

**Research Bank**

Journal article

**Examining the decay in serum ferritin following intravenous iron infusion : A retrospective cohort analysis of Olympic sport female athletes**

**McKay, Alannah K. A., Goods, Paul S. R., Binnie, Martyn J., Goodman, Carmel and Peeling, Peter**

Accepted manuscript.

McKay, Alannah K. A., Goods, Paul S. R., Binnie, Martyn J., Goodman, Carmel and Peeling, Peter. (2020) Examining the decay in serum ferritin following intravenous iron infusion : A retrospective cohort analysis of Olympic sport female athletes. *Applied Physiology, Nutrition and Metabolism*. 45(10), pp. 1174-1177.

<https://doi.org/10.1139/apnm-2020-0132>

# Examining the Decay in Serum Ferritin Following Intravenous Iron Infusion: A Retrospective Cohort Analysis of Olympic Sport Female Athletes

## Authors:

Alannah K.A. McKay<sup>1,2,3</sup>, Paul S.R. Goods<sup>1,2</sup>, Martyn J. Binnie<sup>1,2</sup>, Carmel Goodman<sup>2</sup>, Peter Peeling<sup>1,2</sup>

## Affiliations:

<sup>1</sup> School of Human Sciences (Exercise and Sport Science). The University of Western Australia, Crawley, WA, 6009, Australia. <sup>2</sup> Western Australian Institute of Sport, Mt Claremont, WA, 6010, Australia. <sup>3</sup> Australian Institute of Sport, Bruce, ACT, 2617, Australia.

**Address for correspondence:** Alannah K.A. McKay. School of Human Sciences (Exercise and Sport Sciences), The University of Western Australia, Crawley, WA, 6009. Email: [alannah.mckay@ausport.gov.au](mailto:alannah.mckay@ausport.gov.au), Ph: +61 439 708 968.

**PG:** [pgoods@wais.org.au](mailto:pgoods@wais.org.au), **MB:** [mbinnie@wais.org.au](mailto:mbinnie@wais.org.au), **CG:** [cgoodman@wais.org.au](mailto:cgoodman@wais.org.au), **PP:** [peter.peeling@uwa.edu.au](mailto:peter.peeling@uwa.edu.au)

**Submission Type:** Brief Communication

**Word Count:** 3,299 words

**Abstract Word Count:** 75 words

## Abstract

The long-term decay rate of serum ferritin post-iron infusion in athletic populations is currently unknown. Here, we modelled the decay rate of serum ferritin in female athletes post-intravenous iron infusion (n=22). The post-infusion serum ferritin response and the rate of decay was highly variable between athletes; however, we demonstrate that follow-up blood testing at one (154  $\mu\text{g/L}$ ; 77-300  $\mu\text{g/L}$ ) and six months (107  $\mu\text{g/L}$ ; 54-208  $\mu\text{g/L}$ ) post-infusion is appropriate to observe treatment efficacy and effectiveness.

## Novelty

- Female athletes should have serum ferritin assessed at 1 and 6 months following an intravenous iron infusion to determine efficacy and effectiveness.

**Key words:** parenteral iron, iron therapy, exercise, iron deficiency, anaemia, iron depletion

## Introduction

Iron is an essential mineral obtained from the diet, which plays an important role in numerous fundamental biological processes necessary for optimal athletic performance, including oxygen transport, energy metabolism and neurological and immunological functioning (Beard 2001). Despite its importance, iron deficiency (ID) in athletic populations is common, particularly in female athlete populations, where cohort studies have shown up to 76% of athletes have low serum ferritin concentrations (Ponorac et al. 2019). The increased incidence of ID in female athletes is mostly attributed to the increased iron losses associated with menstruation, which are additive to the overall greater iron demand that results from physical training (McClung 2012). Despite the prevalence of ID being high in athlete cohorts, the condition is usually classified in terms of severity. Broadly speaking, three stages of ID have been proposed: 1) Iron depletion, where iron stores are depleted without haematological consequences (serum ferritin  $<35 \mu\text{g/L}$ , haemoglobin  $>115 \text{ g/L}$ , transferrin saturation  $>16\%$ ); 2) Iron deficiency non-anaemia (IDNA), where erythropoiesis diminishes as the iron supply to the erythoid marrow is reduced (serum ferritin  $<20 \mu\text{g/L}$ , haemoglobin  $>115 \text{ g/L}$ , transferrin saturation  $<16\%$ ); and 3) Iron deficiency anaemia (IDA), where haemoglobin production becomes compromised as iron stores are exhausted (serum ferritin  $<12 \mu\text{g/L}$ , haemoglobin  $<115 \text{ g/L}$ , transferrin saturation  $<16\%$ ) (Peeling et al. 2007).

