Association Between Iron Deficiency and A1C Levels Among Adults Without Diabetes in the National Health and Nutrition Examination Survey, 1999–2006

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OBJECTIVE — Iron deficiency has been reported to elevate A1C levels apart from glycemia. We examined the influence of iron deficiency on A1C distribution among adults without diabetes.

RESEARCH DESIGN AND METHODS — Participants included adults without self-reported diabetes or chronic kidney disease in the National Health and Nutrition Examination Survey 1999–2006 who were aged ≥18 years of age and had complete blood counts, iron studies, and A1C levels. Iron deficiency was defined as at least two abnormalities including free erythrocyte protoporphyrin >70 μg/dl erythrocytes, transferrin saturation <16%, or serum ferritin ≤15 μg/l. Anemia was defined as hemoglobin <13.5 g/dl in men and <12.0 g/dl in women.

RESULTS — Among women (n = 6,666), 13.7% had iron deficiency and 4.0% had iron deficiency anemia. Whereas 316 women with iron deficiency had A1C ≥5.5%, only 32 women with iron deficiency had A1C ≥6.5%. Among men (n = 3,869), only 13 had iron deficiency and A1C ≥5.5%, and only 1 had iron deficiency and A1C ≥6.5%. Among women, iron deficiency was associated with a greater odds of A1C ≥5.5% (odds ratio 1.39 [95% CI 1.11–1.73]) after adjustment for age, race/ethnicity, and waist circumference but not with a greater odds of A1C ≥6.5% (0.79 [0.33–1.85]).

CONCLUSIONS — Iron deficiency is common among women and is associated with shifts in A1C distribution from <5.5 to ≥5.5%. Further research is needed to examine whether iron deficiency is associated with shifts at higher A1C levels.

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A1C is formed by the glycation of the terminal valine of the β-chain of hemoglobin. It is used commonly as a screening test for diabetes in clinical practice (1). A1C may be less susceptible than other measures of glycemia to temporary fluctuations caused by diet, physical activity, or illness as well as differences in local testing standards; as a result, an expert committee has recently endorsed an A1C ≥6.5% as diagnostic for diabetes (1).

Previous studies have reported that depletion of iron stores may alter the glycation rate of hemoglobin and elevate A1C concentrations, independent of glycemia (2). Iron deficiency may be present without associated anemia (3). Although iron deficiency is the most common nutritional deficiency (3), the clinical relevance of iron deficiency on the use of A1C as a screening test for diabetes has not been studied. Reproductive-age women are particularly vulnerable to iron deficiency, reflecting iron loss through menstruation and pregnancy. In the Third National Health and Nutrition Examination Survey (NHANES) 1988–1994 and later NHANES waves, >11% of women had iron deficiency (3,4).

Using a recent population-based sample of U.S. adults, we examined the distribution of A1C by iron deficiency status among adults without known diabetes. We hypothesized that adults with iron deficiency would be more likely to have elevated A1C levels, even after consideration of fasting plasma glucose. We also hypothesized that any differences would persist after adjustment for other factors associated with A1C and iron deficiency, including age, race/ethnicity, and waist circumference.

RESEARCH DESIGN AND METHODS

— We used data from the NHANES 1999–2006 conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention to assess the health and nutritional status of the U.S. population. The NHANES 1999–2006 included a nationally representative probability sample of the U.S. civilian noninstitutionalized population, identified through a complex multistage cluster sampling design (5). During a household interview, participants provided information on sociodemographics and health status, and physicians and health care technicians conducted a standard examination on sampled subjects within 4 weeks of the interview. For the purposes of this analysis, we included NHANES 1999–2006 participants aged ≥18 years who had a complete blood count, iron studies, and A1C levels. We excluded individuals with known self-reported diabetes (n = 1,029) and pregnant women (n = 1,144). Con-

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ditions such as renal disease that shorten erythrocyte survival may proportionately decrease A1C levels and are also associated with iron deficiency, (6), but the degree of renal impairment at which anemia occurs is unclear (7). Therefore, we also excluded participants with chronic kidney disease ($n = 1,266$), defined as a glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 or GFR from 60 to 90 ml/min per 1.73 m^2 with microalbuminuria (8), from the primary analysis.

