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Iron Homeostasis during Risperidone Treatment in Children and Adolescents

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Abstract

Objectives: Previous cross-sectional evidence has linked antipsychotic-related weight gain to reduced body iron concentration. Using longitudinal data, we examined the association between changes in weight following risperidone initiation or discontinuation and ferritin concentration.

Methods: Study 1: Between 04/2004 and 09/2007, participants were enrolled in a prospective randomized clinical trial comparing the efficacy of risperidone monotherapy to the combination of

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Location of the work and address for reprints:

This research has been conducted at the University of Iowa, Department of Psychiatry, Iowa City, IA.

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Conflict of Interest:

The other authors report no competing interests.

risperidone and behavior therapy in targeting disruptive behavior in 4 to 13 year-old children with DSM-IV-TR-based autism spectrum disorder. Study 2: Medically healthy 7 to 17 year-old participants in long-term open-label risperidone treatment at study entry returned for follow up 1.5 years later, between 07/2007 and 07/2011. Available blood samples were used to measure ferritin. Linear multivariable regression analysis tested the association between ferritin concentration and change in age-sex-specific body mass index (BMI) Z-score between study entry and endpoint, adjusting for relevant confounders.

Results: Study 1 sample consisted of 73 participants (85% males, mean age: 7.7 ± 2.4 years). After 18.0 ± 2.0 weeks on risperidone, their BMI Z-score increased by 0.93 ± 0.70 points and ferritin concentration declined by 6.8 ± 13.3 $\mu\text{g/L}$. After adjusting for age and sex, change in BMI Z-score was inversely correlated with percent change in ferritin concentration ($\beta = -18.3$, $p < 0.003$). Study 2 participants had all been receiving risperidone at study entry. At follow up, 1.5 ± 0.3 years later, risperidone was discontinued in 26 of the 96 who were included in the analysis. Neither change in BMI Z-score nor in ferritin concentration was different between those who continued vs. discontinued risperidone. However, a reduction in BMI Z-score between study entry and follow up was associated with higher ferritin concentration at follow up in participants who discontinued risperidone compared to those who continued it ($p = 0.01$).

Conclusions: Risperidone-related weight gain is associated with a reduction in body iron reserves, which appears to improve with weight loss following risperidone discontinuation. Preliminary evidence suggests that risperidone may also directly inhibit iron absorption.

Trial registration: Study 1: on clinicaltrials.gov. Study 2: Not applicable.

Keywords

Antipsychotics; risperidone; iron status; ferritin; weight gain; child and adolescent

Introduction:

Iron plays a significant role in brain function¹. Iron is incorporated in various structural and transport proteins². It is also a cofactor of various enzymes, such as tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis³. Iron deficiency in rats results in reduced density of the dopamine transporter and the dopamine D₁ and D₂ receptors in the basal ganglia^{4,5,6,7,8}. In children, iron deficiency has been associated with cognitive impairment, including motor, attention, and memory dysfunction⁹. Such deficits have been observed even in the absence of anemia because, during iron depletion, available body iron is prioritized to hemoglobin synthesis^{10,11}. In clinical samples, low serum ferritin concentration (a marker of body iron stores) has additionally been associated with more severe attention deficit hyperactivity disorder (ADHD) symptoms and poorer response to psychostimulants^{12,13,14,15}.

Previously, we found significant iron depletion in a group of children and adolescents treated chronically with risperidone¹⁶. Moreover, after adjusting for relevant factors, including risperidone and 9-hydroxy-risperidone concentration, we found that body iron concentration was inversely associated with prolactin concentration. This is presumably secondary to a reduction in dopamine D₂ receptor density in the anterior pituitary, induced by iron

depletion^{4,5,6,7,8}. We further found that body iron concentration was inversely associated with weight gain that followed the initiation of risperidone treatment¹⁶.

As our previous study lacked pre-risperidone estimates of iron stores, we here attempt to replicate the association between antipsychotic-induced weight gain and reduced body iron concentration, using data from the second Research Units on Pediatric Psychopharmacology (RUPP) Autism Network risperidone trial (referred to as Study 1, henceforth)^{17,18}. Further, we extend our previous findings by examining the impact of risperidone discontinuation on ferritin concentration, given that we recently completed a follow up assessment on the participants in the original study (referred to as Study 2, henceforth)¹⁹. We hypothesized that weight loss following risperidone discontinuation would be associated with an increase in ferritin concentration, reflecting improved iron status.

