World Journal of Pediatrics (2023) 19:619–634
https://doi.org/10.1007/s12519-023-00685-y

REVIEW ARTICLE

Inherited Fanconi syndrome

Anna Luiza Braga Albuquerque[1] · Rafael dos Santos Borges[1] · Ana Flávia Conegundes[1] · Erika Emmylaine dos Santos[1] · Frederico Moreira Man Fu[1] · Clara Tavares Araujo[1] · Pedro Alves Soares Vaz de Castro[1] · Ana Cristina Simões e Silva[1,2]

Received: 4 October 2022 / Accepted: 8 January 2023 / Published online: 2 February 2023

Abstract

Background Fanconi-Debré-de Toni syndrome (also known as Fanconi renotubular syndrome, or FRST) profoundly increased the understanding of the functions of the proximal convoluted tubule (PCT) and provided important insights into the pathophysiology of several kidney diseases and drug toxicities.

Data sources We searched Pubmed and Scopus databases to find relevant articles about FRST. This review article focuses on the physiology of the PCT, as well as on the physiopathology of FRST in children, its diagnosis, and treatment.

Results FRST encompasses a wide variety of inherited and acquired PCT alterations that lead to impairment of PCT reabsorption. In children, FRST often presents as a secondary feature of systemic disorders that impair energy supply, such as Lowe's syndrome, Dent's disease, cystinosis, hereditary fructose intolerance, galactosemia, tyrosinemia, Alport syndrome, and Wilson's disease. Although rare, congenital causes of FRST greatly impact the morbidity and mortality of patients and impose diagnostic challenges. Furthermore, its treatment is diverse and considers the ability of the clinician to identify the correct etiology of the disease.

Conclusion The early diagnosis and treatment of pediatric patients with FRST improve the prognosis and the quality of life.

Keywords Cystinosis · Fanconi syndrome · Fanconi renotubular syndrome · Fanconi-Debrè-de Toni syndrome · Proximal tubule · Renal tubular transport · Rickets

Introduction

A 3-month-old girl presented with rickets, glycosuria, albuminuria, and recurrent fevers, progressing to end-stage kidney disease (ESKD) at the age of 5 years and passing away shortly after. At autopsy, cystine crystals filled the renal tubule cells. This was Guido Fanconi's first case in 1931 of a rare condition marked by a general defect in renal proximal tubule reabsorption [1], further described by de Toni [2] and Debré [3]. Although rare, Fanconi-Debré-de Toni syndrome (more commonly known as Fanconi renotubular syndrome, or FRST) profoundly increased the understanding of the functions of proximal tubular cells (PTCs) and provided important insights into the pathophysiology of several kidney diseases and drug toxicities.

Despite Fanconi's findings in the twentieth century, it is currently known that FRST encompasses a wide variety of inherited and acquired proximal convoluted tubule (PCT) alterations that lead to impairment of PCT reabsorption [4]. The true incidence of FRST is unknown, and only a handful of studies have examined the epidemiology of its congenital causes. While acquired and exogenous causes can be seen in any age group depending on the underlying cause and/or drug exposure, some inherited causes affect mostly boys due to X-linked inheritance [5]. Some specific causes of inherited FRST have a higher incidence in Caucasians, such as cystinosis, caused by mutations in the *CTNS* gene (> 70% in Caucasians) [6]. Nevertheless, diagnostic challenges, especially in resource-limited settings [7], may lead to a lack of essential data to identify the true epidemiology of these conditions.

✉ Ana Cristina Simões e Silva
acssilva@hotmail.com

[1] Interdisciplinary Laboratory of Medical Investigation, Unit of Pediatric Nephrology, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil

[2] Department of Pediatrics, Faculty of Medicine, UFMG, Alfredo Balena Avenue, 190, 2Nd Floor, Room # 281, Belo Horizonte, MG 30130-100, Brazil

As congenital causes of FRST greatly impact the morbidity and mortality of patients and impose diagnostic challenges, this review sought to explore the pathophysiology, etiology, diagnosis, and treatment of this important syndrome, mainly focusing on inherited causes of the disease.

Transport mechanisms in the proximal convoluted tubule

The PCT is the major resorptive segment of the nephron and is responsible for the reabsorption of sodium, chloride, water, bicarbonate, phosphate, glucose, amino acids, lactate, citrate, low-molecular-weight (LMW) proteins, and several other substances. The PCT contains a wide brush border with a high concentration of microvilli that increase the surface area for transport mechanisms. Hence, this segment is accountable for nearly 65% of the filtered load and a key element in the regulation of homeostasis [8]. In this section, we briefly overview the main transport mechanisms along the PCT by dividing them into transporters found in the initial and terminal regions of this nephron segment. All transporters described here are represented in Fig. 1.

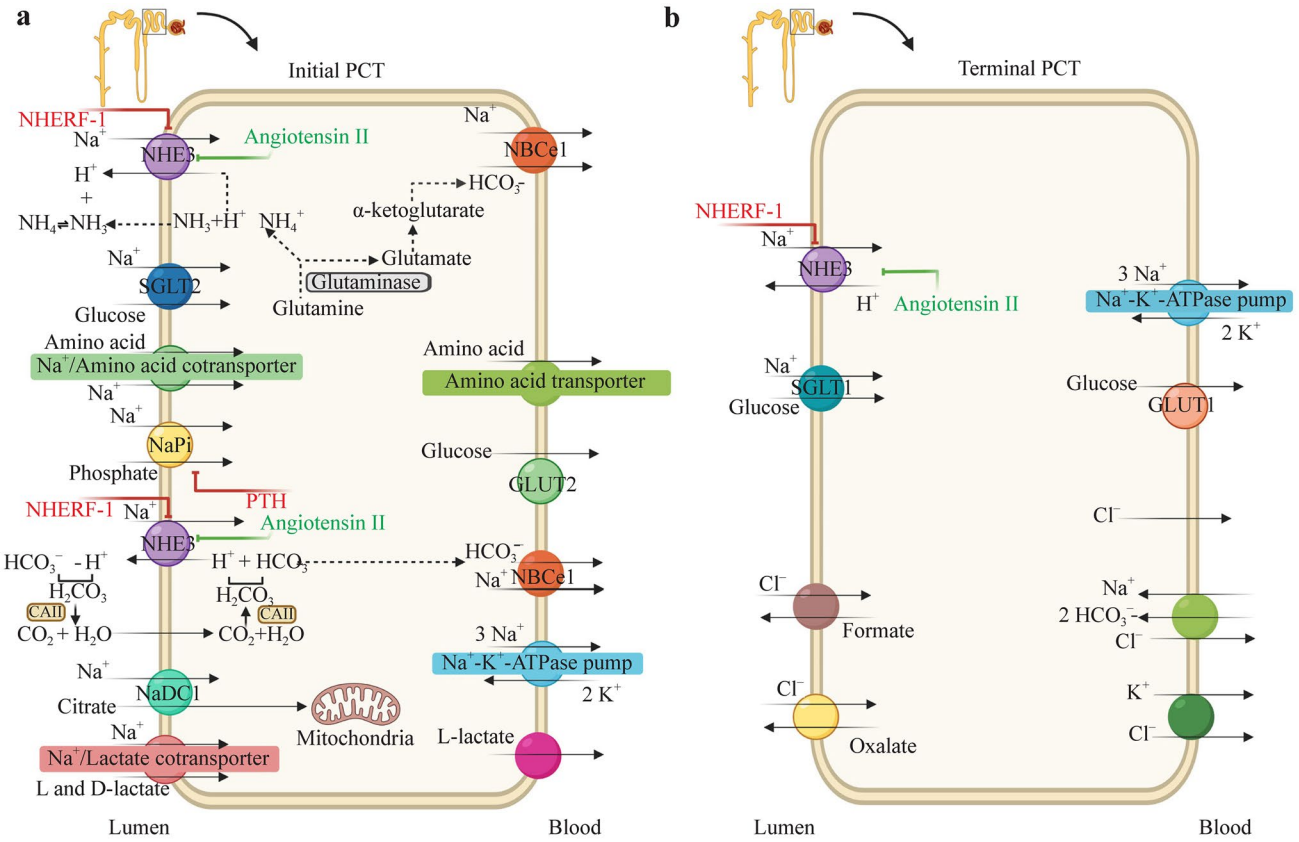

Fig. 1 Transport mechanisms along the proximal convoluted tubule (PCT). Na^+–K^+-ATPase activates the extrusion of Na^+ from the PCT into the bloodstream, generating an electrochemical gradient for passive entry of Na^+ via several antiporters and cotransporters. **a** In the cytosol, CAII catalyzes the intracellular conversion of CO_2 and H_2O into H_2CO_3, which dissociates into H^+ and HCO_3^-. H^+ is secreted into the PCT lumen in exchange for Na^+ via NHE3, which is downregulated by NHERF-1 and upregulated by AII. HCO_3^- returns along with Na^+ to the blood via NBCe1. Glucose is reabsorbed with Na^+ via SGLT2 and returns to the blood through GLUT2. Amino acids and Na^+ are reabsorbed via Na^+/amino acid cotransporters and enter the blood via Na^+-independent transporters. Phosphate is reabsorbed via NaPi. Lactate isoforms are absorbed with Na^+ via Na^+/lactate cotransporters and enter the bloodstream via sodium-independent transporters. Citrate is reabsorbed via NaDC-1 and is transported to the mitochondria. In the cytosol, NH_3 is formed by glutaminase. Glutamine is converted into equimolar amounts of NH_4^+ and HCO_3^-. NH_4^+ dissociates into NH_3 and H^+. NH_3 is secreted via simple diffusion, and H^+ is exchanged with Na^+ via NHE3; generated HCO_3^- passes along with Na^+ to the blood via NBCe1. **b** Glucose and Na^+ are reabsorbed via SGLT1 and return to the blood via GLUT1. Cl^- can be reabsorbed through NHE3-dependent Cl^-/oxalate and Cl^-/formate exchangers; Cl^- enters the blood via simple diffusion, K^+–Cl^- cotransport, or Na^+-$2HCO_3^-$/Cl^- exchange. *PCT* proximal convoluted tubule, *CA II* carbonic anhydrase, *NHE3* Na^+–H^+ antiporter/exchanger, *NHERF-1* Na^+–H^+ exchanger regulatory factor-1, *AII* angiotensin II, *NBCe1* Na^+/HCO_3^- cotransporter, *SGLT2* Na^+/glucose cotransporter 2, *GLUT2* glucose transporter 2, *NaPi* Na^+/phosphate cotransporter, *NaDC-1* Na^+/dicarboxylate cotransporter 1, *GLUT1* glucose transporter 1, *NHE3* Na^+–H^+ antiporter/exchanger

Importance of basolateral Na^+–K^+-ATPase pump

The Na^+–K^+-ATPase pump is located in the basolateral membrane of both the initial and terminal PCT [9]. The Na^+–K^+-ATPase pump involves a 3:2 stoichiometric ratio, essential for active extrusion of Na^+ from PCT cells into peritubular interstitial fluid and eventually into the bloodstream. This enzyme activity contributes to generating an electrochemical gradient that facilitates passive entry of Na^+ into PCT cells through several sodium antiporters and cotransporters placed in the apical membrane. Due to this process, the H_2O molecule is also easily reabsorbed under an isosmotic fashion [8, 10].

