

# Characterization and pathogenesis of anemia in glycogen storage disease type Ia and Ib

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**Purpose:** The aim of this study was to characterize the frequency and causes of anemia in glycogen storage disease type I.

**Methods:** Hematologic data and iron studies were available from 202 subjects (163 with glycogen storage disease Ia and 39 with glycogen storage disease Ib). Anemia was defined as hemoglobin concentrations less than the 5th percentile for age and gender; severe anemia was defined as presence of a hemoglobin <10 g/dl.

**Results:** In glycogen storage disease Ia, 68/163 patients were anemic at their last follow-up. Preadolescent patients tended to have milder anemia secondary to iron deficiency, but anemia of chronic disease predominated in adults. Severe anemia was present in 8/163 patients, of whom 75% had hepatic adenomas. The anemia improved or resolved in all 10 subjects who underwent resection of liver lesions. Anemia was present in 72% of patients with glycogen storage disease Ib, and severe anemia occurred in 16/39 patients. Anemia in patients

with glycogen storage disease Ib was associated with exacerbations of glycogen storage disease enterocolitis, and there was a significant correlation between C-reactive protein and hemoglobin levels ( $P = 0.036$ ).

**Conclusion:** Anemia is a common manifestation of both glycogen storage disease Ia and Ib, although the pathophysiology appears to be different between these conditions. Those with severe anemia and glycogen storage disease Ia likely have hepatic adenomas, whereas glycogen storage disease enterocolitis should be considered in those with glycogen storage disease Ib.

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**Key Words:** anemia; glycogen storage disease I; hepcidin; inflammatory bowel disease; iron

## INTRODUCTION

The glycogen storage diseases (GSDs) are a group of disorders that are characterized by aberrant storage or utilization of glycogen. GSD type I (GSD I) is due to impaired glucose-6-phosphatase activity, and it is the most severe of the hepatic glycogenoses from a hypoglycemia vantage point because this critical enzyme catalyzes the terminal step of both glycogenolysis and gluconeogenesis. As a result, endogenous glucose production is impaired or absent, and shunting of glucose-6-phosphate into alternative pathways results in hyperlactatemia, hypertriglyceridemia, and hyperuricemia.<sup>1</sup>

Since the discovery of continuous glucose feeding in 1971 and uncooked cornstarch in 1982 as methods to maintain euglycemia, patient survival has improved greatly in the GSD I population.<sup>2</sup> Long-term complications continue to occur, however, including hepatocellular adenoma formation with risk for carcinoma, chronic hepatic inflammation, gout, osteoporosis, focal segmental glomerulosclerosis, nephrocalcinosis, and anemia.<sup>3</sup> In addition, patients with GSD Ib, who have defects in the glucose-6-phosphate transporter, have additional manifestations, including neutropenia, neutrophil dysfunction, and inflammatory bowel disease.<sup>4</sup>

Although anemia has been recognized as a common complication in GSD, there has been limited research on the topic. Prior publications have documented a high incidence of anemia in both GSD Ia and Ib, but there have been few studies examining etiology of this complication. In addition, there are no guidelines for management of this common complication. To have evidence-based recommendations for the associated American College of Medical Genetics consensus guidelines for anemia in patients with GSD I, data from the two largest GSD treatment centers in the United States were obtained. The hematologic data gathered over the past three decades were analyzed in a retrospective manner to describe etiological factors and propose management guidelines for anemia in the GSD I population.

## MATERIALS AND METHODS

Following institutional review board approval at both Duke University and the University of Florida, informed written consent was obtained from all participants, with assent obtained from minor subjects 7 years of age and older who were capable of affirming their desire to participate. Subjects were followed longitudinally at these institutions, and all patients with GSD

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I were included in the analysis. Data were available from 202 subjects with GSD I, of whom 163 patients have GSD Ia and 39 patients have GSD Ib. The diagnosis of GSD Ia or Ib was established biochemically or by assessment of enzyme testing from a liver biopsy for all subjects. The diagnosis and subtyping were confirmed in all patients who had mutation analysis (149/163 patients with GSD Ia and 31/39 with GSD Ib).

Patients were evaluated annually with laboratory testing for markers of metabolic control, complete blood counts, inflammatory markers, and ultrasound screening for hepatic and renal lesions. Annual liver imaging with ultrasonography was performed after 5 years of age, and patients discovered to have hepatic adenomas were subsequently monitored more frequently with serial imaging through magnetic resonance imaging, computed tomography scans, or ultrasonography as recommended in the literature.<sup>5</sup> For patients with GSD Ib, the diagnosis of inflammatory bowel disease was made by pediatric gastroenterologists based on a combination of inflammatory studies, serologic testing, colonoscopies, and capsule endoscopies.

