Received: 14 May 2024 | Accepted: 5 November 2024

DOI: 10.1002/jpn3.12455

JPGN

ORIGINAL ARTICLE

Nutrition

Long-term growth and nutrition outcomes in children following intestinal transplantation

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Funding information

None

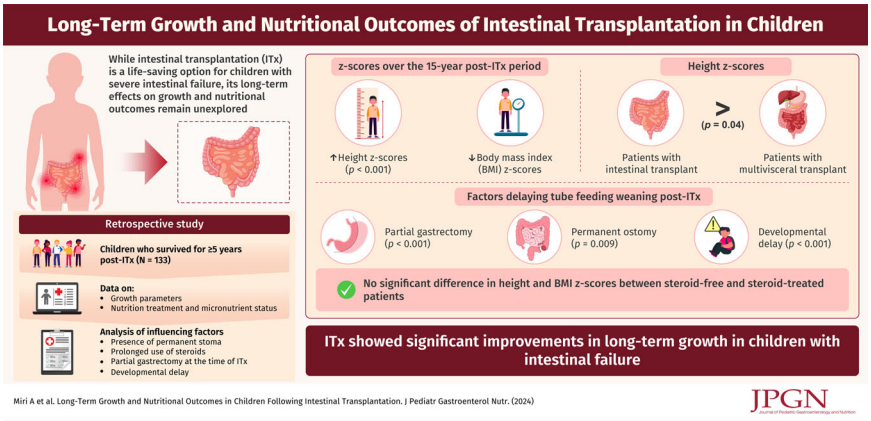
Abstract

Objective: Intestinal transplantation (ITx) has become an accepted option for children with serious complications from intestinal failure and parenteral nutrition (PN) dependence. We aimed to assess long-term growth and nutritional outcomes in these patients. We also assessed factors influencing nutritional status and ability to wean off tube feedings (TFs) after ITx.

Methods: We looked retrospectively into post-ITx growth parameters, nutrition treatment, and micronutrient status for children who survived for 5 or more years after ITx. One hundred thirty-three children between 1993 and 2014 were involved. Descriptive data and growth parameters were collected over 15 years after ITx. We also analyzed influencing factors, including the presence of permanent stoma, prolonged use of steroids, partial gastrectomy at the time of ITx, developmental delay, concurrent visceral transplant, and graft rejection episodes.

Results: There was an increase in the height *z*-scores over the 15-year period post-ITx ($p < 0.001$). There was a downward trend in body mass index (BMI) *z*-scores over the 15-year post-ITx period. Isolated intestinal transplant patients showed a better height *z*-score compared to multivisceral transplant ($p = 0.04$). The height and BMI *z*-scores for patients on steroids were not significantly different from the *z*-scores for steroid-free patients ($p = 0.72$, 0.99, respectively). There was no significant change in height and BMI *z*-scores based on prednisolone dose: ≤0.2 mg/kg ($p = 0.76$); >0.2 mg/kg ($p = 0.52$). Patients were more likely to require supplemental TF up to 15 years post-ITx when they had partial gastrectomy ($p < 0.001$), permanent ostomy ($p = 0.009$), or developmental delay ($p < 0.001$).

Conclusions: There was improved long-term linear growth post-ITx. Developmental delay, partial gastrectomy, and a permanent ostomy are likely to delay TF wean post-ITx.



KEYWORDS

gastrectomy, ileostomy, pediatric, tube feeds

1 | INTRODUCTION

Intestinal transplantation (ITx) has become an accepted option for treating infants and children with life-threatening complications from intestinal failure and long-term dependence on parenteral nutrition (PN).[1] As post-transplant survival has improved, it is crucial to examine long-term growth and nutritional outcomes for these patients. Past research has examined growth indices 2-year post-ITx; however, there are minimal data regarding long-term growth and nutritional outcomes.[2] Long-term growth indices, treatment of vitamin and mineral deficiencies, and the ability of patients to wean off tube feedings (TFs) are all crucial factors in assessing long-term nutrition outcomes post-ITx. Understanding a child's overall nutrition profile plays a crucial role in determining their capacity for healthy development, bone health, and overall morbidity. A healthy nutrition profile can ensure that children will have an undisturbed transition into adulthood. Thus, when exploring the outcomes of post-ITx patients, it is critical to also examine their long-term nutrition outcomes. This study aimed to assess long-term growth and nutrition outcomes in post-ITx children and the factors that influenced these outcomes.

