Fall 12-12-2017

Review of Nutrition Requirements and Growth after Pediatric Intestinal Transplantation

Anita Nucci

Kathleen Crim
Georgia State University

Barbara Hopkins
Georgia State University

REVIEW OF NUTRITION REQUIREMENTS AND GROWTH AFTER PEDIATRIC INTESTINAL TRANSPLANTATION

By

KATHLEEN CRIM

B.S. Georgia State University, 2010

A Master's Project Submitted to the Graduate Committee

In the Department of Nutrition at Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

MASTER OF SCIENCE

ATLANTA, GEORGIA

2017

Abstract

Intestinal failure is characterized by malnutrition, malabsorption, and growth retardation. The most common cause of intestinal failure is short bowel syndrome. If the remaining bowel is unable to adapt to allow weaning from parenteral nutrition and achievement of enteral autonomy, then intestinal transplantation should be considered. Energy and macro- and micronutrient intakes are closely monitored pre-transplant to optimize nutrition prior to surgery. Few studies have been conducted to examine the nutritional requirements and nutritional status post-transplant. Of the studies that have been done, results have been inconsistent. The purpose of this review is to summarize the current literature related to nutrition requirements and growth after pediatric intestinal transplant. Monitoring of vitamin and mineral status is also essential in ensuring proper growth and preventing deficiencies post-transplant. Five out of six studies showed a positive growth trend at the one-year mark post-transplant. One study showed that children with a weight and height z-score of less than -2.0 had a faster catch-up growth post-transplant. Other studies reported positive growth progression within the first two years after transplant. There is still a great deal of information unknown about nutrition and growth post-transplant. Further studies need to be conducted to determine if and how nutrition requirements change post-transplant.

Introduction

Intestinal failure is a condition characterized by malabsorption, malnutrition, and growth retardation.[1] Short bowel syndrome (SBS) is the most common cause of intestinal failure and may occur due to necrotizing enterocolitis or conditions such as small bowel atresia, midgut volvulus, or gastroschisis.[2] Although many children experience progressive adaptation of their remaining small bowel and achieve enteral autonomy, some children are unable to be weaned from parenteral nutrition (PN) support.[1] These children may benefit from other interventions such as intestinal transplantation.[2] Children with intestinal failure are carefully monitored pre-transplant to ensure that they are meeting their estimated nutrition requirements in preparation for transplant. However, many children with intestinal failure experience growth failure pre- and post-transplantation.[3] Growth failure is the inability to achieve a target height trajectory.[4] Although several studies have reported catch-up growth post-transplant, the data are inconsistent. The purpose of this review is to summarize the existing medical literature related to nutrition requirements and growth after intestinal transplantation in children.

Literature Review

Pediatric nutrition assessment

Anthropometric measures should be monitored closely in patients following intestinal transplant. Measurements include weight, length up to two years of age, height for children over the age of two years, weight-for-length or height, and occipital head circumference for children under two years of age. Measurements should be plotted using the World Health Organization (WHO) growth standards for children birth to two years of age and the Centers for Disease Control and Prevention (CDC) growth standards for children two years and older to determine growth percentile compared to the standard.[5] Z-scores are values used to express how far weight and length or height fall from the 50th percentile on reference growth charts for children. These scores should be calculated to provide a precise percentile and determine nutrition status. Z-scores are one of the parameters used to diagnose pediatric malnutrition. Pediatric malnutrition is defined as “an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes”.[6] Malnutrition is either illness related or non-illness related

and classified as acute or chronic. Illness related malnutrition refers to one disease or more that results directly in an imbalance of nutrients that can be caused by decreased intakes, altered utilization, nutrient losses, or hypermetabolism. Non-illness related pediatric malnutrition is related to environmental, socioeconomic and/or behavioral factors that are associated with decreased nutrient intakes or delivery. Acute malnutrition is defined as malnutrition that exists for less than three months while chronic malnutrition is a condition that lasted for three months or longer. A full assessment of anthropometrics and growth related to age and gender should be conducted. Z-scores are then used to diagnose the degree of malnutrition. Mid upper arm circumference can also be used to diagnose malnutrition. Mild malnutrition is a z-score of -1, moderate malnutrition is a z-score between -2 to -3 and severe malnutrition is a z-score greater than -3.[6] Data points are used as the primary indicators for malnutrition using z-scores. Malnutrition can be diagnosed using a single point data (Table 1) or two or more data points (Table 2).

