
Can increased vegetable consumption improve iron status?

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Abstract

Theoretically, vegetable consumption could improve iron status. First, vegetables contain iron. Second, when the provitamin A carotenoids in vegetables improve vitamin A status, the result could be increased iron levels. Most studies on vegetable consumption have focused on improvements in vitamin A status, and only very few have addressed iron status. From a review of the literature and a recent study in Indonesia, we conclude that the data on the effectiveness of vegetables to improve the levels of both nutrients are inconclusive. The bioavailability of both iron and provitamin A carotenoids might be lower than expected. It is necessary to conduct other intervention studies using plant foods, animal foods, and fortified foods. In the meantime, other strategies that have been proved to reduce iron and vitamin A deficiencies should continue.

Background

Food-based approaches to combat deficiencies of micronutrients such as iron and vitamin A deserve great attention, because they are likely to be sustainable in the long term, and the intake of other nutrients will increase simultaneously. Few studies, however, have evaluated the effectiveness of vegetables and fruits to combat iron and vitamin A deficiencies.

Most studies with vegetables have focused primarily on vitamin A status. A well-controlled study showed an increase in serum retinol levels after subjects ate red sweet potato and dark green leafy vegetables [1]. The increase in serum β -carotene after subjects consumed carrots was only 14% to 20% of the increment after an equal dose of purified β -carotene [2, 3], although it was expected to be about 33%. Other investigators failed to report any improvement of serum β -carotene levels after feeding the subjects carrots [4].

According to our recent literature review, evidence that eating fruits and vegetables may improve vitamin A status is inconclusive [5]. Because vegetables contain iron, increased consumption of vegetables would be expected to improve iron status, although the increase might be small because the bioavailability of iron in these foods is poor [6]. It is also possible that if vitamin A status improves after

eating vegetables, iron status will do so as well, because improving the vitamin A status of anaemic subjects also increases haemoglobin levels [7, 8]. Ivygourd (1.1 mg β -carotene/day) given for a relatively short period of two weeks did not improve haematocrit level [9], whereas supplements of vegetables and purified β -carotene (1.2 mg/day) given for three months [10], and papaya (1.2 mg β -carotene/day), amaranth (1.2 mg β -carotene/day), or retinol (300 g/day) given for two months [11], improved haemoglobin concentrations. Another study (Muhilal and Karyadi, personal communication) found no improvement in concentrations of serum retinol and haemoglobin after feeding vegetables (1.9 mg β -carotene/day) for 75 days, but salt fortified with retinol (300 RE/day) improved serum concentrations of retinol and haemoglobin.

Because the findings on the role of vegetables in improving vitamin A status are inconclusive, and only very few studies have investigated their effects on iron status, more research is urgently needed to evaluate dietary approaches, especially those using vegetables, for combating iron and vitamin A deficiencies.

Recent study in Indonesia

We recently investigated whether an additional daily portion of local vegetables can improve iron and vitamin A status in anaemic breastfeeding women in a rural area in the Bogor district, west Java [12]. The intervention lasted 12 weeks. One group received stir-fried vegetables, and a second group received a wafer enriched with iron, β -carotene, folic acid, and vitamin C, to examine the effect of a similar amount of micronutrients in a matrix with better bioavailability. A third group received a non-enriched wafer to control for effects of additional energy intake. Each of the 191 women had a breastfed child age 3 to 17 months, a baseline haematocrit below 38%, and a haemoglobin concentration below 130 g/L as measured by the cyanmethaemoglobin method.*

Assignment to the vegetable or wafer groups was done by village, which was justified by the larger intra-village than inter-village differences. The vegetable supplements contained 100 to 150 g of cassava leaves (*Manihot utilissima*), water spinach (*Ipomoea aquatica*), spinach (*Amaranthus viridis*), or carrots (*Daucus carota*). The wafers were wrapped in blue or red foil and distributed double-blind. The compositions of the prepared vegetable supplements and the enriched wafers as analysed were as follows: all trans- β -carotene: vegetables 3.5 mg, wafers 3.5 mg; iron: vegetables 5.2 mg, wafers 4.8 mg; folic acid: vegetables 130 μ g, wafers 100 μ g; and vitamin C: vegetables 11 mg, wafers 22 mg. The control wafer contained less than 10% of these micronutrients. The fat content of the vegetables was 7.8 g, that of the wafers 4.5 g.

