Nutrition rehabilitation of children with severe acute malnutrition: Revisiting studies undertaken by the National Institute of Nutrition

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Severe acute malnutrition (SAM) in children under five years is an important public health problem due to associated high mortality and long-term health consequences. Research on the dietary causes of SAM, especially the role and relative importance of dietary protein, in the aetiology of oedematous malnutrition, has led to considerable debates and controversies. The present article revisits some of the debates in this field, where the researchers at the National Institute of Nutrition (NIN), Hyderabad, India, with their pioneering work, have contributed to the global literature on the various facets of the disease. Highlighting the importance of energy as a bigger problem than protein malnutrition is a noteworthy contribution of NIN's research. It is, however, important to examine the protein quality of the diets in light of the new information on the lysine requirements. The article argues that the currently dominating hypothesis of free radical theory requires a critical review of the supporting evidence. Over the past few decades, the research has focused on low-cost diets using locally available foods. The article also argues that solutions based on local foods, being acceptable and sustainable, need to be strengthened for their effective delivery through the existing nutrition programmes. Recent evidence shows that the use of ready-to-use therapeutic foods (RUTF) with high micronutrient density may be linked with higher mortality possibly due to the high iron content, which could be counterproductive. There are several unaddressed concerns regarding the potential long-term impact of consumption of RUTF in children with SAM. More evidence and a cautious approach are, therefore, needed before implementing these solutions.

Key words Adaptation - energy malnutrition - India - Kwashiorkor - marasmus - oedematous malnutrition - protein - ready-to-use therapeutic foods - severe acute malnutrition

Introduction

Severe acute malnutrition (SAM), defined as severe wasting [weight-for-height Z score <-3 based on World Health Organization (WHO) reference standard] and/or the presence of nutritional oedema, is a life-threatening condition which needs urgent attention and appropriate management to reduce mortality and promote recovery. India has a high prevalence of SAM, representing a huge burden, and intriguingly, the recent National Family Health Survey-4 indicates a higher prevalence of severe wasting (7.5%) compared to the previous report (6.4%).

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Over the last century, significant contributions have been made to the research on various aspects of severe life-threatening malnutrition in children that have been identified with different names such as protein-calorie malnutrition, protein-energy malnutrition (PEM), oedematous malnutrition, nutritional oedema, severe wasting or with names based on clinical manifestations such as marasmus, Kwashiorkor or Marasmic Kwashiorkor. The legendary British physiologist, John Conrad Waterlow’s early inventions of microbalances, his first impressions of fatty livers, his linking of the disease aetiology with deficiency of protein and calories and his foresight about protein requirements have placed our understanding of SAM on a sound footing. Gopalan and Srikantia, his contemporaries from NNIN, helped solve the major nutritional problems faced by the country during their time. Gopalan and Waterlow also have a common lineage working with Professor B.S. Platt and, despite their differences on certain issues, their mutual collaboration has greatly benefitted the progress of knowledge regarding the pathogenesis, prevention and management of SAM. However, what was once considered protein deficiency leading to Kwashiorkor and calorie deficiency leading to marasmus is now being considered as deficiency of Type I nutrients leading to Kwashiorkor and Type II nutrients leading to marasmus or wasting. Over the last century, research in this area has generated many theories, many controversies and, with it, many enigmas. It is important to review the evidence underlying these theories and reflect on the enigmas in the light of new information that has become available with advances in research in the past few decades. Srikantia discussed the adaptation theory proposed by Gopalan, which has now been largely superseded by the free radical theory by Golden and Ramdath. However, review of the information on the protein requirements in children and the controversies on some of the previous studies, suggests that the free radical theory could in fact be a flipped version of protein deficiency theory with serious flaws.

This article aims to review important research carried out to improve our understanding of the aetiology and management of SAM and its relevance to the global literature.

Prevalence of protein-energy malnutrition (PEM)/severe acute malnutrition (SAM)

A large volume of research in the first few decades of the 20th century dealt with Kwashiorkor or oedematous malnutrition, which had very high mortality with median case fatality rates of 20-30 per cent. Kwashiorkor, which means the ‘disease of the deposed child’ in the Ga language, was first reported by Williams in 1935. More than a decade later in 1947, Kwashiorkor was first reported from Assam in India as ‘malignant malnutrition’ by Hare. In 1948, a case series was published reporting a differential diagnosis of infantile pellagra. Kwashiorkor may have been reported under a different name much earlier in India, as early as 1931, as described by Lowe, who suggested pellagra-like condition of the skin among individuals suffering from leprosy. This was reported in 1942 by Wilson and Widdowson, where a similar disease (Kwashiorkor) was seen in rice-growing districts of south India. Some of the earlier cases treated as malignant malnutrition at the NNIN had case fatality rates of nearly 90 per cent (deaths/admissions: 9/10) with B-complex injections in 1948, but reduced to less than 10 per cent (deaths/admissions: 4/33) with skimmed milk in 1949 and were later reported as Kwashiorkor.

