primary process of podocytes and its expression significantly decreases in idiopathic FSGS. 43rd American Society of Nephrology Renal Week, November 19, 2010, Denver, USA.

表1

カンデサルタンレキシチル（ブロプレス®）によるACEI/ARB fetopathy発症数

西暦	2004	2005	2006	2007	2008	2009	2010
ACEI/ARB fetopathy 患者数	1	2	1	2	2	0	1

表2

ディオバン（バルサルタン@）によるACEI/ARB fetopathy発症数

西暦	2004	2005	2006	2007	2008	2009	2010
ACEI/ARB fetopathy 患者数	2	0	9	0	2	3	1

Ⅲ　参考資料

腎性尿崩症に関するアンケート調査票

御所属　＿＿＿＿＿＿＿＿＿＿＿＿病院＿＿＿＿＿＿＿＿科

御住所　〒

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

御芳名　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

質問 1.　過去に先生御自身あるいは貴診療科において、腎性尿崩症と診断された症例をご経験されていますか。いずれかに○をしてください。

ある　・　ない

質問 2.　質問 1.で**ある**とお答えいただいた場合、症例数をお知らせ下さい。
（死亡された方も含みます。）

（　　人）

質問 3.　直接診療を担当されていなくても、腎性尿崩症の患者さまをご存知の場合は、医療機関、問い合わせさせていただく担当の先生等を可能な範囲でお教え下さい。

（医療機関：　　）
（担当医師：　　先生）

（医療機関：　　）
（担当医師：　　先生）

ご協力誠にありがとうございました。

腎性尿崩症に関するアンケート調査：２次調査票

経験された症例毎にお願いします。
該当する項目の□に印を、また記入欄も分かる範囲で結構ですので、よろしくお願いいたします。

医療機関・診療科名	
連絡先医師のお名前	
email address	

同一の症例を複数の先生方でご登録されている場合は、本アンケートは一部にまとめていただいて結構です。なお、症例の重複を避けるため、担当された先生方のご芳名を下にご記入願えますでしょうか。

担当医師名	

Ⅰ．患者背景

・患者情報

性別	□ 男　□ 女	
生年月日	□ 昭和 □ 平成	_____年（西暦_____）、_____月
発症推定年齢	_____歳_____ヶ月	
診断年齢	_____歳_____ヶ月	
基礎疾患	□ あり　□ なし　□ 不明	
コメント （基礎疾患、薬剤等）		

・母体妊娠中の服用歴

ACEi：アンギオテンシン変換酵素阻害薬）	□ あり　□ なし　□ 不明
ARB：アンギオテンシンⅡ受容体拮抗薬	□ あり　□ なし　□ 不明
その他・コメント	

・家族歴（本症と関連があると思われるもののみで結構です）

尿崩症	□ あり　□ なし　□ 不明
その他	□ あり　□ なし　□ 不明
コメント	

Ⅱ. 発症時（初診時）の症状

□ 口渇　□ 多飲　□ 多尿　□ 夜尿
□ 嘔吐　□ 便秘　□ 発熱　□ 尿路感染症
□ 痙攣　□ 意識障害　□ 体重増加不良　□ 成長障害
□ 精神発達遅滞

□ その他・コメント

Ⅲ. 診断検査方法

□ 水制限試験
□ 5%高張食塩水負荷試験
□ デスモプレシン（DDAVP）負荷試験

□ 尿浸透圧 _____mOsm/kg
□ 血漿浸透圧 _____mOsm/kg
□ 血清 Na 値（最高値） _____mEq/l
□ 血漿 AVP 値（最高値） _____pg/ml

