Protein-energy malnutrition
Vitamin deficiency
Mineral deficiency
Iron deficiency

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Correlation between Protein-Energy Malnutrition and Vitamin-Mineral Deficiencies in the Young

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Summary: Protein-energy malnutrition (PEM) is a nutritional syndrome, affecting mostly young children, characterized by a deficit in protein and energy. PEM is almost always accompanied by deficiencies of vitamins and minerals. These can be due to either a low dietary intake, or secondarily to PEM, or a combination of both factors. Infections may also be another contributing factor. However, the vitamin and mineral deficiencies in severe PEM are masked by the predominant protein-energy deficit and by a decreased nutritional need for these micronutrients. During recovery from PEM the nutritional requirements of vitamins and minerals become greater in order to cope with the increase in tissue synthesis and lean body mass. Therefore, if these micronutrients are not available, their corresponding deficiencies become apparent. To illustrate these points, deficiencies of vitamin A and iron in PEM are discussed in detail as typical models. It is shown that severe PEM can alter the biological utilization and function of these particular nutrients. Considerations are also made in regard to the management of vitamin A and iron nutriture in the treatment of mild-to-moderate PEM using enriched diets.

Introduction

Protein-energy malnutrition (PEM) is a nutritional syndrome characterized by a deficit in protein and energy. Most commonly it is the result of an inadequate diet, in terms of quantity and quality, which does not provide sufficient protein and energy to meet the body's need for normal function, growth and development.

The intensity of this protein-energy deficit can be only mild. When this is

the case, the condition is known as mild-to-moderate malnutrition and its most salient feature is a lower weight for height in comparison with pre-established standards for a normal well-nourished population. In some instances, however, the deficit can be so marked that it constitutes a true clinical entity known in general as severe PEM. More specifically, when the energy deficit predominates it is called marasmus and when the main deficit is of protein it is called kwashiorkor. Certainly, there are some kwashiorkor cases due solely to protein deficiency.

PEM of various degrees can be found at all ages but it occurs most frequently in young children [1]. The higher prevalence in this group can be related to their dietary habits, anorexia caused by frequent infectious episodes and often to their limited gastric capacity for ingesting food in amounts capable of providing sufficient protein and energy. This latter constraint becomes critical particularly when the diet is of low caloric density and contains poor quality protein. Unfortunately this is the most common type of diet fed to children in the developing world.

In adults, severe PEM is rare and usually of secondary origin. In most cases it is related to a malabsorption syndrome or to any other disease which interferes with food utilization. In this group, mild-to-moderate PEM is most frequent.

Severe PEM is almost always accompanied by vitamin and mineral deficiencies [2]. Their clinical or even biochemical consequences, however, are usually overshadowed by the predominant protein-energy deficit, accompanied by a secondary decrease in nutritional requirements [3]. Upon nutritional treatment, however, there is an increase in tissue synthesis and in absolute lean body mass, that result in a greater demand for micronutrients. Under these circumstances, i.e. if these micronutrients are not available, a true vitamin or mineral deficiency may develop.

Etiology of vitamin-mineral deficiencies in severe PEM

Numerous vitamin and mineral deficiencies have been reported to be associated with severe PEM. Among them, vitamins A [4], E [2], B_1 [2], Niacin [2], folates [5], B_{12} [6] and minerals such as K [7], Fe [8], Zn [9], Cu [8], Mg [10], Ca [11], and Se [12].

The etiology of these deficiencies, however, can be classified in two categories as follows:

a) Primary deficiencies due to a low dietary intake of particular nutrients

These are normally epidemiologically associated with the nutritional deficiencies prevalent in the region. For example, in Thailand, thiamine and riboflavin deficiencies are highly prevalent in the general population, thus most children with severe PEM also present the same nutritional deficiencies [13]. This is not the case in Central American children suffering from severe PEM, whose most common vitamin and mineral deficiencies are those of vitamin A [4] and iron [14]. Nutrition surveys in this geographic region have also revealed a wide-spread dietary deficit of these nutrients [15].

b) Secondary deficiencies due to the physiologic and metabolic alterations of severe PEM

In this instance the dietary intake of micronutrients may be adequate but their utilization and normal metabolism are impaired. For example, severe PEM interferes with a proper intestinal absorption of vitamin A [16] and B_{12} [6]. It may also impair the plasma transport of nutrients, especially those carried by specific plasma proteins such as retinol [17], iron [18], and copper [8]. Severe PEM is also accompanied by an increased loss of body potassium [19]. The potassium losses are partly due to a decrease in lean body mass but mainly to a tissue desaturation of potassium which decreases significantly the intracellular concentration of this ion [7].

