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ORIGINAL ARTICLE

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Repurposing SGLT2 inhibitors: Treatment of renal proximal tubulopathy in Fanconi-Bickel syndrome with empagliflozin

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Abstract

Renal proximal tubulopathy in Fanconi-Bickel syndrome is caused by impaired basolateral glucose transport via GLUT2 and consequently, intracellular accumulation of glucose and glycogen. SGLT2 inhibitors act on apical glucose reabsorption of renal proximal tubular cells. The purpose of this study was to retrospectively describe the first experiences with repurposing the SGLT2 inhibitor empagliflozin to treat the generalized tubulopathy in Fanconi-Bickel syndrome. A case series was conducted of seven persons from five families (five males, two females; three children, who were 14y5m, 2y9m, and 1y6m old) with genetically confirmed Fanconi-Bickel syndrome, off-label treated with empagliflozin. Median (range) age at start of empagliflozin was 27 years (1y6m – 61y) and duration of follow-up under empagliflozin treatment was 169 days (57–344). Under empagliflozin (up to 25 mg/d), biochemical parameters of tubular cell integrity (urinary *N*-acetyl-glucosaminidase) and/or tubular functions (including urinary α1-microglobulin) improved in all persons with Fanconi-Bickel syndrome, albeit to varying degrees. Clinically, supplementations (i.e., phosphate, alkali, carnitine, and alfacalcidol) could be completely discontinued in the three

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children, whereas results in the four adult patients were more variable and not as significant. Empagliflozin was well-tolerated and no symptomatic hypoglycemia was observed. In conclusion, SGLT2 inhibitors such as empagliflozin shift the metabolic block in Fanconi-Bickel syndrome, that is, they intervene specifically in the underlying pathophysiology and can thus attenuate renal proximal tubulopathy, especially when started in early childhood.

KEYWORDS

drug repurposing, Fanconi-Bickel syndrome, inherited metabolic disease, off-label treatment, renal proximal tubulopathy, SGLT2 inhibitor

1 | INTRODUCTION

Fanconi-Bickel syndrome (FBS, OMIM #227810), also called glycogen storage disease (GSD) type XI, is an ultra-rare inherited metabolic disorder (IMD) of carbohydrate metabolism. FBS is caused by biallelic dysfunctional variants in the *SLC2A2* gene, encoding the GLUT2 transporter that is expressed in hepatocytes, pancreatic beta cells, and the basolateral membranes of intestinal epithelial cells and renal proximal tubular cells.[1–3] GLUT2 is a high-capacity transporter enabling a flow of glucose into or out of these cells depending on the concentration gradient (i.e., passive transport).[4] The typical clinical phenotype of persons with FBS is characterized by symptoms that are the result of a perturbation of glucose homeostasis and a generalized proximal tubulopathy, also called "the renal Fanconi syndrome." Current treatment is supportive and consists of a dietary and a medicinal component. Dietary treatment aims to normalize glucose homeostasis by prevention of catabolism (by use of uncooked cornstarch and/or continuous nocturnal gastric drip feeding), avoidance of rapidly absorbed sugars, and restriction of galactose. The medicinal treatment aims to replace (a) renal losses through supplementation of water, electrolytes, bicarbonate, phosphate, and L-carnitine, and (b) the diminished synthesis of active vitamin D_3 ($1,25(OH)_2$-vitamin D_3), whichever is necessary.[3,5] Persons with FBS experience a high burden of both the disease and the treatment. The renal Fanconi syndrome can cause severe polyuria (often with nocturia and/or urinary incontinence) and severe rickets with profound growth retardation. Many of the supplements have a bad taste, they can cause abdominal discomfort (including diarrhea) and must be administered multiple times per day throughout life, which negatively affects treatment compliance. Compliance with both dietary and medicinal treatment is important especially during childhood, the period crucial for growth and development.

