Animal Source Foods and Amino Acids Deficiency is Linked with Environmental Enteric Dysfunction and Stunting

Abstract

Addressing endemic stunting remains a primary UN development goal. One potential contributor to global linear growth failure is environmental enteric dysfunction (EDD). However, it has proven challenging to address with interventions focused on water, sanitation and hygiene. Initial theories of EED placed primacy on recurrent enteric exposures, however it appears that these exposures are inadequate to explain the phenotype and sequalae. Children in EED endemic regions are at high risk of having inadequate nutrition, and strong associations can be found between malnutrition and stunting. In this review, we summarize the clinical, translational, and mechanistic evidence linking intake of animal source foods as a source of protein and micronutrients and, in their absence, essential amino acid (EAA) deficiency with stunted growth and features of EED such as altered immune behavior. EAA deficiency has been linked to growth failure through several mechanistic pathways including intestinal inflammation, barrier disruption and chondral plate closure, and amino acid supplementation has shown clinical efficacy. By better understanding this linkage, we will be able to better study not only EED, but also pathways in which dietary sources mechanistically alter systemic signaling in metabolism and immune function.

Introduction

Malnutrition remains one of the biggest public health issues in the global south, with the 2022 UN assessment of progress towards Sustainable Development Goals (SDG) estimating 148 million children under 5 years of age to be stunted (1). Beyond decreased height attainment, malnutrition is associated with several detrimental sequelae including decreased response to oral vaccinations, impaired motor development, poor school performance and reduced intellectual achievement (2, 3). Several factors have an indirect influence on stunting, including poor socioeconomic conditions, lack of community waste disposal and maternal education (4, 5). Consequently, stunting is associated with a significant economic burden and reduction in economic productivity, whereby a stunted individual is estimated to earn an average of 22% less compared with their non-stunted counterpart and is estimated to account for 21% of all disability-adjusted life years in children (6, 7)

It is believed that a major contributing factor to global stunting is a condition known as Environmental Enteric Dysfunction (EED). EED is a common, subclinical condition of the gut which initially affects residents of low-income countries in their early years. EED was first described in the 1960's with intestinal tissue biopsies showing chronic intestinal infection and nutrient malabsorption in clinically health adults and children in South Asia (8, 9). Since then, it has been described in the literature by various terms, including sprue, tropical sprue and environmental enteropathy (10). Whilst EED is a subclinical condition, strong evidence suggests that it leads children to developing phenotypical manifestations of malnutrition, including stunting (11). Although the etiology of EED is complex, it has previously been associated with poor access to clean water and unsanitary living condition (12).

Substantial efforts to reduce the burden of childhood diarrheal disease including improved access to oral rehydration solutions, zinc supplementation and introduction of enteropathogenic vaccines were impressively effective in some ways, leading to reduction in diarrhea related childhood deaths (13). However, these public health efforts did not cause a significant improvement in linear growth. Several efforts were also made to improve living conditions through interventions focused on improving water, sanitation and hygiene (WASH). Most of these studies, however, did not show any impact on linear growth or improvement in inflammatory markers, raising concern that pathogen exposure itself may not be the sole driver of EED, as postulated in previous studies. (14-16). One possible etiology is the impact of the associated low-grade inflammatory state of EED, which can inhibit endochondral ossification, in turn preventing bone growth (17, 18). Another possible mechanism could be one of adaptive response, in which the intestinal epithelium responds to insult via remodeling into surface mucosal cells, resulting in poor absorptive capacity, or immunomodulatory and acid mediated effects driven by H. pylori (19, 20).

One emerging mechanistic contributor for the stunted growth observed with EED is deficiency in essential amino acids secondary to a limited diet, absent dietary diversity and animal source foods (21, 22). Lack of micro and macronutrients, including inadequate protein intake, have been shown to directly result in stunting, and studies have suggested additional protein and micronutrient supplementation to be highly beneficial (23). Mechanistic work has shown linkages by which essential amino acid deficiency, primarily found in animal source proteins, could modulate inflammatory and epithelial proliferative signals (24). In this review, we will summarize clinical evidence suggesting that essential amino acid deficiency is linked with EED and stunted growth, examine therapeutic approaches using amino acid or animal source food supplementation, and integrate advances in our understanding of the biology potentially underlying the linkage between essential amino acid deficiency and observed outcomes in stunting and EED.

