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REVIEW ARTICLE

Micronutrients and Bone Growth in Preadolescent Children from Developing Countries

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Abstract:

Objective:

Childhood undernutrition may result in poor physical development, and negatively impact on the workforce and society. We examined from the literature how micronutrient deficiencies may affect bone growth in preadolescent children in developing countries.

Results:

Overall data from many studies carried out during the past 30 years show that dietary supplementation of children in developing countries may improve growth and development. Although the first few months and years of life have been considered key to these improvements, supplementation at any age may be able to influence bone health and physical development. There is considerable data in support of calcium supplementation, either in tablet form or from increased intake of dairy products, but it now seems likely that calcium alone may not be sufficient to enhance growth, unless other vital micronutrients are also provided. The recent societal changes in South Africa have resulted in an influx of cheap, nutrient-poor foods, leading to widespread childhood undernourishment in mainly black children in resource-constrained communities. Data on dietary supplementation and long-term outcomes in these children are still lacking.

Conclusion:

An understanding of the complex interactions between macro- and micronutrients in enhancing physical growth and development, and a consensus on the optimal timing and delivery system of supplementation is required to improve child health in developing countries, including Africa. The efficacy and efficiency of food based programmes versus supplementation should be critically assessed.

Keywords: Bone health, Children, Growth, Preadolescent, Physical development, Undernutrition.

INTRODUCTION

Investment in children's health that enhances their ability to grow and develop cognitively and optimises healthy status is essential to their future development, the workforce and the nation. Childhood undernutrition occurs when children do not eat or absorb sufficient nutrients to cover their energy needs, and allow for growth and the maintenance of a healthy immune system. Undernutrition, which encompasses stunting, wasting, and deficiencies of essential

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vitamins and minerals (micronutrients) remains a major public health concern in developing countries [1]. Annually, more than one-third of all child deaths worldwide can be attributed to undernutrition [2]. Undernutrition often starts *in utero*, resulting in slower physical and mental development, and the ensuing growth retardation usually extends into the second or third year of life [3].

Until recently, the most common cause of growth retardation was considered to be protein and energy malnutrition, but in the last few years, micronutrient intake has gained considerable attention. Micronutrient deficiencies, also known as "hidden hunger", are found in a number of countries in sub-Saharan Africa at alarmingly high levels [3]. These multiple micronutrient deficiencies are associated with several adverse outcomes throughout life, such as loss of muscle mass, and obstetric risk in females [4, 5]. Deficiencies develop due to inadequate food intake, poor dietary quality, and poor bioavailability due to the presence of inhibitors of absorption in the food [6]. People in developing countries often consume a plant-based diet which is high in phytate (a potent inhibitor of zinc absorption) and fibre, and low in other nutrients, resulting in decreased bioavailability of iron, zinc and calcium.

This article aims to examine how micronutrient poor diets impact on bone growth in children, the optimal timing of intervention, and how differences in the type of intervention (supplementation vs. food based approaches) might affect overall growth and long-term outcomes for children in developing countries. The measurement of bone growth and density is also briefly discussed. Although reports from many countries were examined, this article was designed to focus particularly on available data from Africa, with the emphasis on preadolescent children, aged >2 to 12 years.

BONE GROWTH DURING CHILDHOOD

Attaining height is the result of the interaction between genetic background and macro-/ micronutrient availability during the growth period [7]. The process of longitudinal growth involves increases in the number of the cells on the growth plate of bone, as well as increases in cell size, leading to expansion of the growth plate. The key hormones involved are growth hormone and insulin-like growth factor 1 (IGF-1) [8]. IGF-1 receptors are found in proliferating bone chondrocytes, and a rise in IGF-1 stimulates chondrogenesis. Growth hormones can stimulate growth independent of IGF-1, but can also raise levels of IGF-1, stimulating linear growth [9]. Plasma IGF-1 levels are affected by nutrition, specifically by protein and energy restriction, with lack of protein having the largest impact [10]. Some micronutrients also affect IGF-1 levels, including zinc, potassium, magnesium, copper and manganese. It is also well known that deficiencies in vitamin D and calcium can affect bone development and growth [11]. Peak bone mass is the highest bone mass achievable within a person's genetic potential, and is usually accrued during adolescence [7]. Up to 90% of peak bone mass is accrued by the age of 18 years, although bone mass can still increase up to the third decade of life. In white children, research has shown that the average skeletal calcium retention at the peak rate of accretion is 325 mg/day for girls and 409 mg/day for boys [12]. Due to the significant growth at this time, any modulation of accretion could affect lifelong bone health.

