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SHORT COMMUNICATION

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Plasma ferritin concentration is positively associated with *in vivo* fatty acid mobilization and insulin resistance in obese women

Benjamin J. Ryan | **Douglas W. Van Pelt** | **Lisa M. Guth** | **Alison C. Ludzki** | **Rachel A. Gioscia-Ryan** | **Chiwoon Ahn** | **Katherine L. Foug** | **Jeffrey F. Horowitz**

Substrate Metabolism Laboratory, School of Kinesiology, University of Michigan, Ann Arbor, MI, USA

Correspondence
Jeffrey F. Horowitz, School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI 48109-2214, USA.
Email: jeffhoro@umich.edu

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Abstract

High rates of fatty acid (FA) mobilization from adipose tissue are associated with insulin resistance (IR) in obesity. *In vitro* evidence suggests that iron stimulates lipolysis in adipocytes, but whether iron is related to *in vivo* FA mobilization is unknown. We hypothesized that plasma ferritin concentration ([ferritin]), a marker of body iron stores, would be positively associated with FA mobilization. We measured [ferritin], the rate of appearance of FA in the systemic circulation (FA Ra; stable isotope dilution), key adipose tissue lipolytic proteins and IR (hyperinsulinaemic–euglycaemic clamp) in 20 obese, premenopausal women. [Ferritin] was correlated with FA Ra ($r = 0.65$; $P = 0.002$) and IR ($r = 0.57$; $P = 0.008$); these relationships remained significant after controlling for body mass index and plasma [C-reactive protein] (a marker of systemic inflammation) in multiple regression analyses. We then stratified subjects into tertiles based on [ferritin] to compare subjects with 'High-ferritin' *versus* 'Low-ferritin'. Plasma [hepcidin] was more than fivefold greater ($P < 0.05$) in the High-ferritin *versus* Low-ferritin group, but there was no difference in plasma [C-reactive protein] between groups, indicating that the large difference in plasma [ferritin] reflects a difference in iron stores, not systemic inflammation. We found that FA Ra, adipose protein abundance of hormone-sensitive lipase and adipose triglyceride lipase, and IR were significantly greater in subjects with High-ferritin *versus* Low-ferritin (all $P < 0.05$). These data provide the first evidence linking iron and *in vivo* FA mobilization and suggest that elevated iron stores might contribute to IR in obesity by increasing systemic FA availability.

KEYWORDS
iron, lipolysis, obesity

1 | INTRODUCTION

Accumulating evidence suggests that dysregulated iron homeostasis contributes to metabolic dysfunction in obesity (Gabrielsen et al., 2012; Moreno-Navarrete et al., 2014; Orr et al. 2014), but the mechanisms linking iron and metabolic health remain incompletely understood (Fernández-Real, McClain, & Manco, 2015). High rates of adipose tissue lipolysis and fatty acid (FA) release into the systemic circulation are associated with insulin resistance in obesity (Van Pelt, Guth, Wang, & Horowitz, 2017), and some *ex vivo/in vitro* evidence indicates that iron increases lipolysis in adipocytes (Chirumbolo et al., 2015; Rumberger, Peters, Burrington, & Green, 2004). There is also some epidemiological evidence linking markers of iron metabolism with plasma FA concentrations (Wlazlo et al., 2013), and it has been suggested that iron-mediated lipolysis and FA release might contribute to impaired insulin sensitivity in obesity (Chirumbolo et al., 2015; Rumberger et al., 2004; Wlazlo et al., 2013). However, the relationship between iron and *in vivo* FA release has not been examined. The purpose of this study was to determine whether plasma ferritin concentration ([ferritin]), a marker of total body iron stores (Worwood, 2007), is positively associated with elevated rates of FA release from adipose tissue in obese, premenopausal women.

2 | METHODS

2.1 | Ethical approval

This study was part of a larger investigation of the relationship between FA mobilization and insulin resistance in obese adults. Some of the methods for this study have been reported elsewhere (Van Pelt et al., 2017) but are briefly repeated here for convenience. All findings reported in this paper are new. This study conformed to the standards set by the latest version of the *Declaration of Helsinki*, was registered at clinicaltrials.gov (NCT01452048) and was approved by the University of Michigan Institutional Review Board (HUM00051537). All participants provided written, informed consent.