Main outcome measures

A1C measurements for NHANES 1999–2004 were performed by the Diabetes Diagnostic Laboratory at the University of Missouri–Columbia using Primus CLC330 and Primus CLC 385 analyzers (Primus Corporation, Kansas City, MO). A1C measurements in NHANES 2005–2006 were performed by the Diabetes Laboratory at the University of Minnesota using a Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, San Francisco, CA). Both assays use a high-performance liquid chromatography system and were standardized to the Diabetes Control and Complications Trial reference method. Collection procedures were similar from 1999 to 2004 and between 2005 and 2006, intra-assay variation was <3% for both assays, and assays correlated at 0.98, with similar values for the range of A1C examined in this analysis (9–11). Therefore, for the purposes of this analysis, we combined the results from the two assays.

According to analyses of 1999–2004 NHANES data, an A1C of 5.5% has a sensitivity of 89% and a specificity of 80% compared with fasting glucose, and an A1C of 6.1% has a sensitivity of 67% and a specificity of 98% compared with fasting glucose levels ≥126 mg/dl to detect diabetes (12). In 2009, an expert committee endorsed A1C as a diagnostic test for diabetes (1). For the purposes of this report, A1C was categorized in two ways. Because of the distribution of A1C values (Table 1), we examined a cut point of <5.5 vs. ≥5.5%, and because of the expert committee recommendation, we examined a cut point of <6.5 vs. ≥6.5%.

Independent variables

Iron status may be assessed through several laboratory tests. We used the definition applied previously in the Third NHANES and the NHANES 1999–2000 for iron deficiency, i.e., any two of the following three indexes: erythrocyte protoporphyrin levels >70 μg/dl erythrocytes, ferritin ≤15 μg/l, and transferrin saturation levels <16% (3). The presence of anemia was defined as an Hb level of <12.0 g/dl for women and <13.5 g/dl for men (3).

We controlled for several factors that could have served as confounders because of their associations with both iron deficiency and A1C, including age (13,14), race (13,14), and obesity, particularly visceral adiposity (14,15). In NHANES 1998–2006, race/ethnicity was defined as non-Hispanic white, non-Hispanic black, Mexican American, and other race. For the total estimates of iron deficiency, all racial/ethnic groups were combined. BMI was calculated as weight in kilograms divided by the square of height in meters, and waist circumference is reported in centimeters. In women, we also controlled for self-report of parity and hysterectomy status, as these may be associated with iron deficiency (16) and glucose tolerance (17,18).

Statistical analyses

We performed analyses using SAS for data management and SUDAAN to account for unequal probabilities of selection, planned oversampling, and the complex sample design of the NHANES (5). All analyses were stratified by sex, as anemia cut points for hemoglobin levels differ by sex. We compared categorical variables by iron deficiency status using χ^2 tests and continuous variables using ANOVA. We constructed several types of multivariable models. First, we compared the distribution of A1C between participants with and without iron deficiency. Of participants, 97% had A1C levels >5.5 or 5.5–6.0% (Table 1); therefore, we used 5.5% as a cut point in one analysis and 6.5% as a cut point in another analysis. We used multiple logistic regression models to describe the odds of having A1C levels ≥5.5 vs. <5.5% or ≥6.5 vs. <6.5% by iron deficiency status, before and after adjustment for age, race/ethnicity, waist circumference, and, among women, parity (as a continuous variable) and hysterectomy status. Models using BMI instead of waist circumference were also constructed with similar results, so only the results using waist circumference are shown. We also calculated the predicted prevalence of an elevated A1C level according to iron deficiency status, and differences between prevalences before and after adjustment for the covariates mentioned above.