Since the identification of specific renal and intestinal sodium-dependent glucose transporters (SGLTs) in the early 1990s, several selective inhibitors of the apically expressed SGLT2 of renal tubular cells have been developed to reduce hyperglycemia as a novel strategy to treat type-2 diabetes.[6] Since 2019, SGLT2 inhibitors have been successfully repurposed in glycogen storage disease type Ib (GSD Ib), another ultra-rare IMD of carbohydrate metabolism. In GSD Ib, SGLT2 inhibitors induce renal excretion of a glucose analog responsible for neutropenia and neutrophil dysfunction.[7–11] We subsequently hypothesized that SGLT2 inhibitors may also improve renal symptoms in FBS by pharmacological inhibition of glucose uptake at the apical membrane of renal proximal tubular cells. This would lead to a reduction of intracellular glucose and glycogen accumulation, attenuate the resulting secondary intracellular osmotic effects, and mitigate the sequalae of the basolaterally located metabolic block due to an absent or non-functioning GLUT2. Very recently, this concept was first reported by Trepiccione and co-workers, who generated and characterized a mouse model in which *Glut2* was disrupted.[12] Subsequently, they demonstrated that the SGLT2 inhibitor dapagliflozin limited apical glucose uptake and intracellular glycogen storage and proximal tubular functions improved in these mice and, eventually, they also found a beneficial effect in a 30-year-old person with FBS.

Here, we report our first observations of repurposing empagliflozin to treat renal proximal tubulopathy in seven persons with FBS from five families, including three children.

2 | METHODS

2.1 | Study design and study population

We report on a case series describing the repurposing of empagliflozin as an individualized, rational, off-label pharmacological treatment in seven persons with FBS followed in three tertiary metabolic centers: University Medical Center Groningen (UMCG), University Medical

Center Freiburg (UMCF), and University Medical Center Eppendorf (Universitätsklinikum Eppendorf, UKE), Hamburg. The cohort consisted of five males (71%) and two females (29%). Median (range) age at start of empagliflozin was 27 years (1y6m–61y) and duration of follow-up on empagliflozin treatment was 169 days (57–344).

Oral and written informed consent was obtained for the off-label treatment and the publication of pseudonymized data. All treatment decisions were made on an individual basis and data thus obtained was collected as part of regular clinical care. In the absence of formal reimbursement of empagliflozin for this indication, the empagliflozin costs were covered by either the hospital (UMCG) or by the health insurances based upon individual requests (UMCF and UKE).

The Medical Ethics Committee of the University Medical Center Groningen stated that the Medical Research Involving Human Subjects Act is not applicable in observational studies using retrospective, pseudonymized data and that official study approval by the Medical Ethical Committee is not required (METc 2019/119).

2.2 | Empagliflozin treatment

Based on clinical experience in type-2 diabetes[13] and GSD Ib,[8] the safety profile of SGLT2 inhibitors (gliflozins) was considered favorable. Empagliflozin was selected because it is one of the gliflozins with the highest specificity for inhibiting SGLT2,[14] and based on our positive previous experiences which have been recently reported as a "Benefit-Risk Assessment of Off-label use (BRAvO)" for persons with GSD Ib.[10] In addition, most adverse effects of empagliflozin are related to the induction of glucosuria which is already part of the FBS phenotype. Moreover, the complex glucose homeostasis in FBS characterized by a combination of both fasting hypoglycemia and glucose intolerance with postprandial hyperglycemia or rarely even overt diabetes mellitus,[15] may make SGLT2 inhibitors a substantiated treatment option.

The overall higher propensity to fasting hypoglycemia, and developmental changes of drug disposition and organ function in children[16] raised special concerns before empagliflozin treatment in children with FBS and supported a lower empagliflozin starting dose in infants. First, young, pre-verbal children have higher endogenous glucose requirements,[17] cannot express their symptoms clearly, are more prone to intercurrent infections, and may develop higher levels of fever during intercurrent infections. Second, in vitro studies suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5′-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.[13] Although the developmental pattern of UGT1A3 is not known, the remaining glucuronidation enzymes reach normal activities only after infancy.[18] Consequently, like in GSD Ib,[8] after a low starting dose (i.e., 0.3–0.4 mg/kg/d for children <25 kg, or 10 mg for children >25 kg and adults as a single morning dose), empagliflozin was increased to a maximum of 0.8 mg/kg/d for children, or 20–25 mg in adults given in one or two doses. In addition, for safety reasons, all children with FBS were started empagliflozin treatment during a hospital admission under control of continuous glucose monitoring (CGM), whereas in adults, treatment was initiated in an outpatient setting.

