Renal Function, Erythropoietin, and Anemia of Older Persons

The InCHIANTI Study

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Background: In the older population, anemia has been associated with poor outcomes including disability and mortality. Understanding the mechanisms leading to anemia is essential to plan better treatment and prevention strategies. We tested the hypothesis that the age-related decline in kidney function is associated with an increased prevalence of anemia and that such an increase is accompanied by a concomitant decrement in erythropoietin levels.

Methods: Data were from the InCHIANTI study, a population-based study performed in a sample of community-dwelling older (≥65 years) persons living in Italy. This analysis included 1005 participants with complete data on hemoglobin and erythropoietin levels and markers of renal function.

Results: The prevalence of anemia according to the World Health Organization criteria (hemoglobin level ≤12 g/dL for women and ≤13 g/dL for men) was 12.0% and increased with age in both sexes. After adjusting for age, diseases, and other confounders, only participants with a creatinine clearance (CrCl) of 30 mL/min or lower (≤0.50 mL/s) had a higher prevalence of anemia compared with those with a CrCl higher than 90 mL/min (>1.50 mL/s) (P < .01). Consistently, participants with a CrCl of 30 mL/min or lower (≤0.50 mL/s) had significantly lower age- and hemoglobin-adjusted erythropoietin endogenous levels. After excluding men and women with CrCl of 30 mL/min or lower (≤0.50 mL/s) and adjusting for confounders, we found a trend toward an increase in prevalence of anemia with decreasing renal function; however, it was not statistically significant.

Conclusions: Severe age-related decline in renal function is associated with a reduced erythropoietin secretion and anemia. Whether moderate kidney impairment in older persons is associated with a progressively increasing risk of anemia remains to be determined.

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A nemia is an extremely prevalent condition in older age.1 3 recent re- view of epidemiological studies described preva- lence rates dispersed over a wide range, from 3% to 61% among elderly men and from 3% to 41% among elderly women.1 The variability of rates is likely related to differences in patient populations, crite- ria used to define anemia, and study set- tings; nevertheless, there is a clear trend for increased prevalence of anemia with age. It has been estimated that individu- als older than 85 years have a 2-fold to 3-fold greater prevalence of anemia compared with individuals aged 65 to 69 years.1 Overall, data from a large survey, the third Na- tional Health and Nutrition Examina- tion Survey (NHANES III), show that approxi- mately 3 million US older inhab- itants are affected by this condition.3

In older persons, anemia has im- portant clinical consequences. Recent studies have demonstrated an inverse cor- relation between hemoglobin (Hb) concentra- tion and muscle strength, physical performance, disability, and mortality.4 5 Notably, decreased physical performance is evident among individuals even with borderline anemia (ie, those with Hb level just above the World Health Orga- nization [WHO] criteria for anemia, which is Hb <12 g/dL for women and <13 g/dL for men).4

See also pages 2187, 2214, 2229, and 2237

The most common causes of anemia in the elderly are chronic disease (up to 35% of patients) and iron deficiency (up to 15% of patients); however, even after a careful- assessment, the underlying mecha-
nism leading to anemia remains unexplained in a large amount of cases (approximately one third).2,3,10

It has been suggested that the ability of the kidney to secrete erythropoietin (EPO) in response to tissue hypoxia declines with aging11 in parallel with the decline of renal function. At present, controversial data are available on the EPO response to anemia in the older population compared with the younger population,12,13 and scant data are available on the relationship between renal function and risk of anemia in samples of community-dwelling older persons representative of the general population. The objective of this study was to determine whether the age-associated progressive reduction in renal function is also accompanied by an increased risk of anemia and whether an identifiable threshold of renal function exists below which the risk of anemia markedly increases. Our study may contribute to the understanding of whether the high prevalence of anemia in the older population is due to an age-related reduction of renal function and EPO secretion.

### Methods

The InCHIANTI study (aging in the Chianti area) is a prospective, population-based study of randomly selected older people living in 2 cities in the Chianti area, Tuscany, Italy. The study was designed to identify risk factors for late-life disability. Participants were selected from the city registries of Greve in Chianti and Bagno a Ripoli using a multistage sampling method.14 In 1998, 1270 persons 65 years or older were randomly selected from the population, and 1154 participants agreed to participate in the project. Of these, 1005 participants with complete data for the analysis presented herein were considered. The Istituto Nazionale Riposo e Cura Anziani (INRCA) institutional review board ratified the study protocol. Participants consented to participate and agreed to have their blood samples analyzed for scientific purposes. For those unable to fully consent, surrogate consents were obtained from close relatives.

Blood samples were obtained from participants after a 12-hour fasting and after the participants had been resting for at least 15 minutes. At the time of the home interview, participants were provided a plastic container and received detailed instructions for 24-hour urine collection. Aliquots of serum and 24-hour urine samples were stored at −80°C and were not thawed until analyzed.