What is Known

- Published studies indicate short-term growth improvements in post-intestinal transplant (ITx) patients, but long-term outcomes are less explored.
- Prolonged total parenteral nutrition (TPN) weaning post-ITx is linked to oral aversion and pre-transplant oral intake experience.

What is New

- This study shows long-term improvements in linear growth and nutrition up to 15 years post-ITx.
- Our article also identifies that factors such as permanent ostomy, partial gastrectomy, and developmental delay are associated with delayed TPN weaning, highlighting the importance of these factors in long-term recovery and nutrition management.

2 | METHODS

The primary goal of the study was to assess the long-term nutrition outcomes of post-ITx patients by examining their weight, height, and body mass index (BMI). The patients' height, weight, and BMI were collected in 5-year intervals after their ITx operation (5, 10, and 15 years). The height and weight data were also used to evaluate if the type of transplant, long-term steroid use, partial gastrectomy, developmental delay, permanent ostomy, and episodes of graft rejection had a significant effect on the patients' nutritional outcome. Developmental delay diagnosis follows The American Academy of Pediatrics (AAP) definition as a child not reaching developmental milestones (motor function, speech and language, cognitive skills, and social skills) at the expected age. The secondary goal of the study was to evaluate the effect of partial gastrectomy, developmental delay, and permanent ostomy on the time needed to wean TF in post-ITx patients. Finally, the patients' iron, vitamin D, vitamin A, and zinc levels post-ITx were also evaluated through the 15-year interval data.

2.1 | Patients and materials

A single-center retrospective cohort study was conducted on children (age 0–19 years) who received ITx between October 1, 1993, and December 31, 2014, including isolated and multivisceral en-bloc intestinal transplants. Exclusion criteria include any patient with a second ITx or less than 5 years of survival after ITx and any patient with other organ transplants rather than liver–small bowel–pancreas transplants. For outcome variables, *z*-scores for weight, height, and BMI were gathered for all patients at transplant time and then post-ITx at 5-year intervals (at 5, 10, and 15 years). Other variables include time of post-ITx tube feed weaning, partial gastrectomy at transplant, persistent ostomy for more than 1 year after transplant, developmental delay, number of episodes of intestinal graft rejection, and the dose and duration of steroid regimen after transplant. Also, vitamin D, zinc, vitamin A, and iron levels were gathered at the time of transplant and then post-ITx at 5-year intervals (at 5, 10, and 15 years). IRB approval was obtained from the University of Nebraska Medical Center IRB before initiation of data collection.

2.2 | Statistical analysis

We used scatter plots, mean, median, and standard deviation to summarize individual demographic and health indicators within the study cohort at transplantation and then post-ITx at 5-year intervals (at 5, 10, and 15 years). Next, we focused on changes in primary health indicators over time to assess the overall health of children who received ITx. We used the log link function to perform a linear mixed model and a generalized linear model with a general estimating equation (GEE), where follow-up time was treated as an offset term for characteristics of outcome measurements. A mixed model procedure was used to generate coefficients to evaluate the change in health conditions over the study period for continuous outcomes. The GEE procedure was used for binary outcomes to obtain odds ratios (ORs) and estimate the difference in terms of the outcome variables over time. The statistical significance level was set at $p = 0.05$, and the analyses were carried out using SAS version 9.4 (SAS Enterprise).

3 | RESULTS

3.1 | Demographics and patient characteristics

Two hundred thirty patients received ITx in our center between October 1, 1993, and December 31, 2014. Ninety-six patients were excluded (65 for survival <5 years after transplant, 41 due to second intestinal transplant or intestinal explant, and 1 for concurrent kidney transplant). A total of 133 patients were included in the study. All of them survived 5 years post-ITx. A total of 108 of the patients survived 10 years and 57 survived 15 years (Supporting Information S1: Figure 1). Seventeen patients missed some follow-up data (such as a growth parameter or micronutrient level) at 10 years post-ITx and 16 patients had missing data at 15 years post-ITx.