Apical Na^+–H^+ antiporter/exchanger (NHE)

The Na^+–H^+ antiporter/exchanger genetic family comprises nine genes, but only the NHE3 transporter is found in the apical membrane of both initial and terminal PCT cells [11, 12]. This antiporter functions in a 1:1 stoichiometric ratio, promoting Na^+ entry and H^+ exit, a process linked to the reabsorption of filtered HCO_3^- [11]. Numerous regulatory mechanisms act on this exchanger: Na^+–H^+ exchanger regulatory factor-1 (NHERF-1) phosphorylates and eventually downregulates NHE3 activity via the cAMP second messenger pathway [13]. On the other hand, angiotensin II upregulates NHE3 activity via various mechanisms, including protein kinase C [14], inositol 1,4,5-triphosphate (IP_3) receptor binding protein released with IP_3 (IRBIT) [15], Ca^{2+}/calmodulin-dependent protein kinase II [15], or oxidative stress [16].

Apical Na^+/glucose cotransporter

Although the Na^+/glucose cotransporter genetic family comprises six genes, only two of them are expressed in the apical membrane of renal PCT cells: *SGLT2* and *SGLT1* [17]. *SGLT2* is responsible for the reabsorption of 90% of the filtered glucose, whereas *SGLT1* accomplishes the reabsorption of the remaining 10% [17]. Through those cotransporters, Na^+ and glucose are reabsorbed in a 1:1 stoichiometric ratio [18]. The passage of glucose to the interstitial peritubular fluid and ultimately to the blood involves basolateral GLUT1 and GLUT2, which are Na^+-independent transporters [17].

Basolateral Na^+/HCO_3^- cotransporters

PCT is responsible for the reabsorption of nearly 80% of filtered HCO_3^-, which is an important mechanism for acid–base homeostasis [19]. Carbonic anhydrase II (CAII) is essential for this process since the enzyme catalyzes intracellular conversion of CO_2 and H_2O into H_2CO_3, which, in turn, dissociates into H^+ and HCO_3^- [20]. Then H^+ is secreted into the PCT lumen in exchange for Na^+ via apical NHE3, as previously described [11]. Finally, cytosolic HCO_3^- passes, along with Na^+, to the peritubular interstitial fluid and ultimately the blood mainly via basolateral Na^+/HCO_3^- cotransporter NBCe1 [19].

Apical Na^+/amino acid cotransporters and basolateral amino acid transporters

The vast majority of the filtered amino acids are reabsorbed in the initial PCT. This process involves the passage of amino acids from the tubular lumen into initial PCT cells via apical Na^+/amino acid cotransporters driven by an electrochemical gradient (from the tubular lumen to the cell) established by the basolateral Na^+–K^+-ATPase pump [21]. Multiple cotransport systems have been described, including the neutral system (or methionine-preferring system), the basic system, the acidic system, the iminoglycine system, and the β-amino acid system [22], but their description is beyond the scope of this paper. Once inside the PCT cell, amino acids make their way to the blood probably via facilitated diffusion using Na^+-independent transporters in the basolateral membrane [21].

Apical Na^+/phosphate cotransporter

Approximately 80–90% of filtered phosphate is reabsorbed in initial PCT [23]. Of the three families of Na^+/phosphate cotransporters (NaPi), PCT cells express proteins of family II, primarily NaPi-IIa but also NaPi-IIc [24]. Both cotransporters prefer divalent Pi ($HPO4^{2-}$), and the driving force reabsorption, as previously mentioned, requires a transmembrane Na^+ electrochemical gradient maintained by the basolateral Na^+–K^+-ATPase pump [25]. Regarding regulation, studies suggest that parathyroid hormone decreases the number of apical NaPi-lla within minutes and decreases the number of apical NaPi-llc within hours, increasing phosphate excretion [26]. Despite its apparent importance, the current understanding of Pi basolateral transporters is scarce.

Apical Na^+/lactate cotransporter

Encoded by the *SLC5A8* gene, the apical Na^+/lactate cotransporter is responsible for the reabsorption of both L- and D-lactate isoforms [27]. This process is carried out using the transmembrane Na^+ electrochemical gradient maintained by the basolateral Na^+–K^+-ATPase pump [27]. Once inside the PCT cell, lactate passes to the interstitium and finally to the blood through facilitated diffusion via basolateral sodium-independent carriers, which have a pronounced preference for the L-lactate isomer [27].

Apical Na^+/dicarboxylate cotransporter 1 (NaDC-1)

Encoded by *SLC13A2*, apical Na^+/dicarboxylate cotransporter 1 (NaDC-1) is responsible for the reabsorption of metabolic intermediates of the citric acid cycle, such as citrate [28]. This symport system is driven by a transmembrane Na^+ electrochemical gradient maintained by the basolateral Na^+–K^+-ATPase pump. Thus, this cotransporter can be characterized as facilitated, secondarily active transport, as exemplified previously [28, 29]. The dicarboxylate form is thought to be the only form transported by NaDC-1. Therefore, urine molecules of H^+ play an important role in citrate reabsorption since H^+ oxidizes citrate to the dicarboxylated form. Once inside the PCT cell, the dicarboxylated citrate can be metabolized inside the mitochondria as part of the citric acid cycle [28]. Finally, citrate also enters PCT cells from the interstitium, crossing the basolateral membrane, but few studies have addressed these transport mechanisms, and they have not yet been fully defined.

NH_3/NH_4^+ buffer system

The initial PCT is a key nephron segment for NH_4^+ production and secretion, which is essential for establishing the major buffering system that allows acid excretion in the kidneys. Ammonia genesis occurs primarily in the mitochondria by the enzyme glutaminase. In this process, glutamine is ultimately converted into equimolar amounts of NH_4^+ and HCO_3^-. HCO_3^- is reabsorbed via basolateral NBCe1, as previously described, and NH_4^+ may preferentially follow the three following pathways for apical secretion [30].

Apical Na^+/H^+ exchanger (NHE3)

The apical Na^+/H^+ exchange by NHE3 may undergo substitution of NH_4^+ for H^+ at the cytosolic H^+ binding site, resulting in Na^+/NH_4^+ exchange activity, which is likely the main mechanism for NH_4^+ secretion into the PCT lumen. The cytosolic NH_4^+ competes with H^+ on the intracellular NHE3 binding site, and a high intracellular NH_4^+ concentration from increased ammonia genesis (as seen in metabolic acidosis) combined with low intracellular Na^+ concentration favors Na^+/NH_4^+ exchange. Moreover, metabolic acidosis is also characterized by increased NHE3 expression, which further increases NH_4^+ secretion and ultimately acid excretion [30]. Intracellular NH_4^+ is thought to be conducted into the PCT lumen mediated by apical potassium channels, although how this mechanism exactly works is not yet currently understood [30].

Apical NH_3 transport

Intracellular NH_4^+ may dissociate into NH_3 and H^+. NH_3 can be secreted likely via simple diffusion, whereas the acid may be exchanged with Na^+ via apical NHE3 [30]. Nearly all filtered glucose, amino acids, and HCO_3^- have already been completely reabsorbed in the early PCT. Some NaCl (mainly Cl^-) is reabsorbed in terminal PCT: Na^+ via NHE3 and Cl^- via Cl^-/formate and Cl^-/oxalate exchangers. Some paracellular reabsorption of NaCl also takes place in this nephron segment. These processes contribute to the reabsorption of approximately 50%–70% of the filtered Cl^- [31].

Apical Cl^-/formate exchanger

Intracellular formic acid dissociates into H^+ and formate. This anion can be exchanged with Cl^- in the apical membrane. To maintain this mechanism, formic acid needs to be replenished inside the terminal PCT cells. This process is accomplished by apical NHE3 activity, which creates the driving force for formic acid entry into the cell, and by apical H^+/formate cotransport, which, in turn, promotes formate entry [31].

Apical Cl^-/oxalate exchanger

Intracellular H_2CO_3, previously formed from CO_2 and H_2O via the cytosolic enzyme carbonic anhydrase II, can result in H^+ and CO_3^{2-} (carbonate). This anion can be exchanged with oxalate via the CO_3^{2-}/oxalate exchanger in the apical membrane. Once inside the cell, oxalate can be exchanged with Cl^- via an apical Cl^-/oxalate exchanger, allowing Cl^- reabsorption. However, to maintain this mechanism, oxalate needs to be replenished inside the terminal PCT cells. This process is accomplished by apical NHE3 activity, which creates the driving force for carbonate extrusion, and by the apical oxalate/SO_4^{2-} exchanger, which is coupled to the apical Na^+/SO_4^{2-} exchanger, the principal mechanism of SO_4^{2-} reabsorption in PCT. Some possible pathways for Cl^- to reach the interstitial peritubular fluid and blood are simple diffusion across the membrane following an electrochemical gradient, K^+–Cl^- cotransport, and Na^+-2HCO_3^-/Cl^- exchange [31].

Pathophysiology

The sequence of events leading to FRST is incompletely defined and probably varies according to the etiology. Possible mechanisms include widespread abnormality of most or all of the proximal tubule carriers, "leaky" brush border or basolateral cell membrane, inhibited or abnormal Na^+–K^+-ATPase pump, impaired mitochondrial energy generation, or

other cell organelle dysfunction. The most common cause of FRST in children is an inborn error of metabolism, whereas, in adults, FRST is more frequently caused by an endogenous or exogenous toxin [32].

The mechanisms behind the disease include decreased influx of solute into the blood from the tubular epithelium, increased back flux of solute across the tight junctions separating the cells that line the tubular epithelium from the blood to the glomerular filtrate, defective solute influx into the tubular epithelium, and leakage of the solute back into the lumen from the tubular epithelium [32]. This could be due to a larger problem associated with generating the energy that is needed by the cells to accomplish the task of bringing solutes in through the brush border membrane or in transferring solutes out through the basolateral membrane. For example, heavy metal poisoning can compromise the utilization of energy by the mitochondria [4].

