trauma fracture. Using World Health Organisation (WHO) criteria, osteoporosis is defined as a BMD measured by DEXA ≥2.5 standard deviations (SD) below the mean BMD of a young normal Caucasian female population (T-score < -2.5) with osteopenia defined as a BMD −1 to −2.5 SD below this mean (T-score −1 to −2.5). The practical significance of each SD reduction in the T-score is demonstrated by a meta-analysis of data from 39,000 persons at the age of 65 years, in which the RR for hip fracture increased by 2.94 in men and by 2.88 in women for each SD decrease in BMD (35). This study also reported that at age 50, for each SD reduction in hip BMD, the RR of a hip fracture was 3.68. So in the general population, BMD measurement is an important component of the prediction of fracture risk, a valuable guide to the efficacy of osteoporosis treatments, and in the case of strontium ranelate, an indicator of compliance with therapy.

Bone mass as measured by DEXA is often low in patients with CKD, and with worsening renal function the prevalence of osteoporotic-range BMD values increases (36–38). However, unlike the general population, in patients with CKD-MBD the predictive ability of DEXA has definite limitations. Metabolic acidosis, inadequate levels of 25-hydroxyvitamin D, calcitriol deficiency, and the almost universal presence of ROD, all of which influence bone microarchitecture and strength, are not adequately assessed by BMD measurement and complicate a BMD-based assessment of risk (38,39). Technical factors also contribute to the difficulty of interpreting DEXA measurements in patients with CKD and the elderly. DEXA is a 2-dimensional "areal" rather than a volumetric measure, so that everything in the path of the X-ray beam will register as an increase in BMD. This includes calcified blood vessels, ligaments and degenerative changes affecting the spine, which are common in patients with CKD and the elderly (31,40,41). In these circumstances, DEXA may be more reliable at the hip or forearm.

Hyperparathyroidism (HPT) can cause an increase in porosity of cortical bone but a relative sparing of trabecular bone. These effects have been demonstrated in patients with primary HPT in whom, compared to normal controls, trabecular bone mass (measured by DEXA) was well preserved, while there was a preferential loss of cortical bone (42). In CKD, the severity of HPT is very variable and these differential effects may be more or less marked. However, it is likely that they go some way to explaining the variable effects of ROD on BMD by DEXA. Some studies have shown no BMD differences, while others report forearm BMD to be lower with osteitis fibrosa than with adynamic bone disease (43,44). At the spine, the BMD of patients with osteitis fibrosa has been reported to be lower than for those with mixed lesions. Irrespective of BMD effects, abnormal bone matrix mineralisation, bone turnover and microarchitectural changes are components of ROD, and consequently dialysis patients have changes in bone quality that leads to a mismatch between BMD and fracture risk (43,45,46).

An earlier assessment of the utility of DEXA to predict fracture risk, concluded that BMD measurement did not provide sufficient useful information to support therapeutic decisions in the management of dialysis patients (47). Certainly these patients do not share the strong, consistent association of BMD and fracture seen in the general population (35,48). A recent systematic review was performed by Jamal et al. to determine whether DEXA measurements at various sites were associated with fractures in patients on dialysis (49). This meta-analysis of six cross-sectional observational studies revealed that for all BMD sites except the femoral neck, CKD-5D patients with fractures had significantly lower BMD than those without fractures. Limitations of this study include potential publication bias, lack of demonstration that low BMD is independently associated with fractures (with no adjustment for variables including duration of dialysis, body weight or corticosteroid use), and no evidence for low BMD predicting fractures in patients on dialysis. Other retrospective studies also report that the site at which BMD is measured in patients with CKD-5D does not consistently predict fracture at that particular site (17) and to date no prospective study in CKD-5D patients has shown reduced BMD to be predictive of a higher risk of subsequent fracture. Despite the conflicting reports on the benefits of DEXA to assess fracture risk in dialysis patients (3,50–53), Kidney Disease Outcomes and Quality Initiative (K/DOQI) recommends that DEXA be performed in dialysis patients with fractures and in those with known risk factors for osteoporosis (54). One recent study assessing 25-hydroxyvitamin D deficiency in 242 CKD-5D patients reported that femoral neck BMD was associated with an increased prevalence of vertebral fracture and fragility fracture at any site (55). This study also

reported a negative correlation between levels of 25-hydroxyvitamin D and *Z*-scores at the lumbar spine and wrist; *Z*-scores being the number of SD an individual's BMD differs from the mean of a population of similar age, sex, and ethnicity. Fig. 1 summarizes studies that have reported BMD in patients with CKD-5D.

Spinal X-Ray

In the general population, previous fracture is an important risk factor for subsequent fracture. Using clinical and claims data from the USRDS, Danese et al. reported that a history of any fracture resulted in a hazard ratio of 8.33 (5.04–13.74) for hip and 7.32 (3.41–15.71) for vertebral fracture and symptomatic vertebral fracture was associated with a more than sevenfold increased risk of subsequent fracture (33). Therefore a lateral X-ray of the spine to evaluate for prevalent fracture may be a useful indicator of future fracture risk in CKD-5D.

Quantitative Computed Tomography

Quantitative computed tomography (QCT) has been used to determine BMD in CKD-5D and can be used to distinguish BMD values in both cortical and trabecular bone compartments, while avoiding artifacts of vascular calcification and local degenerative changes that bedevil DEXA evaluation (56). QCT provides a true volumetric measurement of BMD and can be applied to peripheral sites (radius and tibia) as well as central sites (lumbar spine and proximal femur). In one study, a decrease in cortical bone density in the radius using QCT was shown to be associated with fractures in Canadian HD patients and superior to DEXA measurement of hip BMD in predicting fractures (57). Another more recent study of Czech HD patients also reported that vertebral fractures were best predicted by lumbar cortical BMD measured by QCT (58). Some disadvantages of current QCT assessment include higher radiation dose, which is of particular concern for repetitive or high resolution studies, a lack of well established population standards and lack of data establishing trabecular or cortical bone values at the spine and hip as valid surrogates for patient-level outcomes.

A newer technique of ultra-high-resolution peripheral QCT is currently being assessed. Like conventional QCT this technology permits the separate analysis of cancellous and cortical bone, but these scans can also visualize the fine ultra-structural detail, including trabecular thickness, number and separation. High-resolution QCT, which is more sensitive than DEXA for detecting small amounts of bone loss, may provide an improved method to assess the microarchitectural features of bone that contribute to the increased fracture risk observed in CKD.

