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Bone Health in Glomerular Kidney Disease

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Abstract

Purpose of Review To summarize the literature regarding alterations in bone health in patients with glomerular kidney disease and highlight areas in need of additional investigation.

Recent Findings There is mounting evidence that children and adults with glomerular conditions, with or without compromised kidney function, comprise a distinct subgroup of patients with unique risk factors for altered bone health.

Summary Patients with glomerular kidney disease are exposed to both disease-related and treatment-related factors that affect bone structure and function. In addition to chronic kidney disease–related risk factors for impaired bone health, high rates of exposure to osteotoxic medications, varying degrees of systemic inflammation, and altered vitamin D metabolism may contribute to compromised bone health in individuals with glomerular disease. Further study is needed to better understand these risk factors and the complex interaction between the immune system and bone cells in glomerular disease.

Keywords Glomerular · Bone · Bone density · Fracture · Vitamin D

Introduction

Glomerular disease is the third most common cause of end-stage kidney disease (ESKD) in the USA [1, 2] and accounts for 25% of chronic kidney disease (CKD) cases worldwide [3]. Even when kidney function is preserved, glomerular disease is associated with a well-established heavy burden of cardiovascular, metabolic, infectious, and psychosocial complications [4–12]. By comparison, current understanding of skeletal complications in glomerular disease remains very limited. In addition to the disturbances in bone and mineral metabolism imposed by a high rate of glomerular filtration rate (GFR) decline and progression to ESKD, there is mounting evidence that children and adults with glomerular conditions, with or without compromised kidney function, comprise a distinct subgroup of patients with CKD and face other potentially modifiable threats to bone health. These include high rates of exposure to osteotoxic medications, varying degrees of systemic inflammation, and altered vitamin D metabolism (Fig. 1). To date, there is little epidemiologic data describing the prevalence of, or risk factors associated with, the development of compromised bone health and skeletal fracture in patients with glomerular disease. The purpose of this review will be to summarize the existing literature and highlight areas in need of additional investigation.

CKD Mineral and Bone Disorder

Disordered bone and mineral metabolism is a universal feature of CKD in children and adults and represents a major source of excess morbidity and mortality [13–15]. Chronic kidney disease-mineral and bone disorder (CKD-MBD) represents the summation of a series of maladaptive hormonal interactions between the bone, parathyroid gland, kidney, heart, and vasculature resulting from progressive decline in kidney function [16]. See Hanudel and Salusky for a recent review of the pathophysiology and treatment of CKD-MBD in children [17••]. Of particular relevance to this review are the pathophysiologic elements of secondary hyperparathyroidism that contribute in deleterious alterations to bone and vascular

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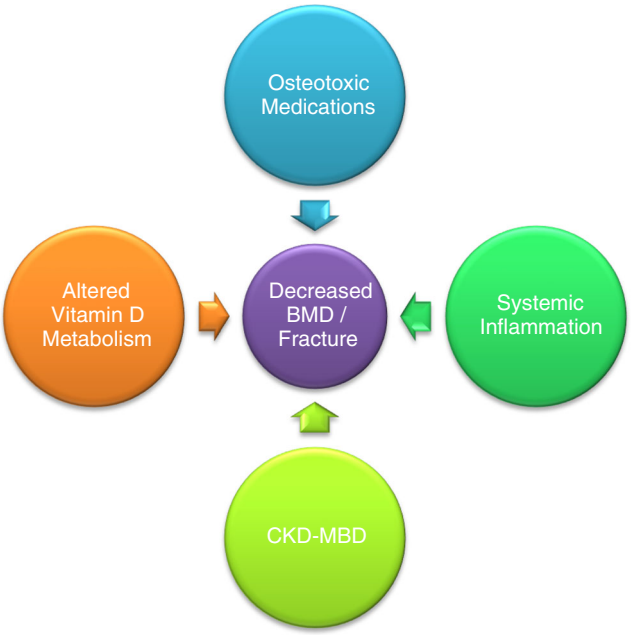

Fig. 1 Conceptual framework depicting potential risk factors for impaired bone mineral density and fracture in glomerular disease

biology. Increased parathyroid hormone (PTH), elevated fibroblast growth factor 23 (FGF23), decreased 1,25-dihydroxyvitamin D (1,25OH_2D), and hyperphosphatemia act to alter bone turnover, mineralization, and volume and promote vascular calcification. These alterations ultimately contribute to increased risk of skeletal fracture, bone deformity, poor growth, and cardiovascular morbidity and mortality [15, 18–22].