If these nutrients affected secondarily by severe PEM are also ingested in limited amounts, the micronutrient deficiency becomes more critical. That is, the two above categories are not mutually exclusive. Furthermore, the overall situation is additionally affected by environmental factors particularly in areas of poor sanitation. Bacterial and parasite infections, especially of the gastrointestinal tract, are common features of children with PEM. In this context, it has been established for example that in severe PEM diarrhea is the main cause of Mg losses which lead to its nutritional deficiency [10]. Similarly, giardiasis and ascariasis [20] as well as salmonellosis [21] are known to impair the intestinal absorption of vitamin A. Furthermore, infections in general can also lower the circulating concentration of nutrients such as retinol [22] and iron [23].

A final consideration may also be the decreased demand for some nutrients in PEM. For example, since hemoglobin needs are related to the oxygen needs of active cell mass [14], in severe PEM with decreased lean body mass, the nutritional need for folates is low and folate levels can be lower than normal [5].

The scope of this presentation does not permit to refer in detail to each one

of the nutrient deficiencies encountered in PEM. Therefore, only the deficiencies of vitamin A and iron will be discussed in depth as typical models. The data that will be presented come mainly from studies conducted at INCAP in children suffering from PEM.

Vitamin A deficiency in severe PEM

Table I shows the serum retinol levels of children with kwashiorkor before and after their recovery. For comparison, the average retinol level of a general population of Guatemalan children [24] has been included. It is clear from these data that in severe PEM, the levels of retinol are significantly lower than those found in normal Guatemalan children.

Tab. I: Serum retinol levels in kwashiorkor

	Kwashiorkor (n = 9)*		Normal population**
	Upon admission	After recovery	
Retinol (μg/dl)	12.8	34.1	30.5

* From SCRIMSHAW *et al.* (2)
** From ARROYAVE *et al.* (16)

Several considerations can be made to explain these low retinol levels. Let us first consider the influence of the diet. It has been amply documented that in Central America, the dietary intake of vitamin A from natural sources is low, particularly in rural children [15, 24]. In addition a great portion of the total vitamin A content of the diet comes from carotenoids which even under normal conditions are known to be poorly absorbed and converted to retinol [25]. Dietary fat in rural regions is also limited to 5–15% [15]. All these dietary factors contribute to a poor vitamin A nutritional status that can be reflected by low serum retinol levels. Thus the low serum levels of retinol in Central American children suffering from severe PEM could be partially explained on these bases, that is due to a primary cause. If we now examine the intestinal absorption of vitamin A we find that in severe PEM the absorption of this vitamin is drastically impaired [16]. Figure 1 shows the response in serum levels of retinol after a single oral dose of 75 000 μg of fat soluble vitamin A, given to children suffering from severe PEM on admission and again after 5 days of PEM treatment. There was no absorption of the vitamin on admission to the hospital but adequate absorption was restored shortly after initiation of successful dietary treatment of the patients.

