Improving linear growth without excess body fat gain in women and children

Ricardo Uauy

Stunting is the most common form of undernutrition, affecting infants before and early after birth. Across the world, 171 million children under 5 years of age are stunted. The rates of stunting have been steadily decreasing in Asia and Latin America since 1990, while they have remained stagnant in Africa. In fact, the absolute number of stunted children has increased in Africa since 1990, from 45 to 60 million. Stunting is linked to maternal size, nutrition during pregnancy, and fetal growth. Interventions on stunting need to begin with nutrition of adolescent girls. Length that is lost early on is rarely recovered later. Stunted children also have lower lean body mass (lower resting metabolic rate per kilogram of body weight) than their nonstunted counterparts and are more prone to developing abdominal obesity and diabetes when consuming energy in excess of their needs.

In a study of children 0 to 60 months of age from 54 countries, Victora et al. found that stunting was the most severely impacted during early childhood, with a mean height-for-age z-score (HAZ) of around –1.75 after 2 years (**fig. 1**) [1]. Mean weight-for-age z-score (WAZ) hovered around –1, while weight-for-height z-score (WHZ) was around zero, indicating children who are stunted but not too thin. This pattern of first loss of WHZ, then HAZ, follows a model of malabsorption. But after 2 years, WHZ recovers and remains around normal, showing that this is not the classic model of acute malnutrition with food deficiency. The loss of HAZ before 6 months indicates a need to be mindful of the timing of interventions. To achieve best recovery, we need to intervene before 6 months of age; irreversible damage may already be done after that time.

Several studies have shown improved growth with milk supplementation. In the 1930s, the Boyd Orr study in the United Kingdom, feeding trials of surplus milk to schoolchildren, showed a significant increase in height and improvement in "general appearance." In India, Aykroyd and Krishnan [2] found that schoolchildren supplemented with skim milk grew faster in height. Malcolm [3] and Lampl et al. [4] showed that a skim milk supplement increased the height of stunted, low-protein-fed children in New Guinea. In the United States, Fomon et al. [5] found that infants fed skim milk (low energy, high protein) showed the same length growth but less weight gain than those fed the high-energy formula. In Bangladesh, Kabir et al. [6] found that animal-source protein at 15% energy increased insulin-like growth factor 1 (IGF-1) and linear growth more than did animal-source protein at 7.5% protein in children recovering from shigellosis. However, excess height or growth velocity may be deleterious in some instances. Data show that although leg length is associated with decreased coronary heart disease risk in men and women, overall height is associated with cancer in adult men [7].

Early nutrition affects expression of genetic growth potential; this can have short-term and long-term effects on growth, development, metabolic programming, and disease risk. Research on long-term effects of early nutrition needs to be prioritized. Any essential nutrient can condition abnormal embryonic and organ growth and development (e.g., folate, iodine, vitamins A and E, iron, zinc, essential fatty acids, protein:energy ratio). The timing of the nutrient deficit or excess is crucial and can affect cell replication, migration, apoptosis, and maturation, increasing the risk of abnormal embryonic and organ growth and development. Genetic polymorphisms affecting nutrient metabolism transport or tissue levels can modulate effects. Nutrients and toxicants (retinoic acid, lead, zinc, folate) interact in defining normal or abnormal growth.

Growth occurs in two different ways: via hyperplasia (brain, bones, length) or hypertrophy (adipose tissue, weight). Hyperplasia is dependent on hormones

Please address all inquiries to the author at: London School of Hygiene and Tropical Medicine, London, UK and the Institute of Nutrition (INTA), University of Chile, Santiago, El Líbano 5524 Macul, Santiago de Chile; email: ricardo.uauy@lshtm.ac.uk.

