Influence of Goat Milk on Iron Deficiency Anemia Recovery

Review Article

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Abstract

Despite Fe deficiency and overload having been widely studied, researchers are still looking for natural foods with beneficial nutritional characteristics which can help to palliate or recover this highly prevalent nutritional deficiency. In this sense, goat milk is a natural food with beneficial nutritional characteristics which can help to reach these goals. Goat milk consumption leads to a better recovery of body Fe stores, minimizing Ca-Fe interactions and improving Fe status and its absorption and increases the Cu bioavailability, an essential mineral for erythropoiesis. In addition, goat milk consumption improves DNA stability, due to the quality its fat, together with the high levels of bioavailable Mg and Zn, even during chronic Fe-overload. Caprine milk also has positive effects on antioxidant defence, even in a situation of Fe overload, limiting lipid peroxidation and improving antioxidant status. Finally improves bone turnover, impaired by Fe-deficiency, increasing bone formation and diminishing parathorme levels. Therefore, inclusion of goat milk is recommended in the diet of people, who suffer nutritional Fe deficiency anemia, since this type of milk helps to relieve the adverse effects produced in bone turnover, oxidative stress and mineral bioavailability due to the Fe deficiency.

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Introduction

Iron deficiency is the most widespread nutritional deficiency in the world. It is the most common cause of anemia during pregnancy. Iron deficiency of nutritional origin is the most frequent cause of microcytic hypochromic anemia, but other conditions such as bleeding, gastro-intestinal malabsorption, Helicobacter pylori infection, malaria, hookworm infections, and schistosomiasis can lead to iron deficiency and anemia. Iron restricted erythropoiesis underlies the anemia of chronic diseases, although several other mechanisms such as suppressed erythropoiesis and poor response to erythropoietin also contribute to this form of anemia [1]. It estimated than 30%–50% of anemia in children and other groups are caused by iron deficiency [2]. Because 1.6 billion people are anemic [3], several hundred million manifest iron deficiency anemia. As such, iron deficiency is the most common cause of anemia worldwide. Iron deficiency anemia afflicts a subset of the two billion people worldwide who are nutritionally iron deficient [4]. Therefore, the health burden of iron deficiency may be extrapolated from the global prevalence of anemia.

Local economics generally dictate the level of nutrition worldwide. The diet, by itself, infrequently causes iron deficiency anemia in the absence of severe malnourishment or a comorbidity. A balanced diet is usually sufficient to prevent anemia, however, the diet becomes far more relevant when the iron stores are lost, or anemia has already developed, and the host requires additional iron absorption from the gut for recovery [5]. This occurs especially during blood loss, rapid growth during infancy, malaria, and hookworm. In these settings, the diet and iron supplements become critical for maintaining iron availability. Supplemental dietary iron may be needed, because the average Western diet is not sufficient to meet the needs during pregnancy [6]. In addition to the iron content itself, the bioavailability of iron for absorption depends largely on the dietary components [7]. Iron in the form of heme is especially bioavailable, and meat-containing diets are also beneficial [8]. Vitamin C improves dietary availability of iron as well as avoidance of tea or other iron-chelating substances [9]. Numerous approaches are being tried to improve iron availability in the diet with the goal of low-cost and culturally acceptable implementation among the underprivileged [10]. In this sense, as discussed in the current review, goat milk is a natural food with beneficial nutritional characteristics which can help to palliate or recover this highly prevalent nutritional deficiency.

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Goat Milk

Dairy goat and dairy sheep farming are a vital part of the national economy in many countries, especially in the Mediterranean and Middle-East region and are particularly well organized in France, Italy, Spain and Greece [11]. Goat milk is wanted or even needed by people of all income groups. Despite the much larger volume available of cow milk, it's usually cheaper production and therefore, lower market price, the production and marketing of goat milk and its products is therefore, an essential niche in the total dairy industry sector. Goat milk differs from cow or human milk in having better digestibility, alkalinity, buffering capacity and certain therapeutic values in medicine and human nutrition [12, 13]. Goat milk has been studied as a natural food with excellent nutritional properties. Although the consumption of goat milk and its products is currently low, its acceptance is rising with the current trend in favor of high quality, nutritious and healthy foods [14]. The importance of goat milk as a food resides in its high digestibility and nutritional value, as well as its therapeutic and dietary characteristics [15, 16].