2.3 | Clinical and biochemical data

Clinical and biochemical data were retrospectively compiled from the medical records at baseline and under empagliflozin treatment. Clinical parameters included the *SLC2A2* genotype, sex, age at diagnosis and start of symptomatic treatment, age at start of empagliflozin treatment, biometric data (height, body weight, BMI), blood pressure, and details regarding medication. Laboratory parameters included basic clinical chemistry in serum, parameters of kidney function and proximal tubular damage, including metabolic parameters (plasma/dried blood spot acylcarnitines, plasma/urine amino acids, and urinary organic acids). A laboratory parameter was considered to represent a clinically meaningful improvement if average of results after treatment with empaglifozin was 20% lower/higher than before treatment. See Supplementary Table S1 for the detailed list of all parameters collected.

3 | RESULTS

3.1 | Clinical outcomes

General characteristics of seven persons with FBS on empagliflozin treatment are summarized in Table 1; and a summary of treatment results is presented in Table 2. The complete dataset is available as Supplementary Table S1 and the detailed case series descriptions are presented as Supplementary File S2.

Empagliflozin was well-tolerated without any reported adverse events by the participants or caregivers. Neither symptomatic hypoglycemias nor hypotension were observed under empagliflozin. Interestingly, in all four persons with FBS who used CGM (participant I, II, VI, and VII), improvement in glucose homeostasis was noted. During follow-up under both empagliflozin and dietary modifications, Time-below-range (<3.0 mmol/L) decreased from 3% to <1% in participant VI and from 5%

TABLE 1 General characteristics of seven persons with Fanconi-Bickel syndrome on empagliflozin treatment.

	Participants						
	I	II	III[a]	IV[a]	V	VI[b]	VII[b]
Homozygosity for *SLC2A2* variant: Nucleotide change (NM_000340.2) Predicted protein change (NP_000331.1)	c.497-2A > G p.?	c.(963 + 71_?) del p.?	c.137delT p.(L46Wfs*29)	c.137delT p.(L46Wfs*29)	c.(963 + 71_?)del p.?	c.1171-2A > G p.?	c.1171-2A > G p.?
Center of follow-up	UMCG	UMCF	UKE	UKE	UMCF	UMCG	UMCG
Sex, M / F	M	M	M	F	F	M	M
Age at start symptomatic FBS treatment	1y2m	1 m	5y	Birth	Childhood	Birth	Birth
Age at start empagliflozin treatment	14y5m	41y	35y6m	27y6m	61y	2y9m	1y6m
Duration of follow-up on empagliflozin treatment, days	344	209	169	169	57	92	92
Empagliflozin start dose (mg/kg/d)[c]	1 dd 10 mg (0.28)	1 dd 10 mg	1 dd 10 mg	1 dd 10 mg	1 dd 10 mg	1 dd 5 mg (0.33)	1 dd 4 mg (0.42)
Empagliflozin dose (mg/kg/d)[c] at last follow-up visit	1 dd 25 mg (0.68)	1 dd 20 mg	1 dd 25 mg	1 dd 25 mg	1 dd 10 mg	2 dd 5 mg (0.65)	2 dd 4 mg (0.75)

Note: n dd, *n* daily doses; UMCG, University Medical Center Groningen; UMCF, University Medical Center Freiburg; UKE, University Medical Center Eppendorf (Universitätsklinikum Eppendorf, Hamburg).

[a]Siblings.

[b]Siblings.

[c]Dose in mg/kg/d is presented for children only.

to 2% in participant VII. Time-above-range (>7.8 mmol/L or > 10.0 mmol/L) decreased in all four participants under empagliflozin (see Supplementary Table S1 for details).

Under empagliflozin treatment, in all three children, supplementations (varying combinations of phosphate, alkali, carnitine, and alfacalcidol) could be completely stopped after 8 months, 3 months, and 1 week, in participant I, VI, and VII, respectively. Cessation of the supplementations improved treatment adherence in these children. In addition, the off-label empagliflozin treatment resulted in significant reduction of annual medication costs, that is, €13 693, 1672, and 23, in participant I, VI, and VII, respectively (Supplementary File S2 and Supplementary Table S3).