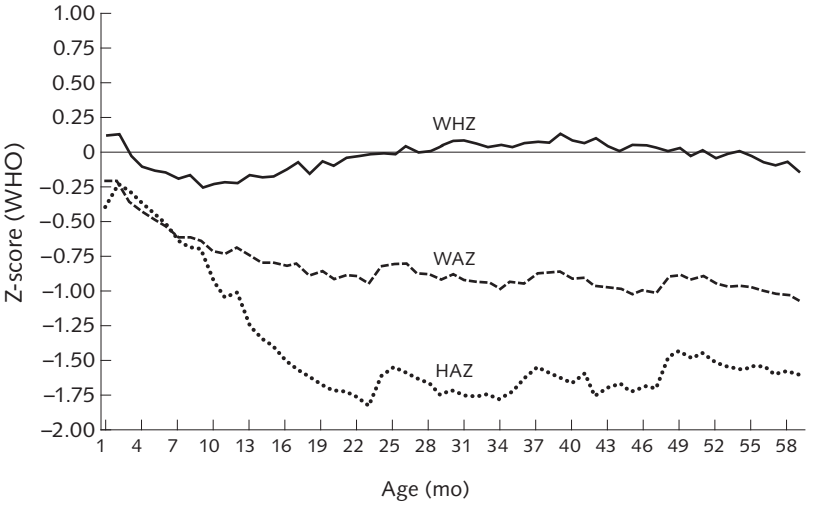

FIG. 1. Mean z-scores for weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ), based on World Health Organization (WHO) standards, for children 0 to 60 months of age from 54 countries [1]

such as insulin, IGF-1, BP3, cortisol, leptin, growth hormone, and T3/T4 and requires essential nutrients such as amino acids, iodine, iron, copper, zinc, sodium, potassium, phosphorus, adequate energy, and essential fatty acids. Thus, effects on linear growth will occur in tandem with cognitive effects, although cognitive effects may be more reversible than stunting. If this phase is affected by nutritional deficiencies, growth will be stunted, specifically linear growth, which depends on long bone epiphyseal plates. It would be useful to have a marker of this type of linear growth to enable early intervention before irreversible stunting occurs. Nutrition can condition linear growth through several mechanisms: gene expression (transcription factors, single or multiple genes); hormone receptors, binding proteins, and signal transduction; and cell growth and turnover during critical periods. In addition, infection can affect linear growth through inhibition of chondrogenesis, while increases in cortisol, interleukin 1 (IL-1), tumor necrosis factor (TNF), and interleukin 6 (IL-6) amplify bone breakdown. We need to review the science around linear growth mechanisms to design better studies.

In a meta-analysis of the effect of protein intake on length gain in low-birthweight infants, small but measurable effects of higher protein intake on improved linear growth were found [8]. In very-low-birthweight babies, energy and the protein:energy ratio interact synergistically to increase IGF-1 at high levels of both [9]. The effect of protein on IGF-1 could be used as a marker of linear growth. The focus needs to be on hyperplastic growth, not just whole-body protein.

Cortisol is among the hormones that will increase bone destruction, whether via drugs (exogenous) or stress (endogenous). Infants who received dexamethasone early on showed differences in linear growth and neurodevelopment later on in life [10]. In wartime, growth retardation is seen in children, which is associated with increased cortisol levels. Stress- or infection-induced cortisol increases may thus have similar effects in infants in developing countries and be an additional factor in the etiology of stunting. It will be prudent to include infection and stress variables in all growth studies.

A study of 8-month-old infants with chronic renal insufficiency randomly assigned to receive either low-protein (5.6% protein:energy ratio) or control protein (10.4%) formula found that at 18 months, infants who had received the low-protein formula had a decreased mean HAZ, while the control group remained unchanged [11]. Infants who received the higher-protein formula had a significantly higher mean WHZ at 2 years than infants who received the low-protein formula and breastfed infants, but there was no significant difference between the groups in mean HAZ or WAZ at 2 years [12].

There are potential adverse effects of using high-protein diets to treat malnutrition. During recovery from protein–energy malnutrition, children in one study gained WHZ but not HAZ (**fig. 2**) [13]. A comparison of slave children in the United States in 1810 versus Guatemalan children in 1990 showed that while they had similar HAZ scores up to age 6, slave children began gaining height and were almost normal by 24 years, while Guatemalan children never improved HAZ after age 4 [15].