□ 頭部 MR　下垂体後葉 T1 強調像高信号消失　□ あり　□ なし

□ その他・コメント

Ⅳ. 遺伝子検査

□ 実施　□ 未実施	
遺伝子診断結果	

Ⅴ. 診断

□ 腎性尿崩症	□ 先天性	
	□ 二次性	□ リチウム
		□ その他
□ 中枢性尿崩症		
□ 心因性多尿		
□ その他・分類不能		

Ⅵ. 治療（現在までに行った治療とその効果について）

□ DDAVP（デスモプレシン）	反応性：□ あり　□ なし
□ サイアザイド系利尿薬	反応性：□ あり　□ なし
□ プロスタグランジン合成阻害薬（インドメタシン等）	反応性：□ あり　□ なし
□ 非ステロイド性消炎鎮痛剤（メフェナム酸：ポンタール等）	反応性：□ あり　□ なし
□ 塩分制限	反応性：□ あり　□ なし
□ その他・コメント	

Ⅶ. 治療副作用

□ 頭痛	□ 悪心・嘔吐	□ 低 Na 血症	□ 低 K 血症
□ 成長障害	□ 水中毒	□ 急性腎不全	
□ その他・コメント			

Ⅷ. 合併症

腎合併症	□ 水腎症　□ 水尿管　□ 膀胱尿管逆流 □ 腎不全　□ アシドーシス
	□ その他
□ 精神発達遅滞：（ □ 軽度　□ 重度　□ 不明 ） □ 痙攣（てんかん） □ 脳梗塞・脳出血 □ 血栓症	
□ その他・コメント	

Ⅸ. 死亡の有無

□ あり　□ なし	
死因 もしくは 現在の状況	

Ⅹ. 遺伝子解析について

患者様のご同意をいただけるようでしたら、当方で遺伝子解析の症例を募っております。

ご協力、誠にありがとうございました。

Ⅳ　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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V　研究成果の刊行物・別刷

42 Fanconi Syndrome

Takashi Igarashi

Fanconi syndrome (FS) is a generalized dysfunction of the renal proximal tubules leading to excessive urinary wasting of amino acids, glucose, phosphate, uric acid, bicarbonate, and other solutes. The patients develop failure to thrive, polyuria, polydipsia, dehydration, and rickets in children, and osteoporosis and osteomalacia in adults. The patients also manifest renal salt wasting, hypokalemia, metabolic acidosis, hypercalciuria, and low-molecular-weight (LMW) proteinuria. De Toni, Debré, and Fanconi described children with renal rickets and glucosuria in the 1930s (1, 2, 3). FS is named after Guido Fanconi, a Swiss pediatrician or it is called as de Toni-Debré-Fanconi syndrome.