Caprine milk is an excellent source of high quality protein, easily absorbed [17] and more digestible than cow milk due to smaller fat globule size and higher contents of short- and medium-chain fatty acids [18]. The smaller-sized fat globules provide a better dispersion and a more homogeneous mixture of fat in the milk, and their larger surface area enhances further pancreatic lipase activity, making goat milk easier to digest [14, 19]. Goat milk has a high proportion of short- and medium-chain saturated fatty acids, such as butyric (C4:0), caproic (C6:0), caprylic (C8:0) and capric (C10:0), and long-chain mono- and polyunsaturated fatty acids [18]. The fat sources of medium-chain triglycerides (MCT) may be advantageous under certain circumstances since they are absorbed intact and do not undergo degradation and reesterification processes. MCT are more readily hydrolyzed by pancreatic enzymes than is long-chain triglyceride fat. Micelle formation is not required for absorption, since the molecules are taken up directly into the portal vein. The fatty acids within MCT penetrate the mitochondria of hepatic cells, independently of carnitine acyl-CoA transferase [20, 21]. Thus they contribute to easier, faster digestion, a feature which makes them especially suitable for post-resection feeding. Finally, these MCT fatty acids are oxidized to produce a rapid energy discharge that can be used in various metabolic processes and produce lower deposits of fat within the organism [18]. In addition, weight gain was improved with goat milk in the diet, compared to cow milk, and levels of cholesterol were reduced, while triglyceride, High Density Lipoproteins values remained normal [22]. It was concluded that the consumption of goat milk reduces total cholesterol levels and the Low Density Lipoproteins fraction because of the higher presence MCT (36% in goat milk versus 21% in cow milk), which decreases the synthesis of endogenous cholesterol.

Noteworthy minerals include calcium and phosphorus, which feature high digestibility levels, partly because they are associated with milk casein and also are present in optimum proportions for absorption (Ca:P 1.0:1.5). Goat milk as a substitute for cow milk was studied in 38 children during a 5 months period [23]. The children on goat milk surpassed those on cow milk in weight gain, height, skeletal mineralization, and blood serum contents of vitamin A, calcium, thiamin, riboflavin, niacin and hemoglobin. Therefore, goat milk supplies adequate amounts of vitamin A, thiamine, riboflavin and pantothenic acid. The only negative aspect of the composition of goat milk concerns its low content of folic acid [18, 24] and vitamin B_{12} [18, 25]. Goat milk, taking into account its nutrient content, constitutes an alternative to cow milk that is highly beneficial in certain aspects of human nutrition, especially for children. Many of the adverse reactions that may be produced by consuming cow milk, and especially those concerning certain protein fractions, as well as lactose intolerance, can often be avoided by substituting it with goat milk [18]. Hence, goat milk is recommended for infants, old and convalescent people. In addition to this, fatty acids like caproic, caprylic and capric are reported to have great medicinal values for patients suffering from a variety of malabsorption, childhood epilepsy, cystic fibrosis, gallstones [26] and anemia [27].

Influence of Dietary Goat Consumption on Anemia Recovery

Influence of Dietary Goat Consumption on Iron Metabolism

In a study by Nestares et al. [28], the authors reported that with goat milk there is a better recovery of body Fe stores in anemic rats, despite Ca-supplementation. In this study it is noteworthy that despite high Ca content, a goat milk diet resulted in minimal Ca-Fe interactions and did not adversely affect Fe status in rats with Fe-deficiency anemia, improving nutritive Fe utilization. The greater nutritive utilization of Fe found with goat milk, could be due to various nutritional factors; goats' milk fat is richer in MCT than the fat obtained from cows' milk, 36 vs. 21%, [22]. The MCT in the diet are oxidized, providing fast energy discharge that can be used in several metabolic pathways [21] and thus contribute to increasing the synthesis of carrier proteins and hence Fe absorption

