Association of Kidney Function With Anemia


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Background: Kidney failure is known to cause anemia, which is associated with a higher risk of cardiac failure and mortality. The impact of milder decreases in kidney function on hemoglobin levels and anemia in the US population, however, is unknown.

Methods: We analyzed a population-based sample of 15419 participants 20 years and older in the Third National Health and Nutrition Examination Survey, conducted from 1988 to 1994.

Results: Lower kidney function was associated with a lower hemoglobin level and a higher prevalence and severity of anemia below, but not above, an estimated glomerular filtration rate (GFR) of 60 mL/min per 1.73 m². Adjusted to the age of 60 years, the predicted median hemoglobin level among men (women) decreased from 14.9 (13.5) g/dL at an estimated GFR of 60 mL/min per 1.73 m² to 13.8 (12.2) g/dL at an estimated GFR of 30 mL/min per 1.73 m² and to 12.0 (10.3) g/dL at an estimated GFR of 15 mL/min per 1.73 m².

The prevalence of anemia (hemoglobin level <12 g/dL in men and <11 g/dL in women) increased from 1% (95% confidence interval, 0.7%-2%) at an estimated GFR of 60 mL/min per 1.73 m² to 9% (95% confidence interval, 4%-19%) at an estimated GFR of 30 mL/min per 1.73 m² and to 33% (95% confidence interval, 11%-67%) at an estimated GFR of 15 mL/min per 1.73 m² among men and to 67% (95% confidence interval, 30%-90%) at an estimated GFR of 15 mL/min per 1.73 m² among women. An estimated GFR of 15 to 60 mL/min per 1.73 m² was present in 4% of the entire population and in 17% of the individuals with anemia.

Conclusion: Below an estimated GFR of 60 mL/min per 1.73 m², lower kidney function is strongly associated with a higher prevalence of anemia among the US adult population.

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PARTICIPANTS AND METHODS

This study uses data on 15,625 participants 20 years and older who participated in NHANES III. This survey was conducted from 1988 to 1994 by the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md. NHANES III uses a complex, multistage, clustering sampling design, and provides cross-sectional nationally representative data on the health and nutritional status of the civilian noninstitutionalized US population.18,19 Non-Hispanic black persons, Mexican Americans, elderly persons, and children were deliberately oversampled in this survey, allowing the calculation of more precise estimates of the distribution of variables in these groups.

Standardized questionnaires were administered in the home, followed by a detailed physical examination and serum collection at a mobile examination center. Race was self-selected and categorized as non-Hispanic white, non-Hispanic black, Mexican American, or other. Participants were considered to have diabetes mellitus if they reported ever having been told by a physician that they had diabetes or “sugar diabetes” at a time other than during pregnancy or if they were taking insulin or a “diabetes pill” at the time of the questionnaire.

The hemoglobin level was measured using an automated hematology analyzer (Coulter S-Plus JR; Beckman Coulter, Inc, Fullerton, Calif). Anemia was defined using World Health Organization criteria (hemoglobin level <13 g/dL for men and <12 g/dL for women) for some analyses.20 To focus on clinically significant and potentially treatable anemia, however, we used a more stringent definition (hemoglobin level <12 g/dL for men and <11 g/dL for women) for most analyses. The serum ferritin level was measured by an immunoradiometric assay (Bio-Rad Laboratories, Hercules, Calif). A low serum ferritin level was defined as less than 10 ng/mL. Transferrin saturation was calculated as follows: 100 × (serum iron level + total iron binding capacity); this was measured by a colorimetric method (Alpkem RFA 300 analyzer; Alpkem, Inc, Clackamas, Ore). Low transferrin saturation was defined as less than 15%. Iron status was categorized as functional deficiency if a participant had low transferrin saturation but a normal serum ferritin level and as absolute iron deficiency if a participant had a low serum ferritin level. The C-reactive protein (CRP) level was measured by latex-enhanced nephelometry (Behring Diagnostics, Inc, Somerville, NJ). An elevated CRP level was defined as 1.0 mg/dL or greater.

