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Clinical Study

The Abnormal Measures of Iron Homeostasis in Pediatric Obesity Are Associated with the Inflammation of Obesity

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Objectives. To determine if the low iron state described in obese children is associated with the chronic inflammatory state seen in obesity. *Study Design*. Obese children age from 2 to 19 years seen at a weight management clinic were studied prospectively. Data were collected on age, gender, BMI, BMI *z*-score, serum iron, ferritin, transferrin saturation, free erythrocyte protoporphyrin, high sensitivity creactive protein (hs-crp), and hemoglobin concentration. *Results*. 107 subjects were studied. Hs-crp levels correlated positively with BMI ($P < .001$) and BMI *z*-score ($P = .005$) and negatively with serum iron ($P = .002$). 11.2% of subjects had low serum iron. Median serum iron was significantly lower for subjects with American Heart Association high risk hs-crp values (>3 mg/L) compared to those with low risk hs-crp (<1 mg/L), (65 mcg/dL versus 96 mcg/dL, $P = .016$). After adjusting for age, gender, and BMI *z*-score, serum iron was still negatively associated with hs-crp ($P = .048$). *Conclusions*. We conclude that the chronic inflammation of obesity results in the low iron state previously reported in obese children, similar to what is seen in other inflammatory diseases.

1. Introduction

Obesity is a substantial cause of morbidity among children. Diseases such as hypertension, hyperinsulinemia, depression, sleep apnea, and type 2 diabetes mellitus are all associated with pediatric obesity. It has been noted that obese children have a higher incidence of low serum iron than nonobese children [1–3]. Furthermore, data-based reviews have shown obese children to have additional measures of iron status such as ferritin, transferrin saturation, and free erythrocyte protoporphyrin that are consistent with iron deficiency at a high frequency [4, 5]. Obesity contributes to an inflammatory state, with elevated markers of inflammation such as high sensitivity c-reactive protein (hs-crp) [6–9]. Obese children have higher values of hs-crp than nonobese children, indicating that even very early obesity is associated with inflammation [10]. Chronic inflammation can lead to abnormal iron homeostasis by decreasing intestinal absorption of iron and promoting its sequestration into storage pools, such as macrophages of the reticuloendothelial system, thereby lowering circulating iron [11]. There thus exists a potential association between the inflammation of obesity and the low iron state of obesity. Such an association has been demonstrated in obese adults, but not children [12].

We sought to determine prospectively if the low iron state described with obesity is associated with the inflammation seen in obese children and to assess associations of inflammatory markers with other markers of iron status and Body Mass Index (BMI) in these children.

2. Patients and Methods

2.1. Patients. Over a 20-month period (10/15/2006 to 07/16/2008), children age from 2 to 19 years old seen at Baystate

Children's Hospital Pediatric Weight Management Program with obesity (BMI greater than 95% for age) were screened with a questionnaire. Patients without an identified risk for iron deficiency or a red cell disorder (heavy menstrual periods, known bleeding from a gastrointestinal site, known elevated levels of lead, thalassemia, sickle cell disease, sideroblastic anemia, aplastic anemia, vegan diet) or a disorder associated with inflammation (inflammatory bowel disease, autoimmune disease, cancer treated within the last year) and those not taking iron supplements were eligible. Data on age, gender, BMI, and BMI *z*-score were collected using the Pediatric Endocrinology Dynamic Record Organizer ((PEDRO), a commercial software program that utilizes the year 2000 growth charts). Subjects had blood samples drawn for complete blood count, serum iron, ferritin, transferrin saturation (serum iron/total iron binding capacity), free erythrocyte protoporphyrin (FEP), and hs-crp.

The study was approved by the Institutional Review Board of Baystate Medical Center. All subjects signed written informed consent or had parental consent with, if appropriate for developmental level, child assent.

2.2. Assessment of Iron Status, Anemia, and Inflammation. Iron status was assessed by serum iron (Roche Diagnostics Modular P analyzer), ferritin (Roche Diagnostics E170 analyzer), transferrin saturation (Roche Diagnostics Modular P analyzer), and FEP (Lab Corp of America). *Low iron* was defined as serum iron less than 45 mcg/dL. This value was chosen because it was below the lower 5th percentile for all age groups represented in the study and, for consistency across studies, it had been used previously [2, 13]. *Iron deficiency* was defined with the combination of ferritin, transferrin saturation, and FEP; if 2 of the 3 labs were abnormal for age, a subject was classified as iron deficient. These criteria have been used in the National Health and Nutrition Examination Survey (NHANES) III and in the previous studies on pediatric obesity and iron deficiency [4, 14] (Table 1a).

