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Heme iron-based dietary intervention for improvement of iron status in young women

Michael Hoppe Ph.D. *, Beatrice Brün M.Sc., Maria Pia Larsson M.Sc., Lotta Moraeus M.Sc., Lena Hulthén Ph.D.

Department of Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

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ABSTRACT

Objective: Conventional iron deficiency treatment with pharmacologic iron doses often causes side effects. Heme iron has high bioavailability and a low capacity to cause gastrointestinal side effects. This study investigated the possibility of using heme iron in the form of blood-based crisp bread as a diet-based treatment program to improve the iron status of women of reproductive age.
Methods: In a 12-wk intervention study, 77 women (mean age 24 y) were assigned to one of four groups: blood-based crisp bread (35 mg of iron [Fe], 27 mg of which was heme Fe), iron supplementation consisting of 35 mg of non-heme iron/day (Fe35), iron supplementation consisting of 60 mg of non-heme iron/day (Fe60), and controls (iron-free tablets).
Results: Body iron increased significantly in the crisp bread group by a median of 2.7 mg/kg (interquartile range 3.1, $n = 18$), in the Fe35 group by 2.7 mg/kg (interquartile range 2.8, $n = 11$), and in the Fe60 group by 4.1 mg/kg (interquartile range 3.6, $n = 13$), whereas no change was observed in the control group. No statistically significant difference in iron status increase was observed between the crisp bread group compared with the two iron-supplemented groups.
Conclusion: Dietary-based treatment containing heme iron has few side effects and can be used efficiently to improve the iron status of women of reproductive age.

Introduction

Iron deficiency is the most common nutrient deficiency globally, affecting an estimated 2 billion people in developed and developing countries [1,2]. The prevalence of iron deficiency in European women of reproductive age has been estimated at 8% to 30% [3]. However, conventional treatment consisting of pharmacologic doses of iron in tablet form often causes side effects such as stomach pain, constipation, diarrhea, and feelings of nausea [4,5]. An important consequence is the risk of low patient compliance in taking the conventional medication [6]. Therefore, identifying treatment options with negligible gastrointestinal side effects would be highly valuable in the battle against iron deficiency in healthy individuals and those who are especially sensitive to such side effects, e.g., patients with short bowel syndrome [7].

Dietary iron can be described as heme or non-heme. Heme iron represents a relatively small part of the total dietary iron intake but has a higher bioavailability than non-heme iron [8] and has been demonstrated to have a low ability to cause gastrointestinal side effects [9]. In many cultures around the world, heme iron–rich blood products have been used in the diet. There are also innovative approaches to developing a heme iron concentrate and a heme iron–based supplement/fortifier, e.g., hemoglobin-based meat pigment [10–12]. The potential of microbe-produced heme iron has also been studied [13]. To investigate the benefits of heme iron as a nutrition-based treatment for low iron reserves, this study explored the effectiveness of blood-based crisp bread to improve iron status in young women. The main research question in this study was whether a substitution of part of the diet with blood-based crisp bread each day for a 12-wk period could improve the iron status of healthy non-anemic women of fertile age.

Materials and methods

Study design

A controlled longitudinal intervention study of 12-wk duration was conducted in two stages. In stage 1 (January 2007 through June 2007), 46 female subjects were recruited. Owing to a large number of withdrawals (see RESULTS)

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* Corresponding author. Tel.: +46-31-786-3705; fax: +46-31-786-3101.
E-mail address: michael.hoppe@nutrition.gu.se (M. Hoppe).

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during the intervention in 2007, an additional 31 female subjects were recruited for a second stage (January 2011 through June 2011). Thus, all subjects underwent the intervention during the same, relatively narrow, time of the year. Because there is a risk of differences in dietary habits depending on the season, we considered this a strength. The subjects (total $n = 77$ women) were randomized into the following four intervention groups: blood-based crisp bread, iron supplementation with 35 mg of iron (Fe35), iron supplementation with 60 mg of iron (Fe60), and a negative control group. The evaluation was carried out by assessments of the habitual diet, height and weight, and venous blood samples collected at baseline and after the intervention (Fig. 1).

Ethics

The study protocol was in accord with the Declaration of Helsinki of 1975 as revised in Seoul 2008 and approved by the regional ethics review board in Gothenburg (reg. no. 650-06). Hence, the subjects were informed that they could withdraw from the study at any time without giving a reason.

Subjects

Volunteer female participants of reproductive age were recruited by recruitment posters at two Swedish universities (University of Gothenburg and Chalmers University of Technology). In total, 293 women contacted our research group for additional and more specific information. After obtaining the full study information, most of these 293 women decided not to participate, and some additional subjects were absent at the start. Forty-seven women were excluded according to the exclusion criteria. The inclusion criteria were healthy non-smoking women without anemia (hemoglobin [Hb] concentration >120 g/L), not pregnant or lactating, and not exercising heavily. The exclusion criteria were a blood donation less than 2 mo before the start of the study, medications or dietary supplements (including iron supplements), underlying malabsorption diseases, or other medical problems known to affect iron homeostasis. Because an activated acute-phase reaction has a marked effect on iron homeostasis and iron absorption, it was of great importance to minimize, as much as possible, the devastating effects of infection/inflammation. Thus, the exclusion criteria also included infection/inflammation (see ANTHROPOMETRIC AND LABORATORY MEASUREMENTS).