Numerous dietary components, present in greater quantities in goat milk than in cow milk [27], are capable of reducing Fe (III) to Fe (II), including ascorbic acid [29], and amino acids such as lysine [30] and cysteine [31]. In addition, goat milk has almost twice the vitamin A content than cow milk [27], vitamin that may mobilize available Fe stores and use them to form hemoglobin [32]. On the other hand, the b-carotene improves Fe uptake and overcomes the inhibition by potent inhibitors of Fe absorption [33]. Goats' milk also has higher vitamin D content than cows' milk [27], promoter of the active component in the absorptive process of Fe which has been reported previously [34]. The protein of goat milk is more soluble than that of cow milk and contains a higher proportion of other soluble proteins (β-lactoglobulin, α-lactoalbumin and serum albumin). The proteins offered by goat milk usually have a lower proportion of caseins and consequently a higher quantity of soluble serum proteins. This fact, together with their animal origin [35], could lead to higher absorption of these proteins and thus favor Fe utilization.

Influence of Dietary Goat Consumption on Copper Metabolism During Anemia Recovery

Goat's milk has greater MCT content than cow's milk [27], and these fatty acids favor the intestinal transport of nutrients (including Cu), because they have a trophic effect on the small intestine, improving uptake and transport through the enterocyte basolateral membrane [36]. MCT are absorbed without re-esterification and directly enter portal circulation where they can be

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metabolized to obtain energy. Fe-deficiency anemia enhances the digestive and metabolic utilization of Cu, because a deficiency of divalent Fe cations in the intestine can increase the absorption of other divalent cations, including Cu [37].

Some studies on isolated epithelial cells, suggest that the main intestinal Fe transporter DMT1 (divalent metal transporter 1) can also transport Cu across the apical membrane [38, 39] and this transporter could be regulated by both Fe and Cu [38]. Extended periods of iron deficiency could lead to an up-regulation of DMT1 expression which subsequently produces an increase in Cu absorption in Fe deficient animals. In addition, Gómez-Ayala et al. [34] showed that in Fe deficiency, Cu absorption increases. Dietary Cu is acquired via the small intestine through a process that is not fully understood, but earlier studies showing the major involvement of the mammalian transporter Copper Transport Protein 1 (CTR1) in cellular copper uptake led to the assumption that in enterocytes CTR1 mediates the acquisition of dietary copper at the apical membrane [40]. This Cu transporter is specific for Cu, and Fe is therefore not expected to interfere with Cu absorption, so CTR1 could not be involved in the increase in Cu absorption in situation of Fe deficiency. On the other hand, Domellöf et al. [41] found that Fe supplementation does not affect Cu absorption in breastfed infants.

Adequate dietary Cu intake and absorption is essential for efficient absorption and utilization of dietary Fe. Reeves and DeMars [42] found that Cu-deficient animal models retained less dietary 59Fe than Cu-adequate rats using whole-body 59Fe counting. Cu facilitates intestinal Fe absorption by promoting Cu-dependent ferroxidase (hephaestin) activity in the duodenal enterocyte. Signs of Fe deficiency such as low serum Fe and anemia appear in weaning rats within a few days of consuming a Cu-deficient diet [43]. This finding suggests a very important role for Cu in Fe absorption. In addition, Cu affects the Cu-dependent ferroxidase activity of ceruloplasmin, a plasma enzyme that catalyzes the oxidation of ferrous ion into the ferric ion required for hemoglobin synthesis. Afterwards, hemoglobin is transported from hepatic stores to the bone marrow to be used in erythropoiesis [44]. Cu-deficient rats are anemic and ceruloplasmin activity is reduced to near zero [42].

Comparison of both milk shows that the Cu content in sternum, kidney, spleen, and heart is higher for both the control and Fe-deficient animals fed on the goat's milk compared to the cow's milk diet. Moreover, Cu in the kidney was two-fold higher when iron deficient rats were given the Ca-fortified goat's milk, as compared to a cow's milk diet. Goat's milk diets, with both normal Ca and elevated Ca, favored higher Cu deposition in the sternum, kidney, spleen, and heart in comparison to the cow's milk diet. This fact is probably a consequence of higher Cu absorption and retention as indicated above. For all groups, the highest concentration of Cu was found in the kidneys. This result is in agreement with a report by Linder [45] who showed that Cu distribution throughout the organism is accomplished in two phases. The first phase involves the transfer of Cu from the intestine to the liver and the kidneys, and the second phase involves distribution from the liver to the other organs. The kidney is rich in Cu, and as has been shown by Barrionuevo et al. [46] this organ consistently reflects Cu absorption and metabolism. However, in this study the renal copper concentration did not always reflect Cu absorption and metabolism.