MEASURING BONE GROWTH AND DENSITY IN CHILDREN

Measurement of growth hormone and IGF-1 in children is challenging [13], and likely to be impractical in developing countries. Therefore, to assess growth, measurements of length (for children less than two years of age) or height (for children aged 2 years or older), and weight are generally used [14, 15], and compared with World Health Organization (WHO) child growth standards [16, 17]. Equipment needed to measure length or height requires only a piece of smooth, moisture-resistant wood, and a measuring tape, forming an infantometer (length) or stadiometer (height) [14]. In general, standing height is about 0.7 cm less than recumbent length [14]. This difference was taken into account in developing the WHO growth standards, and it is important to adjust the measurements if length is taken instead of height, and vice versa [16, 17]. For measuring weight, electronic scales measuring to a precision of 0.1 kg are recommended [14]. Height and weight measurements can then be compared with the WHO standards, and children assigned a z-score (the number of standard deviations above or below the reference median value) [18].

Bone mineral content (BMC) and areal bone mineral density (BMD) are valuable in determining bone strength and mineral content, and are most often measured using dual-energy X-ray absorptiometry (DXA) [19]. DXA uses two levels of x-ray photon energy to measure the amount of minerals in bone, and was originally developed for use in adults with osteoporosis; however great strides have been made in recent years, improving the applicability to children [20]. In 2013, the International Society for Clinical Densitometry (ISCD) published official revised positions on reporting paediatric densitometry results, with recommendations on which skeletal sites should be measured, adjustments that should be made, and the reference databases to be used [21]. According to the ISCD, the posterior-anterior spine and total-body-less-head, are the preferred skeletal sites for measurement in most paediatric subjects; the hip is not a preferred measurement site in growing children due to variability in skeletal development [22]. For children with short stature or growth delay, results should be adjusted using the height z-score [22]. However, while DXA whole-body BMC and BMD for children aged three years and above and DXA lumbar spine measurements for infants and young children aged up to 5 years were identified as feasible and reproducible, it was noted that reference data for children aged 0 to five years are currently insufficient [22, 23]. Furthermore, when evaluating DXA results in children, there are several confounding factors that should be considered, including race, gender, and pubertal status [19]. To date, DXA measurements of children in African countries have been mainly restricted to large research studies [24], likely due to equipment availability, costs, and lack of adequate reference data. Inconsistencies in measurement methodologies will interfere with the comparison of findings.

GROWTH IN AFRICAN CHILDREN

The prevalence of stunting of linear growth of children younger than 5 years affected at least 165 million children globally in 2011; with East (42%) and West Africa (36%) having the highest prevalence estimates [25]. On the other hand, an estimated 43 million children younger than 5 years (7%) were overweight, with most overweight children living in low-income and middle-income countries [25]. In Africa, the estimated prevalence of overweight increased from 4% in 1990 to 7% in 2011 [25]. The nutrition transition, accompanied by decreased physical activity, leads to increases in overweight and obesity. The adverse changes in dietary patterns during the nutrition transition also cause an inability to consistently meet micronutrient requirement, contributing to the “double burden” of nutrition-related diseases, a co-existence of under- and over-nutrition [26].

Despite this clear trend in dietary changes and growth retardation, few studies investigating growth of children up to the age of ten years have been based in South Africa. One study, carried out in white and non-white children between the ages of 0 – 10 years, indicated a slower rate of growth in the non-white children [27]. The Ellisras Growth study [28] recruited 1335 children between three and ten years of age in rural villages in the then Northern Province (now Limpopo Province) of South Africa. The children underwent anthropometric assessment to assess nutritional status, using National Health and Nutrition Examination Survey (NHANES) I and II data from the United States [29] as a historical reference. When analysed, the data for the African children indicated that height tended to follow a pattern between 3-7 years which ran parallel to the 50th percentile of US children, and within the range of 0.0-0.5 z-scores [28]. After the age of seven years there was a consistent tendency for the mean height to be below the 50th percentile with the mean values for both boys and girls being below the 10th percentile at the age of ten years. Weight remained on or just below the 10th percentile from age 3-10 years [28].

