British Journal of Nutrition (2019), 122, 603–604

doi:10.1017/S0007114519001569

British Journal of Nutrition

Invited Commentary

Invited commentary in response to: Vitamin D_3 supplementation for 8 weeks leads to improved haematological status following the consumption of an iron-fortified breakfast cereal: a double-blind randomised controlled trial in iron-deficient women

Fe deficiency is still the most common and widespread micronutrient deficiency in the world, being the most common cause of anaemia[1]. Due to Fe losses through menstruation, women at childbearing age are one of the population groups at greater risk for developing Fe deficiency and anaemia[2]. Recently, data from the WHO showed that global prevalence of anaemia in women of reproductive age in 2016 was 32·8 %, and that it has been growing since 2010 (30·3 %), both in developed and in developing countries[3]. These data are worrisome, taking into account the WHO that included a 50 % reduction in anaemia for women of reproductive age as one of its six global nutritional targets for 2025[4]. To this end, the fortification of food with Fe is considered the most cost-effective prevention strategy[5]. However, due to the multifactorial aetiology of the Fe deficiency and the amounts of factors that influence Fe bioavailability and absorption[6], it is necessary for the development of dietary Fe interventions that focus on specific populations, instead of the general population.

In this regard, Ahmad-Fuzi & Mushtaq[7] recently reported that the daily consumption of a supplement of vitamin D_3 with an Fe-fortified breakfast cereal led to an improvement in Fe status in women with low Fe stores. This intervention study controlled with placebo was performed in fifty women with low Fe stores (ferritin <20 μg/l), who were randomised in two groups to consume daily a portion of 60 g of an Fe-fortified breakfast cereal (which supplied 9 mg Fe) with either vitamin D_3 (38 μg) or a placebo. After 8 weeks of intervention, the group who consumed the vitamin D supplement significantly increased Hb levels (up to 4 g/l) and haematocrit (up to 1·8 %) compared with the group that consumed the placebo. Moreover, the researchers observed that the 62 % of these women presented also vitamin D deficiency (plasma 25-hydroxyvitamin D (25(OH)D) <30 nmol/l) and, of those, the 13 % were anaemic (Hb <110 g/l) and the 61 % were Fe deficient (ferritin <15 μg/l).

These results support the hypothesis about a possible association between Fe status and vitamin D status, previously observed in several observational studies in various healthy and diseased populations. Vitamin D deficiency has been associated with increased risk of anaemia in healthy North-American[8] and Korean children and adolescents[9], in Korean[10–12] and Spanish[13] females, in elderly populations[14,15] and in patients with chronic kidney disease[16]. However, the mechanisms underlying this relationship remain unclear and may be bidirectional. On one hand, vitamin D has been proposed to promote erythropoiesis and Fe recycling by increasing erythroid progenitor proliferation, decreasing pro-inflammatory cytokines and suppressing hepcidin expression[17]. On the other hand, Fe is essential for vitamin D metabolism, as all the vitamin D-related cytochromes catalyse single or multiple hydroxylation reactions on specific carbons of the vitamin D substrate using a haem-bound Fe[18].

Despite this, only one study[19], besides that performed by Ahmad-Fuzi & Mushtaq[7], evaluated if the supplementation with vitamin D_3 exerted an additional effect on Fe status in women with Fe deficiency consuming an Fe-fortified food. Both studies reported very similar results, finding an increase in Hb and haematocrit in the group consuming the vitamin D *v.* placebo after 8 weeks of intervention[7,19]. Moreover, Ahmad-Fuzi & Mushtaq[7] found a significant and positive association between the increase of vitamin D-binding protein concentration, a 25(OH)D transporter related to the biological activity of vitamin D[20], and the erythrocytes count, Hb, haematocrit and mean corpuscular volume levels. All these results support the hypothesis about the role of vitamin D in enhancing erythropoiesis by increasing burst-forming unit-erythroid proliferation and having a synergistic effect with erythropoietin to further enhance erythroid progenitor cell proliferation[17]. However, they did not find differences in hepcidin levels during intervention, nor between vitamin D and placebo group, on the contrary to what was found in other studies, in which vitamin D supplementation was related to reduced circulating hepcidin levels in healthy subjects[21–23]. The authors attributed this to the dose of vitamin D, much lower in their study and probably not enough to affect hepcidin expression. But it is also important to note that baseline hepcidin levels in these women with low Fe stores were much lower than those in the healthy adults[21–23], which correspond to their Fe status, but may hinder the detection of a possible decrease.

Another key point of the commented study[7] is the matrix in which Fe was provided. Breakfast cereal is a very common and suitable vehicle to be fortified with Fe[24]. However, the phytic acid contained in the breakfast cereal may inhibit Fe absorption[25], as well as the Ca and casein contained in the milk consumed with the cereal[19]. In the absence of an Fe-absorption enhancer, such as ascorbic acid[26,27], it cannot be ruled out that the non-increase in ferritin or other Fe parameters observed in the volunteers who performed the commented intervention may be due to an ineffective Fe absorption and, therefore, to a lack of available Fe for metabolism.

The Ahmad-Fuzi & Mushtaq study[7] puts on the spot the old but unsolved Fe-deficiency anaemia issue. There is increased evidence that vitamin D can be implicated in Fe metabolism

and may play an important role in Fe-deficiency recovery. However, the few studies that evaluated if supplementation with vitamin D may exert an additional effect on Fe status in Fe-deficient subjects did not observe great changes in Fe status, partly because they used Fe-fortified products that did not assure Fe absorption. Further studies using Fe- and vitamin D-fortified foods that guarantee the bioavailability of both nutrients are needed, in order to assess the role of vitamin D in Fe metabolism and, therefore, to help develop more targeting and effective products to safely reduce Fe-deficiency anaemia in populations at risk.

Acknowledgements

There was no financial support for this work.

The author declares that there are no conflicts of interest.

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