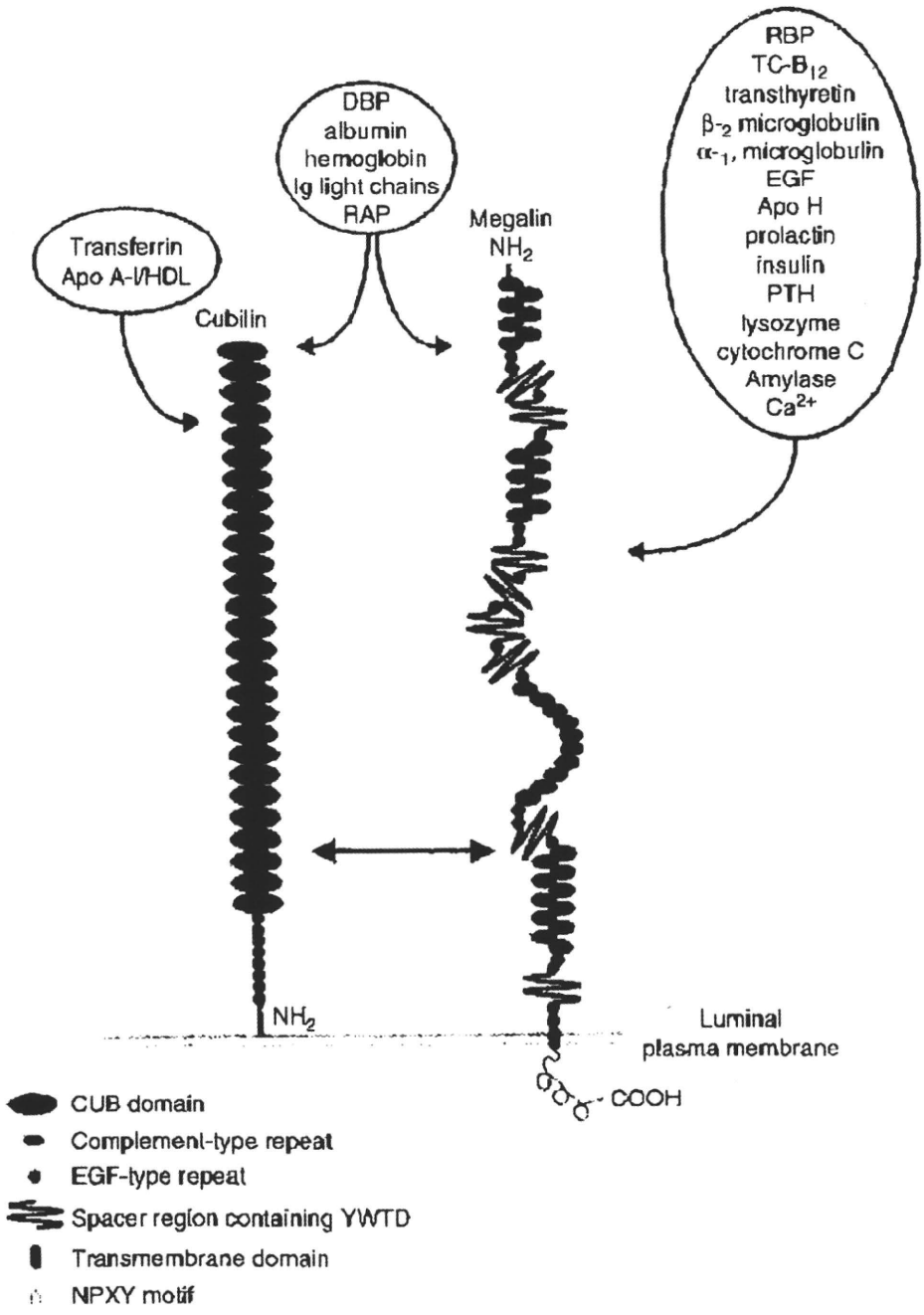
Pathophysiology

The renal proximal tubules reabsorb almost all of the physiologically filtered load of proteins including of albumin, LMW proteins, amino acids, glucose, bicarbonate, sodium, chloride, phosphate, and uric acid. The transport processes in the proximal tubule can be characterized broadly as megalin/cubilin-mediated endocytic pathways and sodium (Na^+) gradient-dependent transport systems.

The proximal tubule cells have extensive luminal receptors and endocytic apparatus such as megalin and cubilin that are critical for the reabsorption and degradation of proteins that traverse the glomerular filtration barrier (4) (● *Fig. 42-1*) as well as for the extensive recycling of many functionally important membrane proteins (5). Numerous filtered proteins including albumin, LMW proteins, polypeptide hormones, vitamin-binding proteins, and polybasic drugs such as aminoglycosides from glomerulus are bound to megalin and cubilin in the luminal membrane of proximal tubules. Then, the protein-receptor complex is incorporated into the endosome. The ligand and receptor are disassociated in the endosome; the receptor is recycled back to the luminal membrane and the reabsorbed proteins go into lysosome for further processing (● *Fig. 42-2*). This disassociation is dependent on acidification of the endosome by increased concentration of H^+ and Cl^- due to the function of H^+-ATPase (proton pump) and ClC-5 chloride channel. An abnormal endocytosis pathway may affect the recycling of transport proteins (megalin and cubilin), the back to the luminal membrane, and the expression of megalin and cubilin in the luminal membrane, leading to decreased solute reabsorption. Perturbation of endosomal acidification in proximal tubule cells leads to diminished reabsorption and increased urinary wasting of albumin, LMW proteins, electrolytes, and solutes. Cadmium inhibits H^+-ATPase and mitochondria, which results in a Fanconi-like syndrome (6). Folimycin, a H^+-ATPase inhibitor, abolishes albumin uptake by proximal tubules (7). Moreover, a defect of ClC-5 chloride channel in patients with Dent disease manifests Fanconi syndrome (8). Acidification defect in the endosome in Dent disease leads to recycling from intracellular endosome into luminal membrane resulting in megalin deficiency in the luminal membrane of the proximal tubule. Analysis of normal human urine samples identified megalin as a physiologically excreted protein. The presence of megalin in normal human urine is due to shedding from the proximal tubule cells into the lumen. Patients with Dent disease demonstrate an almost complete absence of urinary megalin (9). This megalin-shedding deficiency in the urine is also observed in patients with Lowe syndrome (9).