Hemoglobin concentration was measured (Sysmex XE-2100) to assess for anemia, with cutoff values based on the 5th percentile for a reference group [14] (Table 1b).

High sensitivity crp (Roche Diagnostics Modular P analyzer) was used as a marker of inflammation. Hs-crp values were classified by American Heart Association (AHA) standards for risk for cardiovascular disease: Low (<1 mg/L), Intermediate (1–3 mg/L), or High (>3 mg/L).

2.3. Statistical Analysis. The distributions of all variables were examined. Those that were approximately normally distributed are reported with means and standard deviations. Nonnormally distributed variables are reported with medians and ranges. Since many variables did not meet assumptions of normality, nonparametric statistics were employed. Associations among variables which were at least ordinally scaled were estimated using the Spearman rank correlation. When comparing ordinal data across categorical variables, the Wilcoxon rank-sum test was used for categorical variables with two groups and the Kruskal-Wallis test was used for categorical variables with three or more groups. When a significant global test was achieved using the Kruskal-Wallis test, Bonferroni's adjustment for multiple comparisons was applied to the pairwise comparisons of groups. Unconditional logistic regression was used to determine the independent association between iron status and hs-crp, adjusting for potential confounders. All analyses were conducted using Stata (v.10.1, College Station, TX). Associations were considered significant at a critical level of 5%.

Table 1

(a) Cutoff values for laboratory tests of iron deficiency

Age (years)	Serum Ferritin (μg/L)	Transferrin saturation (%)	Free erythrocyte Protoporhytin (μg/dL RBC)
1-2	<10	<10	>80
3–5	<12	<10	>70
6–11	<14	<12	>70
12–15	<14	<12	>70
≥16	<15	<12	>70

(b) Cutoff values for hemoglobin

Both sexes Age (years)	Hemoglobin (g/dL)
1-2	<11.0
3–5	<11.2
6–11	<11.8
Female	
12–15	<11.9
16–19	<12.0
Male	
12–15	<12.6
16–19	<13.6

*Adapted with permission from Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA*. 1997; 277 : 973–976.

3. Results

3.1. Demographic and Clinical Characteristics (Table 2). 176 subjects were enrolled; 107 (60.8%) completed laboratory testing adequate to assess iron status and inflammation. There were no significant differences in mean age, mean BMI/BMI *z*-score, or gender distribution for subjects who had laboratory studies drawn and those who did not.

3.2. Low Iron (Serum Iron <45 mcg/dL) (Table 3). 12 subjects (11.2%) were classified as having low iron. Mean hs-crp was higher in the low iron group than in the normal iron group, although this did not reach significance. Mean hemoglobin was significantly lower in the low iron group compared to

Table 2: Demographic and laboratory profile of subjects.

N	107
Male	46 (43%)
Female	61 (57%)
Mean:	
Age (years)	12.0 ± 3.2
BMI (kg/m^2)	34.4 ± 6.4
BMI z score	2.52 ± 0.48
Iron (μg/dL)	78.3 ± 30.5
Ferritin* (ng/mL)	55.4 ± 32.9
Transferrin (%) Saturation	22.4 ± 8.7
FEP$^+$ (μg/dL RBC)	34.1 ± 11.5
Hemoglobin** (g/dL)	13.6 ± 1.0
Hs-crp (mg/L)	4.22 ± 6.31

*$N = 104$; $^+N = 103$; **$N = 106$.

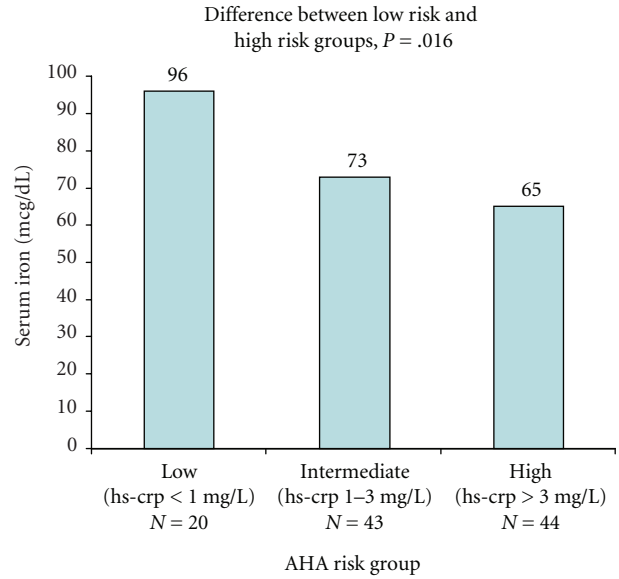

Figure 1: Median serum iron by American Heart Association (AHA) risk for cardiovascular disease group.