Protein Intake and Stunting: Epidemiological and Clinical Evidence

In most EED predominant regions of the world such as sub-Saharan Africa and south-east Asia, data shows that complementary foods are often limited and sources of dietary protein poor (25). It is also well known that there is limited diversity in complementary foods in regions with substantial burden of stunting. A study of dietary patterns in children aged 6-23 months by Choudhury et al in 2019 conducted across 42 low- and middle-income countries showed that on average, only 2.81 out of 7 food groups were consumed in the 24 hours prior to the survey (26). Another study employed DHS data from 39 countries and found lower dietary diversity and low consumption of animal-source foods to be associated with higher risk of stunting, indicating that both protein (macronutrients) and key micronutrients (iron, zinc, vitamins) matter for linear growth(27). The 2017 Report for Nutritional Status of Urban Indian population reported only 55.5% caloric intake when compared to the RDA for children aged 1-3 years (28). Similar studies in other regions (the Indian subcontinent, Nepal, etc) have demonstrated equivalent challenges, with household food insecurity and poor dietary diversity shown to be associated either with stunting or an increased risk of stunting (29-32). These studies support the hypothesis that children in EED endemic regions are at high risk of having inadequate nutrition, including intake of animal source foods in their diet.

Dietary Patterns in Stunted Populations

Several studies have indicated strong associations between low protein intake and high rates of malnutrition and stunting (33, 34). Specifically, data has shown regions with a high reliance on plant-based diets such as South Asia and Sub-Saharan African to report higher rates of stunting as compared to regions with greater access and consumption of animal source foods (35, 36). A study conducted by Kaimila et al in 2019 in Malawian children aged 12-36 months and at risk of developing EED compared two groups, with the first consuming a higher quantity of animal source foods as opposed to plant source foods in comparison with the second group. This was reflected in a higher Protein Digestibility Corrected Amino Acid Score (PDCAAS), a measure of the consumed protein to meet the amino acid requirements of the body and resulted in a higher length-for age (LAZ) score and improved linear growth in the group consuming larger quantity of animal source foods (37). Fish was the primary source of animal source protein in this population, followed closely by chicken, beef and milk. Similarly, the Global Network for Women and Children's Health Research conducted a cross-sectional analysis of infants and children from 6-24 months of age in the Democratic Republic of Congo, Zambia and Pakistan. Apart from finding a remarkably high rate of stunting which varied between 40-60% between the study sites, they were able to show that meat consumption was associated with a lower likelihood of stunting with an odd's ratio of 0.64 and 95% confidence interval of 0.46 to 0.90 (38). This may explain why regions such as South America, where meat consumption is fairly high, have been observed to deal with less stunting than expected based on the quality of their water and sanitation, whereas regions such as South Asia with relatively strong infrastructure but high rates of vegetarianism also have higher rates of stunting. Several other studies from South Asia and Sub-Saharan African showed consumption of animal source diets to be associated with lower rates of stunting, whereas poor linear growth was strongly linked to cereal-dominated diets which lacked sufficient amino-acids, amongst other nutrients (38-42). Therefore, it may be time to rethink protein and return protein malnutrition back to the global health agenda using a balanced approach that includes all protective nutrients (43).

Mechanistic insights: How protein and amino acids influence growth

With a clear set of clinical data demonstrating that animal source food intake is, in some way, beneficial to linear growth in patients in EED endemic regions, the question is raised about how this caloric source is more linked to linear growth and height attainment than other sources.

Protein Structure: Essential Vs Non-Essential Amino Acids

The strong association of increased linear growth seen with animal source foods vs plant source may be explained by the structurally diverse make up of proteins with various amino acids that are not always interconvertible (44). Historically, it was believed that children in developing countries received an adequate amount of protein, however the variety and quantities of amino acids within those proteins was not always accounted for (45). This may be in part to protein quality, which refers to the availability of amino acids once food has been digested and absorbed. Even though plant-based diets are high in protein content, they provide low digestibility of protein as well as low amounts of other micronutrients (37). To ensure adequate growth and development, it is important the body obtains all required amino acids. Among the 20 amino acids, nine are termed essential (tryptophan, valine, leucine, isoleucine, lysine, methionine, phenylalanine, threonine and histidine) as they cannot be synthesized by the human body and need to be obtained through dietary sources (46). Animal source foods are usually the best source for obtaining essential amino acids (EAAs) (47). Therefore, even though certain plant-based diets may provide the minimum requirement of

protein, they may not provide an adequate amount of EAAs such as tryptophan, leucine and lysine which are obtained through consumption of animal source foods.