Whereas goat's milk diet fortified with Ca raised the quantity of Cu deposited in the sternum in the Fe-deficient animals, the con-

trary effect was observed with the cow's milk diet; it can be related with the negative effect of Ca fortification on Cu retention with the cow's milk diet, whereas with the goat's milk diet Cu retention is not affected. Moreover, this finding of elevated Cu in the sternum and spleen may be very important because this is a required mineral in the formation of erythrocytes [44], and these are important organs in the erythrocyte life cycle.

Influence Of Dietary Goat And Cow Milk On Bone Turnover During Anemia Recovery

Díaz-Castro et al. [47] reported that in severe Fe-deficiency, bone matrix formation diminished as revealed by the lower amount of procollagen type I N-terminal propeptide and bone resorption process increased as shown by the increase of serum parathyroid hormone, tartrate-resistant acid phosphatase and levels of degradation products from C-terminal telopeptides of type I collagen released to the serum. In addition, mineralization process was also affected by Fe deficiency, because Ca and P content in femur decreased markedly.

Diaz-Castro et al. [48] reported that in only 10 days of supplying goat milk, bone demineralization induced by Fe deficiency begins to recover, as evidenced by the increase of the bone formation biomarker Procollagen type I N-terminal propeptide (PINP) and diminishing parathormone levels. If the consumption of milk-based diets is more prolonged (30 or 50 days), the parameters of bone remodeling recover with both milk-based diets, though the goat milk restores before this process and favors the mineralization of femur and sternum, improving bone metabolism and hematopoietic process. The beneficial effect of goat milk on mineral metabolism has been well documented, improving Fe bioavailability [27, 28], which becomes available in the hydroxylation processes and then in the biosynthesis of the vitamin D. It is well known that 25 - hydroxycholcalciferol-1-hydroxylase is located within the renal mitochondria and this enzyme is Fe-dependent. Moreover, Fe exerts its influence on bone turnover by affecting type I collagen synthesis and maturation. Fe is an essential cofactor for prolyl and lysyl hydroxylases, enzymes that catalyze an ascorbate-dependent hydroxylation of prolyl and lysyl residues, essential steps prior to crosslinking by lysyl oxidase. Therefore, an improvement in Fe bioavailability would contribute to increase cross-linking activity and, subsequently, stronger collagen fibers. This fact supports the increase in the PINP found in animals fed with goat milk-based diets, reflecting faithfully the higher amount of bone matrix developed. With regard to PTH levels, the supply of goat milk during 10 days, produced a decrease of this hormone in the anemic animals, and an increase in those who consumed cow milk. These results can be explained by the increase in nutritive utilization of Ca, consequence of the greater absorption of this mineral, as previously reported Campos et al. [49]. According to Hale et al. [50], PINP levels can be correlated directly with PTH levels and recent studies reveal that at intermittent doses and within the physiological range, the PTH favors the bone formation through an increase of the number of osteoblasts [51], since the PTH stimulates the transformation of osteocites in osteoblasts [52] and diminishes the apoptosis of these cells [53].

Influence Of Dietary Goat Milk On Oxidative Stress During Anemia Recovery

As a result of the regular cell metabolism, the anion superoxide ($O_2^{\bullet-}$) is converted into H_2O_2 by the ubiquitous enzyme superox-