We conducted several sensitivity analyses. First, we used multiple linear regression to calculate the adjusted prevalence of mean A1C levels by iron deficiency status before and after adjustment for the above factors. Because of the skewed A1C distribution, we log-transformed A1C levels but obtained similar results and, therefore, for ease of interpretation, present the analysis without log transformation. To determine whether the association between iron deficiency and A1C was independent of glycemia, we examined the subpopulation of men and women in our sample who also underwent a fasting glucose measurement ($n = 2,796$ women and $n = 1,680$ men). Approximately one-half of NHANES participants were sampled to attend the morning session. These participants were instructed to fast at least 9 h before the appointment time. Fasting plasma glucose values are available for those adults who attended the morning examination and were fasting ≥8 h. In this subpopulation, we included fasting glucose levels as a continuous covariate when we examined the association between iron deficiency and A1C levels. Because of the small number of male participants with both elevated A1C levels and iron deficiency, we performed sensitivity analyses only among women participants. In the third sensitivity analysis, we also included adults with GFR from 60 to 90 ml/min per 1.73 m^2 with microalbuminuria, resulting in an increase in sample size from 2,993 women and 1,799 men to 3,033 women and 2,044 men. Finally, we examined the subpopulation of adults with anemia to determine whether any associations were more pronounced in the subgroup of women with iron deficiency anemia, but we did not find this (results not shown).

RESULTS — Unadjusted characteristics of men and women with and without iron deficiency are shown in Table 1. Among women ($n = 6,666$), 13.7% ($n = 1,150$) had iron deficiency, and, after consideration of sample weighting, 30% of iron-deficient women also had anemia. Among men ($n = 3,869$), 1.6% ($n = 75$) had iron deficiency, and, after consideration of sample weighting, 33% of iron-deficient men also had anemia. Among women, 316 participants with iron deficiency had an A1C ≥5.5%; 32 participants with iron deficiency had an A1C ≥6.5%. Among men, 13 participants with iron deficiency had an A1C ≥5.5%,

Table 1—*Characteristics of adults aged 18 years and older with and without iron deficiency, NHANES 1999–2006*

	Women			Men		
	Iron deficiency	No iron deficiency	*P**	Iron deficiency	No iron deficiency	*P**
Sample size	1,150 (13.7)	5,516 (86.3)		75 (1.6)	3,794 (98.4)	<0.001
Age						
<50 years	88.7	69.4	<0.001	63.7	71.2	0.216
≥50 years	11.3	30.6		36.3	28.9	
Race/ethnicity (%)						
Non-Hispanic white	56.7	72.4	<0.001	75.0	71.8	0.876
African American	18.2	10.9		9.8	9.7	
Hispanic	20.7	12.3		11.5	15.0	
Other	4.4	4.4		3.7	3.6	
BMI (%)						
<25 kg/m^2	35.7	44.1	<0.001	28.0	36.4	0.225
25 to <30 kg/m^2	24.1	26.6		35.2	40.4	
≥30 kg/m^2	40.3	29.3		36.8	23.3	
Waist circumference (cm)	94.2 ± 0.8	91.1 ± 0.4	<0.001	107.8 ± 3.3	97.0 ± 0.3	0.002
Parity (women only) (%)						
0	24.3	27.3	0.157			
1	15.9	16.5				
2	25.6	27.3				
3	18.7	17.3				
4	9.1	6.3				
≥5 births	6.4	5.3				
Hysterectomy (women only) (%)	5.6	17.6	<0.001			
Anemia (%)	29.5	2.3	<0.001	33.3	3.3	<0.001
A1C (%)	5.31 ± 0.02	5.27 ± 0.01	0.127	5.43 ± 0.06	5.29 ± 0.02	0.035
A1C (%)						
<5.4	73.6	76.5	0.366	54.7	73.9	<0.001
5.5–6.0	23.9	20.5		37.9	22.5	
6.1–6.4	1.5	1.7		7.3	2.0	
6.5–6.9	0.4	0.6		0.0	0.6	
7.0–7.9	0.3	0.3		0.0	0.4	
8.0–8.9	0.2	0.1		0.1	0.2	
≥9.0	0.3	0.3		0.0	0.4	
Fasting glucose (mg/dl) (n = 2,993 women, n = 1,799 men)	92.4 ± 0.8	94.2 ± 0.5	0.034	101.5 ± 2.3	98.8 ± 0.6	0.269
Fasting glucose <126 mg/dl (n = 2,993 women, n = 1,799 men) (%)	99.2	98.5	0.096	100.0	97.3	<0.001

Data are n (%), weighted percentage, or means ± SE adjusted for complex survey design. Percentages may not total 100 because of rounding, and percentages may differ from unweighted calculations of percentages. *P value was determined by a design-corrected χ^2 test or t test.

and only 1 male participant with iron deficiency had an A1C ≥6.5%.