In 1990, a birth cohort study was initiated in the Johannesburg area, called the Birth-to-ten and later the Birth-to-twenty (Bt20) study [30, 31]. Recruitment took place between April and June of 1990, and 4034 mothers with their babies volunteered to participate. Data were collected so that growth and physical development, psychological development and social and economic conditions could be monitored. Though improvements in growth of non-white children were observed in comparison to historical data recorded in the 1970s, their growth patterns did not equal those of the white children, with white children remaining taller and heavier [27, 31]. The Bt20 study also examined ethnic differences in bone mass. Despite a lower socioeconomic status, lower calcium and vitamin D intakes, and less physical activity, greater femoral neck bone mass was reported in the black children compared with white children, although both groups had similar bone mass at the spine and appendicular skeleton after adjusting for differences in stature [32]. Further genetic investigation was done in the Bt20 study to ascertain possible genetic factors contributing to bone health in black South African children aged around ten years [33]. Twenty-seven markers, derived from three genes, were found to be associated with either femoral neck or lumbar spine bone mineral content. The authors therefore concluded that a strong genetic effect acts at the femoral neck in black South African children, affecting bone mass. Such influences should be taken into account in any study evaluating bone health in black South African children, to ensure that genetic effects in specific skeletal areas do not mask the impact of poor nutrition elsewhere in the body.

INTERVENTIONS AGAINST STUNTING

A recent perspective on childhood growth patterns considered critical windows for interventions against stunting [34]. An analysis of the World Health Organization (WHO) global database on child growth and malnutrition revealed that early growth patterns in children from 54 resource-poor countries show a rapid fall-off in height-for-age z-scores during the first two years of life [35]. This observation led to interventions and strategies to improve growth focused on the age 0-2 year age group, without consideration whether there may be an opportunity for interventions later in life. The window between nine months to two years is considered an 'optimal window of opportunity' within which nutritional interventions may have an effect on longitudinal growth. However, other windows of opportunity exist, and data from at least five countries show that height catch-up can take place after the age of two years, making it likely that adolescence may represent another opportunity to intervene with long lasting effects into adulthood [34, 36]. However, any catch-up growth intervention should be monitored to ensure that body weight of the child does not exceed the birth percentile of the child, since overweight is associated with an increased risk for the non-communicable diseases of lifestyle later in life. As such, the approach captured by the United Nations sub-committee on nutrition through the lifecycle [37], which recommends adequate nutrition and interventions throughout life to improve health and well-being, is a more comprehensive approach.

IMPACT OF DAIRY PRODUCTS ON BONE GROWTH

Consumption of dairy products in childhood and adolescence is known to have a positive effect on bone mineralization in adulthood and can reduce the risk for developing osteoporosis [38]. In studies of BMC, osteoporotic women reported less milk and dairy intake when they were children or adolescents compared with non-osteoporotic controls [39 - 41]. However, it has also been suggested that calcium/dairy intake can have a significant effect on bone mass in young adults. Matkovic *et al*. (1979) [42] stated that bone mass at any age is the result of age and sex and other genetically determined factors but that nutrition has a significant effect, and two decades later, a study reported that higher milk intake during adolescence was associated with greater total body spine and radial bone mineral during development of peak bone mass [43]. Thus, supplementation of a nutrient-poor diet with calcium or dairy products appears likely to be a beneficial strategy for improving health in deprived children.

Dietary intake of calcium and other nutrients can be assessed using dietary reference intake (DRI) values developed by the Institute of Medicine of The National Academies [44]. The DRI values are specified on the basis of age, gender and lifestage, cover more than 40 nutrient substances, and were intended to replace the recommended dietary allowance (RDA) values. Originally produced in 1997, updated DRIs for calcium and vitamin D were released in 2010 [44].

Early studies conducted in Caucasian [45 - 47] and Gambian children [48] showed that supplementing the diet with calcium or milk to increase nutrient intake may enhance bone accretion. In one study, girls who had their diet supplemented with milk had higher circulating IGF-1 concentrations, which may affect bone growth [47]. When extra phosphorus was provided, bone area as well as vertebral height increased and total BMC also increased [45]. In another study, the diet of eleven year old white girls was supplemented with dairy products to the level of 1200 mg calcium per day for 12 months [49]. The increased intake of dairy provided not only calcium but protein and other minerals plus additional vitamin D. After one year the intervention group had significantly greater increases in lumbar spine bone density and total body mineralisation [49].

More recent data also support an association between dairy consumption, growth, and bone health. In children in Kenya, physical growth, cognitive function and school performance were all improved when meat and milk were added to the normal daily diet [50]. Milk supplementation improved linear growth, and the meat and milk supplemented groups had improved weight gain, suggesting chronic energy deficits resulting from the unsupplemented diet. In another study, bone changes over two years in young children with a history of milk avoidance were evaluated, and results demonstrated persistent height reduction, obesity and low bone density at the ultradistal radius and lumbar spine [51]. In contrast, other authors have suggested that dairy or calcium intake may only be beneficial to specific subpopulations of children, or may actually fail to provide any benefit to children at all. In a meta-analysis on the relationship between dairy and calcium intake and BMC, a review of 21 studies concluded that increased dairy/calcium intake with or without vitamin D improved spine and whole body mineral content, but only in children with low baseline intakes of dairy or calcium [52]. Lanou *et al*. (2005) [53] reviewed the evidence for the effects of calcium and dairy products on bone health of children and adolescents, and found no consistent benefits of increasing dairy consumption for child or young adult bone health.