Patient data, including age, gender, current medications, comorbidities, and body mass index, were included in our database. Laboratory values of hemoglobin, hematocrit, mean corpuscular volume, serum iron, total iron-binding capacity, transferrin saturation, ferritin, triglycerides, C-reactive protein, erythrocyte sedimentation rate, uric acid, and lactate were obtained from the most recent encounter. Because many patients with hepatic adenomas underwent surgical resection or liver transplantation and experienced subsequent correction of anemia, all historical laboratory studies were examined to establish the nadir hemoglobin value. Additional concurrent laboratory values obtained at the time of nadir hemoglobin concentration were included for analysis. Anemia status was compared for all patients on the basis of the most recent available laboratory values. Anemia was defined with reference to the National Health and Nutrition Examination Survey (NHANES III), using as the definition hemoglobin concentration that is less than the 5th percentile of age and gender reference groups.<sup>6</sup> Severe anemia was defined as hemoglobin  $\leq 10$  g/dl. These criteria were defined before analysis.

Comparison of covariates at nadir hemoglobin event was performed across quartiles on the basis of hemoglobin values. For categorical variables, to account for small cell counts, a Fisher's exact test was performed to examine differences in observed counts across the hemoglobin groups. For quantitative variables, an analysis of variance was employed to test for differences in covariate means across the hemoglobin quartiles while controlling for age and gender. Analysis of variance was also used to compare covariate means between patients with and without adenomas on the basis of nadir hemoglobin event. A logistic regression was used to model the probability of adenoma occurrence on the basis of hemoglobin levels from all available records. Because multiple records were collected for each patient across the study period, a mixed-model approach was employed to accommodate repeated measures.

In the GSD Ib group, univariate regression was used to test for the significance of the relationship between hemoglobin values and C-reactive protein levels, erythrocyte sedimentation rate, triglyceride levels, standardized body mass index, and uric acid concentration individually. A *P* value  $< 0.05$  was used to define statistical significance.

## RESULTS

### GSD Ia

Of the 163 patients with GSD Ia, 95 were male. The median age was 15 years (range: 1.5–51.8 years). A total of 46 patients developed hepatocellular adenomas (31%) at a median age of 16.7 years. The medication regimens of nine patients included ferrous sulfate, and one patient was treated with erythropoietin at the time of the most recent follow-up. Four patients presented with a history of menorrhagia. Fifteen patients presented with comorbid nephropathy, and two patients had renal failure. One patient had undergone a bone marrow transplant for chronic myelogenous leukemia that was performed 5 years before inclusion in this study.

Overall, 68 of 163 (41.7%) patients were anemic at their most recent encounter, and more than half of patients over age 15 were anemic (Table 1). Severe anemia was present in 8 of 163 patients (4.9%), and 6 of 8 (75%) had concomitant hepatic adenomas. Of the 68 anemic patients, 40 patients were examined with complete iron studies. Of patients with iron studies, 32 of 40 had features consistent with iron deficiency anemia with low transferrin saturation and low iron values. Two anemic patients exhibited transferrin saturation values  $> 40\%$ , normal mean corpuscular volume values, and iron values  $> 150$   $\mu\text{g/dl}$ , consistent with anemia of chronic disease. Notably, both of these patients had hepatic adenomas.

Nadir hemoglobin values were compared in quartiles (Table 2). Hepatocellular adenoma was prevalent in 57.9% of patients in the lowest quartile (hemoglobin  $< 10.4$  g/dl) and was significantly associated with quartile divisions (*P* = 0.0165).

**Table 1** Mean hemoglobin values of patients with glycogen storage disease type Ia and prevalence of anemia and severe anemia at most recent follow-up

Age category (years)	n	Hemoglobin (g/dl)	Anemia	Severe anemia
		Mean (SD)	n (%)	n (%)
1–2	3	12.0 (0.70)	0 (0)	0 (0)
3–5	15	12.2 (0.93)	1 (6.7)	0 (0)
6–8	19	12.3 (0.95)	4 (21.1)	0 (0)
9–11	22	12.2 (0.83)	8 (36.4)	0 (0)
12–14	19	12.4 (0.79)	3 (15.8)	0 (0)
15–19	19	12.8 (1.77)	10 (52.6)	0 (0)
20–29	32	12.6 (1.67)	21 (65.6)	1 (3.1)
30–39	24	12.1 (2.14)	14 (58.3)	3 (12.5)
40–49	8	10.2 (2.85)	6 (75)	4 (50)
50–59	2	12.5 (0.21)	1 (50)	0 (0)