Once diagnosed, there are three key strategies that are routinely used to correct an ID in athlete populations; these include, 1) a nutritional consult with a trained sports dietician to increase dietary iron intake; 2) the use of oral iron supplements in doses of 60-200 mg of elemental iron per day over an 8-12 week period; or 3) the use of parenteral iron administration to rapidly boost iron availability; a strategy that by-passes the gut and any associated absorption issues (Sim et al. 2019). Generally, the approach taken is dependent upon the severity of the deficiency, with a food-first approach initially considered for athletes presenting with 'sub-optimal' iron stores (serum ferritin 30-50 $\mu\text{g/L}$ ;

(Peeling et al., 2014)), and an oral iron supplement commonly employed when iron status becomes compromised. In persistent, unresponsive, or generally more severe cases, intravenous iron approaches can be considered. Such an approach shows best outcomes in athletes where a rapid improvement in ferritin is required and when haemoglobin mass has become impaired (Garvican et al. 2014). When considering these more severe IDA cases, intravenous iron infusions appear appropriate given the rapid and effective outcomes of restoring iron stores. Previous literature shows a 200-400% increase in serum ferritin after a 1-56 day period, with the greatest efficacy of outcome observed in athletes with the lowest serum ferritin levels (Garvican et al. 2014, Burden et al. 2015). However, the long-term rate of decay in iron stores when using such an approach in athletic populations appears to be unknown, and current best practice guidelines for the timing of follow-up blood tests to re-examine iron status post-infusion are currently limited to a 4-8 week follow-up assessment, which only provides a short-term observation of effectiveness, rather than a long-term assessment of decay. Therefore, in a retrospective manner, the aim of this study was to model the serum ferritin results of female athletes who have had intravenous iron infusions to examine the rate of decay in serum ferritin post-iron infusion.

## Materials and Methods

In a retrospective investigation, serum ferritin results from a single sporting institution's athlete management system were sourced. All athlete data extracted by this system were junior or senior level female athletes competing at either the National or International level in Olympic, Paralympic and Commonwealth Games sports (age:  $20.3 \pm 4.0$  years old; weight:  $65.9 \pm 10.0$  kg; height:  $172.2 \pm 7.6$ ; sum of 7 skinfolds:  $69.4 \pm 11.5$  mm). All data was collected as part of high-performance service delivery program within the athletes' daily training environment, where all blood samples were collected and analysed by a commercial laboratory. Instructions were given to athletes to arrive for blood tests in the morning prior to training, in a rested and hydrated state, and free from illness.

The physiologists and medical doctor of the host sports institute provided a list of athletes known to have undergone an intravenous iron infusion, and either a referral date or infusion date was provided. All athletes intravenously received 1000 mg of iron as ferric carboxymaltose (Ferrinject®). For confirmation an infusion occurred, a visual inspection of each athlete's serum ferritin results was then undertaken, where a sharp increase in serum ferritin levels was considered characteristic of an intravenous iron infusion (Garvican et al. 2014). All identified athletes' serum ferritin history was then examined for evidence of previous infusions to include in the analysis. Serum ferritin results for up to 2.5 years post-infusion, and the number of days each blood test was performed post-infusion, was determined. A limitation of this study was that no consistent haemoglobin data measured concurrent with the ferritin results could be sourced, and therefore, our results are limited to the study of serum ferritin. Our retrospective analysis yielded a total of 22 infusions from 16 athletes, whereby 1 athlete had 4 infusions, 3 athletes had 2 infusions and 12 athletes had a single infusion. The 16 identified athletes were from the following sports programs: track and field athletics (n=5 [pole vault (n=2), sprints (n=2), marathon (n=1)]), field hockey (n=4), netball (n=2), rowing (n=2), gymnastics (n=1), diving (n=1) and wheelchair basketball (n=1). Ethical approval to analyse this database was obtained from the Human Ethics Committee of the University of Western Australia. Athlete consent was obtained via a signed data release form as part of the standard athlete scholarship agreement at the Western Australian Institute of Sport. The time period covered in this study was January 2014 to January 2020.