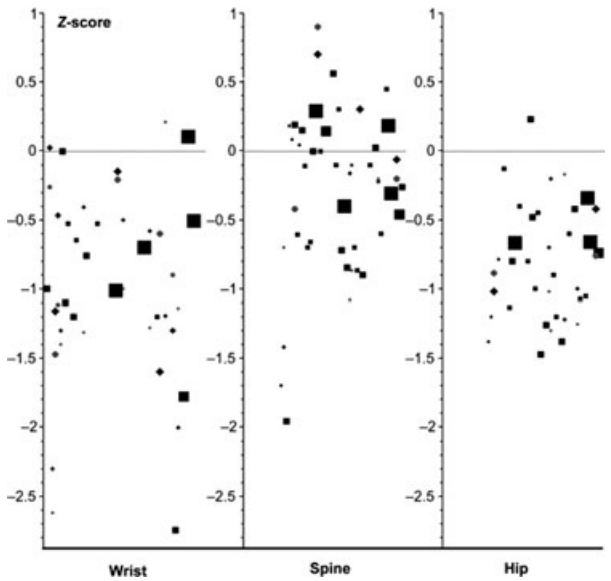

FIG. 1. The graph is a summary of studies that measured bone mineral density (BMD) at the radius, spine, and hip in patients with CKD-5. BMD is presented as the *Z*-score. Within each group, the points are arranged left to right in chronologic order; each point being the mean value for a study. Squares are used for combined data and if data from men and women were reported separately, points for the women are circles and for men are diamonds. Size of points is larger in studies with the greatest numbers of subjects. Data from studies that reported g/cm^2 was converted to *Z*-scores (hip and forearm) using the average age of the group of subjects and published normal reference ranges. Reprinted with permission from the publisher (Wiley Blackwell) and the author (SM Ott) (130).

Magnetic Resonance Imaging

Micro-magnetic resonance imaging (MRI) has also made it possible to obtain high-resolution three-dimensional images of trabecular bone architecture in peripheral sites and although more studies are needed, MRI may have the potential to assess fracture risk non-invasively. A study of 17 patients with CKD-5D showed that although there was substantial variability among patients, cortical thickness and cross-sectional area were significantly lower than in matched controls and trabecular disruption was increased, with reduced trabecular number and increased erosion index, in CKD-5D patients (59).

Bone Turnover Markers and PTH

In the general population, biochemical markers of bone turnover are widely used to guide treatment of osteoporosis (for example, bisphosphonates are ineffective when baseline bone turnover is low) and to monitor treatment responses. However, their role is less clear in the management of bone disease associated with CKD-5D. Urinary markers such as deoxypyridinoline, and the cross-linked telopeptides of collagen type I (CTx) and N-telopeptide of collagen type I (NTx) cannot be used. Other serum markers such as osteocalcin are influenced by renal function. On the other hand, levels of total alkaline phosphatase (ALP), bone specific alkaline phosphatase (BALP), and tartrate-resistant acid phosphatase isoenzyme 5b (TRAcP-5b) are not influenced by renal function, and BALP and PTH levels correlate to bone turnover and findings on bone biopsy. However, on an individual level their diagnostic utility is limited and except for levels of the ALPs and extremes values of PTH, they have not been associated with patient-level

outcomes. Few studies describe relationships between laboratory measures and fracture risk in CKD-5D. Of those that do, PTH levels show the most consistent relationships (1,15,33) and suggest that abnormal bone quality at either extreme of bone turnover may reduce bone strength. Danese et al. reported a weak but significant association between PTH levels (both low and high) and vertebral and hip fractures in over 9000 dialysis patients from the DMMS (33). Coco & Rush reported an increased hip fracture incidence with lower rather than higher PTH levels (1), and Block et al. reported a direct correlation of PTH and fracture (60).

In the general population, there is controversy whether long term suppression of bone turnover (particularly with the use of bisphosphonates) may lead to an accumulation of microdamage and ultimately increase fracture risk. While bisphosphonates do influence mineralisation and crystal size, the accumulation of advanced glycosylation end-products (61), collagen cross links, isomerisation, $\alpha\beta$ ratio (62), and bone elasticity (63), proof of any adverse effect is largely lacking. On the other hand, patients with low turnover due to renal disease who are exposed to these drugs may be at particular risk, so the use of validated bone turnover markers in CKD-5D may yet prove valuable.

Other Laboratory Measures

Hyperhomocysteinaemia and β_2-microglobulin amyloidosis may also be risk factors for bone fractures. Two prospective observational studies in the general population demonstrated increases in hip and wrist fractures associated with higher levels of homocysteine (64,65) and a randomized placebo-controlled study of folate and B vitamins showed a reduction in hip fractures in hemiplegic patients in the active arm (66). However, post hoc analysis of another randomized controlled trial (RCT) in the general population failed to show fracture risk reduction for those taking B vitamins and folate (67). Dialysis patients generally have higher levels of homocysteine than the general population but only one study in a HD cohort has reported a positive association between levels of homocysteine and fracture risk (68).

Bone Biopsy

Given the limitations of laboratory measures to assess bone disease in CKD-5D, quantitative double tetracycline-labeled bone histomorphometry remains the only means of confidently diagnosing underlying bone pathology. The most commonly reported form of ROD defined by bone biopsy in CKD-5D is high turnover, hyperparathyroid bone disease (osteitis fibrosa) often with abnormal mineralisation (mixed uraemic osteodystrophy) (45). Low bone turnover or adynamic bone disease is generally associated with inappropriately low levels of PTH, and previously with aluminum deposition in bone. Despite extensive knowledge of the complexity of ROD, few studies to date have assessed the association between the incidence of fractures and bone histomorphometry in CKD-5D. In one such study, the proportion of patients with prevalent fractures was not significantly different between patients with adynamic bone disease and those with osteitis fibrosa (38).

Falls Risk

Falls are common in the elderly nonuremic population and generally associated with poorer outcomes. In the general population, there is a strong relationship between the risk of hip fracture and the propensity to fall; even more than fracture risk from the presence of osteoporosis or low BMD (48). Falls risk in patients with CKD-5D is estimated at twice that of an age and gender matched general population (69,70) but despite this, there are limited data on the falls risk of dialysis patients.

One recent Belgian study of 308 HD patients reported the incidence of falls to be 1.18/patient-year (69). Independent risk factors for falls in dialysis patients were assessed in this study and included older age, diabetes, difficulty in walking 10 m without assistance, and higher numbers of prescribed medication, especially antidepressant use. The association between increased fracture risk and psychoactive drugs (especially SSRIs) was also demonstrated in DOPPS and may be related to a greater tendency to fall with these agents (15). A recent prospective study of HD patients aged 65 and older reported the incidence of falls as 1.6/patient-year (70) and risk factors for falls in this study were older age, multiple comorbidities, lower predialysis systolic blood pressure and a history of previous falls.

