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Plasma Citrulline Concentration Reflects Enterocyte Mass in Children With Short Bowel Syndrome

CÉLINE BAILLY-BOTUHA, VIRGINIE COLOMB, ELIZABETH THIOULOUSE, MARIE-CLOTILDE BERTHE, KARINE GARCETTE, BÉATRICE DUBERN, OLIVIER GOULET, RÉMY COUDERC, AND JEAN-PHILIPPE GIRARDET

Gastroentérologie et Nutrition Pédiatriques [C.B.-B., K.G., B.D., J.-P.G.], Laboratoire de Biochimie [E.T., M.-C.B., R.C.], Hôpital Armand-Trousseau, APHP, Paris 75012, and Université Paris 6, Paris 75005, France; and Gastroentérologie et Nutrition Pédiatriques [V.C., O.G.], Hôpital Necker Enfants Malades, APHP, Paris 75015, and Université Paris 5, 75015 France

ABSTRACT: Plasma citrulline was recently shown to reflect the residual functional enterocyte mass in various situations characterized by intestinal failure. However, few data are available in children with short bowel syndrome. The objective of this study was to assess the value of citrulline assays in this situation. Prospective plasma citrulline assays were performed in 31 children with short bowel syndrome. Median age was 16 mo (range, 1 mo to 15 y), and median follow-up was 14 mo (6–40 mo). The energy supplied by parenteral nutrition (PN), served to assess intestinal failure severity. Plasma citrulline at inclusion showed a positive correlation with residual short bowel length. Subsequent values correlated negatively with intestinal failure severity. Plasma citrulline increased over time during or after weaning from PN (from 15.8 ± 11.5 μM to 19.3 ± 3.8 μM) but remained stable and low in patients who continued to need PN (6.5 ± 3.0 μM at inclusion and 7.7 ± 6.0 μM at last follow-up). No weaned patients had a residual short bowel length less than 40 cm and plasma citrulline less than 11 μM. Our findings constitute the first evidence that serial plasma citrulline assays help to monitor residual small bowel adaptation in children. **(*Pediatr Res* 65: 559–563, 2009)**

Although the length of the residual small bowel is the main factor determining whether patients with short bowel syndrome (SBS) will eventually be able to live without parenteral nutrition (PN), other anatomic factors also play a role, as well as the degree of enterocyte dysfunction induced by preoperative insults (1–3). A biologic marker capable of reliably separating patients who will eventually become self-sufficient from those who may be candidates for intestinal transplantation would be useful.

Citrulline is a nonprotein amino acid that is produced almost exclusively by the enterocytes, from glutamine and arginine (4). In adults (5–8) and children aged 4 y or under (9) with SBS, postoperative plasma citrulline concentrations correlated significantly with residual small bowel length and showed promise for evaluating whether intestinal failure would prove transient or permanent. Data obtained in pediatric patients are meager, and few longitudinal studies are available. The afore-mentioned pediatric study (9) involved a single citrulline assay in 24 patients followed by a second assay in only five patients.

The objective of this study was to assess the value of serial plasma citrulline assays for improving the assessment of small bowel adaptation in pediatric patients with SBS.

PATIENTS AND METHODS

Patients. We prospectively included 31 consecutive pediatric inpatients receiving treatment at the gastroenterology departments of two teaching hospitals in Paris, France, for SBS after extensive intestinal resection. Inclusion occurred between March 2001 and June 2004 and follow-up ranged from 5 to 40 mo (median, 14 mo). Exclusion criteria were as follows: renal failure with serum creatinine levels above the age-specific normal range, severe comorbidities (*e.g.*, autoimmune disease or neoplasia), and multiple birth defects.

Median age at study inclusion in the 31 patients (18 girls and 13 boys) was 16 mo (range, 1 mo to 15 y), and 20 patients were younger than 24 mo of age. Median time from bowel resection to study inclusion was 11.6 mo (range, 1 mo to 15 y); 24 patients underwent bowel resection within 1 mo after birth.

We recorded the following data collected intraoperatively: length of the residual small bowel, whether the ileocecal valve was preserved, and whether the colon was resected. We divided the patients into three groups based on whether the intraoperative residual short bowel length was greater than 80 cm, 40–80 cm, or less than 40 cm which is the frequently used classification (10,11). At each data-collection time point, we determined the percentage of age-specific calorie needs supplied by PN, which served as an index of intestinal function (12).

