The roles of inflammation and iron deficiency as causes of anemia

Ray Yip, MD, MPH, and Peter R Dallman, MD

ABSTRACT  Inflammatory disease as well as iron deficiency may play an important role in the cause of anemia in the United States. We evaluated the relationships between Fe deficiency, inflammatory disease, and anemia using data from the First National Health and Nutritional Examination Survey (NHANES I). Fe nutrition index was based on the ratio of serum Fe to Fe-binding capacity (Fe:TIBC) and inflammatory index was based on erythrocyte sedimentation rate (ESR). Groups with the highest prevalence of anemia were younger children, young women, and elderly men. Fe deficiency (low Fe:TIBC) was most common among the anemic children and young women but rare in anemic elderly men. Conversely, inflammation (high ESR) was most common among anemic elderly individuals. The prevalence of anemia was more than twice as high in the lowest than in the highest income group. Relative contributions of Fe deficiency and inflammation to anemia did not differ substantially among income groups.  Am J Clin Nutr 1988;48:1295-1300.

KEY WORDS  Anemia, erythrocyte sedimentation rate, inflammation, iron deficiency, serum iron, socioeconomic status, transferrin saturation, First National Health and Nutrition Examination Survey (NHANES I)

Introduction

Anemia is most common among young children, adolescents, women of childbearing age, and elderly individuals (1–3). It has often been assumed that iron deficiency is the predominant cause of anemia in all of these groups, including elderly individuals (4–7). However, the possibility that inflammatory disease could also play an important role has received increasing attention during the last few years (8–11).

The association of anemia with severe and chronic inflammatory disease is well established. This so-called anemia of chronic disease shares many laboratory characteristics with Fe deficiency (12). Acute infections and inflammatory conditions were also found to result in an anemia with laboratory changes similar to those of chronic inflammatory disease (13–16) even when the illness was mild and brief (17) or when the patient had seemingly recovered (18). It is now realized that mild inflammatory conditions can be a major source of error in diagnosing Fe deficiency. Among major biochemical tests for Fe deficiency, both inflammation and Fe deficiency are characterized by a depression in serum Fe and in the ratio of serum Fe to Fe-binding capacity (Fe:TIBC), or transferrin saturation, and an elevation in the erythrocyte protoporphyrin (1–3, 8, 9). Serum ferritin is among the more useful indices in distinguishing the two conditions because it is depressed only in Fe deficiency.

The prevalence of Fe deficiency with or without anemia can be easily overestimated in nutritional surveys because of the role of mild inflammatory disease as an independent cause of anemia and a depression in serum Fe. An analysis of the Second National Health and Nutritional Examination Survey (NHANES II), for example, suggested that inflammatory disease might be more common than Fe deficiency as a cause of anemia among elderly individuals (3, 8). In contrast to women in the childbearing years, elderly individuals with anemia only very rarely had a low serum ferritin level. Unfortunately NHANES II provided only indirect evidence about the possible role of mild inflammatory disease because it did not include laboratory tests that reflect the presence of inflammation.

In this study our objective was to evaluate the relationships among Fe deficiency, inflammatory disease, and anemia in First National Health and Nutritional Examination Survey (NHANES I). The reason for going back

1 From the Division of Nutrition, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, GA and the Department of Pediatrics, School of Medicine, University of California, San Francisco, CA.

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3 Address reprint requests to R Yip, Centers for Disease Control, Bldg 3, Rm SB-45, A41, 1600 Clifton Rd, NE, Atlanta, GA 30333.

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to a survey that was completed over a decade ago is that NHANES I was unique in including laboratory testing results for Fe nutrition status (Fe:TIBC) as well as inflammatory status (erythrocyte sedimentation rate [ESR]) on a large, representative sample of the population of the United States (19). The ESR is a widely used laboratory test that reflects the severity of inflammatory disease in a large variety of conditions (20). In general, an elevation of the ESR with or without a depression in Fe:TIBC can be considered indicative of inflammatory disease. In contrast, a normal ESR with a low Fe:TIBC suggests Fe deficiency.