3.2 | Biochemical outcomes

All persons with FBS displayed improved biochemical parameters of tubular cell integrity and/or tubular function, albeit to variable extent (Figure 1; Table 2). Absolute values of urinary *N*-acetyl-glucosaminidase (NAG), a marker for tubular cell integrity, improved in 6/7 persons. Absolute values of urinary α1-microglobulin and albuminuria decreased in all persons with FBS under empagliflozin treatment, indicating less (tubular) proteinuria. In all three children tubular reabsorption of phosphate (TRP) displayed an initial transient deterioration after which it normalized to values >78% (Figure 1), explaining why these urinary parameters are not displayed in green (Table 2). In the adults, TRP remained abnormal during follow-up (i.e., <78%): it showed improvement in 2/4, remained stable in 1/4 and worsened in one subject. Parathyroid hormone (PTH) was strongly elevated at baseline in 1/6 participants who was not yet treated with active vitamin D_3 derivatives (participant II, 18.1 pmol/L), and this almost normalized (7.4 pmol/L) with empagliflozin treatment alone, suggesting improved synthesis of active vitamin D_3 in renal proximal tubules. Participant I received active vitamin D_3 (alfacalcidol) at baseline which could be successfully stopped under empagliflozin while PTH remained within normal levels (baseline with alfalcalcidol: 3.6 pmol/L; last follow-up without alfacalcidol 1.8 pmol/L). Aminoaciduria improved in 2/7 participants, remained stable in 2/7

TABLE 2 Summary of clinical and biochemical outcomes, displaying percentual change of parameters under empagliflozin treatment in Fanconi-Bickel syndrome.

	Participants						
	I	II	III[a]	IV[a]	V	VI[b]	VII[b]
Parameters of tubular cell integrity							
• NAG excretion in urine	−34.8%	−43.8%	−28.3%	−38.4%	−52.5%	−15.1%	−43.8%
Parameters of tubular cell function							
• Albuminuria	−60.0%	−44.5%	−52.8%	−41.4%	−47.8%	−84.8%	−76.4%
• α1-microglobulin in urine	−49.7%	−27.7%	−46.5%	−40.8%	−39.7%	−60.4%	−38.4%
• TRP	+13.1%	−46.7%	−18.6%	+48.4%	+85.7%	−2.5%	−10.7%
• PTH in serum	−23.8%	−30.2%	+8.3%	−29.8%	i.n.a.	−50.8%	+7.0%
• Aminoaciduria	−30.4%	−2.8%	+31.0%	−53.6%	−8.9%	+40.5%	+130.1%
Parameters in serum							
• Phosphate	+68.0%	−25.3%	−17.0%	+34.6%	+6.4%	+20.1%	+18.2%
• Potassium	+14.3%	+10.8%	+7.4%	+0.7%	+23.7%	+18.8%	−0.7%
• Bicarbonate	+2.6%	+3.1%	−1.6%	−6.2%	+6.2%	+1.2%	+0.0%
• Free carnitine	−22.6%[c]	+1.9%	+21.7%	+26.3%	i.n.a.	+86.1	+52.6%
• Sodium	+0.3%	−1.7%	+0.7%	+1.7%	−0.7%	+2.8%	−0.6%
Cessation of supplements[d]	+,+,+,+	=,=,=,=	=,=,=,=,=,=	=,=,=,=,=	=,=,=,=	+,+	+,+

Note: Colors green, yellow, and red correspond with improved, stable or worsened parameters respectively. For details of treatment response see Supplementary Table S1.

Abbreviations: i.n.a., information not available; NAG, *N*-acetyl-glucosaminidase; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphate.

[a]Siblings.

[b]Siblings.

[c]This parameter was considered improved as carnitine suppletion was stopped during follow-up, after which carnitine levels decreased but remained within reference range.