FRST requires that distal segments of the nephron do not absorb the solutes that are reabsorbed primarily by the PCT. Malabsorption of these substances could be due to altered permeability of tubular membranes or alterations of transport carriers. The substances not absorbed include amino acids, bicarbonate, glucose, phosphate, proteins, and uric acid, and this alteration seems to be associated with low ATP levels [5]. The mechanisms underlying acquired and inherited causes of FRST are still under investigation. It is important to note that type 2 renal tubular acidosis is not always associated with FRST, but FRST does present with type 2 renal tubular acidosis in the setting of excessive excretion of bicarbonate [32] (Fig. 2).

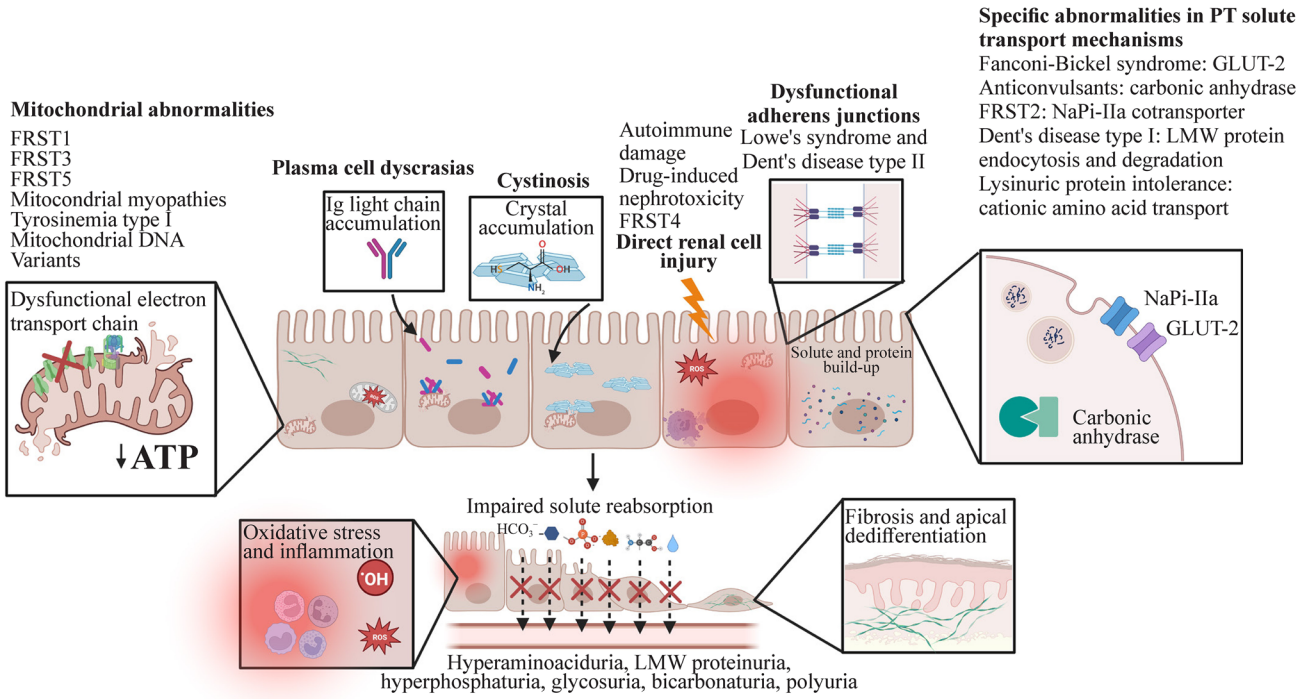

Fig. 2 Summary of the physiopathology of Toni-Debrè–Fanconi syndrome (FS). FS has many primary, secondary, and acquired etiologies that cause proximal convoluted tubule (PCT) damage through various mechanisms. One way the PCT cells may be disrupted is through mitochondrial abnormalities, seen in the inherited forms Fanconi renotubular syndrome types 1, 3, and 5 (FRST1, FRST3, FRST5), as well as secondarily to mitochondrial myopathies, tyrosinemia type I, and mitochondrial DNA variants. These diseases disrupt the electron transport chain, impairing oxidative phosphorylation and ultimately leading to insufficient ATP formation and build-up of reactive oxygen species (ROS), which activates proinflammatory and profibrotic mediators, resulting in PCT cell damage. Another mechanism is the deposition of foreign structures resulting in oxidative and inflammatory stress. This is seen with immunoglobulin (Ig) light chains and crystal accumulation due to plasma cell dyscrasias and cystinosis, respectively. Furthermore, PCT cells may be directly injured via autoimmune mechanisms, drug toxicity or intracellular response to impaired transcription (FRST4). Lowe's syndrome and Dent's disease type II cause damage due to cytoskeletal abnormalities that decrease functional adherens junctions and impair protein trafficking. Protein and solutes may also accumulate in the cytoplasm due to defects in specific transporters, as seen in Fanconi–Bickel syndrome (defective glucose transporter 2—GLUT-2), FRST2 (defective sodium phosphate cotransporter 2a—NaPi-IIa), anticonvulsant therapy (inhibit carbonic anhydrase), lysinuric protein intolerance (defective cationic amino acid transporter), and Dent's disease type I (impaired megalin and cubilin-mediated amino acid endocytosis). All of these forms of cell aggression result in increased oxidative stress, inflammation, and fibrosis, resulting in loss of the brush border and flattened PCT cells with thickened basement membranes. This conjuncture leads to apical dedifferentiation with a global loss of solute resorptive capacity, which explains the findings of hyperaminoaciduria, low-molecular-weight (LMW) proteinuria, hyperphosphaturia, glycosuria, bicarbonaturia, and pyuria characteristics of FS. *FRST* Fanconi renotubular syndrome, *PT* proximal tubular

FRST can occur due to inherited or acquired causes. Primary inherited FRST is caused by a mutation in the sodium phosphate cotransporter (NaP_i-II) in the proximal tubule. Recent studies have identified new causes of FRST due to mutations in the *EHHADH* and *HNF4A* genes. FRST can also be one of the many manifestations of various inherited systemic diseases, such as cystinosis. Many of the acquired causes of FRST with or without proximal renal tubular acidosis are drug induced, with the list of causative agents increasing as newer drugs are introduced for clinical use, mainly in the oncology field [33].

Etiology

As previously stated, FRST is caused by a global dysfunction of solute reabsorption in the PCT, which is a highly energy-demanding process; hence, most of the pathophysiological pathways underlying FRTS are related to mitochondrial cytopathies and defects in the respiratory chain [34]. FRST often presents as a secondary feature of systemic disorders that impair energy supply, such as Lowe's syndrome, Dent's disease, cystinosis, hereditary fructose intolerance, galactosemia, tyrosinemia, Alport syndrome, and Wilson's disease, but it has also been reported in primary form as a Mendelian disorder in both autosomal dominant and recessive manners, caused by specific mutations in a variety of genes. Table 1 summarizes the causes of FRST.

Primary Fanconi syndrome

There are five Mendelian forms of FRST recognized to be caused by mutations in different loci, with unique inheritance patterns and phenotypic presentations. FRST1 was first mapped to chromosome 15q15.3 [35] via a genome-wide screen of 24 members of a family with seemingly

Table 1 Fanconi syndrome classification and common etiologies

Classification	Etiology
Primary Fanconi syndrome	FRST1: *GATM* mutations, autosomal dominant
	FRST2: *SLC34A1* mutations, autosomal recessive
	FRST3: *EHHADH* mutations, autosomal dominant
	FRST4: *HNF4A* mutations, autosomal dominant
	FRST5: *NDUFAF6* mutations, autosomal recessive
	Mitochondrial DNA deletion
	Idiopathic Fanconi syndrome (unknown genetic mechanism)
Fanconi syndrome secondary to hereditary disorders	Cystinosis
	Hereditary fructose intolerance
	Tyrosinemia type I
	Lowe's syndrome
	Dent's disease
	Lysinuric protein intolerance
	Fanconi-Bickel syndrome
	Alport syndrome
	Galactosemia
	Wilson's disease
	Mitochondrial myopathies
Acquired Fanconi syndrome	Antiretroviral drugs (tenofovir, didanosine, lamivudine and stavudine)
	Anticancer agents (ifosfamide, immune checkpoint inhibitors, tyrosine kinase inhibitors)
	Antibiotics (aminoglycosides, tetracycline)
	Anti-protozoals (suramin)
	Anticonvulsants (topiramate, valproate)
	Salicylates (aspirin)
	Iron-chelating agents (defarosirox)
	Dicarboxylic acids (fumaric acids, maleic acid)
	Heavy-metal exposure (cadmium)
	Plasma cell dyscrasias (myeloma, leukemia, lymphoma)
	Monoclonal gammopathies
	Autoimmune causes

FRTS Fanconi renal tubular syndrome

autosomal dominant FRTS reported by Wen, Friedman, and Oberley [36]. Then upon next-generation sequencing and segregation analysis of 28 later-reported affected members of 5 unrelated families, heterozygous missense mutations were found in a specific region of the *GATM* gene, which encodes the enzyme glycine amidinotransferase [37]. Interestingly, this enzyme is involved in the creatinine biosynthetic pathway, and other recessive loss-of-function mutations in this gene have been previously associated with cerebral creatinine deficiency syndrome, characterized by neurologic impairment without renal manifestations [38]. However, the specific heterozygous mutations described in the above-mentioned study created an additional interaction interface within the GATM protein and resulted in linear aggregation and fibrillary aggregate deposition on mitochondria, as shown on biopsy of the PCT cells. This build-up of GATM complexes resulted in enlarged mitochondria resistant to turnover with increased reactive oxygen species (ROS) production, higher activation of the inflammasome, and upregulated expression of profibrotic mediators such as NLRP3, fibronectin, and interleukin (IL)-8 [37]. These changes resulted in increased PCT cell death and fibrosis, which could explain why variants in this specific region of the gene presented phenotypically as FRST.

FRST2 was subsequently described as an autosomal recessive disorder in a consanguineous Arabic family, presenting with the classical findings of rickets, osteopenia, hypercalciuria without renal tubular acidosis and, unlike the previously described symptoms, with elevated serum 1,25-dihydroxyvitamin D [1,25(OH)2D3] [39]. After 20 years, the same family was re-evaluated [40], and the affected patients exhibited normal levels of urinary calcium excretion and vitamin D deficiency, which suggests that during childhood, 1,25(OH)2D3 was overproduced by the kidneys in response to hypophosphatemia. They underwent genetic analysis, and a homozygous 21 bp duplication was found on the *SLC34A1* gene (chromosome 5q35.1–q35.3), which encodes the renal sodium phosphate cotransporter NaPi-IIa, causing complete loss of its function. The mutant cotransporter was absent from the plasma membrane, which seems to be the cause of a deleterious effect on the normal function of the PCT transporters [40].