**Methods**

**The NHANES I sample design**

NHANES I was conducted between 1971 and 1975 by the National Center for Health Statistics and represented the first cycle of a continuing national health and nutrition surveillance system. A detailed description of the survey design was published (19). The survey was based on a national probability sample of civilian, noninstitutionalized persons aged 1–74 y residing in the continental United States. Approximately 32 000 persons from 65 sampling areas were selected for the nutrition component of the survey and 23 808 persons completed the examination. Certain subgroups in the population that were of special interest for nutritional assessment were oversampled: low-income groups, preschool children, women of childbearing age, and elderly people. This study deals with a total of 16 234 individuals for whom a complete set of results for hemoglobin, Fe:TIBC, and ESR analyses was available.

Preschool children, women during the childbearing years, and elderly men were the focus for the analyses because all of these groups had a high prevalence of anemia (21). Men aged 18–44 y were expected to have little Fe deficiency or inflammatory disease and, like elderly women, are included for the purpose of comparison. Adolescents were not included because of problems of heterogeneity in physical maturity and relatively small numbers. The relationship between ESR and anemia were compared for men aged 60–75 y by comparing anemia rate across the ESR range.

We also analyzed the relative contributions of Fe deficiency and inflammation to anemia among five income groups that were categorized according to percentage of the federal poverty level. The poverty income ratio was determined by the US Bureau of Census and taken into account total family income, number of individuals in the household, and the cost of food (22). For this study the group < 100% of poverty level represented the lowest income group (group 1) and that > 400% the highest (group 5), with intervals of 100% dividing the other groups in between. To provide a point of reference, the poverty level (100%) for a family of three was ~$4000 in 1973, the midpoint of NHANES I, and ~$9000 in 1987. To ensure comparability of age and race distribution, the prevalence of anemia among income groups was adjusted for age and race distribution by analysis of covariance (ANOVA). Among the anemic individuals, the relative contribution of those with low Fe:TIBC and/or high ESR in each income category was also determined. All age and sex groups were included in these analyses.

**Laboratory analyses**

Venipuncture blood was collected into tubes containing EDTA for analysis of hemoglobin (Hb) and ESR (23). Hb was determined by the cyanmethemoglobin method with a Coulter Hemoglobinometer (Coulter, Hialeah, FL) (23). ESR was measured by the method of Wintrobe and Landsberg (24). Serum Fe and TIBC were determined by a modification of the automated Technicon AAII-25 Method (23). These assays were performed by the Nutritional Biochemistry Branch, Division of Environmental Health Science, Center for Environmental Health, Centers for Disease Control (CDC). The procedures for freezing and daily shipping of the specimens and all quality control procedures were previously described (25).

**Diagnostic criteria**

For the purpose of our analyses, an individual with low Fe:TIBC and normal ESR value is considered Fe deficient and an individual with elevated ESR with either normal or low Fe:TIBC is considered to have an inflammatory conditions. The terms Fe deficiency anemia and anemia of inflammation are applied to persons who are anemic in addition to fulfilling the above criteria, respectively. It is worth emphasizing that these laboratory criteria are only suggestive but not diagnostic for the conditions.

The criteria for anemia were based on the age- and sex-specific lower limits of the Hb reference ranges derived from NHANES II (3). Mean Hb values in NHANES I were consistently ~3 g/L higher than in NHANES II even in groups such as young adult males who are at little risk of anemia. This discrepancy has not been explained but appears unrelated to Fe deficiency. Consequently, the criteria for anemia for this study were set 3 g/L higher than the values cited in reference (3). The criteria for low Fe:TIBC are values below the 10th percentile of the reference population in NHANES II (8). These values are 12% for ages 1–4 y, 15% for 5–11 y, 16% for adult females, and 18% for adult males. Criteria for high ESR are values > 25 mm/h for children, 20 mm/h for men, and 30 mm/h for women. These limits were set relatively high but are in accord with the differences in ESR among children, men, and women that have been summarized from several sources (26). ESR values in NHANES I were somewhat higher than what one might anticipate from the literature (26). A possible explanation is that the vibration of equipment in the mobile laboratory resulted in a systematic increase in the rate of ESR.