### **Statistical Analysis**

A general linear mixed model was performed in R Studio using the package 'lme4' with the restricted maximal likelihood approach adopted. Athlete and infusion number were specified as random effects within the model to account for instances where multiple infusions occurred within the same athlete. Additionally, the athlete's sport was also included as a random effect within the

model. The outcome variable in the model was natural log-transformed serum ferritin, with the number of days post-infusion, the athlete's age and pre-infusion serum ferritin values included as fixed effects. The intercept and fixed effect estimates for number of days post-infusion were used to create a linear regression. Data were then back-transformed and used to model the exponential decay in serum ferritin post-infusion. Data is presented as mean±95% confidence intervals (CI). Significance was accepted at  $p < 0.05$ .

## Results

The linear mixed model demonstrated that serum ferritin decreased over time following intravenous iron infusion ( $p < 0.001$ ), however neither athlete age ( $p = 0.703$ ) or pre-infusion serum ferritin levels ( $p = 0.273$ ) significantly affected the model. The fixed effects alone accounted for 46% of the variance in serum ferritin (marginal  $R^2$ ), with the inclusion of the random effects increasing the explanatory power of the model to 82% (conditional  $R^2$ ). These additional sources of variation were accounted for by athlete identification (51%), athlete sport (<1%) and infusion number (15%), leaving the remaining 34% of the variance unaccounted. Using the intercept and fixed effect estimate provided by the model for number of days post-infusion, the following exponential curve was constructed:

$$y = e^{(-0.0024011 * x + 5.1099527)}$$

Mean pre-infusion serum ferritin of this cohort ( $n = 22$ ) was 24.0  $\mu\text{g/L}$  (95% CI: 20.5-27.6  $\mu\text{g/L}$ ). Furthermore, when splitting the data into whether it was an athlete's first recorded infusion (23.1  $\mu\text{g/L}$ , 19.0-27.3  $\mu\text{g/L}$ ) or a repeat infusion (26.5  $\mu\text{g/L}$ , 22.4-30.6  $\mu\text{g/L}$ ), which indicates a history of low iron stores, no significant differences in serum ferritin were evident ( $p = 0.457$ ). In instances where athletes required a follow-up infusion, the mean time between infusions was 664 days (500–826 days). If an athlete was screened 3 months after an intravenous iron infusion (in line with current

recommendations for female athletes with a history of low iron stores (Sim et al., 2019)), the model predicted a serum ferritin value of 133  $\mu\text{g/L}$ , with a range of 67 – 259  $\mu\text{g/L}$  (Figure 1). Based on our model, it takes (on average) 499 days post-infusion to reach a serum ferritin of 50  $\mu\text{g/L}$ , and 647 days post-infusion to reach a serum ferritin of 35  $\mu\text{g/L}$ . However as indicated by the model, a large amount of inter-individual variability exists. Using a case study approach, the athlete who best sustained their iron stores following an infusion took 776 and 925 days to fall to a serum ferritin of 50  $\mu\text{g/L}$  and 35  $\mu\text{g/L}$ , respectively. Conversely, the athlete who struggled the most to maintain healthy iron stores following an infusion fell to a serum ferritin of 50  $\mu\text{g/L}$  in 212 days and 35  $\mu\text{g/L}$  in 361 days. Between those two individuals who were both field hockey athletes, a difference of 564 days (or  $\sim 1.5$  years) was evident in the time taken for serum ferritin to fall to 50  $\mu\text{g/L}$ .