[d]"+" correspond with amount of supplements stopped; "=" correspond with amount of supplements that remained unchanged.

participants, and worsened in 3/7 participants during follow-up. Serum levels of phosphate, potassium, bicarbonate, and free carnitine all remained stable or improved, except for participant II, in whom phosphate levels worsened during follow-up. Serum sodium levels remained stable in all seven participants.

4 | DISCUSSION

This study reports on the first experiences of a pathophysiology-based treatment of renal proximal tubulopathy by repurposing the SGLT2 inhibitor empagliflozin in a cohort of seven persons with FBS. We observed improved biochemical parameters of tubular cell integrity and/or tubular function after initiation of off-label empagliflozin treatment in all persons. Moreover, in the three children with FBS, supplementations (i.e. phosphate, alkali, carnitine, and alfacalcidol) could be completely stopped.

At first glance, it seems counterintuitive to repurpose a glucose-lowering drug in persons with an IMD known to cause hypoglycemia. However, the recent emergence of repurposing SGLT2 inhibitors in persons with GSD Ib (OMIM #232220),[7–11] another ultra-rare GSD subtype, has emphasized the importance of understanding disease-mechanisms in the development of novel treatments.

It has previously been postulated that due to the basolateral location of the defective GLUT2 in proximal renal tubular cells, the observed generalized renal tubular dysfunction in FBS is caused by glucose entering but not exiting these cells leading to intracellular glucose and glycogen accumulation. This build-up could in turn impair renal tubular cell functions by various potential mechanisms, for example, a marked osmotic effect destroying cell integrity and lowering the driving force for other substances to be reabsorbed, impairment of mitochondrial function causing a secondary energy deficit, or the accumulation of glycosylated proteins.[3,19,20] SGLT2 is expressed at the apical membrane of early proximal renal tubules (segments S1/2) and has a high capacity to reabsorb sodium and glucose from tubular fluid.[21] In the kidney, it is responsible for 90% of glucose reabsorption.[22] SGLT2 inhibition has become an important and relative