Follow-up data were obtained for 175 women. None of them suffered from clinical infections, but almost all had one or more parasitic infestations. Compliance was ensured by observing the women consume the supplement. Replacement of the participants' own vegetable dishes was avoided by bringing the supplement in the early morning, when the women would not usually eat vegetables. That the vegetables really were a supplement was ascertained by the following observations:

1. The intake of macronutrients, iron, and vitamin A-rich foods, calculated from 24-hour recall questionnaires, remained the same before and during the intervention in all groups.
2. The weight loss was similar in the three groups.
3. The treatment effect was the same in subjects who lost weight as in those who gained weight.

The iron status values, haematocrit, zinc protoporphyrin, and serum concentrations of ferritin and transferrin receptor measured at baseline, and the haemoglobin concentration at three weeks, did not differ among the groups, except for a slightly higher concentration of serum transferrin receptor in the vegetable group compared with the control wafer group. Between the third week and follow-up, the haemoglobin concentrations increased in all groups (baseline mean 109 g/L; 95% confidence interval (95% CI) of the increment 7 to 10 g/L; $n = 175$). Between baseline and follow-up, the serum transferrin receptor concentration decreased in all groups (baseline median 4.25 mg/L; 95% CI of the decrement -0.6 to -0.3 mg/L; $n = 174$). The haematocrit increased in the vegetable and enriched wafer groups. The changes were not significant in all groups, but none of the changes were different among the treatment groups (analysis of covariance). All improvements in iron status seemed to be due to regression to the mean, because all subjects were selected on the basis of a low haemoglobin level, and to the recovery of blood loss from pregnancy and delivery.

The baseline concentrations of retinol in serum and breastmilk and of β -carotene in serum did not differ among the groups. The retinol concentrations in serum and breastmilk of the enriched wafer group showed large increments, one-third and two-thirds, respectively. These were significantly different from the changes in the control wafer group and the vegetable group. Both concentrations did not change in the vegetable group, and breastmilk retinol showed a marginal increase in the control wafer group. The serum β -carotene concentration increased almost fourfold in the enriched wafer group. It increased slightly but without physiological relevance in the vegetable group, and it remained unchanged in the control wafer group.

In summary, improvements in iron status were similar in the three treatment groups, but a physiologically meaningful change of vitamin A status occurred only in the enriched wafer group. It seems that the contents of iron and vitamin C of the vegetables (5.2 and 11.4 mg, respectively) and of the enriched wafer (4.8 and 21.5 mg, respectively) were too small to improve iron status. The bioavailability of iron in vegetables is known to be poor [6]. The enriched wafer contained carbonyl iron, the bioavailability of which seems comparable with that of ferrous sulphate [13] but might be reduced by incorporation in foods [14].

The improvement of vitamin A status of the enriched wafer group seems not to have improved iron status. However, for the women with a baseline serum retinol level below 0.70 $\mu\text{mol/L}$, the increase in haematocrit was significantly greater ($p < .05$) in the enriched wafer group (95% CI 0.01 to 0.02, $n = 20$),

compared with the control wafer group (95% CI -0.01 to 0.01, n = 24), or the vegetable group (95% CI 0.00 to 0.01, n = 19). Increases in haemoglobin levels showed a similar but not significant trend, whereas other iron status values showed no differences among the groups.

The difference in change of iron status between the group that improved in vitamin A status and those that did not was smaller than that observed in other studies. A possible explanation is that higher doses of vitamin A were given in the other studies—a single dose of 110,000 RE [7] or a daily dose of 2,400 RE for eight weeks [8]—which might have caused a change in iron status within a shorter period of time. The very small variation in serum β -carotenes response in the vegetable group suggests that the bioavailability of β -carotene was equally poor for all subjects.

Thus, the main reason for the finding that iron status was not improved by vegetables seems to be that the iron has poor bioavailability and the amount provided was small, whereas the main reason for the finding that vitamin A status was not improved by vegetables seems to be that it was too difficult to break down the matrix in which the carotenoids are captured in the leaves and the complex that they form with proteins for photosynthesis. The difficulty in freeing β -carotene from its matrix might have been aggravated by parasitic infestations.