Disturbed Vitamin D Homeostasis

Studies have documented very low total 25-hydroxyvitamin D (25OHD) levels in nephrotic syndrome (NS) [23–26, 27, 28–34, 35], attributed to urinary loss of its binding proteins, vitamin D–binding protein (DBP) and albumin. A multicenter study of 61 children with incident NS found the prevalence of vitamin D deficiency, defined as 25OHD < 20 ng/mL, to be 100% at diagnosis and 53% at 2–4 months of follow-up. Vitamin D supplementation was independently associated with higher 25OHD concentrations at follow-up [36]. Even in remission, children with steroid-sensitive NS were shown to have lower 25OHD concentrations than healthy controls [37, 38]. Among 182 children and adolescents with CKD and ESKD, glomerular disease, particularly focal segmental glomerulosclerosis (FSGS), was an independent risk factor for lower 25OHD concentrations, adjusted for age, race, season, CKD severity, and hypoalbuminemia [39]. A similar finding was observed in children from the Chronic Kidney Disease in Children (CKiD) cohort; nephrotic-range proteinuria was associated with an 8-fold increased risk of vitamin D deficiency, after adjustment for age, sex, race, season, body mass index (BMI), milk intake, GFR, and vitamin D supplementation [40]. Similarly, in 500 children from 12 European countries participating in the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study, albuminuria and glomerulopathy were independently associated with lower 25OHD concentrations, and the inverse association between 25OHD and albuminuria was even stronger among patients with glomerulopathies [41].

Multiple small studies have demonstrated a protective role for vitamin D and calcium supplementation in children with NS. Vitamin D3 (200 IU/day) and elemental calcium (500 mg/day) were associated with improved spine bone mineral density (BMD) in a prospective study in 88 children, independent of dietary calcium and glucocorticoid exposure [42]. A randomized, controlled trial in 40 children with NS treated with prednisone found a lesser decrease in spine BMD in those treated with vitamin D3 (400 IU/day) and calcium (1000 mg/day) (4.6%) vs. controls (13%) ($p < 0.001$) [43]. Another randomized, controlled trial of daily vitamin D3 (1000 IU) and calcium (500 mg) in 41 children with new-onset NS on prednisone for 12 weeks found an increase in lumbar spine bone mineral content of 11.2% vs. a decrease of 8.9% in the control group ($p < 0.0001$) [44].

Vitamin D–Binding Protein

DBP serves as the predominant high-affinity transport and storage protein for extracellular 25OHD. DBP is primarily synthesized in the liver, and its gene is a member of the albumin and alpha-fetoprotein gene family. Albumin and lipoproteins also have roles in 25OHD transport and storage and bind to 25OHD with lower affinity than DBP. Less than 1% of 25OHD circulates unbound and, together with the albumin-bound fraction, represents the bioavailable pool of circulating 25OHD [45, 46].

Daily hepatic production of DBP is high (10 mg/kg/day) and its half-life is on the order of 2.5–3 days. Malnutrition, liver failure, extensive tissue injury, and nephrotic-range proteinuria can result in decreased serum concentrations. Apart from its transport and storage function, DBP may have additional functions including sequestering globular actin, binding fatty acids, and as a chemoattractant for complement c5 [47]. See Denburg and Bhan for an extensive review of DBP physiology and function [48••].

The free hormone hypothesis states that only non-protein-bound 25OHD or 1,25OH_2D is able to exert biological activity. This hypothesis is supported by experiments in DBP null mice and cultured human foreskin keratinocytes [49, 50]. However, renal proximal tubular epithelial cells expressing megalin and cubilin are known to reabsorb the DBP-vitamin D complex from the glomerular filtrate, an essential step in the

conversion of circulating 25OHD to 1,25OH_2D, supporting the importance of DBP in vitamin D metabolism [51, 52].

Multiple DBP isoforms have been identified with extensive polymorphisms documented that affect binding affinity [53, 54]. Initially, genetic polymorphisms in DBP (e.g., GC1F, GC1S, and GC2) were thought to explain racial differences in DBP concentrations and therefore total 25OHD concentrations [55]. Subsequent studies comparing serum DBP measurements using monoclonal and polyclonal ELSIA assays and mass spectrometry demonstrated that the widely used monoclonal assay differentially quantified DBP by isoform, explaining previously reported race differences in DBP concentrations [56–58]. Both the polyclonal DBP assay and mass spectrometry have been shown to measure DBP without bias to isoform in cohorts of patients with [56] and without renal insufficiency [55, 58]. See Bikle et al. [59] and Denburg and Bhan [48••] for an in-depth review of the topic.