Nutrition Focused Physical Exam (NFPE) is also used to assess possible nutrient deficiencies or toxicities.[8] The NFPE is particularly important when assessing children with intestinal failure and essential to completing a full and accurate nutrition assessment. Along with micronutrient deficiencies or toxicities, NFPE can confirm or identify muscle wasting, fat loss, and edema. The NFPE includes a full inspection from head to toe. Visual inspection is used to examine skin appearance, skin color and signs of edema. When examining skin in relation to deficiencies, it is important to look for pallor, dry/scaly skin, or dermatitis. Changes in skin may be signs of essential fatty acid deficiency (EFAD), zinc, niacin, riboflavin or tryptophan deficiency, respectively. Spoon shaped nails may indicate a deficiency of iron while lackluster nails or pale nail beds may indicate a protein, vitamin A, or vitamin C deficiency.[8] An enlarged thyroid could be related to an iodine deficiency. When examining the mouth, a sign of deficiency of riboflavin, niacin, or vitamin B6 could be dry, cracked lips, bleeding gums, or inflamed mucosa.

Nutrition requirements post-transplant

Multiple equations exist to determine energy requirements for children (Table 3). The Dietary Reference Intake (DRI) equation for age estimates energy requirements for children with normal growth, body composition, and activity when taking oral or enteral nutrition (EN).[9] The outcome of this equation

can be adjusted for catch-up growth or stress factors. The WHO and Schofield equations are based on resting energy expenditure (REE) that are then multiplied by a stress factor.[10,11] The Schofield equation can be used for healthy children and acutely ill children in the hospital. The stress factors take into account activity level and other factors that may alter energy expenditure. These factors include starvation, surgery, sepsis, closed head injury, trauma, growth failure, or burns.[11] Activity is categorized into paralyzed, confined to bed, or ambulatory. The Seashore equation calculates basal metabolic rate (BMR) with an activity and stress factor added.[12] This equation is used for hospitalized children in the intensive care unit between the ages of birth to 15 years of age. If available, indirect calorimetry can be used for critically ill children.

For children solely dependent on PN, daily calorie requirements are generally lower, on average 80% of nutrition needs. Energy requirements post-transplant will vary depending on the age and weight of the child, ventilation status, and nutrition status pre-transplant. Energy requirements can range from 70% to 120% of the DRI.[13] Protein requirements are based on the Recommended Dietary Allowance (RDA) and adjusted for growth, liver function, or kidney function. Protein requirements post-transplant are at least 1.5 times the RDA.[13] In addition, laboratory monitoring to assess micronutrient status should be conducted after transplant.[14] Children who were dependent upon PN prior to transplant and are subsequently weaned off of PN post-transplant should have baseline vitamin and mineral laboratory testing done after transplant with follow-up as indicated. Serum vitamin D levels should be monitored post-transplant to prevent the development of deficiency and if the patient exhibits signs of osteomalacia or muscle weakness. Laboratory tests for zinc, copper, selenium, folate, vitamin B12, and iron studies well as an essential fatty acid panel should be conducted regularly (Table 4).[15]

Modes of Nutrition Therapy Post-Transplant

Parenteral Nutrition should be initiated early postoperatively. The length of time a child remains on PN in the post-operative (post-op) state depends on the ability to tolerate EN. Rejection and sepsis are reasons for children to remain on PN longer before being able to have a trial of EN feeds. Once EN has started and is tolerated, the PN can be tapered, which should be in 2 to 4 hour increments to a cyclic regimen of 10 to 12 hours per day. Once a child is tolerating 50% of EN, PN can be weaned.