Hemoglobin levels were analyzed within 6 hours using the hematology autoanalyzer DASIT SE 9000 (Sysmex Corporation, Kobe, Japan). For the present study, anemia was defined according to the WHO criteria15 as Hb levels lower than 12 g/dL and 11 g/dL for men and women, respectively. Erythropoietin serum levels were measured in duplicate using the Advantage EPO chemiluminescence immunoassay (Nichols Institute Diagnostic, San Clemente, Calif), which has a sensitivity of 1.2 mU/mL, and a coefficient of variation less than 6%. The assay is referenced to the WHO Recombinant DNA-Derived Human Erythropoietin First International Standard.16 Serum creatinine and urinary creatinine from the 24-hour urine collection were measured using a modified Jaffé method and used to calculate creatinine clearance (CrCl) as a measure of glomerular filtration rate (GFR). High sensitivity C-reactive protein was measured in duplicate using the BNII nephelometer (N High Sensitivity C-reactive protein; Dade Behring Inc, Deerfield, Ill). Commercial enzymatic tests were used for determining iron concentrations (Roche Diagnostics, Mannheim, Germany).

The presence of specific medical conditions was established using standardized criteria that combined information from self-reported history, medical records, and a clinical medical examination. The following diseases were assessed: coronary artery disease (angina and acute myocardial infarction), peripheral arterial disease, stroke (and/or transient ischemic attack), hypertension, diabetes, chronic obstructive pulmonary disease, congestive heart failure, and cancer.

Variables are generally reported as mean±SD values and percentages. Because the distribution of EPO levels was highly skewed, log-transformed EPO values were used in the analysis and subsequently back-transformed and reported as geometric means and interquartile ranges. The χ² test was used to compare prevalence of anemia according to age, sex, and CrCl. The relationship between Hb and CrCl according to age in both sexes was explored using scatterplots and summarized by linear regression models. Age-adjusted prevalence of anemia according to CrCl was calculated and compared between sexes using a generalized linear model. A test for trend was used to compare the unadjusted and age- and sex-adjusted prevalence of anemia among the participants with CrCl higher than 30 mL/min (>0.50 mL/s) (after excluding the ≤30 mL/min [≤0.50 mL/s] group). All analyses were performed using the SAS statistical package, version 8.2 (SAS Institute Inc, Cary, NC).

This analysis included 436 men and 569 women 65 years or older. The major characteristics of InCHIANTI participants included in the study population are reported in the Table. The mean±SD ages of men and women were 74.5±7.6 years (range, 65-102 years) and 76.0±6.8 years (range, 65-95 years), respectively.

The overall prevalence of anemia was 12.0% (11.5% in men and 12.5% in women). There was a progressive and statistically significant increase in the prevalence of anemia with increasing age in both men and women. Median levels of endogenous EPO were similar in men and women. Renal function, as measured by serum creatinine and CrCl, tended to be lower in women than in men. The prevalence of persons with CrCl of 60 mL/min or lower (≤1.00 mL/s) and higher than 30 mL/min (≥0.50 mL/s) was 20% and 37.8%, respectively, for men and women, while the prevalence of participants with a CrCl of 30 mL/min or lower (≤0.50 mL/s) was 1.6% for men and 3.3% for women.

Figure 1 illustrates the prevalence of anemia according to age and sex. Both Hb and kidney function progressively declined with increasing age in both men and women (Figure 2 and Figure 3). At age 65 years, the estimated mean Hb level was 15.1 g/dL for men and 13.7 g/dL for women. The average decline in Hb per decade was 0.75 g/dL for men and 0.50 g/dL for women. Similarly, the estimated mean CrCl was 100.0 mL/min (1.67 mL/s) for men aged 65 years, declining 19.4 mL/min (0.32 mL/s) per decade. For women, the estimated CrCl was 81.4 mL/min (1.35 mL/s) at age 65 years, declining 15.2 mL/min (0.25 mL/s) per decade.

In the unadjusted analysis, there was a clear linear relationship between prevalence of anemia and kidney function, with lower CrCl values associated with a higher preva-
ence of anemia (Figure 4A). In particular, both men and women with CrCl of 60 mL/min or lower (≤1.00 mL/s) were significantly (P < .01) more likely to have anemia compared with individuals with CrCl higher than 90 mL/min (>1.50 mL/s). However, when the confounding effect of age on the relationship between kidney function and anemia was removed from the analysis, only participants with CrCl of 30 mL/min or lower (≤0.50 mL/s) had higher prevalence of anemia compared with persons with CrCl higher than 90 mL/min (>1.50 mL/s) (Figure 4B).

