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Nutritional Anaemia in Relation to the Interaction Between Vitamin A Deficiency and Iron Metabolism

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Hypovitaminosis A and nutritional anaemia are two of the major nutritional problems which afflict human populations throughout the world. They affect primarily children and pregnant women and become more prevalent in developing countries where dietary and environmental factors play a much important role.

In most of these countries, an inadequate intake of vitamin A appears to be the underlying cause of low plasma levels of retinol. Nutritional anaemia, on the other hand, is due primarily to deficiencies of iron, folates and vitamin B_{12}. Chronic blood losses produced by parasitic infestations may also play an important role. In addition, deficiencies of other nutrients such as proteins, vitamins E, B_2 and B_6 and some trace minerals as zinc and copper have been found to be related to anaemia. Vitamin C also plays a role by stimulating the absorption of non-haeme iron. However, the public health impact of these latter factors in the occurrence of anaemia remain to be evaluated.

In relation to vitamin A, early reports of haemopoietic changes associated with the deficiency of this vitamin in either humans, experimental animals or both have appeared since 1922.

More recent data on the subject comes from the human vitamin A deficiency study by Hodges and associates. In this particular experiment, vitamin A deficiency was induced by feeding diets deficient or low in vitamin A to eight middle-aged men who voluntarily participated. As anticipated, the concentration of carotene in their serum fell rapidly and the concentration of retinol fell slowly during the vitamin A depletion time which varied in the different subjects from 359 to 771 days. Despite a daily intake of 18–19 mg of iron in their diet, the men gradually began to manifest a mild degree of anaemia accompanied by low serum iron levels. This phenomenon is shown for one of the subjects in Fig. 1. It can be observed that during the depletion period, there was a simultaneous drop in the levels of both vitamin A and haemoglobin. When anaemia became apparent, the men were given oral medicinal iron (310 mg/day). The iron treatment had little or no value so long as the men remained deficient in vitamin A. When vitamin A was less than 20μg/dl, the average haemoglobin level was 11.9 g/dl, and when vitamin A levels were greater than 30 μg/dl, the haemoglobin levels averaged 15.6 g/dl. These data from humans suggests that vitamin A is necessary for normal haematopoiesis.

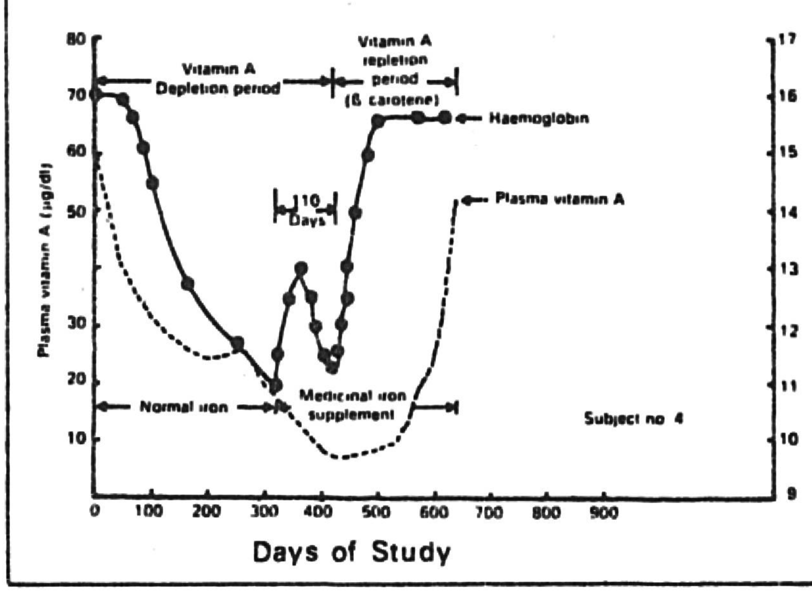

Fig. 1. Effect of vitamin A and iron supplements on plasma vitamin A and haemoglobin levels in a vitamin A depleted human volunteer (Hodges *et al., Am. J. Clin Nutr., 1978, 31: 876).*

Epidemiological evidence from population studies also shows that vitamin A deficiency and anaemia coexist and also that there is a significant association between plasma vitamin A and haemoglobin in blood.

