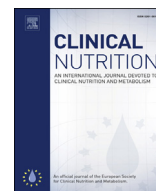




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Original article

Serum fasting GLP-1 and GLP-2 associate with intestinal adaptation in pediatric onset intestinal failure

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SUMMARY

Aim: Glukagon-like-peptide-1 (GLP-1) and -2 (GLP-2), produced by intestinal L-cells, are key hormones regulating intestinal transit, secretion, absorption, and mucosal growth. We evaluated naïve fasting serum GLP-1 and GLP-2 levels in pediatric intestinal failure (IF).

Methods: Fifty-five IF patients with median age 4.2 (IQR 1.3–12) years and 47 matched healthy controls underwent measurement of fasting serum GLP-1 and GLP-2.

Results: Serum GLP-2 [19.9 (13.8–27.9) vs 11.6 (7.0–18.6) ng/mL, $P < 0.001$], but not GLP-1 [6.1 (4.0–15.7) vs 6.4 (3.9–10.7) ng/mL, $P = 0.976$], levels were increased in IF patients. Serum GLP-2 concentrations were higher in patients with small bowel-colic continuity [21.1 (15.0–30.7) ng/mL] compared to patients with an endostomy [10.4 (6.6–17.9) ng/mL, $P = 0.028$], whereas no association with preservation of ileum or ileocecal valve was observed. During PN delivery, GLP-2 inversely associated with remaining small bowel length ($r = -0.500$, $P = 0.041$) and frequency of PN infusions ($r = -0.549$, $P = 0.042$). Serum GLP-1 levels were lower in patients receiving PN currently [4.1 (2.8–5.1)] compared to patients, who had weaned off PN [6.5 (5.1–21.1), $P = 0.005$], and correlated positively with duration of PN ($r = 0.763$, $P = 0.002$) and negatively with percentage parenteral energy requirement ($r = -0.716$, $P = 0.006$).

Conclusions: In pediatric IF, serum GLP-2 levels increase in patients with small bowel-colic continuity proportionally to the length of resected small intestine. Increase in serum GLP-1 and GLP-2 levels paralleled reducing requirement for parenteral support. These findings support regulation of intestinal adaption by GLP-2 and GLP-1 in children with IF.

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1. Introduction

Intestinal failure (IF) results from a major bowel resection or congenital defect, leading to decreased intestinal absorptive area and malabsorption, rapid intestinal transit, and need for long-term parenteral nutrition (PN) to sustain adequate nutrition, growth and survival [1]. Following a massive small intestinal resection, intestinal adaptation, which involves a series of changes in intestinal morphology, function, and regulation, efforts to compensate for the loss of functional intestinal surface area, allowing gradual weaning of PN [2,3]. Intestinal adaptation is mediated by several endocrine hormones, including glucagon-like peptides (GLP) 1 and 2

synthesized by enteroendocrine L-cells of the distal small intestine and colon [4–6]. GLP-1 inhibits gastric emptying and small intestinal and colon motility [7,8]. GLP-2 is shown to slow proximal intestinal motility, increase mesenteric blood flow, reduce gastric secretion, and to act as a trophic agent for the small intestinal mucosa improving nutrient absorption [9–11]. In patients with IF, lack of feed-stimulated GLP-2 response may lead to poor intestinal adaptation [4,5,12]. Discovery of enterotrophic effects of GLP-2 has led to novel emerging treatment options in patients with IF [13,14]. A GLP-2 analog teduglutide has been shown to improve nutrient and fluid absorption, endorse mucosal hyperplasia, and decrease PN requirement in IF patients [13,15,16].

In this study, we hypothesized that serum GLP levels are reflected by the extent and location of intestinal resection, intestinal continuity and PN requirement in pediatric onset IF. To test these hypotheses, we cross-sectionally measured fasting serum GLP-1 and GLP-2 levels in patients with pediatric onset IF and in controls matched for age and gender to investigate their relationships with intestinal adaptation during PN delivery and after weaning off PN.

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2. Methods

2.1. Ethics

This study was approved by the Helsinki University Central Hospital ethics committee and the Institutional Review Board. A written informed consent was received from all patients and controls or their caregivers before any procedures.

2.2. Patients

Medical records of all patients with pediatric onset IF treated by our rehabilitation program in Children's Hospital, Helsinki University Hospital from 1984 to 2014 were reviewed. In total, 72 eligible patients were identified of which 55 (76%) patients participated in this cross-sectional study, including clinical examination and laboratory tests. An informed written consent was received from patients and/or their parents.

For this study, IF was defined as over 50% resection of the small bowel or a duration of PN over 30 days [17,18], and patients with a primary intestinal dysmotility disorder such as Hirschsprung disease with less than 50% of age-adjusted small bowel length remaining were categorized to short bowel syndrome group. Our management protocol for IF has been reviewed recently elsewhere [19,20].