Materials and Methods:

Study 1:

Participants: The aims and methods of the parent study have been described previously^{17,18}. This multi-site multiphase randomized trial, conducted between 04/2004 and 09/2007, compared risperidone (n=49) with the combination of risperidone and behavioral therapy (n=75) to target disruptive behavior in 4 to 13 year-old children with autism spectrum disorder (ASD)¹⁷. The participants had to be psychotropic drug-free for at least two weeks, have an IQ ≥ 35 or mental age ≥ 18 months, and be seizure-free for six months and, if taking antiepileptic agents, on a stable dose of antiepileptics for four weeks. Exclusion criteria included pregnancy, prior adequate trial of risperidone, a diagnosis of Rett's disorder or Childhood Disintegrative Disorder, and other significant psychiatric or medical conditions. At the end of week 8, poor responders were prescribed aripiprazole (n=12) and the participants were followed for up to 24 weeks.

Procedures: The institutional review boards of the participating sites approved the investigation, and the parents or legal guardians provided written informed consent.

Height and weight were measured following a standard protocol. The presence of ASD was established by clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (*DSM-IV-TR*)²⁰ criteria and corroborated by the Autism Diagnostic Interview-Revised²¹.

A blood sample was obtained to measure red blood cell count and hemoglobin concentration. Additional aliquots of plasma were stored at -80°C and used to measure ferritin concentration.

Study 2:

Participants: The aims and methods of the parent study have been described previously^{19,22}. Briefly, 7 to 17 year-old patients treated with risperidone for at least six months were recruited, regardless of psychiatric diagnosis. Patients receiving concurrent treatment with antipsychotics other than risperidone were excluded. Also excluded were patients with neurological or medical conditions and female patients who were pregnant or

receiving hormonal contraception. Between 07/2007 and 07/2011, 72% of the participants returned for a follow up research visit, 18 months after study entry, at which time study entry assessments were repeated. Few differences were present between those who returned for follow up vs. not, including being less likely to have had a history of child maltreatment but more likely to be male, suffer from ASD, and to have been receiving an antidepressant¹⁹.

Procedures: The study was approved by the University of Iowa Institutional Review Board. Written assent was obtained from children younger than 14 years old and consent from adolescents and from parents of all patients.

Height and weight were measured following a standard protocol¹⁹. Iron intake during the week prior to study entry and follow up was estimated using the 2004 Block Kids Food Frequency Questionnaire²³. This questionnaire also queries about multivitamin use, assuming that each tablet contains 18 mg of iron.

A best-estimate diagnosis, following the *DSM-IV-TR*, was generated based on a review of the psychiatric record supplemented by a brief clinical interview, and a standardized interview of the parent using the NIMH Diagnostic Interview Schedule for Children²⁴.

A morning blood sample was obtained to measure serum ferritin and C-reactive protein (CRP), among other assays.

Data Analysis:

Body mass index (BMI) was calculated as weight/height² (kg/m²). BMI measurements were converted into age-sex-specific Z-scores²⁵.

In Study 1, the baseline visit was before risperidone was started while the follow up visit was when the last plasma sample was available. Ferritin is the most widely-used marker of body iron stores. However, being an acute phase reactant, it increases during acute inflammation, potentially masking low iron stores²⁶. Therefore, participants with a change in ferritin concentration of more than 75% (Study 1) or with a CRP ≥ 10 mg/L (Study 2), suggesting acute inflammation, were excluded as were participants with relatively high ferritin concentrations (i.e., >130 µg/L).

Multivariable linear regression analysis examined the association between change in BMI Z-score between the baseline and follow up visits and ferritin concentration, adjusting for potential confounders. In Study 2, continuous and categorical variables were compared across participants who continued vs. discontinued risperidone using the Student t-test and Fisher's Exact test, respectively.

All the statistical tests performed were two-tailed, using SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC), with statistical significance set at $\alpha=0.05$.