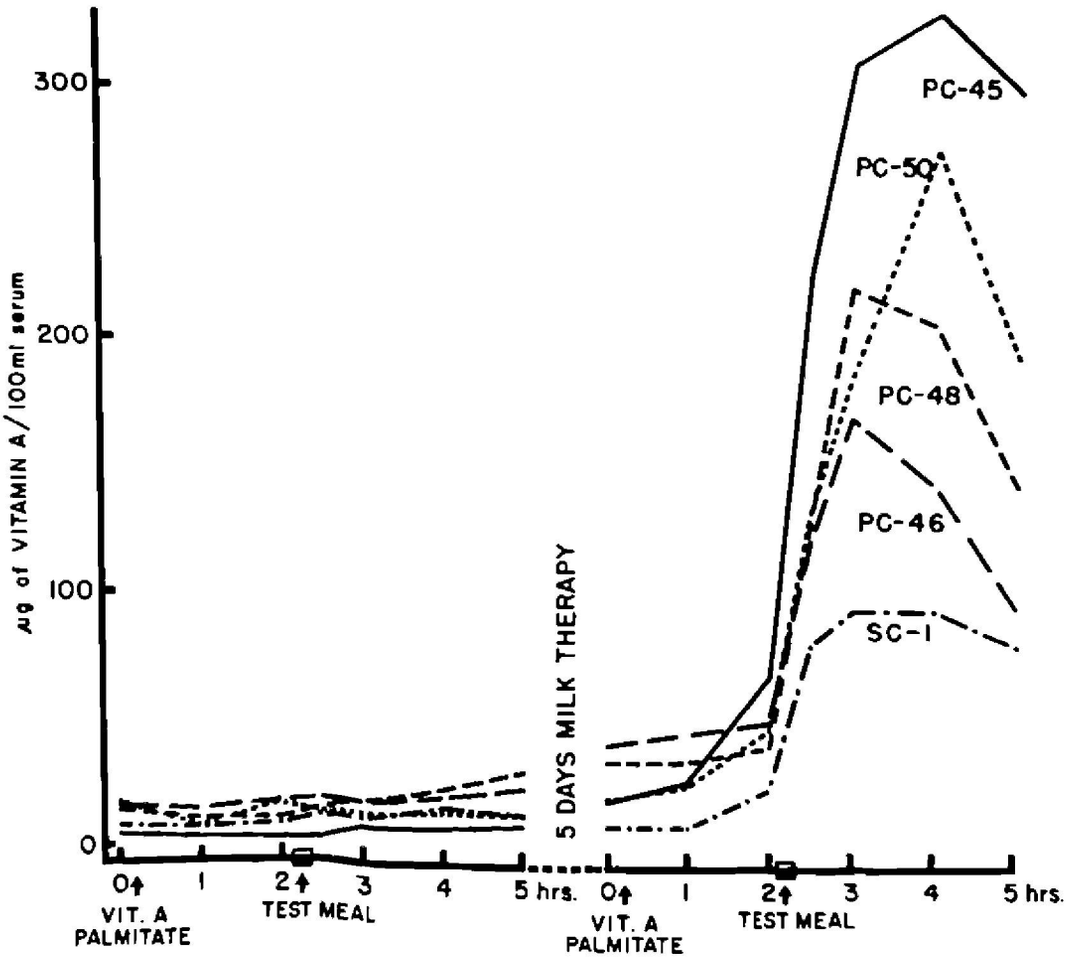

Fig. 1: Response to total vitamin A palmitate in children with kwashiorkor before and after five days of therapy. After 21 h of electrolyte therapy children hospitalized for kwashiorkor were given 75 000 µg of vitamin A as palmitate orally followed by a glass of either skimmed milk or corn-starch gruel two hours later. Blood samples for vitamin A analysis were taken at the intervals indicated and the entire test repeated after five days of intensive therapy based on the administration of adequate quantities of half skimmed milk. (From ARROYAVE *et al.* [16].)

This failure to absorb vitamin A is mainly related to the fact that in severely malnourished children there is a low output of conjugated bile acids which impairs micellar formation and thus also the absorption of fat [26]. Furthermore, a decreased hydrolytic activity for retinyl esters has been also documented in the protein deficient chick [27]. Vitamin A absorption is further impaired if PEM is accompanied by gastrointestinal infections [20–21].

A direct impairement of vitamin A blood transport has been implicated as contributing to deficiency of the vitamin in PEM. This phenomenon has been related to a decrease in plasma levels of retinol binding protein (RBP) [28].

MUHILAL and GLOVER [29] have shown the effect of the quantity and quality of dietary protein on plasma RBP levels in an elegant experiment. In this experiment, weanling rats were fed for a period of 5 weeks diets containing different levels of soybean and rice proteins. The effect of supplementing the rice protein with their limiting amino acid lysine was also tested. The results are presented in Table II. It can be seen that the group of animals fed the diet con-

Tab. II: Effect of amount and quality of dietary protein on plasma RBP levels in the rat*