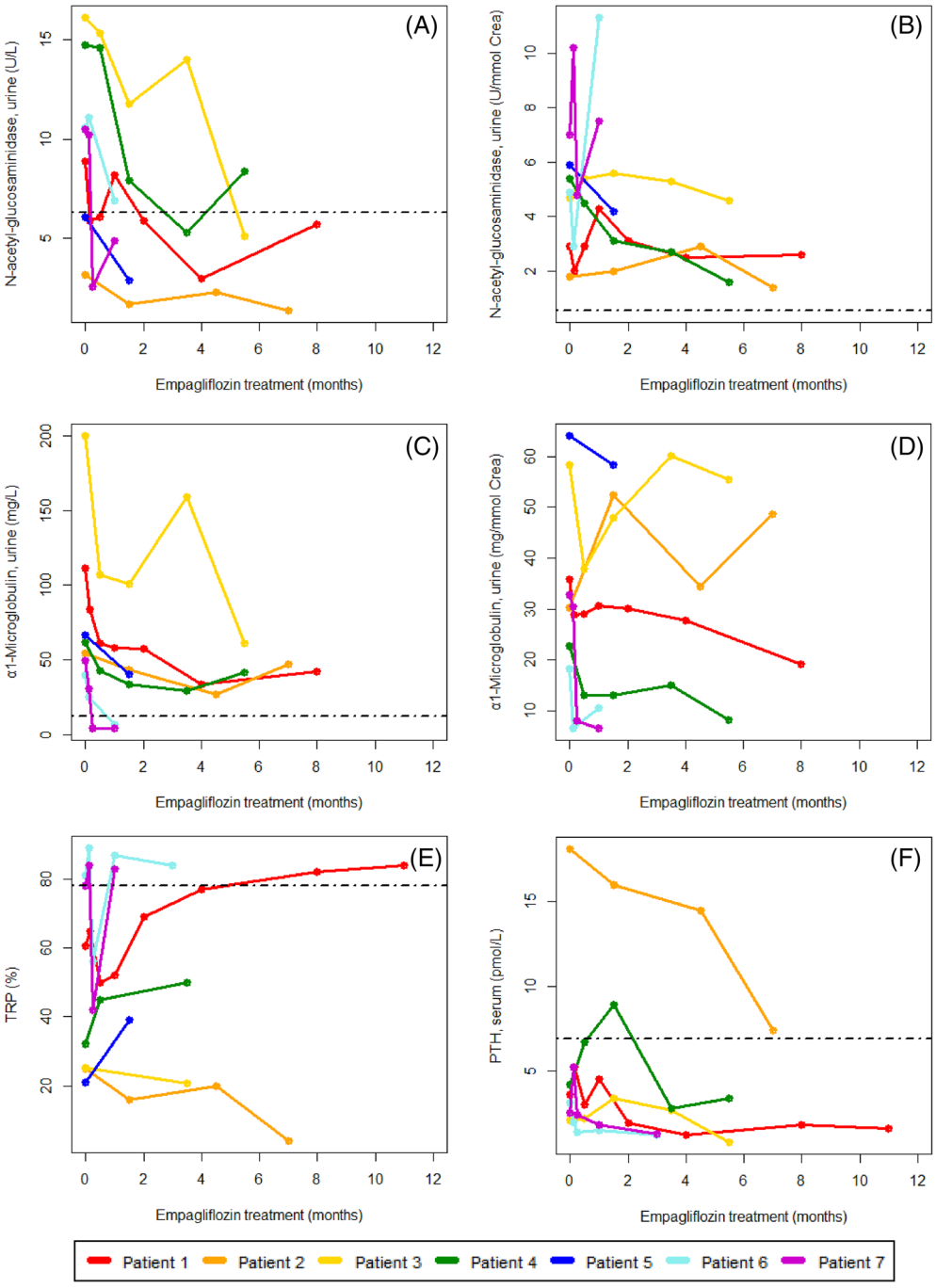

FIGURE 1 Urinary *N*-acetyl-glucosaminidase in U/L (A) and U/mmol Crea (B), α1-microglobulin in mg/L (C) and mg/mmol Crea (D), tubular reabsorption of phosphate (TRP) in % (E), and serum parathyroid hormone (PTH) in pmol/L (F) in FBS before and under empagliflozin treatment. The dotted line represents local reference values, when appropriate.

safe target for therapy in several diseases, including its registered indications for inadequately controlled type-2 diabetes mellitus, symptomatic chronic heart failure, and chronic kidney disease. The effects of SGLT2 inhibition are best seen in persons with renal glucosuria (OMIM #233100), caused by dysfunctional genetic variants in the *SLC5A2* gene encoding the SGLT2 transporter.[23] Affected persons present with variable degrees of isolated glucosuria, but even those with loss of all the filtered glucose with the urine ("renal glucosuria type 0") do not show features of proximal tubular dysfunction and most of them are clinically unaffected.[6,24] Similar findings were observed in SGLT2 knockout mice.[25]

While SGLT2 is responsible for 90% of glucose reuptake, use of SGLT2 inhibitors has the effect that only up to 30%–50% of filtered glucose will not be reabsorbed. It is hypothesized that the more distally located SGLT1 (which is expressed in the S3 segment of the proximal tubule and under normal conditions accounts for 3%–10% of glucose reabsorption), will be exposed to higher glucose loads in the presence of SGLT2 inhibition and thereby be forced to reabsorb glucose at its maximum capacity, thus diminishing in part the effect of SGLT2 inhibition on total glucose reabsorption.[26,27] Epithelial cells of the S3 segment also express GLUT2 at their basolateral membranes to transport intracellular glucose

toward plasma.[28] Thus, theoretically, the introduction of SGLT2 inhibitors in people with a GLUT2 deficiency, could potentially (further) compromise S3 segment epithelial cells through increased glucose supply and accumulation. However, as people with FBS are known to have profound glucosuria, the S3 segment tubule cells are already exposed to high glucose loads even before SGLT2 inhibition, and an additional glucose supply to the S3 segment due to SGLT2 inhibition is most likely not additionally harmful. With the above-mentioned concepts in mind, dual SGLT1-SGLT2 inhibitors (e.g., sotagliflozin, as used in recent trials in diabetes[29–31]) could theoretically be preferred to SGLT2 inhibitors alone to treat renal proximal tubulopathy in FBS.

