

Iron-Induced Thrombocytopenia: A Mini-Review of the Literature and Suggested Mechanisms

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Abstract

Anemia constitutes a major global health burden, and iron deficiency is the most common cause of it. Iron deficiency and replacement affect not only hemoglobin (Hb) levels but also other hematological parameters such as platelet count. In this mini-review, we explore thrombocytopenia as a side effect of iron replacement therapy. We searched for relevant articles published in English, and all case reports/series of iron-induced thrombocytopenia were collected and analyzed. A total of 11 case reports and one case series were found relating to very low Hb at a baseline level of 5.25 +/- 2.2 g/dl and variable platelet count at baseline that dropped in 9 +/- 3 days to an average of 121 +/- 112 x 10⁹/L, which in most of the cases was self-corrected. The parenteral route was more commonly reported to be associated with thrombocytopenia, and discontinuation of therapy was needed in two patients.

The mechanisms, prevalence, and clinical significance of thrombocytopenia associated with iron replacement are unknown; several effects of iron on the primary hematopoietic cells and stromal cell lines have been proposed, such as influence on common progenitors, effects on cytokines, and thrombopoietic effect of erythropoietin, which is directly affected by iron levels. Iron replacement can lead to significant thrombocytopenia. Further research is needed to describe the exact incidence, mechanism, and clinical significance of thrombocytopenia associated with iron supplementation.

Categories: Internal Medicine, Hematology

Keywords: deficiency, iron, replacement, supplement, anemia, thrombocytopenia, platelet

Introduction And Background

Anemia is defined by the World Health Organization as “a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body’s physiologic needs” [1]. The worldwide prevalence of anemia at ~24.8% [2] and its association with increased morbidity and mortality and decreased work productivity have made it an important public health burden [1,2]. Iron deficiency is the most common cause of anemia worldwide. Approximately 5% and 2% of American women and men, respectively, suffer from iron deficiency anemia (IDA) [3]. It occurs due to the unmet demand for iron to form normal red blood cells.

IDA is generally caused by inadequate intake of iron, chronic blood loss, or a combination of both [3-5]. A less common cause is malabsorption of iron secondary to gastric and/or duodenal resection or inflammatory conditions like infectious or atrophic gastritis, or tropical sprue. A rare cause includes a genetic mutation in Tmprss6 leading to iron-refractory IDA [6]. Iron deficiency is often associated with thrombocytosis rather than thrombocytopenia; however, both have been described in the literature for more than 50 years [7]. On the other hand, iron replacement has a similar range of effects on thrombopoiesis [8].

In this article, we review the relevant literature published in English to shed light on the link between iron replacement and thrombocytopenia in patients with IDA.

Review

How to cite this article

Babikir M, Ahmad R, Soliman A, et al. (September 02, 2020) Iron-Induced Thrombocytopenia: A Mini-Review of the Literature and Suggested Mechanisms. *Cureus* 12(9): e10201. DOI 10.7759/cureus.10201

Received 06/17/2020
Review began 06/21/2020
Review ended 08/05/2020
Published 09/02/2020

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Methods

We searched the databases PubMed and Scopus for all relevant articles published in the literature in English using the following Medical Subject Headings (MeSH) terms: [deficiency, Iron] [replacement] [supplement] [anemia] [thrombocytopenia] [platelet]. Data were then collected, recorded, and analyzed.

Results

A total of 11 individual case reports and one case series (containing 9 patients) were found, which are summarized in Tables 1-4 [9-19]. The age of the patients in the study ranged between 15 and 42 years, and a female predominance was observed (a female-to-male ratio of approximately 3:1) (Table 1). At baseline, the hemoglobin (Hb) concentration was 5.25 +/- 2.2 g/dl, serum iron concentration was 20 +/- 12.8 ug/dl, and serum ferritin level was 9 +/- 11.8 ng/dl, denoting a severe form of IDA. After iron replacement, Hb concentration increased to 8.03 +/- 1.47 and serum iron concentration increased to 78 +/- 22.5 ug/dl (Table 2). Before iron therapy, the platelet count was 469 +/- 404 x 10⁹/L. The nadir platelet count occurred after 9 +/- 3 days to a mean count of 121 +/- 112 x 10⁹/L (Table 3). The intravenous route was associated with a higher incidence of iron-associated thrombocytopenia than oral and intramuscular routes. Two patients needed platelet transfusions. Thrombocytopenia led to discontinuation of iron replacement in two patients. Both were receiving iron sucrose (Table 4). In the last follow-up of those patients, Hb concentration was found to be increased to 11.5 +/- 2.3 g/dl, and platelet count had increased to 322 +/- 233 x 10⁹/L.