2.2 | Experimental protocol

We studied 20 obese, premenopausal women with plasma [ferritin] within the clinically normal range (12–200 ng ml^{-1}; Worwood, 2007). Participants were weight stable for ≥6 months, not pregnant or breastfeeding and not taking medications/supplements known to affect their metabolism. Participants were studied after an overnight fast during the follicular phase of their menstrual cycle. We collected a baseline blood sample and a subcutaneous abdominal adipose tissue sample, under local anaesthetic (Van Pelt et al., 2017). The rate of appearance of FA in the systemic circulation (FA Ra) was assessed using ^{13}C-palmitate isotope dilution as detailed elsewhere (Van Pelt et al., 2017). Briefly, after collecting the baseline blood and adipose tissue samples, ^{13}C-palmitate was infused at a rate of 0.04 μmol kg^{-1} min^{-1} for 1 h. After 45 min, we collected three blood samples separated by 5 min for the determination of the tracer-to-tracee ratio (TTR) of ^{13}C/^{12}C-palmitate in plasma for subsequent FA Ra calculations (Patterson, Zhao, & Klein, 1998). Insulin resistance was assessed using a 2 h primed, hyperinsulinaemic–euglycaemic clamp; insulin was infused at a rate of 100 mU m^{-2} min^{-1}, and insulin sensitivity (the inverse of insulin resistance) was determined as the steady-state glucose infusion rate at the end of the clamp period divided by fat-free mass (assessed via dual-energy X-ray absorptiometry).

2.3 | Analytical methods

Haemoglobin concentration ([haemoglobin]) and haematocrit were assessed by the University of Michigan Pathology Laboratory. Fasting plasma concentrations of glucose, triglycerides and cholesterol were measured using colorimetric assays, and fasting plasma insulin concentration was measured via radioimmunoassay (Van Pelt et al., 2017). Enzyme-linked immunosorbent assays were used for the measurement of plasma concentrations of ferritin (Abcam Ab108837, Cambridge, MA, USA), high-sensitivity C-reactive protein ([CRP]; Calbiotech CR120C, Spring Valley, CA, USA), soluble transferrin receptor ([sTfr]; R&D Systems DTFR1, Minneapolis, MN, USA) and hepcidin ([hepcidin]; R&D Systems DHP250). For our FA Ra analysis, palmitate TTR, in addition to the plasma concentrations of palmitate and total FA, were all determined using gas chromatography–mass spectrometry (Patterson et al., 1998; Patterson, Zhao, Elias, Hachey, & Klein, 1999). Palmitate Ra was calculated from TTR using the steady-state Steele equation (Steele, 1959), and FA Ra was calculated by dividing palmitate Ra by the fractional contribution of palmitate to total FA concentration. Standard immunoblotting techniques (Van Pelt et al., 2017) were used to quantify the protein abundance of hormone-sensitive lipase (HSL; #4107, Cell Signaling Technologies, Danvers, MA, USA), phosphorylated HSL (p-HSL^{ser660}; #4126, Cell Signaling), adipose triglyceride lipase (ATGL; #2138, Cell Signaling) and phosphorylated ATGL (p-ATGL^{ser406}; kind gift of Dr Matthew Watt, University of Melbourne). The ATGL antibody recognized a doublet of ~50 and 54 kDa, as has been reported in previous studies (Schreiber et al., 2017; Wang et al., 2013). A single box was drawn around both bands for ATGL quantification. Protein expression was normalized to total protein stain (Memcode; Thermofisher Scientific, Waltham, MA, USA).

New Findings

- **What is the central question of this study?**
  Do obese women with relatively high whole-body iron stores exhibit elevated *in vivo* rates of fatty acid (FA) release from adipose tissue compared with a well-matched cohort of obese women with relatively low iron stores?
- **What is the main finding and its importance?**
  Obese women with high plasma [ferritin] (a marker of whole-body iron stores) had greater FA mobilization, lipolytic activation in adipose tissue and insulin resistance (IR) compared with obese women with lower plasma [ferritin]. Given that elevated FA mobilization is intimately linked with the development of IR, these findings suggest that elevated iron stores might contribute to IR in obesity by increasing systemic FA availability.

2.4 | Statistics

All data are presented as means ± SD. Non-normally distributed variables ([sTfr], [triglycerides] and p-HSL protein expression) were logarithmically transformed before statistical analyses. Simple and multiple linear regressions were performed to examine relationships between variables. For group comparisons between the highest and lowest tertiles of plasma [ferritin], homogeneity of variance was tested (Levene's test), and Student's unpaired *t* tests were performed. The level of significance was set at $P \leq 0.05$ (SPSS version 24, IBM Corp, Armonk, NY, USA).

