Fanconi or not Fanconi? Lowe Syndrome Revisited

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Renal Fanconi syndromes are both clinically challenging and physiologically fascinating. The diagnosis requires a certain index of suspicion to correctly identify the clinical symptomatology and pursue the appropriate laboratory evaluations. With regard to the pathophysiology, the renal proximal tubule is the site of action. Through a complex and coordinated machinery of luminal and basolateral transport proteins, the proximal tubule has established a monopoly for reclaiming amino acids, phosphate, and glucose. The reabsorption of proteins also occurs only in the proximal tubule, but the issue of how much protein, e.g., albumin, is normally reabsorbed remains contentious (1,2).

Over the years, many but not all of the pieces of this puzzle have been assembled. Recent studies have defined the molecular identity of most luminal transporters involved in glucose, amino acid, and phosphate transport. In contrast, the characterization of molecular contributors to basolateral transport mechanisms remains limited.

Perhaps because of the complexity of renal proximal tubular physiology, many aspects are not yet understood. Studies of single-gene disorders should help elucidate the pathophysiology. There are at least two different forms of primary renal Fanconi syndrome in humans. Both are transmitted as autosomal dominant traits. Luder-Sheldon syndrome (OMIM *134600), associated with progression to end-stage renal disease, has been linked to chromosome 15 (3). The second disorder, not associated with loss of renal function, has yet to be mapped (4). Thus, elucidation of the molecular pathogenesis involved in primary proximal tubular damage must await identification of these disease-causing genes.

In comparison, secondary forms of renal Fanconi syndrome have long been appreciated. Drugs, monogenic diseases, and systemic disorders can all contribute to this phenotype. The most common single-gene disorder causing renal Fanconi syndrome in childhood is cystinosis. If recognized and treated early, kidney involvement (glomerular as well as tubular) can significantly be attenuated (5). The most common cause of renal Fanconi syndrome in adulthood may now be related to the therapies targeted to HIV infection.

So, what is renal Fanconi syndrome? When Debré, de Toni, and Fanconi described children with a special form of rickets in the 1930s, they and others demonstrated that all of these children had generalized aminoaciduria without elevation of plasma amino acids, glucosuria without hyperglycemia, phosphaturia without hyperphosphatemia, metabolic acidosis resulting from renal bicarbonate loss, and low molecular weight proteinuria without any evidence for respective elevations of plasma proteins (6–12). In short, the disorder represented a generalized proximal tubular leak. With time, this set of manifestations was accepted as the “renal Fanconi syndrome” and defined by renal losses of all substrates transported across the proximal tubular epithelia. If a patient does not manifest all of these features, then the patient does not have renal Fanconi syndrome. There are no “incomplete” nor “not full blown” renal Fanconi syndrome phenotypes.

In this issue of CJASN, Bockenhauer et al. revisit the renal phenotype of a rare disorder studied more than 50 yr ago (13). Lowe first described the oculocerebrorenal syndrome in 1952 (14). Subsequently, his name was ascribed as an eponym for this disorder, the Lowe syndrome. Although Lowe did not find evidence for renal Fanconi syndrome, with time, others began to describe Lowe syndrome as one of the causes of renal Fanconi syndrome. Bockenhauer et al. (13) have now carefully characterized the renal phenotype of 16 patients (14 of whom had molecular studies done) with Lowe syndrome. Quite surprisingly, they noted that none of them had glycosuria, even when study conditions were modified to account for polyuria. Also, the majority of their patients did not have appreciable phosphaturia or rickets. Thus, it is fair to say that patients with Lowe syndrome do not have renal Fanconi syndrome.

This “new” finding is quite important for several reasons. First, treatment of renal Fanconi syndrome is different from treatment for hypercalciuria and nephrolithiasis. Second, patients and their parents assigned a misleading diagnosis. Third, from a scientific perspective, this phenotypic clarification impacts current thinking about renal tubular pathophysiology in Lowe syndrome. According to Bockenhauer et al., Lowe syndrome, like Dent disease, affects pathways involved in protein, calcium and amino acid reabsorption rather than the yet to be defined global transport defect evidenced in renal Fanconi syndromes.

Appreciating these renal tubular differences will ultimately guide a clearer understanding about transport physiology, particularly in the proximal tubule. This report thus demonstrates that careful delineation of the clinical phenotype is the critical
entry point for deciphering the underlying pathophysiology in tubular transport disorders.

Disclosures
None.

References