A Patient with Nephrotic-Range Proteinuria and Focal Global Glomerulosclerosis

Fernando C. Fervenza

Summary
A young male is evaluated for nephrotic-range proteinuria, hypercalciuria, and an elevated serum creatinine. A renal biopsy is performed and shows focal global glomerulosclerosis. The absence of nephrotic syndrome suggest that glomerulosclerosis was a secondary process. Further analysis of the proteinuria showed it to be due mainly to low-molecular weight proteins. The case illustrates the crucial role of electron microscopy as well as evaluation of the identity of the proteinuria that accompanies a biopsy finding of focal and global or focal and segmental glomerulosclerosis.


Introduction
Focal sclerosis is a pattern of glomerular injury defined histologically by the presence of sclerosis in some glomeruli; the sclerosis can be limited to only portions of involved glomeruli (focal segmental glomerulosclerosis, FSGS) or the entire involved glomerular tufts (focal global glomerulosclerosis). Both FSGS and focal global glomerulosclerosis are histopathologic lesions, not diseases. As such, the discovery of either on a kidney biopsy specimen is only the beginning of a necessary exploratory process leading to an etiologic diagnosis and not an end in itself.

Case Presentation
An 18-year-old man presented with proteinuria (4.5 g/24 hours) and a serum creatinine level of 2.0 mg/dl. Imaging studies and extensive laboratory evaluation revealed no additional abnormalities except for the questionable presence of microlithiasis on renal ultrasonography and hypercalciuria (581 mg/24 hours; normal, 25–300 mg/24 hours) for which he began receiving hydrochlorothiazide (HCTZ), 25 mg once a day. The patient underwent a kidney biopsy that showed normal glomeruli with minimal interstitial fibrosis. Immunofluorescence was negative. Electron microscopy (EM) was not done because of absence of glomeruli on the biopsy sample. A presumptive diagnosis of minimal-change disease (MCD) was made and treatment with prednisone (60 mg/d) was initiated. Proteinuria temporarily improved to 2.4 g/24 hours, but as soon as the prednisone dose was decreased to 40 mg/d, proteinuria increased to 5.2 g/24 hours. The prednisone dose was reduced to 15 mg/d, and cyclosporine (125 mg twice a day) was added for a presumptive diagnosis of primary FSGS that was missed on the biopsy sample. However, the patient remained proteinuric and was referred for further evaluation. Family history was positive for unspecified CKD in a maternal grandfather.

At presentation to the Mayo Clinic, the patient’s BP was 96/62 mmHg while he was receiving HCTZ, 25 mg orally once a day. There was no edema in the lower extremities. The reminder of the physical examination was normal. Laboratory evaluation showed a serum creatinine of 2.2 mg/dl, serum albumin of 4.8 g/dl, and total cholesterol 212 mg/dl. The serum electrolytes, including calcium, uric acid, and phosphorus levels, were normal. Immunologic evaluation was negative for antinuclear antibody, with normal C3 and C4 complement levels. Hepatitis B and C serologic studies were also negative. Urinalysis showed an osmolality of 564 mOsm/kg, a pH of 6.4, negative glucose, and 3–10 red blood cells/high-power field. A 24-hour urine collection showed 2.3 g of protein. A cyclosporine level was 106 ng/ml. Renal ultrasonography showed both kidneys measuring 9.8 cm in length with normal cortical thickness and no calculi.