Reabsorption of filtered solutes including glucose, phosphate, amino acids, and bicarbonate by proximal tubule cells is accomplished by transport system at the brush border membrane that are directly or indirectly coupled to Na^+ movement, by energy production and transport from the mitochondria, and by the Na^+, K^+-ATPase at the basolateral membrane. The Na^+, K^+-ATPase lowers intracellular Na^+ concentration and provides the electrochemical gradient that allows Na^+-coupled solute entry into the cell. Disturbances in energy generation could impair net transepithelial transport in the proximal tubule. Energy is necessary for the operation of Na^+, K^+-ATPase and other membrane carriers that are involved with solute reabsorption of amino acid, glucose, phosphate, uric acid, and bicarbonate. Although the weight of bilateral kidneys is less than 1% of total body weight, kidneys consume about 10% of the total energy consumed by the whole body in a static condition. Moreover, most of the energy is consumed in the proximal tubule cells to operate multiple

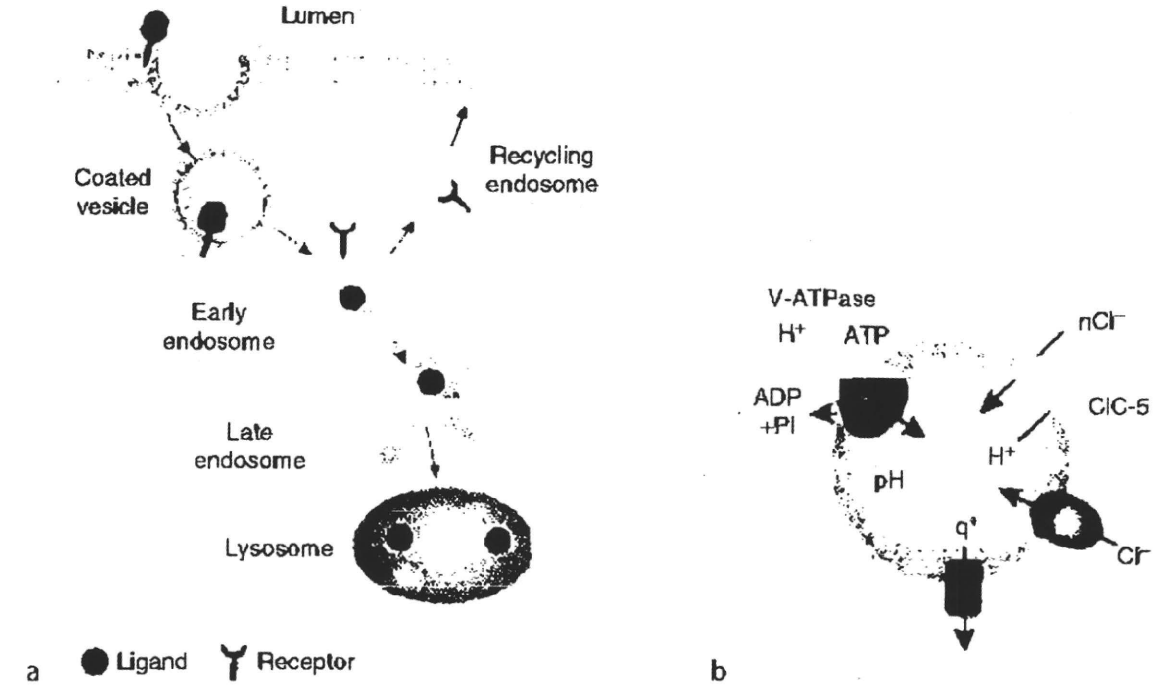
ıegalin and cubilin. (Veroust PJ, Birn H, Nielsen R et al. The tandem endocytic receptors megalin and cubilin proteins in renal pathology. *Kidney Int* 2002;62:745–756).