No	Authors	Year of publication	Patient gender	Patient age (years)	Patient ethnicity
1	Giordano et al. [9]	2019	Male	16	African
2	Bayhan et al. [10]	2016	Female	15	NA
3	Kahraman et al. [11]	2016	Male	17	NA
4	Cunha et al. [12]	2015	Female	16	NA
5	Lindgren et al. [13]	2009	Male	NA	NA
6	Ganti et al. [14]	2007	Female	39	African American
7	Taskapan et al. [15]	2003	Female	37	NA
8	Go et al. [16]	2000	Female	30	NA
9	Soff and Levin (case 1) [17]	1988	Female	17	NA
10	Soff and Levin (case 2) [17]	1988	Female	17	NA
11	Knizley et al. [18]	1972	Male	42	Black
12	Lioger et al. (series) [19]	2016	1 male, 8 females	NA	NA

TABLE 1: Cases publication year, and age, gender, and ethnicity of patients

NA: not available

No	Authors	Hb at baseline	MCV	Hb during replacement	Hb after replacement	Iron at baseline	Iron after replacement	Fe sat at baseline	Fe sat after replacement	Ferritin at baseline	Ferritin after replacement
1	Giordano et al. [9]	5.2 g/dL	54.5 fL	8.4 g/dL	13.3 g/dL	NA	NA	NA	NA	3.1 ng/mL	NA
2	Bayhan et al. [10]	4.7 g/dL	64.2 fL	8.2 g/dL	9.6 g/dL	NA	NA	9.50%	Na	2.4 ng/mL	NA
3	Kahraman et al. [11]	7.6 g/dL	66 fL	NA	NA	27 µg/dL	NA	NA	NA	3 ng/mL	NA
4	Cunha et al. [12]	5.8 g/dL	63 fL	8.1 g/dl	8.8 g/dl	NA	78 mcg/dl	NA	NA	NA	NA
5	Lindgren et al. [13]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6	Ganti et al. [14]	3.1 g/dL	58.6 fL	5.2 g/dL	14.0 g/dL	17 µg/dL	NA	4%	NA	<2 ng/dL	121 ng/mL
7	Taskapan et al. [15]	10.1 g/dL	88.2 fL	8.9 g/dL	9.9 g/dL	19 µg/dL	NA	7%	NA	35.5 µg/L	NA
8	Go et al. [16]	3.1 g/dL	77 fL	NA	NA	5 µ/dL	NA	1%	NA	8 mg/L	NA
9	Soff and Levin (case 1) [17]	3.2 g/dL				22 µg/dL	NA	NA	NA	<10 ng/ml	NA
10	Soff and Levin (case 1) [17]	3.2 g/dL	Low	NA	NA	7 µ/dL	NA	NA	NA	NA	NA
11	Knizley et al. [18]	6.1 g/dL		9.4 g/dL	13.6 g/dL	43 mg/dl	NA	8%	NA	NA	NA
12	Lioger et al. (series) [19]	5.7 ± 2.3 g/dL	63 fL	NA	NA	NA	NA	NA	NA	NA	NA

TABLE 2: Hemoglobin and iron profile at baseline and during and after iron therapy

Hb: hemoglobin; MCV: mean corpuscular volume; Fe sat: iron saturation; NA: not available

No	Authors	Platelet at baseline	Lowest platelet count	Days to nadir	Last platelet count
1	Giordano et al. [9]	40 k/ μ L	28 k/ μ L	5	169 k/ μ L
2	Bayhan et al. [10]	820 x 10 ⁹ /L	48 x 10 ⁹ /L	12	363 x 10 ⁹ /L
3	Kahraman et al. [11]	340 x 10 ³ /mcL	68 x 10 ³ /mcL	7	159 x 10 ³ /mcL
4	Cunha et al. [12]	424 x 10 ⁹ /L	45 x 10 ⁹ /L	8	666 x 10 ⁹ /L
5	Lindgren et al. [13]	NA	NA	NA	NA
6	Ganti et al. [14]	127 x 10 ³ /mcL	39 x 10 ³ /mcL	2	181 x 10 ³ /mcL
7	Taskapan et al. [15]	102,000/L	2,000/L	8	87,000/L
8	Go et al. [16]	426 x 10 ⁹ /L	20 x 10 ⁹ /L	8	NA
9	Soff and Levin (case 1) [17]	168,000/mm ³	21,000/mm ³	6	683,000/mm ³
10	Soff and Levin (case 2) [17]	717,000/mm ³	105,000/mm ³	10	NA
11	Knizley et al. [18]	1,465,000/mm ³	37,000/mm ³	13	265,000/mm ³
12	Lioger et al. (series) [19]	172 \pm 133 x 10 ⁹ /L (range: 102-434)	85% from baseline		NA