Review of History and Laboratory Evaluation
Before presentation to Mayo, the patient was treated as having MCD and subsequently as having presumed FSGS on the basis of the persistence of nephrotic-range proteinuria despite corticosteroid therapy. However, there is a crucial difference between nephrotic-range proteinuria and nephrotic syndrome. In adults, nephrotic syndrome is defined by proteinuria >3.5 g/24 hours, hypoalbuminemia (<3.5 g/dl), hyperlipidemia, lipiduria, and edema (1). In children, nephrotic-range proteinuria is defined as >1 g/m² of body surface area per day (1). Many conditions can give rise to nephrotic-range proteinuria but without the nephrotic syndrome. This is an important clinical distinction because nephrotic-range proteinuria in patients without edema or hypoalbuminemia is more likely to be due to secondary FSGS (e.g., glomerular hyperfiltration, obesity) than primary (idiopathic) FSGS (2–5). It has been said that nephrotic syndrome occurs in only 50%–60% of patients with FSGS, but in my opinion
this is due to failure from past studies to recognize the differences between primary/idiopathic and secondary FSGS. In the view of the discussant, patients with “bona fide” MCD or primary FSGS are very likely to have nephrotic syndrome, while patients with secondary causes of FSGS may have nephrotic range proteinuria but are unlikely to have nephrotic syndrome (2). In my view, this also applies to the diagnosis of FSGS in African-Americans, which I think is a different disease than primary/idiopathic FSGS seen in white persons; because of space constraints I will not discuss this further, but I believe that the inclusion of patients with secondary FSGS in previous studies has given the impression that nephrotic syndrome is less common in FSGS than in MCD (6–9). The fact that the patient discussed here had normal serum albumin, normal cholesterol, and no edema suggests that we are not dealing with a disease that causes widespread podocyte damage and severe proteinuria (e.g., MCD or primary FSGS).

The Role of Renal Biopsy

As noted above, our patient was treated as if he had FSGS when he did not respond as expected to corticosteroids. FSGS is a pattern of glomerular injury defined histologically by the presence of sclerosis in parts (segmental) of some (focal) glomeruli (10). The presence of hyalinosis (entraped plasma proteins) is commonly seen in the sclerotic lesions. Despite the focality of the sclerosis in the early stages, EM examination shows relatively widespread foot process effacement, pointing to the podocyte as a main target of injury (11). With time and progressive loss of podocytes, through either detachment or cell death, more widespread and global glomerulosclerosis develops (1). Thus, both focal segmental and global lesions may be seen as part of the process of disease progression. We now recognize that in addition to “idiopathic” FSGS, many adaptive, infectious, drug-induced, and genetic causes may result in the development of an FSGS lesion. As such, FSGS denotes a histopathologic finding (e.g., a lesion) and not a disease.

Adaptive FSGS is an important form of FSGS thought to result from functional and structural glomerular adaptation to intrarenal vasodilatation, increased plasma flow rates, and glomerular hypertension (12). Glomerular hypertension or hyperfiltration may develop as a result of inherited reduction in the number of healthy nephrons (e.g., unilateral renal agenesis, low birth weight) or hemodynamic stress on an initially normal nephron population (e.g., morbid obesity, unilateral nephrectomy, reflux nephropathy, sickle cell anemia). Viruses can damage the podocyte by directly infecting the cells or indirectly through cytokine toxicity. The best-characterized viral cause of FSGS is HIV-1, which causes HIV-associated nephropathy (13). Similarly, some drugs, such as unpurified heroin, pamidronate, alendronate, interferon, the mammalian target of rapamycin inhibitor sirolimus, and bevacizumab, have been reported as causes of FSGS (14). An increasing number of mutations has been found in genes coding for proteins of the slit diaphragm (nephrin, NPHS2, CD2AP), podocyte membrane (β4-integrin, CD151, PTPRO, TRPC6, laminin β2), cytosol (PLCE1), actin cytoskeleton (formin, myosin IIA, α-actinin-4, MYO1E), lysosomes (SCARB2/LIMP-2), mitochondria (COQ2, tRNA[Leu], COQ6) and cellular nucleus (WT1) (10). In all of these cases, the mutations occur in proteins or enzymes required for podocyte homeostasis, organization of the cytoskeleton, cell-to-cell or cell-to-matrix interactions, or cellular energy (15). Most genetic causes of FSGS follow an autosomal recessive pattern of inheritance and are manifest in the first year of life; mutations in genes for nephrin and podocin are most commonly observed. Autosomal dominant forms (e.g., mutations in α-actinin-4, TPPC6) are more commonly present during adolescence or adulthood (16,17). Adult-onset FSGS is only rarely attributed to a specific mutation (<15% of all adult cases) (16). It is important to emphasize that although a full nephrotic syndrome has been clearly documented among infantile and pediatric cases of FSGS caused by genetic mutations, in the majority of adults with genetic forms of FSGS proteinuria is not massive (usually <5 g/24 hours) (18), and most studies have not documented that these patients actually had true nephrotic syndrome (versus nephrotic-range proteinuria) (19–24).