Characteristics of iron-deficient adults differed among men and women. Women with iron deficiency tended to be aged <50 years and were more likely to be African American or Hispanic, to be obese, and to have a greater waist circumference and were less likely to have had a hysterectomy. Men with iron deficiency tended to be aged ≥50 years and to have greater waist circumference. In the subpopulation of participants who had fasting glucose levels, iron-deficient women had slightly lower fasting glucose compared with non–iron-deficient women, but similar proportions had fasting glucose <126 mg/dl. Iron-deficient men had mean fasting glucose values similar to those of non–iron-deficient men, although no iron-deficient men had a fasting glucose <126 mg/dl. Among women, unadjusted A1C mean levels did not differ between iron-deficient and non–iron-deficient adults; A1C distributions were primarily shifted from <5.5 to 5.5–5.9%. Among men, unadjusted mean A1C levels were higher in iron-deficient men compared with those for iron-sufficient men.

The odds of having an A1C ≥5.5% by iron deficiency status are shown in Table 2. Among women, iron deficiency was associated with increased odds of an A1C ≥5.5% before and after adjustment for age and race/ethnicity, waist circumference, parity, and hysterectomy. Among men with and without iron deficiency, the odds of having an A1C ≥5.5% did not reach statistical significance after adjustment for covariates (Table 2). The odds of having an A1C ≥6.5 by iron-deficiency status for women is also shown in Table 2, with no statistically significant association, although the number of iron-deficient women with A1C ≥6.5% was small. Because only one man had iron deficiency and an A1C ≥6.5%, multivariate regression was not performed.

Table 2—*Odds ratios (95% CI) for iron deficiency predicting high A1C among adults aged ≥18 years, NHANES 1999–2006*

	Women*		Men: A1C ≥5.5%†
	A1C ≥5.5%	A1C ≥6.5%	
n	6,666	6,666	3,869
Unadjusted	1.17 (0.95–1.43)	0.82 (0.37–1.80)	2.34 (1.26–4.33)
Adjusted for age, race/ethnicity	1.47 (1.19–1.83)	0.90 (0.42–1.94)	2.03 (0.81–5.08)
Adjusted for age, race/ethnicity, waist circumference	1.39 (1.11–1.73)	0.79 (0.33–1.85)	1.40 (0.69–2.87)
Adjusted for age, race/ethnicity, waist circumference, parity, hysterectomy	1.33 (1.05–1.67)	0.78 (0.32–1.90)	NA

Data are odds ratios (95% CI). The referent group is adults who are iron-sufficient; an odds ratio >1 indicates that an iron-deficient adult has greater odds of having an elevated A1C than an iron-sufficient adult, and an odds ratio <1 indicates that an iron-deficient adult has a lower odds of having an elevated A1C than an iron-sufficient adult. *316 female participants with iron deficiency had a measured A1C ≥5.5%; 32 female participants with iron deficiency had a measured A1C ≥6.5%. †13 male participants with iron deficiency had a measured A1C ≥5.5%; 1 male participant with iron deficiency had a measured A1C ≥6.5%. NA, not applicable.

Table 3 illustrates the predicted prevalence of women with an elevated A1C by iron status before and after adjustment for covariates. The difference in the predicted prevalence of an A1C ≥5.5% between women with and without iron deficiency was small although statistically significant. There was no significant difference in the predicted prevalence of an A1C ≥6.5% between women with and without iron deficiency, although again the number of women with iron deficiency and an A1C ≥6.5% was small.

