



Malnutrition as the cause of growth retardation among children in developed countries

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Abstract

Introduction and Objective. According to the World Health Organization (WHO), malnutrition is a term that covers three broad groups of conditions: undernutrition, micronutrient-related malnutrition, and overweight with obesity, and diet-related non-communicable diseases. Undernutrition is the leading cause of growth failure worldwide, mainly in third-world countries where stunting is a significant public health problem arising from food poverty. In developed countries, malnutrition resulting in growth failure might often be misdiagnosed in paediatric practice. The aim of this study was to review the current state of knowledge regarding nutritional causes of growth retardation among children in developed countries.

Materials and method. The review was based on data obtained from articles published in the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>) between 2004–2021. The expert reports of the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF), were also included.

Brief description of the state of knowledge. Nutritional growth retardation (NGR) is challenging to diagnose, as it may result from mild food restrictions without apparent abnormalities in biochemical parameters of nutritional status. Reduced insulin-like growth factor type 1 (IGF-1) may suggest NGR, but it also occurs in endocrine disorders such as growth hormone deficiency.

Conclusion. NGR is a phenomenon that can occur in underweight children and those with normal or excessive body weight. As no effective diagnostic biochemical test is available, it seems that paediatric patients with growth failure should undergo dietary analysis preceding further advanced endocrine and biochemical diagnostic procedures.

Key words

short stature, nutrition, nutritional growth retardation, children

INTRODUCTION

According to the World Health Organization (WHO), ‘malnutrition refers to deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired nutrient utilization.’ There are three main forms of malnutrition: undernutrition (including wasting, stunting, underweight), inadequate vitamin or mineral supply, as well as overweight, obesity, together with diet-related non-communicable diseases [1].

Undernutrition can result from insufficient food intake, poor absorption, or excessive loss of nutrients [2]. It is the leading cause of stunting worldwide and a significant health public concern in developing countries, with its highest prevalence in southern Asia and middle and eastern Africa [3, 4]. Childhood growth failure caused by nutritional deficiencies is associated with increased risk of infections [5], reduction of neuro-developmental and cognitive functions, loss of growth potential [3], development of chronic diseases in adulthood, and even death [6, 7].

However, growth failure resulting from poor nutrition also occurs in developed countries. Inadequate caloric intake is thought to be the main cause of failure to thrive (FTT), a

phenomenon that manifests in both decreased weight gain and abnormal growth pattern. According to the American Academy of Family Physicians, in 2016, FTT affected up to 10% of children in primary care and approximately 5% of children hospitalized in the United States [8].

OBJECTIVE

The aim of this study was to review the current state of knowledge regarding nutritional causes of growth retardation among children in developed countries.

MATERIALS AND METHOD

The review was based on data obtained from scientific articles published in the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>) between 2004–2021, found with the use of the following keywords: malnutrition, undernutrition, growth, stunting, short stature, IGF-1, growth hormone. The expert reports of the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) were also taken into consideration. Only studies referring to the above-investigated issues were included.

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STATE OF KNOWLEDGE

Undernutrition and growth in children. The linear growth of a child is regulated mainly by growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) acting within the GH/IGF-1 axis [9, 10]. The growth process is complex and requires the proper cooperation of multiple exogenous and endogenous factors, and various disturbances may lead to growth retardation and result in short stature.

Short stature is defined as height below -2.0 SDS for a given age, gender, and population. The European Society for Paediatric Endocrinology (ESPE) has distinguished three main groups of causes for short stature: primary growth failure, secondary growth failure and idiopathic short stature [11]. It is the secondary growth failure, which includes insufficient nutrient intake, defined in Table 1 as 'malnutrition'.

It has been demonstrated that undernutrition is associated with decreased IGF-1 values and peripheral GH resistance. During food restrictions, there is also resistance of epiphyseal growth plate to GH and IGF-1 at the receptor level. These observations are consistent with the results of clinical observations which suggest that well-nourished children respond better to growth hormone treatment than malnourished patients, and improvement of eating habits is essential to achieve desired therapeutic effects [10, 12]. Growth hormone resistance, which accompanies undernutrition, is assumed to be an adaptive mechanism. The decrease in IGF-1 levels may attribute to saving energy during periods of food deprivation, while elevated GH levels, observed among some undernourished patients, probably support the maintenance of normoglycaemia [13].