To assess the magnitude of the problem of PEM, the Nutrition Research Laboratories (NRL) in Coonoor (which was later shifted to Hyderabad and renamed as NNIN in 1958) carried out its first large-scale survey in 1955 in 10 areas of four southern States and found that the prevalence of Kwashiorkor was about 0.8 per cent (43 cases out of 4536 children). The lower prevalence of Kwashiorkor was considered to be due to the afflicted children being treated at various hospitals. Further, in 12 per cent of the siblings of the affected children, a history of Kwashiorkor was reported. In another community study by Gopalan during the similar period, the prevalence of Kwashiorkor was 1.3 per cent (23 cases out of 1800 children) and 2-3 per cent of children showed severe degree of emaciation and were considered as marasmus cases. Further, large-scale community-based surveys were done under the umbrella of National Nutrition Monitoring Bureau (NNMB), set up in 1975 at the NNIN, which carried out periodic surveys in rural areas till 2012. Fig. 1 shows the time trends in various nutritional deficiencies in under-5 children as per the NNMB repeat surveys in rural areas of 10 States in India over four decades. The prevalence of Kwashiorkor (based on clinical signs) decreased from 1.2 per cent in 1975-1979 to 0.8 per cent in 1996-1997 and further to near zero by 2011-2012. Similarly, marasmus rates decreased from 1.3 per cent to near zero and severe wasting reduced from 8.2 to 3.7 per cent from the first to the last survey (Fig. 1). Underweight and stunting, especially the severe forms, have also decreased substantially during the
above time period. The reduction in the moderate forms of undernutrition was relatively modest, possibly due to shift from severe-to-moderate and moderate-to-mild forms, with apparently low net effect on moderate undernutrition over this period. Figure 2 shows the number of cases since 1995 to 2015 at the Nutrition ward managed by NIN in a tertiary care hospital in Hyderabad. Of the total admissions during this period, 9 per cent of the cases were Kwashiorkor, 7.5 per cent were marasmic Kwashiorkor and 61 per cent were marasmus. During this time period, the overall mortality was 1.9 per cent. Of the total deaths, 16 per cent had Kwashiorkor, 11.3 per cent had marasmic Kwashiorkor and 54.5 per cent had marasmus.

While assessing the time trends over years, it is important to note that the standards for identification of SAM have changed over the years, and what has been

Fig. 1. Time trends in under-5 undernutrition and nutritional deficiencies from the baseline survey till the final repeat survey carried out by the National Nutrition Monitoring Bureau.23

Fig. 2. Time trends in admissions of various nutritional cases and mortality rates from 1995 to 2015 at nutrition ward (the nutrition ward is maintained by the National Institute of Nutrition in collaboration with the State Government of Telangana) in a tertiary care hospital in Hyderabad.
earlier considered moderate wasting using National Center for Health Statistics (NCHS) standards may in most cases be classified as severe wasting using the WHO growth reference standards \(24,25\) (Fig. 3), thus contributing to the seemingly increased prevalence estimates of SAM.

Aetiology of protein-energy malnutrition

Research on the dietary causes of Kwashiorkor and marasmus, especially the role and relative importance of dietary protein in the aetiology of oedematous malnutrition, has led to considerable debates and controversies. It was triggered by Gopalan’s work which demonstrated that the antecedent dietary intakes of children presenting with Kwashiorkor and marasmus were not significantly different from each other \(10\). In general, the dietary intakes of the study children were inadequate in calories but not in protein, and the rates of marasmus were twice as high as that of Kwashiorkor. These findings were confirmed in follow up studies on 300 children, among which seven children developed frank Kwashiorkor \(10\). Gopalan hypothesized that the primary reason for the development of Kwashiorkor or marasmus in a particular child was adaptation, whereby the integrity of liver was maintained in children with marasmus but not in those with Kwashiorkor. This work led to a substantial shift in the prevalent understanding of the relative magnitude of calorie and protein malnutrition by highlighting that calorie malnutrition was a much bigger problem than protein malnutrition. This also marked the beginning of the fall in the support for protein malnutrition, which McLaren later described as ‘the great protein fiasco’, quoting many of the studies carried out at the NIN \(26\).