The relationship between free and total 25OHD under pathologic conditions, such as nephrotic syndrome, remains unclear and an area of ongoing enquiry. Multiple studies have described low serum and high urine levels of DBP in patients with active nephrotic syndrome [23, 24]. Urinary losses of radioactively labeled 25OHD3 in patients with nephrotic syndrome support the hypothesis that urinary loss of vitamin D–binding protein contributes to declines in serum 25OHD levels [24].

The opinion of these authors is that prolonged periods of nephrotic-range proteinuria, especially in those with frequent NS relapses or persistent proteinuria, are likely to be detrimental to bone health, especially in combination with exposure to osteotoxic medications.

Inflammation Biology and Bone Health

There is growing evidence of the bidirectional relationships between immune and bone cells, both during normal physiologic processes, such as bone remodeling, and in disease states, such as rheumatoid arthritis [60–62]. The intersection of the immune system and bone cells is of particular relevance to patients with glomerular disease, as immune dysregulation and pro-inflammatory cytokines have been described in many glomerular diseases [63].

Pro-inflammatory cytokines, such as TNF-α and IL-6, have adverse effects on bone formation [64, 65] and resorption [66, 67]. TNF-α, IL-6, and IL-1β have been shown to activate the parathyroid calcium-sensing receptor [68] and to inhibit renal expression of the 1α-hydroxylase responsible for converting 25OHD to 1,25OH_2D [69]. Furthermore, TNF-α was reported to inhibit Phex gene expression, which could result in decreased proteolysis and increased levels of fibroblast growth factor 23 (FGF23) [70], a negative regulator of PTH and vitamin D metabolism [71, 72].

The effects of CD4+ and CD8+ T cells and their respective cytokines on the dynamics of bone remodeling are increasingly being elucidated. T cell subtypes have been found to regulate bone formation and resorption at multiple levels [73]. Th17 cells promote osteoclastogenic activity by modulation of osteoclast differentiation via secretion of IL-17, TNF-α, and RANKL [74, 75]. There is also evidence supporting a pathogenic role for Th17 cells and IL-17 in animal models of crescentic glomerulonephritis, ANCA-associated glomerulonephritis, and lupus nephritis [76].

Treg cells have been found to play an important role in the inhibition of bone loss via secretion of IL-4, IL-10, and TGF-β1; suppression of TH17 cells; and inhibition of the differentiation of monocytes into osteoclasts [77, 78]. Osteoprotective functions have also been described for Th1 and Th2 cells [60].

While the interplay between immunology and bone biology has helped to elucidate the osteotoxic pathophysiology of a number of inflammatory diseases [79], relatively little attention has been given to the intersection of inflammation biology, immune dysregulation, and bone biology in glomerular disorders. Increased RANKL expression was observed in cultured human osteoblasts following exposure to sera from patients with nephrotic syndrome in relapse, and RANKL expression was attenuated following exposure to sera from patients in clinical remission [80]. RANKL expression was no different in the relatively few patients exposed to glucocorticoids or cyclosporine during relapse or remission in this study. Data from the Women's Health Initiative Study demonstrated that the association between fracture risk and eGFR was eliminated after adjustment for TNF-α receptor levels, supporting a possible role for this pro-inflammatory molecule in mediating fracture risk [81].

Exposure to Medications That Are Toxic to the Skeleton

Children and adults with glomerular disease are often treated with agents that compromise skeletal development and function and mineral metabolism, including glucocorticoid therapy, calcineurin inhibitors, and loop diuretics [82, 83].

Glucocorticoids

The osteotoxic effects of glucocorticoids have long been recognized. Glucocorticoid therapy is the most common cause of secondary osteoporosis, and long-term therapy has been associated with skeletal fracture in as many as 30–50% of those with long-term exposure [84••]. In adults, a threshold of 5 mg daily of prednisone has been linked with reduced BMD and fracture [85, 86]. The recommended daily dosing of prednisone in children (60 mg/m^2 or 2 mg/kg) for new-onset or

relapsed NS far exceeds this threshold. Moreover, it is recommended that glucocorticoid therapy be continued at relatively high doses for at least 12 weeks initially and 4 weeks after achieving remission for relapse [82, 87]. Thus, even patients with infrequently relapsing NS (1–3 relapses in a 12-month period) have considerable cumulative glucocorticoid exposure. The duration of these repeated exposures is of particular concern given that a population-based study of children treated with oral glucocorticoid therapy primarily for respiratory disease showed that receiving four or more relatively short courses (median 5 days) was associated with an adjusted OR for fracture of 1.32 [88].

