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Epidemiology of Anemia Associated with Chronic Renal Insufficiency among Adults in the United States: Results from the Third National Health and Nutrition Examination Survey

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Abstract. Anemia associated with chronic renal insufficiency (CRI) may have substantial clinical and public health importance, but little is known about its epidemiology. This study aims to quantify the relationship between reduced renal function and hemoglobin level, to assess the iron status of subjects with CRI, and to estimate the burden of anemia associated with CRI. The Third National Health and Nutrition Examination Survey (NHANES III) (1988 to 1994) data on 15,971 adults aged >18 yr with measurements of serum creatinine, hemoglobin, and iron profile were analyzed. General linear models were used to determine the relationship between hemoglobin level and Cockcroft-Gault creatinine clearance (CrCl) and to estimate the likelihood of anemia at different levels of renal function in different demographic subgroups. Sample weights were used to produce weighted regression parameters and population estimates. A statistically significant decrease in hemoglobin was apparent among men starting at CrCl ≤70 ml/min and among women starting at CrCl ≤50 ml/min. At any given level of CrCl, men had a larger decrease in hemoglobin than women. For example, compared with subjects with CrCl >80 ml/min, the decrease in hemoglobin for subjects with CrCl 20 to 30 ml/min was 1.0 g/dl in women and 1.4 g/dl in men. A substantial number of subjects with CRI might not have sufficient iron stores to support erythropoiesis as judged by the NKF-K/DOQI transferrin saturation or serum ferritin targets. Among those with CrCl 20 to 30 ml/min, 46% of women and 19% of men had transferrin saturation <20%, and 47% of women and 44% of men had serum ferritin <100 ng/ml. Results estimate that 13.5 million US adults had CrCl ≤50 ml/min. The overall burden of CRI associated anemia, defined as hemoglobin <11 g/dl, was 800,000 adults. The public health burden of anemia associated with CRI may be substantial, given the large number of people with CRI; and that even a modest reduction in renal function is associated with decreased hemoglobin level.

Burgeoning interest exists in understanding and treating anemia among patients with mild to moderate chronic renal insufficiency (CRI). However, there are few studies of the epidemiology of anemia associated with CRI. Patients with renal insufficiency have reduced hemoglobin levels, mostly as a result of decreased kidney production of erythropoietin (1), but the relation between the degree of renal insufficiency and the magnitude of reduction in hemoglobin is not well defined. To our knowledge, only one previous large-scale study has assessed the relationship between renal function and hemoglobin, particularly including categories of mild renal impairment (2). In that study, which was conducted among patients at a single medical center, subjects had measurements of serum creatinine and hemoglobin performed as part of their clinical care, hence raising the possibility of potential bias (2). For example, those thought to be at higher risk for anemia might be more likely to undergo measurement of hemoglobin. In addition, information on iron status was not presented.

The importance of iron status in the pathophysiology and treatment of anemia among patients with end-stage renal disease has been well described (3). However, little is known about the iron status of patients with less severe reductions in renal function. There have also been few studies of whether iron deficiency interacts with renal insufficiency to exacerbate anemia in patients with mild to moderate CRI.

To address these questions, we took advantage of the nationally representative data available in the Third National Health and Nutrition Examination Survey (NHANES III) (1988 to 1994) (4). Because this is a nationally representative sample, we were able to estimate the likelihood of developing anemia at different levels of renal function in various demographic groups and to estimate the burden of anemia across the spectrum of renal insufficiency among US adults.

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Materials and Methods

NHANES III Population

NHANES III was designed to provide national estimates of the health and nutritional status of the civilian noninstitutionalized pop-

ulation of the United States (4). We downloaded NHANES III data from the following Web site: *http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm#Data Files 1a.* In NHANES III, 39,695 people were selected over the course of 6 yr. All NHANES III participants aged >12 yr were eligible for measurement of a complete blood count and a biochemistry profile that included serum creatinine and iron profiles. Examinees reporting hemophilia or recent cancer chemotherapy treatment did not undergo venipuncture. We included in this study only adults aged >18 yr who had measurements of both serum creatinine and hemoglobin.