Creatinine measurements were performed at the White Sands Research Center laboratory, Alamogordo, NM, by the modified kinetic Jaffe reaction21 using an autoanalyzer (Hitachi 737; Boehringer Mannheim Corporation, Indianapolis, Ind), and were reported using conventional units (1 mg/dL = 88.4 µmol/L). The coefficient of variation for creatinine determination was 2.7% at 1.7 mg/dL, 2.1% at 3.5 mg/dL, and 2.0% at 4.4 mg/dL during the study, with stable quality control.21 Data on physiologic variation in creatinine level were obtained in a sample of 1921 participants who underwent a second creatinine measurement. The mean percentage difference between the 2 measurements, collected a mean of 17 days apart, was 0.2% (SD, 9.7%).2 The assay had stable quality control measures during the study. A review of College of American Pathologists Survey data indicated that the laboratory mean for serum creatinine level from 1992 to 1994 was within acceptable limits, but higher than the mean of all laboratories surveyed. The glomerular filtration rate (GFR) was estimated using the abbreviated equation developed at The Cleveland Clinic laboratory,

individuals in the general population with milder kidney dysfunction, however, is unknown. Given the high prevalence of early kidney disease and the impact anemia has on long-term outcomes, it is important to quantify the extent of anemia and its relation to kidney function in the general population.

This study uses data from the Third National Health and Nutrition Examination Survey (NHANES III) to assess the association of kidney function and hemoglobin levels across the range of kidney function among noninstitutionalized adults in the United States.

RESULTS

STUDY POPULATION

Table 1 shows the number of survey participants by demographic and clinical characteristics and the estimated distribution of individuals, the mean hemoglobin level, and the prevalence of anemia among the civilian noninstitutionalized US population 20 years or older. The overall mean hemoglobin level was 14.1 g/dL, and the overall prevalence of anemia, defined as a hemoglobin level less than 12 g/dL among men and less than 11 g/dL among women, was 1.9% (1.1% among men and 2.5% among women). The prevalence of World Health Organization–defined anemia (hemoglobin level <13 g/dL among men and <12 g/dL among women) was 7.3% (3.5% among men and 10.7% among women). An estimated GFR below 60 mL/min per 1.73 m² was strongly associated with lower hemoglobin levels and a higher prevalence of anemia. The prevalence of anemia was 1.8% among those with an estimated GFR of 90 mL/min per 1.73 m² or higher, compared with 5.2% among those with an estimated GFR between 30 and 59 mL/min per 1.73 m² and 44.1% among those with an estimated GFR between 15 and 29 mL/min per 1.73 m². Non-Hispanic black persons had a lower mean hemoglobin level than non-Hispanic white persons. Older age, female sex, and elevated CRP level were also significantly associated with lower hemoglobin levels. The distribution of hemoglobin level by sex is shown in Figure 1. Among those participants with complete information on iron stores (15,322 [99%]), 14% had transferrin saturation below 15% and 4% had a serum ferritin level below 10 ng/mL. Iron status was categorized as normal in 85% of the participants, functional iron deficiency in 12%, and absolute iron deficiency in 4% (percentages do not total 100 because of rounding). The mean hemoglobin level was significantly lower among participants with functional (13.4

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The estimated GFR was analyzed as a continuous measure and divided into 4 categories (15-29, 30-59, 60-89, and ≥90 mL/min per 1.73 m²). Patients with an estimated GFR below 15 mL/min per 1.73 m² (n=23) were excluded from all analyses. Quantile regression models, including fifth-order polynomials of estimated GFR and age, were used to determine the association of estimated GFR and the 5th, 50th, and 95th percentiles of hemoglobin level. These models used the survey weights but could not incorporate the clustered sampling design. The figures generated include data from all participants, although data are only presented for a limited range of estimated GFR. To detect a separate association between estimated GFR and hemoglobin level above an estimated GFR of 90 mL/min per 1.73 m², this association was also modeled using linear splines. The association of estimated GFR with the prevalence of anemia was investigated using logistic regression models with fifth-order polynomials of estimated GFR and age. These models were performed for men and women separately, and adjusted to the age of 60 years. The results of these models were used to predict the prevalence of anemia among participants aged 60 years across the range of estimated GFR. Independent predictors of anemia were identified in sex-specific multivariate logistic regression models. All variables were included in the multivariate models, except elevated CRP level, which may be in the causal pathway between reduced kidney function and anemia. Dummy variables were used in place of missing values for independent variables other than age, race, sex, and estimated GFR (<1% of individuals). Separate multivariate models, including data from both sexes, were developed to test the interaction of sex with the association between estimated GFR and other variables. These analyses were performed again, excluding participants with functional or absolute iron deficiency or an elevated CRP level.