Glucocorticoid exposure results in decreased bone formation and strength. These outcomes are mediated by inhibitory effects on osteoblast development, activity, and survival, as well as increased osteocyte apoptosis and increased osteoclast lifespan [84••, 89, 90]. Glucocorticoids also affect bone formation indirectly through suppression of growth hormone, gonadotropins, and ACTH and facilitation of PTH release. See a review by Weinstein for a summary of the topic [84••].

There is strong evidence that glucocorticoids increase both vertebral and non-vertebral fracture risks in a dose-dependent manner in all age groups beginning as early as within 3 months of starting therapy [85, 91]. In children, the cumulative incidence of vertebral fracture in the first 12 months following initiation of glucocorticoid therapy for idiopathic nephrotic syndrome was found to be 6% [92]. BMD at the lumbar spine in this study decreased significantly after initiation of steroids and subsequently increased by 12 months [92]. Among the 25% of children with lumbar spine BMD Z-scores < = -1.0 at 12 months, there was an inverse relationship between BMD Z-score and early glucocorticoid exposure [92]. A study comparing DEXA of the spine and whole body in 60 children with steroid-sensitive nephrotic syndrome and 195 controls found significantly lower bone mineral content (BMC) at the spine and higher total body BMC, after adjustment for age, sex, height, race, and Tanner stage, in those exposed to steroids. These findings suggest differing responses in cortical and trabecular bone and that secondary increases in body mass index due to glucocorticoid exposure may help maintain bone mineral content due to biomechanical loading or hormonal influences [93]. Decreased BMD has been associated with glucocorticoid exposure in a variety of other pediatric chronic health conditions [94–96]. A large retrospective cohort study of adults exposed to corticosteroids found dose-dependent increases in the relative risk of hip (RR 1.61), forearm (RR 1.09), and vertebral fracture (RR 2.6) during steroid therapy relative to controls [85]. Though fracture rates decreased quickly following cessation of therapy in this study, other studies have found fracture rates to take up to 1 year before returning to rates found in the general population [91].

Cyclosporine

Isolating the osteotoxic effects of cyclosporine has largely been limited by prior or concurrent exposure to other immunosuppressive agents in study populations, especially glucocorticoids. Studies in transplant recipients receiving cyclosporine as part of their immunosuppressive regimen have shown mixed effects on bone mineral density and markers of bone turnover [97–104]. In cell culture experiments, cyclosporine has been shown to inhibit bone resorption and osteoclastic activity [105, 106]. Cyclosporine has been associated with increased bone turnover and is associated with increased plasma concentrations of bone formation and resorption markers in in vivo experiments [107]. This effect has been hypothesized to be mediated by cyclosporine's immunoregulatory functions, specifically, inhibition of anti-resorptive T cell–dependent cytokines [108, 109].

There is little data on the effects of cyclosporine on bone metabolism in glomerular disease. A small study in adults with steroid-dependent nephrotic syndrome treated with a combination of cyclosporine and glucocorticoids did not demonstrate an increased rate of bone loss compared with those treated with glucocorticoids alone [110].

Loop Diuretics and Proton Pump Inhibitors

Patients with glomerular disease are commonly exposed to additional pharmacologic agents that may have the potential for negative effects on bone health, such as loop diuretics and proton pump inhibitors [111]. Though loops diuretics are known to increase urinary calcium excretion and result in a compensatory increase in PTH levels, effects on bone mass and fracture risk have been inconsistent [112–116]. While there is conflicting data associating protein pump inhibitor (PPI) use with alterations in bone mineral density and bone metabolism [117–121], a recent meta-analysis of 32 studies by Liu et al. supports a moderately increased risk of any-site, hip, and spine fracture with PPI exposure [122].

Bone Mineral Density in Glomerular Disease

Small cross-sectional cohorts have measured bone mineral density (BMD) at the spine by dual energy X-ray absorptiometry (DXA) [92, 123–128] or quantitative computed tomography (QCT) at the spine or radius [129–131]. These studies reported decreased BMD in children with glomerular disease. A prospective study evaluating 100 children with idiopathic NS [123] found that mean lumbar spine BMD *Z*-score was lower in children with frequently relapsing, steroid-dependent, or steroid-resistant NS as compared to children with steroid-sensitive or infrequently relapsing NS (− 1.65 vs. − 1.08, $p = 0.01$). Older age, lower calcium intake, and greater

cumulative glucocorticoid exposure were associated with lower BMD in multivariable analysis. Some studies did not find impaired BMD in children with glomerular disease [93, 132, 133]. Differences between these studies may be attributed to the inability of DXA to distinguish cortical and trabecular density individually or to assess three-dimensional bone density and geometry, as well as to the heterogeneity in terms of steroid responsiveness, glucocorticoid exposure, and underlying disease.