Sensitivity analyses

Although mean A1C levels differed between women with and without iron deficiency, differences were small. The mean A1C values among iron-deficient and non–iron-deficient women were 5.33 and 5.27% after adjustment for age and race/ethnicity ($P = 0.002$), 5.31 and 5.27% after further adjustment for waist

Table 3—*Predicted prevalence of elevated A1C among adults aged ≥18 years with and without iron deficiency*

	Predicted prevalence of women with an A1C ≥5.5%*		Difference in predicted prevalence of A1C ≥5.5% between iron-deficient and iron-sufficient women	Predicted percentage of men with an A1C ≥5.5%*		Difference in predicted prevalence of A1C ≥5.5% between iron-deficient and iron-sufficient men
	Iron-deficient	Iron-sufficient		Iron-deficient	Iron-sufficient	
n	1,150	5,516		75	3,794	
Unadjusted	26.4 ± 1.8	23.5 ± 0.9	2.8 ± 1.9	45.3 ± 7.5	26.2 ± 1.3	19.1 ± 7.6†
Adjusted for age, race/ethnicity	29.4 ± 1.8	23.1 ± 0.9	6.3 ± 1.8†	39.5 ± 9.2	26.2 ± 1.3	13.2 ± 9.3
Adjusted for above, and waist circumference	27.9 ± 1.7	23.1 ± 0.9	4.8 ± 1.7†	31.8 ± 6.0	26.1 ± 1.3	5.7 ± 6.2
Adjusted for above, and parity, hysterectomy	27.4 ± 1.7	23.3 ± 1.0	4.1 ± 1.7†			

	Predicted prevalence of women with an A1C ≥6.5%‡		Difference in predicted prevalence of A1C ≥6.5% between iron-deficient and iron-sufficient women
	Iron-deficient	Iron-sufficient	
n	1,150	5,516	
Unadjusted	1.1 ± 0.4	1.3 ± 0.2	0.2 ± 0.4
Adjusted for age, race/ethnicity	1.1 ± 0.4	1.3 ± 0.2	0.1 ± 0.4
Adjusted for above and waist circumference	1.0 ± 0.4	1.3 ± 0.2	0.3 ± 0.4
Adjusted for above and parity, hysterectomy	1.0 ± 0.4	1.3 ± 0.2	0.3 ± 0.4

Data are % ± SE. *316 female participants with iron deficiency and 1,478 without iron deficiency had a measured A1C ≥5.5%, 13 male participants with iron deficiency and 1,178 without iron deficiency had a measured A1C ≥5.5%. †$P < 0.05$. ‡32 female participants with iron deficiency and 102 without iron deficiency had a measured A1C ≥ 6.5%.

circumference ($P = 0.059$), and 5.32 and 5.27% after further adjustment for parity and hysterectomy ($P = 0.022$). The mean A1C values among iron-deficient men and non–iron-deficient men were 5.38 and 5.29% after adjustment for age and race/ethnicity ($P = 0.22$) and 5.29 and 5.29% after further adjustment for waist circumference ($P = 0.92$).

When we examined only women with a fasting glucose level and included fasting glucose as an adjuster, the odds of having an A1C ≥5.5% remained significant after adjustment for age, race/ethnicity, waist circumference, parity and hysterectomy, and fasting glucose ($P < 0.05$). Mean A1C levels were also significantly different after adjustment for these factors ($P < 0.001$). When we included adults with mild renal impairment, the odds of having an A1C ≥5.5% with iron deficiency no longer remained significantly decreased after adjustment for age, race/ethnicity, waist circumference, parity, hysterectomy, and fasting glucose among women (OR 0.73, 95% CI 0.51–1.04). Among men, the odds of having an A1C ≥5.5% with iron deficiency remained nonsignificant (results not shown).

CONCLUSIONS — The optimal screening strategies for diabetes in terms of sensitivity, specificity, and cost may vary among different populations based on demographics and other risk factors for diabetes. We found that iron deficiency, a common condition among reproductive-age women, was associated with shifts in A1C distribution to higher levels, but this shift occurred primarily between <5.5 and 5.5–6.0%. Although we did not find an association between iron deficiency and shifts in A1C between <6.5 and ≥6.5%, few women and men had both iron deficiency and A1C elevations ≥6.5, and therefore conclusions regarding iron deficiency and the higher cut point are limited.

