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RESEARCH

Research Editorial

Anemia in Postmenopausal Women: Dietary Inadequacy or Nondietary Factors?

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Anemia is a state in which a deficiency in the size, number, and hemoglobin concentration of an erythrocyte exists, impairing oxygen and carbon dioxide exchange between the blood and body tissues (1). The World Health Organization has defined anemia in women as hemoglobin concentrations less than 12.0 mg/dL (2). Up to the age of 75 years, women are disproportionately affected by anemia, and the prevalence in females 65 years of age and older in the United States is approximately 10% (3,4).

The manifestation of anemia in older populations is associated with dietary inadequacy of micronutrients such as iron, folate, and vitamin B-12; blood loss; genetics; alterations in the bioavailability of micronutrients due to disease or medication use; renal insufficiency; and other less common causes (3,4). Iron deficiency is the most common cause of anemia, whereas anemia as a consequence of vitamin B-12 or folate deficiency is comparatively rare in older adults (5,6). Iron-deficiency anemia is associated with small (microcytic), hemoglobin-deplete, erythrocytes and is linked to several adverse clinical outcomes in adults, including fatigue, decreased work capacity, palpitations, and alterations in immune function (7). Megaloblastic anemia is associated with both late-stage folate and vitamin B-12 deficiency and is evidenced by altered nucleoprotein production adversely impacting both erythrocyte morphology (macrocytic) and maturation (megaloblasitc) (8). Folate and vitamin B-12 deficiency are clinically similar in their presentations in that both are associated with fatigue, diarrhea, memory loss, and reductions in weight (8). Vitamin B-12 deficiency is also associated with neurological changes. Clearly, understanding the etiology of anemia in older people is critical to improving quality of life and decreasing morbidity and mortality in this segment of the population and should be a public health priority.

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CURRENT RESEARCH

In this issue of the *Journal*, Thomson and colleagues (9) present a cross-sectional and prospective analysis of the association between nutrient intakes and anemia prevalence, in relation to both incidence and persistence, in a large multiethnic sample of 72,833 US postmenopausal women included in the Women's Health Initiative-Observational Study (WHI-OS) cohort (10). Dietary intake was assessed at baseline using a food frequency questionnaire (FFQ) and exposures of interest included iron, folate, vitamin B-12, vitamin C, animal protein, vegetable protein, red meat, and fortified cereal. Dietary inadequacy was defined as less than the dietary reference intakes (DRIs) for individual nutrients from food sources for women older than 50 years of age (11-13). Supplemental sources of nutrients were also evaluated but not consistently combined with food sources when dietary inadequacy was assessed. Fasting hemoglobin was measured at baseline and at 3-year follow-up and used to define anemia according to World Health Organization criteria. Women categorized as with or without anemia were compared for demographic and dietary differences at baseline. Associations between baseline dietary inadequacies, servings of selected food groups, and the cumulative number of baseline dietary inadequacies with incident and persistent anemia at 3-year follow-up was also evaluated, controlling for covariates. Also, associations between anemia and specific nutrients by race/ethnicity were explored.

Results illustrated that anemia was present at baseline in 5.5% (n=3,979) of the analytic cohort. Anemia was more prevalent in women of advanced age (>63.5 years), those identifying as African American, smokers, those with lower income, and women with low or high body mass index. At baseline, mean dietary intake in all groups (no, incident, and persistent anemia) met or exceeded the DRIs for all nutrients investigated, although intakes were lower in the two anemia groups. Specifically, compared with the DRI goals, the approximate baseline mean nutrient intake for all women from food sources of iron was 50% more (intake of 12 mg vs DRI of 8 mg/day), folate was 20% more (479 μg consumed vs DRI of 400 μg/day) and vitamin B-12 was 133% more (5.6 μg consumed vs DRI of 2.4 μg/day). Vitamin C and protein intake from food sources also exceeded the DRIs for women 50 years and older. Mean supplemental sources of iron, folate, vitamin B-12, and vitamin C within each group provided from 50% to more than 100% of the DRIs. When food and supplemental sources were combined, average intakes for each group exceeded 150% of the DRIs for all nutrients of interest.

When intakes were dichotomized into inadequate (lev-

els less than the DRIs) or adequate (at or more than the DRIs), African-American women were more likely to have inadequate intakes for more than one nutrient (food sources only) compared with other race/ethnic groups. Inadequate intake (food sources only) of iron, folate, vitamin B-12, vitamin C, and protein were associated with increased odds of both incident and persistent anemia in adjusted models. Lastly, risk of baseline, incident, and persistent anemia increased as the number of baseline nutrient inadequacies (food and supplemental sources) accumulated when adjusted for covariates.