Conclusion

Because only very few food-intervention studies have looked at iron status, and because the available results are contradictory, no firm conclusions can be drawn as to whether or not vegetables can improve iron status. It is necessary to conduct similar intervention studies with foods of both plant and animal origin and with fortified foods, and to investigate ways to improve the bioavailability of nutrients. Alternative approaches, such as food fortification and promotion of animal foods rich in haem iron and retinol, must be considered. In the meantime, the use of other strategies that have proved to be effective to reduce iron and vitamin A deficiencies should continue.

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Iron deficiency: The problem and approaches to its solution

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Abstract

Anaemia is associated with increased perinatal mortality, increased child morbidity and mortality, behavioural changes and impaired mental development, decreased work performance, increased susceptibility to lead poisoning, and impaired immune competence. Iron-deficiency anaemia is an intractable problem, as indicated by the goal set by world leaders of reducing nutritional anaemia to one-third of 1990 levels by the year 2000, compared with the goals of virtually eliminating deficiencies of vitamin A and of iodine during the same period. To a large extent, this is because intake is less associated with status for iron than for iodine and vitamin A. The demand for iron varies throughout the life cycle, and the bioavailability of iron varies over a wide range because of a number of factors, such as the species of iron compound, the molecular linkage, the amount of nutrient consumed in a meal, the matrix in which the nutrient is incorporated, the absorption modifiers, the nutrient status of the host, genetic factors, other host-related factors, and interactions among factors.

Introduction

Iron deficiency is a problem in both developed and developing countries, affecting about 1,000 million people worldwide, including 370 million women of child-bearing age. In developed countries, it is primarily a problem of these women and young children, and usually occurs as an isolated nutritional problem. In developing countries, such as Indonesia, it extends to older children and usually occurs together with deficiencies of other nutrients [1].

Because of the magnitude of the problem and its serious consequences, a series of meetings has been held in recent years, beginning with the World Summit for Children in New York in 1990, followed in 1991 by the conference on Ending Hidden Hunger in Montreal, and culminating in 1992 with the International Conference on Nutrition in Rome. These led to declarations by heads of state of most countries of the world committing their countries to reducing iron-deficiency anaemia in women of childbearing age to one-third of 1992 levels by the year 2000 [2]. Such a limited goal, compared with the goals of virtually eliminating deficiencies of vitamin A and of iodine, is an admission of the intractability of the problem of iron-deficiency anaemia.

Consequences of iron deficiency

As shown in a series of studies in Indonesia and other countries, attention, learning achievement, and mental development are affected by anaemia in children [3, 4], and these effects can be reversed by iron supplementation when the children are under the age of 10 years but not older [5]. In addition, in Indonesia, iron-deficient rubber plantation labourers were less productive than workers with normal haemoglobin concentrations, and iron supplementation improved their performance [6]. Work performance was particularly impaired when the haemoglobin concentration fell below 100 g/L, which

is 20 to 40 g/L below the lower limit of normal for adults. From the point of view of a government, impairments of mental development and work performance are good reasons to combat iron-deficiency anaemia.

From the point of view of the individual, other aspects of iron deficiency also assume importance. Decreased resistance to infection is due to impairment of both specific and non-specific defense mechanisms. Impairment of specific immunity is particularly noticeable with cell-mediated immunity, whereas oxygen-dependent killing rather than phagocytosis is the most important aspect of non-specific immunity that is affected. An impaired capacity to maintain body temperature in a cold environment is characteristic of iron-deficiency anaemia [7]. Another consequence is lead poisoning, the risk of which is increased in anaemic children, particularly when they are young [8]. Reducing the lead in petrol rather than improving iron status may be the most effective way of approaching this problem. Finally, iron-deficiency anaemia during pregnancy has very serious consequences, leading to increased risk of perinatal mortality and to increased infant mortality [2].

Measuring prevalence of iron deficiency and of iron-deficiency anaemia

In a research environment, a battery of haematological and biochemical measurements can be made, such as haemoglobin, haematocrit, mean corpuscular volume, serum transferrin, serum iron (and transferrin saturation), serum ferritin, free erythrocyte protoporphyrin, and transferrin receptor. However, these methods are generally inappropriate in an operational environment where haemoglobin distribution curves can be used [9]. A shift to the left, compared with a population without anaemia, is indicative of anaemia. In areas where the anaemia is due to iron deficiency, such a shift is seen only in children and women, not in men. If the distribution in men is also shifted to the left, it indicates anaemia due to infection or infestation such as from malaria or from hookworm.

