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Intestinal failure as a significant risk factor for renal impairment in children

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ABSTRACT

Objective: Although impaired renal function has been a frequent finding among adults with intestinal failure (IF), the data on children is scarce. The aim of this study was to assess renal function in pediatric-onset IF.
Methods: Medical records of 70 patients (38 boys) with pediatric-onset IF due to either short bowel syndrome (n = 59) or primary motility disorder (n = 11) and a history of parenteral nutrition (PN) dependency for ≥1 mo were evaluated. Renal function at the most recent follow-up was studied using plasma creatinine, cystatin C, and urea concentrations and estimated glomerular filtration rate (eGFR).
Results: At a median age of 5.7 y and after PN duration of 3.2 y, 20 patients (29%) had decreased eGFR and higher cystatin C and urea concentrations. Patients with decreased renal function had significantly longer duration of PN (3.2 versus 0.9 y; $P = 0.030$) and shorter percentage of age-adjusted small bowel length remaining (22 versus 32%; $P = 0.041$) compared with patients with preserved renal function. No other predisposing factors for decreased eGFR were identified.
Conclusions: Patients with pediatric-onset IF are at significant risk for impaired renal function, which is associated with the duration of PN and the length of the remaining small bowel. In the present study, no other predisposing factors for decreased eGFR were found. Further studies using measured GFR are needed.

Introduction

The European Society of Clinical Nutrition and Metabolism has defined *intestinal failure* (IF) as the reduction of gut function below the minimum necessary for the absorption of macronutrients, water, and electrolytes, so that intravenous (IV) supplementation is required to maintain health and growth [1]. In pediatric patients, necrotizing enterocolitis, intestinal atresia, midgut volvulus, gastroschisis, Hirschsprung disease, and intestinal pseudoobstruction (CIPO) causing either short bowel syndrome (SBS) or severe intestinal dysmotility are the most common etiologies for IF [2,3].

Patients with IF are at persistent risk for hypovolemia and electrolyte imbalance due to impaired absorption and increased intestinal losses, recurrent sepsis episodes, and nephrotoxic medications, which may have an adverse effect on kidney function. Impaired kidney function and development of chronic renal failure have been reported in adults with long-term parenteral nutrition (PN) for IF [4–7], whereas data on renal function in children with IF is very limited [8,9]. Chronic renal failure is observed earlier and more frequently after intestinal transplantation compared with other solid organ

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transplantations [10]. The gold standard for evaluating renal function is to measure the glomerular filtration rate (mGFR) using either inulin or some other radiolabeled marker, such as ethylenediamine tetracetic acid labeled chromium-51 (^{51}Cr-EDTA). Due to the costs and complexities of measuring GFR, estimated GFR, plasma creatinine, and cystatin C often are used in clinical practice to assess renal function. Renal function is considered to be impaired if GFR is <90 mL/min/1.73 m^2 in adults and children >2 y of age [11]. The aim of the present study was to assess the renal function in children with IF during and after weaning off PN.

Materials and methods

The study comprised patients with pediatric-onset IF treated who were followed up at the Children's Hospital, Helsinki University Hospital, between 1990 and 2015. The Ethical Committee of the Children's Hospital, University of Helsinki, approved the use of patient's information and the study protocol.

All patients with IF due to either SBS or primary intestinal dysmotility disorders and with PN for ≥1 mo and a follow-up period of ≥1 y were included. Seventy-eight eligible patients were identified, 8 of whom were excluded because of incomplete laboratory values.

Patient's age, sex, primary disease, cause of IF, surgical procedures, number of blood culture–positive sepsis episodes, anatomy of the remaining bowel, duration of PN, and the amount of current PN, as well as weight and height at the most recent follow-up, were collected from the patient records. Sepsis episode details could be reliably extracted from the electronic hospital discharge database from the year 1993 onward. Six of the 70 patients were born before 1993, and data on their early sepsis episodes therefore may not be complete.

Growth was assessed using the Finnish national growth charts. The height is given as *z* scores and weight as the impact of age and sex-adjusted body mass index (ISO-BMI) scores for children ≥2 y. Height was corrected for gestational age if needed. Age-adjusted weight-to-height percentiles (based on the national data) were reported for those <2 y of age [12]. Three patients with cartilage-hair hypoplasia and one patient with Down syndrome–associated growth failure were excluded from the height analysis. The percentage of the remaining age-adjusted small bowel and colon length was calculated based on age-specific normal in vivo values [13]. Children with Hirschsprung disease and <50% of age-adjusted small bowel length remaining were categorized to the SBS group.