The largest peripheral QCT study examining BMD compared 55 children with steroid-sensitive NS with a reference cohort of > 650 children. The study demonstrated greater cortical volumetric BMD (vBMD) *Z*-scores and lower trabecular vBMD *Z*-scores in the participants with NS versus reference participants [134]. Glucocorticoid exposure was associated with greater cortical vBMD *Z*-scores and lower bone biomarkers, suggesting steroid-induced suppression of bone formation and accumulation of older cortical bone of greater density. Supporting this hypothesis, another study in the same cohort examining the longitudinal association between glucocorticoid therapy and cortical vBMD found that greater glucocorticoid exposure, lesser linear growth, and lesser expansion of cortical area were independently associated with greater increases in cortical vBMD *Z*-score [135]. The clinical implications of lower trabecular BMD combined with higher cortical BMD are not known. This pattern, however, may have important implications for the utility of DXA in this population, as higher cortical vBMD may mask trabecular deficits. There is some evidence to suggest that in NS, bone deficits acquired in childhood persist into adulthood. Two studies of adults with a history of minimal change NS in childhood found osteoporosis to be a frequent long-term complication and demonstrated a significant reduction in trabecular vBMD at the radius [136, 137].

Histomorphometry in Glomerular Disease

In adults with NS, bone biopsy studies suggest that vitamin D deficiency is linked to abnormal bone mineralization [32–34, 35, 138]. The largest study included 30 patients with NS and normal kidney function [34]. About two-thirds of subjects had osteomalacia, either with or without high bone turnover, as the predominant type of renal osteodystrophy. The presence of osteomalacia was related to lower concentrations of vitamin D. However, the severity of osteomalacia was related to severity and duration of proteinuria, suggesting a multifactorial etiology of poor bone health. A small study in 8 children on long-term glucocorticoid therapy with steroid-dependent or partially responsive NS and normal GFR demonstrated focal osteomalacia and mildly increased resorption in more than half of the children. Mineralization lag time correlated with time since diagnosis ($r = 0.93$, $p < 0.0005$), and bone formation rate was inversely correlated with the prednisone dose at biopsy ($r = -0.78$, $p < 0.05$) [139].

These data suggest that abnormalities in vitamin D homeostasis in glomerular disease, due to either effects of proteinuria, medications that alter vitamin D metabolism, or inflammation, may play an important role in associated increased skeletal fragility.

Fracture Risk in Glomerular Disease

The contribution of glomerular disease to increased fracture risk has been poorly explored. Numerous studies have demonstrated increased fracture rates in adults on dialysis [18–21, 140–145] and adults with compromised GFR [81, 146–156], with even small declines in estimated GFR increasing the risk of incident fracture [157]. However, none of these studies assessed the impact of underlying glomerular disease. The only study evaluating the burden of fracture in a large prospective cohort of children with CKD showed that fracture rates were 2- to 3-fold higher than population-based rates [22], despite being less physically active than their healthy peers [158]. Though 20% of this cohort had underlying glomerular disease, > 75% also had an estimated GFR <60 mL/min/1.73m^2 at baseline. To date, the only study of fracture risk in patients with idiopathic nephrotic syndrome found that 6% of 54 children suffered vertebral fractures over their first year of glucocorticoid therapy [92]. There have been no other studies in children or adults addressing the incidence of fracture or other skeletal complications in glomerular disease independent of compromised kidney function.

Areas for Further Investigation

1. Epidemiologic studies are needed to better characterize the burden of and risk factors for fracture and other skeletal complications in patients with glomerular disorders.
2. Mechanistic studies leveraging advances in high-resolution bone imaging and bone biopsy techniques are needed to better characterize CKD-MBD in this population.
3. As patients with glomerular disease are often exposed to multiple pharmacologic agents concurrently, additional research should investigate the effect of combined exposures and interventions to mitigate skeletal risk [159].
4. As discussed in the preceding text, there remains much to learn about the complex interaction of the immune system and bone cells, both in health and disease, and very little is known about the impact of inflammation and immune dysregulation on bone health in glomerular disorders.

In summary, patients with glomerular kidney disease are exposed to both disease-related and treatment-related factors that affect bone structure and function including high rates of

exposure to osteotoxic medications, varying degrees of systemic inflammation, and altered vitamin D metabolism. Further studies are needed to better understand the pathophysiologic mechanisms underlying adverse skeletal outcomes in this population in order to inform preventive strategies.

Compliance with Ethical Standards

Conflict of Interest Michelle Denburg reports grants from Mallinckrodt, NIDDK, and PCORI. Dorey Glenn declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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