Methods of combating iron deficiency

Several possible approaches to combating iron-deficiency anaemia exist. The most obvious is supplementation with iron preparations. Until the present time, this has been the principal method used in developing countries. Programmes often were ineffective, however, because the target group was not reached, compliance was poor, and the preparations used sometimes had low bioavailability of iron [10]. Compliance will almost certainly be increased when daily schedules are replaced by weekly schedules [10] and when the preparations used contain iron in a more bioavailable form.

Food fortification has proved effective in reducing iron-deficiency anaemia, particularly in the United States. The reason for this is not only that American industry is able to manufacture and market iron-fortified products, but also that legislation and accompanying regulations allow fortification to be maintained. By contrast, in many countries in Europe, legislation and regulations are very restrictive with respect to food fortification.

The technology for fortifying foods with iron has improved much in recent years. Problems of offflavour

have been overcome, and compounds with higher iron bioavailability, such as ferrous fumarate, have been introduced. However, increasing bioavailability by removing inhibitors of iron absorption through fermentation and use of phytases can be effective and, combined with enhancing bioavailability through increased consumption of enhancers such as ascorbic acid, may make fortification unnecessary. This is an area in which much more applied and operations research applicable to developing countries has to be done.

Iron supply can be increased not only by choosing animal products rich in haem iron but also by choosing traditional iron-rich plant foods. Recently, much interest has been expressed in increasing the total amount of iron and the proportion per content that is bioavailable through breeding and genetic engineering [11]. It remains to be seen what can be achieved by these means.

Any programme to control iron deficiency has to take into account other nutrients, infection, and other factors. Folic acid and vitamin B12 are required for the synthesis of the haem molecule in haemoglobin. Supplementation with vitamin A increases haemoglobin levels in anaemic women with marginal or just adequate vitamin A levels [12], probably by an effect on the uptake of iron by the erythropoietic system [13]. Riboflavin supplementation increases haemoglobin levels in riboflavin-deficient subjects [14], probably predominantly by an accelerated rate of epithelial turnover in the small intestine [15].

It is well known that hookworm and malaria are important aetiological factors in nutritional anaemia, so greater efforts must be taken not only to increase iron intake but also to reduce iron losses from these causes. In addition, it should be noted that oral contraception reduces menstrual blood loss and intrauterine contraceptive devices generally increase iron loss.

In addition to choosing an approach or series of approaches to controlling iron-deficiency anaemia, the public has to be mobilized [16]. This involves advocacy to those responsible for making decisions about programmes to control iron deficiency. It is also essential to educate the public to change food habits to eat more haem iron-containing foods and to eat non-haeme iron foods that enhance iron bioavailability. The public must be made aware of the value of consuming foods that enhance non-haem iron bioavailability with meals (orange juice), and of not consuming those that inhibit non-haem iron bioavailability (tea).

Bioavailability

Iron bioavailability has been addressed by research workers [17] but has not yet received the attention it deserves by those responsible for programmes controlling iron deficiency. It is the proportion of iron ingested that becomes available to the body for metabolic processes, and most work in the area is still guided by the algorithm for iron bioavailability developed by Monsen and colleagues in 1978 [18]. In this algorithm, the absorption of haem iron is assumed to be 15% in men and 23% to 35% in women, depending on iron stores. For non-haem iron, absorption depends on bioavailability (low, medium, high) estimated in general terms from the phytate, haem, and ascorbic acid contents of a meal. Thus, for men the range is 2% to 4%, and for women it is 3% to 20%, also depending on iron stores as follows:

- 5% to 20% with low iron stores (0 mg iron);
- 4% to 12% with medium iron stores (250 mg iron);
- 3% to 8% with high iron stores (500 mg iron).

However, it seems to be time to consider more factors when calculating bioavailability. Therefore, we propose an approach that focuses on the following [19] species of iron compound, molecular linkage, amount of nutrient consumed in a meal, matrix in which the nutrient is incorporated, absorption modifiers, nutrient status of the host, genetic factors, other host-related factors, and interactions.

Species of iron

Iron is probably absorbed only in the ferrous form, so elemental iron has to be oxidized and ferric iron reduced to ferrous iron before absorption. Thus, it is important to know the proportion of the various atomic species in a food.