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ide dismutase (SOD). Later, H_2O_2 produced in this reaction is converted into harmless compounds by the activities of catalase (CAT) and glutathione peroxidase (GPx); therefore, SOD is the first line of enzymatic defence against free radicals. During anemia recovery, Díaz-Castro et al. [47] recorded an increased activity of SOD in the groups fed the cow milk-based diet, revealing that these animals feature a higher generation of radicals $O_2^{\bullet-}$ than those fed the goat milk-based diet, either with normal Fe content or Fe overload, in all the organs studied, which indicates an increase in the production of H_2O_2, directly correlated with the rate of neutralisation of radicals $O_2^{\bullet-}$. Alférez et al. [54] and Díaz-Castro et al. [55] demonstrated that goat milk consumption improves Zn bioavailability, a mineral with antioxidant capacity [56]. In addition, this type of milk has a better lipid quality than cows' milk [22]; therefore, the generation of free radicals is lower when goat milk is supplied, in comparison with cows' milk, which can be linked to the higher rate of lipid peroxidation achieved in animals fed cows' milk. Díaz-Castro et al. [47] also showed that the slightly modified activity of CAT and GPx in animals fed the cow milk based-diet indicates that the remarkable increase observed in SOD, which is shown to be connected to an increment of the formation of hydroperoxides and CAT and GPx, is insufficient to neutralize and scavenge this high output of H_2O_2. Fe overload increases the production of reactive oxygen species, which is linked to the higher levels of SOD in order to remove the excessive production of $O_2^{\bullet-}$. The increase in thiobarbituric acid-reactive substances (TBARS) is more pronounced in animals receiving the cow milk that in those fed the goat milk. This lower trend to prevent lipid peroxidation in animals fed the goat milk-based diet can be due to the beneficial nutritional characteristics of this type of milk that increases the bioavailability of antioxidant minerals, such as Zn [54, 55]. Several metals may interact with Zn in biological systems, and this interaction could have beneficial effects, preventing undesirable Fe-mediated damage, so Zn can replace Fe and reduce oxidation in the plasma membrane. Moreover, Zn could avoid lipid peroxidation because this mineral competes with Fe for binding sites on the cell membrane [56]. On the other hand, the better nutritive utilisation of goat milk fat [22] provides a lower substrate for lipid peroxidation and consequently decreases the generation of free radicals in animals consuming this type of milk, explaining once more the lower TBARS levels found in the groups consuming the goat milk.

Díaz-Castro et al. [57] have also reported the positive role on genomic stability of the habitual consumption of goat milk, even during Fe-overloading feeding regime, fact that could be due, at least in part to the high bioavailability of Mg [28] and Zn [55], together with its better fat quality [22]. Mg metabolism enhances genomic stability because of the following: DNA is continuously damaged by environmental mutagens and by endogenous processes. To keep mutation frequencies low, cells have evolved different types of DNA repair systems. Nucleotide excision repair is mainly involved in the removal of DNA damage induced by environmental mutagens, and Mg is an essential cofactor in virtually all steps of nucleotide excision repair [58]. Secondly, endogenous DNA damage is mainly repaired by base excision repair (BER). According to current models, BER is initiated by the removal of the modified base by a specific N-glycosylase, an enzyme that is activated mainly by Mg [59]. The third DNA repair system is the mismatch-repair pathway which contributes greatly to genomic stability by correcting replication errors [60]. It has been suggested that the enzymatic activity of MutS and MutL may play a

role in switching from a mismatch-repair initiation to a processing complex. It has however been shown that MutL has an absolute requirement for Mg; in the absence of Mg, the MutL-ATP association is abolished completely [61]. Moreover, Mg is also required for double-strand break repair [62]. On the other hand, Díaz-Castro et al. [55] reported that the bioavailability of Zn is enhanced by goat milk when compared to cows' milk. This improvement in Zn metabolism could contribute to the protective effect of goat milk on DNA against oxidative damage. Moreover, the high quality of the goat milk fat would contribute to its positive effect on DNA stability. In this regard, as previously reported [22] goat milk fat is nutritionally superior that of cow milk. It has a higher content of carnitine that enters the mitochondria, to increase the rate of ß-oxidation [63]. Moreover, goat milk has a high carnitine content, which certainly would increase the energy production derived from fatty acids and so the substrate for lipid peroxidation would be lower, consequently reducing free radicals production with this type of milk, that may have a positive influence on the stability of the DNA

Conclusion

The goat milk improves Fe metabolism, favoring the recovery of the Fe-deficiency anemia. In addition, it has positive effects on Cu metabolism, the evoked oxidative stress and bone turnover during the anemia recovery. In the light of these considerations, it is recommended that this natural food should be included in the diet of the general population and especially in that of people suffering from Fe-deficiency anemia.

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