d intracellular transporter proteins. A defect ıration in the proximal tubule cells produces ıport anomalies of the proximal tubule that ıe FS. The ATP production is severely com- cystine-loaded tubule in cystinosis (10). ing enzymes are critical for renal energy Cystine inhibits in vivo and in vitro the ng enzyme activity resulting in multiple ort anomalies (11). The mitochondrial respiratory chain has a major role in ATP production during aerobic respiration. Genetic defects of enzyme complexes of the oxidative phosphorylation system or toxic substances including of drugs in the proximal tubule cells can produce mitochondrial respiratory chain defect leading to multiple renal transport anomalies (12, 13). In contrast, isolated dysfunction of transporter proteins in proximal tubule cells results in the selective wasting of amino acids, glucose, phosphate, bicarbonate, or uric

Figure 42-2

Schematic model of endocytosis in the proximal tubule cells. Albumin and low molecular weight proteins are filtered in the primary urine and endocytosed by proximal tubule cells via the megalin-cubilin receptor pathway. (a) The receptor ligand complexes progress along the endocytic pathway. The endosomes undergo a progressive, ATP-dependent acidification that results in the dissociation of the receptor-ligand complexes, with megalin and cubilin being recycled the luminal membrane, whereas the ligand is directed to lysosomes for degradation. (b) Vesicular acidification is mediat by the vacuolar H^+-ATPase, which requires a net Cl^- conductance to functions as an electrogenic nCl^-/H^+ exchanger, whi is predicted to facilitate acidification and to play a role in keeping high vesicular Cl^- concentration. (Devuyst O, Pirson Genetics of hypercalciuric stone forming disease. *Kidney Int* 2007:72:1065–1092).



acids. However, glucosuria and aminoaciduria are seen in some patients with defective isolated proteins. They are familial renal glucosuria resulting from the mutations in the kidney-specific low affinity/high capacity Na^+/glucose cotransporter gene (*SLC5A2*) and maturity-onset diabetes of young age type 3 (MODY3) resulting from the mutations in hepatocyte nuclear factor-1 alpha gene that acts as a regulator of transcription for *SLC5A2* (14, 15). Generalized aminoaciduria seen in these patients is considered as a consequence of the impairment in tubular glucose reabsorption, whereas the precise mechanism is not known.

Signs and Symptoms

Growth Retardation (Failure to Thrive)

Growth retardation (failure to thrive) is a common feature of FS in children (16). Patients with FS present severe growth failure at the time of diagnosis that persists in adult life. The pathomechanism of growth failure in FS complex. Malnutrition, hypokalemia, hypophosphatem and metabolic acidosis can lead to growth retardation patients with FS (17). Potassium deficiency induc growth retardation through reduced circulating levels growth hormone (GH) and insulin-like growth factor (IGF-I) (18, 19). Hypokalemia can induce appetite d crease leading to malnutrition and extracellular volur contraction. Metabolic acidosis inhibits growth hormo secretion, the expression of IGF-I and GH receptor (2(Hypophosphatemia is related to severe bone chang leading to rickets and growth retardation in childr with FS (21). In patients with adult onset FS, osteomala(is thought to result from hypophosphatemia due to rer phosphate loss and relative 1,25-dihydroxyvitamin I deficiency (22, 23). Metabolic acidosis impairs the co version of 25-vitamin D3 to 1,25-dihydroxy vitamin D The patients present bone and joint pain in the hi

ınd trunk and difficulty of walking due to ıne fracture. Hypomineralization of dentin d immature formation of craniofacial bones ıatients with FS (24). Specific forms of FS are ıith endocytotosis pathway dysfunction; dis- negalin-mediated uptake vitamin D-binding itamin D3 complex produces metabolic bone fected individuals (25).