TABLE 3: Platelet count before, during, and after replacement

NA: not available

No	Authors	Route of iron replacement	Type of iron replacement	Dose	Discontinuation
1	Giordano et al. [9]	Oral	Ferrous sulfate	NA	No
2	Bayhan et al. [10]	Oral	Ferrous glycine sulfate	4 mg/kg	No
3	Kahraman et al. [11]	IV	Iron sucrose	100 mg/day	No
4	Cunha et al. [12]	IV	Iron sucrose	100 mg	Yes
5	Lindgren et al. [13]	NA	NA	NA	NA
6	Ganti et al. [14]	IV	Iron sucrose	100 mg 2xwk	No
7	Taskapan et al. [15]	IV	Iron sucrose	200 mg daily	No
8	Go et al. [16]	IM	Iron dextran	100 mg/day	Yes (changed to oral)
9	Soff and Levin (case 1) [17]	Oral	Ferrous sulfate	300 mg TID	NA
10	Soff and Levin (case 2) [17]	Oral	Ferrous gluconate		NA
11	Knizley et al. [18]	Oral	Ferrous sulfate	235 mg TID	No
12	Lioger et al. (series) [19]	IV: 8, IM: 1	Iron sucrose/ferric carboxymaltose	NA	NA

TABLE 4: Iron replacement route, preparation, and dose, and whether discontinuation/transfusion was required

IV: intravenous; IM: intramuscular; NA: not available

Discussion

Thrombocytopenia may occur in patients with severe IDA who receive iron therapy; however, it is very uncommon [3]. Its pathogenesis remains undetermined but is thought to be related to the alteration in the activity of iron-dependent enzymes involved in thrombopoiesis [14,20].

Iron has a synthetic and regulatory role in platelet production, and animal models have suggested a common progenitor cell for erythroid and megakaryocytic cell lineages [21]. The reviewed cases who developed thrombocytopenia after iron replacement, especially parenteral iron, had a significant reduction in platelet count that was self-corrected in most of the cases. The mechanisms, prevalence, and clinical significance of this thrombocytopenia are unknown [15-18,22]. Iron has a synthetic and regulatory role in platelet production. Iron can induce cell death by generating free radicals as it interconverts between ferrous (Fe²⁺) and ferric (Fe³⁺) forms. A randomized, placebo-controlled, double-blind, parallel-group study was performed on 38 peritoneal dialysis patients before and after a single intravenous infusion of 300 mg iron sucrose. Iron infusion increased in total (Δ 601 μ g/100 mL, CI 507, 696) and non-transferrin-bound iron (Δ 237.2 μ mol/L, CI 173.6, 300.8) increased approximately by 10-fold, as well as redox-active iron by nearly five-fold (Δ 0.76 μ mol/L, CI 0.54, 0.98) [23].

Animal models have suggested a common progenitor cell for erythroid and megakaryocytic cell lineages [21]. An in vitro study examined the effects of iron load (that may simulate the process of iron infusion in patients with IDA) on the function of primary hematopoietic cells and stromal cell lines and found that iron overload impairs normal hematopoietic cells and modifies the function of stromal cells, indicating that iron overload impairs the whole hematopoietic system. The authors suggested that the deleterious effects of iron were mediated through its impact on hematopoietic stem/progenitor cells as well as in differentiated hematopoietic via reactive oxygen species (ROS) accumulation [24]. In addition, an in-vitro study showed that ferrous ammonium sulfate (FeAS) induced growth arrest and apoptosis in immature hematopoietic cells and led to insulin-like growth factor binding protein 2 (IGFBP2) and insulin-like

growth factor 1 (IGF-1) down-regulation. Both have been found to stimulate the survival, proliferation, and cycling of hematopoietic stem cells (HSCs) [25].

Although thrombopoietin is the primary growth factor and regulator of megakaryopoiesis, several other cytokines such as interleukin (IL)-1, IL-3, IL-6, IL-11, and tumor necrosis factor are also involved in this process [26-28]. Erythropoietin shares some structural features with thrombopoietin and may exhibit a synergistic effect on platelet production. The levels of endogenous erythropoietin significantly decrease during the correction of iron deficiency. This reduction in endogenous erythropoietin might decrease the productivity of megakaryocytes and lead to transient thrombocytopenia [29,30].