FRST3 was first described in 1992 by Tolaymat et al. in four generations of a large African American family with the ordinary presentation of FRTS segregating as an autosomal dominant disorder [41]. In a follow-up study, the phenotype was linked to a heterozygous missense mutation in the gene *EHHADH* (chromosome 3q27), which encodes enoyl-CoA hydratase-L-3-hydroxyacyl-CoA dehydrogenase, a bifunctional enzyme expressed in the proximal tubular (PT) that is involved in the oxidation of fatty acids on the peroxisome [42]. Curiously, the described heterozygous mutation in *EHHADH* did not impair beta-oxidation in peroxisomes of knockout mice but rather created a new targeting signal in the N-terminus of the enzyme, misdirecting it to mitochondria [42]. Respirometric measurements showed that cells with the mutant *EHHADH* had reduced oxidative phosphorylation capacity due to disruption of the mitochondrial trifunctional protein (MTP). They also presented respiratory chain supercomplexes, products of the incorporation of mutated *EHHADH*, impairing mitochondrial respirasome assembly [43]. Renal tubular cells depend on fatty acid oxidation in mitochondria as their predominant energy source [44], so this dominant-negative toxic effect of the mutant protein in energy metabolism seems to impair proximal solute resorption, resulting in FRTS.

FRTS4 is a unique manifestation of full FRTS associated with maturity-onset diabetes of the young (MODY), a monogenic type of diabetes characterized by neonatal hyperinsulinemia and macrosomia [45–47]. This unique phenotype presents in an autosomal dominant form and is caused by one specific mutation (c.226C > T/R76W) in *HNF4A*, a gene where other mutations had been previously related to the pancreatic beta-cell-affecting phenotype but not to FRTS. This finding shows that it was not secondary to the other clinical features but rather a direct effect of the R76W variant. The *HNF4A* gene is a hepatic transcription factor. This specific mutation induces variations in the charge and hydrophobicity of the transcription factor's DNA-binding domains, suggesting that the renal phenotype results from defective interaction of *HNF4A* with regulatory genes in the renal proximal tubule [46].

Finally, FRTS5 refers to a particular Acadian variant characterized by generalized proximal tubular dysfunction, subsequent chronic kidney disease and pulmonary interstitial fibrosis [48]. The Acadians are a founder population in Nova Scotia, Canada, among which several families have been described with this phenotype combination segregating in an autosomal recessive manner [48–50]. Whole exome and genome sequencing studies found that this form of the disease was caused by a splice-affecting intronic variant on *NDUFAF6* [50], which encodes NADH:ubiquinone oxidoreductase complex assembly factor 6 (C8ORF38), which is involved in the biogenesis of complex I (ubiquinone) of the respiratory chain. The above-mentioned variant was associated with complex I deficiency and structural mitochondrial defects affecting the proximal tubular epithelium and pulmonary epithelial cells, tissues that are sensitive to ROS and are highly energy-requiring, which ultimately leads to FRTS5 and pulmonary fibrosis [50].

Apart from the known Mendelian FRTS forms, another primary manifestation of the disease has been reported in association with a specific mitochondrial DNA variant. In a patient presenting with FRTS and retinitis pigmentosa, southern blot analysis revealed that the phenotypic traits resulted from a heteroplasmic mutation of mitochondrial

DNA with three different mtDNA types: some normal, some with a 6.7 kb deletion, and some with a deletion/duplication of 9.8 kb [51]. Furthermore, biochemical and morphological investigations of a patient with neonatal FRTS, a child of a consanguineous Turkish couple, showed severe deficiency of complex III of the respiratory chain but did not point toward a specific causative genetic variant [52].

Several other case reports of idiopathic FRTS presenting sporadically or in familial forms suggest that there might be more mutations and genes involved in the pathophysiology of this disease. There are earlier descriptions of transmission in autosomal dominant [36, 53], autosomal recessive [54], and X-linked manners [55], none of which included genetic testing, but they were able to rule out hereditary causes due to systemic inborn errors of metabolism and acquired origins of FRTS, accounting for primary forms of FRTS with unknown causes.

Fanconi syndrome secondary to systemic inherited diseases

Apart from the primary causes of FRTS, inherited systemic diseases, including cystinosis, hereditary fructose intolerance, galactosemia, tyrosinemia, Lowe syndrome, Wilson disease, glycogen storage disease type 1, arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome, and mitochondrial disorders, are secondary causes.

Cystinosis

The most common inherited cause of FRTS is cystinosis [56], an autosomal recessive lysosomal storage disorder characterized by a defect in cystinosin, the lysosomal cystine transporter, which leads to a multi-organ accumulation of cystine. This metabolic disorder is caused by homozygous mutations or deletions in the gene *CTNS*, located on chromosome 17p13.2 [57], and usually presents as the infantile/nephropathic form, characterized by failure to thrive at approximately 6–9 months of age, kidney dysfunction between 6 and 18 months, and kidney failure by 10 years of age if left untreated. Extrarenal features are caused by cystine crystal deposition in other tissues, resulting in photophobia (from corneal deposition), hypothyroidism, diabetes, myopathy, and central nervous system damage. Other forms, such as ocular cystinuria, present without renal impairment and tend to be milder in adults. The proximal tubular damage is mediated by cystine accumulation and crystallization in PCT, which causes its cells to lose their brush border, become flattened, and acquire thicker basement membranes [58], leading to build-up of inflammatory infiltrate on the interstitium, apoptosis, and oxidative stress [59]. The result is a global loss of solute transporters (such as NaPi-IIa and SGLT-2) and endocytic receptors (such as megalin and cubilin, responsible for reuptake and lysosomal degradation of ultrafiltered plasma proteins). This process, known as apical dedifferentiation, explains the early solute loss and proteinuria before tubular characteristics of FRTS. The lesion extends longitudinally over time and results in PCT cell atrophy and interstitial fibrosis [60].

Hereditary fructose intolerance

Hereditary fructose intolerance is an autosomal recessive disorder characterized by a deficiency of the enzyme aldolase B, encoded by the gene *ALDOB* (9q31.1) [61]. It becomes symptomatic in infancy when fructose or sucrose is added to the diet and is usually well managed by limiting fructose ingestion. However, in high fructose administration scenarios, a dose-dependent abnormality of proximal tubular function similar to FRTS was observed [62].

Tyrosinemia type I

Tyrosinemia type I is an autosomal recessive disorder caused by deficiencies of the last enzyme in the tyrosine degradation pathway, fumarylacetoacetase, due to mutations in the *FAH* gene. This type presents with liver disease and renal dysfunction leading to rickets, characteristic of FRTS, probably caused by a build-up of fumarylacetoacetate, which is not metabolized in the absence of functional FAH. In animal models, this metabolite was thought to damage mitochondria and disrupt nuclear membranes, leading to apoptosis of PCT cells [63].

Lowe's syndrome

Lowe oculocerebrorenal syndrome is an X-linked recessive disorder composed of a classic triad of congenital cataracts, impaired intellectual development, and renal tubular dysfunction consistent with FRTS but may also present with muscle damage with ragged red fibers, hypotonia, and hyporeflexia. It is caused by different mutations in the *OCLR* gene, which encodes a lipid phosphatase that processes the metabolite phosphatidylinositol 4,5-bisphosphate in the trans-Golgi network. Build-up of this substrate was shown to impair actin cytoskeletal polymerization, which is essential for the formation and maintenance of tight and adherens junctions, critical structures for renal tubule function and lens differentiation [64, 65]. OCLR has also been shown to interact with clathrin and regulate protein trafficking between endosomes and the Golgi apparatus in endocytosis, another imperative function for resorption in the PCT [66].

Dent's disease

Dent's disease is a phenotypically diverse renal tubular disorder characterized by hypercalciuric nephrolithiasis,

usually presenting with hypophosphatemic rickets and low-molecular-weight proteinuria, that may be divided into types I and II. The first type is caused by mutations in the *CLCN5* gene (Xp11.22), which encodes the voltage-gated chloride channel CLC-5, that acts on the acidification of endosomes stimulated by ATP [67]. This acidification is essential for proteolytic degradation of the low-molecular-weight proteins reabsorbed by the proximal tubule via megalin and cubilin-mediated endocytosis [68]. The second type of Dent's disease is caused by a mutation in the *OCLR* (Xq 26.1) gene and presents as a milder form of Lowe's syndrome, without its oculocerebral manifestations and the proximal renal tubular acidosis typically associated with FRTS [69]. Therefore, Dent's disease type 2 and Lowe's syndrome are only distinguishable via clinical evaluation, as the genotypic–phenotypic association between the different *OCLR* mutations causing each disorder has not yet been clearly elucidated.

Lysinuric protein intolerance

Lysinuric protein intolerance (LPI) is an inborn error of metabolism due to defective cationic amino acid transporters at the basolateral cell membranes, reducing renal reabsorption and intestinal absorption of positively charged amino acids such as lysine, arginine, and ornithine [70]. This autosomal recessive disease is caused by mutation in the *SLC7A7* (14q11.2) gene, which encodes a catalytic subunit of the above-mentioned transporter. FRTS is one of its most serious renal manifestations and is related to severe abnormalities of apical membrane structure in PCT cells, probably due to the toxic effect of retained metabolites or energetic metabolism dysfunction [71].

Fanconi–Bickel syndrome

This systemic variation in FRTS described by Fanconi and Bickel in 1949 is caused by homozygous mutations in the *SLC2A2* gene (3q26.2), which encodes the GLUT2 facilitative glucose transporter, expressed in hepatocytes, pancreatic beta-cells, in the intestinal brush border, and in the basolateral membrane of tubular epithelial cells [72]. GLUT2 is necessary for monitoring glucose levels by beta-cells, monosaccharide intestinal absorption, hepatic metabolism of glucose, and glucose and galactose renal resorption. This results in a state of hypoinsulinemia, glucosuria, and consequent imbalances in glucose homeostasis, as well as renal accumulation of glycogen, which may lead to other tubular defects associated with FRTS [73].

Other inherited diseases associated with Fanconi syndrome

Less often, FRTS may present secondarily to Alport syndrome [74], galactosemia [75], Wilson's disease [76, 77], and mitochondrial myopathies such as Kearns–Sayre syndrome [78], but the specific pathophysiological basis for these associations has not yet been fully elucidated.