3 | RESULTS

3.1 | Plasma [ferritin] and group stratification

Plasma [ferritin] in our subjects ranged from 23 to 197 ng ml^{-1}, which is within the clinically normal range (Worwood, 2007). We stratified subjects into tertiles for comparisons between subjects with

TABLE 1 Anthropometric and clinical measures in the Low-ferritin *versus* High-ferritin group

Parameter	Low-ferritin ($n = 6$)	High-ferritin ($n = 6$)	*P* value
Age (years)	34 ± 11	33 ± 7	0.80
Body mass (kg)	96 ± 11	98 ± 9	0.73
Body mass index (kg m^{-2})	35 ± 2	37 ± 3	0.25
Body fat (%)	51 ± 3	48 ± 6	0.36
Fat mass (kg)	49 ± 8	47 ± 9	0.73
Fat-free mass (kg)	47 ± 5	51 ± 6	0.27
Fasting [glucose] (mM)	4.7 ± 0.5	4.5 ± 0.7	0.61
Fasting [insulin] (μU ml^{-1})	14 ± 10	18 ± 6	0.40
Fasting [triglycerides] (mg dl^{-1})	53 ± 20	61 ± 37	0.83
Fasting [cholesterol] (mg dl^{-1})	159 ± 45	167 ± 16	0.70
Plasma [ferritin] (ng ml^{-1})	36 ± 13	144 ± 28	0.000007*
Plasma [hepcidin] (ng ml^{-1})	34 ± 54	184 ± 118	0.02*
Plasma [C-reactive protein] (mg dl^{-1})	0.9 ± 0.8	1.2 ± 0.8	0.48
[Haemoglobin] (g dl^{-1})	12.2 ± 1.2	12.4 ± 0.3	0.64
Haematocrit (%)	37 ± 3	37 ± 1	0.91
Plasma [soluble transferrin receptor] (nM)	28 ± 14	19 ± 5	0.21

Data are presented as means ± SD. *$P \leq 0.05$.

high-normal plasma [ferritin] ('High-ferritin'; 144 ± 28 ng ml^{-1}; $n = 6$) *versus* low-normal plasma [ferritin] ('Low-ferritin'; 36 ± 13 ng ml^{-1}; $n = 6$). The High-ferritin and Low-ferritin groups were well matched for age, anthropometric characteristics and fasting plasma concentrations of glucose, insulin, triglycerides and cholesterol (Table 1). By design, there was a large (approximately fourfold) difference in plasma [ferritin] between groups. Hepcidin, a liver-secreted hormone described as the master regulator of iron homeostasis, increases in response to high iron stores (Coffee & Ganz 2017); consistent with this, we found that plasma [hepcidin] was more than fivefold greater in the High-ferritin *versus* Low-ferritin group. Systemic inflammation can influence [ferritin] and [hepcidin], but plasma [CRP] did not differ between groups, suggesting that the difference in plasma [ferritin] between groups reflects a large difference in body iron stores without a difference in a key marker of systemic inflammation. Basic markers of erythropoiesis ([haemoglobin], haematocrit and [sTfr]) were also similar between groups (Table 1).

3.2 | Fatty acid mobilization

Fatty acid rate of appearance (in micromoles per kilogram of fat mass per minute) was >80% greater in the High-ferritin *versus* Low-ferritin group ($P = 0.02$; Figure 1a). The large between-group difference in FA Ra remained significant when expressed in absolute terms (696 ± 191 *versus* 413 ± 133 μmol min^{-1}, $P = 0.01$) or normalized to fat-free mass (13.7 ± 3.6 *versus* 8.6 ± 2.0 μmol kg^{-1} min^{-1}, $P = 0.01$). Accompanying the greater FA Ra in the High-ferritin *versus* Low-ferritin group, total protein abundance of HSL and ATGL and the ratio of p-HSL^{ser660} to HSL (a marker of elevated lipolytic activation) were all significantly greater in the High-ferritin group ($P < 0.05$; Figure 1b). There were no differences in the ratio of p-ATGL^{ser406} to ATGL (Figure 1b). Across all 20 subjects, plasma [ferritin] was significantly correlated with FA Ra ($r = 0.65$; $P = 0.002$; Figure 1c). Importantly, using multiple regression analyses, plasma [ferritin] remained independently correlated with FA Ra even when body mass index (BMI) and [CRP] were included as covariates (overall model $r = 0.67$, $P = 0.02$; [ferritin] $r_{partial} = 0.67$, $P = 0.003$; BMI $r_{partial} = -0.073$, $P = 0.78$; [CRP] $r_{partial} = -0.13$, $P = 0.62$).