ASSOCIATION OF KIDNEY FUNCTION WITH PREVALENCE OF ANEMIA

The prevalence of anemia by estimated GFR category and race is shown in Table 2. A lower estimated GFR was associated with a higher prevalence of anemia in non-Hispanic white persons (P < .001), non-Hispanic black persons (P < .001), and Mexican Americans (P < .02). Non-Hispanic black participants were much more likely than their non-Hispanic white counterparts to have anemia at each estimated GFR category (P < .02 for all). Applying the population-based weights of NHANES III allows us to make national estimates. The 44.1% overall prevalence of anemia at an estimated GFR of 15 to 29 mL/min per 1.73 m² corresponds to approximately 160 000 (SE, 44 000) non-institutionalized civilians in the United States in 1991. The 5.2% overall prevalence of anemia at an estimated GFR of 30 to 59 mL/min per 1.73 m² corresponds to approximately 390 000 (SE, 54 000) non-institutionalized civilians in the United States in 1991. These totals represent an estimated 4.9% and 12.0%, respectively, of the estimated GFR of 90 mL/min per 1.73 m², the median hemoglobin level was mildly but significantly (P < .001) lower at higher estimated GFRs. Similar results were obtained in analyses excluding individuals with functional or absolute iron deficiency or an elevated CRP level.

ASSOCIATION OF KIDNEY FUNCTION WITH HEMOGLOBIN LEVELS

Figure 2A and B shows the median and 5th and 95th percentiles of hemoglobin levels across a range of estimated GFRs for men and women, respectively, adjusted to the age of 60 years. Below 60 mL/min per 1.73 m², a lower estimated GFR was associated with a lower hemoglobin level for men and women. The median hemoglobin level among men decreased from 14.9 g/dL at an estimated GFR of 60 mL/min per 1.73 m² to 13.8 g/dL at an estimated GFR of 30 mL/min per 1.73 m² to 12.0 g/dL at an estimated GFR of 15 mL/min per 1.73 m². The median hemoglobin level among women similarly decreased from 13.5 g/dL at an estimated GFR of 60 mL/min per 1.73 m² to 12.2 g/dL at an estimated GFR of 30 mL/min per 1.73 m² and to 10.3 g/dL at an estimated GFR of 15 mL/min per 1.73 m². Above an estimated GFR of 90 mL/min per 1.73 m², the median hemoglobin level was mildly but significantly (P < .001) lower at higher estimated GFRs. Similar results were obtained in analyses excluding individuals with functional or absolute iron deficiency or an elevated CRP level.

Figure 2
estimated total number of cases of anemia among adults in the noninstitutionalized US population.

**Figure 3** A and B shows the prevalence of hemoglobin levels below 11, 12, and 13 g/dL, for men and women, respectively, adjusted to the age of 60 years. The prevalence of a low hemoglobin level, defined at each cut point, was substantially higher at estimated GFRs below 60 mL/min per 1.73 m². At an estimated GFR of 60 mL/min per 1.73 m², approximately 1% of men had a hemoglobin level below 12 g/dL and 1% of women had a hemoglobin level below 11 g/dL. At an estimated GFR of 30 mL/min per 1.73 m², both were increased to approximately 9%. At an estimated GFR of 15 mL/min per 1.73 m², 33% (95% confidence interval, 11%-67%) of men had a hemoglobin level of less than 12 g/dL and 67% (95% confidence interval, 30%-90%) of women had a hemoglobin level of less than 11 g/dL. Similar results were obtained among individuals without functional or absolute iron deficiency or an elevated CRP level.

**INDEPENDENT PREDICTORS OF ANEMIA**

**Table 3** shows adjusted odds ratios of anemia associated with demographic and clinical factors for men and women separately. After adjustment for all other variables in the table, a lower estimated GFR was associated with a higher prevalence of anemia in men and women ($P<.001$ for trend). Non-Hispanic black race was strongly associated with the prevalence of anemia among men and women. Older age was significantly associated with the prevalence of anemia among men but not women ($P<.001$ for the interaction), whereas Mexican American race was significantly associated with a higher prevalence of anemia among women but not men ($P<.001$ for the interaction). There was no significant interaction between sex ($P=.39$) or race ($P=.64$) and the association of estimated GFR with anemia. Functional and absolute iron deficiency remained significantly associated ($P<.001$) with anemia in men and women after adjustment. Similar associations between estimated GFR and the prevalence of anemia were obtained among individuals without iron deficiency or an elevated CRP level and after adjustment for an elevated CRP level.

