Fasting and Postprandial Plasma Citrulline and the Correlation to Intestinal Function Evaluated by 72-Hour Metabolic Balance Studies in Short Bowel Jejunostomy Patients With Intestinal Failure

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Abstract
Background: Fasting plasma citrulline (p-citrulline) is a marker of functional enterocyte mass. However, the optimal timing of measurement in relation to meals has yet to be clarified. Furthermore, p-citrulline has been proposed to be a surrogate marker for small bowel length and intestinal absorption parameters in short bowel syndrome patients with intestinal failure (SBS-IF). Materials and Methods: Eight patients with SBS-IF and 8 healthy controls (HCs) were given a standardized mixed test meal, and p-citrulline was measured 15 minutes before and 60, 120, and 180 minutes after completion of the meal. The patients with SBS-IF had their intestinal absorption of wet weight, energy, macronutrients, and electrolytes measured in relation to 72-hour metabolic balance studies. We investigated the possible correlations between p-citrulline and short bowel length, absorptive parameters, and the dependence on parenteral support (PS). Results: In the patients with SBS-IF, we found a 12% ($P = .041$) reduction in postprandial citrulline levels after 180 minutes. In the HCs, there was a 13% postprandial reduction at 60 minutes ($P = .018$). No significant correlations between fasting p-citrulline and bowel length, bowel absorptive function, or the dependence on PS were found. Even when excluding 2 patients in whom the intestinal absorption was adjacent to the intestinal insufficiency borderlines, these correlations were not significant. Conclusion: Based on findings in this small study, the optimal timing of p-citrulline measurement is on fasting samples. However, p-citrulline seems insufficiently discriminative to serve as a valid biomarker of bowel length, bowel absorptive function, or dependence on PS in patients with SBS-IF. (JPEN J Parenter Enteral Nutr. XXXX;xx:xx-xx)

Keywords
gastroenterology; research and diseases, rehabilitation; research and diseases, short bowel syndrome; research and diseases, adult; life cycle

Clinical Relevancy Statement
Plasma citrulline (p-citrulline) is most often measured in the postabsorptive state, which is poorly defined. Our findings may help clinicians to perform p-citrulline measurements at optimal timing in relation to meals in both short bowel syndrome patients with intestinal failure and healthy controls. Based on correlation analyses in a small clinical study, the benefit of the use of p-citrulline as a biomarker to predict small bowel length, absorptive function, or dependence on parenteral support was limited. In patients on the borderline between intestinal insufficiency and intestinal failure, p-citrulline does not seem to be sufficiently distinct to discriminate between these 2 patient categories.

Introduction
Short bowel syndrome (SBS) is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a normal diet$^1$ and most often occurs following massive resection of the small bowel.$^2$ Patients with SBS may have consequences of malassimilation such as diarrhea, weight loss, malnutrition, dehydration, electrolyte disturbances, and various nutrition deficiencies.$^3,3$ In SBS patients with intestinal failure (SBS-IF), the absorptive capacity is so limited that parenteral support (PS) is indicated to maintain normal body function and health.$^4$

The gold standard of measurements of intestinal function is by metabolic balance studies, but they require patient admission and are labor intensive and intrusive for patients.$^5$

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Therefore, simple biomarkers for the evaluation of intestinal function have been searched for. In this respect, plasma citrulline (p-citrulline) has received attention. Citrulline is a nonprotein intermediary product of amino acid metabolism. It is almost exclusively synthesized in the small bowel enterocytes, mainly from glutamine and derived amino acids, and it is metabolized into arginine by the kidney. Citrulline has the advantage of being independent of intestinal inflammation, but due to a renal elimination, elevated values have been described in patients with impaired renal function.

In healthy individuals, fasting p-citrulline is about 40 µmol/L. In patients with SBS, it has been suggested that p-citrulline is a simple and accurate biomarker for absorptive remnant intestinal length, especially in patients with bowel length <50 cm. P-citrulline has also been suggested to predict the severity of SBS by distinguishing between permanent and transient IF with a cutoff value of 20 µmol/L. Most studies have measured p-citrulline in the postabsorptive state. The aim of this study was to determine changes from fasting p-citrulline concentrations following a solid mixed test meal in patients with SBS-IF and healthy controls (HCs) to decide the optimal timing of these measurements.