In this study, we observed that young females are more likely to be affected by IDA. Further research is needed to explore whether this is because IDA per se is more common in this population or if there are other explanations related to female sex hormone or genetic profile. Another observation was that platelet nadir occurred within 13 days of iron replacement initiation; however, the number of cases was too small to recommend following platelet count in asymptomatic patients within this timeframe.

Conclusions

Significant thrombocytopenia occasionally occurs in patients receiving iron therapy for IDA. This condition is transient and self-limited in most of these cases. Various mechanisms can contribute to this thrombocytopenia. Dedicated observational and experimental studies are needed to describe the correlation between iron profile, hemoglobin level, genetic factors, cytokines, growth factors and thrombopoiesis; these studies should look for predictors that could determine which individuals will get thrombocytopenia on receiving iron supplements.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We would like express our gratitude to everyone at the Internal Medicine Residency Program, Hamad Medical Corporation, Doha, Qatar

References

1. World Health Organization: serum transferrin receptor levels for the assessment of iron status and iron deficiency in populations. (2014). Accessed: August 15, 2020: https://apps.who.int/iris/bitstream/handle/10665/133707/WHO_NMH_NHD_EPG_14.6_eng.pdf.
2. Gebreweld A, Ali N, Ali R, Fisha T: Prevalence of anemia and its associated factors among children under five years of age attending at Gugufu health center, South Wollo, Northeast Ethiopia. *PLoS One*. 2019, 14:e0218961. [10.1371/journal.pone.0218961](https://doi.org/10.1371/journal.pone.0218961)
3. Johnson-Wimbley TD, Graham DY: Diagnosis and management of iron deficiency anemia in the 21st century. *Therap Adv Gastroenterol*. 2011, 4:177-184. [10.1177/1756283X11398736](https://doi.org/10.1177/1756283X11398736)
4. Li Q, Liang F, Liang W, Shi W, Han Y: Prevalence of anemia and its associated risk factors among 6-months-old infants in Beijing. *Front Pediatr*. 2019, 7:286. [10.3389/fped.2019.00286](https://doi.org/10.3389/fped.2019.00286)
5. World Health Organization: haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. (2011). Accessed: August 15, 2020: <https://www.who.int/vmnis/indicators/haemoglobin/en/>.
6. Saboor M, Zehra A, Qamar K, Moinuddin: Disorders associated with malabsorption of iron: a critical review. *Pak J Med Sci*. 2015, 31:1549-1553. [10.12669/pjms.316.8125](https://doi.org/10.12669/pjms.316.8125)
7. Morris VK, Spraker HL, Howard SC, Ware RE, Reiss UM: Severe thrombocytopenia with iron deficiency anemia. *Pediatr Hematol Oncol*. 2010, 27:413-419. [10.3109/08880011003739455](https://doi.org/10.3109/08880011003739455)
8. Evsatiev R, Bukaty A, Jimenez K, et al.: Iron deficiency alters megakaryopoiesis and platelet phenotype independent of thrombopoietin. *Am J Hematol*. 2014, 89:524-529. [10.1002/ajh.23682](https://doi.org/10.1002/ajh.23682)