The concept of failure to thrive (FTT) refers to children with very low weight for age, or weight for height, and inappropriate growth patterns, caused primarily by nutritional deficiency. This may result from insufficient food intake, impaired absorption of nutrients in the gastrointestinal tract and/or their excessive loss [8].

Insufficient food intake in children and psychosocial issues. Psychosocial and family conditions are the most prevalent causes of low food intake among children in developed countries, including family dysfunction, food insecurity, avoidant/restrictive food intake disorder, and incorrectly balanced elimination diets [14]. Family dysfunction might be associated with several aspects, from those seemingly

meaningless, such as parental work overwhelm, stress, marital strife, through psychiatric disorders (e.g., depression, psychosis) to alcohol addiction. These factors may contribute to child neglect or abuse. Food insecurity is defined as an inability to afford a sufficient amount of nutritious food due to poverty, but also as a lack of healthy eating patterns manifesting in overconsumption of highly processed food [8, 14].

Avoidant/restrictive food intake disorder (ARFID) has been included in the fifth edition of DSM (Diagnostic and Statistical Manual of Mental Disorders) and is defined as persistent failure to meet appropriate nutritional and (or) energy needs associated with: significant nutritional deficiency, dependence on enteral feeding or oral nutritional supplements and psychosocial impairment. Here, insufficient food intake may result from lack of interest in eating, traumatic experiences (vomiting, choking), low appetite, as well as selective appetite, which means that children reject certain foods due to their sensory properties, such as texture, taste or shape [15]. This form of ARFID may lead to specific nutritional deficiencies, depending on the type of food excluded, for instance, children whose diet is rich in added sugars but poor in vegetables and protein are more likely to develop vitamin K and B12 deficiencies [14]. Selective eaters are also at higher risk of heavy metals accumulation, e.g., mercury poisoning due to overconsumption of tuna [15].

Incorrectly balanced elimination diets may also cause undernutrition and growth failure. Among them, the most commonly used are dairy-free and gluten-free.

A longitudinal cohort study of 111 children with cow's milk allergy (CMA), who attended regular clinic visits between the ages 2–4, 5–8, and 9–12 years, indicates that CMA is associated with lower weight and height that persisted after the early childhood years [16]. On the other hand, a cross-sectional study of 5,034 healthy Canadian children aged 24–72 months has demonstrated that consumption of noncow milk beverages was associated with lower childhood height [17]. Cow's milk is a significant source of carbohydrates, proteins, lipids, vitamins (thiamin, niacin, riboflavin, folic acid), and calcium. The exclusion of cow's milk products might lead to growth impairment due to nutritional deficiencies. Thus, there is a need to provide appropriate, wholesome alternatives for cow's milk products among children with CMA.

A gluten-free diet (GFD) is currently the only effective treatment for coeliac disease (CD). The untreated CD might contribute to malabsorption in children, resulting in undernutrition and growth failure. Both energy-protein deficiency and the presence of proinflammatory cytokines in active CD might explain the decrease in the synthesis and activity of IGF-1. Therefore, it has been suggested that the evaluation of IGF-1 concentration should become an additional biochemical marker for monitoring coeliac disease activity [9]. However, a gluten-free diet may be low in B vitamins, iron, zinc, calcium, magnesium and dietary fibre, but rich in added sugars, salt, and saturated fatty acids [18]. Therefore, following a gluten-free diet without medical advice and nutritional counseling is not recommended.

Anorexia nervosa. The negative impact of food deprivation on growth is clearly observed in anorexia nervosa (AN), characterized by significant weight loss, growth, and

Table 1. Classification of short stature causes based on the International Classification of Paediatric Endocrine Diagnoses (ICPED) [11].