3.3 | Insulin sensitivity

Whole-body insulin sensitivity was nearly 40% lower in the High-ferritin *versus* Low-ferritin group ($P = 0.02$; Figure 1d). Across all 20 subjects, plasma [ferritin] was negatively correlated with insulin sensitivity ($r = -0.57$; $P = 0.008$; Figure 1e). Using multiple regression analyses, plasma [ferritin] remained independently correlated with insulin sensitivity when BMI and [CRP] were included as covariates (overall model $r = 0.69$, $P = 0.02$; [ferritin] $r_{partial} = -0.62$, $P = 0.01$; BMI $r_{partial} = -0.28$, $P = 0.28$; [CRP] $r_{partial} = -0.16$, $P = 0.53$).

4 | DISCUSSION

The major new finding of this study was that plasma [ferritin] was linked with elevated FA Ra in obese, premenopausal women. These data are the first to demonstrate a relationship between iron stores and *in vivo* FA mobilization. Importantly, our findings also suggest that an elevation in systemic FA mobilization in obese adults with relatively high plasma [ferritin] might contribute to whole-body insulin resistance. Together, these findings suggest that iron stores influence FA metabolism and insulin resistance in obesity, even among individuals with clinically normal plasma [ferritin].

Circulating [ferritin] is widely used as a biomarker of body iron stores in clinical and research settings (Worwood, 2007). However,

