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THE RELATIONSHIP BETWEEN ANEMIA, HEMOGLOBIN CONCENTRATION AND FRAILTY IN BRAZILIAN OLDER ADULTS

L. PIRES CORONA[1], F.C. DRUMOND ANDRADE[2], Y.A. DE OLIVEIRA DUARTE[3], M.L. LEBRAO[4]

1. Faculty of Applied Sciences, University of Campinas, Limeira, Brazil; 2. Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, USA; 3. Department of Medical Surgical Nursing, School of Nursing, University of Sao Paulo, Sao Paulo, Brazil; 4. Department of Epidemiology, Faculty of Public Health, University of Sao Paulo, Sao Paulo, Brazil. Corresponding author: Ligiana Pires Corona, University of Campinas, Nutrition, R. Pedro Zaccaria, 1300, Limeira, Sao Paulo 13484-35, 0, Brazil, ligiana.corona@fca.unicamp.br

Abstract: *Objective:* to explore the relationship between anemia, hemoglobin concentration and frailty syndrome in older adults. *Research Methods and Procedures:* This was a cross-sectional population-based study, with adults ≥60 years (n=1,256) from the third wave of the SABE Cohort Study (Health, Well-being and Aging) conducted in 2010 in São Paulo, Brazil. Frailty syndrome was evaluated according to Fried´s phenotype. Anemia was defined using the WHO criteria (hemoglobin concentration <12 g/dL for women and <13 g/dL for men). Four approaches were used to verify the associations between anemia, hemoglobin concentration and frailty status or number of frailty criteria. We used logistic regression and Poisson regression in the analyses, and they were adjusted in three hierarchical models using three blocks of variables: basic characteristics; clinical characteristics; cognitive status. *Results:* Mean hemoglobin concentration was significantly lower in frail elderly (13.3g/dL, versus 14.3g/dL in non-frail; p<0.001). Prevalence of anemia was also significantly higher in frail when compared to non-frail elderly (24.2% and 3.8%; p<0.001). Anemia was significantly associated to low physical activity, weakness and slowness. In the fully adjusted regression models, anemia was strongly associated to frailty (OR=3.27, 95%IC=1.89,5.65; p<0.001), and lower levels of hemoglobin were associated to higher number of frailty criteria. *Conclusions:* We found important associations between anemia, hemoglobin concentration and frailty; anemic older adults were more likely to be frail, and lower levels of hemoglobin were associated to higher number of frailty criteria showing a clear dose-response effect..

Key words: Hemoglobin, anemia, frailty, older adults, SABE Study.

Introduction

The population aging process that has been in process in last decades in Brazil brings the emergence of health problems related to old age, such as chronic degenerative diseases and nutritional deficiencies. Within this context, anemia has been identified as a major health problem, because it is the commonest hematological abnormality among older adults (1), and its negative impact seems to be involved in a number of health outcomes in this population. Common symptoms of anemia such as fatigue, dyspnea and difficulty in activities of daily living relate directly to the worse quality of life of older people affected (2, 3).

There are several studies relating anemia to disability (3, 4), mobility impairment (5, 6), cognitive decline (7-10), quality of life (10) and mortality (6, 11). More currently, the relationship of anemia with the frailty syndrome also has been studied (12, 13). It appears that anemia contributes to the development of frailty, and / or exacerbates the negative effects of the syndrome when it is already settled.

Frailty syndrome can be understood as a unique pathophysiological process that lead to dysregulation of multiple physiological systems. This dysregulation can lead to depletion of reserves and impaired ability to maintain homeostasis in the face of stressors (such as changes in environmental temperature and changes in health condition or infection). Anemia seems to have an important role in this process, leading to symptoms and signs of frailty (14, 15).

The relationship between anemia and frailty has been explored first in a case-control study that tested selected physiological parameters as potential correlates of frailty, showing an inverse correlation between interleukin-6 (IL-6) and hemoglobin or hematocrit in the frail group, but not in the nonfrail group, suggesting that frail subjects have evidence of inflammation and lower hemoglobin and hematocrit levels (12). After those first results, another study, based on data from Women´s Health and Aging Studies I and II, found that mildly low and low-normal hemoglobin (Hb) levels were independently associated with increased frailty risk in this sample of community-dwelling older women (13).