The main classification	The subclassification
Primary growth failure	Clinically defined syndromes
	Small for gestational age with failure of catch-up growth Skeletal dysplasias
Secondary growth failure	Insufficient nutrient intake (malnutrition)
	Disorders in organ systems other than skeletal
	Growth hormone deficiency
	Other disorders of the growth hormone-IGF axis
	Other endocrine disorders associated with short stature
Idiopathic short stature	Metabolic disorders
	Psychosocial disorders
	Iatrogenic causes of short stature
Idiopathic short stature	Familial idiopathic short stature
	Non-familial idiopathic short stature

puberty retardation [19]. Even supra-physiologic doses of GH cannot overcome the insensitivity to GH in AN. Clinical observations of patients with AN prove that nutritional therapy significantly increases IGF-1 levels. It has been observed that after three days of hyperalimentation therapy, IGF-1 concentrations have increased by approximately 50% [13]. In patients with AN, the GH/IGF-1 axis activity can be restored only by nutritional rehabilitation and stable weight gain [19].

Mild caloric restriction. While severe undernutrition seems obvious to cause NGR, it turns out that also mild caloric restriction might play a role. A study carried out in prepubertal children has shown a significant decrease in IGF-1 levels after six days of the diet with calories reduced by 50% (i.e. 35 Cal/kg). After the resumption of a regular diet, IGF-1 levels have returned to baseline concentrations [9]. However, in some children with growth disorders caused by mild energy restrictions, changes in IGF-1 levels may not be significant. Therefore, normal IGF-1 values do not exclude NGR [20].

Gastrointestinal disturbances, malabsorption and increased energy requirements. Low food consumption in children may also be caused by mechanical feeding difficulties, gastroesophageal reflux, lactation disorders (e.g., low milk supply), and incorrectly prepared formula. Impaired absorption of nutrients may appear due to untreated milk protein allergy and gastrointestinal disorders, such as coeliac disease (when the patient does not follow a strict gluten-free diet) or irritable bowel syndrome. Other possible causes include biliary atresia, cystic fibrosis, or pancreatic cholestatic conditions. Increased metabolism leads to excessive loss of nutrients in chronic lung diseases (e.g., cystic fibrosis) or hyperthyroidism. Energy requirements also increase in chronic kidney diseases, among children with congenital heart disease, during chronic infectious diseases, and in inflammatory conditions (e.g., in asthma, inflammatory bowel diseases) [8].

SELECTED NUTRITIONAL PROBLEMS

Protein deficiency. Kwashiorkor is an extreme example of severe protein deficiency occurring typically in poor regions of Africa, Asia, and South America, generally rare in developed countries, but milder states of protein deficiencies are more frequent. There are several health conditions known to cause protein insufficiency, for instance, children with Crohn's disease commonly suffer from nutritional growth retardation due to low food intake, resulting from poor appetite and fear of developing gastrointestinal symptoms. Moreover, patients with the active stage of Crohn's disease usually experience hepatopathy, mucosal haemorrhage, enteropathy, and fistula, all leading to hypoproteinemia [21]. Another example is chronic kidney disease, which often manifests in protein-energy wasting and hypoalbuminaemia. The state of persistent inflammation in children might cause anorexia, resulting in lower protein and caloric intake and a decrease in the synthesis of albumin [22].

Several studies have demonstrated reduced IGF-1 serum concentrations and elevated basal GH levels in protein-malnourished children [9]. It is assumed that both

calorie-restricted and protein-deficient diets contribute to the development of GH resistance, but probably in different mechanisms. It has been hypothesized that caloric malnutrition decreases GH receptors, while protein malnutrition is associated with post-receptor defects. Protein deficiency seems to be related to the state of IGF-1 resistance [13].

GH and IGF-1 levels normalize after appropriate nutritional therapy in protein deficiency. It has been observed that after two weeks of nutritional intervention, there was a two-fold increase in IGF-1 concentration in children with severe protein malnutrition. After 50 days of intensive nourishing treatment, the baseline GH and IGF-1 levels were indistinguishable from controls. IGF-1 levels may decrease not only in severe protein deficiency, but also during short-term and mild protein deficits. A study conducted in prepubertal children has shown reduced IGF-1 levels after six days of 33% protein restriction (i.e., 0.66g/kg). The resumption of a regular diet resulted in the normalization of this parameter [9].