**COMMENT**

The results of this study show that moderate and severe kidney dysfunction are associated with a lower hemoglo-
bin level and a higher prevalence of anemia below an estimated GFR of 60 mL/min per 1.73 m². The age-adjusted median, and the 5th and 95th percentiles, of the hemoglobin level were lower at lower estimated GFRs for men and women. The associations were similar across ethnic groups, but the prevalence of anemia was much higher among non-Hispanic black and Mexican American participants than among non-Hispanic white participants.

This study used a large, nationally representative, stratified sample, which allows estimation of the prevalence of anemia across all levels of kidney function for the noninstitutionalized civilian US population. The prevalence of anemia was 1.8% at an estimated GFR above 90 mL/min per 1.73 m², compared with 5.2% at an estimated GFR of 30 to 59 mL/min per 1.73 m² and 44.1% at an estimated GFR of 15 to 29 mL/min per 1.73 m². These estimates correspond to approximately 387,400 individuals with an estimated GFR of 30 to 59 mL/min per 1.73 m² (12% of adults with anemia) and approximately 160,000 individuals with an estimated GFR of 15 to 29 mL/min per 1.73 m² (5% of adults with anemia). Adjusted to the age of 60 years, the prevalence of anemia increased from 1% to 9% as the estimated GFR declined from 60 to 30 mL/min per 1.73 m². Below an estimated GFR of 30 mL/min per 1.73 m², precision was limited, but the increase was steep, with an estimated 33% of men and 67% of women having anemia at an estimated GFR of 15 mL/min per 1.73 m². We also found a wide distribution of hemoglobin levels at each level of kidney function. To our knowledge, these are the first data available in the general population that show the association of hemoglobin level with GFR across the entire range of kidney function.

Previous studies have reported a significant correlation between severity of anemia and various measures of kidney function among clinic populations5,12-16 or among individuals in the general population with serum creatinine levels above 2.0 mg/dL.17 Most of these studies12-15 have used hematocrit, rather than hemoglobin level, to define anemia. This study focuses on hemoglobin level because it can be measured directly and is a more precise measure of erythropoiesis than hematocrit, a derived value that can be affected by plasma water.10 A report from the Canadian Multicentre Study in Early Renal Disease found a mean hemoglobin level of 14.3 g/dL among 88 patients referred to a nephrology clinic with a creatinine clearance greater than 50 mL/min, compared with 12.8 g/dL among 226 patients with a creatinine clearance of 25 to 50 mL/min and 11.7 g/dL among 133 patients with a lower creatinine clearance (P<.001). A recent large study16 in the United States reported similar estimates. These results are consistent with the estimates for the general US population in the present study.

Anemia is associated with many negative consequences among patients with kidney dysfunction, including lower exercise tolerance and quality of life, LVH, and congestive heart failure. Among patients starting renal replacement therapy, approximately two thirds have LVH and half have a history of cardiac failure. Among patients starting renal replacement therapy, approximately two thirds have LVH and half have a history of cardiac failure. These data suggest that the harmful effects of anemia are evident before the onset of kidney failure. The results of the present study confirm the presence of anemia among individuals with moderate kidney dysfunction, and provide population-based estimates of the association between kidney function and hemoglobin levels. Using these same data, we estimate that 8.0 million individuals have moderate kidney dysfunction (estimated GFR <60 mL/min per 1.73 m²). The incidence and prevalence of kidney failure continues to grow in the United States. Presumably, the number of individuals in the United States with moderate kidney dysfunction is also increasing. Thus, the potential burden of anemia, and its associated complications in this population, is large and may be increasing.
Anemia among patients with kidney failure or severe kidney dysfunction is treated effectively with recombinant human epoetin alfa. Correction of anemia with epoetin alfa improves exercise capacity and quality of life, and decreases morbidity and hospitalizations among patients undergoing long-term dialysis. Randomized controlled trials suggest that normalization of the hemoglobin level prevents left ventricular dilation in patients with severe kidney dysfunction without symptomatic cardiac disease, but may not be beneficial in patients with symptomatic disease or severe left ventricular dilation. The correction of anemia also prevented progression and reversed LVH in 2 small studies of patients with renal insufficiency, although this has yet to be confirmed in controlled studies.

Although the anemia associated with chronic kidney disease may be modifiable, most patients reaching kidney failure do not have acceptable levels of hemoglobin at the initiation of dialysis. The optimal hemoglobin level is uncertain, but recommendations are 11 to 12 g/dL. Obrador et al found that more than half of the patients starting dialysis in the United States from 1995 to 1997 had a hematocrit of less than 28% and less than a quarter had received epoetin alfa before starting dialysis. This highlights the need for increased detection and appropriate management of anemia among patients being followed up for chronic kidney disease. Timely referral to a nephrologist may be one important factor in the suboptimal treatment of anemia in these patients. Published studies have found consistently higher hemoglobin levels among patients referred to a nephrologist at least 4 months before the initiation of dialysis than among patients referred later.