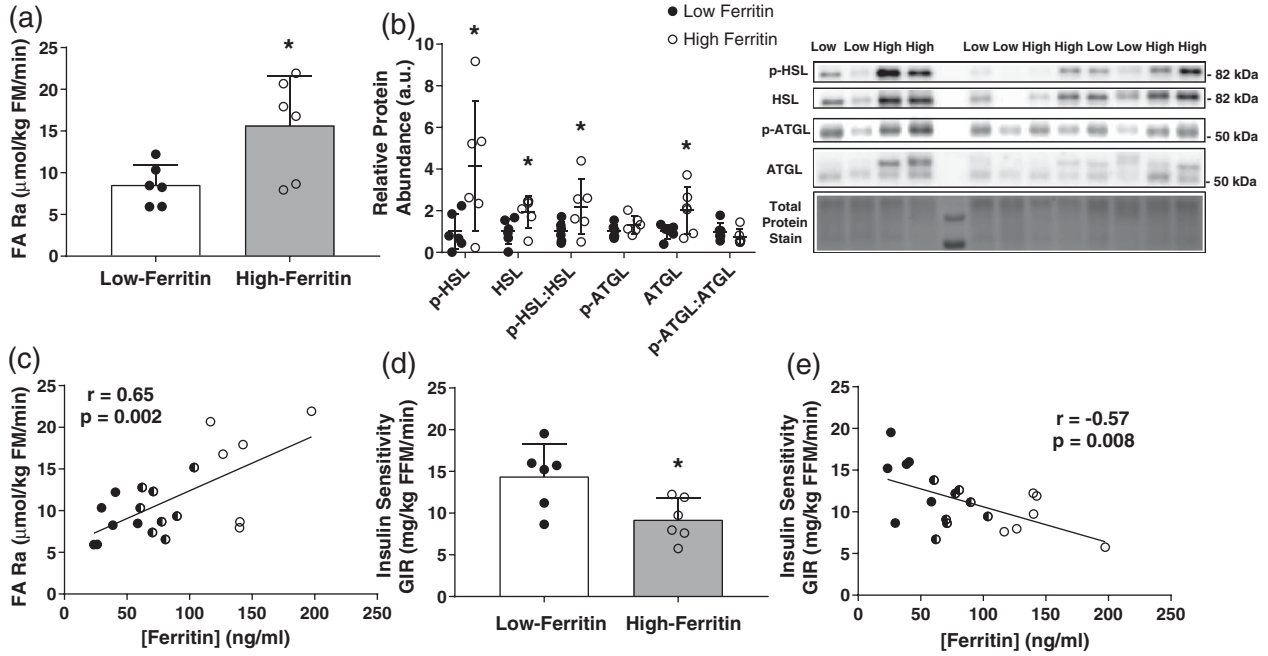

FIGURE 1 (a) Fatty acid rate of appearance (FA Ra) in the Low-ferritin (filled circles) *versus* High-ferritin (open circles) group. (b) Relative protein abundance of lipolytic proteins in adipose tissue; data were normalized to total protein stain (Memcode) and expressed relative to the mean of the Low-ferritin group. Western blot images show all individual data for subjects in the Low-ferritin and High-ferritin groups (for each protein, samples from all subjects were run on a single gel, with a molecular weight marker after the fourth sample). A representative image of the total protein stain is shown. Images were processed using ImageJ; image adjustments were limited to changes in brightness and contrast to optimize visualization and were performed uniformly on the whole image. (c) Correlation between plasma [ferritin] and FA Ra across all subjects. (d) Insulin sensitivity (glucose infusion rate; GIR) in the Low-ferritin *versus* High-ferritin group. (e) Correlation between plasma [ferritin] and insulin sensitivity across all subjects. Data in panels (a), (b) and (d) are presented as means ± SD, with individual data points shown. FM: fat mass; FFM: fat free mass. $^{*}P \leq 0.05$

it is known that systemic inflammation can augment plasma [ferritin] (Gabay & Kushner 1999), which can influence the interpretation of [ferritin] as a marker of body iron stores. For this reason, it is common to assess circulating [CRP] in conjunction with [ferritin] to determine whether observed [ferritin] patterns are driven by inflammation. In the present study, we found no difference in [CRP] between the High-ferritin and Low-ferritin groups, and the relationships between [ferritin] and FA Ra and insulin resistance persisted after controlling for [CRP] in multiple regression analyses. Importantly, the relationship between [ferritin] and insulin resistance has repeatedly been shown to remain independent of [CRP] (Wlazlo et al., 2015; Jehn, Clark, & Guallar, 2004). We recognize that [CRP] is only one marker of systemic inflammation, and we cannot completely dismiss the possible influence of inflammation on [ferritin] in our subjects.

The mechanisms linking iron and insulin resistance remain incompletely understood, but our findings suggest that iron-mediated FA mobilization might be a key underlying mechanism. Previous studies reported that *ex vivo* and *in vitro* treatment of murine adipocytes with iron increased glycerol release (Chirumbolo et al., 2015; Rumberger et al., 2004), suggesting the possibility that iron might directly or indirectly activate ATGL and/or HSL, the two primary enzymes catalysing triglyceride hydrolysis (i.e. lipolysis). Gene expression of HSL was recently reported to be significantly increased (and the increase in ATGL expression was almost statistically significant) in mice after 4 weeks of dietary iron supplementation (Katsumura et al., 2017), but to our knowledge, the influence of iron on lipase protein activation/abundance has not been examined previously. Our findings that total protein abundance of both HSL and ATGL and the ratio of p-HSL^{ser660} to HSL were significantly greater in the High-ferritin *versus* Low-ferritin group suggest that iron might increase lipase protein abundance and activation. Iron is a potent inducer of reactive oxygen species, which have been found to increase adipocyte HSL activation *in vitro* (Krawczyk, Haller, Ferrante, Zoeller, & Corkey, 2012). Based on these findings, our working hypothesis is that elevated iron increases reactive oxygen species signalling, thereby increasing lipase activity and FA Ra, resulting in impaired insulin sensitivity.

Our cross-sectional study design enabled us to compare obese subjects with widely differing iron stores who were otherwise well matched. We hypothesize that iron stimulates lipolysis, resulting in elevated FA Ra, but we cannot rule out the possibility that the converse is true (i.e. elevated FA Ra might increase iron uptake and storage) or that the association between [ferritin] and FA Ra might be mediated by other factors. Additional studies are needed to determine whether iron stores and FA Ra are indeed causally related. Future studies are also needed to examine whether the observed relationships between iron, FA mobilization and insulin resistance in obese, premenopausal women hold true in other populations.

In summary, we have provided the first evidence linking iron stores and *in vivo* FA mobilization. These findings add to the growing body of evidence indicating that iron stores influence metabolic health, even among individuals with normal iron stores. Future studies are warranted to determine whether lowering iron stores is a potential

countermeasure to reduce FA mobilization and improve insulin sensitivity in obese adults.

AUTHOR CONTRIBUTIONS

The experiments were performed at the University of Michigan. B.J.R., D.W.V.P., L.M.G., A.C.L. and J.F.H. contributed to the conception/design of the work. All authors contributed to acquisition, analysis or interpretation of data. All authors contributed to drafting of the work or revising it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

COMPETING INTERESTS

None declared.

ORCID

Jeffrey F. Horowitz http://orcid.org/0000-0003-3851-777X

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