There are, however, three important issues with the above approach of dietary assessment. First, the average dietary intakes may not be truly representative of the vulnerable segments of the population and the intakes have a wide variability within the same individual \(27\). Second, the estimates of adequacy of proteins and calories were based on recommended dietary allowances (RDAs) which have been constantly updated \(28\) and cannot be considered definitive for true adequacy. Moreover, the absence of quantitative or qualitative differences between the diets of children who developed Kwashiorkor or marasmus can be explained in terms of known individual variability in nutrient requirements. On intakes that are marginal in both energy and protein, those children with a relatively high energy requirement may become marasmic, whereas those with a high protein requirement may
present with Kwashiorkor. The above issues were pointed out by Waterlow, who showed that the best marker for protein deficiency was the protein-energy (PE) ratio and reduction in PE ratio was a better marker for understanding protein inadequacy of a calorie-sufficient diet. He further showed that in case of children in Uganda, where Kwashiorkor was more common than in Gambian children, the PE ratio of diets of children below the 10th centile was lower than the critical level of 5, which was much lower than the PE ratio of breast milk (7.2). This was not so in case of Gambian children. However, an important question is whether it is true for the cereal-based diets in India, where marasmic Kwashiorkor is more common than Kwashiorkor (discussed below). The third important issue pertains to the contribution of breastmilk to the dietary intakes of children less than two years which was not measured. There is considerable uncertainty regarding the estimated calorie and protein intakes of breastfed children, and the interpretation of dietary intakes has to be viewed with caution.

The newer RDA for protein set by the Indian Council of Medical Research (ICMR) in 2010 is considerably higher than before due to changes in the estimated lysine requirements (a rate-limiting amino acid for most cereals) from 12 to 30 mg/kg/day. The current recommended energy intake for infants is 80 kcal/kg/day. The PE ratios of Indian diets, therefore, have to be adjusted for the lysine score as well as for the protein digestibility [PE ratio adjusted for (Protein Digestibility-Corrected Amino Acid Score) PDCAAS]. Fig. 4 shows the PE ratios of commonly consumed cereals published in Indian Food Composition Tables, with and without adjusting for PDCAAS score for children aged 6-24 months. PE ratios were calculated based on average lysine requirements of 54.5 mg/g of protein for six (57 mg/g) to 24 month (52 mg/g) children, based on RDA guidelines by the ICMR. Protein digestibility was taken at 80 per cent for all cereals and millets except for wheat, which was taken at 90 per cent. While the unadjusted PE ratios were higher than the recommended level of 5.9, the adjusted PE ratios for many cereals, except wheat and barley, were lower than 5.9. This PE ratio may further decrease by the addition of vegetables, fats and sugars in case of diets that lack high-quality protein from animal source foods such as milk, eggs and meat. Thus, there is theoretical possibility of diets being deficient in protein and yet be adequate in calories in children from low socio-economic groups when the quality of protein is taken into consideration. It is also important to note that the protein requirements can increase by almost 20 per cent in children with infections, due to rise in acute-phase proteins. Metabolic adaptation, on the other hand, may decrease the requirements, although the extent of this adaptation is unclear.

The anecdotal evidence, as originally reported by Williams that Kwashiorkor was seen in elder sibling when a younger one was born was indicative.
of drastic lowering of PE ratio of diets with tapering of breastfeeding and reliance on starchy foods as observed by the Ghanian nurses. Similar studies reported from India and other countries have suggested the role of displaced breast milk due to working mothers, early weaning and starchy diets in the aetiology of Kwashiorkor. In some of the earlier studies carried out by the NIN in tea plantation areas, where the mothers of the children were at work, the prevalence of Kwashiorkor was high, and the authors reported a cereal-based diet with only a few breast milk feeds given to the younger child. Further epidemiological evidence suggested that Kwashiorkor was less common in the poor communities with occupations related to the production of animal source foods such as milk. The case series of Kwashiorkor reported from North America included children consuming diets that were low in quality protein such as rice milk. Cases of Kwashiorkor induced by dietary protein restriction due to perceived milk intolerance or food faddism have been reported in the US also.