Patients' characteristics are presented in Table 1. One hundred thirteen patients (85%) have anatomical causes of intestinal failure before ITx, including short bowel syndrome due to gastroschisis, intestinal atresia, Hirschsprung's disease, superior mesenteric artery thrombosis, and so on. Fifteen (15%) patients' intestinal failure was due to functional causes such as malabsorption syndromes or motility disorders. Post-transplant characteristics are presented in Supporting Information S3: Table 2. We considered patients to have native colon if they have any remaining large intestinal length of sigmoid colon or longer.

TABLE 1 Patients' characteristics at transplant.

Patients characteristics[a]	*N* (%)
Age at transplant time	Range (0.4–19) yr
Gender	
1. Male	71 (53.4)
2. Female	62 (46.6)
Intestinal failure etiology	
A. SBS	113 (85)
1. Gastroschisis	40 (30)
2. NEC	28 (21)
3. Intestinal atresia	16 (12)
4. Volvulus	17 (13)
5. Hirschsprung's	8 (6)
6. Trauma/surgical complication	4 (3)
B. Functional	20 (15)
1. Chronic intestinal pseudo-obstruction	11 (8.5)
2. Microvillous inclusion disease	4 (3)
3. MMIH syndrome	3 (2)
4. Autoimmune enteropathy	2 (1.5)
Type of intestinal transplant	
1. Isolated ITx	19 (14.2)
2. Liver–intestinal–pancreas transplant	114 (85.8)
Comorbidities affecting growth[a]	4 (3.0)

Abbreviations: ITx, intestinal transplant; MMIH, megacystis-microcolon-intestinal hypoperistalsis; NEC, necrotizing enterocolitis; SBS, short bowel syndrome; yr, year.

[a]Growth hormone deficiency and hyperthyroidism.

The only comorbidities found in our patients that affected growth were growth hormone deficiency and hypothyroidism. Those conditions were treated to eliminate their effect on long-term growth.

Other patients' characteristics were the presence of developmental delay (19.5%), partial gastrectomy at the time of ITx (45.1%), and persistent ostomy more than 1 year post-ITx (29.3%). We chose 1 year as a cutoff point for the definition of persistent ostomy as most of our patients will have an ostomy takedown within a year post-ITx unless there was an indication of a permanent stoma. Steroid use was also measured for this study. All the patients in this study were given steroids. A 2-year threshold was used as a differentiator since patients who surpassed 2 years of steroid use were on steroids for the entire duration of the study. About 112 patients (84.2%) surpassed 2 years of steroid use.

3.2 | Growth

Growth was assessed at the time of transplant, then at 5, 10, and 15 years post-ITx. When indicated, growth parameters were corrected to gestational age for premature patients who are less than 2 years old. Mean *z*-scores for growth parameters at transplant were −1.92 for height, −0.95 for weight, and 0.51 for BMI. The mean *z*-score for growth parameters over 15 years post-ITX is presented in Supporting Information S2: Table 3. Results showed no significant change in weight over time ($p = 0.23$). There was a statistically significant increase in the height *z*-score over time post-ITx ($p < 0.001$). There was a statistically significant decrease in the BMI *z*-score over time post-ITx ($p < 0.001$). This change in BMI might not be clinically significant as the change in *z*-score ranged between 0.5 and −0.35 (Figure 1).

There was no significant change in the BMI and height *z*-scores based on whether patients had a gastrectomy or not at the time of ITx ($p = 0.09$ and 0.15, respectively). There was no significant change in the BMI and height *z*-scores between children with permanent ostomy when compared to patients with intestinal continuity post-ITx ($p = 0.37$ and 0.95, respectively). Children who developed intestinal graft rejection did not significantly change their BMI and height *z*-scores compared to children with no graft