This paper aims to explore the relationship between anemia, hemoglobin concentration and frailty syndrome in older adults living in São Paulo, Brazil. More specifically, we used population-based data collected in 2010 to examine: 1) the associations between anemia and frailty status; 2) associations between hemoglobin concentration and frailty status; 3) associations between anemia, hemoglobin and each frailty criterion; and 4) associations between hemoglobin concentration and the number of frailty criteria.

Methods

Sample and procedures

This was a cross-sectional study, part of the third wave of SABE Study (Saúde, Bem-Estar e Envelhecimento [Health, Wellbeing and Ageing]) longitudinal survey. SABE Study began in 2000 involving a probabilistic sample of older adults

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(aged 60 years or older) residing in the city of São Paulo (n=2,143). The baseline sample was obtained with a two-stage stratified sampling method, following the framework of the 1996 National Household Survey based on geographic areas of the city. Individuals aged 75 years and older were oversampled to compensate for the greater mortality rate in this age group. Sample weights took this oversample into consideration in order to represent the population (16). A second wave of the study was carried out in 2006, and a third wave was conducted in 2010. In each new wave, a new sample of older adults between 60 and 64 years old is added following similar procedures used in the first wave. Details on the methodology of the study are described elsewhere (17, 18).

The total sample in the third wave 2010 had 1,345 older adults. Sample weights were recalculated based on Census 2010. There were 89 participants with incomplete data on blood counts. The final sample of the present study was composed by 1,256, which represent about 1.3 million older adults in São Paulo.

The 2010 data were collected in five stages, as described elsewhere (17). The first stage was a household face-to-face interview conducted by a single interviewer using a standardized questionnaire addressing the living conditions and health status of the older adult respondent. The second stage was a household visit during which a nutritionist and a dentist measured anthropometric data, determined physical performance and conducted a dental examination. Physiological specimens of blood and urine were collected in the third and fourth stages, respectively. In the fifth stage, an interviewer collected accelerometer data.

Blood samples were collected after an overnight fast of 10 to 12 hours, by trained registered nurses in the respondent's home in a sitting position by venipuncture. For transportation, blood samples were collected in specific vacuum locked glass tubes, previously identified with data from each individual, and conditioned in rigid and waterproof thermal boxes, provided with external closure devices. The boxes containing biological material were transported to the laboratory for processing. Sub-samples were stored in freezers for back-up.

The study was approved by the Research Ethics Committee at the University of São Paulo. Participation was voluntary, and a signed informed consent form was obtained of all participants in each wave.

Measures

Blood hemoglobin concentrations were determined at the laboratory of the Hospital of the Medical School at the University of São Paulo using an ADVIA 120 system (Siemens Healthcare Diagnostics, Germany). Anemia was defined using the WHO criteria (19). Women were considered anemic when they had a blood hemoglobin concentration of less than 12 g/dL, and men when they had concentration under 13 g/dL.

Frailty syndrome was evaluated according to the phenotype proposed by Fried et al (2001) (20). On the basis of these standardized criteria, participants were considered frail if they had three or more of the following: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Those five components were operationalized in this study as summarized in table 1.

Table 1
Frailty classification criteria for older adults (≥ 60 years old), SABE Study. São Paulo, Brazil, 2010