**Table 2** Nadir hemoglobin quartiles of patients with glycogen storage disease type Ia

Covariate	Hemoglobin				P value
	Quartile 1 (2.6–10.3)	Quartile 2 (10.3–11.5)	Quartile 3 (11.5–12.3)	Quartile 4 (12.3–18.5)	
Adenoma	22 (57.9%)	11 (31.4%)	13 (31.7%)	9 (24.3%)	0.0165
Triglycerides (mg/dl)	702.2 (474.01) <i>n</i> = 17	504.9 (426.12) <i>n</i> = 19	422.1 (280.35) <i>n</i> = 33	427.5 (269.57) <i>n</i> = 32	0.0113
Mean corpuscular volume (fl)	83.4 (9.86) <i>n</i> = 36	83.1 (5.96) <i>n</i> = 32	82.9 (6.16) <i>n</i> = 23	82.5 (5.20) <i>n</i> = 24	0.6404
Iron (µg/dl)	37.6 (15.60) <i>n</i> = 11	80.1 (39.46) <i>n</i> = 9	69.7 (32.09) <i>n</i> = 26	75.2 (29.33) <i>n</i> = 26	0.0087
Transferrin saturation (%)	9.1 (3.74) <i>n</i> = 10	21.6 (10.13) <i>n</i> = 8	18.0 (7.50) <i>n</i> = 25	19.8 (7.44) <i>n</i> = 26	0.0046

Additionally, serum triglyceride concentration was negatively associated with nadir hemoglobin values ( $P = 0.0113$ ). When a comparison was performed on the basis of adenoma status (Table 3), a relationship was again found between adenomas and anemia. In subjects with adenomas, the mean nadir hemoglobin was 10.3 g/dl (SD = 2.42 g/dl) as compared with patients without adenomas, who had a nadir of 11.6 g/dl (SD = 1.64 g/dl;  $P = 0.0002$ ). Serum triglyceride and serum lactate levels were significantly different between these groups.

Hemoglobin values were compared for all patients who underwent hepatic resection or liver transplantation for hepatocellular adenomas (Table 4). Pre-resection nadir hemoglobin value was compared with hemoglobin level at most recent follow-up. Studies from the operative admission were excluded from comparison.

### GSD Ib

Of the 39 patients with GSD Ib, 18 were male. The median age was 13.4 years (range: 1–38 years). Neutropenia was present in all subjects, GSD enterocolitis (inflammatory bowel disease) was diagnosed in 20 patients (51%), and a total of 6 patients had development of hepatocellular adenomas (15%). Of the 28 patients with known medication histories, all patients received granulocyte colony-stimulating factor, four patients were on ferrous sulfate supplements and one included erythropoietin. One patient presented with dialysis-dependent renal failure.

In subjects with GSD Ib, 14/21 females (66.7%) and 14/18 males (77.8%) were classified as anemic at most recent follow-up. As a group, 28/39 patients with GSD Ib were anemic (71.8%). Severe anemia was present in 16/39 patients (41%). Mean hemoglobin level in patients with GSD Ib was 10.3 g/dl (SD ±1.4) in females and 10.2 g/dl (SD ±1.6) in males.

An analysis of variance for inflammatory markers and markers of metabolic control demonstrated significant correlation between C-reactive protein and hemoglobin levels ( $P = 0.036$ , Table 5). Correlation between erythrocyte sedimentation rate and hemoglobin levels approached significance ( $P = 0.071$ ), whereas markers of metabolic control did not demonstrate significant correlation.

**Table 3** Characteristics of patients with GSD Ia at time of nadir hemoglobin concentration according to adenoma status

