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REVIEW ARTICLE

Cow's milk consumption and iron deficiency anemia in children

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Abstract

Objective: To thoroughly investigate the association between the consumption of cow's milk and anemia in childhood.

Sources of data: The information was gathered from papers catalogued in Lilacs and MEDLINE and published during the last two decades, and also from textbooks and publications by international organizations.

Summary of the findings: Iron deficiency anemia is a severe public health problem in developing countries. Breast milk contains adequate iron for full term babies in the first 6 months. Thereafter, an additional iron-rich diet becomes essential. In recognition of the importance of the diet in triggering anemia, this paper discusses the relationship in children between a high intake of cow's milk and iron deficiency anemia. Gastrointestinal and allergic problems may be caused by early introduction of cow's milk or by its substitution for breast milk. Furthermore, cow's milk has decreased iron density and bioavailability, excess protein and minerals, notably calcium, and thus interferes in the absorption of iron from other foods, and is also linked to small intestinal hemorrhage in young children.

Conclusions: The use of cow's milk in lieu of other foods rich in bioavailable iron was shown to be a risk factor for anemia. Exclusive breastfeeding during the first 6 months of life, discretionary weaning only after the 24th month, and a complementary diet rich in iron are highly important to avoid anemia and its consequences.

J Pediatr (Rio J). 2005;81(5):361-7: Anemia/epidemiology, risk factors, food consumption, infant nutrition, nursing bottle.

Introduction

Iron deficiency anemia is the result of multiple etiologic factors. One of the most important of these factors is inadequate iron intake, especially heme iron, due to low intake of foods derived from animals, i.e. a diet based on foods of vegetable origin.[1,2] Other factors, such as low socio-economic status, poor sanitary conditions and a high prevalence of infectious and parasitic diseases, particularly those that provoke chronic blood loss, are also determinants of anemia.[3,4]

During the eighties, the World Health Organization estimated that the prevalence of anemia in the world population was 30%, with a large degree of variation between different regions and age groups, affecting 43% of children aged 0 to 4 years, 51% of expectant mothers, 37% of children aged 5 to 12 years, 35% of women overall, including expectant mothers, and 18% of adult males. The largest proportions were observed in developing countries.[5] More recent estimates indicate that, in those countries, more than 3.5 billion people are anemic.[6]

In Brazil, population studies have found evidence that iron deficiency anemia exists in many regions, with high prevalence. In children under 5 years, prevalence rates of 33.8, 46.7, 31.4, 36.3 and 46.4% were observed in Piauí, Pernambuco, Sergipe, and Paraíba states and the city of Salvador , respectively.[7-11] Two studies demonstrated a tendency for the problem to worsen, since the prevalence of anemia in preschool aged children increased from 35.6%, in 1984/85[12] to 46.9%, in 1995/96,[13] in the city of São Paulo and from 19.3%, in 1981/82 to 36.4% in 1992, in Paraíba state.[10]

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Several authors have demonstrated that children aged 6 to 24 months present greater vulnerability to anemia.[9,14-17] The situation is even more serious in the 6 to 11 month age group with prevalence rates that reach 79% in the provincial rural area of Pernambuco state.[16] The increased prevalence of anemia within this age group is probably the result of risk factors such as early weaning and the introduction of cow's milk and/or a diet based on vegetables and cereals (foods with low iron bioavailability), prematurity, low birth weight and frequent infections.[6,18]

Maternal breastmilk is a very important food to the nutrition of children, especially until the second year of life, and comes to constitute the largest source of energy. During the first 6 months of life, exclusive maternal breastfeeding meets the basic iron requirements of fullterm children. After this period, even with the excellent bioavailability of iron in human milk, it is necessary to offer complementary foodstuffs that are rich in this micronutrient.[18]

The literature has shown that consumption of cow's milk *in natura* consistently presents as a risk factor for anemia in children.[19-22] In the city of Goiânia, Hadler et al.[20] observed that the ingestion of liquid cow's milk had a positive association with anemia prevalence in children aged 6 to 12 months. The authors report that an increased intake of cow's milk, whose iron content is reduced and has low bioavailability, can reduce the total quantity of iron contained in the diet or substitute other possible sources of this nutrient. Modified milk, enriched with iron, however, reduces the chances of anemia by increasing the density of iron in the milk. Nevertheless, a study carried in the city of São Paulo by Levy-Costa & Monteiro[21] in children aged 6 to 60 months, found evidence that increasing the relative participation of cow's milk in the diet was significantly associated with the risk of anemia, even taking account of the diluting effect of this food on the iron density in the diet. Positive and significant associations were observed both in a model that corrected for demographic and socioeconomic variables and also in one that made further corrections for the iron density in the diet. The authors suggested two mechanisms to explain the negative influence of cow's milk intake on hemoglobin concentration: a diluting effect due to low iron concentration in cow's milk, and an inhibitory effect which would be related to the presence of calcium and serum proteins in cow's milk, elements that inhibit iron absorption.