Assessment of Renal Function

Serum creatinine was measured in NHANES III by the Hitachi 737 automated analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) by using a rate Jaffé reaction. Renal function was assessed as the creatinine clearance (CrCl) estimated from the Cockcroft-Gault equation (5):

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{\text{serum creatinine (mg/dl)} \times 72} \ (\times 0.85 \text{ for women})$$

The Cockcroft-Gault estimated CrCl has been found to correlate well with measured CrCl in a large variety of patient populations, including both adult men and women (correlation coefficients, 0.8 to 0.9) (6). For the small number of subjects without body weight data (0.2% of the sample), we assigned the gender-specific median values.

Data Management and Statistical Analyses

Data management and statistical analysis were conducted by SAS version 8 (SAS, Cary, NC). NHANES III was a complex stratified random sample of the US population. Appropriate sample weights must therefore be used to obtain national estimates from the sampled population. The sample weights also adjust for noncoverage and nonresponse (7,8).

Hemoglobin and Renal Function

Subjects were divided into eight categories of renal function by their Cockcroft-Gault calculated CrCl as before (2): >80 ml/min (reference), >70 to ≤80 ml/min, >60 to ≤70 ml/min, >50 to ≤60 ml/min, >40 to ≤50 ml/min, >30 to ≤40 ml/min, >20 to ≤30 ml/min, and ≤20 ml/min. Hemoglobin was examined as the dependent variable in a general linear model (PROC SURVEYREG) with age, race/ethnicity, and categories of CrCl as independent variables.

The value for age was that at the time of the screening interview. Race/ethnicity was defined as non-Hispanic white (reference group), non-Hispanic black, Mexican American, or other. These categories were predefined in NHANES III. The other category included all Hispanics who were not Mexican American and all non-Hispanics from racial groups other than white or black. Gender-specific analyses were performed.

Iron Status among Subjects with CRI

Measures of transferrin saturation and ferritin were available in 15,837 (99%) of 15,971 of the subjects. By use of PROC SURVEYMEANS, we determined the percentage of men and women in the United States in the different categories of CrCl who had transferrin saturation <20% and serum ferritin level <100 ng/ml. These cutoffs were chosen because the National Kidney Foundation (NKF-K/DOQI) Clinical Practice Guidelines recommend maintenance of target transferrin saturation ≥20% and target serum ferritin level ≥100 ng/ml to ensure sufficient iron stores to support erythropoiesis among patients with reduced renal function (3).

Interaction between Renal Insufficiency and Iron Deficiency

In addition to transferrin saturation and serum ferritin, erythrocyte protoporphyrin was also available in NHANES III to assess iron status. Iron deficiency is correlated with lower transferrin saturation and serum ferritin but higher erythrocyte protoporphyrin. To ensure that there would be a sufficient number of subjects in each category, we compared subjects in the lowest two gender-specific quartiles of transferrin saturation and serum ferritin with those above the median and those in the top two gender-specific quartiles of erythrocyte protoporphyrin with those below the median (quartile cutoffs given in Table 1). Whether iron deficiency was an effect modifier of the relation between renal insufficiency and hemoglobin was then tested for by entering interaction terms into the linear models.

Likelihood of Anemia at Different Levels of Renal Function

Three different cutoff points for the definition of anemia were used: hemoglobin levels <10, <11, and <12 g/dl. We used linear modeling to estimate the likelihood of anemia at different levels of renal function. To ensure that our linear model was valid, transformation of the outcome variable (hemoglobin) was undertaken. The distribution of the error term and the estimated parameters from gender-stratified models were then used under this normality assumption to predict the likelihood of having a hemoglobin level <10, <11, or <12 g/dl at different levels of renal function in different demographic groups.

Burden of Anemia Associated with CRI

To determine the burden of anemia associated with renal insufficiency, we estimated the number of adults in the United States that fell into different demographic and renal function categories by inflating with appropriate weights. The total number of adults with anemia was then calculated by multiplying the corresponding model derived likelihood of having a hemoglobin level <10, <11, or <12 g/dl. The burden of anemia associated with CRI in the United States was defined as the difference between this number and the predicted number of people with anemia if all had CrCl >80 ml/min.