Results:

Study 1:

Subject Characteristics: Of the 124 participants randomized to treatment, 79 had plasma samples at baseline and at least one follow up visit. Of those, six were excluded due to exhibiting a ferritin concentration $>130 \mu\text{g/L}$ or a change of $>75\%$, leaving 73 participants to be included in this analysis. Their mean age was 7.7 ± 2.4 years old and 85% ($n=62$) were males. Forty one (56%) had DSM-IV-TR-based autistic disorder, six (8%) had Asperger's disorder, and 26 (36%) had pervasive developmental disorder not otherwise specified. At baseline, their mean age-sex-specific BMI Z-score was 0.52 ± 1.20 and their mean serum ferritin concentration was $30.3 \pm 15.2 \mu\text{g/L}$. The follow up plasma sample was collected a mean 18.0 ± 2.0 weeks after the baseline measurement.

Change in Ferritin and in BMI Z-score: By follow up, BMI Z-score had increased by 0.93 ± 0.70 points and ferritin concentration had declined by $6.8 \pm 13.3 \mu\text{g/L}$, a $15.2 \pm 36.9\%$ reduction. After adjusting for age and sex, baseline ferritin concentration did not predict increase in BMI Z-score ($p > 0.80$).

After adjusting for age and sex, there was a significant inverse association between change in BMI Z-score and percent change in ferritin concentration ($p < 0.003$), whereby every 1 point increase in BMI Z-score was associated with an 18.3% reduction in ferritin (Figure 1).

Of note, there was no significant change in red blood cell count or in hemoglobin throughout the trial (mean change: $-0.004 \pm 0.232 \times 10^6/\text{mm}^3$, $p > 0.80$, and mean change: $-0.09 \pm 0.59 \text{ g/dL}$, $p > 0.20$, respectively).

Study 2:

Subject Characteristics: Of the 108 participants who returned for follow up, 96 were included in this analysis with 12 being excluded either for developing a medical condition in the interim period (e.g., type 1 diabetes, hypothyroidism, etc) or for lacking a ferritin measurement. They were mostly peri-pubertal and predominantly exhibited externalizing disorders (Table). At follow up, 1.5 ± 0.3 years later, 70 (73%) had continued on risperidone, 11 (11%) switched to another antipsychotic, and 15 (16%) discontinued all antipsychotic treatment. The last two groups were combined due to small sample size.

Change in Ferritin and in BMI Z-score: By follow up, neither continuing nor discontinuing risperidone treatment was associated with a significant change in age-sex-specific BMI Z-score ($p \text{ values} > 0.40$, Table). However, as detailed elsewhere¹⁹, among those who discontinued risperidone, switching to another antipsychotic was associated with an increase in BMI Z-score while discontinuing all antipsychotics was associated with a decrease in BMI Z-score (mean=0.68, 95% Confidence Interval [CI]: 0.31 to 1.04 vs. mean=-0.54, 95%CI: -0.80 to -0.28, respectively, $p < 0.0001$). Further, neither ferritin concentration at follow up (mean=13.7 $\mu\text{g/L}$, 95%CI: 10.2 to 17.1 vs. mean=12.7 $\mu\text{g/L}$, 95%CI: 4.0 to 21.4 vs. mean=17.1 $\mu\text{g/L}$, 95%CI: 9.7 to 24.6, respectively) nor the change in ferritin concentration between study entry and follow up (mean=-1.3 $\mu\text{g/L}$, 95%CI: -3.9 to 1.4 vs. mean=0.0 $\mu\text{g/L}$, 95%CI: -5.9 to 5.9 vs. mean=2.5 $\mu\text{g/L}$, 95%CI: -3.0 to 8.2,

respectively) was different between those who continued risperidone, switched to another antipsychotic, or discontinued all antipsychotic treatment (all p values >0.40).

After adjusting for age, sex, and ferritin concentration at study entry, there was a significant interaction effect between change in BMI Z-score and being on risperidone at follow up in predicting ferritin concentration at follow up ($p<0.04$). In fact, a reduction in BMI Z-score between study entry and follow up was associated with higher ferritin concentration at follow up in participants who discontinued compared to those who continued risperidone. No difference in ferritin was observed among those whose BMI Z-score increased (Figure 2a). A similar finding was observed with change in ferritin concentration between study entry and follow up, after adjusting for the same variables (Figure 2b). Excluding the participants who switched to an antipsychotic other than risperidone by follow up did not alter these findings.