One study of HD patients in the United States reported that impaired neuromuscular function was associated with fracture, probably due to an increased tendency to fall (71). This study assessed the relationship between vertebral fractures (present in 27 of 52 subjects), BMD and tests of muscle strength. There was no association between fractures, BMD (hip or spine) or grip strength, but in contrast, improved tests of muscle strength (functional reach, timed up and go, and distance walked in 6 minutes) were associated with a reduced risk of fracture.

How to Determine Fracture Risk in CKD-5D

Take a History and Perform a Risk Factor Assessment

In the general population, major risk factors have been incorporated into useful fracture risk calculators, accessible online, including the WHO Fracture Risk Assessment Tool (http://www.shef.ac.uk/FRAX), and the Fracture Risk Tool from the Australian Garvan Institute of Medical Research (http://www.garvan.org.au/bone-fracture-risk) (Table 2). Whether these tools may be used successfully in patients with CKD-5D is yet to be determined. A recent study of prevalent Austrian HD patients attempted to predict the probability of fracture occurring over the next year in CKD-5D patients calculated from a prediction model, consisting of the independent variables of age and sex (72). This study, which aimed to identify predictive parameters and evaluate a parsimonious prediction rule for fractures, reported that variables such as serum calcium, phosphate, PTH or ALP, as well as time

TABLE 2. Checklist for fracture risk in patients with CKD

Steps to determine fracture risk
Take a history and assess risk factors for fracture (Table 1)
Assess bone turnover with biochemical markers (e.g., extremes of PTH and ALP)
Decide whether a DEXA should be performed
Lateral spine X-ray to assess for prevalent vertebral fracture
Assess the risk of falls; falls diary/functional testing
Determine if a bone biopsy is required

CKD, chronic kidney disease; PTH, parathyroid hormone; ALP, alkaline phosphatase; DEXA, dual-energy X-ray absorptiometry.

on HD, did not contribute to the accuracy of prediction in this HD patient sample. Table 1 provides a checklist of risk factors associated with fracture in CKD-5D.

Assess Bone Turnover

Biochemical markers may be useful indicators of bone turnover when adynamic bone disease and severe HPT are considerations. Inappropriately low or very high levels of PTH and BALP/ALP are probably the most useful tests, although other markers discussed earlier may prove helpful in guiding therapy.

Should a DEXA Be Performed?

Ask yourself whether the patient would qualify for a DEXA if he or she did "not" have CKD? Also, how long has the patient had CKD? If the renal impairment is of recent onset, BMD levels are likely to reflect factors prior to the development of CKD. Providing the limitations of DEXA are recognized, particularly that a low BMD may not represent changes generally associated with age-related osteoporosis, there is a role for this noninvasive, low radiation investigation in selected patients with CKD-5D.

A lateral thoracic and lumbar spine X-ray may also be helpful to assess fracture risk. Symptomatic or unsuspected vertebral compression fractures are likely to increase the risk of future fracture; aortic and iliac calcification can also be assessed on the lateral film.

Assess the Patient's Risk of Falling

Falls risk assessment needs to be comprehensive and includes a review of medications, mobility assessment and determination of environmental risks that increase the propensity to fall. Simple motor, muscle strength, and postural stability assessments should be used routinely, and the use of a falls diary may also be helpful (73). Musculoskeletal strength testing can be easily, accurately and inexpensively performed using medical isometric dynamometers and hand grip strength dynamometers, tools which provide reliable and reproducible results. Functional capacity tests can also be performed and include standing balance, sway and stance tests, and 6-minute or timed walks. These can be used as predictive tools and to assess exercise capacity, postural performance, lower extremity function, and muscle strength (73).

Should I Perform a Bone Biopsy?

To date, bone biopsy is the most powerful and informative diagnostic tool to provide precise information on the type and severity of ROD. Although considered an invasive procedure, bone biopsy is safe and generally free from complications, but experience at performing the procedure and interpreting the results is required. In CKD-5D, biochemical markers of bone turnover are either unproven or lack sensitivity and specificity for the accurate diagnosis of ROD, so bone biopsy remains the gold standard. Before a bisphosphonate is prescribed to a patient with CKD-MBD, or if osteomalacia or aluminum toxicity is suspected, a bone biopsy should be seriously considered.

Treatment Options

Despite the extensive literature for therapies to treat osteoporosis and reduce fracture risk, in CKD-5D there have been few prospective studies showing that treatment improves BMD and no study showing reduction in fractures (Table 3). Most therapeutic trials pertaining to fracture in the nonuremic population have enrolled postmenopausal women without overt renal impairment. The outcome of recent lipid lowering and hemoglobin raising interventions highlight the potential hazard of extrapolating outcome studies in the general population to patients with CKD without a proper RCT.

TABLE 3. Potential treatment options for reducing fracture risk in dialysis patients

Optimisation of CKD-MBD	Potential medical treatments (see text)
Calcitriol	Reduce psychoactive drugs and postural hypotension
Cholecalciferol or ergocalciferol	HRT/tibolone (females)
Noncalcium based phosphate binders	SERMs (females)
Cinacalcet/parathyroidectomy	Testosterone replacement (hypogonadal males)
Physical and behavioral therapies	Bisphosphonates[a]
Treatments to improve muscle strength	Other osteoporosis treatments
Treatments to reduce falls risk	Strontium ranelate[b], recombinant PTH, calcitonin[a]
Hip protectors	Denosumab/Cathepsin K inhibitors[c]

[a]Untested in this population, inappropriate for most patients.
[b]Little experience in this population.
[c]Untested in this population, currently unavailable.
SERMs, selective estrogen receptor modulators; HRT, hormone replacement therapy; PTH, parathyroid hormone; CKD-MBD, chronic kidney disease-mineral and bone disorder.

Optimizing CKD-MBD

Optimal management of CKD-MBD, especially relating to management of secondary HPT, is likely to improve ROD although no study has specifically addressed this issue. Most dialysis patients receive calcium supplementation, in the form of calcium-based phosphate binders, dialysate calcium or increased calcium absorption with administration of calcitriol or a vitamin D analog. This may be beneficial when dietary calcium is low or when mild secondary HPT is present, but could also contribute to the development of low bone turnover and worsening of vascular calcification. Although active vitamin D metabolites have not been shown to reduce fracture incidence in patients with CKD-5D, they have been shown to reduce serum PTH levels and improve BMD in patients with CKD (74,75). Levels of 25-hydroxyvitamin D may also influence BMD in patients with CKD-5 (76) and supplementation of CKD-5D patients deficient in 25-hydroxyvitamin D with cholecalciferol or ergocalciferol has been recommended to achieve 25-hydroxyvitamin D levels ≥50 nmol/l, with optimal levels possibly 75–90 nmol/l.