Enteral Nutrition should be started on post-op day three or four based on bowel function and the presence of ileostomy output.[1] Feedings are started at a small volume between 1 and 5 mL/hour and tolerance is monitored. Every center varies on how EN rates increase, which can range from two to five mL/hour or between two and five mL/day. High ostomy output could be a reason to stop feedings or keep them at a low rate. If the feeding rate is unable to be increased due to increased ostomy output, children may require additional intravenous fluids. When selecting a formula, the age of the donor should be considered. If the donor was an infant less than six months of age, then an infant formula should be used, which is generally a 20 calorie per ounce formula with hydrolyzed protein. If the donor was older than 6 months, a toddler or child formula c be used. This formula is generally 30 calories per ounce or one calorie per mL and peptide based with a low osmolality.

Oral intake can start as soon as seven days post-op if the child has shown tolerance to EN. Once oral feedings have started, EN should be changed to cyclic nocturnal feeds to promote daytime food and beverage intake. Some formulas are palatable and can be used as daily nutritional supplements. A clear liquid diet is started first to monitor tolerance, advancing as tolerated to a regular diet. However, concentrated sweets and high fat foods should be limited. Oral stimulation is important to maintain pre-transplant. If a child has an oral aversion, then a feeding assessment is indicated. Oral aversion can occur when EN is continued for fluid and nutrition.[5] When EN is infusing at a continuous rate, some children do not want to eat or have no desire to eat. Oral aversion can be prevented or improved with changing feeding regimens from continuous to cyclic at night while the child is sleeping, which encourages them to eat during the day. Transitioning to bolus feedings can also help to stimulate hunger for meals. Appetite stimulants are also used when oral aversion is seen and to increase the desire to eat.[15]

Growth after intestinal transplantation

Growth can be a major challenge following intestinal transplant due to factors such as episodes of rejection that require corticosteroid usage and infection that result in a reduction or discontinuation of enteral feedings or PN support.[1] Therefore, weight and height should be monitored closely. It is important to assess appropriate calorie and protein needs as the child grows. Food allergies are a common

occurrence in children after intestinal transplant.[1] Symptoms of a food allergy include increased stool output, abdominal distension or pain, abdominal cramping, weight loss, and malnutrition. The most common allergies reported are milk, egg, wheat, and peanut. Fat malabsorption has also been reported postoperatively.[1] Fat malabsorption can be due to poor intestinal adaptation; there have also been reports of fat malabsorption caused by lymphatic injury and dilated lymphatic vessels. Symptoms include increased stool output, oily stool, weight loss, or abdominal cramping. Growth velocity after transplant has been shown to vary by age. Catch-up growth occurs as a function of age at the time of transplant.[4] Children who are younger receiving transplants have shown a positive trend in linear growth if the majority of their calories are provided enterally or orally earlier post-transplant.[14] Quality of life is greatly affected by longitudinal growth. Children who are short will sometimes have difficulty with behavior and cognition post-transplant as well as have a higher rate of anxiety and attention seeking behavior compared to children of normal height at the same age.[4]

A summary of the published literature that relates to growth after pediatric intestinal transplantation is shown in Table 5. Sudan et al. (2000) examined 31 patients who were >1 year post intestinal transplant.[16] The researchers observed normal growth in 75% of the children, and 15% of these children achieved catch-up growth. Eleven percent of the children remained below the 10th percentile. Venick et al. (2006) examined growth measures in 19 children comprised of 8 girls and 11 boys who had received a small bowel transplant.[17] The researchers measured height and weight prior to transplant and at six month intervals up to 24 months post-transplant. The mean height and weight were found to increase steadily over the first-year post-transplant with catch-up growth leveling off in year two. Mean height at transplant compared to two years post-transplant was significantly higher ($p=0.04$) and weight was also significantly greater ($p=0.04$) when compared to weight at the time of transplant. Twelve of the subjects showed positive trends in z-scores for height and weight during the two years post-transplant. The researchers' concluded that growth improves within the first year of transplant and then levels off in the second year. Iyer et al. (2002) evaluated 46 children who had received an intestinal transplant, all of which showed no linear growth at the time of transplant but post-transplant maintained their growth velocity without evidence of catch-up growth.[18] The researchers also concluded that linear growth

retardation is seen two years after transplant. Children who receive a transplant prior to stunting occurring will have a higher growth velocity post-transplant.