Wiley (2012) [54] recently presented an interesting perspective on cow milk consumption and human biology; posing the question of whether drinking cow milk accelerates linear growth and maturation or affects size in adulthood. The results presented were drawn from new analyses of NHANES data collected between 1999-2004, and other published studies in the US [54]. Overall, children aged 24-59 months with the highest quartile of milk intake (>2 cups per day), attained a greater height percentile compared with those in the lower quartiles of intake. These results are in line with a previous study in New Zealand, which reported that children who avoided milk were shorter than milk-drinking controls [55]. However, data on prepubertal children (5-11 years) were more variable. An older study done in the UK [56] reported greater growth in children receiving milk over a duration of seven months compared with children receiving a biscuit or no supplement. While some more recent studies support this result, others have produced data indicating no effects of milk on growth, and the NHANES data did not support an effect linked with drinking milk daily [54]. However, it should be noted that in addition to increasing calcium availability, milk also provides energy and contributes to macronutrient intake, which may also impact on height and growth. Since few trials correct for energy and macronutrient intake, the question of whether milk does affect growth in prepubertal children remains to be confirmed.

CALCIUM SUPPLEMENTATION

In several studies, calcium supplementation, rather than overall dairy intake, has formed the basis of research into possible associations between growth and diet. In one study, providing only calcium as a supplement increased BMC but not bone area [48], while in another, providing calcium as a supplement in boys and girls aged nine years improved bone density and mineralisation but not longitudinal growth, bone area and width, or body weight [46]. Data from a 4-year randomized controlled trial supplementing ten year old females with calcium citrate-malate suggested that bone accretion in the supplemented group was significantly higher than the control group after 4 years. However, after a three year extension of the trial, the positive effects had largely disappeared, with the exception of the metacarpals and the forearms of taller subjects [57].

A recent meta-analysis of calcium supplementation trials in children aged between six years and 18 years, reported no significant effect on bone density at the femoral neck and lumbar spine, with a small effect on total BMC [58]. However, previous research indicated that calcium supplementation may need to be combined with exercise for the full beneficial effects to be observed [59]. In an earlier review on the role of physical activity and calcium intake for bone mass growth in children, French *et al*. (2000) [60] reported that weight-bearing physical activity and calcium supplementation both improved bone mass gain in children and adolescents, with the consistent sites being the lumbar spine and total bone mass. However, the continuing benefit and durability of these effects was not known until recently, when this question was addressed in a long-term calcium supplementation trial in Gambian children [61]. Participating children, aged 8-12 years, received calcium 1000 mg/day for 12 months, and were subsequently followed to the age of 21-25 years with height measurements occurring every six-months, or annually. In calcium-supplemented boys peak height velocity was accelerated by 7 months and they reached greater stature at a mean age of 15.5 years. But at mean age 23.5 years, the calcium supplemented group was 3.5 cm shorter than their counterparts. No significant effect was observed in girls [61].

Overall, it would appear that providing dairy or calcium supplementation could improve growth and bone mineralisation in children [62]. However, while these types of studies are feasible in growing children in developing countries, they do not address possible deficiencies in other minerals and some vitamins.

IMPACT OF MICRONUTRIENTS

More than 20 years ago, it was suggested that although providing calcium as a supplement alone or with phosphorus did not improve height or weight gain in children of developing countries, providing calcium in combination with other micronutrients could potentially enhance growth [63]. The Bt20 study conducted longitudinal food frequency analyses and consistently found that calcium, iron, zinc and biotin fell below 65% of the recommended daily allowance. In addition, vitamin A, riboflavin, nicotinic acid and pantothenic acid fell below the RDA in 2003, and from 2000 to 2003 there was an increase in the percentage of children falling below the recommended intakes for most micronutrients [31]. Addition of micronutrients such as zinc to the daily diet may help to overcome problems of poor absorption of macronutrients, thus indirectly improving physical and mental growth and well-being. However, while food supplementation and fortification with micronutrients have been shown to be both efficacious and cost-effective [64], there is currently no consensus on the timing or methodology for such improvements to be implemented in developing countries.