9. Giordano L, Llanos-Chea A, Monde A, Mulinge I, Dighe D: Recurrent severe iron deficiency anemia and thrombocytopenia in an adolescent male. *J Pediatr Hematol Oncol*. 2019, 41:e116-e118. [10.1097/MPH.0000000000001162](https://doi.org/10.1097/MPH.0000000000001162)
10. Bayhan T, Ünal Ş, Gümrük F, Çetin M: A rare complication of a common problem: thrombocytopenia subsequent to iron replacement therapy in an adolescent girl with severe iron deficiency anaemia. *Hong Kong J Paediatr*. 2016, 21:113-115.
11. Kahraman C, Üçgün S, Kahraman NK: Intravenous iron infusion induced severe temporary thrombocytopenia case in iron deficiency anemia: a review. *Ann Med Med Educ*. 2016, 3:7-10. [10.12973/amme.2016.00148a](https://doi.org/10.12973/amme.2016.00148a)
12. Cunha V, Ferreira M, Barosa R, Fonseca AG, Delerue F, Carvalho C: Iron-induced thrombocytopenia in severe iron-deficiency anemia. *Expert Rev Hematol*. 2015, 8:247-251. [10.1586/17474086.2015.1010504](https://doi.org/10.1586/17474086.2015.1010504)
13. Lindgren S, Wikman O, Befrits R, et al.: Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol*. 2009, 44:838-845. [10.1080/00365520902839667](https://doi.org/10.1080/00365520902839667)
14. Ganti AK, Shonka NA, Haire WD: Pancytopenia due to iron deficiency worsened by iron infusion: a case report. *J Med Case Rep*. 2007, 1:175. [10.1186/1752-1947-1-175](https://doi.org/10.1186/1752-1947-1-175)
15. Taskapan H, Bahceci F, Taskapan C, Sahin I, Kaya E, Aydogdu I: Transient severe thrombocytopenia in a patient on CAPD after intravenous iron administration. *Perit Dial Int*. 2003, 23:408-409.
16. Go RS, Porrata LF, Call TG: Thrombocytopenia after iron dextran administration in a patient with severe iron deficiency anemia. *Ann Intern Med*. 2000, 132:925. [10.7326/0003-4819-132-11-200006060-00025](https://doi.org/10.7326/0003-4819-132-11-200006060-00025)
17. Soff GA, Levin J: Thrombocytopenia associated with repletion of iron in iron-deficiency anemia. *Am J Med Sci*. 1988, 295:35-39. [10.1097/0000441-198801000-00008](https://doi.org/10.1097/0000441-198801000-00008)
18. Knizley H Jr, Noyes WD: Iron deficiency anemia, papilledema, thrombocytosis, and transient hemiparesis. *Arch Intern Med*. 1972, 129:483-486. [10.1001/archinte.1972.00320030103013](https://doi.org/10.1001/archinte.1972.00320030103013)
19. Lioger B, Beurier P, Biogeu J, Jonville-Bera AP, Ollier S, Ferreira-Maldent N, Maillot F: Thrombocytopenia after iron infusion: a case series of four patients and review of literature. *Haematologica*. 2016, 101:850-851.
20. Jhamb R, Kumar A: Iron deficiency anemia presenting as pancytopenia in an adolescent girl. *Int J Adolesc Med Health*. 2011, 23:73-74. [10.1515/ijamh.2011.012](https://doi.org/10.1515/ijamh.2011.012)
21. Batra S, Gupta A, Peddint R: An unusual case of thrombocytopenia. *Clin Pediatr (Phila)*. 2011, 50:464-466. [10.1177/0009922809354333](https://doi.org/10.1177/0009922809354333)
22. Özdemiş N, Celkan T, Kebudi R, Bor M, Yildiz I: Cytopenia associated with iron deficiency anemia and iron therapy: a report of two cases. *Türk J Haematol*. 2011, 28:243-244. [10.5152/tjh.2011.65](https://doi.org/10.5152/tjh.2011.65)
23. Schaller G, Scheiber-Mojdehkar B, Wolzt M, et al.: Intravenous iron increases labile serum iron but does not impair forearm blood flow reactivity in dialysis patients. *Kidney Int*. 2005, 68:2814-2822. [10.1111/j.1523-1755.2005.00754.x](https://doi.org/10.1111/j.1523-1755.2005.00754.x)
24. Tanaka H, Espinoza JL, Fujiwara R, et al.: Excessive reactive iron impairs hematopoiesis by affecting both immature hematopoietic cells and stromal cells. *Cells*. 2019, 8:226. [10.3390/cells8030226](https://doi.org/10.3390/cells8030226)
25. Huynh H, Zheng J, Umikawa M, et al.: IGF binding protein 2 supports the survival and cycling of hematopoietic stem cells. *Blood*. 2011, 118:3236-3243. [10.1182/blood-2011-01-331876](https://doi.org/10.1182/blood-2011-01-331876)
26. Kaushansky K: Thrombopoietin: the primary regulator of platelet production. *Blood*. 1995, 86:419-431.
27. Wendling F, Han ZC: Positive and negative regulation of megakaryocytopoiesis. *Baillieres Clin Haematol*. 1997, 10:29-45. [10.1016/s0950-3536\(97\)80049-2](https://doi.org/10.1016/s0950-3536(97)80049-2)
28. Broudy VC, Lin NL, Kaushansky K: Thrombopoietin (c-mpl ligand) acts synergistically with erythropoietin, stem cell factor, and interleukin-11 to enhance murine megakaryocyte colony growth and increases megakaryocyte ploidy in vitro. *Blood*. 1995, 85:1719-1726.
29. Metcalf D, Di Rago L, Mifsud S: Synergistic and inhibitory interactions in the in vitro control of murine megakaryocyte colony formation. *Stem Cells*. 2002, 20:552-560. [10.1002/stem.200552](https://doi.org/10.1002/stem.200552)
30. Akan H, Güven N, Aydogdu I, Arat M, Beksaç M, Dalva K: Thrombopoietic cytokines in patients with iron deficiency anemia with or without thrombocytosis. *Acta Haematol*. 2000, 103:152-156. [10.1159/000041038](https://doi.org/10.1159/000041038)