Golden has argued that experimental animal models of induced Kwashiorkor do not exist and the protein-deficient diets given to the animals also lacked other nutrients such as zinc, thus questioning the role of protein deficiency as the sole aetiology of Kwashiorkor. Further, it has been said that the protein content of the diets given to the animals was too low (contributing to <3% of energy) to be consumed by children from poor households in developing countries. However, Kwashiorkor-like syndrome has been successfully reproduced in pigs, rats and monkeys with protein-deficient diets over a relatively short period of time. Some of the animal studies also used diets which were typically consumed by poor children in Africa and India, suggesting the causal role of diets consumed by low-income children in Kwashiorkor.

**Alternate hypotheses regarding the pathogenesis of Kwashiorkor and marasmus**

Many alternate hypotheses about the pathogenesis of Kwashiorkor and marasmus have been postulated. Of these, two hypotheses have gained special significance. The theory of adaptation states that children consuming diets deficient in proteins and calories may either develop marasmus or Kwashiorkor based on their adaptability. A child with a better adaptability preserves the structural and functional integrity of liver at the expense of less important organs such as muscle and skin, whereas a child lacking this adaptability develops Kwashiorkor. However, in some parts of the world, the mortality rates in children with marasmus were found to be higher or only slightly lower than those in children with Kwashiorkor, thus raising questions about the better adaptability in marasmus cases as per this theory. Further, the integrity of liver was found to vary with the severity of protein and calorie deficiency apart from the percentage of energy intakes contributed by fat. Animal studies have shown that on a low-protein, normal calorie diet typically consumed in low-income households, there was increased accumulation of fat in the periportal areas of liver. The deposited fat content was found to be as high as 50 per cent of the total weight of the liver and held a long-lasting impression with Waterlow. The reasons for increased fat accumulation in liver are unlikely to be due to the reduced synthesis of lipoprotein as has been suggested and more likely to be due to increase in the autophagy of peroxisomes and mitochondrial dysfunction due to protein deficiency. The accumulated fat was found to disappear after rehabilitation with protein-rich diets. In contrast, when given a low-protein, low-calorie diet, as is believed to be the aetiology of marasmus, the structural and functional integrity of liver was preserved without any fat accumulation. Thus, the development of marasmus or Kwashiorkor appears to be linked with environmental factors, in this case diet, rather than an individual’s ability of adaptation. Apart from the hepatic changes, skin and hair changes seen in Kwashiorkor are generally not seen in marasmus. The high turnover rates of skin and hair necessitate higher protein requirements. In Kwashiorkor, both qualitative and quantitative changes are seen in the skin, with less nitrogen as well as less collagen and hydroxyproline content. The crazy pavement dermatosis, typically seen in Kwashiorkor due to the inelasticity of skin, was found to reverse on a high-protein diet. Similarly, the hair changes linked with deficiency of important amino acids such as cysteine also reversed during nutrition rehabilitation, suggesting that majority of the changes in Kwashiorkor could be explained with the classical theory of protein deficiency.
radical production is linked to high iron stores and raised ferritin levels seen in Kwashiorkor. However, as Waterlow explained, the fatty liver produced by protein-deficient diet was entirely different from that produced from free radical damage due to peroxidation. Moreover, the high iron stores and raised ferritin levels seen in Kwashiorkor are also seen in marasmus and in many other conditions that do not produce Kwashiorkor. The high ferritin levels seen in Kwashiorkor may in fact be an effect of liver damage rather than its cause.

As per the free radical theory, absence of protective pathways leads to ineffective defence of the free radicals due to deficiencies of various micronutrients such as vitamins A and E and various biochemical pathways involving free radical scavenging. The theory states that the oedema seen in Kwashiorkor is due to vitamin E deficiency leading to the peroxidation of membranes in capillaries and renal cell membrane. However, deficiencies of the micronutrients and trace elements in Kwashiorkor are linked with low levels of albumin and other proteins that are transporters of many of the fat-soluble vitamins such as vitamins A and E and trace elements. Studies have also shown higher vitamin E levels in Kwashiorkor, and administration of vitamin E to children with marasmus and Kwashiorkor did not show any benefit in terms of duration of oedema or rate of weight gain. In a randomized controlled trial antioxidant therapy did not reduce the incidence of Kwashiorkor in children from Malawi. Glutathione levels, a central feature of the protective pathway, were found to be markedly reduced in Kwashiorkor compared to marasmus, but glutathione levels are reduced in protein deficiency and can be reversed by the supplementation of amino acid cysteine, thus suggesting a cause rather than effect. Further, protein-deficient diets in rats have been shown to increase oxidative stress. Thus, oxidative stress seen in Kwashiorkor may be the effect of protein deficiency rather than its cause. The free radical theory thus fails to explain many of the characteristic features seen in Kwashiorkor and could possibly be an effect of protein deficiency.

