



## Brief: The Big Five

### Iron, Vitamin B<sub>12</sub>, Folate, Vitamin A, Zinc

Anemia remains a significant global health challenge; it results from decreased production or increased loss of red blood cells (RBCs) and has multiple determinants. USAID created the USAID Advancing Nutrition Anemia Task Force to address the biology, assessment, and factors affecting the development and implementation of interventions to address this global health problem. Conceptually the USAID Advancing Nutrition Anemia Task Force presents anemia as a condition resulting from interactions among multiple internal (biology, nutrition, genetics, health status) and external (economic, social/cultural, physical) environments (i.e., an ecology). The ATF focused on two primary categories of etiology, nutrition-specific and non-nutritional factors. The following is an overview of key aspects of nutrition-specific causes of anemia.

#### Overview of Primary Micronutrients Involved in Anemia

Deficiencies of micronutrients such as iron, vitamin B<sub>12</sub>, folate, vitamin A, and zinc can contribute to anemia. Contributing pathways (table I; Fishman, Christian, and West 2000) include—

- specific aspects of RBC production
- elimination of antioxidant protection for mature RBCs
- interference with intestinal iron absorption
- interference with mechanisms of iron mobilization.

Anemia caused by deficiencies of iron, vitamin B<sub>12</sub>, or folate is generally clearly defined and relatively common, while anemia resulting from other micronutrient deficiencies (vitamin A, zinc, and others) is poorly characterized.

#### Iron

Iron is an essential element that is critical to various core biological functions including energy metabolism, nucleotide synthesis, neurogenesis, and oxygen transport or storage. Most iron is recycled in the organism, the predominant source of iron to replace lost iron is through dietary intake. After ingestion of food containing iron, iron is absorbed in the small intestine. This process is tightly regulated inside the organism (Ganz 2013).

- The hormone hepcidin influences iron absorption. Even in diets with high iron bioavailability iron absorption is halted when the concentration of hepcidin is high, which occurs either when iron stores are sufficient or when the body is challenged by inflammation or infection. In contrast, iron absorption occurs when hepcidin concentration is low.

#### Key Messages

- Nutrition-specific causes for anemia include **deficiencies of iron, vitamin B<sub>12</sub>, folate, vitamin A, and zinc**, and in some instances, **other micronutrients such as vitamin B<sub>2</sub> and C**.
- Iron deficiency (ID) occurs when metabolic iron is insufficient for erythropoiesis and other iron-dependent functions. Iron deficiency can result from insufficient iron stores (**absolute ID**) or inadequate iron absorption and mobilization despite adequate iron stores because of inflammation or infection (**functional ID**).
- Absolute ID may arise from insufficient dietary iron intake; insufficient iron absorption; or iron demand exceeding habitual iron supply as a result of growth, pregnancy, hemolysis, bleeding, or treatment with erythropoiesis stimulating agents.

- Absorbed iron is subsequently incorporated into hemoglobin molecules in RBCs, as well as in other proteins (mostly enzymes), as activity depends on iron.
- As a result of the RBC life cycle (120 days), iron is continuously released as RBCs break down, and ultimately recycled in the plasma. This tight retention of iron is why males are at lower risk for anemia than females who lose iron due to menstruation.

Absolute iron deficiency can result from either loss of iron (e.g., due to blood loss) or when usual supply is insufficient to satisfy the increased iron requirement (e.g., due to growth, during pregnancy) (Pasricha et al. 2021). When iron availability for RBC production is limited, reduced hemoglobin production can lead to poor oxygen transport and, eventually, anemia (Ganz 2013). Iron deficiency can also occur when the organism suffers from infection or inflammation due to an increase in hepcidin concentration (i.e., functional iron deficiency), which may occur simultaneously or independently from absolute iron deficiency.

### **Vitamin B<sub>12</sub> and Folate**

Vitamin B<sub>12</sub> and folate (vitamin B<sub>9</sub>) are crucial for the synthesis of nucleic acids (deoxyribonucleic acid [DNA] and ribonucleic acid [RNA]). Deficiencies of these two B vitamins, can result from inadequate intake, malabsorption, or increased utilization or demand and can cause megaloblastic anemia (table 2). This in turn leads to cells with larger size, an immature nucleus, and relatively greater amount of cytoplasm.

### **Vitamin A**

Vitamin A has multiple functions including its integral role in vision, immune processes, as well as cell growth and differentiation. Vitamin A deficiency may cause anemia by impairing iron metabolism (i.e., impaired iron absorption and/or utilization). Reducing vitamin A deficiency can increase erythropoietin, a protein that stimulates RBC production, allowing the body to use stored iron for RBC production (Zimmermann et al. 2006). Interventions aimed at improving vitamin A status showed a reduced prevalence of anemia in most (Suharno et al. 1993; Muslimatun et al. 2001; Zimmermann et al. 2006) but not all (Semba et al. 2001) contexts.

Chronic vitamin A deprivation results in changes consistent with functional iron deficiency. Unlike iron-deficiency anemia, but similar to anemia of chronic disease, iron stores are sufficient and may even be elevated. In this case, administration of iron alone will not correct the anemia. Simultaneous administration of vitamin A with iron may enhance the response to treatment of the anemia (Mejía and Chew 1988; Al-Mekhlafi et al. 2014).