Criterion	Operational definition
Weight loss	≥ 3 kg in previous 3 months no due to dieting
Exhaustion	
	Self-report positive answer for more than three days from either of 2 questions on CES-D Scale: (a) How often in the past week have you felt that everything you did required an effort? (b) How often in the past week have you not been able to "get going"?
Weakness	Lowest 20% in grip strength (adjusted by gender and BMI)
	Men
	Strength ≤ 24.5 Kg for BMI ≤ 24.36
	Strength ≤ 25 Kg for BMI 24.37 – 26.99
	Strength ≤ 26.5 Kg for BMI 27.0 – 29.62
	Strength ≤ 30 Kg for BMI > 29.62
	Women
	Strength ≤ 14 Kg for BMI ≤ 25.01
	Strength ≤ 14 Kg for BMI 25.02 – 28.39
	Strength ≤ 15.5 Kg for BMI 28.40 – 32.55
	Strength ≤ 16 Kg for BMI > 30.55
Slowness	Slowest 20% of the SPPB walking test
	Men
	> 5.0 s for height ≤ 1.66 m
	> 4.1 s for height > 1.66 m
	Women
	> 5.2 s for height ≤ 1.52 m
	> 4.7 s for height > 1.52 m
Low physical activity level	Lowest 20% of caloric expenditure by gender
	Men 457.2 kcal
	Women 413.6 kcal

Note: BMI = Body mass index (kg/m2)

Associations between frailty and anemia were adjusted by independent controlling variables, included in three hierarchical blocks:

- Basic characteristics: gender and age.
- Clinical characteristics: self-reported chronic conditions

(hypertension, diabetes, chronic pulmonary disease, heart disease, stroke and arthritis), summarized as number of chronic conditions. Obesity was also included, based on BMI values ≥ 30 (21).

- Cognitive status: evaluated using the modified version of the Mini Mental State Exam (MMSE) validated for the SABE Study, due to the low level of schooling of the South American older adult population. This measure has 13 items that are less dependent upon schooling. Those with a score of 12 or less were classified as having cognitive impairment (22).

Statistical analysis

Descriptive statistics (mean and standard error) were calculated for the continuous variables and proportions were calculated for the categorical variables. Between-group differences were estimated using the Wald test of mean equality and the Rao-Scott test.

To assess the association between anemia, hemoglobin concentrations and frailty, we tested four different approaches. For the first analysis, we examined the association between frailty status (robust or frail) and anemia (classified according to the WHO criteria) using logistic regression. For the second analysis, we used logistic regression to examine whether continuous values of hemoglobin concentrations were associated with frailty status. For the third analysis, we used Poisson regression to examine whether continuous levels of hemoglobin concentrations were associated with the number of frailty characteristics (from 0 to 5, according to the proposed phenotype).

For all analyses, three hierarchical models were used. Model 1 adjusted by age. In model 1, gender was included as a covariate for the logistic regression using anemia because its cutoffs already consider gender differences; however models using hemoglobin concentration were stratified by gender. Model 2 added to Model 1 number of chronic conditions and obesity. In addition to all variables included in Model 2, Model 3 added cognitive impairment.

All analyses included sample weights and were adjusted for the complex sampling design. The data analyses were performed using Stata® version 11.

Results

In the study population, 60.9% were women and the mean age was 70 years. Table 2 displays the distribution of population, according to frailty status. Prevalence of frailty was 8.0%. The most prevalent frailty criterion was low physical

Table 2
Selected characteristics of older adults (≥ 60 years old) according to frailty status. SABE Study. São Paulo, Brazil, 2010 (weighted estimates)

	Robust	Frail	All participants
Hemoglobin concentration, g/dL (mean)*	14.3	13.3	14.2
Anemia (%)*	3.8	24.2	7.7
Gender (%)			
Male	39.7	32.4	39.1
Female	60.3	67.6	60.9
Age (mean) *	69.3	77.8	70.0
Self-report of physician diagnosed disease			
Hypertension (%)	66.5	76.1	67.2
Diabetes (%) *	24.8	36.8	25.8
Chronic respiratory disease (%)	9.1	9.8	9.1
Cardiovascular disease (%)	22.2	28.9	22.8
Stroke (%) *	5.4	21.8	6.7
Arthritis (%) *	31.3	51.0	32.8
Osteoporosis (%) *	18.4	29.4	19.3
Cancer (%) *	7.1	16.1	7.8
Number of chronic conditions (mean)*	1.8	2.7	1.9
Obesity (BMI ≥ 30 Kg/m2)	32.2	37.8	32.6
Cognitive impairment, modified version of MMSE < 12 (%) *	6.9	37.9	9.4
TOTAL	92.0	8.0	