Iron supply is most affected when cow's milk is introduced early and becomes the primary food source, substituting or complementing savory foods. Studies have shown just how early cow's milk is being introduced and that the volume of milk consumed reduces as children get older. As a result children receive a progressively greater iron supply, probably as a result of the introduction of other foods that are not milk-based.[19-23] Male et al.[22] demonstrated that the most important dietary risk factor for anemia was early introduction of cow's milk and that the duration of feeding with this milk had the strongest and most consistent negative influence on hemoglobin and ferrous nutritional status indicators. For every month of feeding with cow's milk, there was a reduction of 2 g/l in the hemoglobin levels of children aged 12 months.

In addition to the low content and bioavailability of iron, ingestion of cow's milk can interfere in the absorption of iron from other foodstuffs and can provoke occult blood loss in feces.[24-28]

In order that iron deficiency prevention and control programs can be planned, it is necessary that information is available on possible causative factors, including nutritional intakes, socioeconomic factors and the prevalence of infections. It is important to be aware of, not just total iron intake, but also the composition of feeds and the presence of dietary components that could inhibit or stimulate iron uptake. In response to the high level of cow's milk intake in infant nutrition and the negative impact of iron deficiency anemia on children's development, the purpose of the present study is to review certain aspects of the consumption of this foodstuff that are related to this severe nutritional problem.

The functions of iron in the body

Within the body, iron is linked with two categories of components: those whose function is metabolic or enzymatic (functional components) and those associated with storage. The functional components are hemoglobin and myoglobin, in lower quantities within body tissues, and several other proteins that are active in the transport, storage and utilization of oxygen. Iron also participates in a variety of biochemical processes, including the transport of electrons in the mitochondria, metabolism of catecholamines and DNA synthesis.[29-31]

The majority of iron is found in hemoglobin (70-80%), a tetrameric hemeprotein whose prosthetic group is the radical heme, present in erythrocytes and whose function is oxygen transport. Around 10 to 12% of iron is found in myoglobin, a monomeric hemeprotein present in the muscles, whose function is to fix oxygen supplied by the hemoglobin of circulating red globules, thus making possible oxidation reactions that release energy.[32]

The storage components do not have any physiological function, serving only as a reserve to replace losses from functional components. These are: ferritin and hemosiderin, present in the liver, spleen and bone marrow. When dietary iron supply is inadequate, the element is mobilized from the storage components to maintain the production of hemoglobin and other iron compounds that perform metabolic functions. It is probable that functional alterations do not take place while this production is not prejudiced.[29,30]

The most characteristic manifestation of iron deficiency is microcytic iron deficiency anemia. Nevertheless, subclinical iron deficiencies can be detrimental to health at all stages of life because they cause oxidative metabolism disorders and are associated with altered oxidative performance, muscular function, physical activity, productivity at work or school, mental acuity and the capacity to concentrate. Furthermore, there can be alterations to thermogenesis, the skin, nails and mucosas, in addition to reduced immunoresponse, which in turn increases morbidity due to infectious diseases.[6,33] In its most advanced phase anemia is associated with clinical symptoms, such as weakness, reduced respiratory capacity and dizziness.[34]

The importance of iron in the diet

In developing countries, in which there are elevated percentages of low birth weight children, the likelihood of iron deficiency during the first 6 months of life is increased because reserves are so low at birth. Furthermore, these children have faster postnatal growth rates than children born full term, which means that they use up their reserves earlier and consequently their iron requirements are greater.[18,35] From birth onwards children use iron reserves to supply their needs for red blood cell synthesis and growth and exclusive breastfeeding has a relevant role to play in maintaining these reserves. There is normally a reduction in iron reserves in the liver during the first 6 months of life,[18] and the absence of or partial or total substitution of maternal breastmilk by other types of milk contributes to the appearance of anemia.[19-23]

The iron contained in human milk is highly bioavailable, since approximately 50% is absorbed, while unfortified cow's milk or formula based on cow's milk offer only 10 to 20% absorption. Foods used for weaning with low bioavailability can also interfere in the absorption of the iron that is present in maternal milk.[14,18,29,30]

