Public Health Nutrition: 23(17), 3187–3189 doi:10.1017/S1368980020002499

Invited Commentary

Severe acute malnutrition, calcium and vitamin D: important interactions

In this issue of Public Health Nutrition, Smilie *et al.*[1] dare to challenge the adequacy of the refeeding regimen in the WHO's time-tested, data-driven, health-enhancing, life-saving Ten Steps programme for the management of severe acute malnutrition (SAM). Bravely, they trample on the central tenets of the 'holy grail' of malnutrition management. Are they justified?

One could claim that there were three 'top' public health developments during the 20th Century – vaccines, antibiotics and oral rehydration solutions. With malnutrition contributing to nearly half of childhood deaths around the planet, the release of the WHO's Ten Steps programme for SAM in 1999 markedly reduced the morbidity and mortality associated with childhood malnutrition, perhaps qualifying it as the top public health nutrition intervention of the current century. These Ten Steps allow an algorithmic scheme to take even highly trained physicians away from complex management thoughts to simply focus on stepwise interventions to save lives and restore health[2,3].

Popular wisdom tells us not to change processes that are already working: 'If it ain't broke, don't fix it'. Obviously, unbroken vaccination and antibiotic therapies have been improved with subsequent additions and changes to regimens. Even the simple and effective 'magic bullet' of oral rehydration therapy for combatting diarrhoeal dehydration was subjected to decades of revisions with changes in sugar source and osmolar concentration[4,5]. As vaccines, antibiotics and oral rehydration solutions have been improved (without being totally broken), so malnutrition management can be improved.

Specifically, the WHO predicts <10% mortality in children with complicated SAM treated based on the Ten Step recommendations. However, despite guideline compliance, some sub-Saharan Africa hospitals report 10–40% mortality in hospitalised children with SAM[6]. This lowered rate of morbidity and mortality may be further reduced with updates based on recent research. To clarify, of the thirty-three WHO recommendations for managing SAM, only eleven are based on directly relevant research, while sixteen are based solely on expert opinion and six are based either on studies not conducted in children with complicated SAM or using non-identical treatment recommendations. Furthermore, the recommendations for micronutrient supplementation are almost solely based on expert opinion with the exception of the vitamin A recommendations that came from the results of three randomised controlled trials[6].

It has already been suggested that refeeding programmes should include better thiamine delivery to children, and there are new data suggesting that long-term recovery from SAM could be enhanced by using foods that consider growth-promoting patterns in the local population's microbiome[7,8]. Now, Smilie *et al.*[1] show that current malnutrition management is 'broken' in regards to Ca and vitamin D nutrition, and they suggest 'fixes'.

SAM, defined as having a weight-for-height *z*-score <−3, a mid-upper arm circumference of <115 mm or bilateral oedema, is sometimes associated with Ca deficiency and increases the risks of rickets and hypocalcaemia[2]. Despite this potential link, few studies have examined the serum Ca levels in children hospitalised with SAM. Smilie *et al.*[1] help fill this gap. Their analysis of 150 patients aged 1–59 months, who were hospitalised with SAM in a Delhi tertiary hospital, found that 26% had hypocalcaemia (<2·12 mmol/l), 65·3% had vitamin D deficiency (serum 25-(OH)D < 30 nmol/l) and 42% had clinical rickets. Importantly, hypocalcaemia occurred more commonly in patients with clinical rickets (OR = 6·6), suggesting an increased vulnerability in patients already displaying signs of decreased Ca and/or vitamin D reserve.

These results highlight a couple of significant outcomes of Ca and vitamin D deficiency. First, although rickets is common in many parts of the world[9,10], Smilie *et al.*[1] finding that 42% of their malnourished children had rickets is alarming. Furthermore, the fact that even more children had deficient circulating levels of vitamin D and Ca, the nutritional elements essential for bone health and the prevention of rickets, gives added reason for concern.

Rickets is the tip of the proverbial iceberg of otherwise hidden derangements in Ca and vitamin D homoeostasis. Rickets is clinically significant as it is associated with skeletal deformities, dental abnormalities, bone pain, muscle weakness, failure to thrive, developmental delay, hypocalcaemic seizures and, sometimes, even death from complications of hypocalcaemia[9–12]. Separate from renal disease and hereditary syndromes, *nutritional* rickets results from isolated and/or interacting deficiencies of Ca and vitamin D as adequate Ca is not delivered to, deposited in and maintained in bones[9,10,13].

The primary cause of rickets varies by location. In areas where children have limited sun exposure due to air pollution, shadows from urban buildings, indoor isolation or covered skin, vitamin D deficiency is a major cause of nutritional rickets. In other areas of plenteous sunshine, dietary insufficiency of Ca can cause rickets; such is the case in western India where a majority of 2–16-year-old school children ingest only about half the recommended daily Ca intake[14,15]. Everywhere, other factors such as maternal vitamin status and genetics can affect the risk of rickets. And, the need for vitamin D depends on Ca intake in ways that make higher-than-usual vitamin D levels protective of rickets in Ca-deprived children[13]. This combined with the data collected by *et al.*[1] suggests that there may be grounds for Ca supplementation.

