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Fatigability as a Predictor of Subclinical and Clinical Anemia in Well-Functioning Older Adults

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Abstract

BACKGROUND/OBJECTIVES—Anemia is a common condition in older adults for which the primary symptom – fatigue – often goes unrecognized as individuals typically equilibrate their activity to avoid fatigue. Whether assessing fatigability (i.e., susceptibility to fatigue) facilitates identification of anemia is unknown. Thus, this study examines the association between fatigability and prevalent, incident and persistent subclinical and clinical anemia in well-functioning older adults.

DESIGN, SETTING, PARTICIPANTS—Longitudinal analysis of 905 well-functioning men and women aged 60-89 years and followed for 1-5 years from the Baltimore Longitudinal Study of Aging conducted at the National Institute on Aging, Clinical Research Unit, Baltimore, MD.

MEASUREMENTS—Perceived fatigability was assessed as rating of perceived exertion (RPE) from 6 to 20 following a 5-minute treadmill walk at 1.5 mph (0.67 m/s) and reported unusual tiredness in the past month. Clinical anemia was defined using World Health Organization hemoglobin cutpoints of <13g/dL and <12g/dL for men and women respectively and subclinical anemia was defined respectively as 13.0-13.9g/dL and 12.0-12.9g/dL.

RESULTS—Overall, 14% of participants had clinical and 30% subclinical anemia at baseline. Each increment (1 RPE) of fatigability was associated after covariate adjustment with respectively 14% (95% confidence interval (CI):5-25%, p=.005) and 8% (CI:1-17%; p=.031) greater likelihood of prevalent clinical and subclinical anemia. An average of 2.2 years later, each 1 RPE increment in baseline fatigability predicted an 11% (CI:2-20%; p=.016) higher likelihood of incident and/or persistent subclinical and clinical anemia. Reports of unusual tiredness were associated with prevalent subclinical anemia only.

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CONCLUSION—This study provides evidence that perceived fatigability may help identify well-functioning older adults with borderline to clinical anemia who are on a trajectory of persistently suboptimal or worsening hemoglobin status. Assessing fatigability may facilitate earlier diagnosis of health conditions that underlie persistent suboptimal hemoglobin status.

Keywords

Anemia; fatigability; hemoglobin; older adults

Introduction

Anemia commonly occurs in older adults and typically arises from chronic disease processes, poor kidney function,[1] systemic inflammation[2] and iron deficiency among other conditions[3] and has been associated with poor physical function and health-related life quality, frailty and heightened risk of mortality.[4–7] Anemia frequently goes unrecognized as the principal manifestation – fatigue, unusual tiredness or low energy – often goes unnoticed.[8] This is especially problematic in older adults who typically constrain their activity level and intensity to avoid, diminish or delay fatigue.[9]

The construct of fatigability, that is, susceptibility to fatigue,[10] has recently emerged and has been operationalized as activity-specific perceived exertion. Several studies have identified fatigability as superior to fatigue symptoms in evaluating risk or likelihood of mobility decline in well-functioning older adults[11–13] and lower engagement in daily physical activity.[14] Higher fatigability has been associated with cancer history,[15] low-grade inflammation[16] and subclinical peripheral arterial disease[17] indicating a potential role as an early marker of serious health conditions. Whether fatigability assessment would aid in identifying well-functioning older adults with anemia or sub-optimal hemoglobin status has not been investigated.

The World Health Organization (WHO) defines anemia as a hemoglobin level below 13g/dL for men and 12g/dL for women. Several reports have found elevated risk of poor health and functional outcomes including mortality at hemoglobin levels above those defining anemia;[18–21] therefore in this work, we also examine suboptimal hemoglobin levels up to 1g/dL above the WHO cutpoints which we label subclinical anemia and propose that fatigability may help distinguish persons with stable low normal hemoglobin from those experiencing declining levels. Attention to suboptimal hemoglobin status in addition to anemia, is important especially when evaluating well-functioning older adults, that is, individuals with no overt limitations in their ability to walk several blocks independently. Such individuals comprise 50 to 70% of persons aged 60 years and older in the United States[22] and due to emerging health issues are highly vulnerable to losing their well-functioning status.[23]

This study examines the concurrent association between fatigability and subclinical and clinical anemia and evaluates whether fatigability predicts sustained, chronic or incident subclinical and clinical anemia an average of 2.2 years later. We target anemia as an outcome because it commonly occurs in older adults and more importantly anemia is itself a sign and potential early marker of underlying disease conditions and/or homeostatic

dysregulation. For comparison purposes, we also examine associations with reports of unusual tiredness over the past month.