There have been several studies in children evaluating the effect of single micronutrient supplementation on linear growth. According to a meta-analysis of more than 30 randomized controlled trials, the most conclusive evidence exists for the addition of zinc to the diet [1]. Zinc has been found to have a small but significant effect on growth in children aged 0-13 years, by reducing the incidence of diarrhoea and pneumonia, which were two factors affecting growth. In contrast, iron supplementation only improved linear growth in anaemic children, while vitamin A had little or no benefit on linear growth [1]. These data are supported by other publications, although the conclusions must be interpreted with caution due to the inclusion of non-randomized trials and community-based studies in the analyses [11, 65]. One limitation of the meta-analysis is that reports on the relationship between iron and growth in children are sparse and not convincing, making it difficult to draw definitive conclusions [1]. Furthermore, the response to vitamin A appeared to be linked to the season, with a response in the summer months; thus the non-response recorded for vitamin A supplementation and growth could result from the fact in an intervention lasting for a year, any small effect taking place in a specific season is likely to be diluted out in the overall data [1]. The other consideration mentioned was that none of the children in the supplemented groups were vitamin A deficient which could limit the response. The results of single micronutrient supplementation are therefore limited, and since it seems likely that multiple nutrient deficiencies exist, it may be expected that supplementation with individual micronutrients will have a limited impact on growth.

In addition to evaluating the impact of single micronutrient supplementation, the same meta-analysis reported that multi-micronutrient interventions do improve growth in children [1]. This outcome could be due to interactions between nutrients [66] as well as direct effects by single nutrients in the mixture. A recent systematic review of 18 trials in which young children in developing countries were given multinutrient-fortified milk and cereal products indicated that correcting multiple micronutrient deficiencies may be beneficial in improving an overall poor diet and reducing common health problems, although information on long-term functional outcomes remains scarce [67].

While there have been many studies on single or multiple micronutrient supplementation in infants and young children [11, 67 - 69], there is a paucity of data on micronutrient supplementation and growth in older children, and specifically in South African children aged between 9 and 12 years. One study in South African schoolchildren aged 6-11 years (mean age eight years) reported that while a multi-micronutrient-fortified beverage was able to improve cognition, it had no effect on height [70]. Furthermore, the impact of the micronutrients on cognition was attenuated by the addition of sugar to the beverage, indicating that nutrient interactions can add an additional level of complexity to supplementation research, and may significantly influence study outcomes [70]. Authors of studies in other countries have reported varying results [71 - 74]. In Bangladesh, a trial in 989 girls (mean age 12 years) receiving multinutrient supplementation reported that mean height, weight and mean upper arm circumference increased significantly more in the supplemented group over the first six months compared with the control group [71]. Significant improvement was also found in haemoglobin concentration, iron status and vitamin A status over the first six months in the supplemented group, with no further improvement over the second six months of the study. Despite these improvement, the girls did not appear to gain significant height during the supplementation period [71]. In contrast, children in Tanzania aged between 6-11 years, supplied with a beverage containing three minerals and seven vitamins delivering between 30-120% of the RDA during week days for six months, showed improvements in both linear growth and weight gain [72, 73]. Similarly, children in Botswana aged 6-11 years, who were supplemented with an experimental beverage which was fortified with 12 micronutrients, gained significantly more weight over the eight weeks of supplementation [74]. While these studies show promise, the variability in results between countries suggest that low energy and protein intake may still limit growth even in the presence of adequate micronutrients.

CONCLUSION

Dietary supplementation in previously undernourished children may improve growth and development, and ultimately produce a healthier workforce and society. Although considerable attention has been focused on the early months and years of life as the optimal time to effect change, there may be other windows of opportunity throughout childhood and adolescence to reverse, to at least some degree, the impact of poor maternal diet and foetal underdevelopment. Furthermore, although many studies have evaluated dairy and calcium supplementation, it seems likely that maximum benefit is gained only when the diet includes sources of energy, protein, and micronutrients, which can act together to reduce deficits and boost physical and cognitive development. In South Africa, societal changes during the past few decades have radically altered a traditional diet which sustained the population for centuries, introducing cheap but nutrient-poor, fast-food alternatives which has resulted in a generation of undernourished children. Further studies are required to explicitly identify the role for the specific nutrients affecting bone growth, the optimal timing of supplementation and the dosage thereof, and the method by which multinutrients can be made available to these children and future generations, to reverse the tide of stunting and poor health which currently threatens to engulf them. The efficacy and efficiency of supplementation vs. food based approaches should be determined.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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