The calcimimetic cinacalcet is an allosteric modulator of the calcium-sensing receptor and reduces PTH secretion, while lowering levels of calcium and phosphate. Although there is limited information about the impact of this drug on patient-relevant clinical outcomes, cinacalcet may be useful in preventing fractures in dialysis patients with HPT. A post hoc analysis of safety data from four RCTs involving 1184 patients revealed significant reductions in fracture risk with cinacalcet compared to placebo [RR 0.46 (95%CI 0.22, 0.95)] (77). Given the relatively short follow-up of these trials and differing entry criteria, it is unclear how these data should be extrapolated. The relatively high cost of cinacalcet should also be considered in these analyses (78). The results of ongoing, prospective RCTs may provide answers on the role of cinacalcet for patient-level outcomes, including fractures and survival. For severe HPT unresponsive to medical therapy, parathyroidectomy is also reported to reduce fracture risk. Based on long-term USRDS data from hip, vertebral, and radial fractures in HD patients, parathyroidectomy may provide a 31% lower risk of any fracture compared to matched controls (79).

Compared to earlier phosphate binders, the use of lanthanum and sevelamer, which do not contain aluminum or calcium, may improve bone mineralisation and volume. However, their association with bone fracture has not been studied. In one RCT comparing the effects of sevelamer and calcium carbonate on ROD over 12 months, there were no significant changes in bone turnover or mineralization between the groups, although bone formation increased and trabecular architecture improved with sevelamer (80). Another prospective study reported that treatment with sevelamer, compared to calcium acetate, had the advantage of maintaining stable PTH levels and elevating ALP levels while lowering serum phosphorus levels and the calcium-phosphorous product (81).

In summary, optimizing the management of CKD-MBD constitutes a first line strategy to maintain bone quality and strength and to reduce the risk of fractures in patients with CKD-5D.

Medical Therapies Used in Patients with Osteoporosis: Do They Apply?

Bisphosphonates

Bisphosphonates are bone antiresorptive agents widely used to treat postmenopausal or glucocorticoid-induced osteoporosis and other conditions characterized by excessive osteoclastic bone resorption. Bisphosphonates closely resemble pyrophosphate compounds in binding to hydroxyapatite in bone and, used appropriately, clearly provide fracture protection for patients with osteoporosis in the general community (82–84). Many patients with kidney disease are treated with bisphosphonates in the hope of similar efficacy (85,86). The presence of CKD has been a general exclusion criterion in studies of bisphosphonate efficacy, but based on calculated levels of estimated GFR, considerable numbers of patients with early CKD participated in these studies. Data on this subgroup suggest that when secondary causes of low BMD are excluded and blood levels of calcium, phosphate, PTH, and vitamin D are normal (laboratory features of CKD-MBD), bisphosphonate use is safe and results in fracture reduction (87).

The value of bisphosphonate treatment in CKD-4 to 5D is unknown because there are virtually no data (88). A pooled analysis of clinical trials involving postmenopausal women reported that bisphosphonates reduce fracture risk in those with moderate to severe renal impairment and median GFR 27 ml/min (87). Secondary analysis of another study, the Fracture Intervention Trial (FIT) in which women were randomly assigned to placebo or alendronate, showed significant increases in total hip BMD and reduced risk of clinical fractures with alendronate irrespective of baseline renal function (20). This finding was more pronounced in those with GFR <45 ml/min, however women with a serum creatinine level >1.6 mg/dl were excluded from the study and bone biopsies were not performed.

Bisphosphonate use in ROD was initially tested in animal models with demonstration of potential benefits for renal failure-induced HPT. In nephrectomised rats, ibandronate prevented increases in erosion depth and bone turnover (89) and olpadronate improved BMD associated with high turnover bone disease (90). Clinically, the affinity of bisphosphonates to bone in dialysis patients is related to the degree of HPT, although bisphosphonate effects in patients with CKD-5D have only been examined in a limited number of studies. Administration of clodronate in nine HD patients with severe HPT produced inhibition of osteoclast-mediated bone resorption (91) and in a RCT of 31 HD patients, hip BMD remained stable after 6 months in patients treated with alendronate compared to a reduction in those on placebo (92). However, in the latter study this difference was minimal (despite statistical significance) and the treatment time was short.

Bisphosphonates diffuse into the bone matrix where they accumulate due to their exceptional affinity to bind to the calcium-phosphorus crystal surface. It is not known whether this accumulation increases with progressive renal impairment (88,93) but with reduced initial renal excretion and increased recirculation to bone of bisphosphonate released by osteoclastic resorption, it is reasonable to assume increased accumulation in CKD. In patients without CKD, the reduction in bone turnover caused by bisphosphonates contributes to improved mineral apposition and an increase in BMD, but even in this group there is debate regarding effects of long-term bisphosphonate use on brittleness vs. toughness, and ultimately on bone quality and resistance to fracture. Previous experimental animal studies have demonstrated that bisphosphonates, especially when given in higher doses, can induce osteomalacia (94) or result in accumulated microdamage (95,96). In CKD-5D the *potential* problem of bisphosphonate therapy is diminished bone remodeling that could lead to reduced repair of microcracks and impairment of bone strength (97). The frequency of microcracks in clinical studies of patients on long-term bisphosphonates varies from low (98) to high, with an increased accumulation of microdamage (99), although there is as yet no clinical evidence demonstrating bisphosphonates actually result in impairment of bone strength.

Nevertheless, despite inconsistent data, bisphosphonates cannot be recommended when low bone turnover, adynamic bone disease, or osteomalacia are present or suspected, as they have potential to do harm. Because bisphosphonates do not prevent fractures in people with normal BMD or with low baseline markers of bone formation, the subset of patients with CKD-5D that might receive therapy would be those with low BMD but high bone resorption. Even in this group bisphosphonate use should be cautious, because by reducing bone resorption and causing incremental reductions in levels of serum ionized calcium, bisphosphonates may stimulate glandular release of PTH and induce parathyroid hyperplasia over time.

Hormone Replacement Therapy, Tibolone and Selective Estrogen Receptor Modulators

Hormone replacement therapy (HRT) has historically been used in the management of osteoporosis in the general population although there was little prospective data for fracture prevention. Low dose steroidal contraceptive use in women who are amenorrhoeic before the age of 45 and HRT in women who develop early menopause may protect against loss of BMD.

In postmenopausal women without renal impairment and with prior hysterectomy, the use of conjugated equine estrogen (CEE) (used without a progestagen) has been associated with an increased risk of cerebrovascular events in a large RCT (100). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of six fewer hip fractures per 10,000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant two events per 10,000 person-years. On account of these and other data regarding breast cancer risk (101) and despite its efficacy for reducing fractures, the use of HRT in older women is generally avoided, except for treatment of menopausal symptoms such as flushing.