Group**	Protein (g/kg diet)	Total plasma protein (g/d)	Plasma RBP (μg/ml)
L	Soybean 200	6.4 ± 0.05***	26.0 ± 0.4
N	Soybean 50	5.4 ± 0.07	22.0 ± 2.0
P	Rice 50	4.7 ± 0.08	16.3 ± 0.6
R	Rice 50 + lysine	5.0 ± 0.15	20.0 ± 2.0

* Adapted from MUHILAL and GLOVER [29].
** The diets in these groups contained vitamin A at a level of 3 mg/kg.
*** $\bar{x} \pm$ S.D.

taining the low soybean protein level (50 g/kg/diet), had significantly lower levels of plasma RBP than those animals fed the higher level of the same protein (200 g/kg diet). Even more striking is the effect on plasma RBP levels when the animals were fed the rice protein. Their RBP levels were 16.3 ± 06 μg/ml as compared to the level of 22.0 ± 2.0 μg/ml encountered in the group fed the same level of the higher quality soybean protein. When lysine was added to the rice protein, however, the RBP levels improved significantly approaching those found in the rats receiving 50 g/kg diet of soybean protein. It is interesting to see in retrospect that even before the identification of RBP as a plasma carrier of retinol [30], the work performed at INCAP by ARROYAVE *et al.* [4] had shown that nutritional treatment of severe PEM with a protein rich diet without supplementary vitamin A, produced not only the expected increase in serum proteins but also a rapid initial significant rise in serum retinol. These results are presented in Figure 2. It was concluded from this experiment that even when severe PEM patients had moderate amounts of vitamin A in liver stores, its mobilization into the circulation was impaired. We now know that this initial rise in serum retinol with protein treatment is due to an increased synthesis of RBP produced by the improvement in the protein nutritional condition of the children [31].

The observations of SMITH *et al.* [28] clearly confirm the protein-RBP-retinol interrelation just discussed. In conclusion, the retinol transport from the liver to the tissues is also impaired in severe PEM.

Figure 2 also illustrates another important phenomenon which occurs upon treatment of PEM in relation to the nutritional needs for micronutrients. Nutritional treatment of PEM re-activates anabolic activity, as shown by the rise in total serum proteins, with a resulting increase in lean body mass and growth. Under these circumstances the demand for vitamin A is suddenly increased and the usually meager vitamin A stores are rapidly used up. It can be