It is still unclear if a relation between p-citrulline concentration and intestinal absorptive function exists, and researchers have found contradictory results. This study examined the correlations between p-citrulline and small bowel length; p-citrulline and absorption of wet weight, energy, protein, carbohydrate, fat, potassium, sodium, magnesium, and calcium; and p-citrulline and the dependence on PS in 8 patients with SBS-IF performing 72-hour metabolic balance studies.

Materials and Methods
The data analyzed and presented in this article are derived from the baseline admission period of a larger study entitled “Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study.” This investigator-initiated study was approved by the Scientific-Ethical Committee of the Capital region of Denmark (protocol 2013-624), the Danish Health and Medicine Authority, and the Good Clinical Practice unit in Copenhagen, Denmark. The study was registered with the Danish Data Protection Agency (Journal no 2013-005499-16). The study was conducted according to the Helsinki Declaration II, and written informed consent was obtained from all participants. The study was conducted from March to June 2014 at the Department of Medical Gastroenterology at Rigshospitalet, Copenhagen, Denmark.

Participants: Patients and HCs
The 8 patients recruited for the study were older than 18 years and had SBS-IF and an end-jejunostomy. They had depended on and received PS for at least 6 months prior to the 72-hour balance study. None of the patients received glutamine or citrulline as part of their PS. All of the patients had a remnant bowel length of <200 cm measured from the ligament of Treitz during their last surgery. Eight healthy individuals (4 females and 4 males) were included as controls for measurements of p-citrulline before and after a test meal. All control participants had an uneventful medical record, had no sense of physical illness, and were not pregnant. The HCs did not participate in the metabolic balance studies.

Metabolic Balance Studies
The patients were admitted 1 day prior to the initiation of the 72-hour balance study to get acquainted with the balance study procedures and to construct a personalized 24-hour fluid intake program. The 72-hour metabolic balance study lasted from 8:00 AM on day 1 and ended 72 hours later in the morning on day 4. The 72-hour metabolic balance studies quantified wet weight volume of urine and fecal output and diet intake of duplicate meals, energy by bomb calorimetry, macronutrients (nitrogen by Kjeldahl’s method, lipid by titration technique, and carbohydrate by Englyst’s method), and electrolytes (sodium and potassium by flame photometry; magnesium and calcium by atomic absorptiometry). The diet was unrestricted, but none of the patients took oral glutamine supplements or medium-chain triglycerides. The absolute absorption was defined as the difference between the oral intake and the fecal output.

Postprandial Measurements of P-citrulline
The patients with SBS-IF and the HCs received a standardized meal after an overnight fasting of oral intake from midnight. The patients with SBS-IF had their regular PS overnight prior to testing. The meal contained 3250 kJ (773 kcal) of solid food with a protein/carbohydrate/fat energy ratio of 11/46/43% and 22/87/38 g, respectively. The meal consisted of 20 g rye bread, 50 g coarse bread, 25 g butter, 40 g cheese (26% fat), 20 g jam, 150 g fruit yogurt, 100 g banana, and 200 g water. Peripheral venous blood was collected for p-citrulline analysis 15 minutes before and 60, 120, and 180 minutes after completion of the meal. The patients and the HCs were kept nil by mouth during the blood collection. Blood was collected in EDTA tubes and immediately turned and kept on ice for a maximum of 45 minutes before being centrifuged at 3000 rpm at 4°C.

P-citrulline Analysis
P-citrulline concentration was determined by high-pressure liquid chromatography (HPLC). The samples were analyzed using a Shimadzu HPLC system with fluorescence detector (Shimadzu, Tokyo, Japan), with Ascentis Express C18 column, 15 cm × 2.1 cm, 5 µmol (Supelco, Bellefonte, PA). The samples were made as a duplicate to ensure precision. Two controls (Sigma AAS18...
and Sigma A6407), a blind test containing sterile water, plasma from the patients with SBS-IF and the HCs, and external standards with known concentrations of amino acids were prepared. Novaline was used as an internal standard. All samples were deproteinized using 1.5 mol/L perchloric acid. Precolumn derivatization of the amino acids was performed with o-phthalaldehyde, and the amino acids were separated in the column containing silica gel matrix with chemically bonded alkylic chains. For separation, we used alternate concentrations of the 2 mobile phases: mobile phase A contained sodium acetate, hydrochloric acid, methanol, and tetrahydrofuran (pH 7.2), and mobile phase B contained methanol (chromasolv).