## Discussion

Given the lack of literature to inform practitioners of the typical long-term athlete response to intravenous iron infusions, the aim of this study was to model the decay in serum ferritin levels to better advise on when, and how frequently post-infusion follow-up testing should occur. However, the major outcome of this investigation is the realisation that the response to an intravenous iron infusion is highly variable between athletes, and therefore, we recommend that an individualised approach to monitoring severe cases of ID is required.

Within our model, specifying the athlete as a random effect accounted for a large proportion of the variance, whereas accounting for each infusion (in cases where multiple infusions occurred) contributed to a much lesser extent. This may suggest that while each athlete responds differently to an intravenous iron infusion, a similar within-athlete response occurs, and therefore, knowing your athlete well is a cornerstone of improving athlete health outcomes. Interestingly, the inclusion of the athlete's sport did not improve the model ( $<1\%$  of the variance). This is partially supported by

research demonstrating the prevalence of iron deficiency in female athletes across various sports appears to be similar (Ponorac et al., 2019; Koehler et al., 2012). While it is acknowledged that only a limited number of sports have been studied here (n=7), it is likely the type, frequency and duration of training completed may have a greater impact on the decay in serum ferritin rather than the sport *per se*.

A substantial proportion of the model variance (34%) was left unaccounted for, with many (uncontrollable) factors likely to have contributed to this variation. For instance, high dietary iron intake, or additional treatment in the form of oral iron supplements during the post-infusion period is likely to slow the decay in serum ferritin; however, the retrospective approach used in this study meant we were unable to attain reliable dietary data for analysis. With the knowledge that energy and macronutrient manipulations can also alter iron regulation (Sim et al., 2019), this should be accounted for in future research. Furthermore, the impact of an athlete's menstrual cycle has not been considered here and may have further improved our model. Conditions such as amenorrhea, common in some athletic populations, may be protective against iron deficiency (Petkus et al., 2017). Additionally, oral contraceptive pill use has been proposed to improve iron status via reduced menstrual blood loss (Larsson et al., 1992) and/or the oestradiol-mediated suppression of hepcidin (Yang et al., 2012). Furthermore, an additional factor likely to impact the decay rate is the type and amount of training performed, since heavy training loads are often associated with increased iron losses (through processes such as sweating, haemolysis and GI bleeding) and iron utilisation for adaptive haematological processes (Peeling et al. 2008). Athletes frequently performing weight-bearing activities may also be at an increased risk of iron loss due to increased haemolysis, and an accelerated decline in serum ferritin may be expected. Conversely, infusions that occur during the off-season may allow greater iron absorption, as the exercise-induced iron losses are likely reduced, which may subsequently improve iron uptake. Clearly, further work is needed in this space

to isolate the impact that each of these factors may have on the decay in serum ferritin following an iron infusion.

A potential factor that may influence the rate of decline in serum ferritin is the iron regulatory hormone hepcidin. The mechanistic role of hepcidin is to internalise the body's only known iron exporter, ferroportin, preventing the absorption of iron through enterocytes in the gut and the recycling of iron from macrophages (Nemeth et al. 2004). Increases in hepcidin have been noted both 24 h and 4 weeks post-iron infusion, proposed to occur as part of a homeostatic response to the increase in whole body iron stores (Burden et al. 2015). It appears that, in response to an iron infusion, hepcidin levels are immediately elevated in an attempt to minimise the risk of iron overload, and subsequently, iron absorption is reduced. This increase in hepcidin likely explains the rapid, exponential decrease in serum ferritin that is seen early in the post-infusion period. However, whether this hepcidin response is a positive homeostatic mechanism invoked to protect the athlete and bring their iron stores back to a more 'normal' individual level, or one that is counterproductive and negates the success of the iron infusion, remains to be established.