the normal iron group. All additional measures of iron status were significantly different between the two groups, with ferritin and transferrin saturation lower and FEP higher in the low iron group than in the normal iron group. There were no significant differences in BMI, BMI *z*-score, age, or gender between the two groups.

3.3. Iron Deficiency and Anemia. 2 subjects (1.9%) met NHANES criteria for iron deficiency. Neither subject had anemia. 106 subjects had hemoglobin concentration measured. One subject (0.9%) had a hemoglobin concentration that was low for age and gender; all iron studies in this subject were above cutoff values.

3.4. Hs-crp (Figure 1). 87 (81%) of subjects had hs-crp levels classified as either AHA intermediate or high risk for cardiovascular disease. The group of subjects with high risk hs-crp had significantly lower median serum iron than those classified as low risk (65 mcg/dL, range 23–123 versus 96 mcg/dL, range 46–156, $P = .016$). Mean BMI was higher in the high risk group compared to the low risk group (36.4 kg/m^2 ± 7.3 versus 32.1 kg/m^2 ± 6.2, $P = .008$). There were no significant differences in age, gender, or BMI *z*-score among the three risk groups.

3.5. Hs-crp Correlations (Spearman). Hs-crp levels correlated positively with BMI ($r = 0.33$, $P < .001$), BMI *z*-score ($r = 0.27$, $P = .005$), and ferritin ($r = 0.23$, $P = .018$) and negatively with serum iron ($r = -0.29$, $P = .002$), transferrin saturation ($r = -0.21$, $P = .033$), and hemoglobin ($r = -0.20$, $P = .039$).

3.6. Logistic Regression Analysis. After controlling for age, gender, and BMI *z*-score, hypoferremia remained negatively associated with hs-crp ($P = .048$).

4. Discussion

This prospective study establishes the association between the inflammatory state, as identified by hs-crp, and the low iron state described in pediatric obesity. It also shows that the inflammation of obesity disturbs basic iron homeostasis as early as childhood and adolescence. Identification of the probable cause of the iron deficiency reported in obese children is especially important because this age group is particularly susceptible to the negative effects of iron deficiency, as discussed later.

Previous reports have proposed different mechanisms to explain the high rate of iron deficiency among obese children, including consumption of high calorie, iron-poor diets, sedentary lifestyle resulting in decreased myoglobin breakdown, and increased iron requirements for increased red cell mass. Our data support that it is the inflammation of obesity that negatively influences iron homeostasis. A similar association has been described in adults [12]. Anty et al. reported on obese adult women undergoing bariatric surgery who, when their BMI decreased postoperatively, showed a decrease in levels of crp with an associated improvement in markers of iron status, further suggesting that it is obesity that leads to inflammation which in turn contributes to abnormal measures of iron homeostasis [15].

It is known that obesity is associated with chronic low levels of inflammation [16]. Adipose tissue secretes a variety of proinflammatory cytokines including tumor necrosis factor alpha and interleukin-6 [16, 17]. The positive association of hs-crp with ferritin and negative associations with serum iron, transferrin saturation and hemoglobin, as shown in this study, are characteristic of inflammation's effects on measurements of iron homeostasis. A potential mechanism explaining the impact of obesity on iron status may involve the increased production of the protein

Table 3: Demographic and laboratory features of subjects with low iron status compared to subjects with normal iron status.