Experimental animal studies have also shown that anaemia may result due to the lack of vitamin A. Initially, when deprived of vitamin A, rats exhibit lower haematocrit or haemoglobin levels as compared with control groups. At a later stage, haematocrit and haemoglobin levels become elevated reaching even higher levels than those observed in the control groups. This is due to a reduction in blood and plasma volume which occurs when the vitamin deficiency becomes severe. At this stage, the anaemia is masked by haemoconcentration and this may be the reason why several investigators have failed to observe anaemia in hypovitaminosis A. When the anaemia developed, these animals showed a reduction in serum iron and a concomitant elevation of the amount of iron in the liver. The concentration of liver iron increases at approximately the same time the haematocrit levels become lower than normal. Spleen iron also increases when the deficiency becomes severe.

In Central America, nutrition surveys have revealed a high prevalence of hypovitaminosis A. Children in this region of the world have a low vitamin A intake, and the prevalence of serum retinol levels less than 20 μg/dl in rural children varied from 20 to 50%. In an attempt to overcome this nutritional problem of the area, the Institute of Nutrition of Central America and Panama (INCAP) began in Guatemala at the end of 1975 a vitamin A fortification programme at the national level using table-sugar as dietary vehicle. The concentration used is 15 μg of retinol equivalents per gram of sugar. Preschool children and lactating mothers from 12 small rural communities were studied for two years in five consecutive surveys; one prior to vitamin A fortification (Survey 1) and four additional ones (Surveys 2–5) each six months apart after the intervention began. The dietary data revealed that in comparison with the prefortification survey, the implementation of sugar fortification resulted in a significant threefold increase in the average daily intake of retinol equivalents. As a result, there has been a highly significant reduction in the prevalence of low and deficient levels of serum retinol in children. Similar results have been obtained in breast milk of lactating mothers. The average intake of iron, however, did not change throughout the two year period of evaluation. This vitamin A programme provided a unique opportunity to evaluate the effect of this single intervention on iron nutrition and metabolism at the population level. The results showed that vitamin A fortification alone had a positive impact favouring iron nutriture of this population. In these children, there were significant positive correlations between the experienced change in serum retinol and changes in serum iron, total iron binding capacity (TIBC) and saturation of transferrin. In contrast, stored iron, as defined by serum ferritin levels, correlated negatively. The results suggest that, between the basal survey and at six months, vitamin A mobilised the stored iron into the circulation and also supported previous similar observations in experimental animals. It is interesting to note that in these children, despite an increase in serum iron levels, there is also an elevation in TIBC suggesting that vitamin A may affect the levels of the iron carrier glycoprotein, transferrin.

After more prolonged intervention, the effect of vitamin A on iron nutriture was different. There was an overall improvement in the levels of iron indicators between the basal and the last survey, particularly with regard to the amount of stored iron (Table 1). There was a lower prevalence of children with low serum ferritin levels in Survey 5 than in Survey 1, prior to vitamin A fortification. In healthy children the levels of serum ferritin have been shown to remain constant from six months to 16 years of age; therefore, the observed favourable change in iron reserves cannot be attributed to the fact that the children were two years older at the end of the study. Most probably this elevation in iron stores observed after two years is due to an enhancement of dietary iron absorption triggered as a response to the initial depletion of iron reserves experienced after six months of vitamin A fortification, and in addition to a possible increment on haemopoietic utilisation of this mineral.

The evidence indicates that there is a biological interaction between vitamin A and iron nutrition and metabolism. Through this relationship, vitamin A deficiency may be a contributing factor in the occurrence of nutritional anaemia especially in areas where hypovitaminosis A is highly prevalent and endemic. When planning nutritional interventions, proper consideration should be given to this concept.

Table 1. Percent distribution of cases in Surveys 1 and 5 by categories of iron parameters

	Survey 1* %	Survey 5** %
Serum iron (μg/dl)		
<50	43.1	25.5***
50–75	27.5	39.2
>75	29.4	35.3
Serum TIBC (μg/dl)		
<250	5.9	2.0
250–350	37.5	49.0
>350	56.9	49.9
% ST		
<15	39.2	27.5
15–20	33.3	33.3
>20	27.5	39.2
Serum ferritin (ng/ml)		
<10	64.7	21.6***
10–20	23.5	58.8
>20	11.8	19.6

*Basal survey; **Two years after initiation of vitamin A fortification; ***The distributions are significantly different ($p < 0.05$ or better).