Acquired Fanconi syndrome

In adults, FRTS is most frequently caused by drug-induced nephrotoxicity, as the proximal tubules are involved in the excretion of several drugs. It has been associated with antiretroviral medications such as tenofovir, didanosine, lamivudine, and stavudine, especially in HIV + patients undergoing multidrug therapy [79]. Other causes of FRTS are anticancer agents that impair normal metabolism and induce cell death, such as ifosfamide, which indirectly inhibits complex I of the respiratory chain, impairing cellular respiration in PCT cells [80], immune checkpoint inhibitors nivolumab/ipilimumab [81], and tyrosine kinase inhibitors [82]. Anticonvulsant drugs such as topiramate and valproic acid may precipitate FRTS due to inhibition of carbonic anhydrase II [83]. Other drug classes associated with FRTS include antibiotics such as aminoglycosides and tetracyclines [82, 84], iron-chelating agent defarosirox [85], salicylates such as aspirin [86], antiprotozoal suramin [87] and dicarboxylic acids such as fumarate and malate [88, 89]. Most of these drugs are associated with mitochondrial damage or extensive nephrotoxicity, which may manifest as FRTS. Furthermore, chronic heavy metal exposure has been associated with FRTS, especially cadmium, which is endocytosed and accumulates in PCT cells, generating ROS that lead to cellular damage and proximal tubular dysfunction [90].

FRTS may also occur secondarily to plasma cell dyscrasias such as myeloma [91, 92], leukemia [93], lymphoma [94], and other monoclonal gammopathies. Renal damage usually occurs due to urinary excretion of immunoglobulin (Ig) light chains that form crystals and deposit in proximal tubular cells [95]. It was demonstrated in mouse models that Ig light-chain deposits accumulated in lysosomes and impaired their acidification and function, resulting in defective endocytosis and proteolysis and, ultimately, in decreased resorptive capacity of PCT cells [96]. Furthermore, autoimmune causes of FRTS are rare but have also been described, mostly in association with tubulointerstitial nephritis, due to antimitochondrial antibodies [97].

Clinical findings

The clinical findings of FRTS vary according to its etiology and the degree of involvement of the proximal renal tubule. These include aminoaciduria, glycosuria, increased renal clearance of inorganic phosphates, and bicarbonaturia. In pediatric patients, the syndrome is often characterized by growth retardation and rickets [98]. The occurrence of fever and dehydration can be caused by frequent polyuria. The literature descriptions and the current clinical experience converge to the conclusion that FRTS is not a uniform entity. FRTS can manifest as isolated proximal tubular dysfunction or multiple organ disorders, according to the underlying etiology [4]. The main findings of FRTS are hyperaminoaciduria, LMW proteinuria, hyperphosphaturia, and bicarbonaturia [98]. When all known etiologies of FRTS are ruled out, the diagnosis is given as idiopathic FRTS. During childhood, the glomerular filtration rate is usually within the normal range, but between the first and third decades of life, chronic kidney disease may occur [98].

Inherited causes of Fanconi syndrome

The presence of specific heterozygous mutation R76W in transcription factor HNF4A in some patients with MODY1 showed the development of the renal phenotype by affecting the transcription of renal genes still unknown [4]. In a study with six heterozygous patients for this mutation, the phenotype of proximal tubulopathy was observed, characterized by generalized aminoaciduria, LMW proteinuria, glycosuria, hyperphosphaturia, and hypouricemia, in addition to additional features not observed in FRTS, including neonatal hyperinsulinism, diabetes mellitus, nephrocalcinosis, renal impairment, hypercalciuria with relative hypocalcemia, and hypermagnesemia [46, 98]. When the etiology of FRTS is autosomal dominant or autosomal recessive, especially affecting the *SLC9A3* gene, ocular involvement is observed with the presence of keratopathy, cataracts, glaucoma, and blindness [4].

Isolated genetic Fanconi renal tubular syndrome (FRTS) findings

Of the three isolated FRTS genetic causes, FRTS1 is closely associated with progressive chronic kidney disease [4]. On the other hand, FRTS2 presents phosphaturia and rickets. However, not all transport routes of the proximal tubule are impaired. Moreover, mutations in the *SLC34A3* gene, which encodes the renal phosphate transporter NAPi-IIc, lead to the development of hereditary hypophosphatemic rickets with hypercalciuria. In clinical practice, glycosuria is commonly found in patients with hypophosphatemic rickets [4].

FRTS3 is characterized by the loss of water, solutes, and 1 g/day of filtered proteins throughout life. However, the glomerular filtration rate did not change. This form does not normally result in chronic kidney disease [4, 41, 42]. The affected patients manifest rickets, impaired growth, glycosuria, generalized aminoaciduria, phosphaturia, metabolic acidosis, and proteinuria of LMW due to the mutation affecting mitochondrial metabolism [98].

Mutations in the *CTNS* gene give rise to nephropathic cystinosis, which is the most common cause of FRTS in children from Western countries. Cystinosis arises from 6 to 12 months of age, presenting with growth deficit, polyuria, polydipsia, dehydration, hypophosphatemic rickets, hypokalemia, electrolyte abnormalities, aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis. At an older age, the affected individuals can acquire photophobia through corneal precipitation of cystine crystals, as well as hypothyroidism due to hypotrophy of the thyroid gland. Although renal function is commonly normal, at about 10 years of age, most patients develop renal failure if left untreated [6, 98].

Clinical findings of *GLUT2* and *FTH* gene mutation

The mutation in the *GLUT2* gene causes an autosomal recessive disorder of glucose metabolism that affects tubular cells. The disease characteristics are rickets, hepatomegaly, growth deficit, fasting hypoglycemia, hyperglycemia, hypergalactosemia in the post-absorptive state and hyperlipidemia [7]. On the other hand, patients with mutations in the *FTH* gene develop progressive renal damage beginning in early childhood. During the development of FRTS, hypophosphatemia and rickets are characteristic, in the same way as generalized aminoaciduria, renal tubular acidosis, and mild proteinuria. However, glycosuria is less common since plasma glucose levels are low. In addition, the syndrome may be responsible for worsening carnitine deficiency [98, 99].

Mitochondrial disorders

Mitochondrial disorders are multisystemic diseases that can affect individuals at any age. As a cause of FRTS, mitochondrial disorders are often observed in age groups ranging from newborns to young children. Patients may present with partial forms of the syndrome, manifesting renal tubular acidosis with hypercalciuria [43, 98].

Galactosemia (GALT deficiency)

Milk contains an important amount of galactose, and this is the main carbon source for neonates because it is incorporated more efficiently into glycogen than into glucose.

However, when there is a deficiency in the activity of galactose-1-phosphate uridyl transferase (GALT), milk ingestion promotes the emergence of classical galactosemia. Thus, affected infants manifest episodes of vomiting, diarrhea, growth deficit, developmental delay in renal liver and tubular dysfunctions, cerebral edema, vitreous hemorrhage, sepsis, especially by *Escherichia coli*, and, frequently, jaundice and indirect hyperbilirubinemia [98, 100].

Acquired causes of Fanconi syndrome

Among the acquired causes of FRTS, focal and segmental glomerulosclerosis can be a cause, but with an unidentified defect in most cases. Immunological and hematological disorders can also result in FRTS. For instance, Sjögren's syndrome, in which 4% of patients have FRTS, is associated with the development of osteomalacia, thoracic bone deformities, fractures of the humerus diaphysis bilaterally, and intense thinning of the cortical bone [97]. Rarely, post-transplanted renal patients develop the syndrome as a consequence of the procedure. Patients with acute tubulointerstitial nephritis, and uveitis, in addition to manifesting asthenia, general malaise, nocturia, weight loss, and polydipsia, can present incomplete or complete symptoms of FRTS, including LMW proteinuria, glycosuria, aminoaciduria, bicarbonaturia, phosphaturia, and uricosuria [98].

Heavy metals are nephrotoxic and can produce FRTS, especially in children. Lead is a long half-life non-biodegradable metal that causes aminoaciduria and glycosuria up to 13 years after contact during childhood. Another example is cadmium. Prolonged exposure to cadmium may result in FRTS, as observed in the Jinzu River basin in Japan, where patients developed severe osteomalacia with intense bone pain secondary to multiple spontaneous bone fractures [101].

Diagnosis

General diagnostic approach to FRTS

The diagnosis of FRTS is based on the clinical manifestations associated with laboratory analyses of routine tests of blood, urine, and kidney function [102, 103]. By means of the blood test, it is possible to identify altered concentrations of metabolites and electrolytes due to the generalized defect in the proximal tubular reabsorption of solutes. Therefore, the serum levels of urea, creatinine, uric acid, sodium, potassium, chloride, calcium, phosphate, and magnesium were measured. Likewise, blood gas analysis is useful for the evaluation of acid–base homeostasis. Additionally, urine evaluation includes an acidification test and urinary concentration analysis. The 24-h urine collection is the preferable method used to measure creatinine and other electrolytes due to its application in the determination of kidney function. To that end, the creatinine clearance and the fractional excretion rate of electrolytes are calculated and used to estimate the glomerular filtration rate and urinary loss of electrolytes. Another parameter obtained by the complementary exams is the urinary anion gap (AG) [103].

Considering the laboratory tests, the diagnosis is confirmed when the results indicate urinary hyperexcretion of generalized amino acids, phosphate, glucose, bicarbonate, potassium, and urate; hypophosphatemia and normocalcemia; and elevated urinary pH in the context of mild to moderate metabolic acidosis [104]. The urinary AG remains negative and within the reference range due to the normal distal secretion of hydrogen [103].

In some cases, the etiological diagnosis is useful for the treatment of the underlying condition, and a detailed investigation should be performed, including molecular genetic testing and specific substance concentration measurements. This issue is supported by the following analysis of the diagnostic methods of three main inherited disorders associated with FRTS.

Dent–Wrong disease diagnosis

There are three diagnostic criteria for Dent–Wrong disease. First, urinary excretion of LMW proteins, such as β2-microglobulin, Clara cell protein and/or retinol-binding protein, was elevated by at least fivefold above the upper limit of normal. Second, hypercalciuria was identified in a 24-h urine collection. Third, the presence of nephrocalcinosis, calcium nephrolithiasis, hematuria, hypophosphatemia, or chronic kidney disease. The diagnosis is also confirmed by the identification of a mutation in either the *CLCN5* or *OCRL1* gene. However, in a few patients, these mutations are not identified, and the diagnosis is not excluded if the clinical findings suggest Dent–Wrong disease [105].