Currently, it is suggested female athletes with a history of low iron stores are tested for serum ferritin every three months (Sim et al. 2019), however, limited guidelines have been established for athlete populations following an intravenous iron infusion, beyond a follow-up assessment at 4-8 weeks post-infusion (The Iron Clinic, 2017). Based on our model, a follow-up blood screening at 30 days (~4 weeks) post-infusion would result in a mean serum ferritin value of 154  $\mu\text{g/L}$ , with a range of 77-300  $\mu\text{g/L}$ . Accordingly, we propose an initial follow-up screening should be completed 1 month following the infusion to assess how effectively the iron has been delivered to the body. Furthermore, a 6-month follow-up screening would result in a mean serum ferritin of 107  $\mu\text{g/L}$ , with a range of 54-208  $\mu\text{g/L}$ , and therefore, we suggest a 6-month post-infusion serum ferritin assessment

should be conducted to identify whether the body has retained the administered iron. Even in the case of the athlete who had the fastest decline in serum ferritin levels (serum ferritin of 54  $\mu\text{g/L}$  at 6 months post-infusion), this approach would have allowed the identification of diminishing iron stores prior to them re-entering a state of ID. In cases where an athlete's 6-month serum ferritin result returns a healthy outcome, the previously established guidelines of 3-monthly screenings should be recommenced (Sim et al. 2019) and longitudinal data obtained to support an individualised approach to managing athlete's iron stores in the future. Of course, we must acknowledge a limitation of this study, being the absence of consistent haemoglobin data that could be included within the analysis; however, we suggest that a minimum blood panel of haemoglobin concentration and transferrin saturation be measured in conjunction with serum ferritin, particularly when cases of ID may be suspected.

In conclusion, our data clearly demonstrates the high variability between athletes following an intravenous iron infusion, and therefore, we recommend an individualised approach to follow-up testing. We suggest that a 1 and 6-month follow-up blood screening should occur to assess the efficacy of an intravenous iron infusion, and the individual rate of decay. Of note, it should be emphasised that this investigation was an exploratory exercise based on limited data, and therefore, there remains a need for prospective studies to confirm our findings. Future research should employ a consistent 2-year follow-up period in order to capture the full extent of the decay in serum ferritin, and should account for factors such as haemoglobin levels, training load, dietary iron intake and oral iron supplement use.

The authors have no conflicts of interest to report.

## References

- Beard, J.L. 2001. Iron biology in immune function, muscle metabolism and neuronal functioning. *J. Nutr.* **131**(2S-2):568S-580S. doi:10.1093/jn/131.2.568S.
- Burden, R., Pollock, N., Whyte, G.P., Richards, T., Moore, B., Busbridge, M., Srai, S.K., Otto, J., and Pedlar, C. 2015. Effect of intravenous iron on aerobic capacity and iron metabolism in elite athletes. *Med. Sci. Sports. Exerc.* **47**(7):1399-1407. doi:10.1249/MSS.0000000000000568.
- Garvican, L.A., Saunders, P.U., Cardoso, T., Macdougall, I.C., Lobgis, L.M., Fazakerley, R., Fallon, K.E., Anderson, B., Anson, J.M., and Thompson, K.G. 2014. Intravenous iron supplementation in distance runners with low or suboptimal ferritin. *Med. Sci. Sports. Exerc.* **46**(2):376-385. doi:10.1249/MSS.0b013e3182a53594.
- Koehler, K., Braun, H., Achtzehn, S., Hildebrand, U., Predel, H.G., Mester, J., and Schanzer, W. 2012. Iron status in elite young athletes: gender-dependent influences of diet and exercise. *Eur. J. Appl. Physiol.* **112**,513–523. doi:10.1007/s00421-011-2002-4.
- Larsson, G., Milsom, L., Lindstedt, G. and Rybo, G. 1992. The influence of a low-dose combined oral contraceptive on menstrual blood loss and iron status. *Contraception.* **46**(4):327-334. doi:10.1016/0010-7824(92)90095-B.
- McClung, J.P. 2012. Iron status and the female athlete. *J. Trace. Elem. Med. Biol.* **26**(2-3):124-126. doi:10.1016/j.jtemb.2012.03.006.
- Nemeth, E., Tuttle, M.S., Powelson, J., Vaughn, M.B., Donovan, A., Ward D.M., Ganz, T., and Kaplan, J. 2004. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science.* **306**(5704):2090-2093. doi:10.1126/science.1104742.

