

Iron therapy for iron deficiency without anaemia

Scope

Publication date

September 2017

Authors

Dr. med. Heike Raatz, MSc; Dr. sc. Viktoria Gloy, MSc; Dr. sc. Dominik Glinz, MSc;
Renato Mattli, MSc; Prof. Dr. oec. publ. Simon Wieser

Heads of the institutes (CEB/ZHAW)

Prof. Dr. med. Heiner C. Bucher, MPH; Prof. Urs Brügger



REAL LIFE EVIDENCE. EVIDENCE SYNTHESIS. HEALTH TECHNOLOGY ASSESSMENTS.

find out more at www.ceb-institute.org

 **Universitätsspital
Basel**

Klinische Epidemiologie

This scope has been developed based on a preliminary scope by the SFOPH on iron deficiency without anaemia (iron deficiency no anaemia, IDNA) and applies to the first phase of a stepped approach to assessing the available evidence. The following sections cover the background for the choice of the topic, followed by the resulting PICO-question (Population, Intervention, Comparator, and Outcome), the inclusion and exclusion criteria, and the rationale for the scope.

Background

The definition and the indications for the treatment of IDNA are controversial in Switzerland. In the past, the Swiss Federal Office of Public Health (SFOPH) has repeatedly been confronted with the question whether the therapy with iron should be covered by the mandatory health insurance. Several cases were already been tried in court at cantonal level. In order to be eligible for reimbursement the conditions to be treated have to qualify as diseases and the effectiveness, appropriateness and cost-effectiveness of the treatment with iron has to be established. So far though the effectiveness of the therapy with iron is unclear for IDNA and there is even no consensus regarding the relevant diagnostic markers and thresholds that should be used to diagnose IDNA¹⁻³.

Possible indications that have been suggested for the therapy with iron are fatigue, depression, restless legs syndrome, sleep disorders, hair loss, brittle nails, attention-deficit hyperactivity disorder, and cognitive deficits⁴. The latter two indications are mostly relevant in children. Several evidence syntheses have been identified that covered similar questions and include potentially relevant primary studies but the inclusion criteria are often slightly different to those of the SFOPH⁵⁻⁸. The systematic review by Lomagno 2014 for example investigated the effect of iron or zinc on mood or cognition in women with iron deficiency with or without anaemia but didn't pre-specify whether they had to be symptomatic⁶. The systematic review by Pratt 2016 (literature search until April 2014) looked more broadly at non-anaemic iron deficiency but a pre-specified ferritin level (<16µg/l) was part of the inclusion criteria⁸.

Study aim

The aim of this first phase is to assess the effectiveness of the therapy with iron in symptomatic patients with IDNA. For those instances where a treatment effect is being shown diagnostic markers will be evaluated based on individual patient data if available and the costs of intravenous versus oral treatment with iron will be compared.

The clinical effectiveness will be assessed in a systematic review of randomized controlled trials (RCT). The type of relevant symptoms is not pre-defined beyond the fact that they have to be health or safety outcomes. Patients in the included RCTs should be comparable to those patients in Switzerland, for which this treatment is currently being discussed. Relevant patients suffer from IDNA but don't have any serious underlying conditions that would affect the interpretation of laboratory parameters related to iron homeostasis, such as inflammatory conditions, organ failure (e.g. kidney, liver and heart), or malignancy. Neither should patients have any underlying condition that in itself causes the symptoms to be investigated by other pathways than via iron deficiency. The criteria for the diagnosis of IDNA will be based on the definitions used by the authors of the primary studies.

The systematic review on the clinical effectiveness will evaluate the evidence based on RCTs for the treatment with iron as RCTs are most likely to yield high quality evidence. As preventive iron treatment was not subject to discussion in Switzerland they are not considered in this assessment.

The exact PICO-questions for the assessment of the diagnostic markers and for the cost-effectiveness of oral versus iv treatment with iron will depend on the results of the systematic review on the clinical effectiveness. The responsibility for the selection of specific populations or indications for such additional analyses lies with the SFOPH.

PICO-Question for the assessment of clinical effectiveness

Population: Adults, children and adolescents with symptomatic iron deficiency without anaemia

Intervention: therapy with iron

Comparator: any other intervention including placebo or no therapy

Outcome: health and safety outcomes

Inclusion and exclusion criteria for the assessment of clinical effectiveness

Population:

Included are:

- Studies investigating patients with symptoms, hypothesized in the respective study to be caused by IDNA irrespective of the definitions used for iron deficiency and the thresholds used to define anaemia. Any type of symptom investigated is eligible. In those cases where iron deficiency has not explicitly been reported the fact that iron therapy is being investigated as a possible cure serves as surrogate for the presence of iron deficiency.
- No other cause should have been identified for the symptoms that treatment with iron aims to alleviate

Excluded are:

- Studies with athletes
- Studies including patients who are known to suffer from one of the following underlying diseases:
 - Chronic heart failure
 - Renal failure, chronic kidney disease, dialysis
 - Chronic liver failure
 - Chronic inflammatory disease in particular –inflammatory bowel disease
 - Achlorhydria, atrophic gastritis, gastric resection
 - Acute and chronic infections
 - Malignancy

Intervention:

Studies investigating iron therapy will be included. Any form of iron therapy (oral and/or parenteral) will be accepted.

Comparator:

No additional criteria were defined.

Outcomes:

Both health outcomes (including mortality, morbidity or quality of life) and safety outcomes such as adverse events and serious adverse events will be assessed. The measures used (e.g. patient reported outcomes, surrogate outcomes etc.) have to be validated. In general, health outcomes rather than surrogate outcomes will be deemed relevant.