Molecular linkage

Haem iron is absorbed to a much greater extent than non-haem iron. In iron-deficient persons, the absorption of haem iron is about 35% and the absorption of non-haem iron is about 25%, when enhancers are abundant (see below). The corresponding figures in an iron-replete subject are 15% and 2%. Enhancers and inhibitors exert their effect only on the absorption of non-haem iron, although the inhibition of absorption of non-haem iron by dietary calcium is an exception. Ferrous iron in the form of fumarate is absorbed much better than ferrous sulphate.

An additional problem with elemental iron is the particle size, as fine particles, such as iron reductum produced by reducing ferrous iron, are absorbed much better than coarser particles.

Amount of iron in the diet

Iron absorption is reduced to some extent at increased levels of iron intake. More important, perhaps, is the effect of high intake that down-regulates the capacity of the intestinal epithelium to absorb iron subsequently.

Food matrix

Matrix effects are probably more pronounced for non-haem than for haem iron. This is based on experience with the low bioavailability of plant carotenoids [20].

Absorption modifiers

A number of compounds in the diet affect the bioavailability of iron. Ascorbic acid in the diet enhances

the absorption of non-haem iron, probably by reducing ferric iron to ferrous iron, the form in which iron is probably absorbed from the intestine. Dietary ascorbic acid probably also prevents the precipitation in the intestinal lumen of ferric complexes such as ferric hydroxide. The effect of ascorbic acid on non-haem iron absorption is marked and strongly dose related, especially for the first 50 mg of ascorbic acid in a meal.

A second factor is meat, which stimulates non-haem iron absorption. This is due in part to the haem in the diet, but is possibly also a result of other dietary factors such as individual amino acids. Acidic foods also stimulate iron absorption, which probably explains the stimulatory effects of fermented foods such as sauerkraut, which is prepared from cabbage, and enjera, which is prepared from the cereal teff in Ethiopia.

Phytate (inositol phosphate) is perhaps the most important dietary constituent inhibiting non-haem iron absorption, but fortunately its effect can be counteracted by increasing ascorbic acid intake. It is interesting to note that inositol with up to three phosphate groups stimulates iron absorption, whereas inositol with four to six phosphate groups inhibits absorption. Another powerful inhibitor of absorption is the group of plant phenolic compounds such as those from tea and coffee, and their effect is also reversed by dietary ascorbic acid.

Other minerals can influence the absorption of iron. As mentioned, calcium inhibits the absorption of not only non-haem but also haem iron. This inhibition is not reversed by ascorbic acid. Magnesium acts in the same way as calcium and to the same extent. However, interference from dietary magnesium is less because the intake is less than that of calcium. Manganese, but not zinc, in the diet reduces iron absorption.

Nutrient status of the host

Iron status has a marked effect on absorption of iron, especially non-haem iron. It is affected not only by intake and absorption but also by iron utilization and losses. Utilization varies throughout the life cycle, and losses are increased by menstruation, haemorrhage, blood donation, the action of parasites such as hookworm, and malaria.

Genetic constitution of the host

Iron overload is a genetic condition in which people absorb large amounts of iron that is not subject to negative feedback. The problem can be overcome by introducing a programme of screening for iron nutriture abnormalities, with the aim of detecting individuals with anaemia and those with iron overload.

Other host-related factors

Intestinal parasites such as *Giardia lamblia* and *Ascaris lumbricoides* possibly reduce the absorption of iron. Such a negative effect on bioavailability is quite separate from that of hookworm in increasing iron

loss from the body.

Interactions among the above

All of these factors should be taken into account when designing a programme to control iron-deficiency anaemia. When trying to evaluate the magnitude of the effects of these factors, not only should the effects be quantified independently of one another, but the interaction among the factors should also be measured.

It is hoped that in the future we will be able to evaluate the impact of all these variables on iron absorption. It will then be possible to come up with mathematical values to fit our proposed approach, which could replace the algorithm of Monsen et al. that has served us well for nearly 20 years [18]. Particular attention should be paid to absorption modifiers and to parasites.

Conclusion

Iron-deficiency anaemia is a serious problem because of its impact on individuals and because of the large number of individuals it affects. Much work has been and is being done to control the problem, but programmes should pay more attention to increasing iron bioavailability rather than iron intake.

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