**Protein supplementation in the treatment of Kwashiorkor**

Studies from various centres across the world showed that milk-based diets, rich in high-quality protein, resulted in the cure of Kwashiorkor. Some earlier experiments have demonstrated initial recovery with balanced amino acid mixture and glucose. Studies at the NIN have also confirmed the cure of Kwashiorkor by the provision of milk-based and mixed protein-based diets. Studies were also carried out to ascertain the role of vegetable protein in the treatment of Kwashiorkor to make these diets affordable to the poor after discharge from the hospital as well as for community-level prevention of Kwashiorkor. Fig. 5 shows various studies conducted at the NIN facility to assess the impact of various milk and vegetable protein-based diets on reducing oedema and increasing serum albumin levels in children with oedematous malnutrition. In general, vegetable protein-based diets were inferior to the milk-based diets in terms of clearance of oedema and rise in serum albumin. However, mixed diets including vegetable and milk proteins were equally effective in terms of cure rates compared to milk protein alone.

Corroborative evidence for oedema reduction before the recovery of serum albumin was provided by animal studies carried out by Srikanthia. An experiment on six monkeys (Macaca radiata) demonstrated that serum albumin dropped from 4.1 to 3.5 g/dl within two weeks of feeding low-protein diet (case in 2.5%) and thereafter declined slowly to 2.3 g/dl till tenth week with plateau thereafter. Oedema developed in all the monkeys between 13th and 16th wk. When the monkeys were re-fed with standard 16 per cent protein diet, visible oedema disappeared in 8-12 days, but serum albumin rose to 2.8 g/dl even after four weeks of feeding. In the same study, ferritin appeared at 12th wk coinciding with the appearance of oedema and disappeared with the disappearance of oedema. The poor correlation of serum albumin with disappearance of oedema and extracellular fluid volume in the above studies led Srikanthia and other researchers with similar findings, to question the role of albumin in the aetiology of oedema in Kwashiorkor.

Further, Golden in his two studies showed that it was possible to correct oedema in children on low-protein (2.5% of energy from protein) diets and showed poor correlation between dietary protein and disappearance of oedema, thereby questioning the role of protein deficiency in the development of Kwashiorkor. However, this has been questioned by Coulthard based on careful re-examination of the evidence on the poor correlation of serum albumin with oedema. Moreover, as explained by Coward in great detail, to expect a good correlation between two variables, in this case albumin and colloid pressure, the relationship has to be linear for all range of values, which is not the case in Kwashiorkor. In children with...
a small amount of fluid filtered from the capillaries, increases to zero due to decreased protein in the interstitial space, which allows the normal pressure gradients to be maintained. This is best explained in case of congenital analbuminaemia, where the serum albumin levels are <1 g/dl, but only mild ankle oedema is seen. The reasons for disappearance of oedema before the correction of serum albumin are, however, complex. A closer look at the studies carried out at the NIN to test the impact of various diets (Fig. 6) revealed that the mean duration of oedema was lower in those children who had achieved the maximum increase in serum albumin. An inverse association between mean duration of oedema and serum albumin (r=-0.55, P<0.05) was also observed, suggesting that the rise in albumin may contribute to the clearance of oedema.

Kwashiorkor, Coward found the relationship between serum albumin and colloid pressure to be cubic, and therefore, the poor correlation between albumin and colloid pressure observed in the above studies can be explained by their non-linear relationship. Further, the normal negative interstitial pressure, which results in

![Graph 1](http://www.ijmr.org.in)

**Fig. 5.** Rise in serum albumin on day 30 in various studies from 1956 to 1974 at the nutrition ward. Blue colour represents diet based on vegetable protein and the red colour represents diet based on skimmed milk protein. X-axis represents the experimental group and the calorie and protein given in parenthesis. Due to large number of experimental groups (n=7) in 1964 study, it has been split in two parts (1964a and 1964b) for easy interpretation of the results. For the years 1956, 1960 and 1964a, calories and proteins are given as total per day, while in 1964b, 1968 and 1974, intakes are given per kilogram body weight per day. The methodologies on various papers have been mentioned elsewhere.