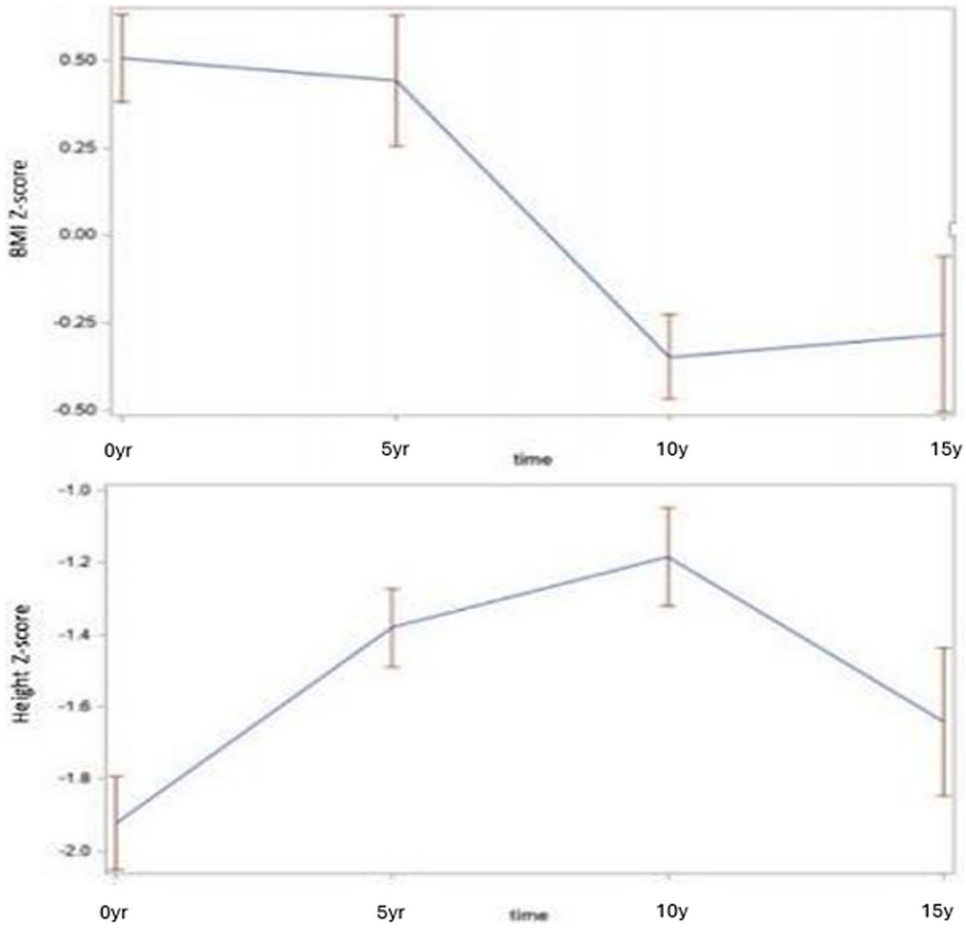


FIGURE 1 BMI and height *z*-score changes over time after intestinal transplantation. BMI, body mass index.

rejection ($p = 0.16$ and 0.9, respectively). Isolated intestinal transplant patients had improvement in height *z*-scores when compared to patients with liver–small bowel–pancreas transplant ($p = 0.04$), but there was no significant difference in BMI *z*-scores ($p = 0.87$). No significant difference was found in height and BMI *z*-scores between patients who had long-term steroid use when compared to patients who came off the steroid within 2 years of their ITx. ($p = 0.72$ and 0.99, respectively). There was no significant difference in height and BMI *z*-scores between the two daily dose-based prednisolone groups (dose ≤0.2 or >0.2 mg/kg/day) ($p = 0.76$ and 0.52, respectively).

3.3 | Nutrient delivery

All patients were weaned off PN shortly after the transplant. The median length of time needed to discontinue PN was 34 days (range: 7–258 days). After weaning off PN, patients received a combination of TF and oral nutrition support. TF nutrition was weaned off gradually based on improved oral calorie intake and sustained growth. Eighty patients (60.2%) were weaned off TF at some time point following intestinal transplant. The remaining patients ($n = 53$) were either unable to wean off TF ($n = 35$), died while on TF ($n = 6$), or had inadequate data to report ($n = 12$). The median length to achieve a full oral diet in those patients weaned off TF was 48 months (range: 1–175 months). Patients with partial gastrectomy, permanent ostomy, and developmental delay were more likely to require a longer period of supplemental TF post-ITx when compared to other patients without those conditions ($p < 0.001$, $p = 0.009$, and $p < 0.001$, respectively) (Figure 2).