Results

NHANES III Population

A total of 19,215 NHANES III subjects >18 yr were examined. Older people, Mexican Americans, and African Americans were oversampled in NHANES III. Among the participants, 15,971 (83%) had measurements of both serum creatinine and hemoglobin. Those excluded were on average older (age, mean ± SD, 53 ± 22 yr). The characteristics of the 8506 women and 7465 men studied are shown in Table 1. The mean Cockcroft-Gault estimated CrCl ± SD was 83 ± 33 ml/min for women and 88 ± 32 ml/min for men. The mean hemoglobin level was 13.1 ± 1.2 g/dl for women and 14.9 ± 1.3 g/dl for men.

Hemoglobin and Renal Function

Compared with men with CrCl > 80 ml/min, the hemoglobin in men was significantly lower starting at a CrCl ≤70 ml/min (Table 2). However, a significant decrease in hemoglobin in women was seen only starting at a CrCl ≤50 ml/min (Table 2). At every level of CrCl, men had a greater absolute decrease in hemoglobin than women ($P < 0.0001$). As an example, compared with subjects with a CrCl >80 ml/min, the

Table 1. Characteristics of the Third National Health and Nutrition Examination Survey population[a]

Characteristic	Women (n = 8506)	Men (n = 7465)
Age (yr)	48 ± 20	48 ± 20
Weight (kg)	70 ± 18	80 ± 17
Race/ethnicity (non-Hispanic white/non-Hispanic black/Mexican American/other) (%)	42/28/26/4	41/26/29/4
Hemoglobin (g/dl)	13.1 ± 1.2	14.9 ± 1.3
Hematocrit (%)	39 ± 3	44 ± 4
Serum creatinine (μmol/L) (mg/dl)	88 ± 26 (1.0 ± 0.3)	106 ± 35 (1.2 ± 0.4)
CrCl (ml/min)	83 ± 33	88 ± 32
number (%) of subjects with:		
CrCl > 80 ml/min	4206 (49%)	4530 (61%)
80 ≥ CrCl > 70 ml/min	1206 (14%)	878 (12%)
70 ≥ CrCl > 60 ml/min	961 (11%)	670 (9%)
60 ≥ CrCl > 50 ml/min	786 (9%)	532 (7%)
50 ≥ CrCl > 40 ml/min	621 (7%)	437 (6%)
40 ≥ CrCl > 30 ml/min	462 (5%)	298 (4%)
30 ≥ CrCl > 20 ml/min	225 (3%)	92 (1%)
CrCl ≤ 20 ml/min	39 (0.5%)	28 (0.4%)
Transferrin saturation (%)[b] (median, interquartile range)	23 ± 11 (21, 15–28)	28 ± 12 (27, 20–34)
Serum ferritin (ng/ml)[b] (median, interquartile range)	90 ± 122 (54, 26–110)	184 ± 166 (141, 83–232)
Erythrocyte protoporphyrin (μg/dl)[b] (median, interquartile range)	59 ± 41 (51, 42–63)	47 ± 25 (42, 35–51)

[a] All values are unweighted mean ± SD unless otherwise stated. CrCl, creatinine clearance.
[b] In 8434 women and 7403 men.

decrease in hemoglobin for subjects with a CrCl of 20 to 30 ml/min was 1.0 g/dl in women and 1.4 g/dl in men.

Iron Status among Subjects with CRI

A substantial number of US subjects with CRI do not have sufficient iron stores to support erythropoiesis as judged by the NKF-K/DOQI transferrin saturation or serum ferritin targets (Table 3). For example, among those with CrCl 20 to 30 ml/min, 46% of women and 19% of men had transferrin saturation <20%; 47% of women and 44% of men had serum ferritin <100 ng/ml. However, it should be noted that subjects with higher CrCl also had similar iron indexes.