Covariate	Adenoma	No adenoma	ANOVA P value
	Mean (SD)	Mean (SD)	
Hemoglobin (g/dl)	10.3 (2.42) <i>n</i> = 55	11.6 (1.64) <i>n</i> = 96	0.0002
MCV (fl)	84.9 (9.01) <i>n</i> = 43	82.2 (5.59) <i>n</i> = 64	0.555
Iron (µg/dl)	89.2 (45.54) <i>n</i> = 14	64.9 (25.94) <i>n</i> = 52	0.0112
TIBC (µg/dl)	423.1 (90.40) <i>n</i> = 13	393.4 (79.50) <i>n</i> = 52	0.2459
Transferrin saturation (%)	22.8 (11.18) <i>n</i> = 12	17.3 (6.82) <i>n</i> = 51	0.0316
Ferritin (ng/ml)	549.2 (1146.3) <i>n</i> = 6	69.4 (54.05) <i>n</i> = 36	0.0111
Triglycerides (mg/dl)	697.2 (436.32) <i>n</i> = 30	416.6 (278.99) <i>n</i> = 64	0.0003
Lactate (mmol/l)	6.2 (9.93) <i>n</i> = 26	2.4 (1.30) <i>n</i> = 53	0.0073
BMI SDS	0.6 (0.47) <i>n</i> = 5	1.8 (0.82) <i>n</i> = 16	0.0047

ANOVA, analysis of variance; BMI, body mass index; GSD, glycogen storage disease; SDS, standard deviation score; TIBC, total iron-binding capacity.

SI conversion factors: To convert hemoglobin to g/L, multiply by 10; iron to µmol/L, multiply by 0.179; TIBC iron to µmol/L, multiply by 0.179; ferritin to pmol/L, multiply by 2.247; and triglycerides to mmol/L, multiply by 0.0113.

## DISCUSSION

### GSD Ia

Concordant with previously reported studies of patients with GSD I, we found a high prevalence of anemia in this patient population. When compared with the NHANES reference groups, over half of the patients with GSD Ia who were above the age of 15 years were anemic. Of note, patients were less likely to be anemic in preadolescent age groups, and this may be related to several factors, including lower prevalence of hepatic adenomas, differences in nutrition and metabolic control, cornstarch regimen

**Table 4** Comparison of hemoglobin before and after hepatocellular adenoma resection in patients with GSD Ia

Subject	Sex	Age	Before resection			After resection			
			Hgb (g/dl)	Hct (%)	MCV (cu micron)	Age	Hgb	Hct	MCV
1	M	14	11.5	33.7		16	13.6	40.1	
2	F	16	10.3	32	83	24	10.4	33	91
3	M	17	10.3	32	92	28	11.7	34	89
4	F	19	10	30	78.3	26	14.1	37.2	
5	M	20	10.1	30	82	31	16.9	48	85
6	F	21	9.8	30	92	36	12.9	38	85
7	M	23	14.4	42	91	32	16.4	46	91
8	F	30	13.6	40.3		31	13.8	38.3	
9	F	36	9.4	30	100	41	12.4	39	92
10	F	45	9.8	29.8		52	12.3	38.3	
11	M	49	11.2	34	84	50	12.6	38	91

F, female; GSD, glycogen storage disease; Hct, hematocrit; Hgb, hemoglobin; M, male; MCV, mean corpuscular volume.

**Table 5** ANOVA of hemoglobin values in patients with GSD Ib

Covariate	ANOVA (P value)
CRP (n = 28)	0.036
ESR (n = 29)	0.071
Trig (n = 36)	0.341
BMI SDS (n = 23)	0.414
Uric acid (n = 29)	0.198

ANOVA, analysis of variance; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GSD, glycogen storage disease; Trig, triglyceride.

adherence, and fewer comorbidities such as menorrhagia and renal failure. The prevalence of anemia in our adult patient population is slightly higher than that seen in the European Study on Glycogen Storage Disease Type I.<sup>2</sup> It is noteworthy that the standards used to define anemia were different between the two studies. In this study, we controlled for both age and gender, resulting in variable normal ranges; in contrast, a lower limit of 11.9 g/dl was used for all patients over age 10 years in the European Study on Glycogen Storage Disease Type I. The prevalence in this study, however, was less than that reported by Talente *et al.*,<sup>7</sup> who found 81% of their cohort of 32 patients with anemia.

Patients with GSD may be predisposed to iron deficiency because cornstarch reduces iron bioavailability in the gastrointestinal tract.<sup>8</sup> Although iron supplementation usually will treat people with mild anemia, patients with severe anemia are often resistant to iron therapy even when administered intravenously.<sup>9</sup> Patients with more severe anemia were found with a very high adenoma burden. When analyzed, patients with hepatic adenomas had lower hemoglobin values, but serum iron concentrations were greater than average. Taken together, patients with adenomas appear to exhibit anemia of

chronic disease that is likely related to increased expression of hepcidin within adenoma tissue. Abnormal regulation of hepcidin in the adenomas results in impaired intestinal absorption of iron and decreased recycling of iron by macrophages.<sup>10</sup> Notably, most anemic patients with hepatic adenomas demonstrated normalization of hemoglobin levels after adenoma resection or liver transplantation (Table 4).