Cystinosis diagnosis

The presence of intracellular levels of cystine higher than 2 nmol half-cystine/mg protein in peripheral leukocytes confirms the diagnosis of cystinosis. This finding is usually associated with demonstration of corneal crystals by slit lamp exam and consecutive genetic analysis of the *CTNS* gene [5]. During the prenatal period, the diagnosis is possible by means of amniocytes or chorionic villi [32].

Hereditary tyrosinemia type I diagnosis

Concerning hereditary tyrosinemia type I diagnosis, elevated levels of succinylacetone in plasma and urine have been used as the primary marker of this disease [5, 102]. This finding

establishes the diagnosis along with the increased plasma concentration of tyrosine, methionine, phenylalanine, elevated urinary concentration of tyrosine metabolites, and the compound 5-aminolevulinic acid (δ-ALA). Additionally, it may be confirmed by the identification of pathogenic variants in the *FAH* gene in molecular genetic testing [106].

Due to its many etiologies, it is challenging to establish a protocol for diagnostic screening for FRTS. This disorder can be frequently misdiagnosed, and therefore, new studies may be useful to guide the early diagnosis of FRTS.

Treatment

Tubulopathies are rare, which explains the low clinical level of evidence in regard to treatment. The way to treat may vary among physicians since it is primarily based on the understanding of renal physiology, clinical observations, and individual experiences [107]. Regarding the treatment of FS, the correction of hydroelectrolytic and metabolic disorders stands out. Alkali replacement, which is important for the correction of acidosis [103], can be performed by replacing sodium bicarbonate or potassium citrate, usually at 10 mEq/kg/day (2–15 mEq/kg/day), divided every 6–8 h [108].

In addition, potassium citrate or potassium chloride can be used to replace the cation, usually at a dose of 5 to 10 mEq/kg/day, divided every 6–8 h. Sodium replacement, in turn, can be performed with sodium bicarbonate [108]. The replacement of these ions is a significant measure; however, these measures do not significantly improve the condition on a long-term basis [98]. It is important to note that potassium citrate, bicarbonate or acetate can be used to correct acidosis and hypokalemia at the same time. Sodium wasting and dehydration are treated with a combination of sodium bicarbonate, citrate, and chloride, depending on the degree of acidosis. Regarding phosphorus replacement, phosphate solution at a concentration of 15 mg/mL or sodium and potassium phosphate tablets containing 250 mg of phosphate can be used, with an initial dosage of about 2 to 3 mmol/kg/day in divided doses. Concerning magnesium replacement, it is common to use magnesium sulfate at variable doses according to the serum level [108]. Usually, the initial magnesium sulfate dose is 2.5 to 5 mg/kg (0.1 to 0.2 mmol/kg) three times daily orally, adjusted to serum levels. If the plasma levels of vitamin D, calcitriol, and L-carnitine are low, these components must be replaced [108]. In patients with rickets, treatment with calcitriol can be effective, although it is more appropriate to correct hypophosphatemia by replacing phosphate with neutral phosphate solution [103]. Regarding calcium replacement, calcium carbonate can be used, starting with 400 mg of elemental calcium per day [108]. It should also be noted that the administration of phosphate, 1,25-dihydroxycholecalciferol, and bicarbonate must be well monitored since, if there is an excess dose, the patient may develop nephrocalcinosis or present renal calculi formation [109]. To prevent further reduction of phosphorus, care should be taken not to administer calcium with food or with the phosphate formulation to prevent calcium from reducing the absorption of the orally ingested phosphate.

In the case of nephropathic cystinosis, the treatment includes the oral administration of N-acetyl-cysteine [110] and the use of cysteamine. This approach can reduce intralysosomal cystine stores and improve the prognosis of patients, delaying the progression to end-stage renal disease and decreasing extrarenal impairment [108]. Oral therapy with cysteamine is performed at doses of 60 to 90 mg/kg/day every 6 h and generally achieves 90% cellular cystine depletion, as evidenced by the evaluation of circulating lymphocytes [111]. Furthermore, it is noteworthy that successful renal transplantation, despite reversing renal failure, does not significantly improve the extrarenal manifestations of cystinosis; therefore, cysteamine therapy should continue after transplantation [32]. Cysteamine should be administered as soon as the diagnosis of cystinosis is made and continued for life, even after kidney transplantation to protect extrarenal organs [109]. The drug ELX-02, a selective eukaryotic ribosomal glycoside (ERSG), was tested for cystinosis in a clinical trial aiming to verify its efficacy in reducing the baseline cystine levels in leukocytes. However, this study was discontinued during the second phase due to limitations of its design [112].

Patients with cystinosis may also manifest gastrointestinal symptoms such as choking, vomiting, nausea, lack of appetite, diarrhea, constipation, and difficulty swallowing [113]. Recombinant human growth hormone was used in 20% of children to improve growth and weight gain. Families reported that growth hormone improved both appetite and gastrointestinal problems [113]. Furthermore, some patients who had difficulty swallowing required feeding via a gastric and/or jejunal tube or even total parenteral nutrition in very severe cases [113].

In addition, individuals with FRST may present ophthalmological alterations, starting with photophobia, and may progress to amaurosis [108]. This is because cystine crystals cause light reflections and result in photophobia, with substantial discomfort. Untreated adolescents may develop painful corneal erosions, punctate, filamentous, or banded keratopathy, iris crystals, and peripheral corneal neovascularization [109]. The treatment is carried out using a cysteamine ophthalmic solution: one drop in each eye every hour while the patient is awake [108]. Administration of this solution is capable of completely dissolving corneal cystine crystals within 8 to 41 months, even at an older age [109].

Another relevant symptom of FRTS is hypothyroidism [108]. There is evidence to indicate that progressive thyroid

Table 2 Treatment scheme for patients with Fanconi renal tubular syndrome

Medications	Doses	Time of medication
Sodium bicarbonate or sodium citrate	10 mEq/kg/d	Every 6 or 8 h
Potassium citrate	5 to 10 mEq/kg/d	Every 6 or 8 h
Phosphate solution	15 mg/mL	Variable
Potassium phosphate	2 to 3 mmol/kg/d	Variable
Magnesium sulfate	Variable, initially 2.5 to 5 mg/kg (0.1 to 0.2 mmol/kg)	Variable, normally every 8 h
Calcium carbonate	400 mg	Once a day
Cysteamine	60 to 90 mg/kg/d	Every 6 h
Cysteamine ophthalmic solution	0.44% solution and 0.55% gel formulation	One drop in each eye hourly while awake
L-arnitine	28–59 μmol/L (female children) and 32–62 μmol/L (male children)	Variable
Calcitriol	Variable	Variable

atrophy, with gradual loss of thyroid function, is considered part of the normal course of the infantile form of cystinosis. Therefore, thyroid-stimulating hormone (TSH) and thyroxine hormone (free T4) should be monitored every 6 months from 2 years of age. In the presence of hypothyroidism, it is recommended to start thyroid hormone replacement [108]. For glucose monitoring, fasting glucose and glycated hemoglobin should be monitored annually from 5 years of age, as patients with FRTS tend to present glucose intolerance [108]. Furthermore, there is a need to standardize the treatment of hyperglycemia and diabetes, as there is still no consensus on the management of these alterations [114]. An overview of the treatment scheme of FRTS can be seen in Table 2.

Conclusions

FRTS is a global dysfunction of PCT, which is mainly characterized by glycosuria, phosphaturia, generalized aminoaciduria, and type II renal tubular acidosis. Although uncommon, this condition presents high morbidity and mortality, especially when diagnosed late. Several advances have been made recently toward the discovery of new forms of this syndrome, which has contributed immensely to the knowledge of the physiological functions of PCT. Nevertheless, the treatment is still poorly studied, and many of its underlying causes are considered irreversible.

Author contributions ALBA: writing—original draft; RSB: writing—original draft; AFC: data curation; EES: data curation; FMMF: data curation; CTA: supervision, writing—review and editing; PASVC: supervision, writing—review and editing; ACSS: conceptualization, supervision, writing—review and editing.

Funding None.

Data availability Not required.

Declarations

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. Author ACSS is a member of the Editorial Board for *World Journal of Pediatrics*. The paper was handled by the other Editor and has undergone rigorous peer review process. Author ACSS was not involved in the journal's review of, or decisions related to, this manuscript.

Ethical approval Not required.

References

1. Fanconi G. Die nicht diabetischen Glykosurien und Hyperglykämien des älteren Kindes. Jahrbuch fuer Kinderheilkunde. 1931;133:257–300.
2. De Toni G. Remarks on the relations between renal rickets (renal dwarfism) and renal diabetes. Acta Paediatr. 1933;16:479–84.
3. Debré R, Marie J, Cleret F, Messimy R. Rachitisme tardif coexistant avec une nephrite chronique et une glycosurie. Arch Med Enfants. 1934;37:597–606.
4. Klootwijk ED, Reichold M, Unwin RJ, Kleta R, Warth R, Bockenhauer D. Renal Fanconi syndrome: taking a proximal look at the nephron. Nephrol Dial Transplant. 2015;30:1456–60.
5. Klootwijk E, Dufek S, Issler N, Bockenhauer D, Kleta R. Pathophysiology, current treatments and future targets in hereditary forms of renal Fanconi syndrome. Expert Opin Orphan Drugs. 2017;5:45–54.
6. Bendavid C, Kleta R, Long R, Ouspenskaia M, Muenke M, Haddad BR, et al. FISH diagnosis of the common 57-kb deletion in CTNS causing cystinosis. Hum Genet. 2004;115:510–4.
7. Piloya T, Ssematala H, Dramani LP, Nalikka O, Baluka M, Musiime V. Fanconi-Bickel syndrome in a Ugandan child - diagnostic challenges in resource-limited settings: a case report. J Med Case Rep. 2020;14:172.
8. Zhuo JL, Li XC. Proximal nephron. Compr Physiol. 2013;3:1079–123.