Interaction between Renal Insufficiency and Iron Deficiency

Iron deficiency, reflected by low transferrin saturation or serum ferritin or by high erythrocyte protoporphyrin, was independently associated with lower hemoglobin level (data

Table 2. Predicted change in mean hemoglobin level by renal function[a]

CrCl	Women		Men	
	Change in Hemoglobin (g/dl)	P Value	Change in Hemoglobin (g/dl)	P Value
CrCl > 80 ml/min	Reference		Reference	
80 ≥ CrCl > 70 ml/min	−0.0 (−0.1, 0.1)	0.68	−0.1 (−0.2, 0.0)	0.16
70 ≥ CrCl > 60 ml/min	−0.1 (−0.2, 0.0)	0.08	−0.2 (−0.3, −0.0)	0.02
60 ≥ CrCl > 50 ml/min	−0.1 (−0.2, 0.1)	0.36	−0.3 (−0.5, −0.1)	0.007
50 ≥ CrCl > 40 ml/min	−0.2 (−0.3, −0.0)	0.01	−0.4 (−0.6, −0.2)	0.0005
40 ≥ CrCl > 30 ml/min	−0.4 (−0.6, −0.2)	<0.0001	−0.8 (−1.1, −0.6)	<0.0001
30 ≥ CrCl > 20 ml/min	−1.0 (−1.2, −0.7)	<0.0001	−1.4 (−2.1, −0.6)	0.0005
CrCl ≤ 20 ml/min	−2.3 (−2.8, −1.9)	<0.0001	−2.7 (−3.8, −1.6)	<0.0001

[a] Adjusted for age and race/ethnicity; values in parentheses are 95% confidence intervals for parameter estimates. CrCl, creatinine clearance.

Table 3. Observed frequency (%) of US population with low iron indexes by renal function[a]

CrCl	Women		Men	
	Transferrin Saturation < 20%, % (95% CI)	Serum Ferritin < 100 ng/ml, % (95% CI)	Transferrin Saturation < 20%, % (95% CI)	Serum Ferritin < 100 ng/ml, % (95% CI)
Overall	40 (38–43)	76 (74–78)	21 (19–23)	32 (30–34)
CrCl > 80 ml/min	43 (40–46)	81 (79–84)	20 (18–22)	31 (29–33)
80 ≥ CrCl > 70 ml/min	38 (34–42)	81 (77–85)	21 (16–25)	28 (23–34)
70 ≥ CrCl > 60 ml/min	37 (32–42)	78 (74–81)	22 (17–27)	36 (29–43)
60 ≥ CrCl > 50 ml/min	36 (31–41)	62 (58–67)	21 (15–27)	34 (27–41)
50 ≥ CrCl > 40 ml/min	39 (35–44)	55 (51–59)	30 (23–36)	41 (33–50)
40 ≥ CrCl > 30 ml/min	40 (34–46)	59 (53–65)	35 (27–43)	37 (30–44)
30 ≥ CrCl > 20 ml/min	46 (38–53)	47 (41–54)	19 (11–26)	44 (33–55)
CrCl ≤ 20 ml/min	59 (43–76)	47 (28–67)	69 (59–80)	44 (28–59)

[a] CrCl, creatinine clearance; 95% CI, 95% confidence interval.

not shown). Including iron measures in the models did not materially alter the relation between renal insufficiency and hemoglobin (data not shown).

In men, there was a suggestion that the effects of iron deficiency and renal insufficiency were more than strictly additive. In a model with categories of renal function and erythrocyte protoporphyrin entered as main terms and their products as interaction terms, we found that men with either CrCl 20 to 30 ml/min or ≤20 ml/min and also in the highest quartile of erythrocyte protoporphyrin had an additional decrease in hemoglobin of 1.8 g/dl ($P = 0.008$ and 0.03, respectively). However, this interaction was not observed when transferrin saturation or serum ferritin were used to assess iron status, and it was not observed among women.

Likelihood of Anemia at Different Levels of Renal Function

The likelihood of anemia varied with demographic variables as well as with renal function (Table 4). In multivariate analysis, we noted that a higher likelihood of anemia was found among blacks (*versus* whites), older (*versus* younger) men and younger (*versus* older) women. For example, among non-Hispanic black women aged 61 to 70 yr, the model predicted likelihood of having a hemoglobin <11 g/dl increased from 10% among those with CrCl >80 ml/min to 14% among those with CrCl 40 to 50 ml/min to 32% among those with CrCl 20 to 30 ml/min. The corresponding figures among non-Hispanic white men aged 31 to 40 yr were <1, 1, and 3% (Table 4).