Protein and the Intestinal Epithelium

Tryptophan is an essential amino acid which must be derived through dietary sources and plays a critical role in promoting linear growth (48). Diets lacking in high quality proteins and amino acids, particularly tryptophan, may be associated with growth failure (49). Mechanistic work has previously linked tryptophan deficiency related pathways as a primary characteristic of the EED intestinal epithelium, with evidence now existing of tryptophan metabolism being disturbed in EED secondary to functional and structural barrier disruption and inflammation (50-52). Single cell work in Zambia by Kummerlowe et al in 2022 noted major evidence of this pathway by comparing small intestinal biopsies to a control group from South Africa and the United States; their results were significant for decreased epithelial cell proliferation and reduced goblet cell abundance in the EED subset; addition of tryptophan was able to induce their differentiation (19). Previously, their group has shown supplementation with amino acids (tryptophan, glutamine and leucine) to result in a reduction in both villous hypertrophy as well as reduced mucosal barrier leakage (53). Similar results were seen in the SEEM study from Pakistan which showed decreased tryptophan to be associated with stunting and amino acid supplementation to ameliorate villus blunting in adults with EED (54).

EED is known for its ability to alter immune responses, with some evidence suggesting suppression of oral vaccine efficacy in affected populations (55, 56). Recurrent infections in populations where EED is endemic may induce both local and systemic inflammation, leading to dysregulation of the mucosal immune system and impairments in amino acid absorption and overall nutrient utilization (57). This chronic, low-grade inflammatory state was evaluated by Kosek et al through measurement of the indoleamine- 2,3-dixoygenase 1(IDO1) activity, inferred from the Kynurenine-tryptophan ratio (KTR). One key pathway for tryptophan metabolism involves its conversation to Kynurenine by IDO1, diverting dietary tryptophan away from protein synthesis; consequently, low plasma tryptophan, elevated kynurenine and an increased KTR have been recognized as markers of many inflammatory activation (58). Their study, conducted over a six-month period in Peru and Tanzania, noted inverse associations between KTR and LAZ ratios in children at 3 months of age in Peru and at 7, 15 and 24 months of age in Tanzania. They further reported that children with higher plasma tryptophan levels (90^{th} percentile) exhibited greater gains in LAZ compared to those at the lower end of the distribution (10^{th} percentile) in both cohorts (51). These results open the gates for further exploration and support the hypothesis that increased IDO1 activity, denoted by decreased levels of plasma tryptophan, promotes microbial translocation and drives the mucosal and systemic inflammatory responses characteristic of EED.

Furthermore, animal work has also supported the necessity of dietary tryptophan, reporting strengthened intestinal epithelial tight junctions, improved mucosal barrier integrity and proliferation (59-61). Given bacterial translocation and systemic inflammation has been a postulated mechanism for development of EED, supplementation with tryptophan could potentially be one way to target the disease. A study by Fu et al in white geese showed supplementation of dietary tryptophan and its resultant metabolites, such as serotonin, was linked to enhanced feed intake and improved growth performance (62).