**Statistical procedures**

All statistics in the report were weighted to correct for differences in selection probabilities and adjusted for persons not examined so that the final calculations should be representative of the civilian, noninstitutionalized population of the United States as estimated independently by the Bureau of the Census for 1973, the midpoint of the survey (19). The design effect of the complex sampling for NHANES I was taken into account in the determination of all confidence intervals or standard errors for the prevalence of anemia, Fe deficiency, and inflammation using SESUDAAN program (27). The coding structure for the strata and primary sampling units for NHANES I were modified to allow computation based on complex sampling design (19, 27). All comparison of rates were based on the chi-square test (28).

**Results**

The groups with the highest prevalence of anemia in NHANES I were preschool children, young women, and
elderly men (Fig 1). Young men were rarely anemic, the figure of 2.6 ± 0.8% being just above the theoretic 2.5% that would be defined as anemic in a healthy reference population. Among elderly individuals, women were less frequently anemic than men. The relative contributions of iron deficiency and inflammatory conditions among anemic individuals are depicted in Figure 1. Among both preschool children and women, more than one-third of anemic individuals had an Fe deficiency in contrast to fewer than one-tenth of anemic elderly individuals. Inflammatory conditions appeared to play a more important role in anemic elderly individuals because well over half of elderly men and women with anemia had an elevated ESR alone or in combination with a low Fe:TIBC. Among the relatively few young men who were anemic, abnormalities of either Fe:TIBC or ESR were very rare.

The prevalence of Fe deficiency and inflammatory conditions for each age and sex group are shown in Table 1. Fe deficiency was relatively higher among preschool children and among women during the childbearing years. Fe deficiency was rare among men aged 18–44 y and among elderly individuals.

The prevalence of inflammatory conditions was much higher among elderly individuals than in any of the other groups (Table 1). Furthermore, inflammatory conditions were two to three times more common among anemic elderly individuals of both sexes than it was in the respective total groups. Men aged 18–44 y had the lowest prevalence of inflammatory conditions.

To better define the relationship of inflammation and anemia among elderly individuals, Figure 2 illustrates the distribution of ESR for men aged 60–75 y. The ESR distribution indicates that the majority (67.8%) of elderly men had an ESR < 20 mm/h and 18.1% had mildly elevated ESR (20–29 mm/h). The groups with moderately elevated ESR (≥ 30 mm/h) group comprised the remaining 14.1% and appear to be outliers from the main distribution. Figure 3 shows the prevalence of anemia across the entire ESR range. The anemia rates ranging from 2.2 to 3.5% for the elderly men with ESR < 20 mm/h who constitute majority of the group. By contrast, the anemia rate ranged from 8.5 to 78% for the elderly men with ESR ≥ 30 mm/h. The variation of prevalence of anemia across the eleven ESR groups is statistically significant (p < 0.01, chi-square test).

The association of inflammatory conditions as represented by an elevated ESR with changes in Hb concentration, serum Fe, TIBC, and transferrin saturation in elderly men is illustrated in Table 2. As ESR values rise

![Figure 1: Prevalence of anemia (with SEE) and the relative contributions of low Fe:TIBC and high ESR among anemic individuals by age and sex.](https://academic.oup.com/ajcn/article-abstract/48/5/1295/4716204)

![Figure 2: Relative frequency distribution of men aged 60–75 y across ESR range.](https://academic.oup.com/ajcn/article-abstract/48/5/1295/4716204)