Statistics
Quantitative values are expressed as median (minimum to maximum). A significance level of \( P = .05 \) was chosen. Difference between groups (SBS-IF and HCs) was calculated with a Mann-Whitney rank-sum test. Difference within groups was calculated with a Friedman repeated-measures analysis of variance on ranks with Dunnett’s method to isolate the time interval that differs from fasting measurements (\( t_{15 \text{ min}} \)). Spearman’s rank test was used to analyze correlations. The statistical calculations and graphs were made using SigmaPlot 13.0 (Systat Software, San Jose, CA).

Results
Table 1 shows the characteristics of the 8 patients recruited for the study. The patients with SBS-IF had a median remnant small bowel length of 105 cm (30–200). They were significantly older than the HCs (respectively 66 years [42–74] vs 39 years [26–60], \( P = .003 \)). The patients with SBS-IF had a body mass index (BMI) of 23.0 kg/m\(^2\) (19.1–31.1), which was similar to the BMI in the HCs (22.4 kg/m\(^2\) [20.8–27.3], \( P = .878 \)). The creatinine clearance was calculated from collection of a 24-hour urine volume and a single serum creatinine sample performed after a minimum of 8 hours fasting.\(^{16} \)

Figure 1 shows p-citrulline in the fasting state (\( t_{15 \text{ min}} \)) and 60, 120, and 180 minutes after solid food intake in the patients with SBS-IF and the HCs, respectively. Figure 1 illustrates that, except in the 2 outliers (patients 2 and 7) with abnormally high fasting p-citrulline (respectively 79 and 101 µmol/L), the patients with SBS-IF had fasting p-citrulline concentrations of 30.5 µmol/L (14–35). When including patients 2 and 7 (Table 1 and Figure 1) in the statistical analysis, no significant differences in the median fasting p-citrulline were demonstrated in the patients with SBS-IF (33 µmol/L [14–101]) compared with the HCs (39 µmol/L [32–43], \( P = .23 \)). When the 2 outliers were excluded, the patients with SBS-IF had fasting values of 30.5 µmol/L (14–35), which was a significantly lower fasting p-citrulline than that of the HCs (\( P = .008 \)) (Tables 2 and 3). No significant reductions in the postprandial p-citrulline concentrations were seen in the patients with SBS-IF when comparing the fasting state to 60 minutes (\( P = .133 \)) and 120 minutes (\( P = .133 \)), but at 180 minutes following the meal, a 12% (\( P = .041 \)) reduction in citrulline concentration was found. The HCs had significantly lower postprandial p-citrulline concentrations at 60 minutes (13% reduction, \( P = .018 \)), but no significant differences were found at 120 minutes (\( P = .664 \)) or 180 minutes (\( P = .164 \)).

Figure 2A shows the correlation between fasting p-citrulline and the remnant bowel length and dependence on PS (Figure 2B). No significant correlations were found between p-citrulline and remnant bowel length when all patients were included (\( n = 8 \)) and when the outliers, patients 2 and 7, were excluded (\( n = 6 \)). When patients 2 and 7 were excluded, we found a significant correlation between p-citrulline and dependence on PS volume (\( R = .87, P = .033 \)). No significant correlation was found when all patients were included.

Figure 3A–D shows correlations between fasting p-citrulline and absorption of energy and macronutrients in all patients with SBS-IF (\( n = 8 \)) and when patients 2 and 7 were excluded (\( n = 6 \)). No significant correlations were found in either group.

Figure 4A–E shows correlations between fasting p-citrulline and absorption of wet weight and electrolytes in all patients with SBS-IF (\( n = 8 \)) and when patients 2 and 7 were excluded (\( n = 6 \)). Likewise, no significant correlations were found.

Discussion
The aim of this study was to investigate changes in fasting p-citrulline in relation to a solid mixed test meal in patients with SBS-IF and in HCs and to measure the relationship between p-citrulline, bowel length, dependence on PS, and absorption parameters quantified by a 72-hour metabolic balance study. In the patients with SBS-IF, a 12% (\( P = .041 \)) reduction in the postprandial p-citrulline levels was detected at 180 minutes compared with fasting values. In the HCs, there was a 13% (\( P = .018 \)) reduction in postprandial p-citrulline at 60 minutes, but at 180 minutes following the test meal, no significant changes compared with fasting values were found.