Methods

Study Design and Population

Data are from the Baltimore Longitudinal Study of Aging (BLSA), a continuous enrollment cohort established in 1958. Once enrolled, participants are followed until death through comprehensive health, cognitive and functional evaluations conducted during a three-day visit to the National Institute on Aging Clinical Research Unit in Baltimore, Maryland. Follow-up visits typically occur biannually for persons aged 60 to 79 years and annually for persons aged 80 and older. Participants for the current study included 905 men and women aged 60 to 89 years who were well-functioning (i.e.; reported no difficulty walking ¼ mile and had a usual gait speed of at least .67 m/s), had known anemia status and hemoglobin values that did not exceed 16g/dL for men and 15g/dL for women which are considered excessively high and have been associated with poor health outcomes.[19,20] All participants were administered the perceived fatigability test (see below) which was implemented in the BLSA in April 2007. The first visit in which these criteria were met served as the index or baseline visit for the analyses.

The longitudinal sample consisted of 658 participants who had at least one follow-up visit within one to five years of their index visit (mean=2.2 years). Among the 247 without an eligible follow-up, 77 were not due for a visit, 43 were seen outside of five years, 8 were missing anemia status, 9 had a phone or incomplete visit and 10 had excessively high hemoglobin values. Twenty-seven had died, 3 developed dementia, 2 withdrew and 68 were overdue for a visit, unable to contact or lost to follow-up. Participants without an eligible follow-up were younger (70.6 vs. 72.3 years; p=.004) and more likely to be current or recent smokers (4.6 vs. 2.1%; p=.048) but did not differ on any other characteristic examined in this study. The BLSA protocol was approved by the National Institute of Environmental Health Sciences Institutional Review Board and participants provided written informed consent at all visits.

Measures

Anemia status at the index visit was determined from a blood draw on the morning of the first day of the clinic visit after an overnight fast of at least 10 hours. Blood was processed on site the same day it was drawn. WHO cutpoints of <13g/dL of hemoglobin for men and <12g/dL for women were used to define clinical anemia. Subclinical anemia was defined as hemoglobin values of 13-13.9g/dL for men and 12-12.9g/dL for women. Those above the subclinical anemia cutpoints having hemoglobin values respectively between 14-16g/dL and 13-15g/dL were labeled “no anemia” in the tables. Anemia status at follow-up was determined using the same procedures used at the index visit except for the 13 participants who had a home visit. The home visit blood draw was performed by a certified phlebotomist typically within two to four weeks of the home visit interview and examination. Participants were instructed to fast overnight and to ingest nothing other than water before the blood

draw which was scheduled for early morning. Samples were processed locally by a certified lab.

Fatigability was evaluated using a slow paced 5-minute walk (1.5 mph; 0.67 m/s) performed on a treadmill at zero percent grade immediately after which participants rated their perceived exertion using the Borg rating of perceived exertion (RPE) scale.[11,24] The Borg RPE ranges from 6 to 20, where 6=no exertion at all, 9=very light, 11=light, 13=somewhat hard and 20=maximal exertion.[25] This operationalization of fatigability is termed "*perceived fatigability"* and has been found to predict clinically meaningful decline in physical performance and reported walking ability[11] and objectively assessed physical activity level.[14] High fatigability has been defined as having a score of 10 or more.[24]

Reports of unusual tiredness, a common fatigue symptom also was examined. Using an interviewer-administered questionnaire, participants were asked "In the past month, on average how often have you felt unusually tired during the day? all, most, some or none of the time?" For analysis, responses were dichotomized to none (coded 0) versus some to all of the time (coded 1) as "most" and "all" were rarely endorsed (n=11 and 3, respectively).

Co-variates included sex, self-designated race coded as black and non-black, age in years over 60, age-squared, measured weight in kilograms and height and waist circumference in centimeters to account for overweight and obesity, smoking status dichotomized as current or quit within 10 years versus never smoked or quit over 10 years ago and physical activity level categorized as sedentary (<30 minutes), low (30 to 74 minutes), moderate (75 to 149 minutes) or high (≥150 minutes) based on reported frequency and duration of vigorous and moderate physical activity including brisk walking performed per typical week.