Considering the multitude of potential mechanisms that may result in the development of a FSGS lesion, it is not surprising that glomerular lesions are diverse (11,25,26). Lesions may differ regarding their anatomic position within the glomerular tuft (e.g., vascular or tubular pole) as well as the presence or absence of glomerular cellularity and capillary collapse. In 2004, an international group of renal pathologists created a working proposal aimed at providing a more precise definition and standardized approach to the morphologic subclassification of FSGS (26). According to this approach, FSGS lesions are classified on light microscopy as not otherwise specified (NOS), perihilar, cellular, tip, and collapsing variant. FSGS NOS is the generic form of FSGS, applicable to a renal biopsy specimen that does not meet specified criteria for any other variant. It is the most common FSGS subtype (27,28). It can occur in association with primary or secondary (including genetic forms) of FSGS and may present with nephrotic syndrome or subnephrotic proteinuria. Collapsing FSGS is most commonly idiopathic or associated with HIV. Perihilar lesions are common in adaptive forms of FSGS. Because of the adaptive origin of the lesion, glomerulomegaly is common, foot process effacement is mild, and patients are more likely to present with sub-nephrotic range proteinuria but without nephrotic syndrome (i.e., normal serum albumin) (10). On the other hand, patients with tip, cellular, or collapsing lesions usually present with nephrotic syndrome (10). Although tip lesion is more common in white patients, is more likely to respond to corticosteroids, and has the best prognosis, patients with collapsing FSGS are predominantly black, respond poorly to corticosteroid therapy, and have the worst prognosis.

Another important difference between these lesions is the degree of foot process effacement on EM examination. Tip, cellular, and collapsing FSGS usually have widespread foot process effacement. In FSGS NOS, foot process effacement is variable and in the perihilar subtype effacement is relatively mild and focal, likely reflecting the heterogeneous adaptive glomerular response (10). As such, cases of primary (or idiopathic) FSGS are more likely to resemble MCD by the absence of immune-type electron-dense deposits and the
presence of widespread foot process effacement, whereas cases of secondary FSGS are more likely to show glomerulomegaly and focal foot process effacement (11,29). Further evidence that idiopathic FSGS is a primary “podocytopathy” is the observation that in recurrent FSGS following kidney transplantation, early biopsy findings resemble those of MCD, with widespread foot process effacement on EM, while with time, repeat biopsies will show evolution to an FSGS lesion, with the recurrent subtype lesion recapitulating the native FSGS subtype in approximately 80% of cases (30). An FSGS lesion may also be seen in cases associated with thin glomerular basement membrane disease, and EM examination is required for detection (16). In the case under discussion, the initial biopsy was unavailable for review and EM had not been performed. Therefore a repeat renal biopsy specimen was obtained.

Repeat Renal Biopsy and Additional Evaluation

The sample consisted of a single piece of renal parenchyma containing up to 21 glomeruli per level of section, 4 of which were globally sclerotic when examined under light microscopy (Figure 1). There was no mesangial expansion or capillary wall deposits, spikes, spicules, or double contouring. A few glomeruli were borderline enlarged. No segmental scarring was seen, and cellularity was normal. Thus, the glomerular findings were of focal global glomerulosclerosis rather than FSGS. There was patchy fibrosis involving 5%-10% of the cortical area. A sparse mononuclear cell infiltrate was noted focally without tubulitis, and there were a few discrete interstitial calcifications. The crystals stained purple on H&E, appeared black on von Kossa stain, and did not polarize under dark field light, consistent with calcium phosphate crystals (Figure 2). Protein resorption granules were present in the tubular epithelial cell cytoplasm, but there were no interstitial foam cells. On immunofluorescence, nonspecific trace mesangial staining was seen with IgM. There was patchy 1+ C3 granular tubular basement membrane staining without glomerular staining. There was no staining for IgA, IgG, C1q, fibrinogen, or κ or λ light chains. No deposits were seen on EM, and the glomerular basement membranes showed no ultrastructural abnormalities. Specifically, no significant thinning or lamellations were seen. In addition, negligible (<5%) foot process effacement was present, and there was no evidence of dysmorphic mitochondria or intracellular crystals.