9. Herman MB, Rajkhowa T, Cutuli F, Springate JE, Taub M. Regulation of renal proximal tubule Na-K-ATPase by prostaglandins. Am J Physiol Renal Physiol. 2010;298:F1222–34.
10. Féraille E, Doucet A. Sodium-potassium-adenosinetriphosphatase-dependent sodium transport in the kidney: hormonal control. Physiol Rev. 2001;81:345–418.
11. Biemesderfer D, Pizzonia J, Abu-Alfa A, Exner M, Reilly R, Igarashi P, et al. NHE3: a Na+/H+ exchanger isoform of renal brush border. Am J Physiol. 1993;265:F736–42.
12. Donowitz M, Li X. Regulatory binding partners and complexes of NHE3. Physiol Rev. 2007;87:825–72.
13. Weinman EJ, Cunningham R, Shenolikar S. NHERF and regulation of the renal sodium-hydrogen exchanger NHE3. Pflugers Arch. 2005;450:137–44.
14. Du Z, Ferguson W, Wang T. Role of PKC and calcium in modulation of effects of angiotensin II on sodium transport in proximal tubule. Am J Physiol Renal Physiol. 2003;284:F688–92.
15. He P, Klein J, Yun CC. Activation of Na+/H+ exchanger NHE3 by angiotensin II is mediated by inositol 1,4,5-triphosphate (IP3) receptor-binding protein released with IP3 (IRBIT) and Ca2+/calmodulin-dependent protein kinase II. J Biol Chem. 2010;285:27869–78.
16. Banday AA, Lokhandwala MF. Angiotensin II-mediated biphasic regulation of proximal tubular Na+/H+ exchanger 3 is impaired during oxidative stress. Am J Physiol Renal Physiol. 2011;301:F364–70.
17. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int Suppl. 2011;79:S1-6.
18. Wright EM, Loo DDF, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91:733–94.
19. Boron WF. Acid-base transport by the renal proximal tubule. J Am Soc Nephrol JASN. 2006;17:2368–82.
20. Sly WS, Hu PY. Human carbonic anhydrases and carbonic anhydrase deficiencies. Annu Rev Biochem. 1995;64:375–401.
21. Zelikovic I, Chesney RW. Sodium-coupled amino acid transport in renal tubule. Kidney Int. 1989;36:351–9.
22. Bröer S. Amino acid transport across mammalian intestinal and renal epithelia. Physiol Rev. 2008;88:249–86.
23. Knox FG, Osswald H, Marchand GR, Spielman WS, Haas JA, Berndt T, et al. Phosphate transport along the nephron. Am J Physiol. 1977;233:F261–8.
24. Werner A, Kinne RK. Evolution of the Na-P(i) cotransport systems. Am J Physiol Regul Integr Comp Physiol. 2001;280:R301–12.
25. Biber J, Hernando N, Forster I, Murer H. Regulation of phosphate transport in proximal tubules. Pflugers Arch. 2009;458:39–52.
26. Bacic D, Lehir M, Biber J, Kaissling B, Murer H, Wagner CA. The renal Na+/phosphate cotransporter NaPi-IIa is internalized via the receptor-mediated endocytic route in response to parathyroid hormone. Kidney Int. 2006;69:495–503.
27. Murer H, Barac-Nieto M, Ullrich KJ, Kinne R. Renal transport of lactate. In: Greger R, Lang F, Silbernagl S, editors. Ren Transp Org Subst. Berlin, Heidelberg: Springer; 1981. p. 210–23.
28. Hamm LL. Renal handling of citrate. Kidney Int. 1990;38:728–35.
29. Pajor AM. Sequence and functional characterization of a renal sodium/dicarboxylate cotransporter. J Biol Chem. 1995;270:5779–85.
30. Weiner ID, Verlander JW. Role of NH3 and NH4+ transporters in renal acid-base transport. Am J Physiol Renal Physiol. 2011;300:F11-23.
31. Aronson PS, Giebisch G. Mechanisms of chloride transport in the proximal tubule. Am J Physiol. 1997;273:F179–92.
32. Foreman JW. Fanconi syndrome. Pediatr Clin North Am. 2019;66:159–67.
33. Kashoor I, Batlle D. Proximal renal tubular acidosis with and without Fanconi syndrome. Kidney Res Clin Pract. 2019;38:267–81.
34. Rötig A. Renal disease and mitochondrial genetics. J Nephrol. 2003;16:286–92.
35. Lichter-Konecki U, Broman KW, Blau EB, Konecki DS. Genetic and physical mapping of the locus for autosomal dominant renal Fanconi syndrome, on chromosome 15q15.3. Am J Hum Genet. 2001;68:264–8.
36. Wen SF, Friedman AL, Oberley TD. Two case studies from a family with primary Fanconi syndrome. Am J Kidney Dis Off J Natl Kidney Found. 1989;13:240–6.
37. Reichold M, Klootwijk ED, Reinders J, Otto EA, Milani M, Broeker C, et al. Glycine amidinotransferase (GATM), renal Fanconi syndrome, and kidney failure. J Am Soc Nephrol JASN. 2018;29:1849–58.
38. Mercimek-Andrews S, Salomons GS, et al. Creatine deficiency disorders. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, et al., editors. GeneReviews®. Seattle: University of Washington; 1993.
39. Tieder M, Arie R, Modai D, Samuel R, Weissgarten J, Liberman UA. Elevated serum 1,25-dihydroxyvitamin D concentrations in siblings with primary Fanconi's syndrome. N Engl J Med. 1988;319:845–9.
40. Magen D, Berger L, Coady MJ, Ilivitzki A, Militianu D, Tieder M, et al. A loss-of-function mutation in NaPi-IIa and renal Fanconi's syndrome. N Engl J Med. 2010;362:1102–9.
41. Tolaymat A, Sakarcan A, Neiberger R. Idiopathic Fanconi syndrome in a family. Part I Clinical aspects. J Am Soc Nephrol. 1992;2:1310–7.
42. Klootwijk ED, Reichold M, Helip-Wooley A, Tolaymat A, Broeker C, Robinette SL, et al. Mistargeting of peroxisomal EHHADH and inherited renal Fanconi's syndrome. N Engl J Med. 2014;370:129–38.
43. Assmann N, Dettmer K, Simbuerger JMB, Broeker C, Nuernberger N, Renner K, et al. Renal fanconi syndrome is caused by a mistargeting-based mitochondriopathy. Cell Rep. 2016;15:1423–9.
44. Balaban RS, Mandel LJ. Metabolic substrate utilization by rabbit proximal tubule. An NADH fluorescence study. Am J Physiol. 1988;254:F407–16.
45. Flanagan SE, Kapoor RR, Mali G, Cody D, Murphy N, Schwahn B, et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur J Endocrinol. 2010;162:987–92.
46. Hamilton AJ, Bingham C, McDonald TJ, Cook PR, Caswell RC, Weedon MN, et al. The HNF4A R76W mutation causes atypical dominant Fanconi syndrome in addition to a β cell phenotype. J Med Genet. 2014;51:165–9.
47. Stanescu DE, Hughes N, Kaplan B, Stanley CA, De León DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. J Clin Endocrinol Metab. 2012;97:E2026–30.
48. Crocker JF, McDonald AT, Wade AW, Acott PD. The acadian variant of Fanconi's syndrome 1643. Pediatr Res. 1997;41:276.
49. Wornell P, Crocker J, Wade A, Dixon J, Acott P. An acadian variant of Fanconi syndrome. Pediatr Nephrol Berl Ger. 2007;22:1711–5.
50. Hartmannová H, Piherová L, Tauchmannová K, Kidd K, Acott PD, Crocker JFS, et al. Acadian variant of Fanconi syndrome is caused by mitochondrial respiratory chain complex I deficiency due to a non-coding mutation in complex I assembly factor NDUFAF6. Hum Mol Genet. 2016;25:4062–79.
51. Pitchon EM, Cachat F, Jacquemont S, Hinard C, Borruat F-X, Schorderet DF, et al. Patient with Fanconi syndrome (FS) and retinitis pigmentosa (RP) caused by a deletion and duplication