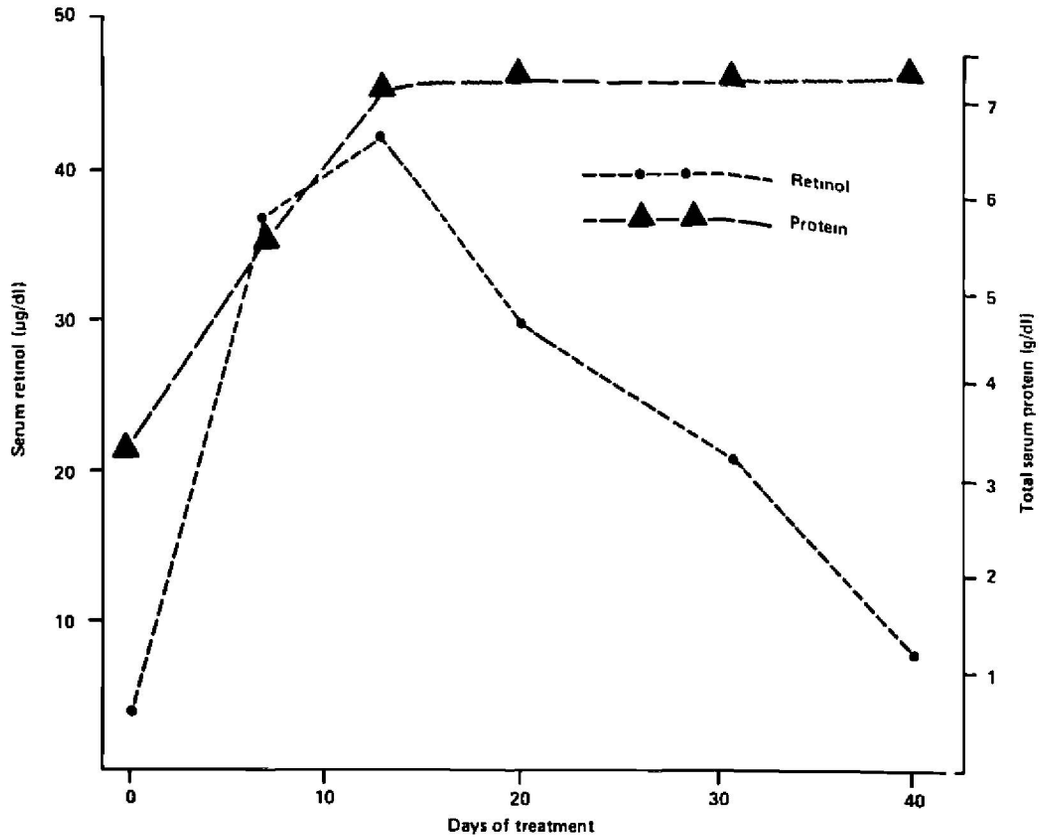

Fig. 2: Serum levels of retinol and total proteins during treatment of severe protein-energy malnutrition (PEM) (From ARROYAVE et al. [4]).

observed in the graph that although there was an initial rise in serum retinol levels this was followed by their gradual drop, reaching again a deficient level. This important demonstration implies that if the vitamin is not provided, clinical deficiency of the vitamin may develop. Therefore, it became mandatory in INCAP's clinical center to provide large supplementary vitamin A doses to children under PEM treatment. They are given a single oral dose of 50 000 IU of a water-dispersive vitamin A preparation at the beginning of their treatment. This relatively large dose is followed by additional smaller daily doses of 5000 IU until full nutritional recovery is attained.

Iron deficiency in severe PEM

Table III shows data obtained by ARAYA [32] in a study aimed to investigate the iron metabolism during the nutritional recovery of the undernourished rat. In this experiment, the animals were made severely undernourished by feeding them for 35 days a protein deficient diet. Some of these animals were sacrified and the non-heme iron concentration was determined in plasma, liver and bone marrow. The rest of them were re-fed for 30 additional days with a 10 NDpCal% (Net dietary protein as percent of calories) casein diet and the same parameters were determined. The results obtained from both

groups were compared with a control group of animals of the same age, fed at all times a complete diet, and therefore had never been undernourished. All the diets in the experiment contained iron at a level of 85 μg/kg. In comparison with the casein re-fed and control groups it was clear that the undernourished animals had low plasma iron, a high concentration of iron in the liver and a low amount of bone marrow iron. It was concluded from these data, that in protein-energy deficiency iron accumulates abnormally in the depots, and that during nutritional recovery iron is mobilized thus becoming available to the bone marrow for hematopoiesis.

Tab. III: Non-heme iron in plasma, liver and bone marrow in the undernourished rat*

Group	Iron in:		
	Plasma (μg/dl	Liver (μg/g W.T.)	Bone marrow (μg/g)
Undernourished	64 ± 4.9**	325.1 ± 23.9	0.125 ± 0.02
Casein Re-fed (10 NDp Cal%)	88 ± 12.9	105.1 ± 19.8	0.137 ± 0.04
Control	204 ± 15.8	120.6 ± 24.6	0.250 ± 0.05

* Adapted from ARAYA, J. [32].
** $\bar{x} \pm$ S.D.

Children suffering from severe PEM always have serum iron levels lower than normal and usually present sub-normal concentration of blood hemoglobin [8, 14]. In contrast, their body iron stores vary widely from almost absent to elevated amounts [14, 33]. This variation in the amount of stored iron is undoubtedly related to their previous dietary iron intake.

Table IV shows the iron biochemical characteristics of a group of severely undernourished children recently studied in INCAP's clinical center. Upon admission, they had a great variation in the amount of stored iron as determined by serum levels of ferritin. Based on this, they were classified into two categories; those with ferritin levels less than 30 ng/ml (group A) and those with levels greater than 30 ng/ml (group B). The data indicate that group B has on the average a much greater amount of stored iron than a normal population of the same age [34]. Both undernourished groups, however, regardless of their amount of stored iron, have a low concentration of serum iron. Their levels of total iron binding capacity (TIBC) are also significantly lower than normal, indicating that transferrin is low. Low transferrin levels is a common feature of severe PEM [18], and this may be a factor determining impaired iron mobilization. This phenomenon, together with the fact that in

severe PEM there is a decreased iron need for hematopoiesis [14] explains the accumulation of stored iron in severe PEM. It can also be noticed that the percent transferrin saturation (% ST) is higher than normal in spite of the low serum iron concentration. This phenomenon is related to the low transferrin levels of severe PEM. Some PEM patients have occassionally been observed at INCAP's clinical center with % ST near 100% [14].