Review of a 24-hour urine collection showed a urinary volume of nearly 3 L with 2.3 g of protein but only 193 mg of albumin. This suggests that proteins other than albumin accounted for the vast majority of the protein. The urine was then evaluated for low-molecular-weight (LMW) proteins revealing retinol-binding protein excretion of 212,573 μg/24 hour (normal <163 μg) and α1 microglobulin excretion of 656 mg/24 hour (normal <19 mg). Urinary sodium, calcium, and uric acid excretions were 203 mmol/24 hour (normal, 41–227 mmol), 163 mg/24 hours (normal, 25–300 mg), and 668 mg/24 hours (normal <750 mg), respectively. The 24-hour urinary amino acid profile was normal.

Differential Diagnosis

The absence of nephrotic syndrome (serum albumin at the time of initial biopsy was 3.82 g/dl) and significant foot process effacement argues against the diagnosis of MCD or idiopathic FSGS, both of which were excluded by the repeat kidney biopsy. In fact, the presence of a normal serum albumin should have alerted the physicians that they were not dealing with MCD or idiopathic FSGS. Thus, we should consider clinical conditions, either acquired or inherited, that can be associated with focal global glomerulosclerosis and impaired proximal tubular function manifested by LMW proteinuria. LMW proteinuria may be associated with Fanconi syndrome (glucosuria, aminoaciduria, phosphaturia, uricosuria), which can occur with acquired (immunoglobulin light chain toxicity, heavy metal toxicity, aristolochic acid nephropathy, Sjögren syndrome, some...
antiviral agents, and acute tubulointerstitial nephritis with uveitis) or inherited (cystinosis, mitochondrialopathies) Fanconi syndrome. Our patient did not have Fanconi syndrome, however. On the other hand, the history of hypercalciuria together with a few tubulointerstitial calcium phosphate crystals and high LMW proteinuria raises suspicion for Dent disease. Genetic analysis was performed and a novel frame-shifting mutation (c.92delA, p.Val31fs15) of the CLCN5 gene was identified, confirming the diagnosis of Dent disease.

**Dent Disease**

Dent disease is a rare X-linked recessive renal tubular disorder that affects male patients in childhood or early adult life. It is clinically characterized by the presence of LMW proteinuria, hypercalciuria, medullary nephrocalcinosis, nephrolithiasis, and progressive renal failure (31,32). Other proximal tubular dysfunction may include aminoaciduria, glycosuria, phosphaturia, and sodium and potassium wasting, but complete Fanconi syndrome and metabolic acidosis are typically not present (33). Additional complications may include rickets or osteomalacia (34). Female carriers often show milder degrees of LMW proteinuria than male carriers but may develop hypercalcioria and nephrolithiasis depending on X-chromosome inactivation (33). In most affected male patients, proteinuria is subnephrotic but may reach nephrotic levels (31,35,36). As in the present patient, albumin contributes to less than half of the proteinuria and patients do not develop a full-blown nephrotic syndrome. LMW proteinuria characterized by the excretion of proteins, such as α-1 and β-2 microglobulins and retinol-binding protein, is present in >98% of affected male patients; occurs early in the course of the disease; and thus is a valuable diagnostic test. Mild hypercalcioria is common in adults (4–6 mg/kg body weight per day), but calciuria as high as 10 mg/kg body weight per day can be seen in children (37). Nephrocalcinosis is found in 40%–70% of male patients and can present as early as late childhood or young adulthood, but it is very unusual in female carriers. Early signs of nephrocalcinosis may be reflected by the presence of hyperch remodeling in the pyramids on renal ultrasonography and may be a clue to the diagnosis in a patient without evidence of nephrolithiasis. Considering that the disease is X-linked, it is important to review the family history of renal calculi in otherwise unaffected mothers and apparently normal brothers.

Renal biopsy findings in patients with Dent disease are nonspecific. Renal histology can be normal or show lesions of FSGS, focal segmental and global glomerulosclerosis, or pure global glomerulosclerosis, with some degree of tubular atrophy and interstitial fibrosis (31,35,36,38–41). As in the present case, medullary nephrocalcinosis may be seen. By contrast, EM examination typically shows no glomerular or tubular abnormalities (37,40).