Both low protein and essential amino acid-deficient diets can lead to growth failure in children. Semba et al. measured concentrations of amino acids in 331 children aged 12–59 months, 62% of whom were stunted. Stunted children had significantly lower concentrations of all nine essential amino acids (tryptophan, isoleucine, leucine, valine, methionine, threonine, histidine, phenylalanine and lysine), three relatively essential amino acids (arginine, glycine, glutamine) and three non-essential amino acids (asparagine, glutamate and serine), when compared to children with normal height [23]. Arginine is a well-described amino acid involved in growth processes. Since 1982, intravenous administration of arginine has become one of the diagnostic methods for growth hormone secretion disorders. An intravenous bolus of arginine should cause an increase in GH concentration. The mechanism of arginine action is associated with its inhibitory effect on the secretion of endogenous somatostatin and, consequently, the stimulation of growth hormone release [24].

Micronutrient deficiencies. Iron, calcium, and zinc are the key nutrients for optimal cognitive development, bone health and proper growth. Data collected from the National Health and Nutrition Examination Survey III (NHANES III) has evaluated the usual intake of iron, calcium, and zinc among 1,122 US children in the second year of life. The results of this study have proved that 26.1% of children had usual iron intakes lower than the Recommended Dietary Allowance (RDA), and 11% of them had usual calcium intakes below RDA. Only <1% of participants consumed less zinc than recommended [25]. These findings suggest the need for estimating dietary intake of minerals, particularly iron and calcium, as part of paediatric care.

Calcium is a structural element of bone, and its proper dietary supply is necessary to achieve peak bone mass and maintain normal growth. This mineral is mainly stored in bones, and the process of calcium bone accumulation is the most intensive during puberty. Vitamin D is involved in calcium homeostasis by regulating its absorption or reabsorption from the intestines, bones, and kidneys [10]. Calcium deficiency may reflect cases of selective appetite with the exclusion of dairy, but is a particular problem in children

with cow's milk allergy. Dietary analysis of 6,189 children aged 2–17 showed a significantly lower average daily calcium intake in children with milk allergy (882.2mg) compared to healthy participants of the study (1047mg) [26]. Children with a milk allergy also consumed fewer calories and less vitamin D. Since milk products are the common source of calcium, children following a dairy-free diet are at particular risk of developing a calcium deficiency.

Exposure to sunlight is the leading natural source of vitamin D. Several genetic association studies have shown an association between single-nucleotide polymorphisms (SNPs) of the *vitamin D receptor (VDR)* gene promoter and growth. Paediatric patients with kidney diseases commonly suffer from disturbed bone metabolism and reduced linear growth, partly caused by impaired vitamin D metabolism [10]. It seems that vitamin D metabolites might interfere with GH/IGF-1 axis. Several clinical paediatric studies have shown a positive correlation between 25(OH)D and IGF-1 levels, but this relationship was significant only after vitamin D supplementation [27]. These observations suggest that the improvement of vitamin D status might be essential to normalize IGF-1 levels.

Iron and zinc. The American Academy of Pediatrics (AAP) has identified iron and zinc as critical nutrients for young children. An adequate intake of iron positively influences cognitive development [25]. Iron is an essential component of enzymes that are involved in metabolism, e.g. oxidases, catalases, reductases, peroxidases, and dehydrogenases. Many metabolic processes lead to *de novo* protein synthesis and, consequently, to the formation of new tissues. During puberty, an intensive body weight gain requires an increase in haemoglobin concentration, making children a risk group for iron deficiency. In turn, insufficient iron supply may cause anaemia, negatively affecting the growth process. Monitoring body iron stores is important during growth hormone therapy in children [12].