Interestingly, the results remained virtually unchanged after further adjustment for diseases (coronary artery disease, peripheral arterial disease, stroke [and/or transient ischemic attack], hypertension, diabetes, chronic obstructive pulmonary disease, congestive heart failure, and cancer), C-reactive protein, and iron.

When the presence of a trend toward an increase in the prevalence of anemia with reduction of renal function among subjects with CrCl higher than 30 mL/min (>0.5 mL/s) was tested (Figure 4), we found a significant trend only in the unadjusted (P < .01), but not in the age- and sex-adjusted, analysis (P = .17).

To further assess the effect of declining kidney function on anemia, sex-specific linear models were fitted predicting the log EPO level according to CrCl, after adjusting for age and Hb level, in the 131 participants (52 men and 79 women) with anemia (Figure 5). Participants with CrCl of 30 mL/min or lower (≤0.5 mL/s) had significantly lower age- and Hb-adjusted EPO levels compared with the group with CrCl higher than 90 mL/min (>1.5 mL/s). Participants with less severe kidney disease (CrCl, 31-90 mL/min [0.52-1.50 mL/s]) exhibited a slight trend toward lower age- and Hb-adjusted EPO levels with decreasing CrCl values; however, differences were not statistically significant.

Table. Characteristics of Men and Women Included in the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 436)</th>
<th>Women (n = 569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.5 ± 6.8</td>
<td>76.0 ± 7.6</td>
</tr>
<tr>
<td>Education, y</td>
<td>6.3 ± 5.8</td>
<td>4.8 ± 2.8</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.4 ± 1.4</td>
<td>13.1 ± 1.2</td>
</tr>
<tr>
<td>&lt;12 g</td>
<td>4.8</td>
<td>12.5</td>
</tr>
<tr>
<td>&lt;13 g</td>
<td>11.5</td>
<td>41.5</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.02 ± 0.22</td>
<td>0.86 ± 0.24</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>82 ± 27</td>
<td>67 ± 24</td>
</tr>
<tr>
<td>&gt;90</td>
<td>35.6</td>
<td>18.3</td>
</tr>
<tr>
<td>61-90</td>
<td>42.9</td>
<td>40.6</td>
</tr>
<tr>
<td>31-60</td>
<td>20</td>
<td>37.8</td>
</tr>
<tr>
<td>&lt;30</td>
<td>1.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Erythropoietin, median (interquartile range), mU/mL</td>
<td>10.0 (5.7)</td>
<td>10.2 (8.6)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>11.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>20.4</td>
<td>19.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>13.5</td>
<td>9.3</td>
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<tr>
<td>Diabetes</td>
<td>11.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.8</td>
<td>60.4</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>16.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.5</td>
<td>5.6</td>
</tr>
<tr>
<td>C-reactive protein, median (interquartile range), µg/mL</td>
<td>2.5 (4.5)</td>
<td>2.3 (3.9)</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert creatinine clearance to milliliters per second, multiply by 0.0167.

* Data are given as mean ± SD or percentage of subjects unless otherwise specified.

Figure 1. Prevalence of anemia according to age and sex. Proportion of anemic participants in each group is reported within the bars.

Figure 2. Hemoglobin (A) and creatinine clearance (B) according to age in male participants. To convert creatinine clearance to milliliters per second, multiply by 0.0167.
In a large and representative sample of community-dwelling older persons, we found a gradual increase in the prevalence of anemia across progressively more severe stages of reduced kidney function. However, after controlling for age, diseases, and other important confounders, and compared with participants with CrCl higher than 90 mL/min (>1.50 mL/s), only participants with CrCl of 30 mL/min or lower (≤0.50 mL/s) had a significantly higher prevalence of anemia. Moreover, in the adjusted analysis, no significant trend toward an increase in the prevalence of anemia with reduction of renal function among subjects with mild to moderate CrCl was found. Accordingly, only the group of persons with CrCl of 30 mL/min or lower (≤0.50 mL/s) had significantly lower age- and Hb-adjusted EPO plasma levels compared with normal participants. Our findings suggest that in older persons the age-related reduction in the ability of the kidney to secrete EPO is an important risk factor for anemia only when the GFR is severely reduced.