The disease is caused by mutations in the CLCN5 (Dent disease 1) or OCRL1 (Dent disease 2) genes localized on chromosome Xp11.22 and Xq25, respectively (42). The CLCN5 gene codes for CLC-5, a voltage-dependent, electrogenic Cl⁻/H⁺ exchanger primarily located in the endosomes of the proximal tubular cells with lower expression in the thick ascending limb of Henle and the α-type intercalated cells of the collecting ducts (43). Mutations in the CLCN5 gene can account for the phenotypically distinct X-linked recessive nephrolithiasis, X-linked recessive hypophosphatemic rickets, or familial idiopathic LMW proteinuria (44,45). These diseases are now unified as Dent disease.

More than 140 distinct CLCN5 mutations have been reported in patients with Dent 1 disease. Approximately 36% are nonsense mutations, 33% are missense mutations, and 19% are frameshift mutation; splice-site mutations, insertional mutations, and deletions account for the remaining 12%, all of which result in total or near-total loss of function (42). No correlation has been found between genotype and the Dent disease phenotype, and there is considerable intra-familial variability (46).
Pathophysiology of Dent Disease

Adequate acidification of endosomes is important for endosomal recycling and protein degradation. Accordingly, it has been proposed that as a vesicular Cl⁻/H⁺ exchanger, CLC-5 allows maximal acidification of the endosome by providing an electrical shunt that dissipates the positive charge created by the H⁺-ATPase pump (47). Indeed, experimental data show that CLCN5 mutations lead to a loss of Cl⁻ conductance (45). However, the precise pathophysiological mechanism is unclear. CIC-5 is a 2Cl⁻/H⁺ exchanger, not a Cl⁻ channel, and the relevance of the exchange activity in the pathophysiological process is unknown. Knockin mice harboring a mutation that maintains normal endosomal acidification showed the same phenotype as CIC-5 knockout mice and patients with Dent disease, including LMW proteinuria, hypercalcemia, and hyperphosphatemia (48). Furthermore, both knockin and knockout mice develop impaired cellular endocytosis, indicating that in Dent disease dysfunction of proximal tubular cells can occur despite normal endosomal acidification. Inactivation of CIC-5 is also associated with severe intracellular trafficking defect, with loss of megalin and cubulin at the brush border of proximal tubular cells (49), and impaired lysosomal biogenesis and processing, which contribute to defective endocytosis and urinary loss of LMW ligands and lysosomal enzymes (50). Some patients with Dent disease have proximal tubule cells with inverted H⁺-ATPase polarity and redistribution to the basolateral regions, further evidence that CIC-5 plays an important role in intracellular traffic (40). A recent study in a mammalian expression system suggests that endoplasmic reticulum retention and degradation of CIC-5, defective endosomal acidification, or altered endosomal distribution of CIC-5 without defective endosomal acidification may play a role in the disease (51). As a result, LMW proteins that are freely filtered by the glomerulus cannot be reabsorbed by the proximal tubular cells. The role of CIC-5 mutations in the thick ascending loop of Henle and in intercalated cells remains to be defined.

It is also unclear why CLCN5 mutations cause hypercalciuria, nephrocalcinosis, and other tubular abnormalities. It has been proposed that hypercalciuria, which is considered a major risk factor for nephrocalcinosis and nephrolithiasis, may be secondary to urinary loss of parathyroid hormone, vitamin D-binding protein, and reduced phosphate absorption, leading to increased 1,25(OH)₂-vitamin D₃ synthesis (42). The resulting increase in 1,25(OH)₂-vitamin D₃ levels would promote intestinal absorption of calcium. However, although some CLCN5 knockout models have been described with hypercalciuria (52), others have neither hypercalciuria nor nephrocalcinosis (48). In addition, 30% of patients with Dent disease have nephrocalcinosis without hypercalciuria (53). It has been suggested that cells lacking CIC-5 may be unable to internalize calcium crystals adhering to the apical cell surface (54).