3.4 | Vitamin and micronutrient deficiency

All patients were routinely supplemented with multivitamins through PN and enterally following discontinuation of PN after ITx. Vitamin D and iron were the most common vitamins and minerals supplemented. Twenty-seven out of 48 patients with available iron level data at the time of ITx (56.2%) were deficient (Table 2). Six out of 22 patients (27.3%) remained iron deficient at 15 years. Thirty-seven out of 113 patients (32.7%) were vitamin D deficient at the time of ITx. At 15 years, 14 out of 28 patients (50.0%) remained vitamin D deficient. Zinc deficiency was evident in 19 out of 118 patients (16.1%) at the time of ITx. At 15 years, 5 out of 18 patients (27.8%) had a zinc deficiency. Zinc deficiency was found in 6 out of 20 patients (30.0%) with a permanent ostomy at 5 years and 1 out of 12 patients (8.3%) at 10 years post-ITx. Twelve out of 114 patients (11%) were vitamin A deficient at the time of ITx. At 5 years post-ITx, 3 out of 26 patients (12%) remained vitamin A deficient, and none out of 17 patients were vitamin A deficient at 10 years. Only 1 out of 10 patients (10%) had vitamin A deficiency at 15 years post-Tx. We tried to trend Vitamin E, phosphorus, and copper levels but not enough available data. Data for magnesium levels were not collected as they are usually low in post-transplant patients because of sustained tacrolimus therapy.

4 | DISCUSSION

Our study showed improvement in linear growth, but a decline in BMI over the 15-year post-ITx period that was measured. These changes could be related to a drop in the number of survivors between 10 and 15 years post-ITx. Similar findings were found in previous studies. One study observed significant improvement in the catch-up growth for children who survived 10 years post-ITx with no significant change in weight over time.[3] Another study showed that two thirds of children had normal growth and the remaining one third had *z*-scores lower than –2 over 7 years post-ITx.[2] More recent published data showed improved length and stable weight at 10 years post-ITx.[4] A single center in Argentina found a decrease in BMI and an improvement in height z-scores within 10 years post-ITx.[5] Another study showed improvement in height in the first 3 years and a significant improvement in weight only during the first year post-ITx.[6]

Our center conducts ITxs both with and without partial gastrectomy. In past research, feeding intolerance and nutrition deficiencies were reported after gastrectomy in bariatric surgery.[7] No data are available regarding gastrectomy's effect on growth post-ITx. We found no significant impact of gastrectomy on linear growth or BMI over time.

Ileostomy formation is a standard technique post-ITx to facilitate accessing the bowel via ileoscopy for biopsy to rule out rejection. Ileostomies carry a higher risk for poor weight gain. This might be attributed to total body sodium loss in ileostomy output.[8] We did not find a major effect on growth patterns in children with a permanent ileostomy. The practice of regular electrolyte checks and replacement could explain this result.

Developmentally delayed children are usually considered to be at higher risk for malnutrition.[9] Despite this, our results did not find that developmental delay had a major effect on long-term growth. Avoiding transplantation in patients with severe developmental delay and early nutritional intervention post-ITx are possible explanations for this finding.

Previous studies showed that the absence or limited number of intestinal graft rejection episodes was a positive predictor for weight gain a few years post-