Zinc deficiency increases the risk of growth disorders, diarrhea, and acute lower respiratory infections in childhood [28], and is known to weaken both IGF-1 synthesis and cellular response to this hormone. It has been observed that growth hormone treatment is less effective in children with zinc deficiency than in those with normal serum zinc concentration. Low circulating IGF-1 is also observed in states of iodine, magnesium, vitamin B6, or vitamin A deficiencies [9, 13]. Therefore, daily intake of all nutrients should be instigated among children with growth disorders.

High-sugar diets. Already during foetal life, the foetus is able to detect sweet taste. Newborns prefer the sweet taste of mother's milk because it is the primary food source enabling them to survive. It has been proved that during infancy, children are able to differentiate between varying degrees of sweetness and are more likely to consume sugar solutions than water. It has been observed that sweet taste stimulates the sucking reflex and makes children's faces look more cheerful and relaxed [29]. Moreover, heightened sweet preference during childhood might be associated with increased energy needs due to intensive growth. All this makes children vulnerable to developing their taste preferences toward sweet, highly processed foods [30].

However, high sugar diets are generally rich in calories but low in nutrients. Children who experienced a highly

sweetened diet may not willingly reach for healthy snacks, including fruit, finding them 'not sweet enough' [30]. Sweet taste is likely to reduce food consumption and increase satiety; thus, high sugar diets may contribute to lower consumption of nutritious meals in some children [31]. According to data collected from What We Eat in America (WWEIA) and NHANES 2015–2016, added sugars accounted for 16% of total daily energy intake among 2–19-year-olds in the United States, which is above the recommended limit of 10%. Notably, sugar-sweetened beverages (SSB) have been reported to be the main source of added sugars in children's diet [32]. Besides high sugar content, SSB are often saturated with carbon dioxide, which increases stomach volume and satiety. Thus, it is advisable to avoid carbonated drinks shortly before meals [31].

However, on the population level, overconsumption of highly sweetened food during childhood increases the risk of obesity and comorbidities, including diabetes type II and cardiovascular diseases in future life [33]; therefore, it is essential to form healthy eating habits at the early stages of life. It has been proved that children imitate parents' food choices; for example, children whose parents drink sweetened beverages less frequently also consume them in smaller amounts. Parental control over children's diet and replenishing home food supplies with healthy snacks may also improve children's nutrition [34]. It has also been shown that some genetic factors may influence taste preferences. For example, the perception of sweet taste intensity depends on variants of the *TAS1R3* and *GNAT3* genes [30].

Coexistence of obesity and growth retardation. Obese children usually present normal height or are statistically higher than their non-obese peers, despite impaired growth hormone secretion. However, although the secretion of GH in obese children is reduced, their GH responsiveness seems to be increased compared to average-weight peers. Somatomedin generation tests proved that in obese children, the increase in IGF-1 concentration is 80% greater than in those from the control group [35]. The growth process in obese children seems to be related to the body's adaptation to the state of reduced GH secretion by increasing the concentration of growth hormone-binding proteins (GHBP) and maintaining the complex of growth hormone and growth hormone binding protein (GH-GHBP) within the normal range. This enables the maintenance of normal synthesis and bioavailability of IGF-1 [36].

Obesity might affect growth by altering insulin and leptin secretion. Hyperinsulinemia seems to be a significant factor in suppressing GH synthesis and release [37]. On the other hand, high insulin levels are known to inhibit hepatic production of IGF-1 and IGF-2, leading to enhanced IGF-1 bioavailability [9]. It is also assumed that insulin may modulate skeletal growth. A study conducted in 74 overweight and obese children aged 4–13 has shown a relationship between hyperinsulinaemia (with fasting insulin >30 µU/L) and increased risk for advanced bone age [38]. Another growth-stimulating hormone, leptin, is known to regulate chondrocyte proliferation and differentiation in the growth plate. Scientific data suggests that serum leptin levels positively correlate with IGF-1 levels [9]. A cohort study conducted in children with congenital leptin deficiency indicates that leptin substitution increases IGF-1 levels and promotes linear growth [39]. Finally, both hyperinsulinemia

and hyperleptinemia seem to be involved in the phenomenon of 'growth without growth hormone', occurring among some obese children with growth hormone deficiency [9, 37].