Effects on 5-HT and IGF-1 on growth

Most dietary tryptophan is used for the biosynthesis of tissue protein. About 1%, however, is utilized as a precursor for the biosynthesis of serotonin (5-hydroxytryptophan; 5-HT). 5-HT is a hormone and neurotransmitter that is primarily synthesized (95%) in the GI tract. In the gut, 90% of serotonin is synthesized in the enterochromaffin cells of the gut mucosa with the remainder being synthesized by the enteric nervous system (ENS). Serotonin synthesis is controlled largely by the action of its rate limiting enzyme, tryptophan hydroxylase (TPH), which converts tryptophan to 5-HT and of which two subtypes exist (63); TPH1 and TPH2 are located in the enterochromaffin cells and the enteric neurons, respectively. This is an important distinction because it has been shown that TPH1- vs TPH2-derived serotonin synthesis may have differential effects on gut function, including intestinal epithelial homeostasis (64, 65). An excess of gut serotonergic signaling, induced by administration of selective serotonin reuptake inhibitors, has been shown to increase gut mucosal growth and gut epithelial proliferation (66). Importantly, it has been shown that this serotonin-promoted growth is neuronally-mediated, by TPH2, suggesting that some of the effects of EED on the gut epithelium may be indirectly correlated with ENS dysfunction, although this connection has not yet been studied(67). By administration of parenteral as well as enteral selective serotonin reuptake inhibitors (SSRI), Cowles et al. were able to show an increase in villous height, crypt depth as well as enterocyte proliferation with a resultant increase in ileal surface area (68). These findings suggest that substrates that target serotonergic signaling may be potential therapeutic targets for optimizing intestinal mucosal growth and may thus be beneficial in treating EED. (69)

5-HT also plays a key role in the regulation of growth hormone as well as IGF-1, both of which are critical for linear growth and bone development. IGF-1 plays a crucial role in cellular proliferation and differentiation and acts through the IGF receptor to stimulate chondrocyte growth in the epiphyseal plates of bones (70). Low protein intake has been associated with reduced IGF-1 activity, whereas increased intake of animal source foods has been shown to increase levels of IGF-1 (71). It has been suggested that the relatively high proportion of EAAs present in animal source foods is the driving force behind increased levels of IGF-1 in individuals who consume these diets, which in turn contributes to improving height velocity and overall growth trajectories in children (72, 73). These downstream effects of tryptophan by way of its metabolite, 5-HT further support the hypothesis that tryptophan and, in effect, its major reservoir in the form of animal source foods, are essential in regulating intestinal function, which in turn are responsible for preventing growth failure associated with EED.

Therapeutic Approaches: Protein and Amino Acid Supplementation

Impact of Supplementation with Animal Source Foods:

One way to approach assessing the relevancy of complete protein intake on growth is to explore the impact of protein supplementation through animal source foods, an excellent source of proteins amongst other nutrients, on growth in stunting/EED impacted regions. The BEED study from Bangladesh was a community-based intervention study with a historical comparison group established as part of the Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort. Children between the age of 12-18 months who were either stunted or at risk of being stunted were provided with directly observed animal source foods in the form of eggs and milk for 90 days which resulted in improvement in LAZ scores compared with children from the MAL-ED cohort (23). The Lulun project from Ecuador encompassed a randomized control trial (RTC) in which infants who were supplemented with 1 egg/day for 6 months had an increase LAZ score compared with controls, with models predicting an almost 50% reduction in stunting (74). Complete protein (such as animal) is

therefore considered an important part of complementary feeding for infants and children. Animal source foods such as chicken eggs and milk are excellent sources of protein, along with other micronutrients, and the increases in linear growth provides us with substantial evidence to further explore the protein hypothesis.

It is interesting to note that many dietary diversification programs which successfully reduced the prevalence of stunting in LMICs incorporated tryptophan-rich foods such as egg and dairy as part of their intervention (75, 76). A study in Ethiopian children aged 6-35 months looking at the association of tryptophan and lysine intake with linear growth found that although there was no difference in total protein intake between stunted and non-stunted children of their study population, however, intake of tryptophan in stunted children was relatively lower when compared to the tryptophan intake of non-stunted children (77). These findings highlight the importance of animal source foods, the largest reservoir of EAAs such as tryptophan, in promoting linear growth and preventing development of EED.

