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EDITORIAL

What is causing anemia in young children and why is it so persistent?☆,☆☆

O que causa anemia em crianças mais novas e por que ela é tão persistente?

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The worldwide prevalence of anemia in children under 5 years of age is estimated to be 42.6%.[1] Not surprisingly, it is more often found in low and middle-income countries, with South East Asia and Africa being the most affected. The consequences of childhood anemia range from increased susceptibility to infectious diseases, fatigue, decreased physical capacity, and, if persistent, lower cognitive function and economic productivity in adulthood.[2–5] When a large part of the population is affected, this can have large-scale consequences for the economic productivity.[6]

Anemia is rare in newborn babies, since their mother provides them with a generous supply of iron upon birth, especially in cases of delayed cord clamping. There is evidence that antenatal iron supplementation, as recommended by the World Health Organization (WHO), improves neonatal iron stores, thus delaying the age at which iron-deficiency anemia is likely to develop during infancy.[7] Although breast milk is not a rich source of iron, its absorption is enhanced by the presence of lactoferrin. Formulas usually contain a higher amount of iron to compensate for the lack of lactoferrin. Therefore, anemia often appears after the age of 6 months. This roughly coincides with the introduction of complementary foods, but also with the period that children start to explore their world and are frequently exposed to contaminants. During school age, the risk of anemia is usually much lower, but it peaks again during puberty, especially in girls after menarche and during pregnancy, due to the sharp increase in iron requirement during the second and third trimester.[8]

The causes of anemia are multifactorial, but iron deficiency is the most common cause and explains about half of the cases.[1] Meat is an important source of iron, since it contains heme iron, which is more efficiently absorbed in comparison to non-heme iron, which is the primary form of iron in plant foods. Non-heme iron is absorbed in the ferrous (Fe^{2+}) form through the divalent metal transporter 1 (DMT1). The only transporter for heme iron that has been observed up until now is the HCP1 carrier,[9] although it is speculated that other carriers should exist. Bioavailability of heme iron ranges from 15 to 35%, whereas that of non-heme iron is usually lower than 10%. Although dark green leafy vegetables are rich in iron, its absorption is low and these vegetables are therefore not very good sources of this nutrient.[10,11] Likewise, legumes are rich in phytate and polyphenols, which hampers iron absorption.[12]

Iron metabolism and the innate immune response to infection may explain the interrelationships between nutrition and anemia in young children. Due to its ability to exist in one of two oxidation states, ferrous (Fe^{2+}) or ferric (Fe^{3+}), iron is an essential but also toxic nutrient in the human body. Iron acts as an electron donor in the ferrous state and as an electron acceptor in the ferric state.[13] The redox potential of iron can result in reactive oxygen species that ultimately lead to generation of free radicals that damage lipids, DNA,

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and protein, especially under conditions of iron overload.[14] As such, iron concentration and distribution in the human body is highly regulated.

Hepcidin, a circulating peptide hormone, is now known as the key regulator of systemic iron homeostasis in humans.[13] Hepcidin reduces dietary iron absorption by reducing iron transport across the gut mucosa; it reduces iron exit from macrophages, the main site of iron storage; and it reduces iron exit from the liver. In all three instances, this is accomplished by reducing the transmembrane iron transporter ferroportin.[13] Hepcidin synthesis and secretion by the liver is controlled by iron stores within macrophages, inflammation, hypoxia, and erythropoiesis. Measuring hepcidin would be of benefit to establish optimal iron deficiency anemia treatment, but because this is not widely available, C-reactive protein (CRP) is used as a surrogate marker. In light of emerging knowledge regarding iron transport and regulation, there is need to study iron metabolism in relation to other physiological processes in health and disease.

The mechanisms of iron homeostasis in human health and disease are largely dependent on the fact that iron is an essential nutrient for both humans and pathogenic microbes.[14] Nutritional immunity (also known as ''iron withholding''), a process through which the human immune system limits iron availability to invading microbes as an innate immune defense system, may explain why anemia in young children is so persistent. In addition, direct and indirect links between parasitic infections and human iron homeostasis exist. For example, hookworms infect over 700 million people worldwide and are a leading cause of iron-deficiency anemia in lower and middle-income countries.[15]

In this issue of the journal, Zuffo et al.[16] describe the factors associated with anemia among 334 randomly selected children aged 6–36 months attending Municipal Early Childhood Education Center (Centros Municipais de Educação Infantil [CMEI]) nurseries in Colombo-PR, Brazil. They found a prevalence of anemia of 34.7%, which was significantly higher among younger mothers (<28 years), male children, younger children (<24 months), and children who did not consume iron food sources such as meat, beans, and dark green leafy vegetables. In Brazil, the prevalence of anemia in children under 5 years of age has been estimated at 24%.[1] Although the prevalence in the present small study appears to be much higher than the national statistic, this might in part be explained by the smaller age range (6–36 months *vs.* 6–59 months).

Iron intake of the children appeared to be low, with a median intake of 3 mg per day. This is far below the recommended iron intake of 7.7 mg for children aged 6–12 months and 4.8 mg for children aged 13–36 months. The poor dietary composition of the meals provided in the nurseries may be the cause, but the low iron intake can also be due to poor appetite of the children for iron-rich foods. Whatever the reason, it is clear that low iron intake is a likely explanation for the high prevalence of anemia revealed by this study. However, it should be noted that many other potential causal factors can play a role. In addition to iron, deficiencies of vitamin A and B can be important, as well as non-nutritional causes, such as parasitic infestation, infectious diseases, diarrhea, destruction of erythrocytes (*e.g.* by malaria), severe blood loss, and genetic factors. In the Brazil study, almost half of the children had experienced fever and 22% of the children had diarrhea in the 15 days prior to the hemoglobin measurement. Those with fever or diarrhea had a higher prevalence of anemia than those who did not.

The most common global strategy to address iron deficiency anemia is the fortification of staple foods with iron. Flour fortification has proven to be effective in improving iron status and, to a lesser extent, in reducing anemia.[17] In Brazil, fortification of wheat and maize flour with 4.2 mg iron and 150 μg of folic acid per 100 g of flour became mandatory since 2004. However, evaluation of the fortification program ten years after its inception by a nationwide survey showed that flour fortification added little to the total iron intake of the Brazilian population, especially when taking the low bioavailability of electrolytic iron into consideration.[18] In a study comparing whole meal maize flour fortified either with electrolytic iron or NaEDTA-iron, the latter was shown to be superior in improving iron status and reducing iron-deficiency anemia in Kenyan children.[19]

Despite global programs to control it, childhood anemia is still present even in countries with excellent health systems and sufficient iron intake, with a prevalence in North America of 7% and in Europe of 19%.[1] It is likely that the anemia that remains after the correction of iron intake is, to a large extent, related to common childhood infections. It is ironic that these infections are inevitable in order to build up a healthy immune system. It is therefore questionable whether childhood anemia can ever be fully eradicated unless we would live in a completely sterile environment.

Conflicts of interest

The authors declare no conflicts of interest.

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