**TABLE 1**

<table>
<thead>
<tr>
<th>Sex and age</th>
<th>Total n</th>
<th>Total group</th>
<th>Anemic group</th>
<th>Total group</th>
<th>Anemic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>F + M &lt;6 y</td>
<td>1599</td>
<td>14.6 ± 1.2</td>
<td>45.7 ± 4.0</td>
<td>10.0 ± 1.4</td>
<td>14.2 ± 3.2</td>
</tr>
<tr>
<td>F 18–44 y</td>
<td>4172</td>
<td>15.4 ± 0.9</td>
<td>54.0 ± 5.3</td>
<td>9.6 ± 1.0</td>
<td>35.3 ± 4.7</td>
</tr>
<tr>
<td>M 18–44 y</td>
<td>1844</td>
<td>7.4 ± 0.5</td>
<td>4.3 ± 3.9</td>
<td>6.7 ± 1.3</td>
<td>8.3 ± 4.9</td>
</tr>
<tr>
<td>F 60–74 y</td>
<td>1574</td>
<td>5.7 ± 1.0</td>
<td>13.0 ± 6.3</td>
<td>23.5 ± 1.4</td>
<td>60.5 ± 6.8</td>
</tr>
<tr>
<td>M 60–74 y</td>
<td>1447</td>
<td>5.9 ± 1.0</td>
<td>10.3 ± 7.0</td>
<td>26.6 ± 2.3</td>
<td>66.5 ± 12.1</td>
</tr>
</tbody>
</table>

* % ± SE.
anemia varied markedly according to age and sex. The predominance of Fe deficiency as a cause of anemia in preschool children and young women that we observed is well established (1, 2). Young children are at risk because of rapid growth and a diet that is often low in Fe. In young women menstrual blood loss and the increased Fe requirements of pregnancy are the major factors. Anemia in elderly individuals until recently was attributed primarily to Fe deficiency but was based on relatively scant evidence (4–7). This report further strengthens the impression from NHANES II analyses (3, 8) and from other studies (6–11) that Fe deficiency is relatively rare among elderly individuals and that inflammation predominates as a cause of anemia. Because inflammation and Fe deficiency result in similar abnormalities of many laboratory tests commonly used for determining Fe deficiency, a careful history and serum ferritin and additional laboratory studies focused on inflammation, such as ESR, are helpful in determining the cause of anemia among elderly individuals.

In recent years the relative importance of inflammation as a cause of anemia may have increased among preschool children. Since the early 1970s when the NHANES I was conducted, Fe deficiency anemia has declined among younger children in the United States (29, 30). This is likely the result of specific infant-feeding recommendations and more effective Fe fortification of foods. It therefore seems likely that mild inflammatory conditions, such as upper-respiratory infections and otitis media, which remain common in early childhood, now contribute more heavily to the comparatively small percentage of anemia that remains (18, 30).

The extent to which specific inflammatory conditions will prove to be linked to anemia in elderly individuals is uncertain. A general increase in ESR with age and decrease in mean Hb has been recognized for some time (3, 31, 32), but it has been difficult to determine whether it is due to an increased prevalence of degenerative, in-

TABLE 2
Hemoglobin and iron biochemistry results of men aged 60–74 y at four different ranges of erythrocyte sedimentation rate

<table>
<thead>
<tr>
<th>ESR (mm/h)</th>
<th>Hemoglobin (g/L)</th>
<th>Serum Fe (µmol/L) TIBC</th>
<th>Transferrin saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>157 ± 1</td>
<td>19.8 ± 0.4</td>
<td>0.33 ± 0.01</td>
</tr>
<tr>
<td>10–19</td>
<td>155 ± 1</td>
<td>19.6 ± 0.5</td>
<td>0.32 ± 0.01</td>
</tr>
<tr>
<td>20–29</td>
<td>150 ± 1</td>
<td>18.1 ± 0.6</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>≥30</td>
<td>141 ± 3</td>
<td>16.7 ± 0.6</td>
<td>0.29 ± 0.01</td>
</tr>
</tbody>
</table>

Discussion

Our analysis of results for Hb, ESR, and Fe:TIBC based on the NHANES I sample indicates that causes of

FIG 3. Prevalence of anemia (with SEE) across the ESR range for men aged 60–75 y.