Citrulline is almost exclusively synthesized in the small bowel enterocytes mainly from glutamine. It is metabolized into arginine in the kidney, and arginine is degenerated into urea in the liver.\(^{6,7} \) This intestinal-renal pathway is hypothesized to prevent excess arginine degeneration,\(^{18} \) and the key enzymes in this citrulline syntheization process are upregulated in situations where the body has to spare nitrogen, such as in the postabsorptive state.\(^{19} \) Therefore, theoretically, p-citrulline should be stable or slightly depressed (10%–20%) in the postprandial state and return to preprandial values after 2–4 hours in the so-called postabsorptive state.\(^{7,10} \) Rabier and Kamoun\(^{7} \) found that p-citrulline was poorly modified by regular meals in healthy participants, but after a high-protein meal, p-citrulline concentration slightly decreased and returned to
Table 1. Patient Characteristics.

<table>
<thead>
<tr>
<th>SBS</th>
<th>Diagnosis</th>
<th>Sex/ Age, y</th>
<th>Small Bowel Length, cm</th>
<th>BMI, kg/m²</th>
<th>Creatinine Concentration, µmol/L</th>
<th>Creatinine Clearance, mL/min</th>
<th>Dietary Energy Intake, kJ/d</th>
<th>Wet Weight Intake, kg/d</th>
<th>Wet Weight Ostomy Output, kg/d</th>
<th>Parenteral Support, L/d</th>
<th>Ostomy Energy Output, kJ/d</th>
<th>Parenteral Energy, kJ/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD</td>
<td>F/57</td>
<td>70</td>
<td>19.1</td>
<td>73</td>
<td>85</td>
<td>10,823</td>
<td>3.7</td>
<td>4.4</td>
<td>3.6</td>
<td>9638</td>
<td>6662</td>
</tr>
<tr>
<td>2</td>
<td>Mesenteric infarction</td>
<td>M/66</td>
<td>190</td>
<td>23.5</td>
<td>246</td>
<td>26</td>
<td>7238</td>
<td>3</td>
<td>1.6</td>
<td>0.9</td>
<td>3497</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Mesenteric infarction</td>
<td>M/74</td>
<td>30</td>
<td>22.6</td>
<td>146</td>
<td>70</td>
<td>15,181</td>
<td>3.6</td>
<td>5</td>
<td>5.2</td>
<td>12,741</td>
<td>8120</td>
</tr>
<tr>
<td>4</td>
<td>Ileus</td>
<td>F/55</td>
<td>100</td>
<td>19.2</td>
<td>53</td>
<td>93</td>
<td>9038</td>
<td>1.9</td>
<td>3.9</td>
<td>8</td>
<td>6771</td>
<td>6120</td>
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<tr>
<td>5</td>
<td>CD</td>
<td>F/79</td>
<td>30</td>
<td>26.5</td>
<td>62</td>
<td>124</td>
<td>8447</td>
<td>1.2</td>
<td>2.9</td>
<td>4</td>
<td>7697</td>
<td>4853</td>
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<tr>
<td>6</td>
<td>CD</td>
<td>M/42</td>
<td>150</td>
<td>19</td>
<td>79</td>
<td>153</td>
<td>12,216</td>
<td>3.1</td>
<td>4.3</td>
<td>3.4</td>
<td>7445</td>
<td>5857</td>
</tr>
<tr>
<td>7</td>
<td>UC</td>
<td>M/66</td>
<td>200</td>
<td>25.4</td>
<td>142</td>
<td>65</td>
<td>10,111</td>
<td>2.9</td>
<td>1.4</td>
<td>2</td>
<td>1977</td>
<td>664</td>
</tr>
<tr>
<td>8</td>
<td>Surgical complication</td>
<td>M/72</td>
<td>110</td>
<td>31.1</td>
<td>104</td>
<td>74</td>
<td>8126</td>
<td>2.6</td>
<td>2.5</td>
<td>3.1</td>
<td>5467</td>
<td>2727</td>
</tr>
</tbody>
</table>

BMI, body mass index; CD, Crohn’s disease; F, female; M, male; SBS, short bowel syndrome; UC, ulcerative colitis.
normal values after 4 hours. In accordance with this, Wahren et al documented that the usual oral protein intake had no significant effect on postabsorptive p-citrulline levels in healthy participants measured 3 hours after a protein meal.

Our findings of an initial decrease in p-citrulline after 60 minutes in the HCs, which returned to fasting values after 180 minutes, are in concordance with this. However, also in patients with SBS-IF, we found a significant decrease in postprandial p-citrulline compared with fasting values at 3 hours.