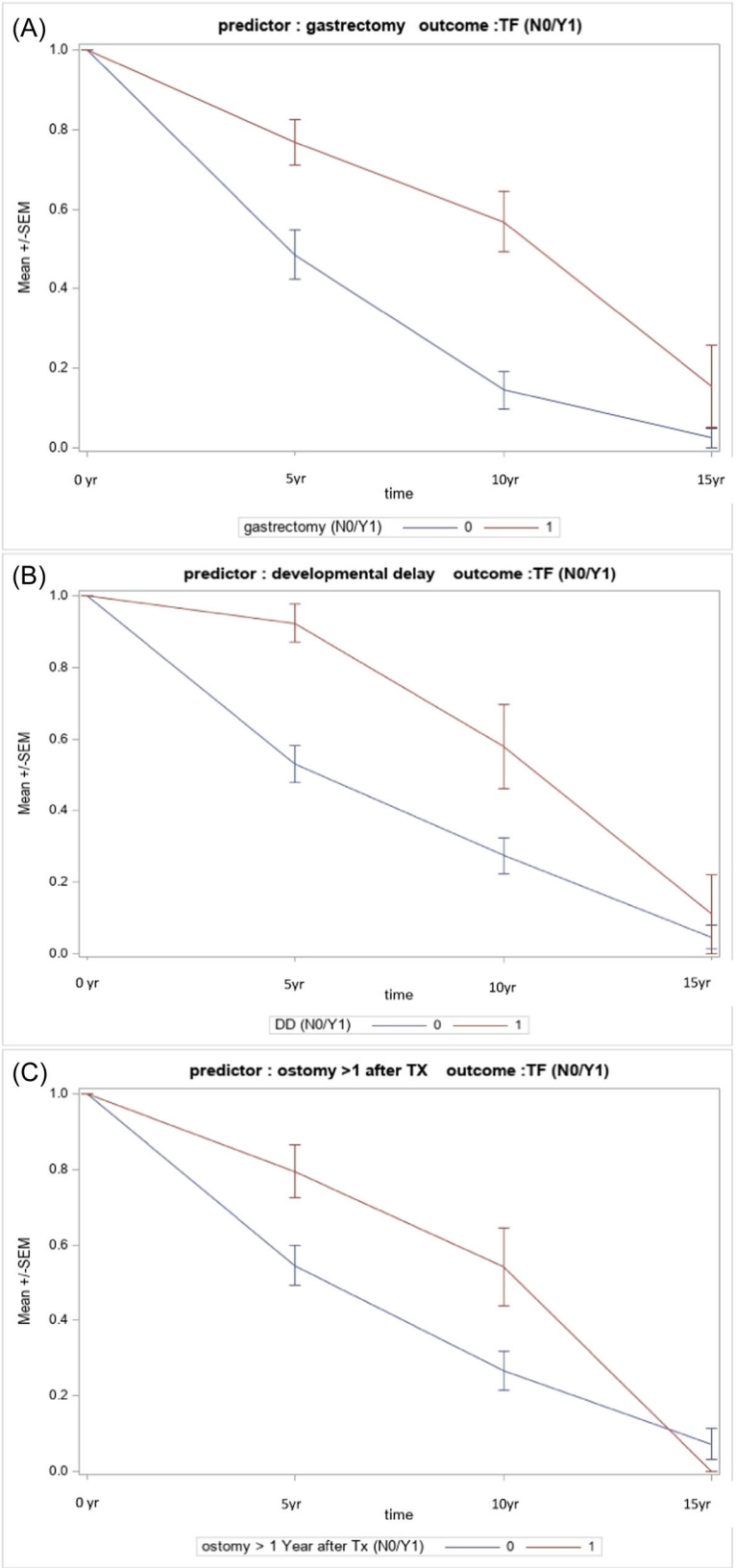


FIGURE 2 TF independence based on gastrectomy, ostomy, and developmental delay status. Time 0 is at the time of ITx; time 1 is at 5 years post-ITx; time 2 is at 10 years post-ITx; and time 3 is at 15 years post-ITx. (A) Percentage of patients staying on TF at 5, 10, and 15 years post-ITx with versus without partial gastrectomy. (B) Percentage of patients still on TF at 5, 10, and 15 years post-ITx with versus without persistent ostomy (>1 year post-ITx). (C) Percentage of patients staying on TF at 5, 10, and 15 years post-ITx with versus without developmental delay. ITx, intestinal transplant; TF, tube feed.

TABLE 2 Micronutrient deficiencies at 5-year intervals after ITx.

Micronutrient deficiency	At ITx *N* (%)	5 Years *N* (%)	10 Years *N* (%)	15 Years *N* (%)
Iron	27/48 (56.2)	33/68 (48.5)	21/54 (38.9)	6/22 (27.3)
Vitamin D	37/113 (32.7)	19/67 (28.4)	8/41 (19.5)	14/28 (50.0)
Zinc	19/118 (16.1)	14/52 (26.9)	9/32 (28.1)	5/18 (27.8)
Vitamin A	12/114 (11)	3/26 (12)	0/17 (0)	1/10 (10%)

Note: The table shows the number of patients with micronutrient deficiencies out of the total number of patients for whom micronutrient level data are available at the specific time interval. Cutoffs for iron, vitamin D, zinc, and vitamin A deficiency were <50 mcg/dL, <20 ng/mL, <60 mcg/dL, and <200 mcg/L, respectively.
Abbreviation: ITx, intestinal transplant.