Tibolone is a synthetic steroid with estrogenic, progestational, and androgenic effects which has been used as an alternative to estrogen to treat menopausal symptoms for 30 years. Cummings et al. found that tibolone reduced the incidence of vertebral fractures by 45% and nonvertebral fractures by 26% in 4538 postmenopausal women when compared to placebo (102). However, this study was ceased early as a result of an increased risk of cerebrovascular events in those on tibolone [relative hazard 2.19 (95%CI 1.14, 4.23)], and tibolone has not been studied in patients with CKD.

Raloxifene is a selective estrogen-receptor modulator (SERM) also shown in women with osteoporosis to reduce breast cancer risk and rates of fractures (103). In one placebo-controlled study of HD patients, there was a significant improvement in trabecular (but not cortical) bone after 1 year (104). Like HRT, there may be an increased risk of fatal stroke in postmenopausal women so it should be used cautiously in CKD-5D (105).

Hypogonadism is common among men with CKD-5D, beginning before the need for dialysis and not improved with the initiation of dialysis. Many of the manifestations of hypogonadism, such as bone disease and muscle wasting, are seen in CKD-5D and hypogonadism is also thought to contribute to sexual dysfunction experienced by patients. There have been few studies of HRT using testosterone replacement in the dialysis population, but extrapolation from results of treatment of hypogonadal, older men with normal renal function suggests that testosterone replacement could improve libido and could have beneficial effects on muscle mass and BMD in patients with CKD (106). Administration of testosterone replacement may be with a hydroalcoholic gel containing 1% testosterone, which is as efficient as a testosterone patch but with fewer side effects, or with intramuscular injections of testosterone undecanoate which have a favorable pharmacokinetic profile.

Other Potential Treatments

Lipid-lowering statins, which inhibit HMG-CoA reductase, act on the same cholesterol synthesis pathway as nitrogen-containing bisphosphonates and therefore may have a role in osteoporosis. This possibility has been supported by the finding that statins also stimulate bone formation, and by observational studies suggesting that patients using statins have higher BMD and lower fracture rates than controls (107–109). However, more recent RCTs and meta-analyses offer little support for the hypothesis that statins influence fracture risk in the general population (110–112). Statin therapy in CKD-5D was analyzed in the DOPPS database for its protective effect on fractures but no association was found (15). Only one retrospective cohort of 174 HD patients in Canada has recently reported a significant negative association between bone fractures and statin therapy (26).

Strontium ranelate is an antiosteoporotic treatment that, unlike bisphosphonates, may increase osteoblast function and bone formation while reducing bone

resorption. There is good evidence to support the efficacy of strontium for the reduction of vertebral fractures (and to a lesser extent nonvertebral fractures) in postmenopausal osteoporotic women and an increase in BMD (all sites) in postmenopausal women with and without osteoporosis (113,114). The use of strontium in CKD is limited, however studies in rats with CKD have found that biopsies with higher bone strontium had higher levels of osteoid, characteristic of osteomalacia (115,116). One clinical study in 74 HD patients, assessing bone biopsies with measurement of bone strontium/calcium ratio, did not support the hypothesis of strontium-induced osteomalacia, with no correlation between different histomorphometric parameters and this ratio (117).

Recombinant PTH, given by daily subcutaneous injection, is a potent anabolic agent that improves BMD and contributes to fracture reduction in nonuremic postmenopausal osteoporotic subjects (118). There are no clinical studies on the use of recombinant PTH, in CKD-5D. Obviously its use would be inappropriate in patients with secondary HPT. In patients with proven low bone turnover, its effects are speculative. It has been used in one case of hypoparathyroidism and calciphylaxis with subsequent bone turnover marker and bone biopsy evidence of improved bone turnover (119). Calcitonin has been used in the management of osteoporosis in the general population, with evidence from one RCT of postmenopausal women demonstrating reduction in the incidence of vertebral fractures (120). However, its effect is weak and there are no data on its role in CKD. Newer and as yet unregistered agents such as cathepsin K protease inhibitors and denosumab (a monoclonal antibody to the receptor activator of nuclear factor $\kappa\beta$ ligand), have not been studied for reduction of fracture risk in CKD-5D.

Behavioral Therapy

Falls Prevention

There have been many RCTs demonstrating benefits of fracture reduction from reducing falls in the general population (121). Multifactorial assessment of falls risk with targeted interventions aimed at reducing polypharmacy, improving mobility, and removing environmental hazards, is especially useful in older people and likely to be valuable in the dialysis population. No interventional studies have addressed this issue in CKD-5D, although these patients fall regularly and simple falls prevention may be a useful way to reduce fractures and the associated morbidity and mortality. There is evidence in the general population that falls risk is reduced by decreasing the number of medications to less than four (122), although this goal may be unattainable for many dialysis patients. If patients are unsteady or incapable of performing transfers, referral for professional gait, balance and strength training is reported to reduce the risk of falls (123–126).

As the etiology of falls is often multifactorial, it would be helpful to first perform a comprehensive risk assessment in dialysis patients followed by targeted interventions. Multitargeted strategies would include reduction in psychoactive medications that may increase the propensity to fall (especially benzodiazepines, narcotics, and antidepressants), assessment of hypotensive agents for postural hypotension, improvement in muscle strength, gait and balance, and correction of poor vision or reduction in environmental risks. The addition of 25-hydroxyvitamin D, when deficiency is present, may also improve muscle strength and reduce falls risk as vitamin D deficiency increases muscle weakness (127). Treatment with active vitamin D has also been associated with greater muscle size and strength in HD patients (128) and may help reduce falls and subsequent fracture.

Hip Protectors

The use of hip protectors has been reported to reduce the risk of hip fractures in high-risk subjects, such as those in a nursing home (129). However, there have been no studies assessing hip protectors in the CKD-5D population.

Conclusion

Fracture is a significant complication of CKD with substantial morbidity and mortality. As the general population ages, an increasing number of patients will have both CKD and a high fracture risk, on account of preexisting reductions in bone mass, CKD-MBD, medications, reduced physical functioning, and falls. Patients with CKD-5D share important risk factors for fracture with the general population but are also distinctive. Identifying those patients at greatest fracture risk provides an opportunity to modify risk factors and in some cases, to institute specific therapy.

A history of fracture or identification of prevalent vertebral fracture may indicate an increased fracture risk. BMD by DEXA correlates poorly with fracture risk in patients with CKD-5D, although it may be useful in specific patients. Biochemical markers of bone turnover also lack diagnostic accuracy in CKD-5D. Hopefully, newer high-resolution imaging techniques and the use of biochemical markers unaffected by renal function may improve the noninvasive diagnosis of bone disease.

Despite these numerous caveats, an assessment of risk factors and medications listed in Table 1, proceeding through the checklist in Table 2 and the use of Table 3 to consider therapies for CKD-MBD should improve fracture risk. Because these drugs are largely untested in patients with CKD-5D, prospective studies of treatments targeting fracture risk in this population are urgently required.