Previous studies of the influence of iron deficiency and glucose control have documented the high prevalence of iron deficiency in pregnancy (19) and the association with erythrocyte indexes (20). In a premenopausal nonpregnant population, Koga et al. (20) found that red cell counts and A1C were associated in premenopausal women with otherwise normal glucose tolerance. Hashimoto et al. (19) found that A1C levels were significantly increased in the third trimester compared with earlier in pregnancy, but serum glycated albumin did not change; A1C was negatively correlated with serum ferritin and transferrin saturation, suggesting that A1C was influenced by iron stores rather than by glucose control. Furthermore, replacement with iron is associated with decreases in A1C, independent of glucose changes. Coban et al. (21) found that among nondiabetic adults with iron-deficiency anemia, the A1C was 7.4 ± 0.3% before treatment and 6.2 ± 0.6% after treatment. Likewise, Tarim et al. (22) found that A1C in iron-deficient patients decreased from 7.6 ± 2.6 to 6.2 ± 1.4% after iron therapy ($P < 0.05$), despite similar glucose levels. We did not find such large shifts in A1C associated with iron deficiency, either because of the population-based nature of the sample or differences in A1C assays. In addition, we did not examine pregnant patients, and the previous studies of nonpregnant patients may have included some adults with undiagnosed diabetes, as suggested by the A1C levels. In this respect, our results are similar to a subanalysis of the Diabetes Control and Complications Trial, in which comparisons of A1C and glucose associations were similar between premenopausal women and men (23), suggesting that iron deficiency might not be influential in larger samples, although actually iron measurements were not available in that study.

When we examined only women who underwent a fasting glucose measurement and included fasting glucose as an adjuster, iron deficiency was still associated with a greater mean level of A1C after adjustment as well as a greater odds of having an A1C ≥5.5%. When we excluded women who were likely to have undiagnosed diabetes by fasting glucose value, iron deficiency was still associated with a higher mean level of A1C after adjustment, but the increased odds of having an A1C ≥5.5% was no longer significant. When we included adults with renal impairment, the association between iron deficiency and A1C was attenuated. This result is consistent with the observation that factors contributing to shorter erythrocyte half-life such as renal disease may lower the range of A1C values and reduce the strength of the association between A1C and factors such as iron deficiency.

The strengths of our report include its population-based sampling frame, size, and standardized A1C measurements that accounted for factors that might alter A1C measures such as hemoglobinopathies. Our study has several limitations. Iron studies may be affected by inflammation, and we have limited ability to assess such inflammation. Whereas previous studies have not shown that adjustment for C-reactive protein affected estimates of iron deficiency, it is possible that adults more prone to glucose intolerance and higher A1C levels were also prone to inflammation that was not detected. However, inflammation would be expected to raise ferritin levels so that adults with iron deficiency would be less likely to be diagnosed with iron deficiency, thus biasing estimates of association between A1C and iron deficiency to the null, and we used a low cutoff for ferritin (15 mg/dl). We were also unable to account for other factors that might affect red cell production, including malignancies and aplastic anemia. These factors might act as effect modifiers by decreasing red cell half-life and thus artificially lower A1C, thus reducing the magnitude of the association and might also act as confounders through influencing iron resorption, although we expect that these conditions were probably uncommon and would bias any associations to the null. As with any observational study, residual confounding from measurement error may account for the observed associations, and multiple testing may have contributed to chance positive findings.

In summary, we found that iron deficiency was common among women, this iron deficiency was not necessarily accompanied by anemia, and iron deficiency shifted the A1C slightly upward independent of fasting glucose level. However, the shift occurred at the lower end of the A1C spectrum, and we were unable to conclude whether iron deficiency affected A1C distributions at a higher cut point of <6.5 vs. ≥6.5%, a new recommended diagnostic cut point (1). Similar relationships were observed in men, although the proportion of men with iron deficiency was fairly low, prohibiting more definitive conclusions. Although younger populations are generally at low risk for diabetes compared with older populations, the incidence and prevalence of diabetes are increasing among younger women and pregnant women with the obesity epidemic as well as advancing maternal age (24,25). Research needs to be done to confirm that iron deficiency does not affect A1C readings in the population with known diabetes as well as at diagnostic cut points ≥5.5%.

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