Ueno et al. (2006) gathered anthropometric data on 23 patients who survived greater than six months post-transplant, dividing patients into two groups (weight and height z-scores less than -2.0 and greater than -2.0).[3] The researchers reported that patients with a z-score of less than -2.0 had a faster catch-up growth post-transplant. Nucci et al. (2002) examined growth in 24 pediatric patients post intestinal transplant and observed a positive trend in z-scores for weight and height for 39% and 22% of the patients, respectively.[14] Venick et al. (2011) observed an improvement in z-score for height 4 years post-transplant (n=19) with a mean of -3.1 at transplant improving to between -2 and -2.5 at four years post-transplant.[19] The patients that had positive growth were weaned off of PN quicker, required a lower steroid dose, and tolerated a peptide based formula rather than requiring an amino-acid base formula.

Growth has also been examined by the use of steroids post-transplant to determine whether or not the use of steroids affects growth long-term. Growth while on steroids has been shown to be below normal and then when steroids are stopped it tends to normalize.[2] Nucci et al. (2011) evaluated the use of steroid based immunosuppression versus steroid free immunosuppression and the effect on linear growth post-transplant.[20] The researchers observed a decrease in prevalence of growth failure in the steroid free group. They also saw a greater positive change in linear group in patients who received steroid therapy for less than 120 days within the first two years post-transplant. Nayyer et al. (2010) also evaluated the use of steroids and growth in 76 patients who received a small bowel transplant.[21] Thirty-four of their patients received tacrolimus and steroids while the other 42 patients received ATG induction, then tacrolimus and only received steroids for acute rejection. The researchers observed an improvement in height standard deviation amongst the group who was steroid free. These studies do show that remaining steroid free post-transplant or limiting the time on steroids will have a positive effect on growth.

Conclusion

Many children who undergo intestinal transplant are observed to have malnutrition that contributes to difficulty with catch-up growth post-transplant. Nutrition optimization prior to transplant and prevention of malnutrition post-transplant can have a positive effect on post-transplant outcomes. There

are a limited number of studies on nutrition requirements and growth after pediatric intestinal transplant. Patients who have positive linear growth pre-transplant have better growth outcomes post-transplant. It has also been observed that patients with a weight and height z-scores of less than -2 have better growth post-transplant. Patients who show poor growth pre-transplant have a harder time attaining linear growth post-transplant. For children who have an oral aversion, the goal is to wean PN post-transplant with transition to EN. The development of food allergies post-transplant has been reported; therefore, it is important to gradually introduce new foods by mouth one at time and watch for signs of any allergic reactions. Once a patient is fully weaned from PN and EN, close caloric monitoring should be done to make sure calorie and protein needs are met by oral intake. If weight loss, stunting, and abnormal laboratory values reflect that nutritional needs are not being met, oral supplementation should be started. Vitamin and mineral monitoring is essential for patients post-transplant especially when PN has been discontinued to prevent any deficiencies and to supplement if needed. Given the limited research on growth, further studies should be done to determine specific requirements post-transplant to see if nutrition requirements differ from pre-transplant requirements. Medication management should be investigated further to compare children on steroid treatment versus no steroid treatment and the effects on growth. Until further research can be done, nutrition optimization, maintaining linear growth, and adequate z-scores pre-transplant are essential to optimal growth post-transplant.

References

1. Nucci A, Strohm S, Katyal N, Lytle B. Organ Transplantation. In: Corkins M, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum.* Silver Spring, MD: A.S.P.E.N.; 2010:256-268.
2. Hansen K, Horslen S. Liver and intestinal transplantation in children. *Pediatr Child Health*. 2010; 20:13-19.
3. Ueno T, Kato T, Revas J, et al. Growth after intestinal transplant in children. *Transplant Proc*. 2006; 38:1702-1704.
4. LaRosa C, Baluarte J, Meyers K. Outcomes in pediatric solid-organ transplantation. *Pediatr Transplant*. 2011; 15:128-141.