![Graph 2](http://www.ijmr.org.in)

**Fig. 6.** Scatter plot graph and linear regression with clearance of oedema in days as dependent variable and rise in albumin (g/dl) on day 10 as independent variable. All the data points of the Fig. 5 have been used for the analysis except for Group 3 in 1960 where there was a decrease in albumin. The methodologies on various papers have been mentioned elsewhere.

A small amount of fluid filtered from the capillaries, increases to zero due to decreased protein in the interstitial space, which allows the normal pressure gradients to be maintained. This is best explained in case of congenital analbuminaemia, where the serum albumin levels are <1 g/dl, but only mild ankle oedema is seen.

The reasons for disappearance of oedema before the correction of serum albumin are, however, complex. A closer look at the studies carried out at the NIN to test the impact of various diets (Fig. 6) revealed that the mean duration of oedema was lower in those children who had achieved the maximum increase in serum albumin. An inverse association between mean duration of oedema and serum albumin (r=-0.55, P<0.05) was also observed, suggesting that the rise in albumin may contribute to the clearance of oedema. Further, changes in total plasma colloid pressure are reflective of total albumin and total plasma volume. Serum albumin is a poor indicator of total albumin, as the rise in total circulating albumin has been shown to be twice than that in serum albumin due to simultaneous
increase in plasma volume\textsuperscript{60}. The rise in serum albumin in a study conducted in Jamaica by Golden \textit{et al}\textsuperscript{60} providing a diet with low protein (0.6 g/kg/day) and maintenance energy (=96 KCal/kg/day) was 0.3 g/dl lower than that of average rise in albumin found in studies at the NIN (0.5 g/dl)\textsuperscript{68}. This small study (n=12), although reported correlation of serum albumin with clearance of oedema, has not provided information on the correlation of clearance of oedema with the rate of change of albumin, which would have been helpful in understanding the role of increase in serum albumin in the reduction of oedema\textsuperscript{60}. In another study, Golden reported lack of correlation between protein intakes and rate of change of oedema\textsuperscript{77}. However, based on the reanalysis of the data and review of literature, Coulthard demonstrated that this was a mistaken conclusion\textsuperscript{83}.

**Type II nutrients: Potassium, magnesium, zinc**

Type II nutrients are those nutrients whose deficiencies cannot be measured and symptoms are not obvious\textsuperscript{81}. One such example is growth failure. The idea is that an individual can have normal concentrations of a nutrient such as zinc and yet be deficient in that nutrient as identified by growth failure; therefore, their requirements can only be understood through the therapeutic approach on optimal growth. However, this leads to an uncharted territory of the unknown, and such an approach may be dangerous as studies on supplementation of zinc, a Type II nutrient, started with an objective of improving the catch-up growth, particularly linear growth, in SAM children resulted in higher mortality rates with high-dose zinc\textsuperscript{82}. McCance \textit{et al}\textsuperscript{83} in the review of seven balance studies (including his study) on retention during recovery phase have shown a median retention of protein at 1.46 mg/kg (range 0.23-3.0 as calculated from nitrogen with a correction factor of 6.25), potassium retention at 1.2 mEq/kg (range 0.15-2.3) and magnesium retention at 0.6 mg/kg (range 0.22-2.47). This study also included other nutrients, presented as mean ± standard deviation such as retention of zinc at 0.8±0.4 mg/kg, copper at 0.02±0.04 mg, manganese at 0.04±0.03 mg and chromium at 9.0±60 mg. The retention rates of all the nutrients were much lower than the intakes in the studies and also the WHO recommendations for these nutrients. This approach provided a better picture of the tissue accretion rates than a blind therapeutic approach and associated problems.

Potassium plays a key role in the resolution of oedema, though its effects are less clear\textsuperscript{84}. Potassium levels are low in Kwashiorkor and marasmus, but when corrected for acidosis, potassium levels are much lower in Kwashiorkor and are also one of the reasons of apathy in these children\textsuperscript{85}. The low potassium levels are due to decrease in the number of cells, cellular organelle and also loss of functional capacity to pump sodium out and potassium in by energy-dependent sodium potassium ATPase mechanism\textsuperscript{86}. As a result, there is increased sodium and water retention in the cells and also a compensatory rise in sodium pumps\textsuperscript{87}. The cause of potassium deficiency is surprisingly less clear in these children. It is assumed that the deficiency is less likely to be due to dietary inadequacy, but may be due to gastrointestinal losses as malnourished children are relatively inefficient in retaining the potassium\textsuperscript{85}. The normal level of potassium content in the body is 45 mEq/kg body weight and level <35 mEq/kg has been considered to be potassium deficiency. When given at doses 2-4 mEq/kg, about 3-4 wk are taken for complete recovery. Alleyne has suggested three phases of recovery\textsuperscript{86}. In the first phase (5 days), the functional capacity improves, thereby correcting the true potassium deficiency. This is followed by the lag phase and the phase of rapid growth, where potassium is retained in the amount appropriate for deposition of new tissue. The diets based on locally produced foods are usually low in potassium, magnesium, zinc and other micronutrients, known to affect recovery in SAM and has been described elsewhere\textsuperscript{68}. The WHO recommends potassium supplementation with 2-4 mEq/kg/day for the first two weeks of rehabilitation\textsuperscript{25}.