It is currently unknown if provision of conventional parenteral nutrients, fluids, and electrolytes affects p-citrulline. This should be investigated to harmonize conditions for the most reliable sampling of plasma for citrulline analysis.

A cutoff value of p-citrulline below 30 µmol/L has been suggested to delineate patients with SBS and healthy participants, and a cutoff value of 20 µmol/L has been suggested to distinguish between transient and permanent IF. In our study, 2 of the 8 patients with SBS-IF with the longest remnant bowels (190 cm and 200 cm) had p-citrulline values of 79 and 101 µmol/L, respectively, thereby significantly exceeding this value and even exceeding the highest concentrations observed in the HCs (Figure 1). In patient 2, this

Figure 1. Postprandial citrulline levels. Left graph depicts the patients with short bowel syndrome (SBS), and the right graph depicts healthy controls. P-citrulline measured in the fasting state (–15) and 60, 120, and 180 minutes after the mixed test meal.

Table 2. Plasma Citrulline Values (µmol/L) for SBS.

<table>
<thead>
<tr>
<th>Citrulline (µmol/L)</th>
<th>t–15</th>
<th>t60</th>
<th>t120</th>
<th>t180</th>
<th>P Value (Difference Within Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBS-IF (n = 8)</td>
<td>33 (14–101)a</td>
<td>30 (14–86)a</td>
<td>28.5 (17–92)b</td>
<td>29 (17–109)b</td>
<td>.047</td>
</tr>
<tr>
<td>Healthy controls (n = 8)</td>
<td>39 (32–47)a</td>
<td>34 (28–38)b</td>
<td>35 (30–45)b</td>
<td>33.5 (27–47)a</td>
<td>.032</td>
</tr>
<tr>
<td>P value (difference between groups)</td>
<td>.234</td>
<td>.382</td>
<td>.161</td>
<td>.328</td>
<td></td>
</tr>
</tbody>
</table>

Values represent the median and range. Difference within groups is calculated with a Friedman repeated-measures analysis of variance on ranks with Dunnett’s method to isolate the time interval that differs from fasting measurements (–15). Superscripted letters a and b denote a statistically significant difference (P < .05) compared with fasting measurement (–15). Difference between groups is calculated with a Mann-Whitney rank-sum test. SBS-IF, short bowel syndrome with intestinal failure.

Table 3. Plasma Citrulline Values (µmol/L) for SBS.

<table>
<thead>
<tr>
<th>Citrulline (µmol/L)</th>
<th>t–15</th>
<th>t60</th>
<th>t120</th>
<th>t180</th>
<th>P Value (Difference Within Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBS-IF (n = 6)</td>
<td>30.5 (14–35)</td>
<td>28.5 (14–32)</td>
<td>27 (17–32)</td>
<td>27 (17–30)</td>
<td>.075</td>
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<tr>
<td>Healthy controls (n = 8)</td>
<td>39 (32–47)a</td>
<td>34 (28–38)b</td>
<td>35 (30–45)b</td>
<td>33.5 (27–47)a</td>
<td>.032</td>
</tr>
<tr>
<td>P value (difference between groups)</td>
<td>.008</td>
<td>.029</td>
<td>.003</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

Values represent the median and range. Difference within groups is calculated with a Friedman repeated-measures analysis of variance on ranks with Dunnett’s method to isolate the time interval that differs from fasting measurements (–15). Superscripted letters a and b denote a statistically significant difference (P < .05) compared with fasting measurement (–15). Difference between groups is calculated with a Mann-Whitney rank-sum test. SBS-IF, short bowel syndrome with intestinal failure.
could be explained by a severe impairment in renal function evidenced by the elevated serum creatinine and decreased creatinine clearance (Table 1). P-citrulline has been demonstrated to be significantly elevated in patients with a creatinine clearance <50 mL/min. In patient 7, the apparent high serum creatinine might be due to both a degree of renal impairment and/or dehydration. The measured creatinine clearance was slightly impaired at 65 mL/min (normal >60 mL/min for men and >45 mL/min for female), but the combination of the borderline renal impairment and the length of the remnant small bowel may have resulted in the elevated p-citrulline. These 2 patients had the lowest ostomy wet weight (1.6 and 1.4 kg/d, respectively) and ostomy energy outputs (3497 and 1977 kJ/d, respectively) and, concomitantly, the lowest need for parenteral fluid (0.9 and 2.0 L/d, respectively) and parenteral energy support (0 and 664 kJ/d, respectively) (Table 1). The high p-citrulline concentrations in these 2 patients may illustrate that the clinical use of the suggested cutoff values in individual patients with SBS to predict PS dependence is difficult in the patients situated on the borderline between intestinal insufficiency and failure. Thus, in these patients, p-citrulline may be insufficiently discriminative for use in the individual context. Many of these patients with SBS have various degrees of renal impairment, frequently caused by chronic dehydration, and this could further impair the positive predictive value of measurements of p-citrulline in an unselected SBS patient population.