5. Asfaw M, Mingle J, Hendricks J, Hendricks J, Pharis M, Nucci A. Nutrition management after pediatric solid organ transplantation. *Nutr Clin Pract*. 2014; 29:192-200.
6. Mehta N, Corkins M, Lyman B, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *J Parenter Enteral Nutr.* 2013; 37:460-481.
7. Beer S, Bunting K, Canada N, et al. *Texas Children's Hospital Pediatric Nutrition Reference Guide*. 11th ed. Houston, TX: Texas Children's Hospital Nutrition Committee; 2016.
8. Green Corkins K. Nutrition-focused physical examination in pediatric patients. *Nutr Clin Pract*. 2015; 30:203-209.
9. Food and Nutrition Board. Energy. In: Otten JJ, Pitzi Hellwig J, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006:625 – 651.
10. World Health Organization. Energy and protein requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Technical Report Series 724. World Health Organization, Geneva; 1985.
11. Schofield WN. Predicting basal metabolism rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39C:5-91
12. Seashore JH. Nutritional support of children in the intensive care unit. *Yale J Biol Med.* 1984; 57:111-134.
13. Phillips SK, McGhee B, Reyes J. *Pediatric Liver, Intestine, and Multivisceral Transplantation: A Manual of Management and Patient Care*. Hudson, OH: Lexi-Comp, Inc; 2003.
14. Nucci A, Barksdale E, Beserock N, et al. Long-term nutritional outcome after pediatric intestinal transplantation. *J Pediatr Surg*. 2002; 37:460-463.
15. UpToDate. Management of short bowel syndrome in children. https://www.uptodate.com/contents/management-of-short-bowel-syndrome-in-children?source=search_result&search=short%20bowel%20syndrome%20children&selectedTitle=2~150. Updated May 24, 2017. Accessed September 15, 2017.
16. Sudan D, Iverson A, Weseman R, et al. Assessment of function, growth and development, and long-term quality of life after small bowel transplantation. *Transplant Proc.* 2000:1211-2.

17. Venick R, Farmer D, Saikali D, et al. Nutritional outcomes following pediatric intestinal transplantation. *Transplant Proc*. 2006; 38:1718-1719.
18. Iyer K , Horslen S, Iverson A, et al. Nutritional outcome and growth of children after intestinal transplantation. *J Pediatr Surg*. 2002; 37:464-466.
19. Venick R, Wozniak L, Colangelo J, et al. Long-term nutrition and predictors of growth and weight gain following pediatric intestinal transplant. *Transplantation*. 2011; 92:1058-1062.
20. Nucci A, Strohm S, Squires H, Mazariegos G, Sun Q, Sindhi R. Growth pre- and post-implementation of a steroid-free induction protocol in a large pediatric intestinal transplant population. *J Pediatr Gastroenterol Nutr*. 2011; 52:601-606.
21. Nayyar N, Mazariegos G, Sarangarajan R. Pediatric small bowel transplantation. *Semin Pediatr Surg*. 2010; 19:68-77.

Table 1. Malnutrition Diagnosis Using Single Point Data[6]

Indicator	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight for height z-score	-1 to -1.9	-2 to -2.9	-3 or less
BMI for age z-score	-1 to -1.9	-2 to -2.9	-3 or less
Length/height for age z-score	No data	No data	-3 or less
Mid-upper arm circumference	-1 to -1.9	-2 to -2.9	-3 or less

BMI – body mass index

Table 2. Malnutrition Diagnosis Using Two or More Data Points[6]

Indicator	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight gain velocity	<75% of normal	<50% of normal	<25% of normal
Weight loss (2-20 y/o)	5% of usual body weight	7.5% of usual body weight	10% of usual body weight
Decline in weight for length/height z-score	Decline of 1 z-score	Decline of 2 z-score	Decline of 3 z-score
Inadequate nutrient intake	51% to 75% estimated energy needs	26% to 50% estimated energy needs	<25% estimated energy needs