Residual small bowel length was greater than 80 cm in five patients, 40–80 cm in 14 patients, and less than 40 cm in 12 patients (Table 1). The reason for bowel resection was atresia in nine patients, including five with apple-peel syndrome (two each in the >80 cm and 40–80-cm groups and one in the <40-cm group); necrotizing enterocolitis in six patients (five in the 40–80-cm group and one in the <40-cm group), gastroschisis in six patients (one each in the >80 cm and <40-cm groups and four in the 40–80-cm group), volvulus in five patients (two in the 40–80-cm group and three in the <40-cm group), ischemic necrosis in two patients (one each in the >80-cm and <40-cm groups), intestinal obstruction because of adhesions in two patients (one each in the >80-cm and 40–80-cm groups), and congenital short bowel in one patient (in the <40-cm group).

At inclusion, 30 of the 31 patients were receiving PN with a standard amino acid solution containing no glutamine. The mean percent calories supplied by PN was 51% (0–100%) in the >80-cm group, 76% (27–100%) in the 40–80-cm group, and 75% (23–99%) in the <40-cm group. Only five patients were on total PN at the time the first blood sample was collected. A 7-y-old patient who underwent bowel resection on the day of birth for multilevel atresia, which left 105 cm of small bowel, had been weaned off PN 1 y before study inclusion.

Blood sample collection and chromatography of plasma amino acids. At each study time point, a 1-mL sample of heparinated blood was collected in the morning, at the end of PN, at least 8 h after the last oral meal. Blood sample collection was performed when the child was in stable condition, with no evidence of dehydration. Samples at inclusion were obtained from all 31 patients. In 18 patients, we were able to obtain two to six additional samples. In all, 63 samples were collected.

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Correspondence: Jean-Philippe Girardet, M.D., Gastroentérologie et Nutrition Pédiatriques, Hôpital Armand Trousseau, 26 Avenue Arnold Netter, Paris 75012, France; e-mail: jean-philippe.girardet@trs.aphp.fr

Abbreviations: PN, parenteral nutrition; **SBS,** short bowel syndrome

Table 1. *Characteristics of the study patients in each of the three groups based on residual small bowel length*

	>80 cm (n = 5)	40 cm to ≤80 cm (n = 14)	<40 cm (n = 12)
Age, median (range) at surgery	2 y (1 d to 7.5 y)	6.5 (birth to 5.5 y)	1 (birth to 1.5 y)
Age (mo), median (range) at inclusion	21 (3.5 mo to 7.7 y)	3.5 (1 mo to 6 y)	25 (1 mo to 15 mo)
BMI *Z*-score at inclusion, median (range)	−0.22 (−2.4 to 1.87)	0.22 (−2.28 to 2.09)	−0.93 (−2.94 to 0.27)
Residual small bowel length in cm, mean ± SD	114 ± 23	60 ± 12	21 ± 13
Colon preserved, n of patients	5	7	7
Ileocecal valve preserved, n of patients (%)	4 (80%)	5 (36%)	7 (58%)
Citrulline (μmol/L) at inclusion, mean ± SD	21.6 ± 9.47*†	11.4 ± 8	7.83 ± 4.7

* $p < 0.015$ *vs* the 40–80-cm group.
† $p < 0.002$ *vs* the <40-cm group (Bonferroni test).
BMI, body mass index.

Table 2. *Degree of dependency on parenteral nutrition at study completion in the three groups defined based on residual small bowel length*

	>80 cm (n = 5)	40 cm to ≤80 cm (n = 14)	<40 cm (n = 12)
Follow-up (mo), median (range)	16 (10–24)	12 (6–40)	12 (7–35)
Number of patients weaned off PN	4	5	0
Number of patients undergoing weaning (PN <50%)	1	7	4
Number of patients dependent on PN (PN ≥50%)	0	2	8*
% calories by PN, mean ± SD	5.6 ± 11.2%†	28 ± 23.5%†	63 ± 21%

* $p < 0.0023$ *vs* the 40–80 cm group by χ^2 test.
† $p < 0.0005$ *vs* the <40-cm group by Mann-Whitney test.
PN, parenteral nutrition.