Several covariates of adenoma status at the nadir hemoglobin event correlated significantly, including serum triglyceride concentration and serum lactate concentration. Although some subjects were included in both studies, this evidence from a larger cohort of subjects and an additional GSD specialty center corroborates previously published data, which demonstrate that metabolic control may play a role in hepatocellular adenoma development.<sup>11</sup> It is important to note that metabolic control by itself, however, cannot fully explain adenoma formation, and there are genetic and other factors also involved with development of adenomas.<sup>12</sup> The most strongly correlated laboratory parameter with adenoma formation was serum triglyceride concentration ( $P = 0.0003$ ), which is the most reliable surrogate marker of metabolic control due to stable concentrations over longer periods of time. Serum lactate concentration was also correlated ( $P = 0.0073$ ), although it should be noted that lactate values fluctuate rapidly throughout the day in response to diet and treatment conditions.

Iron supplementation remains the primary therapy for patients with mild anemia. If iron therapy fails or if severe anemia develops, imaging of the liver is warranted if not recently performed to screen for adenoma growth or changing lesions. In the presence of adenomas, intravenous iron therapy may help overcome decreased intestinal iron absorption induced by hepcidin. In the absence of alternative treatment options, severe iron-refractory anemia secondary to hepatocellular adenoma may be best addressed definitively with surgical resection.<sup>13</sup>

**GSD Ib**

Anemia is more prevalent in patients with GSD Ib (71.8%) as compared with GSD Ia (41.7%). Additionally, prevalence of severe anemia is increased in GSD Ib (41%) as compared with patients with GSD Ia (4.9%). The observed prevalence of anemia in our GSD Ib population is higher than previously reported findings in the European Study on Glycogen Storage Disease Type I, in which 23 of 56 patients across all age groups were anemic (41%), but the cohort in this study (median age 13.4 years) was older than in the prior report (median age 7.1 years).<sup>2</sup>

The association between anemia and inflammatory bowel disease in the GSD Ib population is similar to the high prevalence of anemia seen within the non-GSD inflammatory bowel disease population. Burbige *et al.*<sup>14</sup> studied 58 ambulatory patients with Crohn disease and reported an anemia prevalence of 51.7% with hemoglobin values <11.0 g/dl. Another large study by Schreiber *et al.*<sup>15</sup> found 26.3% of 334 ambulatory Crohn disease patients with hemoglobin values <10.0 g/dl. The etiology of anemia in patients with inflammatory bowel disease is likely attributed to iron deficiency anemia, blood loss, and anemia of chronic

disease. Blood loss, folate deficiency, inflammation, malnutrition, hemolysis, and marrow-suppressing medications may also contribute to iron deficiency anemia in this population.<sup>16</sup> Mechanisms for anemia of chronic disease have been hypothesized. It is thought that cytokine release (particularly interleukin-6) from the inflamed intestine stimulates hepcidin synthesis in the liver with resultant anemia of chronic disease.<sup>17</sup>

In our study, the severity of anemia is significantly correlated with the levels of C-reactive protein. The relationship between inflammatory bowel disease severity and anemia in patients with GSD Ib has not been previously documented, and our study is the first to describe this correlation. New-onset development of anemia in a patient with GSD Ib should trigger an evaluation of GSD enterocolitis if a diagnosis has not been made. In contrast to GSD Ia, hepatic adenomas are less common in this population (15%), and treatment of the inflammatory bowel disease and iron supplementation should result in improvement of anemia.

### Conclusion

Anemia is a common complication in both GSD Ia and Ib, but the cause of this complication appears to be different. Although mild iron deficiency is common in both GSD Ia and Ib due to dietary restrictions, altered iron absorption from cornstarch therapy, and anemia of chronic disease, severe anemia in GSD Ia appears to be related to large hepatic adenoma formation. Likewise, GSD enterocolitis should be considered in GSD Ib patients with severe anemia. Development of severe anemia during puberty or adulthood warrants imaging of the abdomen to search for a bleed or growth of the lesions. In contrast, evaluation for GSD-associated inflammatory bowel disease should occur in patients with GSD Ib who develop severe anemia. Improved understanding of the pathogenesis of this complication should allow new therapies to be introduced to treat anemia in the future.

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### DISCLOSURE

The authors declare no conflict of interest.

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