Table 3. Pediatric Energy Requirements and Indications for Use

Source	Age	Guideline or Equation	Indication for Use	Stress Factors
Dietary Reference Intake[9] (kcals/kg/d)	2 – 3 m 4 – 6 m 7 – 12 m 13 – 35 m 3 y 4 – 5 y 6 – 7 y 8 y 9 – 11 y 12 – 13 y 14 – 16 y 17 – 18 y >18 y	102 82 80 82 Boys 85 Girls 82 Boys 70 Girls 65 Boys 64 Girls 61 Boys 59 Girls 59 Boys 49 Girls 42 Boys 44 Girls 40 Boys 39 Girls 33 Boys 37 Girls 31 Boys 36 Girls 34	Normal growth and body composition	None
World Health Organization[10]	0 - 3 y 3 – 10 y 10 – 18 y	Male: 60.7W - 54 Female: 61W - 51 Male: 22.7W + 495 Female: 22.5W + 499 Male: 17.5W + 651 Female: 12.2W + 746		Surgery: 1.2-1.5 Burn: 1.5-2.5 Infection: 1.2-1.6 Starvation: 0.7 Trauma: 1.1-1.8 Growth Failure: 1.5-2.0
Schofield[11]	0 – 3 y	Male: 0.17W + 15.17H - 617.6 Female: 16.25W + 10.232H - 413.5	Healthy children and/or acutely ill	Surgery: 1.2-1.5 Burn: 1.5-2.5 Infection: 1.2-1.6 Starvation: 0.7

	3 – 10 y 10 – 18 y	Male: 19.6W + 1.303H + 414.9 Female: 16.97W + 1.618H + 371.2 Male: 16.25W + 1.372H + 515.5 Female: 8.365W + 4.65H + 200.0	hospitalized children	Trauma: 1.1-1.8 Growth Failure: 1.5-2.0
Seashore[12]	≤15 y	[55-2 (Age)] W + 20%	Hospitalized children in the intensive care unit between the ages of birth to 15 years old.	

d - day; H - height in centimeters; kcals - kilocalories; kg - kilograms; m - months; W - weight in kilograms; y - years

Table 4. Laboratory Monitoring while Receiving Parenteral Nutrition and Enteral Nutrition[15]

Nutrient and Laboratory Test	Parenteral Nutrition (PN)	Enteral Nutrition
Serum Iron studies (iron, ferritin, total iron binding capacity, transferrin)	Every 1-3 months	Every 6-12 months
Serum Copper	1 month after PN initiation then every 6 months If level is low, repeat every 2-3 months until normal	After PN discontinuation then once a year
Serum Zinc	1 month after PN initiation then every 6 months If level is low, repeat every 2-3 months until normal	After PN discontinuation then yearly
Serum Selenium	1 month after PN initiation then every 6 months If level is low, repeat every 2-3 months until normal	After PN discontinuation then yearly
Serum 25-hydroxyvitamin Vitamin D	Yearly Every 3-6 months if deficient	After PN discontinuation then yearly Every 306 months if deficient
Serum Vitamin E (alpha-tocopherol)	Yearly Every 3-6 months if deficient	After PN discontinuation then yearly Every 306 months if deficient
Serum Vitamin A	Yearly Every 3-6 months if deficient	After PN discontinuation then yearly Every 306 months if deficient

Serum Vitamin B12 Methylmalonic Acid (MMA)	Yearly	After PN discontinuation, then every 6-12 months
Serum essential fatty acid panel (triene/tetraene ratio)	Every 3 to 6 months	If there are signs of deficiency
Serum Chromium	Annually	Not necessary
Serum Manganese	Annually	Not necessary

Table 5. Summary of Results for Publications related to Growth after Pediatric Intestinal Transplant

Author	Population	Follow-up Period	Results
Sudan et al. (2000)[16]	<16 years of age	>1 year graft survival time	Normal growth in 50% of patients
Venick et al. (2006)[17]	<18 years of age	Biannually for 2 years post-transplant	Mean z-scores for height and weight increased significantly at first year post-transplant
Iyer et al. (2002)[18]	0.4 to 16.6 years of age	6 months, 1 year and 2 years post-transplant	Pre-transplant growth velocity maintained
Ueno et al. (2006)[3]	0.5 to 6.9 years of age	6, 12, 24 and 36 months post-transplant	Z-scores less than -2 had faster growth catch-up post-transplant
Nucci et al. (2002)[14]	8.5 months to 17.4 years of age	Biannually for 2 years post-transplant	Positive trend in z-scores in 39% of patients for weight and 22% for height
Venick et al. (2001)[19]	<18 years of age	4 years post-transplant	Z-score for height improved from -3.1 to between -2 and -2.5