of mitochondrial DNA (mtDNA). Klin Monatsbl Augenheilkd. 2007;224:340–3.
52. Wendel U, Ruitenbeek W, Bentlage HA, Sengers RC, Trijbels JM. Neonatal De Toni-Debré-Fanconi syndrome due to a defect in complex III of the respiratory chain. Eur J Pediatr. 1995;154:915–8.
53. Friedman AL, Trygstad CW, Chesney RW. Autosomal dominant Fanconi syndrome with early renal failure. Am J Med Genet. 1978;2:225–32.
54. Illig R, Prader A. Primare tubulopathien. 2. Ein fall von idiopathischem gluko-amino-phosphat-diabetes (Detoni-Debre-Fanconi-syndrom). Helv Paediatr Acta. 1961;16:622.
55. Neimann N, Pierson M, Marchal C, Rauber G, Grignon G. Nephropathic familiale glomerulotubulaire avec syndrome de De Toni-Debré-Fanconi. Arch Fr Pediatr. 1968;25:43–69.
56. Baum M. The Fanconi syndrome of cystinosis: insights into the pathophysiology. Pediatr Nephrol Berl Ger. 1998;12:492–7.
57. Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nat Genet. 1998;18:319–24.
58. Cherqui S, Sevin C, Hamard G, Kalatzis V, Sich M, Pequignot MO, et al. Intralysosomal cystine accumulation in mice lacking cystinosin, the protein defective in cystinosis. Mol Cell Biol. 2002;22:7622–32.
59. Nevo N, Chol M, Bailleux A, Kalatzis V, Morisset L, Devuyst O, et al. Renal phenotype of the cystinosis mouse model is dependent upon genetic background. Nephrol Dial Transplant. 2010;25:1059–66.
60. Cherqui S, Courtoy PJ. The renal Fanconi syndrome in cystinosis: pathogenic insights and therapeutic perspectives. Nat Rev Nephrol. 2017;13:115–31.
61. Cross NC, Tolan DR, Cox TM. Catalytic deficiency of human aldolase B in hereditary fructose intolerance caused by a common missense mutation. Cell. 1988;53:881–5.
62. Morris RC. An experimental renal acidification defect in patients with hereditary fructose intolerance. II. Its distinction from classic renal tubular acidosis; its resemblance to the renal acidification defect associated with the Fanconi syndrome of children with cystinosis. J Clin Invest. 1968;47:1648–63.
63. Sun M-S, Hattori S, Kubo S, Awata H, Matsuda I, Endo F. A mouse model of renal tubular injury of tyrosinemia type 1: development of de Toni Fanconi syndrome and apoptosis of renal tubular cells in Fah/Hpd double mutant mice. J Am Soc Nephrol JASN. 2000;11:291–300.
64. Suchy SF, Nussbaum RL. The deficiency of PIP2 5-phosphatase in Lowe syndrome affects actin polymerization. Am J Hum Genet. 2002;71:1420–7.
65. Bockenhauer D, Bokenkamp A, van't Hoff W, Levtchenko E, Kist-van Holthe JE, Tasic V, et al. Renal phenotype in Lowe syndrome: a selective proximal tubular dysfunction. Clin J Am Soc Nephrol CJASN. 2008;3:1430–6.
66. Choudhury R, Diao A, Zhang F, Eisenberg E, Saint-Pol A, Williams C, et al. Lowe syndrome protein OCRL1 interacts with clathrin and regulates protein trafficking between endosomes and the trans-Golgi network. Mol Biol Cell. 2005;16:3467–79.
67. Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, et al. A common molecular basis for three inherited kidney stone diseases. Nature. 1996;379:445–9.
68. Solano A, Lew SQ, Ing TS. Dent-Wrong disease and other rare causes of the Fanconi syndrome. Clin Kidney J. 2014;7:344–7.
69. Hoopes RR, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus J, et al. Dent disease with mutations in OCRL1. Am J Hum Genet. 2005;76:260–7.
70. Borsani G, Bassi MT, Sperandeo MP, De Grandi A, Buoninconti A, Riboni M, et al. SLC7A7, encoding a putative permease-related protein, is mutated in patients with lysinuric protein intolerance. Nat Genet. 1999;21:297–301.
71. Riccio E, Pisani A. Fanconi syndrome with lysinuric protein intolerance. Clin Kidney J. 2014;7:599–601.
72. Fanconi G, Bickel H. Chronic aminoaciduria (amino acid diabetes or nephrotic-glucosuric dwarfism) in glycogen storage and cystine disease]. Helv Paediatr Acta. 1949;4:359–96.
73. Santer R, Schneppenheim R, Dombrowski A, Götze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat Genet. 1997;17:324–6.
74. Hamasaki T, Shimizu K. Seki K [Two cases of Alport's syndrome with incomplete Fanconi's syndrome or with situs inversus viscerum totalis]. Nihon Naika Gakkai Zasshi J Jpn Soc Intern Med. 1989;78:410–1.
75. Hurvitz H, Elpeleg ON, Barash V, Kerem E, Reifen RM, Ruitenbeek W, et al. Glycogen storage disease, Fanconi nephropathy, abnormal galactose metabolism and mitochondrial myopathy. Eur J Pediatr. 1989;149:48–51.
76. Tsuchiya M, Takaki R, Kobayashi F, Nagasaka T, Shindo K, Takiyama Y. Multiple pseudofractures due to Fanconi's syndrome associated with Wilson's disease. Rinsho Shinkeigaku. 2017;57:527–30.
77. Selvan C, Thukral A, Chakraborthy PP, Bhattacharya R, Roy A, Goswani S, et al. Refractory rickets due to Fanconi's syndrome secondary to Wilson's disease. Indian J Endocrinol Metab. 2012;16:S399-401.
78. Tzoufi M, Makis A, Chaliasos N, Nakou I, Siomou E, Tsatsoulis A, et al. A rare case report of simultaneous presentation of myopathy, Addison's disease, primary hypoparathyroidism, and Fanconi syndrome in a child diagnosed with Kearns-Sayre syndrome. Eur J Pediatr. 2013;172:557–61.
79. Earle KE, Seneviratne T, Shaker J, Shoback D. Fanconi's syndrome in HIV+ adults: report of three cases and literature review. J Bone Miner Res Off J Am Soc Bone Miner Res. 2004;19:714–21.
80. Nissim I, Horyn O, Daikhin Y, Nissim I, Luhovyy B, Phillips PC, et al. Ifosfamide-induced nephrotoxicity: mechanism and prevention. Cancer Res. 2006;66:7824–31.
81. Farid S, Latif H, Nilubol C, Kim C. Immune checkpoint inhibitor-induced Fanconi syndrome. Cureus. 2020;12: e7686.
82. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM Mon J Assoc Physicians. 2014;107:261–9.
83. Mirza N, Marson AG, Pirmohamed M. Effect of topiramate on acid-base balance: extent, mechanism and effects. Br J Clin Pharmacol. 2009;68:655–61.
84. Ghiculescu RA, Kubler PA. Aminoglycoside-associated Fanconi syndrome. Am J Kidney Dis Off J Natl Kidney Found. 2006;48:e89-93.
85. Chuang GT, Tsai IJ, Tsau YK, Lu MY. Transfusion-dependent thalassaemic patients with renal Fanconi syndrome due to deferasirox use. Nephrol Carlton Vic. 2015;20:931–5.
86. Tsimihodimos V, Psychogios N, Kakaidi V, Bairaktari E, Elisaf M. Salicylate-induced proximal tubular dysfunction. Am J Kidney Dis Off J Natl Kidney Found. 2007;50:463–7.
87. Rago RP, Miles JM, Sufit RL, Spriggs DR, Wilding G. Suramin-induced weakness from hypophosphatemia and mitochondrial myopathy. association of suramin with mitochondrial toxicity in humans. Cancer. 1994;73:1954–9.
88. Eiam-ong S, Spohn M, Kurtzman NA, Sabatini S. Insights into the biochemical mechanism of maleic acid-induced Fanconi syndrome. Kidney Int. 1995;48:1542–8.
89. Häring N, Mähr HS, Mündle M, Strohal R, Lhotta K. Early detection of renal damage caused by fumaric acid ester therapy by determination of urinary β2-microglobulin. Br J Dermatol. 2011;164:648–51.

90. Johri N, Jacquillet G, Unwin R. Heavy metal poisoning: the effects of cadmium on the kidney. Biometals Int J Role Met Ions Biol Biochem Med. 2010;23:783–92.
91. Lacy MQ, Gertz MA. Acquired Fanconi's syndrome associated with monoclonal gammopathies. Hematol Oncol Clin North Am. 1999;13:1273–80.
92. Messiaen T, Deret S, Mougenot B, Bridoux F, Dequiedt P, Dion JJ, et al. Adult Fanconi syndrome secondary to light chain gammopathy. clinicopathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore). 2000;79:135–54.
93. Sahu KK, Law AD, Jain N, Khadwal A, Suri V, Malhotra P, et al. Fanconi syndrome: a rare initial presentation of acute lymphoblastic leukemia. Indian J Hematol Blood Transfus Off J Indian Soc Hematol Blood Transfus. 2016;32:5–7.
94. Vanmassenhove J, Sallée M, Guilpain P, Vanholder R, De Potter A, Libbrecht L, et al. Fanconi syndrome in lymphoma patients: report of the first case series. Nephrol Dial Transplant. 2010;25:2516–20.
95. Magnano L, Fernández de Larrea C, Cibeira MT, Rozman M, Tovar N, Rovira M, et al. Acquired Fanconi syndrome secondary to monoclonal gammopathies: a case series from a single center. Clin Lymphoma Myeloma Leuk. 2013;13:614–8.
96. Luciani A, Sirac C, Terryn S, Javaugue V, Prange JA, Bender S, et al. Impaired lysosomal function underlies monoclonal light chain-associated renal Fanconi syndrome. J Am Soc Nephrol JASN. 2016;27:2049–61.
97. Saeki T, Nakajima A, Ito T, Takata T, Imai N, Yoshita K, et al. Tubulointerstitial nephritis and Fanconi syndrome in a patient with primary Sjögren's syndrome accompanied by antimitochondrial antibodies: a case report and review of the literature. Mod Rheumatol. 2018;28:897–900.
98. Igarashi T. Pediatric fanconi syndrome. In: Avner E, Harmon W, Niaudet P, Yoshikawa N, Emma F, Goldstein S, editors. Pediatric Nephrology. Berlin: Springer; 2016.
99. Gahl WA, Bernardini I, Dalakas M, Rizzo WB, Harper GS, Hoeg JM, et al. Oral carnitine therapy in children with cystinosis and renal Fanconi syndrome. J Clin Invest. 1988;81:549–60.
100. Bockenhauer D, Kleta R. Approach to the patient with renal Fanconi syndrome, glycosuria, or aminoaciduria. In: Turner N, Lameire N, Goldsmith D, Winearls CG, Himmelfarb J, Remuzzi G (Eds). Oxford Textbooks: Oxford Textbook of Clinical Nephrology. p. 412–22. 2015
101. Uetani M, Kobayashi E, Suwazono Y, Okubo Y, Kido T, Nogawa K. Investigation of renal damage among residents in the cadmium-polluted Jinzu River basin, based on health examinations in 1967 and 1968. Int J Environ Health Res. 2007;17:231–42.
102. Tang SF, Li HT, Zhu M, Ma ZS, Qiu MC. New ideas for the diagnosis and treatment of Fanconi syndrome: a pilot study. Chin Med J (Engl). 2013;126:3388–90.
103. Silva e ACS, Lima res CJCA, de Souto MFO. Acidose tubular renal em pediatria. J Bras Nefrol. 2007;29:38–47.
104. Clarke BL, Wynne AG, Wilson DM, Fitzpatrick LA. Osteomalacia associated with adult Fanconi's syndrome: clinical and diagnostic features. Clin Endocrinol (Oxf). 1995;43:479–90.
105. Devuyst O, Thakker RV. Dent's disease. Orphanet J Rare Dis. 2010;5:28.
106. Sniderman King L, Trahms C, Scott CR, et al. Tyrosinemia type I. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, Gripp KW, et al., editors. GeneReviews®. Seattle: University of Washington; 1993.
107. Kleta R, Bockenhauer D. Salt-losing tubulopathies in children: what's new, what's controversial? J Am Soc Nephrol JASN. 2018;29:727–39.
108. Vaisbich MH, Satiro CAF, Roz D, de Nunes DAD, Messa ACHL, Lanetzki C, et al. Multidisciplinary approach for patients with nephropathic cystinosis: model for care in a rare and chronic renal disease. J Bras Nefrol. 2019;41:131–41.
109. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. Pediatr Nephrol Berl Ger. 2011;26:205–15.
110. Soeiro EMD, de Helou CMB. Clinical, pathophysiological and genetic aspects of inherited tubular disorders in childhood. J Bras Nefrol. 2015;37:385–98.
111. Kleta R, Gahl WA. Pharmacological treatment of nephropathic cystinosis with cysteamine. Expert Opin Pharmacother. 2004;5:2255–62.
112. Eloxx Pharmaceuticals. A phase 2, single center, open-label, multiple dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of daily subcutaneously administered ELX-02 in patients with nephropathic cystinosis bearing one or more CTNS gene (cystinosin) nonsense mutations. clinicaltrials.gov; 2020. Available at https://clinicaltrials.gov/ct2/show/NCT04069260 (last update May 20, 2020).
113. Elenberg E, Norling LL, Kleinman RE, Ingelfinger JR. Feeding problems in cystinosis. Pediatr Nephrol Berl Ger. 1998;12:365–70.
114. Şeker-Yılmaz B, Kör D, Bulut FD, Yüksel B, Karabay-Bayazıt A, Topaloğlu AK, et al. Impaired glucose tolerance in Fanconi-Bickel syndrome: eight patients with two novel mutations. Turk J Pediatr. 2017;59:434–41.