Patients with Dent 2 disease have a clinical phenotype similar to that of patients with Dent 1 disease and make up approximately 16% of cases of Dent disease. It is caused by mutations in the OCRL1 gene, which is responsible for the oculo-cerebro-renal syndrome of Lowe, a multisystem disease characterized by Fanconi syndrome, progressive renal insufficiency, congenital cataracts, and mental retardation (55). However, patients with Dent 2 disease do not have severe cataracts or the intellectual deficits typically found in Lowe syndrome, probably because the OCRL1 mutations associated with Dent disease 2 do not overlap with those causing Lowe syndrome. OCRL1 encodes a 105-kD Golgi protein with phosphatidylinositol bisphosphate 5-phosphatase activity important in lysosomal trafficking and endocytosis in proximal tubular cells. Thus, mutations in this protein may result in abnormalities similar to those observed in Dent 1 disease. Approximately 20%–30% of patients with Dent disease do not have mutations in CLCN5 or OCRL1, suggesting that other gene(s) may be involved. Thus, inability to find a mutation in CLCN5 or OCRL1 genes does not rule out Dent disease in a patient with clinical phenotype.

Why Do Patients with Dent Disease Develop Glomerulosclerosis and Renal Failure?

The exact mechanism underlying the development of glomerulosclerosis and renal failure in patients with Dent disease is unknown. Significant loss of glomerular filtration rate may start in childhood, with 30%–80% of affected male patients reaching ESRD between the third and the fifth decades of life (32,33). The presence of nephrocalcinosis does not correlate with the development or degree of renal insufficiency (37). Until recently, CIC-5 was considered not to be expressed in glomeruli (56). However, a recent study demonstrated that CIC-5 is expressed in human podocytes, and CIC-5 is overexpressed in proteinuric states (57). It has been hypothesized that the excessive load of LMW proteinuria to the distal nephron may trigger the production of fibrogenic cytokines (e.g., TGF-β) that through a paracrine effect may induce the development of FSGS (36). A second mechanism may involve the triggering of the intrarenal renin-angiotensin system due to the increased electrolytes and water wasting invoking a perpetual prerenal state. Interestingly, cases of FSGS in patients with Gitelman syndrome (58) and Bartter syndrome (59) have been described. Thus, it is possible that in Dent disease FSGS is a secondary phenomenon. However, the degree of glomerulosclerosis and minimal tubular atrophy and interstitial fibrosis seen in this case make it difficult to account for the serum creatinine of 2.2 mg/dl. It could be speculated that in diseases characterized by tubular interstitial injury, functional tubular abnormalities (e.g., creatinine secretion) may in fact be more profound despite “normal” findings on light microscopy. In addition, the cortical renal biopsy sample may not reflect the actual damage going on at deeper levels in the parenchyma. Nephrocalcinosis alone cannot explain the progressive decline in renal function in Dent disease (24).

Treatment

Treatment is supportive and focuses on the prevention of nephrolithiasis. Thiazide diuretics have been shown to correct hypercalciuria in patients with Dent disease (60,61). However, the long-term benefit has not been established, and care should be taken to avoid hypovolemia and hypokalemia. Treatment of rickets with vitamin D also requires close monitoring because it may increase
hypercalciuria. Studies in CIC-5 knockout mice suggest that a high citrate diet helps to control the hypercalciuria and delays renal disease progression even in the absence of stone formation (62). Therefore, treatment with a citrate buffer can be attempted.

The current patient was treated with a thiazide diuretic, which resulted in normalization of the calciuria (24-hour calciuria with therapy, 169 mg). An angiotensin-converting enzyme inhibitor was also prescribed, but the patient could not tolerate it because of symptomatic hypotension. However, there is no evidence that inhibition of angiotensin II is of benefit in Dent disease, even in the presence of marked LMW proteinuria.

