Abstract
Inflammatory bowel disease, especially Crohn’s disease, is linked to significant growth stunting, sarcopenia (loss of skeletal muscle mass), deterioration of bone architecture and reduction in bone mass. Exclusive enteral nutrition (EEN) has been shown to correct nutritional deficiencies, provide adequate calories for growth, and alleviate intestinal inflammation in Crohn’s disease with a favorable adverse effect profile. In this chapter, we report a summary of the effects of EEN on linear growth, skeletal health and lean body mass in children with Crohn’s disease.

Introduction
Children with inflammatory bowel disease (IBD), especially Crohn’s disease, are particularly vulnerable to disease and treatment factors that can affect physical development. Most children with IBD are diagnosed during puberty or right before puberty, which is usually a time of acceleration of physical growth. Normally during puberty children achieve peak height velocity and accumulate a significant amount of muscle mass and bone mass [1, 2]. During active growth, the length and shape of long bones are determined by the combined activity of cells in the growth plate, osteoclasts that expand the medullary cavity and osteoblasts that appose bone matrix in the periosteal surface, which is later mineralized. This process is called bone modeling [3]. In addition, the significant expan-
sion of skeletal muscle mass produces large mechanical forces that induce bone apposition during growth [4]. Endocrine pathways such as sex steroids and insulin-like growth factor 1 are also critically important in promoting linear growth and inducing gains in lean body mass and bone mass. Proper nutrition, absorption and nutrient utilization are required to fuel the large metabolic demands generated by physical growth and development during childhood.

IBD (especially Crohn’s disease) can affect these developmental processes due to disease factors such as inflammatory cells and cytokines, poor caloric intake and malabsorption, decreased physical activity, delayed puberty, end-organ resistance to anabolic growth factors and also medications to treat IBD (i.e. glucocorticoids) [5–10]. Therefore, significant reductions in linear growth and alterations in bone mass, bone architecture and body composition are frequently present in children with IBD, even at diagnosis [5, 7, 8, 11]. While conventional induction of remission with a glucocorticoid followed by maintenance mesalamine or an immunomodulator does not accelerate linear growth in children with Crohn’s disease [12], exclusive enteral nutrition (EEN) has shown promise in restoring normal pubertal development, linear growth and body composition [13, 14].

**Exclusive Enteral Nutrition, Growth and Skeletal Development**

EEN is an effective therapy to induce and maintain remission in Crohn’s disease [15, 16]. EEN consists of ingesting a commercially available formula exclusively for 6–8 weeks instead of food. Remission rates with EEN range from 50 to 85% in pediatric Crohn’s disease, depending on the study. Patients with small bowel involvement may derive more benefit from EEN than patients with primary colonic Crohn’s disease [17]. Typically, an immunomodulator is started shortly after commencing EEN with the goal of maintaining remission induced by EEN in patients with Crohn’s disease.

EEN can be administered continuously overnight or orally (intermittent boluses). Both dosing schemas are equally efficacious to induce remission in pediatric Crohn’s disease, although continuous administration of EEN results in better weight gain [18]. While elemental formulas were used initially to provide EEN, subsequent studies have shown that they do not offer any advantage over polymeric formulas in terms of their anti-inflammatory effect in Crohn’s disease, and polymeric formulas are cheaper and more palatable [13, 19]. Despite the better palatability of polymeric formulas, most children on EEN opt to administer the formula via nasogastric tube and in some cases a gastrostomy tube to bypass the need to ingest the formula for many weeks.
The many advantages for induction of remission in pediatric Crohn’s disease of EEN over glucocorticoids notwithstanding, the use of EEN is limited in the United States compared to Australia and Europe, where it is considered first-line therapy of pediatric Crohn’s disease. The monotony of EEN, the likely need for a feeding tube, and physician and patient attitudes are barriers to the more widespread use of EEN in the United States [20]. Alternate schemas of enteral nutrition (EN) that allow one small regular meal a day in addition to formula are being studied to improve acceptance of EN as a treatment modality for pediatric Crohn’s disease [21]. The adverse effects of EEN include nocturnal awakening to urinate, sensation of morning satiety, nausea, vomiting, diarrhea, and complications secondary to using feeding tubes.

The mechanisms by which EEN alleviates Crohn’s disease are not yet known, but probably involve a combination of factors, including nutritional rehabilitation, modification of the intestinal microbiome, with consequent provision of short-chain fatty acids, a preferred fuel of intestinal epithelial cells [22] and a decrease in the antigenic load delivered to the intestinal mucosa [13]. As a consequence, EEN reduces inflammation, heals the intestinal mucosa, improves nutrition, and allows glucocorticoid withdrawal [23].

EN, even when not exclusive, may have anti-inflammatory benefits to patients with Crohn’s disease. For example, logistic regression analysis in a cohort of 74 adults with Crohn’s disease in Japan who were on maintenance therapy with infliximab and supplemental nutrition revealed that concomitant use of EN ≥600 kcal/day was an independent factor associated with sustained response to infliximab [24]. In another retrospective cohort study in 102 adults with Crohn’s disease, using EN together with maintenance infliximab was associated with improved remission rates compared to infliximab alone [25]. While these findings need to be confirmed in prospective studies, they suggest that supplementation with EN may be an adjuvant to treatment with infliximab in patients with Crohn’s disease.

EEN has a number of beneficial effects on body composition. EEN is associated with significant weight gain [26] and in some studies it appeared to accelerate linear growth in children with Crohn’s disease [27], although not in others [26]. With respect to bone health, EEN for 8 weeks was linked to an increase in serum bone alkaline phosphatase, a biomarker of bone formation, and a decrease in serum collagen C-telopeptide, a marker of bone resorption in newly diagnosed children with Crohn’s disease, suggesting that EEN is anabolic to bone [28]. Whether this increase in bone anabolic activity translates into sustained gains in bone mass over time is less well established. EEN also results in significant short-term gains in lean body mass [29], which probably reflects, at least in part, muscle mass accrual [29]. This is important because sarcopenia as-
associated with pediatric Crohn’s disease reduces bone mass and alters bone architecture [30, 31]. It follows that correcting sarcopenia in Crohn’s disease by EEN may be anabolic to bone. In this regard, Werkstetter et al. [14] recently reported improvements in bone geometry and muscle mass in 10 children with newly diagnosed Crohn’s disease treated with EEN. In this study, they induced remission with EEN (8/10 patients achieved remission) and maintained patients on an immunomodulator. They used peripheral quantitative computed tomography of the forearm to measure bone mass, bone architecture and muscle mass. They observed improved trabecular bone density and increased cortical bone turnover at 12 weeks, with no further improvements. Interestingly, muscle mass also improved, but only in the first 12 weeks of the study [14]. Taken together, these data suggest that the benefits of EEN may not be sustained once EEN is stopped, making an argument to study intermittent administration of EEN (or supplemental EN) to improve body composition outcomes in Crohn’s disease.

**Conclusion**

EEN induces remission in children with Crohn’s disease and has many beneficial effects on body composition, at least while EEN is being delivered. Additional studies are required to improve acceptance of EEN in North America among patients with Crohn’s disease and their physicians, and to achieve sustained effects of EEN on growth and bone and muscle mass in children with Crohn’s disease.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the content of the chapter.

**References**