Acknowledgments

NT was supported by a National Health and Medical Research Council Grant (Australia).

Conflict of Interest

None declared.

References

1. Coco M, Rush H: Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 36:1115–1121, 2000
2. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C: Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 58:396–399, 2000
3. Atsumi K, Kushida K, Yamazaki K, Shimizu S, Ohmura A, Inoue T: Risk factors for vertebral fractures in renal osteodystrophy. *Am J Kidney Dis* 33:287–293, 1999
4. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353:238–248, 2005
5. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 360:1395–1407, 2009
6. von der Recke P, Hansen MA, Hassager C: The association between low bone mass at the menopause and cardiovascular mortality. *Am J Med* 106:273–278, 1999
7. Tanko LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR: Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *J Bone Miner Res* 20:1912–1920, 2005
8. Banks LM, Lees B, MacSweeney JE, Stevenson JC: Effect of degenerative spinal and aortic calcification on bone density measurements in post-menopausal women: links between osteoporosis and cardiovascular disease? *Eur J Clin Invest* 24:813–817, 1994
9. Marcovitz PA, Tran HH, Franklin BA, O'Neill WW, Yerkey M, Boura J, Kleerekoper M, Dickinson CZ: Usefulness of bone mineral density to predict significant coronary artery disease. *Am J Cardiol* 96:1059–1063, 2005
10. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC: Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 15:1943–1951, 2004
11. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC: Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 27:394–401, 1996
12. Sinnott B, Syed I, Sevrukov A, Barengolts E: Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. *Calcif Tissue Int* 78:195–202, 2006
13. Moe SM, Drueke T, Lameire N, Eknoyan G: Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis* 14:3–12, 2007
14. Jadoul M: Towards the prevention of bone fractures in dialysed patients? *Nephrol Dial Transplant* 22:3377–3380, 2007
15. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, Mason N, Prutz KG, Young EW, Pisoni RL: Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 70:1358–1366, 2006
16. Kaneko TM, Foley RN, Gilbertson DT, Collins AJ: Clinical epidemiology of long-bone fractures in patients receiving hemodialysis. *Clin Orthop Relat Res* 457:188–193, 2007
17. Yamaguchi T, Kanno E, Tsubota J, Shiomi T, Nakai M, Hattori S: 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, 1996
18. Inaba M, Okuno S, Kumeda Y, Yamakawa T, Ishimura E, Nishizawa Y: Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus. *Calcif Tissue Int* 76:256–260, 2005
19. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antoniucci DM, Cummings SR: Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 167:133–139, 2007
20. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR: Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* 22:503–508, 2007
21. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A: Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrol Dial Transplant* 24:1539–1544, 2009
22. Nickolas TL, McMahon DJ, Shane E: Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 17:3223–3232, 2006
23. Dooley AC, Weiss NS, Kestenbaum B: Increased risk of hip fracture among men with CKD. *Am J Kidney Dis* 51:38–44, 2008
24. Stehman-Breen CO, Sherrard DJ, Alem AM, Gillen DL, Heckbert SR, Wong CS, Ball A, Weiss NS: Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int* 58:2200–2205, 2000
25. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C: Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 288:3014–3018, 2002
26. Nichols R, Hopman WM, Morton AR, Harman GJ, Holden RM: Statins are associated with a reduced risk of bone fracture in hemodialysis (HD) patients. *Hemodial Int* 12:275–279, 2008
27. Rodriguez-Garcia M, Gomez-Alonso C, Naves-Diaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB: Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. *Nephrol Dial Transplant* 24:239–246, 2009
28. Naves M, Diaz-Lopez JB, Gomez C, Rodriguez-Rebollar A, Rodríguez-García M, Cannata-Andía JB: The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. *Osteoporos Int* 14:520–524, 2003
29. Ismail AA, Cooper C, Felsenberg D, Varlow J, Kanis JA, Silman AJ, O'Neill T: Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. European Vertebral Osteoporosis Study Group. *Osteoporos Int* 9:206–213, 1999
30. Mittalhenkle A, Gillen DL, Stehman-Breen CO: Increased risk of mortality associated with hip fracture in the dialysis population. *Am J Kidney Dis* 44:672–679, 2004
31. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V: Aortic calcification and the risk of osteoporosis and fractures. *J Clin Endocrinol Metab* 89:4246–4253, 2004
32. Naves M, Rodriguez-Garcia M, Diaz-Lopez JB, Gomez-Alonso C, Cannata-Andía JB: Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. *Osteoporos Int* 19:1161–1166, 2008
33. Danese MD, Kim J, Doan QV, Dylan M, Griffiths R, Chertow GM: PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J Kidney Dis* 47:149–156, 2006
34. Doan QV, Gleeson M, Kim J, Borker R, Griffiths R, Dubois RW: Economic burden of cardiovascular events and fractures among patients with end-stage renal disease. *Curr Med Res Opin* 23:1561–1569, 2007
35. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A: Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20:1185–1194, 2005
36. Yendt ER, Cohanim M, Jarzylo S, Jones G, et al.: Bone mass is related to creatinine clearance in normal elderly women. *J Bone Miner Res* 6:1043–1050, 1991
37. Sherman SS, Tobin JD, Hollis BW, Gundberg CM, Roy TA, Plato CC: Biochemical parameters associated with low bone density in healthy men and women. *J Bone Miner Res* 7:1123–1130, 1992
38. Lindberg JS, Moe SM: Osteoporosis in end-state renal disease. *Semin Nephrol* 19:115–122, 1999
39. Hruska KA, Teitelbaum SL: Renal osteodystrophy. *N Engl J Med* 333:166–174, 1995
40. Raggi P, Bellasi A, Ferramosca E, Block GA, Muntner P: Pulse wave velocity is inversely related to vertebral bone density in hemodialysis patients. *Hypertension* 49:1278–1284, 2007
41. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG: Relationship between vascular calcification, arterial stiffness and bone mineral density in a cross-sectional study of prevalent Australian haemodialysis patients. *Nephrology (Carlton)* 14:105–112, 2009
42. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP: A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 341:1249–1255, 1999
43. Gerakis A, Hadjidakis D, Kokkinakis E, Apostolou T, Raptis S, Billis A: Correlation of bone mineral density with the histological findings of renal osteodystrophy in patients on hemodialysis. *J Nephrol* 13:437–443, 2000
44. Fletcher S, Jones RG, Rayner HC, Harnden P, Hordon LD, Aaron JE, Oldroyd B, Brownjohn AM, Turney JH, Smith MA: Assessment of renal osteodystrophy in dialysis patients: use of bone alkaline phosphatase, bone mineral density and parathyroid ultrasound in comparison with bone histology. *Nephron* 75:412–419, 1997
45. Elder G: Pathophysiology and recent advances in the management of renal osteodystrophy. *J Bone Miner Res* 17:2094–2105, 2002
46. Duan Y, De Luca V, Seeman E: Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone. *J Clin Endocrinol Metab* 84:718–722, 1999
47. Erlichman M, Holohan TV: Bone densitometry: patients with end-stage renal disease. *Health Technol Assess (Rockv)* 9:i–vi, 1–31, 1996
48. Cummings SR, Black D: Bone mass measurements and risk of fracture in Caucasian women: a review of findings from prospective studies. *Am J Med* 98:24S–28S, 1995
49. Jamal SA, Hayden JA, Beyene J: Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. *Am J Kidney Dis* 49:674–681, 2007
50. Fontaine MA, Albert A, Dubois B, Saint-Remy A, Rorive G: Fracture and bone mineral density in hemodialysis patients. *Clin Nephrol* 54:218–226, 2000
51. Jamal SA, Chase C, Goh YI, Richardson R, Hawker GA: Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have had fractures. *Am J Kidney Dis* 39:843–849, 2002
52. Urena P, Bernard-Poenaru O, Ostertag A, Baudoin C, Cohen-Solal M, Cantor T, de Vernejoul MC: Bone mineral density, biochemical markers