Following the study by Trepiccione and co-workers,[12] SGLT2 inhibitor treatment was found to be safe and efficacious to treat renal proximal tubulopathy in FBS. In the present study no symptomatic hypoglycemias or other clinically meaningful adverse events occurred during the treatment period. Until recently, the safety and effectiveness of empagliflozin have not been established in detail in pediatric patients.[13] A double-blind, placebo-controlled trial performed in 108 centers in 15 countries demonstrated that common adverse events of oral empagliflozin (10 mg/d) in participants with type 2 diabetes aged 10–17 years were urinary tract infections, fungal infections mainly in females, and a higher risk of low blood glucose concentrations. However, there were no symptomatic hypoglycemias requiring assistance.[32] It remains important to realize that hypoglycemia and hypertriglyceridemia are common symptoms of persons with hepatic GSDs and may be challenging to completely prevent, especially in young children.

Under empagliflozin treatment, we have observed improvement of tubular cell integrity and/or tubular transport function in all seven persons with FBS, to variable extent. Improvement of tubular cell integrity and tubular proteinuria was assessed by urinary excretion of NAG and α1-microglubulin, respectively. Preferably, the ratios of these markers with creatinine are used to correct for dilution in the urine samples. However, these persons all have renal Fanconi syndrome with polyuria and diluted urine and 4/7 participants had one or more urinary samples with very low creatinine concentrations of <1.0 mmol/L. In very diluted urine samples, creatinine ratios are less of a good parameter, hence we assessed both the absolute values and the creatinine ratios.

The authors consider the ability to taper or discontinue supplementations to be a clinically meaningful efficacy parameter. In this study, SGLT2 inhibition allowed to stop supplementations only in children with FBS. Several reasons may explain why supplements could not (yet) be reduced in adults with FBS. First, the extent of inhibition of apical glucose reabsorption could have been generally too low or the follow-up duration of empagliflozin therapy might have been too short for the adults in this study. Little is known if and how age influences the expression of different SGLTs in the kidney. Second, we cannot rule out that adults with FBS have a more advanced or even irreversible renal tubular damage with loss of tubular cell mass, fibrotic processes or thickening of the basal membrane, given the fact their proximal tubular cells have been exposed to the above-mentioned pathogenic mechanisms for much longer compared to children. Third, one may wonder whether significantly elevated blood glucose concentrations and thus a higher load of glucose in the proximal tubules could relativize the effects of empagliflozin; which would mean that despite SGLT2 inhibition, significant amounts of glucose will still be reabsorbed and accumulated in the proximal tubule cells. Indeed, three out of four adults (participants II, III, and V) with an $HbA1_c$ concentration > 42 mmol/mol (>6.0%) showed a reduced biochemical response to empagliflozin when compared to adult participant IV and the pediatric participants all of whom had $HbA1_c$ concentrations ≤42 mmol/mol. It should therefore be considered to reduce blood sugar concentrations first through another medicinal route before testing empagliflozin efficacy. Finally, genotype–phenotype associations may play a role, both at the level of the *SLC2A2* gene (determining severity of FBS) and genes encoding the sodium-linked glucose transporters.[33] Follow-up studies are required to address both the long-term effect on rickets and growth in children with FBS, and to study the case-mix variables explaining differences in treatment efficacy of empagliflozin in FBS.

We had hypothesized that blood 1,5-anhydroglucitol, the therapeutic target in GSD Ib, might be reduced from higher-than-normal concentrations to lower levels under empagliflozin, at least in some participants with increased starch intake. Interestingly, in all seven participants of our cohort the actual 1,5-anhydroglucitol concentrations were already massively reduced to concentrations below the detection limit before empagliflozin (Supplementary Table S1), a mechanism principally known from glucosuric diabetics,[34] but never been observed to this extent. This is another observation that shows that SGLT2 inhibition has a weaker effect on glucosuria than FBS itself.