Plasma amino acid concentrations were determined using ion-exchange chromatography followed by colorimetric ninhydrin detection at 570 nm and 440 nm (13). Plasma citrulline concentrations at inclusion were compared with values obtained in same-age healthy children using the same assay method (14).

Statistical analysis. Results are reported as means ± SD. To compare groups, we used nonparametric tests, either the Mann-Whitney test when two groups were compared or the Kruskal-Wallis test followed by the Bonferroni test when more than two groups were compared. A correlation matrix produced using StatView 5 software (SAS Institute, Cary, NC) was used to build a linear regression model.

Informed consent was collected from each study participant. The study was compliant with current French regulations for medical studies and was approved by the local Institutional Review Board for clinical research in humans (Hôpital Saint Antoine, Paris) according to the principles of the Declaration of Helsinki.

RESULTS

Patient characteristics. During the study period, 8 patients were weaned off PN (three in the >80-cm group and five in the 40–80-cm group). The percent calories supplied by PN were reduced to less than 50% during the study in 12 patients (one in the >80-cm group, seven in the 40–80-cm group, and four in the <40-cm group). Ten patients remained dependent on PN for more than 50% of their calorie needs (Table 2).

Longer length of the residual small bowel measured during surgery strongly predicted weaning off PN ($p < 0.0001$). Thus, mean length was 87.5 cm (50–150 cm) in the nine weaned patients and 17.8 cm (0–48 cm) in the 22 PN-dependent patients. Weaning off PN during the study period was not associated with the reason for small bowel resection, the location of the resected segment, whether the ileocecal valve or colon was preserved, or age at surgery.

Plasma citrulline concentrations. Plasma citrulline levels at inclusion were low in the overall patient population, compared with healthy same-age children (11.6 ± 8.6 μM *versus* 25 ± 9 μM, $p < 0.01$). Plasma citrulline levels were lower in the 40–80-cm group ($p < 0.015$) and the <40-cm group ($p < 0.002$) than in the >80-cm group (Table 1). A strong correlation was noted between the plasma citrulline concentration at the inclusion and the length of the residual small bowel ($r = 0.441$, $p = 0.013$) (Fig. 1). A trend ($p = 0.013$) was found toward an association of the plasma citrulline concentration at inclusion and dependency on PN at the end of the study. All patients who had a residual small bowel length less than 50 cm and a baseline plasma citrulline concentration less than 11 μM remained dependent on PN more than 70% of their calorie needs (Fig. 1). Plasma citrulline concentration at inclusion failed to correlate with plasma albumin concentration, serum creatinine, whether the ileocecal valve or colon was preserved, or the body mass index *Z*-score.

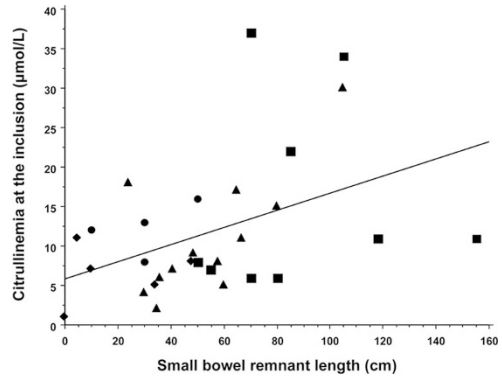

Figure 1. Number of weaned (■) and of PN dependent (▲, <50%; ●, 50–70%; ◆, >70%) children compared with small bowel remnant length and initial plasma citrulline concentration.

During the study, 32 additional citrulline assays were performed in 18 patients. Overall, the plasma citrulline level correlated negatively with the degree of PN dependency at sample collection ($r = 0.517$, $p < 0.004$) (Fig. 2). From baseline to study completion, a nonsignificant trend toward

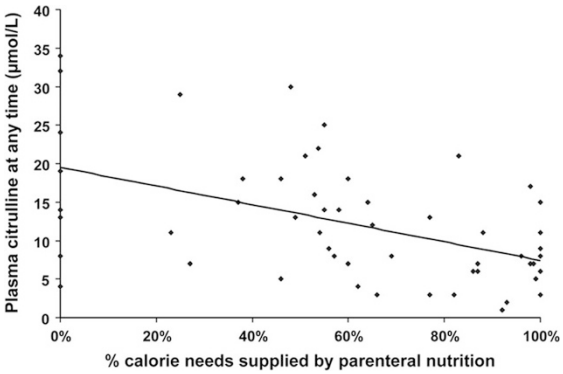

Figure 2. Plasma citrulline concentrations at baseline or later during the study plotting against the percentage of calorie needs supplied by parenteral nutrition ($y = -12.093x + 19.51$, $r = 0.517$, $p < 0.004$).