Dietary assessment

The dietary assessment was performed by a previously used food-frequency questionnaire (FFQ) elucidating habitual meal patterns [14]. To investigate the habitual dietary patterns before and during the study, foods containing dietary elements that affect iron absorption, such as coffee and tea, dairy products, citrus fruit juice, whole meal products, meat, fish, and poultry, were assessed. The weekly intake of meals (breakfast, lunch, and dinner) was also evaluated. The FFQ used in this trial was divided into five sections: breakfast, lunch, dinner, between meals, and other foods. Portion sizes of foods were described in terms of household measurements and standard weights and by photographs of portions of known weights. The weekly intake of meals was evaluated in the FFQ by a checklist of foods and beverages containing dietary elements known to influence iron absorption. The checklist contained a frequency response section to report how often each food item was consumed during a specified period. In short, the FFQ was designed to answer three questions: What foodstuffs are habitually eaten? How much of this foodstuff is eaten at each occasion? How often is this foodstuff eaten? To answer this last question, the subjects had to state the frequency among 10 different options: rarely/never, once a month, twice a month, and one, two, three, four, five, six, or seven times a week.

Blood-based crisp bread

The dietary heme iron used in this study came from blood-based crisp bread, which was baked using whole meal rye flour, sifted wheat and rye flours, water, blood from cattle and pigs, sodium chloride, and bicarbonate. Each daily ration of crisp bread (75 g ≈ 10–11 slices) contained 1.15 MJ and 35 mg of iron, 27 mg of which was heme iron. The iron content of the crisp bread was analyzed as previously described [15,16]. The total phytate phosphorus content in the bread (134 mg/100 g of bread) was analyzed as previously described [17]. The subjects were encouraged to spread their intake throughout the day.

Tablets

The iron tablets (2 per day) used in the Fe35 group were Twinlab Iron Caps (Ideasphere, Inc., American Fork, UT, USA), each containing 18 mg of iron as ferrous fumarate. On four occasions/days during the study, the subjects in the Fe35 group were instructed to consume one tablet. Thus, the mean daily iron intake from the tablets during the 12-wk intervention was 35 mg.

The iron tablets used in the Fe60 group were Erco-Fer tablets (Orion Pharma, Orion Corporation, Espoo, Finland), each containing 60 mg of iron as ferrous fumarate. Placebo tablets that contained no iron but were otherwise identical to Erco-Fer tablets were planned for use in the control group. However, because of a sudden shutdown in the production of Erco-Fer tablets, the company was unable to supply these placebo tablets. Thus, as an ad hoc solution, tablets containing 500 mg of folic acid (Recip AB, Haninge, Sweden) were used in the control group.

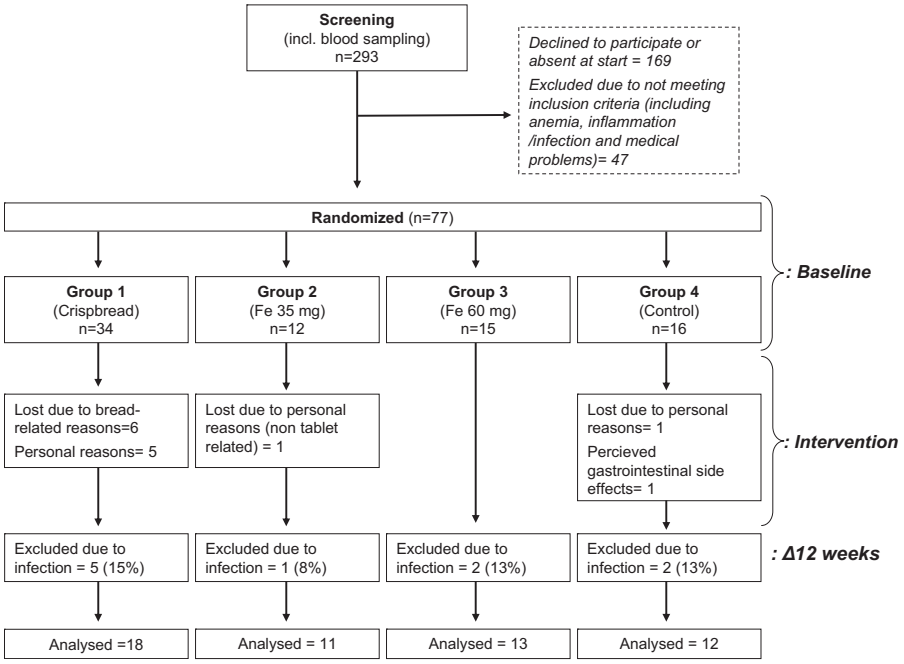

Fig. 1. Study design of the 12-wk intervention study. The subjects were allocated to one of four groups that received a daily ration of 1) 75 g of a blood-based and rye flour-based crisp bread (containing 35 mg of iron, 27 mg of which was heme iron), 2) iron tablets containing 35 mg of iron, 3) iron tablets containing 60 mg of iron, or 4) tablets without iron. Evaluations were at baseline and after 12 wk by the collection of blood samples and assessments of habitual diet, height, and weight.