The DRIs for iron, folate, vitamin B-12, vitamin C, and protein were set as Recommended Dietary Allowances and represent the average daily nutrient intake level sufficient to meet the nutrient requirement of 97% to 98% of healthy individuals within a particular life-stage and sex (13). Also, it is well known that decreases in hemoglobin occur from nutrient deficiencies only when stores are nearly exhausted (ie, late-stage nutrient deficiencies). Therefore, the reported means of the nutrients consumed by WHI-OS participants raises the question of how dietary intake alone could be responsible for the incident and persistent anemia observed. The answer likely lies in a fair proportion of the anemias being unrelated to dietary inadequacy, the limits of FFQs to quantify absolute values of nutrient intake, and the insensitivity of hemoglobin as a measure of dietary deficiencies.

NONDIETARY RISK FACTORS FOR ANEMIA

It is important to acknowledge that anemia in older individuals is frequently linked to non-nutritional causes (3). Several of the clinical parameters required to interpret and classify the type of anemia and evaluate non–diet-related factors associated with anemia were not assessed in all women enrolled in the WHI-OS cohort, as acknowledged by Thomson and colleagues (9), and therefore not evaluated or reported. The non-nutritional factors associated with decreased nutrient bioavailability of iron, folate, and vitamin B-12 linked to anemia are discussed in the following sections.

ANEMIA OF CHRONIC DISEASE

Anemia of chronic disease (ACD) is the most common form of anemia in elderly people and closely resembles iron-deficiency anemia (14). ACD is a normochromic, microcytic anemia that is thought to be a host defense response mediated by pro-inflammatory cytokines (interleukin-6, interleukin-1, and tumor necrosis factor-α) that evolved to deprive bacteria of iron (15,16). ACD is characterized by hypoferremia, normal or increased iron storage, and the presence of iron in bone marrow, indicating impaired mobilization of iron from stores (17). Recent studies indicate that inflammation leads to hypoferremia and ultimately ACD through an interleukin-6–mediated increase in hepcidin production (16,18). Hepcidin controls the activity of the sole iron exporter ferroportin-1. Increased hepcidin concentrations diminish ferroportin-1 activity, sequestering iron within key sites of iron flux, including the intestinal enterocytes and reticuloendothelial cells, ultimately decreasing iron bioavailability for erythrocyte production. Therefore, iron from food sources or dietary supplementation in individuals with the ACD would have little impact on repletion efforts secondary to increased hepcidin levels (19). Although Thomson and colleagues (9) included several chronic conditions as exclusion criteria, other conditions such as diabetes were not excluded. Also, some women may have developed a chronic condition that altered their iron bioavailability and status during the 3-year follow-up, thus impacting the cases of incident and persistent anemia observed.

OBESITY

Thomson and colleagues (9) reported that higher BMIs were associated with a greater prevalence of anemia in the WHI-OS cohort. Several studies in adults and children have demonstrated that obesity is associated with diminished iron status, increased hepcidin levels, and decreased iron absorption; inadequate diet was not associated with iron deficiency or anemia (20-27). Although obesity is a condition of chronic inflammation, the iron deficiency phenotype in obese individuals is vastly different from ACD. Unlike ACD, obesity does not seem to be associated with iron sequestration or impaired mobilization of iron from stores, but instead subclinical iron deficiency as indicated by increased serum transferrin receptor levels and minimal iron sequestration in reticuloendothelial cells (22,23,26). Therefore, obesity-associated iron deficiency has been classified as a mixed anemia in which the hallmarks of iron deficiency and ACD co-exist (23). Consequently, it is plausible that women in the WHI-OS cohort gained weight during the 3-year follow-up period, which could have influenced both the incident and persistent anemia observed. The exact mechanism linking obesity with iron deficiency remains unclear, but expansion of blood volume coupled with decreased bioavailability of iron (increased hepcidin) and not dietary inadequacy may be associated with some of the anemia reported. In addition, recent studies have shown that vitamin B-12 and serum folate concentrations are diminished in obese compared with lean individuals (28,29), but it remains unclear if expansion of blood volume, dietary inadequacy, or decreased bioavailability is linked to these lower levels, suggesting the need for additional research in this area.

