

Healthy persons at risk for iron substitution

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Now in *Swiss Medical Weekly*, Clénin, a renowned expert in sports medicine, contributes a current opinion article on the – cool – topic of iron deficiency treatment [1]. The subject's coolness is related to “iron deficiency without anaemia (in otherwise healthy persons)”, i.e., to the focus of the article on nonanaemic iron deficiency (NAID). NAID is a clinical entity on the brink of becoming “a disease in its own right”, as a recent systematic review expressed it [2]. Or, seen from an altogether different viewpoint: with NAID, are we treating abnormal laboratory results instead of sick people? On the basis of the in-depth pathophysiological information provided in the article, NAID is easily imaginable as a nosological entity. The picture of NAID as a disease may, however, require a more active imagination when one considers a person with NAID who is leading a lifestyle prone to cause iron store depletion. In this context, the question arises whether treatment of “iron deficiency at all its levels” as demanded by Clénin means counselling for lifestyle change or iron supplementation.

The goal of this editorial is to provide alternative views on the subject, thereby possibly delineating the border between reasonable and debatable foundations for iron substitution in NAID.

“Otherwise healthy persons”

The treatment strategy demanded in this review appears obsolete when recent views on the meaning of the term “health” are considered. The World Health Organization (WHO) definition of health formulated in 1948 is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [3]. Though unchanged over a long period of time, this initially progressive and broad definition has been criticised because of its absoluteness and neglect of dynamic features essential for biological systems. Recently, the introduction of the aspect of self-adaptation into the definition, in the sense of the capacity to *maintain* “well-being” has been proposed [4]. Thus, attributes of “allostasis” (maintenance of physiological homeostasis) and resilience (the antonym of rigidity) have come into play, which would correct the absoluteness of the word “complete” in the context of well-being [4], where an attribute for dynamic adjustments to a biological system's changing states would be appropriate. It has been acknowledged that the WHO definition carries a risk of medicalisation of society [5]. The treatment of NAID “in otherwise healthy persons” already exemplifies this

problem semantically: the adverb “otherwise” in front of “healthy” does not render the concerned person diseased, it rather expresses an uncertainty regarding the relevance of iron deficiency to the health status of the nonanaemic person. If NAID were a disease in all affected persons, it would be termed so, and consequently they could not be described as being “healthy, except for” (“otherwise”).

Nonanaemic iron deficiency

NAID cannot be generally regarded as a disease. In the article by Clénin, the crucial and well-developed sections on the biological function of iron provide a rationale for the recognition that iron deficiency potentially develops into a disease or diseases, most often into anaemia. However, the focus of the review is, intentionally, on iron deficiency in the absence of anaemia: NAID. In this context, it is deceptive to introduce the article with epidemiological information on the magnitude of iron deficiency in developing countries, because there it is a disease – anaemia – which is, explicitly, not within the scope of the review. Furthermore, the prevalence of iron deficiency obviously depends on the ferritin cut-off level used for its definition, and this has been set quite variably at 15, 30 or even 50 µg/l [2, 6, 7]. Accordingly, in the survey by Schleiffenbaum et al. among 7484 Swiss male army draftees, 7.8% (587/7484) presented with a ferritin concentration below 30 µg/l, but the prevalence of iron deficiency dropped to less than 3% when a ferritin threshold of 15 µg/l was applied [6]. A ferritin threshold of 16 µg/l is used by the WHO to define iron deficiency [8], but this limit may be lower, at 12 µg/l, in young men [9]. It is, however, arbitrary to employ a ferritin threshold of 30 µg/l simply based on the unfounded explanation that “if not only erythropoiesis but also clinical symptoms of iron deficiency such as fatigue ... are considered, the cut-off may be slightly higher” [1]. In support of a threshold at 15 µg/l, Krayenbuehl et al. documented in their randomised controlled trial among 116 premenopausal nonanaemic women presenting with fatigue that only the subgroup with ferritin ≤15 µg/l showed symptomatic improvement over the course of 6 weeks in response to parenteral iron [7]. Notably, for the *entire* group of women who were eligible for study inclusion at a higher ferritin threshold of ≤50 µg/l, intravenous administration of 800 mg iron was not efficacious in reducing fatigue [7].

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At risk for iron deficiency

In the above context, it is agreed that, as stated by Clénin, a person with NAID suffering from (chronic) fatigue should be treated with iron; but the threshold for defining iron deficiency ought to be set at a lower ferritin level of 15 µg/l. The systematic review of Pratt and Khan supports such a recommendation, because in NAID they found iron supplementation beneficial exclusively for those with fatigue (objectively, on self-rating scores) [2]. In addition they observed an association of NAID during pregnancy with reduced birth weight [2]. No other pathophysiological candidate variables potentially associated with iron deficiency in NAID, or beneficially influenced by iron supplementation, could be detected in this review, including maximal oxygen uptake during exercise, respiratory exchange rate, and different psychomotor and mental developmental endpoints in children [2]. As a consequence, this narrows the relevant NAID target population to those with fatigue irrespective of gender and to premenopausal women without fatigue but with heavy menstruation. In other words, adolescents, underweight persons, those preferring a vegetarian or vegan diet, and competitive sports athletes (the populations depicted on the flowchart in the article by Clénin [1]) can be regarded at risk for developing iron deficiency, but should not be cared for according to the credo expressed in the review: "...iron deficiency at all levels, nonanaemic iron deficiency...should be treated." [1]. Among adolescents, underweight persons and those with eating disorders, therapeutic decisions concerning NAID should be individualised.

At risk for iron supplementation

Persons with NAID preferring a vegetarian or vegan diet and competitive sports athletes with NAID ought not to be considered for pharmacological iron supplementation for the following reasons, which were partly given in more detail above: there is no disease to be cured, there is no evidence for the efficacy of iron supplementation, and pharmacological iron supplementation has side effects. In this regard, the populations mentioned are less at risk from iron deficiency than from its substitution. Furthermore, it should not be a general principle that one of medicine's duties is to pharmacologically alleviate lifestyle choices. The

nutritional deficits related to a vegetarian or vegan diet can, should this diet cause more harm than help, be reversed by an obvious dietary change, which could be regarded as an example of resilience, itself an essential feature of health. In competitive athletes, the demands for performance-enhancing or -maintaining medical actions are ubiquitous and far reaching, but they should not be fulfilled by pharmacological means. The impositions and slowness of effect on iron stores related to oral iron supplementation would result in a prompt shift of the athlete's demand to parenteral iron application, which can have more serious adverse effects. Finally, and as a piece of personal current opinion, Mount Everest is not necessarily to be conquered unless this can be done without extra oxygen.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

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