### **Zinc**

Zinc is an essential trace element involved in wound healing, the maintenance of eye and skin health, and it is a component of numerous zinc containing metalloproteinases and enzymes. Zinc, iron, and copper share common transport mechanisms in the gastrointestinal tract. Consequently, consumption of large quantities of zinc can cause copper deficiency due to zinc's interference with copper absorption; patients typically present with a microcytic anemia. If not in excess, zinc and copper are thought to aid iron absorption, although the presence of zinc is not a critical prerequisite (Scheers 2013).

**Table 1. Selected Micronutrients with Relevance to Anemia**

Nutrient	Function	Consequences of Deficiency	Hematologic Consequences
Iron	Core biological functions	Limited iron availability for RBC production, subsequent reduced hemoglobin production and oxygen transport	Normocytic and microcytic hypochromic anemia
Vitamin B <sub>12</sub> and Folate	RBC production, iron utilization	Ineffective DNA synthesis and subsequent altered RBC formation	Megaloblastic anemia
Vitamin A	Epithelial cell growth and differentiation, involvement in growth and differentiation of erythroid precursors	Impaired iron absorption and utilization	Microcytic and hypochromic anemia
Zinc	Component of numerous metalloproteinase/enzymes	Hampered iron absorption	Microcytic anemia due to concomitant iron deficiency

**Table 2. Different Types of Anemia**

Type of Anemia	Characteristic
Macrocytic	Very large RBCs
Microcytic	Small RBCs (hypochromic if cause is ID)
Normocytic	RBCs are normal in shape and size
Hypochromic	Low content of hemoglobin in the RBCs

## References

- Al-Mekhlafi Hesham, M., T.S. Anuar, E.M. Al-Zabedi, M.T. Al-Maktari, M.A. Mahdy, A. Ahmed, A.A. Sallam et al., Abdul. 2014, December. “Does Vitamin A Supplementation Protect Schoolchildren from Acquiring Soil-Transmitted Helminthiasis? A Randomized Controlled Trial.” *Parasites & Vectors*. 7(1):1–9. <https://doi.org/10.1186/1756-3305-7-367>
- Fishman, S.M., P. Christian, and K.P. West. 2000. “The Role of Vitamins in the Prevention and Control of Anaemia.” *Public Health Nutrition* 3(2): 125–150. <https://doi.org/10.1017/s136898000000173>.
- Ganz, Tomas. 2013. “Systemic Iron Homeostasis.” *Physiological Reviews* 93(4): 1721–1741. <https://doi.org/10.1152/physrev.00008.2013>.
- Mejía, L. A., and F. Chew. 1988. “Hematological Effect of Supplementing Anemic Children with Vitamin A Alone and in Combination with Iron.” *The American Journal of Clinical Nutrition* 48(3): 595–600. <https://doi.org/10.1093/ajcn/48.3.595>.
- Muslimatun, Siti, Marjanka K. Schmidt, Clive E. West, Werner Schultink, Joseph G. A. J. Hautvast, and Darwin Karyadi. 2001. “Weekly Vitamin A and Iron Supplementation during Pregnancy Increases Vitamin A Concentration of Breast Milk but Not Iron Status in Indonesian Lactating Women.” *The Journal of Nutrition* 131(10): 2664–2669. <https://doi.org/10.1093/jn/131.10.2664>.
- Pasricha, Sant-Rayn, Jason Tye-Din, Martina U. Muckenthaler, and Dorine W. Swinkels. 2021. “Iron Deficiency.” *The Lancet* 397(10270): 233–248. [https://doi.org/10.1016/S0140-6736\(20\)32594-0](https://doi.org/10.1016/S0140-6736(20)32594-0).
- Scheers, Nathalie. 2013. “Regulatory Effects of Cu, Zn, and Ca on Fe Absorption: The Intricate Play between Nutrient Transporters.” *Nutrients* 5(3): 957–970. <https://doi.org/10.3390/nu5030957>.
- Semba, R.D., N. Kumwenda, T.E. Taha, L. Mtimavalye, R. Broadhead, E. Garrett, P.G. Miotti, and J.D. Chipangwi. 2001. “Impact of Vitamin A Supplementation on Anaemia and Plasma Erythropoietin Concentrations in Pregnant Women: A Controlled Clinical Trial: Vitamin A and Erythropoietin.” *European Journal of Haematology* 66(6): 389–395. <https://doi.org/10.1034/j.1600-0609.2001.066006389.x>.
- Suharno, D, Muhilal, D Karyadi, C.E West, J.G.A.J Hautvast, and C.E West. 1993. “Supplementation with Vitamin A and Iron for Nutritional Anaemia in Pregnant Women in West Java, Indonesia.” *The Lancet* 342(8883): 1325–1328. [https://doi.org/10.1016/0140-6736\(93\)92246-P](https://doi.org/10.1016/0140-6736(93)92246-P).
- Zimmermann, Michael B., Ralf Biebinger, Fabian Rohner, Abdeljawad Dib, Christophe Zeder, Richard F. Hurrell, and Nourredine Chaouki. 2006. “Vitamin A Supplementation in Children with Poor Vitamin A and Iron Status Increases Erythropoietin and Hemoglobin Concentrations without Changing Total Body Iron.” *The American Journal of Clinical Nutrition* 84(3): 580–586. <https://doi.org/10.1093/ajcn/84.3.580>.



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