Study design and setting:

Only randomized controlled trials and quasi-randomized trials in developed countries will be included.

Subgroup analyses:

The a priori planning of subgroup analyses is limited in view of the breadth of the proposed question. The following subgroup analyses have been planned depending on feasibility:

- Oral vs. intravenous therapy with iron (vs. intra-muscular therapy with iron)
- Female vs. male participants
- Ferritin levels, i.e. <16 vs. ≥16 and <30 vs. ≥30 and <50 vs. ≥50 µg/l
- Adolescents/children vs. adults

Sensitivity Analysis:

- Depending on definition (cut-off Hb) for anaemia

Other subgroup and sensitivity analyses will be planned depending on the available data for example subgroups for different definitions of IDNA may be created.

The evaluation of the quality of the evidence will be based on GRADE (**G**radings of **R**ecommendations **A**ssessment, **D**evelopment, and **E**valuation)⁹⁻²⁴.

Rationale

The aim of this first phase is to identify high quality evidence on the effectiveness of iron therapy for symptomatic IDNA followed by an assessment of the diagnostic markers and an economic evaluation of the treatment with oral versus intravenous iron therapy for those populations for which a treatment effect is being shown.

The rationale for the inclusion and exclusion criteria is that the results from these studies should be transferable to the Swiss population for which iron treatment is currently being discussed. Accordingly, only trials in developed countries are being included in order to ensure that the population in the studies will be comparable to the population of interest in Switzerland. In addition, some of the excluded conditions listed above are likely to cause at least some of the symptoms attributed to iron deficiency via other pathways than iron

deficiency and/or will affect the diagnostic parameters relevant for the diagnosis of iron deficiency in such a way that they cannot be applied to the target population in Switzerland. The list of underlying diseases cited here is not necessarily complete. In cases where the appropriateness of inclusion seems debatable, the above mentioned rationale will be applied in the decision making.

Depending on the evidence and data found in this first phase the following topics will be assessed either more in detail or based on other types of evidence in subsequent phases:

- appropriate diagnostic and/or predictive markers and thresholds for the identification of patients who suffer from iron deficiency and are most likely to benefit from iron treatment,
- additional effectiveness data,
- evidence on the possible pathophysiology that associates iron deficiency with the conditions (with special consideration of the role of iron with regard to myoglobin and as co-factor for CNS development in children)
- data on patient preferences.

The relevance of these questions, their possible impact on a decision regarding reimbursement and the best methodological approach to elucidate them (analysis of Swiss registry data, evaluation of diagnostic accuracy data...) will depend on the evidence found in the first phase.

The aim would be to primarily assess effectiveness based on RCTs. For those of the seven pre-defined conditions (fatigue, depression, restless legs syndrome, sleep disorders, hair loss, brittle nails, attention-deficit hyperactivity disorder, and cognitive deficits) where no evidence based on RCTs is available a search for non-randomized studies will be considered if feasible.

References

1. Fehr, Krayenbühl, Favrat, et al. Diagnose und Behandlung von Eisenmangel ohne Anämie. *Praxis* 2009;**98**(24):1445-51.
2. Herklotz RH, Andreas. Labordiagnose von Eisenstoffwechselstörungen. *Schweiz Med Forum* 2010;**10**((30-31)):500–07.
3. Martius F. Eisenmangel ohne Anämie – ein heisses Eisen?: Nichthämatologische Auswirkungen des Eisenmangels: Welche sind belegt, wann kommen sie zum Tragen. *Swiss Medical Forum* 2009;**9**(15-16):294-99.
4. Swiss Iron Health O. Secondary. www.siho-global.net.
5. Hariri M, Azadbakht L. Magnesium, Iron, and Zinc Supplementation for the Treatment of Attention Deficit Hyperactivity Disorder: A Systematic Review on the Recent Literature. *Int J Prev Med* 2015;**6**:83.
6. Lomagno KA, Hu F, Riddell LJ, et al. Increasing iron and zinc in pre-menopausal women and its effects on mood and cognition: a systematic review. *Nutrients* 2014;**6**(11):5117-41.
7. Trenkwalder C, Allen R, Hogl B, et al. Restless legs syndrome associated with major diseases: A systematic review and new concept. *Neurology* 2016;**86**(14):1336-43.
8. Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: a systematic review. *Eur J Haematol* 2016;**96**(6):618-28.
9. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013;**66**(7):719-25.
10. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;**66**(7):726-35.
11. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011.
12. Brunetti M, Shemilt I, Pregno S, et al. Grade guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol* 2012.
13. Guyatt G, Oxman AD, Akl E, et al. GRADE guidelines 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2010.
14. Guyatt G, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2010.
15. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol* 2012.
16. Guyatt G, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence-study limitations (risk of bias) and publication bias. *J Clin Epidemiol* 2011.
17. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;**64**(12):1283-93.
18. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol* 2011;**64**(12):1303-10.
19. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol* 2011;**64**(12):1294-302.
20. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol* 2011;**64**(12):1277-82.

21. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines 12. Preparing Summary of Findings tables-binary outcomes. *J Clin Epidemiol* 2012.
22. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: A new series of articles in the *Journal of Clinical Epidemiology*. *Journal of Clinical Epidemiology* 2011;**64**(4):380-82.
23. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol* 2011;**64**(12):1311-16.
24. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing Summary of Findings tables and evidence profiles - Continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173-83.