ITx.[3,10] Interestingly, our study found that intestinal graft rejection did not significantly affect linear growth or BMI. Although prior studies investigated how patient and graft survival differed between ITx types, no study investigated growth outcomes based on the type of ITx.[4,5] Despite the higher risk of surgical complications and graft rejection with isolated ITx, our data showed better linear growth outcomes in isolated ITx.

In contrast to previous studies, we found no significant effect on the growth pattern of patients on a long-term steroid regimen.[11,12] A study on children with kidney transplants did see improved linear growth with steroid dosing every other day.[13]

Our long-term prednisolone dose ranges between 5 mg daily and 2.5 mg every other day. Prednisolone dose of <0.1 mg/kg/day was found to be a positive predictor for linear growth in one study.[10] Our result found no significant long-term changes in BMI or linear growth with a prednisolone dose of >0.2 or <0.2 mg/kg/day. There is no consensus on a specific steroid dose, that is, unlikely to impair growth.[14] Our decision to wean to a low dose of prednisolone was based on how far the patient was from their ITx and the number of documented rejection episodes.

The median duration to come off PN in our study was 34 days. This duration is similar to data from previous studies, which showed medians of 31 and 44 days.[10,15] Similar to the past literature, our study found that feeding intolerance in patients with complications post-ITx (such as intestinal graft rejection) contributed to delay in PN weaning.[15]

Few studies have looked at factors that affect TF weaning post-ITx. Past research has found that a long period of TF wean was attributed to oral aversion.[3] Full oral diet was achieved faster in patients with a positive pre-transplant oral intake experience.[16] High stoma output may also affect a patient's ability to reach full TF wean and delay the transition to an oral diet.[17] In addition to permanent ostomy, we investigated two additional factors that could affect TF wean: partial gastrectomy and developmental delay. Our data found that all these factors did delay TF wean. The gastrectomy effect might be due to smaller stomach size leading to feeding intolerance and early satiety. This should be investigated further to determine the need to avoid gastrectomy during ITx surgery. Regarding the developmental delay factor, oral aversion and challenging oral intake experience in these patients could explain slow TF weaning.

Several vitamin and micronutrient deficiencies were seen post-ITx. Previous studies showed that vitamin D deficiency is the most frequent deficiency compared to iron and zinc deficiencies. Since vitamin D is a fat-soluble vitamin, its deficit could be explained by the suboptimal intestinal graft fat absorption.[2,15] In our study, iron deficiency improved over time post-ITx. The initial median iron level before transplant was 37 mcg/dL which improved slowly over time to reach 67 mcg/dL at 15 years post-ITx. The zinc deficiency rate remained the same over the years post-ITx. A group at Cincinnati Children's found that iron and magnesium deficiencies were the most common after a full transition to enteral feeds.[18] Although a zinc deficiency is typically seen more in ileostomy patients, zinc deficiency was only found in 8% of ileostomy patients who survived at 10 years post-ITx.[19] A lack of patient compliance could be the cause of micronutrient deficiencies that were observed.

The major strengths of our study are its large sample size and the duration of our post-ITx follow-up. Additionally, our study is the first to investigate the effect of gastrectomy and developmental delay on TF wean. The primary weaknesses of our study are its retrospective nature and the data gaps that were created by interrupted clinic follow-ups. Also, some factors that may affect growth in these patients, such as small intestinal bacterial overgrowth and total body sodium, were not investigated in this study. Another important weakness is that the severity of developmental delay was not assessed. This makes it difficult to determine how the severity of developmental delay may impact the process of achieving full TF weaning post-ITx.

In conclusion, children generally have good long-term linear growth post-ITx. Partial gastrectomy, developmental delay, and persistent ileostomy can delay the achievement of full TF wean post-ITx. Further

research is needed to identify risk factors affecting nutrition in children post-ITx.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

How to cite this article: Miri A, Iverson AK, Law N, et al. Long-term growth and nutrition outcomes in children following intestinal transplantation. *J Pediatr Gastroenterol Nutr*. 2025;1-8. doi:10.1002/jpn3.12455