While iron-deficiency anemia and vitamin A deficiency are both significant problems in many countries, research establishing an interaction between iron and vitamin A could have major implications for treatment of anemia that is due to nutritional status. The high worldwide prevalence of anemia is especially evident in preschool children and women of reproductive age in developing countries, and a more effective treatment for anemia would benefit millions of people. This paper will first present evidence from humans and animals that vitamin A has an effect on iron and anemia, then hypotheses surrounding this relationship will be given.

Numerous studies using humans have supported the notion that vitamin A has an impact on iron status and, in turn, iron-deficiency anemia. Early research suggested that people deficient in vitamin A were prone to anemia that was reversed when sufficient doses of vitamin A were taken (1). Many studies in humans have been performed in countries where nutritional anemia and vitamin A deficiency are major public health problems. One study focused on pregnant women in Indonesia who were anemic due to nutritional status, which the authors reported to affect 50-70% of all pregnant women in that country (2)(p. 1325). Using a double-blind, randomized design, the pregnant women were assigned to one of four groups: iron, vitamin A, iron and vitamin A, and placebo. Hematological variables were measured in a total of 251 women, and the results indicated that the group receiving both vitamin A and iron showed the most improvement. Specifically, those receiving both nutrients exhibited an increase in hemoglobin that was over 50% greater than those receiving iron alone, and, using the data from the other groups, the authors state that one-third of this increase is due to vitamin A while the other two-thirds is due to iron. Furthermore, 97% of the women receiving both nutrients recovered from anemia, while the other groups recovered as follows: iron (68%); vitamin A (35%); and placebo (16%). These results strongly support the use of vitamin A in addition to iron when treating nutritional anemia, and the authors raise an interesting question regarding its implications. They wonder if anemia due to nutritional deficiency could be addressed using foods already available to the people in need, as opposed to prepared supplementation (p. 1327).

Another study of this type focused on children in Guatemala, and the authors' rationale was based on the observation that, in a number of Guatemalan children, iron intake is sufficient, yet iron-deficiency anemia still develops (3). This, taken together with the prevalence of vitamin A defiency in this region, prompted the authors to determine if vitamin A would have an impact on the anemia in these children. The study design was similar to the above study, with four groups of children receiving either vitamin A, iron, vitamin A and iron, or placebo for two months. Various hematological measures were taken, and the results supported an effect of vitamin A on iron status. In the group of children receiving vitamin A alone, the increase in hemoglobin averaged 9.3g/L (using a daily dosage of 10,000 IU for two months). The changes were similar for the groups receiving iron alone and both vitamin A and iron (about 14g/L), and the placebo group showed an average increase in hemoglobin of 3.2g/L. The authors report a strong effect of vitamin A on serum iron and, in turn, percent transferrin saturation. No alteration in total iron binding capacity (TIBC) was observed in the group receiving vitamin A. The major finding in this study was that vitamin A raised the level of serum iron in anemic children, which, according to the authors, could lead to greater hematopoesis and thus recovery from anemia (p. 600). Also, the increase in serum iron is maximal when both vitamin A and iron are administered, with either alone resulting in an increase of lesser magnitude.

While these authors imply that nutritional-deficiency anemia might be best treated using both vitamin A and iron, their conclusions are not drawn directly from the hemoglobin data, since there was no significant difference between the iron group and the vitamin A and iron group. Perhaps the observed changes in hemoglobin concentration represent physiological maximums, and the iron available for hematopoesis, as indicated by serum iron, is greatest when both vitamin A and iron are supplemented in one's diet, even though it may not be used immediately for hematopoesis.

One line of investigation into the interaction between vitamin A and iron comes from animal studies, and has allowed researchers to better define the changes associated with vitamin A deficiency and related changes in iron indices. Early studies sometimes described changes in hematopoetic tissue in vitamin A-deficient rats, but studies were subjected to confounds by other changes due to the vitamin A deficiency (1). Inadequate vitamin A may result in volume balance alterations, with a loss of extracellular fluid, which

translates into decreased blood volume, and this could mask decreases in erythrocyte number and hemoglobin content. Nevertheless, animal studies have provided important information about vitamin A and its effects on iron status.

Roodenburg et al. compared changes in iron metabolism during either vitamin A or iron deficiency in rats, in order to describe the changes in order of their occurrence (4). In rats experiencing iron deficiency hemoglobin levels decreased, and iron absorption and TIBC increased as levels of tissue iron decreased. Vitamin A deficiency was initially manifest by anemia, then increased iron absorption and increased iron level in the spleen. Eventually, packed cell volume, hemoglobin concentration, and serum iron were increased relative to control, which the authors suggest may be due to hemoconcentration (pp.696-7). Also, decreased TIBC in the vitamin A-deficient rats, coupled with increased tissue levels of iron, suggests that iron is not mobilized, which could alter hematopoesis (1,4).

A subsequent study by the same group used rats initially on diets with sufficient iron and varying levels of vitamin A (5). Then the diets were changed to include the same amounts of vitamin A but no iron, followed by a period of iron supplement or iron supplement plus vitamin A. The results suggested that iron in combination with vitamin A is more effective than iron alone in treating lowered iron status, which agrees with studies performed in humans. Also, the authors assert that vitamin A promotes the use of spleen and bone iron stores (p. 635).

While the exact mechanisms underlying the impact of vitamin A on iron and anemia are unknown, several hypotheses exist to explain this phenomenon. One prevalent hypothesis is that vitamin A increases levels of serum iron, which allows hematopoesis to thrive, increasing hemoglobin and erythrocyte production (1)(p. 321). In vitamin A deficiency, iron would not be available for erythropoesis, and anemia would result. The reasoning behind this hypothesis is evident in the above studies.

Another hypothesis, proposed by Thurnham, involves the immune function of vitamin A (6). Thurnham uses the following reasoning for this hypothesis (p. 1313). Vitamin A (specifically, retinol) and iron are bound by retinol-binding protein and transferrin, respectively. During infection, the level of these proteins is diminished, which could be beneficial for various reasons. Due to increased epithelial permeability during infection, these proteins could be lost in the urine, so suppression of these proteins would minimize such losses. Also, the potential oxidizing effects of iron would be lessened during an infection. However, decreased availability of vitamin A could disrupt the integrity of epithelial tissues, especially the eye, gastrointestinal tract, and respiratory tract. This would make this tissue susceptible to infection. Thurnham suggests that the anti-infectious activity of vitamin A could have an impact on the reversal of anemia using this nutrient (p. 1313). Supplementation with vitamin A could lessen infection and help release iron that is stored in the liver during infection, which would in turn stimulate hematopoesis. One relevant point of Thurnham's hypothesis is that the anemic subjects in vitamin A and anemia studies may have some level of infection, which might play a role in their recovery from anemia when vitamin A is administered.

Research into the mechanism of the observed effect of vitamin A on anemia could lead to very specific interventions for this condition, yet it is already clear that vitamin A, when used with iron, can be beneficial in the treatment of anemia. This relationship between vitamin A and anemia could have an impact on how nutritional anemia is approached from a public health perspective, and the development of the most effective treatment is a definite possibility.

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