Iron requirement can be defined as the quantity of iron that needs to be absorbed to replace organic losses, with children and adolescents requiring additional quantities for expansion of red cell mass and growth of body tissues. Requirements are first defined as the iron that must be absorbed and then converted into estimates of dietary iron requirements, taking bioavailability into account. In the case of a diet with intermediate bioavailability, iron requirements are 11 mg/day for children less than a year old, 6 mg for those 12-23 months old and 7 mg/day for 2 to 6-year olds.[30]

The density of a nutrient, or the quantity of it per a given unit of energy is a measure widely used to compare foods and evaluate the quality of diets, both in industrialized nations and developing countries. Low energy intake very often means that the requirements for certain nutrients are not fully attained. The density of bioavailable iron is defined as the quantity of iron absorbed (in milligrams) from a meal for every 1,000 kcal.[36]

The World Health Organization recommendation for iron density (mg/100 kcal) in complementary foods is based on the FAO/WHO[30] model which groups meals or diets into three categories of bioavailability (low, intermediate and high). In developing countries, the majority of complementary foods offered to children are low or intermediate bioavailability foods. Based on an intermediate bioavailability diet, the recommended iron is 4 mg/100 kcal for children 6 to 8 months old, 2.4 mg/100 kcal at 9-11 months and 0.8/100 kcal for 12-24 months.[18]

Nutritional characteristics of human milk versus cow's milk

The most common proteins in milk are casein and whey proteins. In cow's milk, casein accounts for around 80% of total proteins, while whey proteins predominate in human milk, at 60-70%. Whey proteins are more easily digested than casein, which demands that more hydrochloric acid is secreted so that stomach pH is sufficient for it to be digested by pepsin. The principal sugar present in milk (human and cow's milk) and in infant formulae is lactose and its functions are: to promote energy, to promote calcium absorption and develop adequate intestinal microbial flora. In terms of lipids, there are significant differences in fatty acid composition: in cow's milk saturated fatty acids predominate and in human milk unsaturated fatty acids predominate. The larger the chain and more saturated the fatty acid is, the lower is its absorption. Cow's milk is low in linoleic acid and vitamin E and contains excessive quantities of sodium, potassium and proteins.[37]

Both cow's milk and breastmilk are low in iron (around 0.2-0.5 mg iron per liter), however the iron in breastmilk is bonded to lactoferrin and offers greater bioavailability. Cow's milk also offers low levels of vitamin C, considered a factor that stimulates iron absorption, and high levels of calcium and phosphorous, factors that inhibit iron absorption.[29,37,38] Mature breastmilk contains an average of 40±10 mg/l of vitamin C[18] and also has the advantage of not requiring manipulation or heating which encourage loss of this nutrient.

The many different types of milk available on the market are products based on cow's milk *in natura,* and their composition may have been modified by fortification or reduction of nutrients (e.g. free of lactose; fat levels altered: whole milk, skimmed, semi-skimmed, cholesterol free; enriched or fortified with: calcium, iron, vitamins A, D, E, B6, omega-3, omega-6).

Although it appears to be a practical and economic option, cow's milk, either whole milk or diluted with water, with flour or sugar added, is not indicated for children less than 12 months old because of the innumerable adverse effects it can have on their health. Some of the most common clinical manifestations include gastrointestinal, respiratory, cutaneous and anaphylactic symptoms. Furthermore, since cow's milk is the most common food in the diet during weaning and is often used in detriment to other foods that are iron sources, substituting or complementing a savory meal, may encourage the development of iron deficiency anemia.[38-40]

The bioavailability of iron in children's diets

Iron absorption is influenced by two principal factors: the homeostatic function of the intestinal mucosa, where iron uptake increases as reserves fall, and the interaction of dietary iron with other elements of the diet.[35] In order to ensure an adequate diet it is necessary to take account not just of the quantity of the mineral, but also its bioavailability. Some dietary factors that increase this bioavailability are meat (beef, fish, poultry and liver) and ascorbic acid.