We found no significant correlations between fasting p-citrulline and bowel length, absorption of wet weight, and macronutrients and micronutrients (all \( P > 0.05 \)) when including all patients \( (n = 8) \). Likewise, when excluding the 2 patients closest to the borderline of intestinal insufficiency (patients 2 and 7), no correlations between p-citrulline and the absorptive parameters existed in the lower ranges of intestinal absorption. Thus, in the interval of intestinal wet weight absorption ranging from a net secretion of 2 kg/d to a net absorption 0.1 kg/d, p-citrulline ranged from 14–35 µmol/L, and no significant correlation was found. Likewise, in the interval of intestinal energy absorption of 750–4771 kJ/d, p-citrulline ranged from 14–35 µmol/L, but no significant correlation was found. Researchers have found inconsistent correlations between citrullinemia and energy, macronutrient, wet weight, and electrolyte absorption, and this probably reflects the complex nature of absorptive function in patients with SBS-IF. Although a recently published study showed that short bowel anatomy might influence p-citrulline values, no correlation between p-citrulline and remnant bowel length was found in patients with SBS without ileum. Thus, the large patient heterogeneity and consequent heterogeneity in the pathophysiological manifestations of SBS may explain the variable results regarding correlations between p-citrulline and intestinal length and function. We found a positive correlation between p-citrulline and the dependence on PS volume when patients 2 and 7 were excluded. This is in contrast to what would be expected since those patients with SBS-IF with the most severe intestinal failure and the highest need for PS volume were anticipated to have the lowest p-citrulline.

It is clear that the weakness of the current study is the small sample size. Larger studies employing the same methods but also including patients with SBS with remnant colons should be performed to investigate the applicability of p-citrulline as a biomarker of intestinal function. In the ideal situation, these studies should separately address patients with irreversible IF, patients with borderline and potentially reversible IF, and patients with SBS with intestinal insufficiency. It remains to be established if sequential measurements of p-citrulline may be of benefit in the long-term management and adjustment of parenteral support in patients with SBS-IF.
Figure 3. Correlations between p-citrulline and absorption of energy (A) and macronutrients (protein [B], carbohydrate [C], and lipid [D]) when all patients were included (n = 8) and when patients 2 and 7 were excluded (n = 6). n = 6 is marked with a dotted line.

Figure 4. Correlations between fasting p-citrulline and absorption of wet weight (A) and electrolytes (potassium [B], sodium [C], magnesium [D], and calcium [E]) when all patients were included (n = 8) and when patients 2 and 7 were excluded (n = 6). n = 6 is marked with a dotted line.
Conclusion

Our data showed a 12% ($P = .041$) reduction in p-citrulline levels after 180 minutes compared with fasting values in the patients with SBS-IF. In the HCs, there was a 13% ($P = .018$) reduction after 60 minutes, but after 180 minutes, no significant change compared with fasting values was found. Thus, on this small study, the optimal timing of p-citrulline measurement is after at least 3 hours of fasting. However, the clinical applicability of p-citrulline as a biomarker of bowel length, bowel absorptive function, or dependence on PS is questionable. P-citrulline may not be sufficiently discriminative in the SBS patients with irreversible IF and the patients with SBS on the borderline between intestinal insufficiency and failure. A finding of a low p-citrulline concentration is indicative of intestinal failure, but a normal p-citrulline may be found in healthy participants, patients with irreversible IF, and patients on the borderline between intestinal insufficiency and failure. Larger studies employing metabolic balance studies and p-citrulline in selected SBS patient populations should be performed to confirm these conclusions.

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Statement of Authorship

H. Fjermestad, M. Hvistendahl, P. B. Jeppesen equally contributed to the conception and design of the research, and contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References