Statistical Analysis

To evaluate the cross-sectional associations between anemia status and fatigability and reported tiredness, we examined the likelihood of subclinical and clinical anemia associated with perceived fatigability level along the full range, high fatigability and unusual tiredness using logistic regression. All models were adjusted for the covariates described above. To evaluate whether perceived fatigability and unusual tiredness predict persistent or worsening anemia status, we created a composite follow-up measure defining persons who met subclinical or clinical anemia criteria at follow-up and had the same or worse classification as their index visit as having incident or persistent subclinical or clinical anemia. We examined these outcomes combined and separately. Associations were evaluated using logistic regression models controlling for the covariates defined above as well as time between index and follow-up visit. Statistical significance was set at $p < .05$ and all tests were 2 sided.

Results

Participant Characteristics

The study population (see Table 1) consisted of 905 men (48%) and women aged 60 to 89 years with an average age of 71.9 years. In this well-functioning population, less than 3% had smoked within the previous 10 years, just under half were sedentary and 23% met

physical activity recommendations.[26] Fourteen percent met WHO defined criteria for anemia of whom 8.7% or 1.2% overall had iron-deficiency anemia. An additional 30.2% were classified as having subclinical anemia. Clinical anemia was higher in men and both subclinical and clinical anemia were higher in Blacks. Anemia status varied by race within women and by sex within race with 23.8% of black women, 7.1% of white women, 16.6% white men and 13.3% of black men meeting WHO anemia criteria. Mean fatigability was 8.7 RPE on a scale from 6 to 20 and 27.4% had high fatigability (reported exertion level ≥ 10).

Cross-Sectional

As shown in Table 2, after accounting for age, age-squared, sex, race, weight, height, waist circumference, smoking status and exercise level, prevalence of clinical anemia was 14% higher (95% confidence interval (CI):5-25%, p=.005) with each increment (1 RPE) of fatigability and the prevalence of subclinical anemia was 8% higher (CI:1-17%; p=.031). Unusual tiredness in the past month was associated with a 42% higher (CI:4-95%; p=.027)prevalence of subclinical anemia but was not an independent predictor of clinical anemia.

Longitudinal

As shown in Table 3, of the 658 participants with follow-up data an average of 2.2 years later, 19.0% had clinical anemia and 30.2% had subclinical anemia. Of those with clinical anemia at their index visit, 69% met clinical anemia criteria at follow-up which we have defined as persistent clinical anemia. Of the 201 with subclinical anemia at their index visit, about 25% improved (i.e., had hemoglobin values of at least 13g/dL for women and 14g/dL for men), 50% remained in the subclinical range and 25% got worse and met sex-specific criteria for clinical anemia. Of those initially above the threshold for subclinical anemia, 20% moved below the threshold and an additional 4% developed clinical anemia. As reported in Table 4, the prevalence of persistent or incident subclinical or clinical anemia was 11% higher (CI:2-20%; p=.016) with each increment of baseline fatigability and 48% higher in those with high fatigability at their index visit. Persistent or incident clinical anemia was 13% more prevalent (CI:2-25%; p=.025) with each increment of perceived fatigability. Unusual tiredness in the past month did not reliably predict persistent suboptimal or worsening anemia status at follow-up.

Discussion

In well-functioning community-dwelling older adults with no overt walking limitations, greater level of perceived exertion or fatigability in response to a low demand walking test was associated with higher rates of clinical and subclinical (i.e., sub-threshold) anemia. Greater fatigability also predicted higher rates of persistently suboptimal or worsening hemoglobin level over a follow-up slightly longer than two years on average. In contrast, reports of unusual tiredness in the past month did not reliably predict concurrent anemia status or persistent suboptimal hemoglobin status.

Even in well-functioning older adults, anemia was common, affecting 7 to 24% depending on race and sex. The rates observed in black and white women of 23.8 and 7.1 percent, respectively, were similar to those observed in black and white women aged 65 years and older in the nationally representative NHANES III of 28.0 and 8.7 percent[27] and in Health ABC participants aged 71 to 81 years of 20.9 and 7.0 percent, respectively.[28] Rates of anemia in men however differed with white men having a slightly higher rate of 16.6 percent versus 9.2 in NHANES III and 13.7 in Health ABC and black men having a much lower rate of 13.3 percent in contrast to 27.5 and 25.5 for NHANES III and Health ABC respectively.[27,28] We have no definitive explanation for the markedly lower anemia prevalence in black men except that, similar to the other participants in BLSA, black participants had much higher educational attainment and income than individuals with the same characteristics in the general population, both of which have been associated with lower anemia rates.[29]