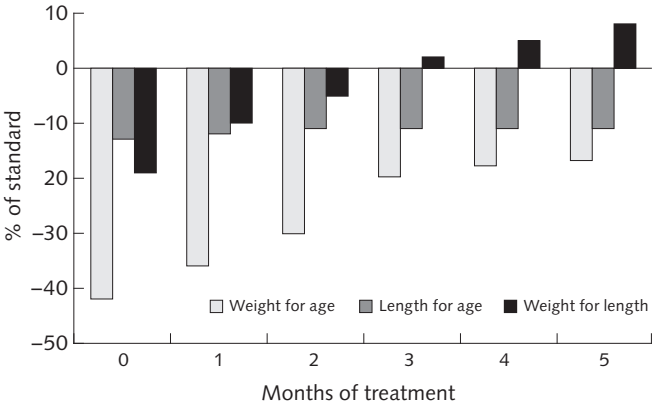

FIG. 2. Anthropometric measurements during recovery from protein–energy malnutrition. Source: Uauy and Alvear [14]

Type II nutrients that mostly likely have an influence on growth include nitrogen and essential amino acids, potassium, sodium, magnesium, zinc, phosphorus, and water. There is good experimental evidence in animals for effects of protein and zinc, but indirect data for effects of protein in humans and good meta-analysis data in humans for zinc (with a weak effect). There is also good experimental and epidemiological evidence for growth restriction mediated by proinflammatory cytokines and cortisol, but more research needs to be performed on the effects of infection and stress on growth.

The Growth and Obesity Cohort Study (GOCS) is a study of a concurrent cohort of mothers and children in Chile to track children from birth and assess the risk of obesity. By 6 months of age, researchers could track who would be overweight by the age of 7 years. For children 24 months of age, they could predict obesity at age 7 years. All infants, regardless of whether they ended up normal or obese, had a drop in HAZ between birth and 2 months. After 2 months, however, children who would end up obese or overweight grew faster in HAZ and WHZ. One theory is that infants could become adapted to hyperinsulinemia in obese mothers, which is then removed at birth, causing the fall in HAZ. The timing of the infants' adiposity rebound was also associated with the risk of obesity, with a younger age of adiposity rebound associated with a higher risk of obesity at age 7 (**fig. 3**). The bone age in those children who were overweight or obese at 7 years of age was found to be greater than that in children of normal weight. The gain in body mass index (BMI) after 6 months was associated with increases in adiposity but not height at 5 years, which is explained largely by advanced maturation [16].

The prenatal environment can affect the growth of the infant. Prepregnancy BMI will affect maternal glucose insulin, in turn affecting placental fetal blood flow, which can lead to fetal growth restriction or fetal macrosomia, both of which can lead to risk of obesity later in life. Chronic stress affected protein metabolism in poor Indian women in slum areas of Bangalore. In women who have low-birthweight children because of stress, we would have seen a change in net protein oxidation and metabolism.

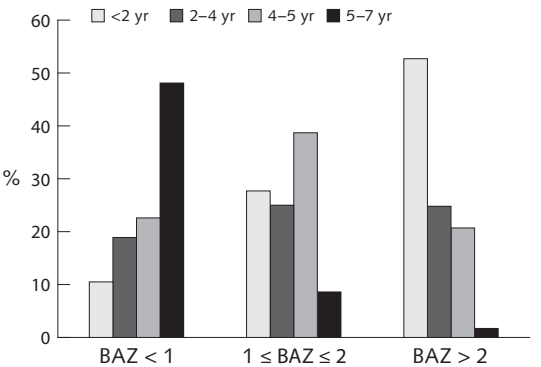

FIG. 3. Timing of adiposity rebound and body mass index (BMI)-for-age z-score (BAZ) in Chilean children

Conclusions

We need to investigate the long-term effects of stunting, and we need to prioritize research on the biological mechanisms of growth, including identifying potential biomarkers. There is a need to explore the effects of stress and cortisol on growth in various populations, including infants and pregnant women. In addition, we need further research on how to improve linear growth along with weight gain in malnutrition interventions, and we need to be mindful of unintended consequences of accelerated weight gain during such interventions.

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