and skeletal fractures in haemodialysis patients. *Nephrol Dial Transplant* 18:2325–2331, 2003
53. Kaji H, Suzuki M, Yano S, Sugimoto T, Chihara K, Hattori S, Sekita K: Risk factors for hip fracture in hemodialysis patients. *Am J Nephrol* 22:325–331, 2002
54. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 42(Suppl. 3):S1–S202, 2003
55. Elder GJ, Mackun K: 25-Hydroxyvitamin D deficiency and diabetes predict reduced BMD in patients with chronic kidney disease. *J Bone Miner Res* 21:1778–1784, 2006
56. Russo CR, Taccetti G, Caneva P, Mannarino A, Maranghi P, Ricca M: Volumetric bone density and geometry assessed by peripheral quantitative computed tomography in uremic patients on maintenance hemodialysis. *Osteoporos Int* 8:443–448, 1998
57. Jamal SA, Gilbert J, Gordon C, Bauer DC: Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res* 21:543–548, 2006
58. Mares J, Ohlidalova K, Opatrna S, Ferda J: Determinants of prevalent vertebral fractures and progressive bone loss in long-term hemodialysis patients. *J Bone Miner Metab* 27:217–223, 2009
59. Wehrli FW, Leonard MB, Saha PK, Gomberg BR: Quantitative high-resolution magnetic resonance imaging reveals structural implications of renal osteodystrophy on trabecular and cortical bone. *J Magn Reson Imaging* 20:83–89, 2004
60. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15:2208–2218, 2004
61. Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D: Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. *Osteoporos Int* 20:887–894, 2009
62. Byrjalsen I, Leeming DJ, Qvist P, Christiansen C, Karsdal MA: Bone turnover and bone collagen maturation in osteoporosis: effects of antiresorptive therapies. *Osteoporos Int* 19:339–348, 2008
63. Richer E, Lewis MA, Odvina CV, Vazquez MA, Smith BJ, Peterson RD, Poindexter JR, Antich PP, Pak CY: Reduction in normalized bone elasticity following long-term bisphosphonate treatment as measured by ultrasound critical angle reflectometry. *Osteoporos Int* 16:1384–1392, 2005
64. McLean RR, Jacques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, Hannan MT, Cupples LA, Kiel DP: Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 350:2042–2049, 2004
65. van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, van der Klift M, de Jonge R, Lindemans J, de Groot LC, Hofman A, Witteman JC, van Leeuwen JP, Breteler MM, Lips P, Pols HA, Uitterlinden AG: Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 350:2033–2041, 2004
66. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K: Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 293:1082–1088, 2005
67. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr: Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 354:1567–1577, 2006
68. Jamal SA, Leiter RE, Bauer DC: Hyperhomocysteinaemia and aortic calcification are associated with fractures in patients on haemodialysis. *QJM* 98:575–579, 2005
69. Desmet C, Beguin C, Swine C, Jadoul M: Falls in hemodialysis patients: prospective study of incidence, risk factors, and complications. *Am J Kidney Dis* 45:148–153, 2005
70. Cook WL, Tomlinson G, Donaldson M, Markowitz SN, Naglie G, Sobolev B, Jassal SV: Falls and fall-related injuries in older dialysis patients. *Clin J Am Soc Nephrol* 1:1197–1204, 2006
71. Jamal SA, Leiter RE, Jassal V, Hamilton CJ, Bauer DC: Impaired muscle strength is associated with fractures in hemodialysis patients. *Osteoporos Int* 17:1390–1397, 2006
72. Mitterbauer C, Kramar R, Oberbauer R: Age and sex are sufficient for predicting fractures occurring within 1 year of hemodialysis treatment. *Bone* 40:516–521, 2007
73. O'Shaughnessy DV, Elder GJ: Patient-level outcomes: the missing link. *Nephrology (Carlton)* 14: 443–451, 2009
74. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, Josse S, Meyrier A, Lins RL, Fairey IT: Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ* 310:358–363, 1995
75. Rix M, Eskildsen P, Olgaard K: Effect of 18 months of treatment with alfacalcidol on bone in patients with mild to moderate chronic renal failure. *Nephrol Dial Transplant* 19:870–876, 2004
76. Elder GJ: Vitamin D levels, bone turnover and bone mineral density show seasonal variation in patients with chronic kidney disease stage 5. *Nephrology (Carlton)* 12:90–94, 2007
77. Cunningham J, Danese M, Olson K, Klassen P, Chertow GM: Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 68:1793–1800, 2005
78. Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, D'Souza R, Welch K, Stein K: The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. *Health Technol Assess* 11: iii, 2007. xi-xiii, 1-167.
79. Rudser KD, de Boer IH, Dooley A, Young B, Kestenbaum B: Fracture risk after parathyroidectomy among chronic hemodialysis patients. *J Am Soc Nephrol* 18:2401–2407, 2007
80. Ferreira A, Frazao JM, Monier-Faugere MC, Gil C, Galvao J, Oliveira C, Baldaia J, Rodrigues I, Santos C, Ribeiro S, Hoenger RM, Duggal A, Malluche HH: Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. *J Am Soc Nephrol* 19:405–412, 2008
81. Liu YL, Lin HH, Yu CC, Kuo HL, Yang YF, Chou CY, Lin PW, Liu JH, Liao PY, Huang CC: A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients. *Ren Fail* 28:701–707, 2006
82. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ: Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 280:2077–2082, 1998
83. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE: Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348:1535–1541, 1996
84. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD: Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 282:1344–1352, 1999
85. Miller PD: Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporos Rep* 3:5–12, 2005
86. Cunningham J: Bisphosphonates in the renal patient. *Nephrol Dial Transplant* 22:1505–1507, 2007
87. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE: Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 20:2105–2115, 2005
88. Ott SM, Drueke T, Elder G, Fukagawa M, Jorgetti V, Langman CB, Moe S, McCann L, Wang AY, Weisinger J, Wheeler D: Renal function and bisphosphonate safety. *J Bone Miner Res* 23: 453–454, 2008. author reply 455.
89. Geng Z, Monier-Faugere MC, Bauss F, Malluche HH: Short-term administration of the bisphosphonate ibandronate increases bone volume and prevents hyperparathyroid bone changes in mild experimental renal failure. *Clin Nephrol* 54:45–53, 2000
90. Tomat A, Gamba CA, Mandalunis P, De Grandi MC, Somoza J, Friedman S, Zeni S: Changes in bone volume and bone resorption by olpadronate treatment in an experimental model of uremic bone disease. *J Musculoskelet Neuronal Interact* 5:174–181, 2005
91. Hamdy NA, McCloskey EV, Brown CB, Kanis JA: Effects of clodronate in severe hyperparathyroid bone disease in chronic renal failure. *Nephron* 56:6–12, 1990
92. Wetmore JB, Benet LZ, Kleinstuck D, Frassetto L: Effects of short-term alendronate on bone mineral density in haemodialysis patients. *Nephrology (Carlton)* 10:393–399, 2005
93. Miller PD: Is there a role for bisphosphonates in chronic kidney disease? *Semin Dial* 20:186–190, 2007
94. Lenehan TM, Balligand M, Nunamaker DM, Wood FE Jr: Effect of EHDP on fracture healing in dogs. *J Orthop Res* 3:499–507, 1985
95. Mashiba T, Hirano T, Turner CH, Forwood MR, et al.: Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* 15:613–620, 2000
96. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB: Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone* 28:524–531, 2001
97. Persy V, De Broe M, Ketteler M: Bisphosphonates prevent experimental vascular calcification: Treat the bone to cure the vessels? *Kidney Int* 70:1537–1538, 2006
98. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, Delmas PD:: Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study. *J Bone Miner Res* 22:1502–1509, 2007
99. Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, Fahrleitner-Pammer A, Petto H, Westmore M, Michalsky D, Sato M, Dobnig H: Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. *Bone* 41:378–385, 2007
100. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D,

Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 291:1701–1712, 2004
101. Cuzick J: Hormone replacement therapy and the risk of breast cancer. *Eur J Cancer* 44:2344–2349, 2008
102. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R: The effects of tibolone in older postmenopausal women. *N Engl J Med* 359:697–708, 2008
103. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Glüer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 282:637–645, 1999
104. Hernández E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F, Martinis R, Bellorin-Font E, Weisinger JR: Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 63:2269–2274, 2003
105. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK: Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 355:125–137, 2006
106. Johansen KL: Testosterone metabolism and replacement therapy in patients with end-stage renal disease. *Semin Dial* 17:202–208, 2004
107. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Kraenzlin ME, Schlegel B, Jick H: HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 283:3205–3210, 2000
108. Wang PS, Solomon DH, Mogun H, Avorn J: HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 283:3211–3216, 2000
109. Schoofs MW, Sturkenboom MC, van der Klift M, Hofman A, Pols HA, Stricker BH: HMG-CoA reductase inhibitors and the risk of vertebral fracture. *J Bone Miner Res* 19:1525–1530, 2004
110. Reid IR, Hague W, Emberson J, Baker J, Tonkin A, Hunt D, MacMahon S, Sharpe N: Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term Intervention with Pravastatin in Ischaemic Disease. *Lancet* 357:509–512, 2001
111. LaCroix AZ, Cauley JA, Pettinger M, Hsia J, Bauer DC, McGowan J, Chen Z, Lewis CE, McNeeley SG, Passaro MD, Jackson RD: Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med* 139:97–104, 2003
112. Bauer DC, Mundy GR, Jamal SA, Black DM, Cauley JA, Ensrud KE, van der Klift M, Pols HA: Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 164:146–152, 2004
113. O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY: Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 3:CD005326, 2006
114. Seeman E: Strontium ranelate: vertebral and non-vertebral fracture risk reduction. *Curr Opin Rheumatol* 18(Suppl 1):S17–20, 2006
115. Schrooten I, Cabrera W, Goodman WG, Dauwe S, et al.: Strontium causes osteomalacia in chronic renal failure rats. *Kidney Int* 54:448–456, 1998
116. Oste L, Bervoets AR, Behets GJ, Dams G, Lamberts LV, Marynissen R, Dorriné W, De Broe ME, D'Haese PC: Time-evolution and reversibility of strontium-induced osteomalacia in chronic renal failure rats. *Kidney Int* 67:920–930, 2005
117. Gerstenfeld S, Hinojosa L, Serrano Arias M, Menendez Rodriguez P, Fernández Martín JL, Marchante JM, García Alonso JI, Sanz-Medel A, Cannata Andía JB: [Effect of strontium on bone metabolism in hemodialysis patients]. *Nefrologia* 23(Suppl 2):52–56, 2003
118. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344:1434–1441, 2001
119. Elder GL, Kumar KS: Calciphylaxis associated with chronic kidney disease and low bone turnover: management with recombinant human PTH-(1–34). *NDT Plus* 1:97–99, 2008
120. Chesnut III CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D: A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 109:267–276, 2000
121. Kannus P, Sievanen H, Palvanen M, Jarvinen T, Parkkari J: Prevention of falls and consequent injuries in elderly people. *Lancet* 366:1885–1893, 2005
122. Tinetti ME, McAvay G, Claus E: Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT Trial? Frailty and Injuries Cooperative Studies of Intervention Techniques. *Am J Epidemiol* 144:389–399, 1996
123. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, Koch ML, Trainor K, Horwitz RI: A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 331:821–827, 1994
124. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM: Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. *BMJ* 315:1065–1069, 1997
125. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C: Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet* 353:93–97, 1999
126. Robertson MC, Devlin N, Gardner MM, Campbell AJ: Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. *BMJ* 322:697–701, 2001
127. Holick MF: The role of vitamin D for bone health and fracture prevention. *Curr Osteoporos Rep* 4:96–102, 2006
128. Gordon PL, Sakkas GK, Doyle JW, Shubert T, Johansen KL: Relationship between vitamin D and muscle size and strength in patients on hemodialysis. *J Ren Nutr* 17:397–407, 2007
129. Kannus P, Parkkari J, Niemi S, Pasanen M, Palvanen M, Järvinen M, Vuori I: Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 343:1506–1513, 2000
130. Ott SM: Bone Density in Patients with Chronic Kidney Disease Stages 4–5. *Nephrology (Carlton)* 14: 395–403, 2009