Discussion:

Previously, using cross-sectional data, we found an inverse association between weight gain and iron status in children and adolescents who had received risperidone for a mean of 2.4 years¹⁶. Here, we extend those findings by 1) showing that baseline ferritin concentration does not moderate weight gain associated with antipsychotic treatment, 2) replicating the association between weight gain and reduction in body iron concentration, using a longitudinal design, 3) finding that ferritin concentration improves following weight loss after antipsychotic discontinuation, and 4) suggesting that risperidone might inhibit iron absorption, independently of its potential to cause weight gain.

By design, the participants had already been taking risperidone for at least six months prior to entry into Study 2. Therefore, it may be possible that the participants' pre-risperidone iron status was compromised, somehow predisposing them to excessive weight gain. Findings from Study 1 address this concern by showing not only that the participants with ASD had largely normal body iron status before starting risperidone but that there was no association between their baseline ferritin concentration and the magnitude of weight gain following the initiation of risperidone.

Additionally, with ferritin measurements available at baseline and follow up, Study 1 confirms the inverse association between weight gain and reduction in body iron concentration. This is predictable given the substantial risperidone-associated increase in BMI Z-score observed in Study 1, consistent with evidence linking rapid growth with reduction in body iron reserves^{27,28,29}. A large portion of the newly added weight, following antipsychotic treatment, may be adipose tissue. Thus, although its need for vascularization might be smaller than that of lean tissue, it will nevertheless still place further demand for iron on a system already strained to meet the needs related to normal growth in children and adolescents. It is also possible that the accumulation of adipose tissue promotes inflammation, consequently inducing the release of hepcidin from the liver. Hepcidin downregulates the iron transport protein ferroportin, thereby potentially inhibiting intestinal iron absorption^{16,30,31}. In fact, childhood obesity has been associated with iron depletion, a finding mediated at least in part by increased hepcidin^{30,31,32,33}.

In further support of the association between change in weight during antipsychotic treatment and changes in body iron reserves, we found that the discontinuation of risperidone resulted in the resolution of the excessive age-inappropriate weight gain¹⁹. This was correlated with an improvement in ferritin concentration. As detailed elsewhere¹⁹, those who discontinued risperidone still gained significant weight between study entry and follow up, but with a less steep trajectory, compared to those who continued on risperidone, enough for their sex-age-specific BMI Z-score to return to its pre-risperidone baseline through normal maturation by the follow up visit. This increase in weight, necessary for growth and development during childhood and adolescence, still requires iron for vascularization and normal cellular functions, perhaps explaining the only partial repletion of body iron reserves by follow up, despite the fact that iron dietary intake was within the recommended range³⁴.

Of interest, there was a significant interaction effect between change in BMI Z-score and risperidone treatment status in predicting change in ferritin concentration. Among participants whose BMI Z-score increased at follow up, ferritin concentration did not significantly change, regardless of whether risperidone was continued or not. This is likely due to the fact that ferritin was already strikingly low (i.e., floor effect). In contrast, among participants whose BMI Z-score decreased, ferritin concentration improved only in those who discontinued risperidone. This suggests that risperidone may be directly inhibiting iron absorption, thereby suppressing the beneficial effect of BMI Z-score reduction on iron status. This finding is not explained by sample characteristics because the range of BMI Z-score change between study entry and follow up among those who continued on risperidone was -1.2 to 0.95 and that for those who discontinued all antipsychotic treatment was -1.93 to 0.15. Further, the findings were not altered by excluding those participants who switched to a different antipsychotic.

The clinical implications of our findings have yet to be fully examined. In a previous risperidone clinical trial in ASD, there was a statistical trend for ferritin concentration to mediate clinical response to risperidone treatment³⁵. However, the number of participants with ferritin measurements at baseline and follow up was small, restricting statistical power. We have previously found iron status to be inversely correlated with response to stimulants in ADHD and with prolactin concentration during long-term treatment with risperidone^{12,16}. We have also found that prolactin was inversely related to bone mass²². Therefore, low body iron reserves could possibly impair treatment response as well as medication tolerability. These are hypotheses that deserve further investigation.