Perhaps unsurprisingly in the context of the above information, efforts to introduce animal husbandry in African countries such as Kenya have resulted in improved nutritional status with reduced stunting (78). Animal husbandry represents an easy and potentially self-sustaining intervention to drive up protein availability, in particular that of eggs (79). Eggs provide many high-quality macro and micro-nutrients, including many amino acids such as tryptophan. Another study in Ethiopia utilized a chicken-gifting techniques for children 6-18 months of age, where community and religious leaders declared children as the owners of the chicken. Results were significant for an increased consumption of eggs by children which was associated with higher LAZ scores as compared to the control group at the end of the 6-month trial period (76). Backyard poultry can therefore serve as an easy and inexpensive method for increasing intake of animal source foods which in effect results in an improvement in linear growth and reduced rates of stunting in vulnerable populations and rural settings. Perhaps it is important to note that animal husbandry practices present with health risks through exposure to fecal pathogens and direct ingestion of soil which may contribute to EED, but studies have shown mixed results due to general poor hygiene, handwashing practices and disposal of children's feces (80).Nevertheless, the efficacy of these interventions, on their own, even in the absence of overall calorie insufficiency, additionally suggests the role of a complete protein diet in facilitating linear growth, and the contribution of deficiency to EED and the stunting phenotype.

Impact of Maternal Protein Intake:

Infant nutritional status does not start with their own oral intake. Maternal status impacts infants prenatally as well as impacts the composition of human breast milk (81). The quality of maternal diet throughout the pregnancy period is reflective of fetal growth and development as well as birth weight of the newborn infant. Several studies looking at the association of maternal protein intake and birth weight of the offspring found that women who consumed a higher quantity of animal protein during their pregnancy delivered children with a higher birth weight with a lower risk of fetal growth restriction (82, 83). The Predict study from The Netherlands looked at the effects of periconceptional maternal animal and plant source foods on prenatal growth and birthweight by measuring crown-lump length, embryonic volumes and birth weights. They found animal source protein to be associated with better embryonic growth and higher birth weights, whereas no associations were present between plant source foods and embryonic growth/birth weight (84). A meta-analysis by Imdad and Bhutta looking at the impact of balanced protein energy supplementation in pregnancy in 11 RCTs showed a significant reduction in the risk of giving birth to

infants who are small for gestational age (RR + 0.69, 95% confidence internal 0.56 to 0.85). The balanced protein supplemented group also gained more weight compared to control (mean difference 59.89 g 95% CI 33.09-86.68) (85).

Oral Amino Acid Supplementation

Perhaps the most novel intervention for EED, after identifying the role of specific amino acids in intestinal mucosal proliferation and growth, would be direct supplementation with an amino acid formulation. Very recently published literature by Alam et al is the first of its kind, where a randomized control trial was conducted to test the effects of supplementation with VS001, marketed under the trade name of Enterade (86). VS001 contains a formulation of five amino acids (valine, aspartic acid, serine, threonine, and tyrosine) (87). Previous work in murine models has suggested VS001 to decrease intestinal permeability and bacterial translocation while increasing epithelial proliferation(88). Supplementation was provided in the form of a 250 ml daily beverage to Bangladeshi children aged 1-2 years with LAZ scores between -1 and -2 and effects on markers of EED (lactulose-mannitol ratio) were observed. Although there was no statistically significant difference in LM ratios between active and control arms, positive trends were observed when it came to intestinal permeability, and the supplements were well tolerated by the study participants. The study did not, however, report the impact of EAA supplementation on growth, which remains an excellent question that has yet to be explored.

Future Directions

Whilst some progress has been made in understanding the relationship between essential amino acid deficiency, intake of animal source foods, linear growth and EED, several key gaps in our understanding remain. There is an unmet need to generate further evidence through well-designed, randomized and controlled EAA or tryptophan supplementation trials. Future research should also focus on the precise mechanism through which essential amino acids, particularly tryptophan, influence intestinal barrier integrity. Additionally, studies utilizing multi-omics approaches such as transcriptomics and metabolomics could provide deeper insights into the metabolic disruptions associated with EED and how provision of adequate nutrition may restore gut homeostasis.

Conclusion

Addressing stunting and EED in LMICs requires a multifaceted approach that includes not only improved sanitation but more importantly access to high-quality protein sources, particularly animal source foods which are rich in EAAs. This hypothesis is supported not only by observational data but also interventional as well as mechanistic studies. Further interventions should focus on dietary diversification with a focus on provision of animal source foods to vulnerable populations in LMICs which lack access to fortified foods. Supplementation with essential amino acids, especially tryptophan, may play a crucial role in mitigating growth faltering in children living in these regions.

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