Burden of Anemia Associated with CRI

We estimated from NHANES III data that 9.7 million adult women and 3.8 adult million men in the United States have CrCl ≤50 ml/min.

When anemia was defined as hemoglobin <10 g/dl, we estimated that there were 330,000 adult women and 150,000 adult men with anemia associated with CRI. When the cutoff point was raised to hemoglobin <11 g/dl, the estimates were 610,000 women and 230,000 men. When anemia was defined as hemoglobin <12 g/dl, the estimated burden of anemia associated with CRI in the United States among adults was 1,200,000 women and 390,000 men.

Discussion

Increasing attention is being paid to understanding and treating anemia among patients with CRI not yet requiring dialysis. In this population, anemia contributes to adverse health effects such as left ventricular hypertrophy (9–11). Anemia treatment with epoetin might ameliorate ventricular hypertrophy and improve quality of life and other measures of health (12–16). The National Kidney Foundation (NKF-K/DOQI) Clinical Practice Guidelines recommend an evaluation of anemia among patients with renal insufficiency when the hemoglobin is <11 g/dl among premenopausal women and <12 g/dl among adult men and postmenopausal women (3). Epoetin treatment is recommended for patients with CRI, whether dialysis dependent or not, to achieve a target hemoglobin of 11 to 12 g/dl (3). Similar guidelines have been put forth by the European Renal Association/European Dialysis and Transplantation Association (17).

Much remains unknown about anemia in patients with mild to moderate CRI. We have shown from a study at a single institution that a decrease in hemoglobin could be detected at more modest degrees of renal insufficiency than previously realized (2). In addition, at any given level of CrCl, men had a larger decrease in hemoglobin than women (2). We now confirm and extend these findings in a nationally representative sample. Unlike in our previous study of ambulatory patients in whom the indications for measuring serum creatinine and hemoglobin were unknown, the analysis presented here is based on measurements routinely performed as part of NHANES III. The similar quantitative relations between hemoglobin and CrCl observed in two independent cohorts provide strong evidence that these are unbiased findings. The

Table 4. Predicted likelihood (%) of anemia by renal function in select demographic subgroups (multivariate analysis)[a]

Demographic Subgroup		Women			Men		
		Likelihood (%) of Hemoglobin Level:			Likelihood (%) of Hemoglobin Level:		
		<10 g/dl	<11 g/dl	<12 g/dl	<10 g/dl	<11 g/dl	<12 g/dl
Non-Hispanic white							
age 31–40	CrCl > 80 ml/min	2	4	11	<1	<1	1
	50 ≥ CrCl > 40 ml/min	3	6	15	<1	1	2
	30 ≥ CrCl > 20 ml/min	10	18	34	2	3	6
age 61–70	CrCl > 80 ml/min	1	2	7	1	1	3
	50 ≥ CrCl > 40 ml/min	1	3	10	1	2	4
	30 ≥ CrCl > 20 ml/min	6	12	25	4	7	12
Non-Hispanic black							
age 31–40	CrCl > 80 ml/min	8	15	30	1	2	5
	50 ≥ CrCl > 40 ml/min	12	21	38	2	4	7
	30 ≥ CrCl > 20 ml/min	29	42	63	7	10	17
age 61–70	CrCl > 80 ml/min	5	10	22	3	5	9
	50 ≥ CrCl > 40 ml/min	7	14	28	5	8	13
	30 ≥ CrCl > 20 ml/min	20	32	52	13	18	28
Mexican-American							
age 31–40	CrCl > 80 ml/min	3	6	16	<1	<1	1
	50 ≥ CrCl > 40 ml/min	5	10	21	<1	1	2
	30 ≥ CrCl > 20 ml/min	15	24	43	2	3	5
age 61–70	CrCl > 80 ml/min	2	4	10	1	1	2
	50 ≥ CrCl > 40 ml/min	3	6	14	1	2	4
	30 ≥ CrCl > 20 ml/min	9	17	32	4	6	10

[a] CrCl, creatinine clearance.

magnitude of the decrease in hemoglobin observed among those with mild to moderate CRI is important because prospective studies have shown that in this range of hemoglobin, each 0.5 g/dl decrease is associated with an odds ratio for increase in left ventricular mass of 1.3 (11).