The 30 percent overall prevalence of subclinical anemia especially in a cohort of well-functioning older adults warrants some discussion. As noted in the introduction, sex-specific hemoglobin values up to 1g/dL above the WHO anemia cut-point threshold have been associated with elevated rates of mortality.[19–20] Findings from this study also support the potential negative health consequences of subthreshold anemia as we observed a graded association in mean fatigability across anemia categories (see Table 1) with persons with no anemia having a mean fatigability of 8.4 versus 8.9 in those with subclinical anemia versus 9.4 in those with clinical anemia. After adjustment for co-variates, persons with subclinical anemia had higher fatigability than those with no anemia (8.8 versus 8.5; $p<.03$). Thus, although subclinical anemia is still not considered a clinical entity, at least in some people, it appears to have consequences for well-being and quality of life.

Remarkably, few studies have examined change in anemia status in older adults over time. In this study, we observed a trend towards worsening hemoglobin status with clinical anemia prevalence increasing from 14 to 19 percent and subclinical anemia remaining at 30 percent over an average of 2.2 years for an overall prevalence of suboptimal hemoglobin of 49 percent. Although 31 percent of those with clinical anemia at their index visit did not meet clinical anemia criteria at follow-up, a large majority (24 out of 28) continued to have suboptimal hemoglobin levels. Those with subclinical anemia were equally likely to improve or decline, but nevertheless 25% met clinical anemia criteria within 2.2 years. Among persons initially free of anemia, 24 percent had worsening status with 4 percent developing clinical anemia and 20 percent subclinical anemia. Importantly, persons who developed or continued to have suboptimal hemoglobin levels at follow-up had higher fatigability at their index visit than those who continued to have optimal hemoglobin levels (adjusted mean fatigability 8.8 versus 8.5; $p=.049$).

As noted above, anemia prevalence was similar among black and white men in the current study but much lower in black men than observed in more representative samples; whereas, black women had over three times the anemia prevalence as white women in the current study, but similar to that reported in other studies.[27,28] In light of these disparate prevalence rates, we conducted race-stratified analyses as a check on the integrity of our findings and the applicability to both black and white older adults. Results can be found in Supplementary Tables S1 and S2. The cross-sectional findings are nearly identical when

examining the 668 white participants separately. For example, the odds ratios, (95% confidence intervals and p-values) for fatigability RPE associated with clinical and subclinical anemia respectively in the white only sample were 1.18 (1.05-1.32; .004) and 1.10 (1.01-1.20; .025) versus 1.14 (1.04-1.25; .005) and 1.08 (1.01-1.17; .031) in the full sample. No associations were observed in the black subsample. Longitudinally, the situation is similar. The odds ratios, (95% confidence intervals and p-values) for fatigability RPE associated persistent or incident clinical and subclinical anemia in the white only sample (N=482) was 1.13 (1.03-1.25; .013) versus 1.11 (1.02-1.20; .016) in the full sample, with no association observed in black participants. Notably, high fatigability was associated with 2.4 times (1.39-4.22; .002) the likelihood of persistent or incident clinical anemia in white participants which was not observed in the full sample.

In summary, this study provides evidence that perceived fatigability, an activity anchored measure of fatigue, facilitates identification of well-functioning older adults with borderline to clinical anemia who may be on a trajectory of persistently suboptimal or worsening hemoglobin status. Observed associations largely are driven by white study participants and may not to apply to older adults of African descent with anemia defined using WHO sex-specific cut-points. Notably, over one-quarter of well-functioning older adults had high fatigability of which 46% did not have anemia. As fatigability has been associated with diminished functional performance, reported walking ability and activity engagement[14,24] and anemia in older adults often portends underlying chronic illness,[1,2,30] assessing fatigability may lead to earlier identification of health conditions whose treatment in turn may delay functional decline and prolong independent living.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline Characteristics of 905 Baltimore Longitudinal Study Participants Stratified by Anemia Status[a]