agnosis and efficient correction of acidosis and ılances by supportive therapy can contribute growth and final height in patients with FS vever, supportive therapy is frequently unable ırther loss of relative height in patients with · those with cystinosis.

olydipsia, and Dehydration

ydipsia, and dehydration are frequently seen ith FS. Polyuria is secondary to the osmotic the excessive urinary solute losses and urine ı defect in the collecting ducts due to chronic Recurrent acute fever due to dehydration is a ifestation in infants with FS. In the most : of cystinosis, Fanconi syndrome occurs at of age. Recurrent febrile episodes are often f FS in infantile patients with cystinosis (26).

d Aminoaciduria (Generalized ıoaciduria)

ight (MW) of 20 different amino acids is est amino acid is tryptophan [MW = 204 D ıino acids are not bound to proteins in the amino acids are freely filtered from glomer- ı–99% of filtered load of amino acids are the proximal tubules. More than one trans- ›roximal tubule cells absorbs amino acids. etion of amino acid is usually less than 3% ı except for neonate or premature babies. histidine has a fractional excretion of 5%

nal excretion of amino acid (%) =
a/Paa)/(Ucr/Pcr)] × 100

l, cr; creatinine, U; urine, P; plasma)

he excretion more than 5% of the filtered acid is termed aminoaciduria or hypera- Every amino acid is highly excreted in patients with FS, and this phenomenon is called as *generalized aminoaciduria.*

Glucosuria

Filtered load of glucose (D-glucose, MW = 180 D) is almost completely absorbed by a sodium-coupled active transport located in the brush border membrane of the proximal tubule in the normal condition. Glucose reabsorption involves a couple of transporters at the luminal and basolateral membranes of the proximal tubules. The driving force for glucose reabsorption is provided by Na^+, K^+-ATPase in the plasma membrane. Thus, very small amount of glucose are present in the urine in the normal condition. Glucosuria is a common manifestation in FS. It is derived from impaired reabsorption of glucose when serum glucose is normal. Renal threshold of glucose is reduced in FS. Glucosuria is one of the originally described clinical features of FS (1, 2, 3). 0.5–20 g of glucose a day is lost in the urine in patients with FS.

Hypophosphatemia

Most of the patients with FS manifest a low tubular reabsorption of phosphate (percent tubular reabsorption of phosphate: %TRP, >80–85% in the control) and decreased serum phosphate. Rickets and osteomalacia are produced by the increased urinary wasting of phosphate as well as by impaired 1α-hydroxylation of 25-hydroxy vitamin D3 by proximal tubule cells (27).

$$\%TRP = [1-(Up/Sp)/(Ucr/Scr)] \times 100$$

(p; phosphate, cr; creatinine, U; urine, S; serum)

The maximal threshold of phosphate (TmP/GFR) is a very sensitive indicator that reflects the reabsorption of phosphate in the renal tubules.

$$TmP/GFR = TRP \times Sp$$

(GFR; glomerular filtration rate, p; phosphate, S; serum)

The Tm/GFR is usually very low (2.3–4.3 in the control) in patients with FS. Rickets manifests bowing deformity of the lower limbs, distal femur, the ulna, and the radius.

Phosphate handling in the kidney is affected by a couple of factors including parathyroid hormone (PTH) and vitamin D. PTH level is normal or elevated in patients with FS. Serum 1, 25-dihydroxy vitamin D3 is variable in patients with FS (28, 29).