Tab. IV: Stored iron and other biochemical characteristics of children with severe PEM

	Group A (n = 13)	Group B (n = 13)	Normal average*
Serum ferritin (ng/ml)	12 ± 2**	86 ± 9***	30
Serum iron (µg/dl)	40 ± 6	63 ± 5***	71
TIBC (µg/dl)	195 ± 30	115 ± 9***	318
% ST	28 ± 6	57 ± 5***	23
Hemoglobin (g/dl)	9.8 ± 0.5	9.3 ± 0.3	12.8

* From VITERI *et al.* [14]; except serum ferritin from SIIMES *et al.* (34)
** $\bar{x} \pm$ S.E.
*** $P < 0.05$ or better.

Despite their significantly different levels of stored iron, the children in both groups had equal hemoglobin levels, but lower than normal children. This points out the impaired iron utilization in severe PEM.

The children in this study were then given nutritional treatment for 90 days. To cope with the increased iron requirement during recovery, they were administered an iron supplement of 300 mg/day of ferrous sulphate. This is done routinely, especially, to protect those children with initially low iron reserves. In spite of the iron supplement, the serum ferritin levels decreased gradually in those children with initially high iron reserves as treatment progressed (Fig. 3). The intestinal absorption of iron is known to be markedly inhibited by high iron stores. Therefore, the children in this group (B) must have utilized the supplement very poorly. Consequently, the drop in ferritin must be reflecting the mobilization of the stored iron to meet the enhanced iron needs as recovery ensues. It is logical to assume that the important effect of the iron supplement in this case was to prevent a depletion of iron reserves beyond adequate levels as shown in the figure. On the other hand, the intestinal absorption of iron would be expected to be high in the group of children with initially low stores (A). The change observed in the serum ferritin values in this group demonstrates the marked utilization and therapeutic value of the iron supplement under these conditions. Although there was a

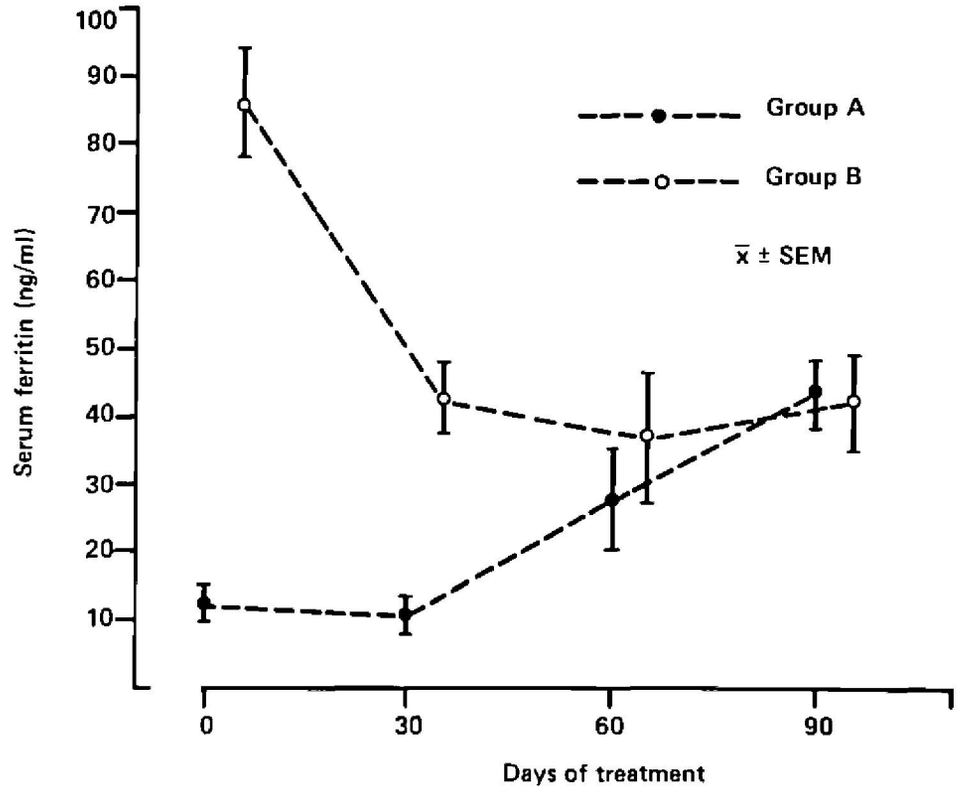

Fig. 3: Change in body iron stores during treatment of severe protein-energy malnutrition (PEM); includes supplementation of 300 mg ferrous sulphate per day.