2.3. Controls

Forty-seven age and gender-matched healthy children and young adults without any renal, endocrinological, hepatobiliary or gastrointestinal disease, were used as controls. Their age [6.4 years (4.2–12), $P = 0.091$] and sex (boys:girls, 35:12, $P = 0.144$) distributions were comparable to patients.

2.4. Baseline data

Baseline patient data, including amount and composition of PN during 3 months preceding serum GLP-1 and GLP-2 measurement, surgical procedures and anatomy of the remaining bowel were collected from the patient records. Percentage of age-adjusted

small bowel and colon length was calculated based on age-specific normal values [21]. The weight and height were expressed as z-scores. Body-mass index (BMI, in kg/m^2 ; weight divided by the square of height) was calculated for adults and Finnish reference value-based BMI-for-age was calculated for children over two years of age [22].

2.5. Laboratory tests

Blood samples were drawn after overnight fast, prepared with centrifugation and stored to -20°C until analyzed. Quantification of serum GLP-1 and GLP-2 were performed with the Human GLP-2 (YK141) and GLP-1 (YK160) EIA kits (Yanaihara Institute Inc., Shizuoka, Japan) according to the manufacturer's instructions. The intra-assay and inter-assay CV (%) were 4.7 and 9.6 for GLP-1 and 3.0 and 14.3 for GLP-2, respectively. Serum citrulline, a marker of enterocyte mass, was measured by using an automatic amino acid analyser (Biochromon 30 Physiological and Midas Autosampler, Biochromon Limited, Cambridge, England) as described previously [23].

2.6. Statistical analysis

Descriptive statistics are expressed as median (IQR) unless otherwise stated. For multiple comparisons Kruskal Wallis test was used, followed by post hoc Mann Whitney U test when Kruskal Wallis test reached statistical significance. For pairwise comparisons Mann Whitney U test and Fisher's exact test was used. Associations were tested with Spearman rank correlation test. Statistical significance was set at 0.05.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. Causes of IF included necrotizing enterocolitis ($n = 23$), midgut volvulus ($n = 10$), small bowel atresia ($n = 9$), extensive Hirschsprung's disease ($n = 7$), chronic intestinal pseudo-obstruction ($n = 5$), and gastroschisis ($n = 1$). Patients currently on PN were younger, had

Table 1
Patient characteristics.

	All patients	Patients on PN	Patients weaned off PN	P-value
N	55	17	38	
Boys		10	23	1.000
Age	4.2 (1.3–12)	1.0 (0.3–4.6)	7.7 (3.1–17)	0.001
BMI	18.5 (16.9–20.0)	20.0 (18.5–22.1)	18.3 (16.5–19.4)	0.181
Weight z-score	−0.8 (−1.5–0.0)	−1.0 (−2.0–0.0)	−0.8 (−1.5–0.1)	0.056
Height z-score	−1.0 (−2.2–0.2)	−1.5 (−2.9–0.5)	−0.7 (−1.9–0.3)	0.431
Duration of PN (mo)	9.5 (4.2–34)	11 (5.4–59)	8.5 (3.8–25)	0.146
Time after weaning off PN (y)			3.9 (1.6–14)	
Weekly PN infusions		7 (6–7)		
PN calories of total nutrition (%)		73 (12–85)		
Time after last bowel resection (y)	2.9 (1.0–9.0)	0.6 (0.2–2.9)	4.4 (2.4–14)	<0.001
SBS/dysmotility disorder (n)	48/7	15/2	33/5	1.000
Remaining bowel				
Small bowel (cm)	47 (25–101)	30 (18–60)	50 (31–108)	0.031
Small bowel (%) ^a	26 (17–47)	23 (14–29)	32 (21–50)	0.046
Ileum (cm)	0 (0–5)	0 (0–4)	2 (0–18)	0.125
Colon (%) ^a	87 (57–100)	71 (22–100)	95 (68–100)	0.069
ICV preserved (n)	26	6	20	0.249
Small intestinal endostomy (n)	4	3	1	0.083
Serum Citrulline (umol/L)	22 (15–29)	13 (10–23)	24 (18–30)	0.001
Serum GLP-1 (ng/mL)	6.0 (4.0–16)	4.1 (2.8–5.1)	6.5 (5.1–21)	0.005
Serum GLP-2 (ng/mL)	20 (14–28)	19 (14–25)	20 (14–34)	0.571

Data are median (IQR). GLP; glucagon-like-peptide; SBS; short bowel syndrome.

P-values refer to comparisons between patient groups using Fisher's exact test or Mann Whitney U test. P-values <0.05 are marked bold.

^a %; percentage of remaining age-adjusted small bowel or colon length.

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