Several methodological limitations of this study should be addressed. First, the retrospective nature of this study may have caused recall bias and explains why certain biochemical parameters have not been assessed in all participants. Second, the median (range) duration of follow-up has been 169 days (57–344). Long-term follow-

up data of a larger cohort are desirable to study safety and efficacy in more detail, for instance addressing reduction of supplementations in adults and parameters for growth and rickets in children. Thirdly, considerable heterogeneity is observed between the participants in our case series, even between siblings with identical *SLC2A2* genotypes. This illustrates on one side the lack of international treatment guidelines for FBS, but also the need for a personalized, multidisciplinary approach involving a (pediatric) metabolic/genetic specialist, a (pediatric) nephrologist, and a metabolic dietitian. Additionally, at first, the investigators expected that the empagliflozin dose escalation could be titrated based on the adverse effects up to the maximum dose as prescribed for recognized indications. The expectation was that supplements could be titrated downwards in steps of approximately 25% of the daily dosage if concentrations of relevant biomarkers in blood improved or remained within the normal range. The explorative character of this study and the personalized approaches complicated the detailed predefining of durations and increments of both the empagliflozin dose escalation and the dose reductions of supplements. As each person with FBS and their treatment plan is unique, an N-of-1 treatment and trial design could yield stronger evidence.[35,36]

In conclusion, repurposing empagliflozin is a pathophysiology-based treatment that can attenuate symptoms of renal proximal tubulopathy in FBS, especially when started in early childhood. Prospective long-term studies are needed to better understand the full scope of SGLT2 inhibitor treatment in FBS.

AUTHOR CONTRIBUTIONS

Conceptualization: SCG, MTPB, RS, TGJD. *Project administration*: RJO. *Data curation*: RJO, SCG, MTPB, RS, TGJD. *Formal analysis*: RJO, SCG, MTPB, RS, TGJD. *Investigation*: RJO, SCG, MTPB, JG, SM, RS, TGJD. *Patient care*: all authors. *Writing—original draft*: RJO, TGJD. *Writing—review and editing*: all authors. *Correspondence*: TGJD. *Guarantor*: TGJD. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors confirm the absence of previous similar or simultaneous publications.

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CONFLICT OF INTEREST STATEMENT

RJO declares that he experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. There is a consultation agreement (with Ultragenyx Pharmaceutical Inc). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. SCG declares that she experiences no competing interests concerning the content of this manuscript. In the past 36 months, SCG has received honoraria for educational lectures or development of patient information material from Vitaflo, Ultragenyx, and Nutricia Metabolics as well as support for scientific meetings from Nutricia Metabolics. She has also received compensation for participation in advisory boards by Ultragenyx. MTPB declares that she experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. MTPB has received honoraria for lectures or presentations (Kyowa Kirin). For all private–public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. MSB declares that he experiences no competing interests concerning the content of this manuscript. JG declares that he experiences no competing interests concerning the content of this manuscript. ABS declares that she experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. MW declares that he experiences no competing interests concerning the content of this manuscript. MW has received honoraria for presentations (BioMarin Pharmaceutical Inc, metaX Institut für Diätetik GmbH) and participation in an Advisory Board (BioMarin). SM declares that she experiences no competing interests concerning the content of this manuscript. RS declares that he experiences no competing interests concerning the content of this manuscript. He received personal support for scientific meetings from Nutricia Metabolics and also compensation for participation in advisory boards by Ultragenyx and Chiesi. As former President of APS (German Pediatric Metabolic Association) he received support from numerous companies for the organization of annual meetings. TGJD declares that he experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research

(NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone), and participations in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG.

DATA AVAILABILITY STATEMENT

The full data set has been made available as Supplementary Table S1. Additional information is available from the authors on reasonable request.

ETHICS STATEMENT

In the Netherlands, the off-label empagliflozin treatment in FBS patients was performed according to the guideline of the Royal Dutch Medical Association, which implies written informed consent and prior consultation with the hospital pharmacist. The Medical Ethical Committee of the UMCG (METc 2019/119) stated that the Medical Research Involving Human Subjects Act (in Dutch abbreviated as WMO) is not applicable for retrospective, observational studies and that an official study approval is not required. All patients involved in this study gave their written informed consent for both off-label treatment with empagliflozin and the publication of their pseudonymized data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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