The mechanism by which meat stimulates iron absorption is not yet entirely understood. There is evidence that it acts to reduce the inhibitory effects of polyphenols and phytates on the absorption of nonheme iron and increases the bioavailability of heme iron, even though these types of iron have different absorption mechanisms.[41,42]

Ascorbic acid acts as a reducer, maintaining the nonheme iron from food in its ferrous state, which is more soluble and bioavailable when intestinal pH is elevated. Vitamin C can also affect the transport and storage of iron in the organism, since individuals who are deficient in this vitamin can exhibit defects in the liberation of iron from endothelial cells. Therefore, the inclusion of fruit and vegetables rich in vitamin C in the diet makes dietary iron more available.[43,44]

Some dietary components can reduce the absorption of minerals. On this list are the phytates present in cereals, the oxalic acid present in leafy vegetables, the polyphenols in high concentrations in coffee and tea and phosvitin, which is a protein found in egg yolks, bonded to iron.[45] Foods of vegetable origin, like beans, lentils, soya and dark green vegetables (Chinese leaves, kale, broccoli, mustard) have large quantities of iron in their compositions, but low bioavailability.[46]

Interactions between minerals take place when chemically similar elements share the same means of absorption. Excessive consumption of zinc or calcium, especially in the form of supplements, can interfere in the utilization of iron if consumed simultaneously.[45,47]

When calcium is present in meals, at concentrations that are often consumed in the habitual diet, it has a marked inhibitory effect on the absorption of both heme iron and nonheme iron. One possible explanation is that calcium and iron compete for bonds with substances that are important to the absorption route, i.e. inhibition is not located in the gastrointestinal lumen, but is in some way related to the transportation of iron through the mucosa.[48,49]

There is a known link between vitamin A deficiency and anemia. Anemia prevalence rates are high in populations affected by vitamin A deficiency. It appears to be involved in the pathogenesis of anemia through several different biological mechanisms: modulation of iron metabolism, interference with immunity and mobilization of iron from tissues.[50] These mechanisms do not appear to be related to a primary iron metabolism abnormality or iron deficiency, but to inefficient hematopoiesis[51] and reduced reserve iron mobilization.[45] Studies suggest that vitamin A and ß-carotene form compounds with iron, maintaining it soluble within the intestinal lumen and avoiding the inhibitory effect of phytates and polyphenols on iron absorption.[31,52]

In general, children less than 2 years old, and in particular those under 1 year old, do not consume iron-rich foods (liver, meat and fish) in sufficient quantities to meet their iron requirements.[18,46] Furthermore, it is presumed that there will be a high consumption of cow's milk in this age group, which provides relatively low quantities of iron and contains three elements that potentially inhibit the absorption of this micronutrient, namely: casein, whey proteins and calcium.[25-27,48]

The bioavailability of iron in cow's milk

Foods that are sources of dietary protein can both increase and reduce the absorption of nonheme iron. Animal tissue (beef, pork, liver, chicken and fish) increases the absorption of this micronutrient. On the other hand, casein and whey proteins from cow's milk account for the greater proportion of the protein present in the majority of infant formulae and foods and have a negative influence on iron uptake, particularly if the increased requirements of children that result from their accentuated growth are taken into account. A study undertaken by Hurrel et al.[25] suggested that casein and whey proteins from cow's milk are, at least in part, responsible for the low bioavailability of the iron in infant formulae. When these proteins were tested intact *in vitro*, the majority of iron did not pass the dialysis membrane, indicating that it had formed compounds that were insoluble or too large to pass through the membrane's pores. Casein is a mixture of phosphoproteins whose most important components are α-, ß- and κ-casein and is known to form large phosphopeptides in the *in vitro* digestion, which can bond with calcium and, possibly, also iron in the duodenum and upper jejunum. The authors argued that cysteine is the only amino acid that has been demonstrated to increase iron absorption and neither casein nor whey proteins have large quantities of this amino acid.

Cow's milk has approximately four times more calcium than human milk, which can contribute to low iron absorption.[26] The practical nutritional implications of the inhibitory effect of calcium on iron uptake were demonstrated by Hallberg et al.[27] when they observed that the consumption of milk or milkshake with hamburgers or the addition of cheese to a pizza reduced nonheme iron absorption by 63, 47 and 61%, respectively. This maximum inhibitory effect is achieved with an approximate intake of 150-200 mg of calcium, which is the equivalent to that contained in one glass of milk or a piece of cheese, for which reason the authors recommend that these should not be consumed regularly at the main iron-providing meals, particularly by those who have increased iron requirements (children, adolescents and women of fertile age). The earlier that cow's milk is introduced, the greater the chance of iron deficiency.[26,53]

The type of cow's milk consumed, whether fresh (pasteurized and homogenized) or infant formula, can result in differences in hemoglobin and hematocrit concentrations in children.[54] Some authors have observed that ferritin levels are higher among children less than one year old who consumed infant formula fortified with iron, together with other foods, which may be due to the higher quantity of iron, especially if these formulae have a lower concentration of proteins and calcium.[32,55,56] In contrast, when pasteurized cow's milk is offered with other foods, there may be iron absorption inhibition and children receive exaggerated quantities of proteins and electrolytes.[57-59]