Consistent with our findings, most of the past literature suggested that the highest level of CrCl associated with a discernible decrease in Hb was around 40 mL/min (0.67 mL/s). However, recent data from NHANES III showed a significant decrease in Hb level even among men with CrCl of 70 mL/min or lower (≤1.17 mL/s) and among women with CrCl of 50 mL/min or lower (≤0.84 mL/s) compared with participants with CrCl higher than 80 mL/min (≥1.34 mL/s). In the same study, the prevalence and the severity of anemia were associated with reduced kidney function below, but not above, an esti-
mated GFR of 60 mL/min. Our study confirms the notion of a nonlinear relationship between renal function and anemia, but the threshold below which the risk of anemia dramatically increases is somewhat lower than that reported in the NHANES III study. Owing to the smaller sample size and the low prevalence of anemia in the InCHIANTI population with moderate to severe renal impairment, our ability to detect a relationship between GFR and anemia across narrower GFR intervals might be limited. Therefore our findings should be interpreted with caution because we cannot exclude that the true threshold of GFR for increased risk of anemia is slightly higher than 30 mL/min. In addition, the 24-hour urine collection is a physically and cognitively demanding task. Therefore, by using CrCl, calculated from 24-hour urine collections, as a measure of GFR, we might have excluded from our analysis the more debilitated and frail participants for whom milder stages of renal failure might induce the onset of anemia. In making these comparisons between our study and the NHANES III study, it is important to remember that NHANES III included persons with a mean age of 48 years, which is substantially younger than that of our study population. More importantly, the authors used a different definition of anemia and estimated GFR indirectly. Data on the relationship between kidney function and anemia are very limited in the older population. To the best of our knowledge, only one population-based study addressed the relationship between renal function and anemia in this expanding section of the population. In a large cross-sectional study conducted on community-dwelling participants 49 years or older, Cumming and coworkers showed that the age-adjusted relative risk for anemia was approximately 5-fold higher in men and 3-fold higher in women with a CrCl lower than 50 mL/min (<0.84 mL/s), using the Cockroft-Gault Formula, compared with those with CrCl of 50 mL/min or higher (≥0.84 mL/s). This study suggests that the threshold of renal function impairment leading to the development of anemia may lie in between our estimate and that of the NHANES III study. Once more the different design of the study conducted by Cumming and colleagues, which enrolled participants on average 10 years younger than those in the InCHIANTI study and estimated the GFR using a serum creatinine–derived formula, does not allow a direct comparison with our data.

Because of the reduced muscle mass, which is typical in older adults, GFR estimates based on serum creatinine level have been questioned. In fact, muscle wasting is one clinical indication for using timed urine collection over prediction equations to estimate the GFR. An important strength of our study is the availability of a direct measure of CrCl as well as the assessment of the endogenous EPO in a large population-based sample of older people.

Taken together, the 3 available population-based studies cover a wide portion of the aging spectrum, ranging from 18 to 102 years, and support the intriguing hypothesis of an age-dependent relationship between renal function and anemia, with a progressively lower critical threshold of appearance of anemia with advancing age. The reason for this trend is not straightforward and is probably due to the complex interplay between diseases, aging, and the selection process. The threshold where the risk of anemia increases considerably is probably in the range of a GFR between 60 and 30 mL/min in both nonelderly adults and older persons. However, our findings suggest that, excluding the effect of diseases and other confounders, the aging process per se brings about anemia at a lower threshold (GFR, approximately 30 mL/min) than diseases (the primary cause of renal impairment in younger persons) do at younger ages. Other studies aimed to verify this speculation should be performed.

Our study has important limitations. First, owing to the cross-sectional design, we are unable to assess the effects of progressive kidney disease on anemia and EPO secretion over time; moreover, for the same reason, we cannot infer any causal relationship between renal insufficiency and anemia. Second, because we lack data on the cause of anemia in our study, we could not speculate on anemia of renal impairment as a cause of unexplained anemia in the elderly, and we could not account for the other causes of anemia in our analysis.

In conclusion, we found no linear increase in the prevalence of anemia with decreasing renal function, and a marked increment of risk of anemia in older participants with severe renal impairment. According to our results, in older outpatients with mild to moderate renal insufficiency, the occurrence of anemia is not likely to be caused by an aging-related reduced EPO response to low Hb levels (blunted response), and other causes of anemia should be investigated. Consistent with this, all age-related chronic conditions affecting the kidney function, including diabetes and hypertension, should be carefully treated because they probably represent the most important causes of anemia from EPO reduced secretion in older persons with mild to moderate renal impairment.

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Financial Disclosure: Drs Woodman and Klausner are employees of Ortho Biotech Clinical Affairs, LLC; Drs Ferrucci and Guralnik are former consultants for Ortho Biotech Clinical Affairs, LLC; and Dr Fink is on the advisory board and speakers bureau for Ortho Biotech Clinical Affairs, LLC.

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REFERENCES


**Correction**

Errors in Figure and Text. In the Original Investigation by Roos et al titled “The Starting Dose of Levothyroxine in Primary Hypothyroidism Treatment,” published in the August 8/22 issue of the ARCHIVES (2005;165:1714-1720), there were errors in Figure 1 and in the text. In Figure 1, the lower row on the bottom should have read “Low Dose” instead of “Full Dose.” In the second paragraph of the “Safety” subsection, the first sentence should have read “At baseline, sinus bradycardia was observed in 40% of patients in the full-dose group and 28% in the low-dose group.”