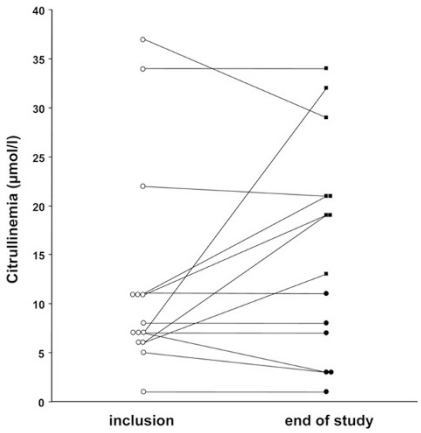

Figure 3. Evolution of citrullinemia from inclusion to the end of the study in weaned patients (■) ($n = 9$) and dependent on PN more than 70% of calorie needs (●) ($n = 6$) at the end of the study.

plasma citrulline elevation was noted among patients who were weaned off PN during the study (from 15.8 ± 11.5 µM to 20.12 ± 7.88 µM, $p = 0.099$ by paired t test). However, all weaned patients, except one who had a low citrullinemia at inclusion, had their citrullinemia dramatically increased at the end of the study (Fig. 3). In contrast, plasma citrulline concentrations were stable at low values in patients who remained dependent on PN for more than 50% of their calorie needs (6.5 ± 3 µM at baseline and 4.33 ± 1.8 µM at study completion, $p = 0.203$). Moreover, patients who remained dependant on PN more than 70% of their calorie needs have had a citrullinemia less than 11 µM at inclusion, which remained low at the end of the study, in all cases (Fig. 3). At study completion, plasma citrulline was significantly lower in patients who remained dependent on PN than in weaned patients (4.33 ± 1.8 µM *versus* 20.12 ± 7.88 µM, $p < 0.01$).

Plasma arginine and glutamine concentrations. Plasma arginine and glutamine concentrations at inclusion in our patients were not significantly different from normal values (11) (48.7 ± 21.7 µM *versus* 74 ± 18 µM for arginine and 541.9 ± 125.3 µM *versus* 467 ± 76 µM for glutamine). No significant differences were found across the three patient groups based on residual small bowel length regarding the plasma concentrations of arginine (>80-cm group, 40 ± 22.2 µM; 40–80-cm group, 48.1 ± 21.2 µM; and <40-cm group, 53 ± 21 µM; NS) or glutamine (>80-cm group, 529 ± 234 µM; 40–80-cm group, 534.6 ± 87,5 µM; and <40-cm group, 555.5 ± 92 µM; NS).

DISCUSSION

The main factor determining whether a child with SBS will eventually be able to live without PN is the length of the residual small bowel. Although the measurement of the residual bowel length is not always enough accurate at surgery, it has been proposed that the length above which weaning off PN may be possible varies with age, from 25 to 30 cm in neonates to 50–60 cm in adolescents (3,15,16). However, additional anatomic and functional factors associated with PN dependency include removal of the ileocecal valve, extensive colon resection, a need for multiple surgical procedures, and dysfunction of the residual small bowel as reflected indirectly by the percent of daily intake tolerated by the enteral route and whether bacterial overgrowth develops (3,16). Therefore, availability of a reliable marker for the residual mass of functional enterocytes would be valuable both for early outcome prediction and for monitoring small bowel adaptation over time. Such a marker would help in the early identification of children who have permanent intestinal failure and may therefore be candidates for intestinal transplantation.