slight tendency of the ferritin levels to decrease in the first 30 days, they increased significantly thereafter until reaching the level attained by the children in the other group. At the end of this study all the children had a complete PEM and hematopoietic recovery.

In practical terms, what we have discussed indicates that children suffering from PEM require an adequate diet for proper iron utilization and normal hematopoiesis. Figure 4 further illustrates this point. It shows the results obtained in a typical case of a child with PEM who upon admission was given iron and folates and there was no response in terms of reticulocyte production. It was not until treatment with a high protein-calorie diet started and the child's lean body mass increased (as indicated by the creatinine height index), that the response to hematinics was appropriate as shown by the marked rise in reticulocyte index and the increase in total circulating hemoglobin.

Management of vitamin A and iron nutriture during treatment of mild-to-moderate PEM

The largest portion of undernourished children in the general population are those suffering from mild-to-moderate PEM. These children may not have clinical deficiencies of vitamins and minerals but their nutritional status in

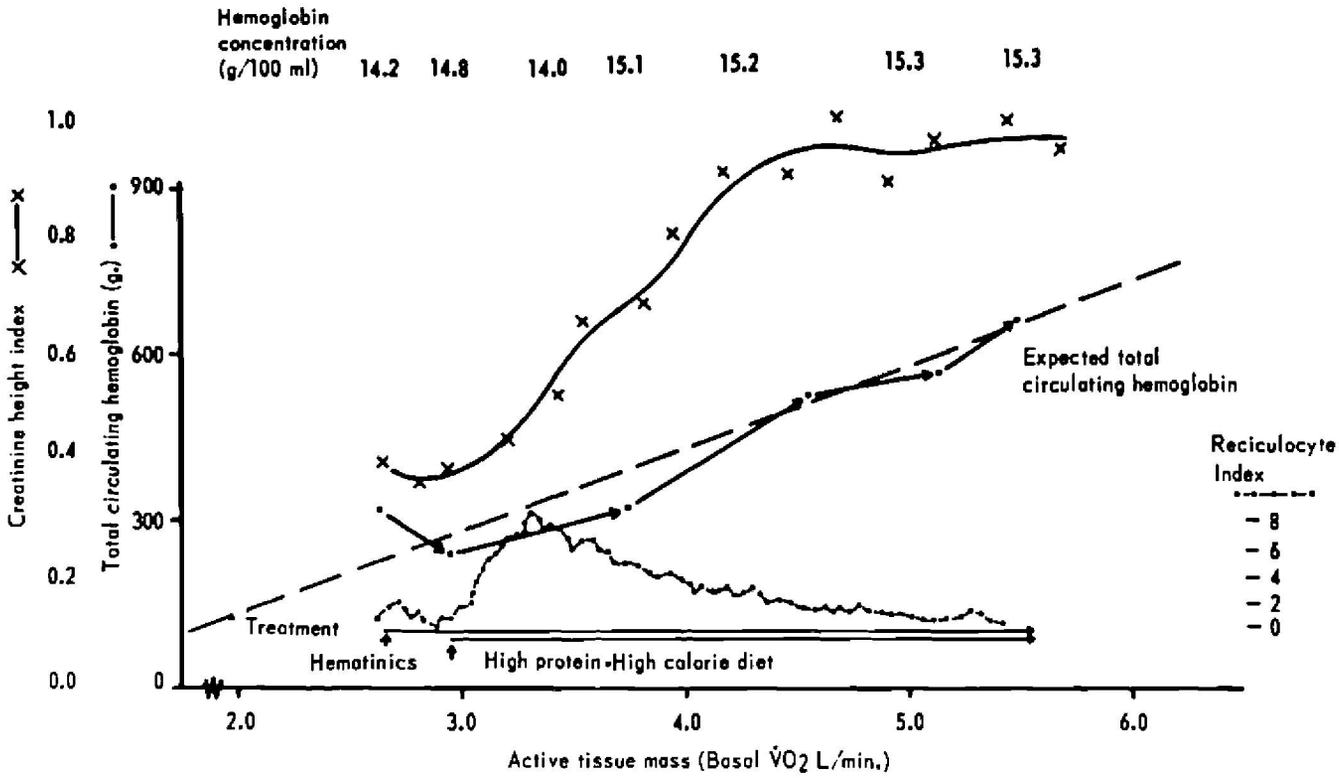

Fig. 4: Hematological and active tissue mass changes in a child with severe protein-energy malnutrition (PEM) and during nutritional recovery.

relation to these micronutrients is usually marginal. Therefore, sufficient amounts of vitamins and minerals should also be given to children treated for mild-to-moderate PEM, particularly those micronutrients known to be limited in the region's customary diet. Under these circumstances, a good intake of some vitamins and minerals can be attained through foods with a natural abundace of these nutrients. Others may be provided using enriched diets without necessarily using pharmaceutical preparations.

In a recent study at INCAP [35] 13 children aged 15–40 months with chronic mild-to-moderate PEM were admitted to our clinical center. They were apparently healthy but underweight for their height in comparison with the 50th percentile of the Boston standards. The main objective of the study was to determine whether a diet based on traditional foods would satisfy the nutritional needs and promote adequate catch-up growth of the children.