> 20 mm/h, the mean Hb, mean serum Fe, mean TIBC, and mean transferrin saturation values all declined (p < 0.01, ANOVA).

The prevalence of anemia and the relative contributions of Fe deficiency and inflammatory conditions to anemia by income group are depicted in Figure 4. The analysis by income group included all age-sex categories. Anemia was almost three times more common in the lowest than in the highest income group, 7.4 ± 1.0 and 2.6 ± 0.3%, respectively. The anemia trend across income groups is statistically significant (p < 0.01, chi-square test). In each income category, more than half of the anemic individuals had an abnormality in Fe:TIBC, ESR, or both. Overall, the relative contribution of Fe deficiency and inflammatory conditions to anemia did not vary substantially among income groups. The standard errors for all the estimated proportion of low Fe:TIBC and high ESR among the anemic cases shown in Figures 1 and 4 were all < 1% and in most cases < 0.5%.

FIG 4. Prevalence of anemia (with SEE) and abnormalities in Fe:TIBC and ESR among anemic individuals by income group.
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flammatory processes or whether it is a concomitant of aging even in the healthiest of individuals. Cross-sectional and longitudinal studies were done to address this question using periodic health examinations of individuals who were presumed to be in good general health (31, 32). A steady rise in ESR with age was confirmed but there is little or no previous evidence that the healthiest individuals at any given age had a lower ESR than those who were less healthy. Using NHANES I data that were based on a relatively healthy sample (nonclinic and non-hospital based), we found that a majority of older individuals had a low or normal ESR and that anemia was mainly associated with that minority with an elevated ESR (Figs 2 and 3). This finding suggests that if normal Hb concentration is used as an indicator of good health, then most nonanemic and presumably healthy older individuals have a normal ESR. The increasing prevalence of elevated ESR as well as anemia observed with aging may reflect a relatively greater proportion of elderly individuals who had developed inflammatory conditions. It seems likely that conditions that might be considered subclinical but that are common concomitants of aging (eg, mild arthritis) are the reason for the observed anemia with elevated ESR among elderly individuals. Further investigation is needed to determine whether the hematological changes observed with aging are related to disease conditions among a subset of individuals or related to a generalized change related to aging. Evidence from this study is consistent with the hypothesis that inflammatory conditions among a subset of elderly individuals is responsible for the observed association of mild anemia with elevated ESR.

It might be argued that the anemia itself could be partly responsible for a higher ESR among elderly individuals. Anemic blood is known to sediment faster than nonanemic blood but the difference is so small over a narrow Hb range that it can not account for the major alterations observed in the ESR; furthermore, a leading textbook of laboratory hematology concludes that there is little merit in correcting for anemia (26).

A higher prevalence of anemia among low socioeconomic groups was evident in previous NHANES I and NHANES II analyses (8, 21). Our data confirm and expand on those findings by indicating that both Fe deficiency and inflammatory disease play a major role in the increased prevalence of anemia among the poor. Even though prevalence of anemia varied, the relative contributions of inflammation and Fe deficiency anemia do not appear to differ substantially among income groups.

This study suggests that inflammation rather than Fe deficiency is the most common underlying reason of anemia among elderly individuals. The role of inflammation may also become more important among infants and young children as anemia related to Fe deficiency declines. The increased prevalence of anemia among individuals of lower socioeconomic groups appears to be related to an increase of both Fe deficiency and inflammatory conditions. The role of inflammation as a cause of anemia has important implications for the clinical evaluation of anemic patients and for the determination of the prevalence of Fe deficiency in future nutrition surveys. It remains to be determined what specific conditions are most commonly associated with an acute-phase reaction (eg, high ESR) and anemia. Severe chronic diseases will certainly produce such an effect (20, 26). However, the high prevalence of anemia with elevated ESR in elderly individuals suggests that mild medical conditions may play a more important role than previously recognized. It will be useful in the future to determine to what extent common conditions that produce an acute phase reaction can confound the interpretation of other laboratory measures of nutritional status in addition to those related to Fe nutrition.

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References