Also, in addition to rickets, 26% of malnourished children with hypocalcaemia reported by Smilie *et al.*[1] highlights the acute risk of Ca and vitamin D deficiency. It is important to note that not all Ca-deprived children become hypocalcaemic. Ca-insufficient diets alone cause Ca deficiency which prompts a redistribution of body Ca from bone stores to keep the serum Ca level safe. When that homoeostatic response is overwhelmed in children with rickets, hypocalcaemia results with risks of sepsis, seizures and even death[9,16]. Hypocalcaemia is caused by either derailments in the homoeostatic control of Ca (i.e. hypoparathyroidism, renal failure, sepsis and vitamin D deficiency) or extreme Ca deficiency. Nonetheless, even some severely Ca-deficient individuals can maintain normal serum Ca levels due to complex homoeostatic regulation[16]. A re-analysis of 20+ year old data from Nigeria recently revealed that higher levels of vitamin D (>47·5 nmol/L) can overcome the risk of rickets in children with Ca-deficient diets[13]. The fact that the children studied by Smilie *et al.*[1] had such a high vulnerability to hypocalcaemia provides added support for nutritional supplementation.

The WHO malnutrition management guidelines have greatly reduced paediatric mortality and morbidity globally, and the guidelines already helpfully direct care for frequent comorbidities such as vitamin A deficiency and infections. Smilie *et al.*[1] have helpfully demonstrated that a large number of malnourished children are at risk of severe complications of Ca and vitamin D deficiency. Some details of current feeding recommendations might be 'broken', at least as related to children in areas of highly prevalent Ca insufficiency. Smilie's research, in addition to the growing body of knowledge on Ca and vitamin D deficiency, wisely prompts us all to consider 'fixing' our current malnutrition management so as to treat and prevent co-morbid deficiencies of Ca and vitamin D in order to prevent unnecessary morbidity and mortality. Specifically, at least in areas like India where Ca deficiency is highly prevalent, we should consider increasing the Ca content of therapeutic formulas and foods used in the management of malnutrition and we should consider vitamin D supplementation of malnourished children who do not have significant exposure to sunshine.

Acknowledgements

Acknowledgements: None. *Financial support:* None. *Conflicts of interest:* None. *Authorship:* P.R.F. conceived of this paper. M.A.W. and P.R.F. prepared and revised drafts and, together, approved the final manuscript. *Ethics of human subject participation*: Not applicable.

Micaela A Witte[1] and Philip R Fischer[2]

[1]Mayo Clinic Alix School of Medicine, Rochester 55905, Minnesota, USA

[2]Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester 55905, Minnesota, USA

References

1. Smilie C, Shah D, Batra P *et al.* (2020) Prevalence and predictors of hypocalcaemia in severe acute malnutrition. *Public Health Nutr* **23**, 3181–3186.
2. Management of severe acute malnutrition in infants and children (2018) https://www.who.int/elena/titles/full_recommendations/sam_management/en/ (accessed July 2020).
3. Kamat DM & Fischer PR (editors) (2015) *Textbook of Global Child Health*, 2nd ed. Elk Grove Village, Illinois: American Academy of Pediatrics.
4. Ruxin JN (1994) Magic bullet: the history of oral rehydration therapy. *Med Hist* **38**, 363–397.
5. Ofei SY & Fuchs GJ (2019) Principles and practice of oral rehydration. *Curr Gastroenterol Rep* **21**, 67.
6. Tickell KD & Denno DM (2016) Inpatient management of children with severe acute malnutrition: a review of WHO guidelines. *Bull World Health Organ* **94**, 642–651.
7. Hiffler L, Adamolekun B, Fischer PR *et al.* (2017) Thiamine content of F-75 therapeutic milk for complicated severe acute malnutrition: time for a change? *Annals NY Acad Sci* **1404**, 20–26.
8. Gehrig JL, Venkatesh S, Chang HW *et al.* (2019) Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science* **365.** doi: 10.1126/science.aau4732.
9. Munns CF, Shaw N, Kiely M *et al.* (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endo Metab* **101**, 394–415.
10. Creo AL, Thacher TD, Pettifor JM *et al.* (2016) Nutritional rickets around the world: an update. *Paediatr Int Child Health* **37**, 84–98.

https://doi.org/10.1017/S1368980020002499 Published online by Cambridge University Press

11. Creo AL, Tebben PJ, Fischer PR *et al.* (2018) Cardiac arrest in a vitamin D-deficient infant. *Global Pediatr Health* **5**. doi: 10.1177/2333794x18765064.
12. Aul AJ, Fischer PR, O'Grady JS *et al.* (2019) Population-based incidence of potentially life-threatening complications of hypocalcemia and the role of vitamin D deficiency. *J Pediatr* **211**, 98–104.
13. Thacher T, Sempos C, Durazo-Arvizu R *et al.* (2019) Serum 25-hydroxyvitamin D requirements to prevent rickets in Nigerian children on a calcium-deprived diet. *Bone* **7**, 170.
14. Ekbote VH, Khadilkar AV, Khadilkar VV *et al.* (2017) Dietary patterns with special reference to calcium intake in 2–16-year-old urban Western Indian children. *Indian J Public Health* **61**, 188–193.
15. Kadam NS, Chiplonkar SA, Khadilkar AV *et al.* (2011) Modifiable factors associated with low bone mineral content in underprivileged premenarchal Indian girls. *J Pediatr Endocrinol Metab* **24**, 975–981.
16. Kelly A & Levine MA (2011) Hypocalcemia in the critically ill patient. *J Intensive Care Med* **28**, 166–177.

Public Health Nutrition