This study suffers from several limitations. First, budgetary restrictions prohibited the measurement of additional markers which could have shed further light on the magnitude and impact of body iron store depletion. Red blood cell count and hemoglobin concentration were available in Study 1 and were normal. However, follow up took place only 18 weeks after risperidone initiation and the fact that these markers are the last to be impacted by iron deficiency suggests that it would have been very unlikely that frank anemia would develop. In Study 2, these markers were not measured. We used a drastic change in ferritin concentration and elevated CRP to exclude cases with acute inflammation but additional cases of masked iron depletion could have still been missed. Further, a thorough assessment of iron intake may shed further light on whether this contributed to the findings. This is

unlikely, however, as our data suggest that intake was within the recommended range³⁴. Finally, further research is necessary to examine whether a similar reduction in body iron concentration is observed during treatment with other antipsychotic medications and to establish the clinical implications of low iron reserves in this population and whether iron supplementation would be indicated.

Conclusions:

Risperidone-related weight gain may be associated with a reduction in body iron stores. Loss of excessive weight may result in improved iron status but apparently not if risperidone treatment is continued.

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Clinical Significance:

Optimizing the safety of antipsychotics is necessary as their use in children and adolescents is widespread. One so-far little appreciated adverse event is the depletion of iron stores as a result of weight gain and/or a direct effect of the medication, specifically risperidone. The full clinical implications of such depletion are unknown but could include reduced treatment efficacy and tolerability given that brain iron deficiency is associated with impaired dopaminergic signaling. Thus, clinicians may need to monitor iron status during long-term risperidone treatment.

Clinical Points:

Antipsychotic-induced weight gain is associated with a reduction in body iron reserves.

In the general population, low iron stores have been associated with impaired cognitive and emotional functioning. In patients with ADHD, low iron stores have been associated with more severe symptoms and poorer response to treatment.

However, the clinical impact of low iron stores during antipsychotic treatment remains to be examined.

Figure 1:

Correlation of percent change in ferritin concentration and change in age-sex-specific body mass index Z-score between study entry, prior to starting risperidone, and follow up in Study 1.

Panel a)

Panel b)

Figure 2:

Least squares means of ferritin concentration at follow up (panel a) and of change in ferritin concentration between study entry and follow up (panel b) among participants in chronic risperidone treatment some of whom had discontinued it by follow up (Study 2). The reduction, but not increase, in age-sex-specific body mass index Z-score between study entry and follow up was associated with a higher ferritin concentration at follow up and a larger increase in ferritin concentration between study entry and follow up in those who

discontinued risperidone (vertical stripes) compared to those who continued it (horizontal stripes).

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Demographic and Clinical Characteristics of the Study 2 Sample Overall and Split Based on Risperidone Treatment Status at Follow up [means±sd unless otherwise noted].

Table:

	Total Sample N=96	Risp Cont N=70	Risp Discont N=26	p value
Male sex, n (%)	88 (92)	66 (94)	22 (85)	>.20
Age, years	13.2±2.7	13.3±2.8	12.9±2.4	>.50
Tanner Stage I/II/III/IV/V, %	18/21/14/17/30	18/21/18/13/31	19/23/4/27/27	>.30
Change in BMI z Score ¶	-0.04±0.63	-0.04±0.46	-0.05±0.96	>.90
Dietary Iron Intake, mg/d §	15.8±7.7	16.0±8.0	15.0±6.9	>.50
Multivitamin Use, n (%)	22 (23)	19 (27)	3 (12)	>.10
Ferritin Concentration, µg/L	14.1±14.4	13.7±15.9	15.3±9.7	>.50
Ferritin Change, µg/L ¶	-0.5±9.4	-1.3±9.7	1.3±8.5	>.20
Psychiatric Disorders, n (%)				
Attention Deficit Hyperactivity Disorder	86 (90)	63 (90)	23 (88)	>.80
Disruptive Behavior Disorder	84 (88)	64 (91)	20 (77)	<.06
Anxiety Disorder	28 (29)	21 (30)	7 (27)	>.70
Tic Disorder	25 (26)	17 (24)	8 (31)	>.50
Autism Spectrum Disorder	18 (19)	12 (17)	6 (23)	>.50
Depressive Disorder	5 (5)	3 (4)	2 (8)	>.50

¶ Refer to change between study entry and follow up. Ferritin concentration was available at both visits for 71 participants.

§ Four participants with invalid dietary data were excluded. This combines intake from food and supplements (i.e., multivitamins).