Given the above, growth retardation usually coexists with undernutrition and underweight; however, population health experts, including the WHO, point to the increasing prevalence of the phenomenon called 'the double burden of malnutrition' (DBM). In the DBM, obesity and stunting co-occur [40]. DBM may particularly affect families migrating from rural to urban areas, where access to highly processed food is increased. An interesting example has been observed in Mexico, where most poor households afford food that meets their energy requirements but has low nutritional value, i.e., low in minerals (particularly iron) and fibre. Therefore, some children suffer from anaemia, stunting, and obesity simultaneously. Another aspect worth mentioning is that stunted children are likely to have impaired fat oxidation and energy regulation, which predispose them to excessive fat accumulation. Therefore, in stunted children, a hypercaloric diet often leads to excessive weight gain before catch-up growth occurs [41].

Presently, American paediatricians struggle with the phenomenon of growth and puberty delay among some obese children. In response to the increasing problem of overweight, young patients significantly limit their food consumption which results in nutritional deficiencies and, consequently, in growth failure. Anaemia in obese children can develop in response to improper diet and increased body needs, or malabsorption of iron which are both commonly observed in the state of obesity. The inflammation typical for overweight and obesity contributes to the increase in hepcidin levels, a protein that weakens iron absorption in the digestive tract. Furthermore, hepcidin is known to block the action of ferroportin, leading to a decrease in serum iron concentration [42]. Besides iron deficiency, there is also evidence of a higher prevalence of zinc and copper deficiency among obese children, compared to their non-obese peers [43].

Diagnostic difficulties in nutritional growth retardation.

Patients with NGR adapt to the state of mild energy deficit by decreasing energy expenditure [20]. Distinguishing NGR from other causes of growth failure may be difficult because children with NGR usually do not present abnormal biochemical parameters of nutritional status, such as retinol-binding protein, prealbumin, albumin, transferrin, or triiodothyronine [20, 28]. Furthermore, it is likely that in obese children, diagnostic tests for NGR will not be considered because both undernutrition and growth failure are commonly assumed to be associated with being underweight.

The IGF-1 is a biochemical parameter sensitive to diet modifications and may suggest NGR. But IGF-1 evaluation is also the routine biochemical test for the GH/IGF-1 axis disorders. GH stimulation tests are carried out to confirm growth hormone deficiency (GHD) in children with low IGF-1 levels [44, 45]. Both malnourished children and those with growth hormone deficiency can present decreased IGF-1 levels and suffer from peripheral GH resistance. In both these cases, the results of GH stimulation tests can be abnormal. A study conducted with 57 children with NGR and 36 with GHD demonstrated reduced IGF-1 levels in all group, without statistical difference between NGR and GHD

groups for serum IGF-1 levels. The study results suggest that IGF-1 levels do not distinguish children with NGR from those with GHD; hence, patients with NGR are at high risk of misdiagnosis [46]. Growth hormone therapy in patients with NGR will be ineffective and may expose them to potential adverse health effects of the treatment [9]. Regardless of the growth failure cause and its treatment, it is highly advisable to analyze the eating habits of all children with short stature.

CONCLUSIONS

In developed countries, the leading cause of nutritional growth failure seems to be inadequate food intake due to psychosocial and family conditions. Nutritional deficiencies are known to lower IGF-1 levels, leading to growth retardation. However, currently, a relevant concern is the over-consumption of sweet, highly processed products, which can negatively influence children's appetite and reduce consumption of nutritious meals. Therefore, various micro- and macronutrient deficiencies may coexist with sufficient or even excessive caloric supply. In consequence, NGR is the phenomenon that can occur in underweight and overweight children, as well as those with normal body weight. In developed countries, NGR might be an underestimated problem due to diagnostic difficulties and common dietary mistakes, despite the general availability of food. As no practical diagnostic biochemical test for NGR is available, it seems that paediatric patients with growth failure should undergo dietary analysis preceding further advanced endocrine and biochemical diagnostic procedures.

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