The prevalence of anemia was much higher in non-Hispanic black men and women than in non-Hispanic white participants. This was true before and after adjustment for the estimated GFR. The high prevalence of anemia among non-Hispanic black participants with a moderately decreased GFR may be important in explaining the higher prevalence of LVH among black persons. The prevalence of sickle cell anemia among black persons cannot explain most of the elevated prevalence of anemia in this group. Mexican American women also had a higher prevalence of anemia than did their non-Hispanic white counterparts. This finding deserves further investigation.

Iron deficiency was a strong predictor of anemia in this study. Many patients with kidney disease and anemia have iron deficiency and benefit from iron supplementation, and most patients receiving epoetin alfa require iron supplementation to achieve adequate hemoglobin levels. The relation between kidney function and hemoglobin level in this study, however, was unchanged in analyses that excluded participants with a low serum ferritin level or a low transferrin saturation.

This study is limited by its cross-sectional design. Prospective data are needed to estimate expected declines in hemoglobin level as kidney disease progresses in an individual. Another limitation of this study is that despite the large size of the NHANES III population, there were relatively few (n=52) participants with an esti-
Table 3. Adjusted Odds Ratios of Anemia by Sex: NHANES III (1988-1994)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated glomerular filtration rate, ml/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 90</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
</tr>
<tr>
<td>60-89</td>
<td>0.8 (0.5-1.3)</td>
<td>0.7 (0.4-1.3)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>30-59</td>
<td>2.5 (1.3-4.5)</td>
<td>2.5 (1.4-4.6)</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td>15-29</td>
<td>38.9 (7.8-173.8)</td>
<td>44.9 (14.1-143.5)</td>
<td>39.2 (16.1-95.6)</td>
</tr>
<tr>
<td>Female sex</td>
<td>...</td>
<td>...</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>20-39</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
</tr>
<tr>
<td></td>
<td>40-59</td>
<td>3.5 (12.10.0)</td>
<td>1.1 (0.7-1.7)</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
<td>3.6 (12.11.0)</td>
<td>0.9 (0.4-2.2)</td>
</tr>
<tr>
<td></td>
<td>≥ 70</td>
<td>18.4 (6.5-51.2)</td>
<td>2.2 (1.1-4.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>5.1 (2.9-8.7)</td>
<td>6.3 (3.8-10.5)</td>
<td>5.9 (4.0-8.8)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>0.9 (0.5-1.9)</td>
<td>2.5 (1.6-4.0)</td>
<td>2.1 (1.5-2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0.6 (0.1-2.9)</td>
<td>2.0 (0.9-4.6)</td>
<td>1.7 (0.8-3.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7 (0.7-4.0)</td>
<td>1.6 (0.9-2.7)</td>
<td>1.6 (1.0-2.7)</td>
</tr>
<tr>
<td>Iron status†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
</tr>
<tr>
<td>Functional deficiency</td>
<td>4.0 (2.5-6.4)</td>
<td>3.5 (2.2-5.8)</td>
<td>4.0 (2.8-5.6)</td>
</tr>
<tr>
<td>Absolute deficiency</td>
<td>150.4 (42.1-538.1)</td>
<td>40.2 (23.0-70.2)</td>
<td>61.2 (35.1-106.6)</td>
</tr>
</tbody>
</table>

*Data are given as adjusted odds ratio (95% confidence interval). This is a multivariate logistic regression model containing all variables in the table. Anemia was defined as a hemoglobin level of less than 12 g/dL for men and less than 11 g/dL for women. NHANES III indicates Third National Health and Nutrition Examination Survey; ellipses, data not applicable.
†Functional iron deficiency was defined as transferrin saturation of less than 15%; and absolute iron deficiency, a serum ferritin level of less than 10 ng/mL.

In summary, this study provides a description of the association between kidney function and hemoglobin level across the entire range of kidney function in the US population. The results demonstrate that participants with an estimated GFR below 60 mL/min per 1.73 m² are much more likely to have anemia, and that the prevalence and severity of anemia increase with declining kidney function. Because the population with moderate kidney dysfunction in the United States is large, the burden of disease associated with anemia in this population may be considerable.

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