Final Comments
Glomerular sclerosis can be focal or global in nature; they are both histopathologic lesions that are etiologically diverse. As such, finding these lesions on a kidney biopsy specimen represents only the beginning of the diagnostic process. Establishing the correct etiologic diagnosis avoids unnecessary and potentially harmful treatments, such as immunosuppressive agents. This is especially true in patients whose initial biopsy samples lack significant glomerular pathology, and failure to respond to corticosteroids leads to the assumption that we are dealing with “unsampled” FSGS. Secondary FSGS should be considered in all patients with proteinuria, including nephrotic-range proteinuria, who do not have hypoalbuminemia and edema (i.e., nephrotic syndrome) when renal biopsy shows only segmental foot process effacement. In cases of secondary FSGS, the relative preservation of the foot process contrasts with the findings in a primary podocytopathy, such as MCD or primary FSGS, even in patients with nephrotic-range proteinuria. In patients found to have FSGS or focal global glomerulosclerosis, it is also important to verify the identity of the urinary proteins. To start, a simple urinary protein-to-creatinine ratio can be compared with a urinary albumin-to-creatinine ratio. If <50% of total proteinuria is due to albumin, then the possibility of tubular proteinuria or presence of light chains should be considered. Because dipsticks largely detect albumin, a dipstick proteinuria of trace/1+ in a patient with a quantified urinary protein >1 g/24 hours is also a clue that proteins other than albumin account for the proteinuria. If a male patient has proteinuria composed largely of LMW protein and has a renal biopsy showing focal global glomerulosclerosis, the diagnosis of Dent disease should be strongly considered. The presence of hypercalciuria, nephrocalcinosis, and/or kidney stones, as well as a family history of nephrolithiasis and renal failure, further supports the diagnosis. Genetic testing can confirm the diagnosis. In patients with Dent disease due to mutation in the OCR1L gene, absence of clinical cataracts and/or severe intellectual impairment are key features in differentiating patients with Dent 2 disease from those with Lowe syndrome.

Questions
Jeffrey Berns, MD (Renal, Electrolyte, and Hypertension Division, University of Pennsylvania, Philadelphia): In CIC-5 knockout mice models, proximal tubule cell expression of the Na+/H+ exchanger is reduced. Is it known whether this occurs in humans? Are there urinary acidification abnormalities in Dent disease in the absence of other manifestations of Fanconi syndrome?

Reply
This is an interesting question. In the mouse, disruption of the CIC-5 gene results in displacement not only of the Na+/H+ exchanger, NHE3, but also of the Na+/phosphate co-transporter, NaPi-2a, from the plasma membrane to intracellular vesicles (63), but I am not aware of data in humans. On the other hand, a study on renal biopsy specimens from patients with Dent disease demonstrated a consistent inversion of H-ATPase polarity in proximal tubule cells to a basolateral distribution (40), suggesting that in humans loss of a functional CIC-5 is reflected by an inverted polarity of H-ATPase at the cellular level. However, in knockout mice lacking CIC-5, the distribution and polarity of H-ATPase are apparently unaltered (52). Regarding urinary acidification abnormalities, Wrong and colleagues administered oral ammonium chloride to 14 patients with Dent disease (32). Seven of these patients, all male, had urinary acidification defects, although none had systemic acidosis at baseline. All had aminoaciduria, but glucosuria was documented in only half. The patient with the most severe urinary acidification defect had aminoaciduria but no glucosuria. As opposed to another cause of nephrocalcinosis and hypercalciuria (i.e., distal renal tubular acidosis), in Dent disease the urinary acidification defect does not result in systemic acidosis.

John C. Lieske, MD (Division of Nephrology and Hypertension, Rare Kidney Stone Consortium, Mayo Clinic, Rochester): What is the frequency of glomerulosclerosis in Dent disease?

Reply
Until recently, Dent disease was felt to be largely, if not entirely, a disease of the tubules. However, an Israeli cohort of patients from three families has been described with nephrotic range proteinuria and focal global glomerulosclerosis on biopsy and documented CLCN5 mutations (35). A second cohort in the United States was reported about the same time that also presented with unexplained proteinuria and focal global glomerulosclerosis on biopsy, before the diagnosis of Dent disease was eventually considered and confirmed (39). Indeed, early Dent disease case series did document glomerulosclerosis on a subset of available biopsy specimens (32). Recent studies have documented a key role for CIC-5 during endocytosis, unique among chloride channels (64,65). In addition, podocyte expression of CIC-5 has now been documented, and this expression is increased in proteinuria disease, including diabetic and IgA nephropathy (57). It was suggested that CIC-5 may be important for albumin reabsorption. Thus, it is tempting to speculate a link between CLCN5 mutations, subtle alterations in podocyte function, and eventual global sclerosis as a factor that contributes to CKD among patients with Dent disease. However, the prevalence of focal global glomerulosclerosis among patients with Dent disease, and its relative importance in disease progression, remains to be determined.
References


Published online ahead of print. Publication date available at www.cjasn.org.