Renal function laboratory parameters (plasma creatinine, cystatin C, and urea) measured at the time of the most recent follow-up visit were collected from the medical records; the follow-up time was considered to end at this point. Renal function was evaluated using either the estimated GFR (eGFR) calculated by the CKiD (Chronic Kidney Disease in Children) Schwartz equation [14], which uses all creatinine, cystatin C, and urea values in the formula or the Chronic Kidney Disease Epidemiology Collaboration creatinine–cystatin equation [15] for patients >18 y of age. In two cases lacking cystatin C value, the creatinine-based Bedside Schwartz formula was used [16]. In four cases with decreased renal function, GFR was evaluated more precisely using the ^{51}Cr-EDTA measurement. Renal function was classified as normal when eGFR was ≥89 mL/min/1.73 m^2 (≥62 mL/min/1.73 m^2 at 12–19 mo of age) [17]. In patients who underwent intestinal transplantation during follow-up, renal function was evaluated before surgery. Renal ultrasound was performed on all patients with decreased renal function. The possible presence of structural abnormalities, nephrocalcinosis, increased echogenicity, or a combination of the three, was recorded from the medical records and ultrasound pictures.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS/Windows version 22.0, SPSS Inc., Chicago, IL, USA). Data are reported as medians with their interquartile range. A Mann–Whitney U test was used to compare median values. Fisher's exact test was used for comparison of categorical variables. Statistical significance was defined as $P \leq 0.05$.

Results

Demographic and clinical characteristics of the patient population are summarized in Table 1. The causes of IF included necrotizing enterocolitis (n = 20), midgut volvulus (n = 15), small bowel atresia (n = 14), gastroschisis (n = 2), CIPO (n = 8), and Hirschsprung disease (n = 11); eight of these were categorized to the SBS group. At the latest follow-up visit, 22 of the 70 patients (31%) were on PN and received a median seven (six to seven) weekly PN infusions. Five patients had undergone intestinal transplantation and three are currently on waiting list for transplantation.

Overall, 20 patients (29%) had decreased eGFR at a median age of 5.7 y after median PN duration of 3.2 y (Table 1). Patients with decreased eGFR also had significantly higher cystatin C and urea values. The increase in creatinine levels failed to reach statistical significance. Among patients with decreased renal function, eGFR was 60 to 89 mL/min/1.73 m^2 in 16 patients (80%) and below 60 mL/min/1.73 m^2 in 4 (20%). There was no difference between

Table 1
Characteristics of 70 patients with pediatric-onset intestinal failure having either normal or decreased GFR at the end of the follow-up

	All patients (interquartile ranges) (N = 70)	Patients with decreased GFR* (interquartile ranges) (n = 20)	Patients with normal GFR* (interquartile ranges) (n = 50)	*P* value
Boys	38	10	28	0.792
Age at follow-up, y	5.4 (3.3–12.3)	5.7 (3–12.1)	5.4 (3.6–14.2)	0.563
Height, *z* score	−1.4 (−2.3 to −0.4)	−2.5 (−3.2 to −0.7)	−1.1 (−2 to −0.1)	**0.027**
Weight, ISO-BMI	19.6 (17.3–22)	20 (18.9–22.4)	19.2 (16.4–21.9)	0.207
Weight, percentiles	−9% (−11 to −0)	0	−9% (−11 to −2)	0.667
SBS/dysmotility disorder	59/11	19/1	40/10	0.159
Patients weaned off PN	48	12	36	0.397
Time after weaning off PN, y	4.5 (2.2–9.7)	4 (1.7–7.1)	4.9 (2.3–10.7)	0.338
Duration of PN, mo	14.7 (6.3–40)	38.7 (11.5–99.2)	11.1 (5.2–32)	**0.030**
Amount of current daily PN, kcal/kg	41.5 (30.7–60)	50.5 (35.3–74.7)	38.4 (30–45)	0.297
No. of septicemia/patient	1 (0–2)	0 (0–3.5)	1 (0–2)	0.863
Remaining bowel				
Small bowel, cm	50 (30–100)	36 (23–65)	50 (31–103)	0.364
Small bowel, %	26 (17–53)	22 (16–32)	32 (21–75)	**0.041**
Colon, %	77 (50–100)	72 (3–100)	82 (50–100)	0.462
Colon +/−	55/15	14/6	41/9	0.337
ICV preserved	34	7	26	0.290
Plasma creatinine μmol/L	33 (24–48)	43 (28–53)	30 (22–46)	0.062
Plasma cystatin C, mg/L	0.85 (0.74–0.98)	0.99 (0.90–1.18)	0.76 (0.72–0.86)	**<0.001**
Plasma urea, mmol/L	4.9 (3.9–6.6)	6.8 (4.8–7.2)	4.5 (3.7–5.2)	**<0.01**
eGFR, mL/min/1.73 m^2	100 (86–115)	71 (65–86)	107 (99–124)	**<0.001**

eGFR, estimated glomerular filtration rate; ICV, ileocecal valve; ISO-BMI, age-adjusted body mass index; SBS, short bowel syndrome; PN, parenteral nutrition
Bold values are statistically significant.
* Renal function was classified as normal when eGFR was ≥89 mL/min/1.72 m^2 (≥62 mL/min/1.73 m^2 at 12–19 mo of age) [17].