**Catch-up growth and composition of weight gain**

After the initial stabilization phase when the metabolic machinery gets back to normalcy and oedema subsides, high-energy dense foods are recommended for rapid catch-up growth and the management is similar for oedematous and non-oedematous malnutrition\textsuperscript{25}. The most important limiting factor for promoting weight gain with the older milk-based diets was energy. Studies by Ashworth in Jamaica showed increased weight gain after increasing the energy content without increasing the protein content\textsuperscript{88}. Based on the seminal studies carried out in Jamaica and elsewhere, calorie intakes of 160-220 kcal/kg/day and protein intakes of 2-4 g/kg/day have been recommended during nutrition rehabilitation phase by the WHO\textsuperscript{25}. Studies carried out at the NIN have also shown that the mixed protein diets providing about 200 kcal/kg/day energy and 4-6 g/kg/day of protein were associated with the highest rate of weight gain\textsuperscript{70}.
Analysis of the data based on the catch-up growth of 309 children admitted at the NIN during 2001-2005 showed that the average rate of weight gain was about 6 g/kg/day. Relatively lower rates of weight gain observed in this study could be due to multiple factors such as frequent morbidities in hospitalized children, reducing the weight gain by almost about 40 per cent; admission of moderately wasted children (due to being at high risk of SAM) and lower intake of potassium, magnesium, etc, and have been discussed elsewhere. Studies at various Nutritional Rehabilitation Centres (NRCs) have shown rates of weight gain in the range of about 5-10 g/kg/day. Due to concerns about disproportionately higher amounts of body fat deposition during rapid weight gain of children recovering from SAM, a study at our ward examined the composition of weight gain during nutrition rehabilitation in 80 children (aged 6-60 months). Overall, the average rate of weight gain was 6.1 g/kg/day (total weight gain of about 1.09 kg in one month) and fat mass contributed to about 40 per cent of the weight gain. The children with most severe wasting had significantly higher weight gain and higher fat-free mass gain, probably in an attempt to recover the lost tissue. On the other hand, the fat mass gain did not differ in relation to the rate of weight gain or baseline severity of wasting, demonstrating that it is possible to achieve rapid weight gain with recovery of the lost tissue in severely malnourished children with diets based on local foods.

Community-based management of severe acute malnutrition

An important problem with facility-based nutrition rehabilitation is the high default rates, mainly because families find it difficult to stay away from their homes for longer periods due to economic and other constraints. In community- or home-based management of children with uncomplicated SAM, an estimated 85 per cent of the total cases can lead to recovery rates similar to that of facility-based management and are better accepted by the community at large.

Most of the studies on community-based nutrition rehabilitation, mainly conducted in Africa, have used centrally or locally produced ready-to-use therapeutic foods (RUTFs) and other locally produced nutrient-dense foods. A Cochrane review in 2013 has concluded that RUTF may improve recovery slightly (risk ratio 1.32; 95% CI 1.16-1.50; based on low-quality evidence), but it is unclear whether RUTF improves relapse, mortality or weight gain. In a small study conducted at our centre, when rates of weight gain of children receiving RUTF and those receiving local foods were compared, it was observed that the weight gains were higher in the RUTF group than that of the other group only for the first two weeks, but in later weeks, the rates of weight gain were similar in the two groups. It is likely that the nutrients which were replete by the use of RUTF in the first two weeks may not have been limiting during the latter part of the catch up.