- Peeling, P., Blee, T., Goodman, C., Dawson, B., Claydon, G., Beilby, J., and Prins, A. 2007. Effect of iron injections on aerobic-exercise performance of iron-depleted female athletes. *Int. J. Sport. Nutr. Exerc. Metab.* **17**(3):221-231. doi:10.1123/ijsnem.17.3.221.
- Peeling, P., Dawson, B., Goodman, C., Landers, G., and Trinder, D. 2008. Athletic induced iron deficiency: new insights into the role of inflammation, cytokines and hormones. *Eur. J. Appl. Physiol.* **103**(4):381-91. doi:10.1007/s00421-008-0726-6.
- Peeling, P., Sim, M., Badenhorst, C.E., Dawson, B., Govus, A.D., Abbiss, C.R., Swinkels, D.W., and Trinder, D. 2014. Iron status and the acute post-exercise hepcidin response in athletes. *PLoS One.* **9**(3):e93002. doi:10.1371/journal.pone.0093002.
- Petkus, D.L., Murray-Kolb, L.E. and De Souza, M.J. 2017. The unexplored crossroads of the female athlete triad and iron deficiency: a narrative review. *Sports. Med.* **47**,1721–1737. doi:10.1007/s40279-017-0706-2
- Ponorac, N., Popvic, M., Karaba-Jakovljevic, D., Bajic, Z., Scanlan, A., Stojanovic, E., and Radovanovic, D. 2019. Professional female athletes are at a heightened risk of iron-deficient erythropoiesis compared with nonathletes. *Int. J. Sport. Nutr. Exerc. Metab.* In press. doi:10.1123/ijsnem.2019-0193.
- Sim, M., Garvican-Lewis, L.A., Cox, G.R., Govus, A., McKay, A.K.A, Stellingwerff, T., and Peeling, P. 2019. Iron considerations for the athlete: a narrative review. *Euro. J. Appl. Physiol.* **119**(7):1463-1478. doi:10.1007/s00421-019-04157-y.
- The Iron Clinic. 2017. Patient information sheet for intravenous (IV) iron therapy. <https://theironclinic.com/ironc/wp/wp-content/uploads/2017/07/Patient-information-for-iron-infusion.pdf>.
- Yang, Q., Jian, J., Katz, S., Abramson, S.B. and Huang, X. 2012. 17 $\beta$ -Estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. *Endocrinology.* **153**(7):3170-3178. doi:10.1210/en.2011-2045

## Figure Captions.

**Figure 1.** The decay in serum ferritin levels post intravenous iron infusion. Black dashed line is the mean response from the mixed model, with the individual athlete response represented by solid lines.

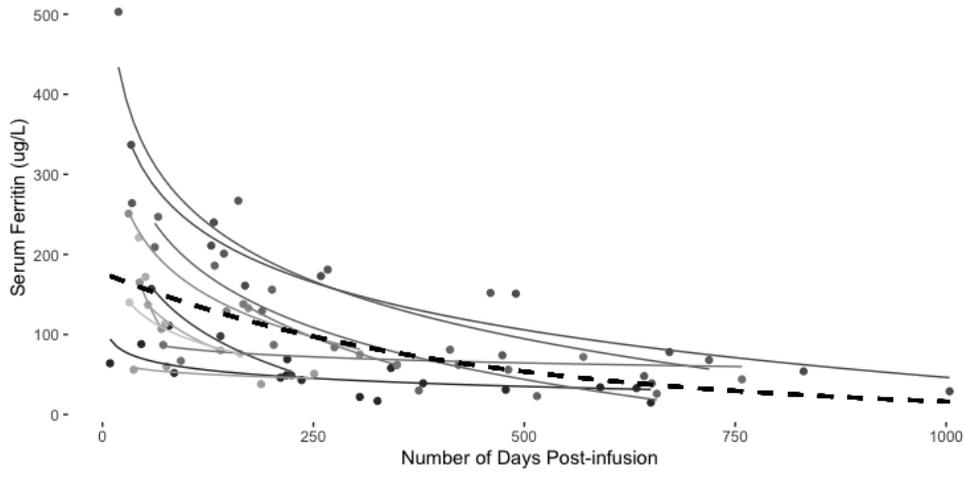


Figure 1. The decay in serum ferritin levels post intravenous iron infusion. Black dashed line is the mean response from the mixed model, with the individual athlete response represented by solid lines.

265x130mm (72 x 72 DPI)