Although extensive literature exists on the importance of iron status in determining response to administered epoetin among patients with end-stage renal disease, few studies have examined iron status or the relationship between iron status and hemoglobin among patients with reduced endogenous erythropoietin production. The observation that patients with end-stage renal disease appear to have a "functional iron deficiency" (3) led us to hypothesize that not only were iron deficiency and renal insufficiency both independent risk factors for anemia, but there might be an interaction. The same degree of iron deficiency might be associated with a greater drop in hemoglobin in patients with reduced renal function than in patients with preserved renal function.

Because no single biochemical indicator is consistently diagnostic of iron deficiency (18,19), we studied serum ferritin, a measure of storage iron (20); transferrin saturation, a measure of current iron supply to tissues (20); and erythrocyte protoporphyrin, an indicator of iron supply to erythroid precursors over a longer term (20). We found that a large fraction of US patients with CRI not yet requiring dialysis had iron stores below the NKF-K/DOQI targets (although there was no consistent relationship between measures of iron status and CrCl).

The effects of iron deficiency and renal insufficiency appeared more than strictly additive among men only when erythrocyte protoporphyrin was used as a measure of iron status. Further studies are therefore needed to clarify whether there is indeed an interaction between iron deficiency and renal insufficiency and whether this differs by gender.

Our estimate of the prevalence of renal insufficiency in the United States is similar to that of other investigators. Both also using NHANES III data, Jones *et al.* (21) estimated that 6.2 million Americans aged ≥12 yr had serum creatinine ≥1.5 mg/dl, and Wei *et al.* (22) estimated that 12.5 million aged ≥17 yr had CrCl <50 ml/min per 1.73 m^2. In agreement with previous research, we observed that blacks, older men, and younger women have, on average, lower hemoglobin levels (23,24). Given the large number of subjects with reduced renal function, and given the fact that increased risk of anemia is seen even among patients with only modest reductions in CrCl, the burden of anemia associated with CRI is substantial.

Our estimate of the number of people in the United States with anemia associated with CRI is higher than that found by Strauss *et al.* (25), who concluded that between 68,000 and 75,000 people had "predialysis" renal insufficiency and anemia (defined as hematocrit <30%). Possible reasons for the differ-

ence in prevalence estimates include the fact that Strauss *et al.* (25) used data from NHANES II, which was conducted from 1976 to 1980; their population estimate was based on only 44 sampled people with serum creatinine between 2.0 and 8.0 mg/dl, and the estimate of proportion of patients with hematocrit <30% was based on pooling 182 patients from three different studies.

The advantages of our modeling approach over direct assessment of the percentage of people falling below hemoglobin cutoffs include full use of the information available in the continuously distributed outcome (hemoglobin) and smoothing out of sample variation that was evident because of the small sample sizes for some of the demographic and renal function categories. For example, there might not be a 61 to 70 yr-old non-Hispanic white woman with CrCl 20 to 30 ml/min sampled in NHANES III (and therefore no directly observed hemoglobin level), although such people exist in the United States.

The findings from the report presented here should be interpreted in the context of the study design. Only calculated CrCl were used; actual measurements of CrCl or GFR were not done. As this was a cross-sectional study, we did not have information on how hemoglobin changes over time in people with progressive renal insufficiency. Although NHANES III oversampled some subjects at higher risk for renal insufficiency (*e.g.*, elderly subjects and minorities), sampling gaps remained in some demographic and renal function subgroups. For example, the number of NHANES III subjects with CrCl ≤30 ml/min was relatively small, and this decreased our modeling precision. We probably underestimated the number of subjects with anemia associated with CRI because we excluded people in NHANES III who were examined but who did not have measures of creatinine or hemoglobin, and these examinees on average were older.

In conclusion, by using the nationally representative NHANES III data, we found that a decrease in the hemoglobin level was apparent even among adults with only modest decrements in renal function. The magnitude of the decrease in hemoglobin was greater for men than for women at any level of CrCl. Clearly, the overall burden of anemia associated with CRI in the United States is substantial. Future studies should examine the benefits and cost-effectiveness of treating anemia in subjects with mild to moderate CRI.

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