Of particular interest in this regard is an Indian study by Bhandari et al which compared (n=906) the efficacy of centrally produced RUTF (RUTF-C), locally prepared RUTF (RUTF-L) and micronutrient-enriched (augmented) energy-dense home-prepared foods (A-HPF) for home-based management of uncomplicated SAM. The intervention lasted for 16 wk, followed by 16 wk of sustenance by linking with the existing programmes. At the end of 16 wk period, the recovery rates with RUTF-L, RUTF-C and A-HPF group were 56.9, 47.5 and 42.8 per cent, respectively. Group receiving RUTF-L had significantly higher rate of weight gain than A-HPF, and time to recovery was shorter in both the RUTF groups, suggesting the higher efficacy of RUTF compared to micronutrient-enriched home-based diets. However, as early as 16 wk after the end of the treatment phase, there was a relapse in many of the children and the recovery rates in the RUTF-L, RUTF-C and A-HPF groups were 17.3, 12.1 and 14.6 per cent, respectively, and were not significantly different from each other. This is an important finding of the study and raises questions about the sustainability of community-based nutrition rehabilitation programmes using RUTFs and other nutrient-dense foods and highlights that the projected benefits of community-based management using these solutions are most likely overestimated. The case fatality rates in the three groups also show intriguing trends. During the total period of 32 wk of intervention and sustenance, five children from the two RUTF groups died, but no mortality was reported in the group receiving home-based foods. The likely reasons for higher mortality rates in the groups that received RUTFs need further exploration. Moreover, about 10 per cent of children in all the groups were hospitalized for various reasons, >40 per cent of children had an episode of diarrhoea and about 70 per cent had an episode of fever during the study. In another randomized controlled trial, where the iron content of RUTFs was increased compared to the standard RUTF, there was a rise in haemoglobin, but the mortality...
rates were almost twice as compared to the standard RUTF\textsuperscript{97}. It is likely that the high iron content in RUTF may have resulted in increased infections and mortality. Micronutrient supplements with iron are known to increase the risk of inflammation and infections as iron is also an indispensable nutrient for many pathogenic bacteria in the gut\textsuperscript{98}.

Several other concerns have been raised regarding the potential long-term impact of consumption of RUTF in children with SAM including alteration of epigenome and associated metabolic functions, gut microbiome and body composition that are not adequately examined and are currently not well understood\textsuperscript{99}. Studies assessing the cost-benefit ratios of RUTFs versus local foods should also assess costs related to the displacement of resources from other long-term strategies for improving nutrition such as nutrition-sensitive agriculture and social and behavioural changes\textsuperscript{99}. The above concerns also need to be examined in the background of an observational study conducted in Meerut, Uttar Pradesh\textsuperscript{96}, which evaluated survival and recovery of children with SAM without the existing community-based management programme (n=409) and showed that, after median duration of follow up of 7.4 months, the case fatality was 1.2 per cent and spontaneous recovery occurred in about 31 per cent of children\textsuperscript{96}. The authors speculated that the benefits of investing in community-based management of severe wasting in India are considerably overestimated.

**Future research and way forward**

The WHO guidelines for the management of SAM children are based on extensive studies carried out by various centres across the world that helped advancing the knowledge regarding the disease pathogenesis and its management. However, only one-third of the recommendations in these guidelines were supported by the results of directly relevant research (intervention or observational studies), whereas almost half of the recommendations were based on expert opinion, unsupported by published evidence\textsuperscript{100}. Although the recommendations based on expert opinion are not necessarily incorrect, need for further epidemiological and clinical research cannot be overemphasized to improve treatment outcomes in a large number of children with SAM that continue to get admitted in tertiary care hospitals. Tackling the problem of high defaulter rates and strengthening linkages with the existing health and nutrition programmes are especially important.

The newer ICMR\textsuperscript{30} and WHO\textsuperscript{12} guidelines on the requirements of protein re-emphasize the importance of protein quality in line with the studies carried out by the NIN in the early years of its existence\textsuperscript{23}. Improvement in protein quality of supplements provided in the nutrition programmes, by taking due care of the PE ratio adjusted for PDCAAS, is therefore needed.

Uncomplicated SAM is an extension of moderate wasting and may be treated as a continuum of the same disease. Compared to RUTF, locally available nutrient-dense foods offer advantages of lower cost, wider acceptability and availability; the existing programmes in the country such as Integrated Child Development Services, therefore, need to be strengthened for effective delivery of nutrient-dense local foods to the children with uncomplicated SAM. Further research is needed to better understand the long-term impact of RUTF consumption on metabolic functions and body composition of children with SAM. Moreover, careful studies estimating the cost-benefit ratios of RUTFs versus local foods are needed to inform policy.

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