Plasma citrulline was suggested as a reliable predictor for the duration of PN dependency based on results from several studies (5–9,17,18). Citrulline is a nonprotein amino acid produced nearly exclusively by the enterocytes and present in only small amounts in the diet (19). Because citrulline is not incorporated into endogenous or exogenous proteins, it is neither released by proteolysis (20) nor taken up or exported by the liver (21). Citrulline is converted to arginine in the kidney (4). Thus, only kidney failure and intestinal failure affect plasma citrulline concentrations (22). Chromatographic determination of citrulline concentrations is easy to use in clinical practice. Studies in adults established that plasma citrulline correlated not only with the length of the residual small bowel but also with its function (5–7). Thus, changes in plasma citrulline concentrations over time reflect enterocyte function recovery, and serial plasma citrulline assays can distinguish between patients with transient or permanent intestinal failure (6). Further support for the link between plasma citrulline and enterocyte function in adults comes from studies showing plasma citrulline reduction in patients with SBS (7), celiac disease (23), intestinal transplant rejection (24–26), radiation enteritis (27,28), or intestinal toxicity of myeloablative therapy (29). A study in children with SBS suggested that higher plasma citrulline concentrations might predict the development of enteral tolerance (9). Moreover, it has been shown that after serial transverse enteroplasty in children with SBS, citrullinemia was closely related with outcomes (18).

Plasma citrulline in our patients correlated closely with residual small bowel length, in keeping with the previous pediatric study (9). Our patients had a broader age range (1 mo to 15 y) than those studied previously (3 wk to 4 y) and our findings therefore suggest that the predictive value of plasma

citrulline concentrations in children may be independent from age. In addition, the trend toward successful weaning off PN and higher plasma citrulline concentrations at inclusion supports a major role for postoperative plasma citrulline in predicting whether intestinal failure will prove transient or permanent. This possible predictive role deserves to be further evaluated in a larger and more uniform group of patients. Nevertheless, all patients who had both a residual small bowel length less than 50 cm and a baseline plasma citrulline concentration less than 11 μM remained dependent on PN throughout the study period. Furthermore, our results support monitoring plasma citrulline concentrations over time, as increasing values were associated with eventual weaning off PN. The citrulline level of five of these patients increased at least of 70% during follow-up. Only the weaned patient with a residual length of small bowel of 50 cm had his citrullinemia unchanged at 8 μM. Therefore, it seems that citrullinemia increase during the follow-up, combined with the residual length of bowel, might be as predictive as the sole citrullinemia at inclusion.

This result was obtained despite the short follow-up in some of our patients, which would be expected to underestimate the association, as small bowel adaptation may require more than 48 mo (2,16,30–32). Plasma citrulline assays must be performed at a distance from enteral infections, as shown by the transiently low citrulline values obtained in four of our patients immediately after gastroenteritis episodes (data not shown). In contrast, the time of blood sampling relative to oral or parenteral feeding is irrelevant, as citrulline is a nonprotein amino acid that is not found in PN solutions (4,19).

The plasma glutamine and arginine concentrations found in our patients deserve comment. In several earlier studies, a negative correlation was noted between plasma glutamine and residual small bowel length. A severe reduction in intestinal mass may lead to glutamine uptake by the basal pole of the enterocytes and, therefore, to an early increase in plasma glutamine concentrations (33). Subsequently, inhibition of muscle glutamine synthetase (34) is followed by a return to normal of the plasma glutamine concentrations (35,36). The normal plasma glutamine concentrations in our patients may be related to preservation of the colon in some patients (37) and to the long-time interval from surgery to glutamine assay in others. Plasma arginine showed a nonsignificant decrease in our patients compared with healthy controls, in keeping with previous data (6,17,38). Because citrulline is the only precursor used by the kidney to produce arginine, low citrulline concentrations may lead to a decrease in arginine production (4,20). In a well-controlled experimental study (39) of rats subjected to 80% intestinal resection, a similar decrease in plasma arginine was noted. The variability in arginine concentrations across studies may be related to the complex metabolism of this amino acid (40) and to its sensitivity to catabolism and/or inflammation (26). Conceivably, the small magnitude of the plasma arginine decrease in our patients may be ascribable to the presence of arginine in PN solutions.

In conclusion, our findings confirm the usefulness of plasma citrulline as a marker for functional enterocyte mass in children with SBS. The potential usefulness of monitoring plasma citrulline over time to predict intestinal function recovery deserves to be investigated in a long-term prospective study involving regularly spaced citrulline assays in a more uniform group of patients.

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