For this purpose, they were fed for approximately 90 days with a diet based primarily on corn, beans, bread and some regional fruits and vegetables. Small amounts of egg and meat were given once a week, and 100 ml of milk were fed three times weekly. This diet was similar to that consumed by the children for at least two months prior to admission. Since the overall content of vitamin A and bio-available iron of this dietary regimen was relatively low, the table sugar used for the preparation of food and beverages was enriched with vitamin A (15 μg/g) and NaFe EDTA (0.13 mg Fe/g). No other vitamin

or mineral supplement was given. Prior to admission, the children had consumed sugar enriched with vitamin A only.

This enriched sugar was used in relatively large amounts in order to help to improve the overall energy density of the diet. Thus, the sugar intake was on the average 198 g/day, in contrast to the 40–45 g/day usually consumed by children from the general population. Some of the results obtained with this treatment are presented in Table V. At the end of the study period there was a significant increase in weight for height from an average of 89 to 95 % of their expected weight for height value, indicating that nutritional recovery was attained. In spite of the experienced growth and probably increased demand of vitamin A, the serum levels of retinol remained normal. Serum ferritin, iron and % ST, however, increased significantly. Their hemoglobin levels also increased reaching normal levels. These data indicate that traditional diets enriched with vitamin A and iron can satisfy the nutritional needs for these nutrients during recovery of mild-to-moderate PEM.

Tab. V: Treatment of children suffering from mild-to-moderate PEM using Guatemala's habitual diets and sugar enriched with vitamin A and NaFe EDTA*

	Experienced change	
	Initial (day 0)	Final (day 90)
Weight for height (%)	89 ± 5.0	95 ± 4**
Serum retinol (μg/dl)	30.5 ± 8.2	29.6 ± 6.9
Serum ferritin (ng/ml)	11.1 ± 6.9	16.3 ± 4.2**
Serum iron (μg/dl)	48.7 ± 22.6	73.5 ± 25.8**
% ST	13.3 ± 6.1	23.4 ± 7.3**
Hemoglobin (g/dl)	11.7 ± 1.4	13.1 ± 0.9**

* Adapted from TORÚN *et al.* [35]
** Significantly different ($P < 0.05$).

Conclusion

The studies reviewed demonstrate that PEM is accompanied by vitamin and mineral deficiencies. The biological and clinical impact of these deficiencies is, however, masked by the predominant undernutrition which results in lowered tissue requirement for micronutrients. Upon nutritional treatment, the metabolic demand for these micronutrients is significantly increased. Therefore, adequate amounts of the most limiting vitamins and minerals must be provided to satisfy these enhanced nutritional needs and thus attain a complete and harmonious nutritional recovery.

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