One further factor to be pointed out is that, when cow's milk becomes the principal food offered to a child, contributing a large proportion of the calories in the diet, other iron-rich foods cease to be offered.[16,20,21]

Cow's milk consumption and intestinal microhemorrhages

In addition to the characteristics already discussed above, such as low iron content, the low bioavailability of that iron and the fact that it is used in place of other iron-rich foods, cow's milk can also cause occult gastrointestinal bleeding, which is yet another negative effect on infants' ferrous nutritional status.[37]

Studies evaluating blood loss in feces have observed that when cow's milk was introduced to the diets of children who had been exclusively breastfed, hemoglobin in feces increased in an accentuated manner. The results suggested that the intestinal blood loss provoked by exposure to cow's milk is a characteristic phenomenon among younger children that gradually disappears during the second half of their first year of life and does not cause clinical repercussions.[57,58,60] These losses can exceed 3 ml/day, which equates to 0.27 mg of hemoglobin or 0.9 mg of iron per day.[32]

At least 20 proteins can be found in cow's milk that can act as allergens, with the principal ones being b-lactoglobulin and casein.[38]

Allergic proctocolitis, one manifestation of adverse reaction to cow's milk protein, is a common cause of bleeding, especially during the first months of life. Systemic signs and symptoms are generally absent, with the exception of pain during defecation and eczema, which may be presented by some patients. Erythema, erosion and/or nodular lymphoid hyperplasia are revealed by rectosigmoidoscopy and the presence of inflammatory infiltration can be observed when histological studies are made of biopsy material. Cow's milk protein allergy can induce a syndrome characterized by chronic diarrhea (with steatorrhea), lesions of the jejunal mucosa and weight loss, similar to celiac disease. Anemia, hypoprothrombinemia and vitamin K deficiency coagulopathy can be observed in laboratory tests. Histopathological studies of the jejunal mucosa also reversal that atrophy of the intestinal villa with hypertrophy of the crypts is also present to varying degrees.[38]

It is important to point out that, in countries such as ours, parasitosis is the primary pathological cause of blood losses which, in turn, are not taken into account when iron requirements are estimated. Often, such parasitosis affects nutritional status at a several different stages of the lifecycle, through reductions in nutritional intake, maldigestion and malabsorption. Ancylostomiasis, defined as human infestation by two nematodes of the ancylostomidae family (*Ancilostoma duodenalis* and *Necator americanus*), trichuriasis (*Trichuris trichiura)* and schistosomiasis (*Schistosoma mansoni*) can provoke chronic blood losses. This intestinal blood loss reaches an average of 2 ml or 1 mg of iron daily when *Necator americanus* is present and twice this when the cause is *Ancilostoma duodenalis*, with a third of this iron being reabsorbed in the gastrointestinal tract. Studies demonstrate a direct relationship between the intensity of the infection, blood losses and anemia.[6,30,61,62]

Despite the fact that it has been well documented in the literature that using cow's milk to feed children can deteriorate their nutritional status,[37,57-60] none of the studies that have been cited above is capable of explaining this relationship by intestinal blood losses alone.

Final considerations

Iron deficiency anemia is a severe public health problem in developing countries, especially among children less than one year old, who have elevated iron requirements in comparison with other phases in life. Exclusive maternal breastfeeding, up to 6 months of age, meets the iron requirements of infants. After this period it becomes necessary to supply this nutrient in complementary foods.

The early introduction of cow's milk or the use of it, fresh or pasteurized, as a substitute for breastmilk can cause children certain health disorders. The composition of cow's milk is different to that of human milk, since it provides excessive quantities of proteins and minerals, interfering in the absorption of iron. This justifies the recommendation that cow's milk and its byproducts should not be consumed together with other iron-rich foods. Furthermore, cow's milk consumption can be associated with occult blood losses in feces, particularly among children less than one year old. In isolation these losses cannot explain the relationship between cow's milk consumption and the nutritional deterioration in terms of iron, since other mechanisms such as the inhibition of uptake of iron from other sources by calcium and/or milk proteins may also be involved. Therefore, stimulation of the practice of exclusive maternal breastfeeding up to 6 months and its continuation until at least 24 months, together with a complementary diet rich in iron and elements that facilitate its absorption, in common with the fortification of infant feeds with iron, are measures of great importance for the prevention of anemia and of its consequences during childhood.

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