Baseline Characteristics[b]	Overall	No Anemia	Subclinical Anemia	Clinical Anemia
Participants No. (%)	905	505 (55.8)	273 (30.2)	127 (14.0)
Age, mean (SD), y	71.9 (8.1)	71.0 (8.0)	72.1 (8.1)	74.7 (7.8)
Male sex	433 (47.8)	246 (48.7)	118 (43.2)	69 (54.3)
Black race	237 (26.2)	98 (19.4)	92 (33.7)	47 (37.0)
Recent smoker	25 (2.8)	15 (3.0)	7 (2.6)	3 (2.4)
Sedentary	420 (46.4)	217 (43.0)	131 (48.0)	72 (56.7)
Highly active	209 (23.1)	124 (24.6)	62 (22.7)	23 (18.1)
BMI, mean (SD)	27.1 (4.6)	27.0 (4.3)	27.3 (5.0)	27.1 (4.5)
Waist circumference, mean (SD)	90.4 (12.5)	90.4 (12.5)	90.1 (13.2)	90.9 (12.1)
Fatigability, mean (SD), RPE	8.7 (2.3)	8.4 (2.0)	8.9 (2.4)	9.4 (2.5)
High fatigability	248 (27.4)	115 (22.8)	79 (28.9)	54 (42.5)
Unusual tired past month	343 (37.9)	172 (34.1)	119 (43.6)	52 (40.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); RPE, rating of perceived exertion.

[a]World Health Organization cutpoints of <13g/dL of hemoglobin for men and <12g/dL for women were used to define clinical anemia. Subclinical anemia was defined as hemoglobin values of 13-13.9g/dL for men and 12-12.9g/dL for women.

[b]Unless otherwise indicated, data are reported as number (percentage) of participants.

Table 2.

Odds[a] of Subclinical and Clinical Anemia Associated with Fatigability and Fatigue Symptoms

Fatigability/Fatigue Symptom	Anemia Status[b]	Odds Ratio (95% Confidence Interval)	p-value
Fatigability RPE[c]	Subclinical	1.08 (1.01-1.17)	.031
	Clinical	1.14 (1.04-1.25)	.005
High fatigability (RPE≥10)	Subclinical	1.15 (0.80-1.65)	.44
	Clinical	1.91 (1.23-2.99)	.004
Unusual tiredness past month	Subclinical	1.42 (1.04-1.95)	.027
	Clinical	1.26 (0.83-1.92)	.27

[a]Adjusted for age, age-squared, sex, race, weight, height, waist circumference, smoking status and exercise level

[b]World Health Organization cutpoints of <13g/dL of hemoglobin for men and <12g/dL for women were used to define clinical anemia. Subclinical anemia was defined as hemoglobin values of 13-13.9g/dL for men and 12-12.9g/dL for women.

[c]Rating of perceived exertion

Table 3.

Anemia Status at Index and Follow-up Visits

	Follow-Up Visit			
Index Visit	**Anemia Status**[a]	Clinical	Subclinical	None
	Clinical	62	24	4
	Subclinical	48	103	50
	None	15	72	280

[a]World Health Organization cutpoints of <13g/dL of hemoglobin for men and <12g/dL for women were used to define clinical anemia. Subclinical anemia was defined as hemoglobin values of 13-13.9g/dL for men and 12-12.9g/dL for women.

Table 4.

Odds[a] of Persistent or Incident Subclinical and Clinical Anemia[b] Associated with Fatigability and Fatigue Symptoms

Fatigability/Fatigue Symptom	Odds ratio (95% Confidence Interval)	p-value
Persistent or Incident Subclinical or Clinical Anemia		
Fatigability RPE[c]	1.11 (1.02-1.20)	.016
High Fatigability	1.48 (1.01-2.18)	.046
Unusual Tiredness Past Month	1.37 (0.98-1.92)	.07
Persistent or Incident Subclinical Anemia		
Fatigability RPE	1.09 (0.99-1.20)	.07
High fatigability	1.45 (0.93-2.26)	.10
Unusual Tiredness Past Month	1.33 (0.90-1.96)	.16
Persistent or Incident Clinical Anemia		
Fatigability RPE	1.13 (1.02-1.25)	.025
High fatigability	1.54 (0.93-2.53)	.09
Unusual Tiredness Past Month	1.46 (0.94-2.29)	.10

[a]Adjusted for age, age-squared, sex, race, weight, height, waist circumference, smoking status, exercise level and time between index and follow-up visit

[b]World Health Organization cutpoints of <13g/dL of hemoglobin for men and <12g/dL for women were used to define clinical anemia. Subclinical anemia was defined as hemoglobin values of 13-13.9g/dL for men and 12-12.9g/dL for women.

[c]Rating of perceived exertion