ALTERED ABSORPTION AND BLOOD LOSS

Many elderly individuals suffer from decreased gastric acid production as a result of atrophic gastritis (4). Reduction in stomach acidity can result in reduced nonheme iron, vitamin B-12 from food sources, and folate absorption (30-32). Decreased stomach acid production can also lead to bacterial overgrowth, which can further impede both non-heme iron and vitamin B-12 absorption (30,31). Similarly, proton-pump inhibitors and H2-blockers commonly prescribed for gastroesophogeal reflux disease and peptic ulcers can also reduce stomach acidity and impair non-heme iron, vitamin B-12, and folate uptake (33-35). Lastly, blood loss is more common in elderly compared to younger age groups due to conditions such as hiatal hernia, hemorrhoids, constipation, and frequent nonsteroidal anti-inflammatory drug use. Blood loss is associated with decreased iron bioavailability for erythrocyte production and increased dietary iron requirements (4,36).

RENAL INSUFFICIENCY

Renal disease was not present in the WHI-OS cohort at baseline, but development over the 3- year follow-up period was possible as acknowledged by Thomson and colleagues (9). Mild to moderate renal insufficiency is common in elderly individuals and is associated with increased risk of anemia due to decreased kidney production of erythropoietin reducing hemoglobin levels and increased inflammation (37,38), which could impact nutrient bioavailability for erythrocyte production. Therefore, it is important to assess renal function as a risk factor for anemia in elderly populations.

UNEXPLAINED ETIOLOGY OF ANEMIA IN ELDERLY PEOPLE

Many cases of anemia in the elderly remain unexplained and several theories have emerged. Proposed unique mechanisms of anemia in the elderly include sarcopenia, decrease in sex steroids, diminished sensing of the hypoxia/erythropoietin sensing mechanism, changes in stem cell physiology, and polypharmacy (3,7,39-41). However, additional research is needed to provide mechanistic evidence to support any of these hypotheses.

QUANTIFYING DIETARY INTAKE WITH AN FFQ

FFQs are the most common method for assessing dietary intake in epidemiological studies because they are low-cost and can be administered on a large scale (42). The two principles of the food frequency approach are that average long-term intake and relative ranking of individual diet are more important than absolute intake for predicting chronic disease risk. Thomson and colleagues used an FFQ to discern dietary intake, and results indicated adequate mean consumption across groups (ie, no, incident, and persistent anemia) but greater odds for incident and persistent anemia in those with nutrient consumptions less than the DRIs. It is possible that the mean nutrient intake observed could have been due to systematic over-reporting of intake among the WHI-OS participants, although there is little evidence to suggest this. Further, Willett and colleagues (43) compared mean nutrient intake of several nutrients (including iron and vitamin C) via their 116-item FFQ to a 1-year diet record collected in 27 adults and found no significant differences in mean iron and vitamin C intake, further suggesting FFQs do not result in over-reporting of these nutrients. Therefore, the mean reported intake, consistent with the DRIs, suggests that a portion of the anemia observed is not related to dietary inadequacy.

LACK OF SPECIFICITY OF HEMOGLOBIN CUT-POINTS FOR DETECTION OF DEFICIENCIES IN NUTRIENT INTAKE

Hemoglobin levels less than 12 mg/dL were used to define anemia in the Thomson and colleagues study (9). Hemoglobin is an imprecise measure of iron, vitamin B-12, or folate deficiency as reduction in hemoglobin only occurs during the final stages of deficiency (44). In addition, whenever a cutoff value such as hemoglobin is used, some misclassification of "deficient" and "adequately nourished" could occur (45). Thomson and colleagues' finding that incident and persistent anemia were associated with dietary intake less than the DRIs for the nutrients of interest suggests that hemoglobin was a sensitive marker of poor diet (ie, those with low hemoglobin had dietary intakes less than the DRIs). However, the overall mean intake of all nutrients were more than the DRIs in those with no, incident, and persistent anemia, indicating a somewhat low level of specificity for hemoglobin as an indicator of poor diet (ie, many participants with low hemoglobin levels also had adequate dietary intake). This finding again suggests that something unrelated to diet is contributing to some cases of anemia observed.

SUMMARY

The study by Thomson and colleagues extends the literature by providing one of the largest prospective assessments of diet and anemia in US postmenopausal women. Also, the investigators have demonstrated that assessment of diet using an FFQ correctly ranked participants with inadequate dietary intake for anemia-related nutrients to low hemoglobin status. This finding lends credibility to use of an FFQ for large epidemiological studies investigating the relationship between diet and anemia risk; however, the mean nutrient intakes reported also suggest that a portion of the anemia observed in the WHI-OS cohort was not diet-related. Although precise assessment of anemia in older individuals through use of hematologic parameters, clinical indicators of inflammation, markers of disease progression, as well as diet, will allow the medical professional to appropriately classify the type of anemia and recommend appropriate treatment options, their inclusion in large epidemiologic studies is cost-prohibitive and unlikely.

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