Metabolic Acidosis

More than 85% of filtered load of bicarbonate ($HCO3^-$) is reabsorbed by the proximal tubule cells. This is accomplished by the coordinated function of luminal membrane Na^+/H^+ exchanger, luminal membrane carbonic anhydrase IV and XIV, and basolateral membrane $Na^+/HCO3^-$ cotransporter (30). Hyperchloremic metabolic acidosis is a common feature of FS resulting from defective bicarbonate reabsorption in the proximal tubules. Anion gap is normal. More than 30% of filtered load of $HCO3^-$ is not reabsorbed in patients with FS, and they manifest low plasma $HCO3^-$ levels between 12–18 mEq L^{-1}. Fractional excretion of $HCO3^-$ ($FEHCO3^-$) under the alkali treatment to increase plasma $HCO3^-$ to the normal ranges is >15% in patients with FS.

$$\text{Fractional excretion of } HCO_3\text{-}\% = [(UHCO_3\text{-}/PHCO_3\text{-})/(Ucr/Pcr)] \times 100$$

($HCO3^-$; bicarbonate, cr; creatinine, U; urine, P; plasma)

Acidification in the distal tubule is usually normal or impaired in association with chronic hypokalemia or toxic effect on distal tubules due to the original disorder in patients with FS.

Sodium and Potassium Losses

60–80% of filtered load of Na^+ is reabsorbed in the proximal tubules in the normal condition. Renal Na^+ reabsorption in the proximal tubules decreased in patients with FS. It leads to hyponatremia, hypotension, and dehydration. Hypokalemia is a secondary phenomenon. Increased delivery of Na^+ into the distal tubules and activation of the renin-angiotensin system secondary to hypovolemia cause potassium (K^+) wasting in the distal tubules. Severe hypokalemia can cause sudden death.

Hypercalciuria

Hypercalciuria is a common finding in patients with FS due to several original diseases. Defective endocytosis of parathyroid hormone (PTH) in patients with Dent disease resulting in its persistence in the lumen of the proximal tubule stimulates 25-hyroxyvitamin D3 1-hydroxylase to produce more 1,25-dihydroxyvitamin D3, raising serum levels of this vitamin. 25-hydroxyvitamin D3 is presented to 25-hydroxyvitamin D3 1-hydroxylase in the form of a complex with the vitamin D3-binding protein. As this complex is lost in the urine as a result of defective endocytosis leading to LMW proteinuria, the precursor 25-hydroxyvitamin D3 could be in short supply. The overall outcome of increased 1, 25-dihydroxyvitamin D3 levels may depend on the delicate balance between these processes. The slightly elevated serum levels of 1, 25-dihydroxyvitamin D3 in patients with FS can lead to increased intestinal Ca^{2+} reabsorption which will lead to hypercalciuria (*absorptive hypercalciuria*) (29). Hypercalciuria is rarely associated with nephrolithiasis in FS, possibly because of the polyuria and alkalized urine. However, patients with Dent disease manifest hypercalciuria and nephrolithiasis.

Hyperuricosuria (Uricosuria)

Uric acid (urate) is the end product of purine metabolism in humans. Because of its small molecular size (MW = 126 D), uric acid is freely filtered from the glomerulus. Then, 90–95% of filtered load of uric acid is eventually reabsorbed in the proximal tubules. A four-component hypothesis has been proposed to explain the renal uric acid transport mechanism; it includes glomerular filtration, presecretory reabsorption, secretion, and postsecretory reabsorption (31). Hyperuricosuria is often present in FS, leading to secondary hypouricemia (<2 mg dL^{-1}) (32). A voltage-sensitive uric acid pathway and uric acid exchangers are located at both luminal and basolateral membranes of proximal tubule cells (33). Uric acid-anion exchanger (URAT1) that reabsorbs uric acid from the lumen of the proximal tubules in the luminal membrane of proximal tubules regulates serum uric acid levels. This uric acid-anion exchanger can be disturbed in patients with FS. Defective URAT1 is a predominant cause of the patients with renal hypouricemia who manifest acute renal failure after exercise (34, 35). Hexose transporter gene (*SLC2A9*) is identified as a cause of gout and hyperuricemia (36). This transporter transports both fructose and uric acid. *SLC2A9* produces two isoforms by alternative splicing; the long isoform is expressed in basolateral membrane of proximal tubular cells and the short isoform is expressed in apical membrane of proximal tubular cells. This hexose transporter can be affected in patients with FS. Uric acid is a selective antioxidant, capable especially of reaction with hydroxyradicals and hypochlorous acid, itself being converted to innocuous products such as allantoin, allantoate, glyoxylate, urea, and oxalate (37).