	Low Iron (<45 mcg/dL)	Normal Iron (>45 mcg/dL)	*P* (Wilcoxon Rank-Sum Test)
N	12	95	
Male	5 (42%)	41 (43%)	
Female	7 (58%)	54 (57%)	
Mean			
Age (years)	11.9 ± 3.5	12.0 ± 3.2	.968
BMI (kg/m^2)	36.5 ± 6.1	34.1 ± 6.4	.141
BMI *z*-score	2.59 ± 0.22	2.51 ± 0.50	.102
Hs-crp (mg/L)	8.49 ± 12.88	3.69 ± 4.79	.095
Hemoglobin (gm/dL)	12.9 ± 0.9	13.7 ± 1.0*	.005
Ferritin (μg/L)	33.4 ± 18.0	58.3 ± 33.3$^+$	.003
Transferrin saturation (%)	9.4 ± 3.0	24.0 ± 7.8	<.001
FEP (μg/dL RBC)	45.9 ± 13.6	32.6 ± 10.3**	.001

*$N = 94$; $^+N = 92$; **$N = 91$.

hepcidin. Hepcidin is a key regulator of iron homeostasis, decreasing intestinal iron absorption and promoting iron sequestration in macrophages, effectively lowering serum iron and the bioavailability of iron. Hepcidin is produced primarily in the liver but is expressed in adipose tissue as well [18]. Its expression is increased by interleukin-6, which is higher in obese than nonobese children. In addition, there are data to suggest that hepcidin expression is increased by the adipose-derived hormone leptin [19].

In an attempt to isolate obesity's influence on iron status, subjects at risk for iron deficiency were excluded. Because of this, iron deficiency, as defined by NHANES criteria, in this screened population, was not as prevalent as in reviews of unscreened obese children [4]. When our rate of iron deficiency (1.9%) is added to the rate reported for nonobese children (2.1%), one gets a rate of iron deficiency closer to the 5.5% described for obese children [4]. Thus, the reported increase in iron deficiency among obese children may be attributable to the inflammation of obesity and its effects on measures of iron status.

Potential complications of iron deficiency during childhood and adolescence include poorer cognition, worse school achievement, and more behavior problems than in children without iron deficiency [20–22]. Cournot et al. in a prospective study found an association between higher BMI and lower cognitive scores in middle aged men and women, but iron status was not assessed [23]. We are unaware of such descriptions in children but future research could investigate associations between BMI, iron status, and cognitive function.

In addition to its impact on iron homeostasis, inflammation is associated with the development of cardiovascular disease in adults. This study confirms elevated levels of hs-crp in obese children as well as the positive association between hs-crp and BMI/BMI *z*-score [24, 25]. That is, the more obese a child is, the more systemic inflammation they are exposed to. The majority of the children in this study were significantly obese, with a mean BMI **z**-score of 2.5 and had levels of hs-crp at intermediate or high risk for cardiovascular disease according to adult studies [26]. The full effects of years of such inflammation on children's cardiovascular health have yet to be determined. Baker et al. showed that an elevated BMI in childhood was associated with significantly increased risk of both fatal and nonfatal coronary heart disease later in life [27].

A potential limit of this study is that although at the time of enrollment subjects were screened for risks of inflammation, some subjects had blood drawn days or weeks later and could have been ill at the time of phlebotomy thus raising hs-crp levels above baseline. While possibly impacting lab variables such as hs-crp, ferritin, or iron, such a situation would not account for the positive association of hs-crp and BMI/BMI *z*-score. Although we demonstrated correlations between BMI/BMI *z*-score and hs-crp as well as between hs-crp and measurements of iron status, without nonobese subjects, it is difficult to assess the degree of effect weight status has on hs-crp and iron status.

These data raise several questions for future childhood obesity research. It has been demonstrated that weight loss is associated with reduction in crp [15, 28]. Does weight loss improve iron status in children as it has been suggested to do in some adults [15]? Is oral iron supplementation sufficient to correct low serum iron? Do anti-inflammatory medicines alter iron status in obese children? Does the low iron state of obesity contribute to poor neurocognitive function? Does the inflammation of obesity alter metabolism of other essential trace elements, such as zinc, copper, and selenium? Future research may address some of these questions.

This study provides the probable link between two long-known important aspects of pediatric obesity—chronic inflammation and abnormal, low iron status. It illustrates the pervasive nature that obesity has on children and their health, affecting even essential mineral metabolism, and shows that such effects start early in the disease, during

childhood. Such data could ultimately be used to support evidence-driven public health policy and prevention of the disease.

Abbreviations

AHA: American Heart Association
BMI: Body mass index
FEP: Free erythrocyte protoporphyrin
Hs-crp: High sensitivity c-reactive protein
NHANES: National Health and Nutrition Examination Survey.

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