a (LMW Proteinuria)

l tubules have a high capacity for uptake of ns from the glomerulus. The cut off molec- r filtration of plasma proteins is assumed to e of 65 KD (kilodaltons) that corresponds to · weight of serum albumin. However, small rger weight proteins including gammaglo- red from glomerulus in the normal condi- n and LMW proteins (MW<45,000 D) glomerulus are considered to be the major ıary albumin and LMW proteins. Filtration ıd LMW proteins are followed by tubular and thus the resulting albuminuria and ıuria reflect the combined contribution of cesses. Dysfunction of both these processes increased urinary excretion of albumin and s, and both glomerular injury and tubular ıave been implicated in the initial events teinuria. In FS, proteinuria is predominant- ıe dysfunction of reabsorption in the proxi- Adolescent patients with FS due to Dent ɔwe syndrome excrete greatly increased ·oteins (1,740 ± 660 mg/day) and peptide ıg/day). LMW proteins ranging from 2 to ɔresent in 12.9 ± 3.9-fold excess in FS h normal urine (38). The micropuncture ogs revealed that the filtered load of albu- ; m^{-2} suggesting that a filtered load of g/day in normal humans (39). However, on of protein is less than 0.1–0.15 g/day condition. Numerous filtered proteins in- in and LMW proteins from glomerulus are ılin and cubilin in the luminal membrane bules. Then, the protein-receptor complex into the endosome. The ligand and recep- ıciated in the endosome; the receptor is to the luminal membrane and the reab- s go into lysosome for further processing.)0 KD glycoprotein and a member of the poprotein receptor family. Megalin is e proximal tubule brush-border and lumi- ıpparatus. Megalin binds to a number of ·y different proteins. It contains a large l, extracellular domain, a single transmem- ınd a short carboxy-terminal cytoplasmic -1). Cubilin is a multiligand, endocytic a 460 KD protein with little structural nown, endocytic receptor (● *Fig. 42-1*). ssed in the proximal tubule brush-border ıdocytic apparatus. Megalin involved in albumin reabsorption directly as a receptor for albumin, and/or indirectly by affecting the expression and/or endocytic function of cubilin (40, 41). Megalin's expression was decreased in patients with Dent disease. Acidification defect due to endosomal defective ClC-5 in patients with Dent disease disturbs the recycling from intracellular endosome into luminal membrane of the proximal tubule resulting in megalin and cubilin deficiency in the luminal membrane of the proximal tubule.

Etiologies

The causes of FS are divided into three main categories; hereditary, acquired, and exogenous substances (● *Table 42-1*). Most of the hereditary FS occurs as one of the manifestations of congenital metabolic disorders or as sporadic or familial disorders. Acquired forms are derived from immunological reactions, nephrotic syndrome or accumulated abnormal proteins. Exogenous substances are composed of drugs, chemical compounds, and heavy metals.

Hereditary Fanconi Syndrome

Dent Disease

Dent disease is an X-linked proximal tubulopathy characterized by LMW protinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and eventual end stage renal failure. Hypophosphatemic rickets and metabolic acidosis are sometimes seen (42, 43). Almost all of the patients are males. Adult patients with Dent disease manifest FS. However, children with Dent disease often manifest LMW proteinuria and one or two of the manifestations due to proximal tubular dysfunction and this is called partial FS (44). They usually fall into end stage renal failure by the age of 40s. However, this is highly variable, and one third of patients with Dent disease will not develop end stage renal failure. Patients with Dent disease never manifest extrarenal manifestations, except for rickets, which may itself be a consequence of phosphaturia. School children with Dent disease manifest proteinuria. A lot of school children with Dent disease are detected as proteinuria by school urine mass screening program in Japan, and it was called as idiopathic low molecular weight proteinuria (45, 46). Carrier females are often manifest less severe LMW proteinuria and hypercalciuria, depending on X-chromosome inactivation, but they rarely develop clinically significant problems.