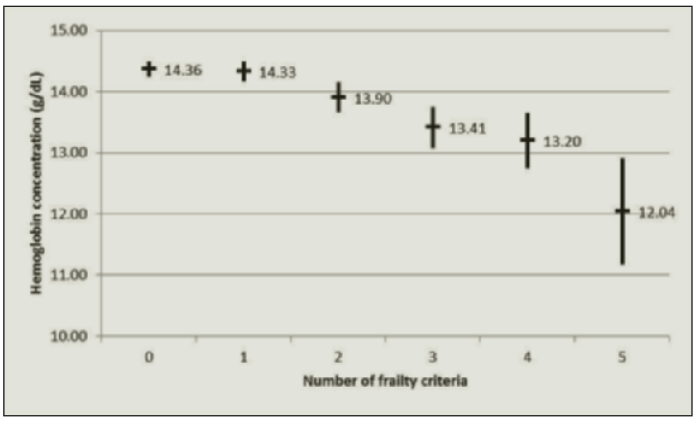
* p<0.05

activity (36.4%), followed by weakness (22.4%), slowness (19.7%), exhaustion (9.7%) and weight loss (5.2%). Those who were frail were older, had more chronic conditions, and were more likely to be obese and to be cognitive impaired. The mean hemoglobin concentration among older adults who were not frail was 14.3g/dL, but those who were frail had significantly lower levels (13.3g/dL). In the total sample, 7.7% were classified as having anemia. However, the prevalence of anemia was considerably higher among older adults who were frail (24.2%) than among those who were not frail (3.8%).

Next, we explored the associations between anemia and hemoglobin concentration to each of the frailty criterion, adjusted by age and gender (Table 3). When anemia was considered, there was significant association to low physical activity, weakness and slowness. In analyses using hemoglobin concentration, it showed statistical associations with all criteria among women, except for weight loss. On the other hand, among men, the only characteristic associated with hemoglobin concentration was weight loss.

Figure 1

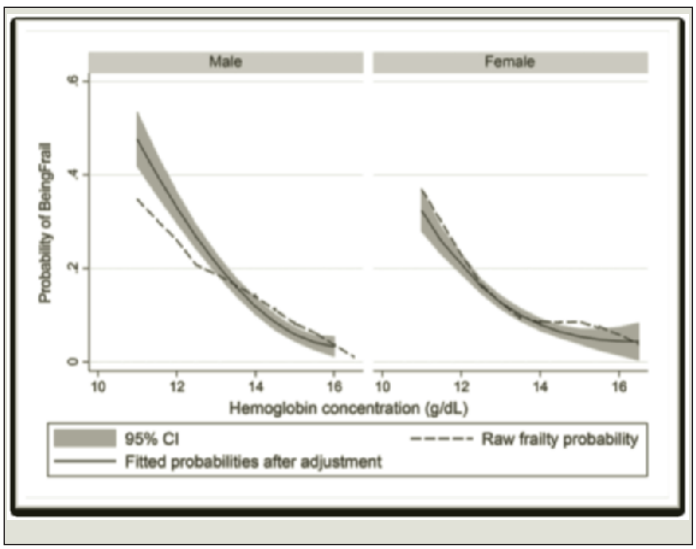
Mean hemoglobin concentrations and 95% confidence intervals according to the number of frailty criteria



Next we examined the association between anemia, hemoglobin concentration and frailty. Figure 1 shows lower levels of hemoglobin concentrations for those with higher the number of frailty characteristics. Table 3 shows the results of the logistic and Poisson regression analyses. Results indicate that individuals with anemia were 2.5 times more likely than those without anemia to be frail. When the analyses focused on hemoglobin concentration, the results showed that older adults with higher levels of hemoglobin concentration were less likely to be frail. Based on the results of the Model 3 of the logistic regression based on continuous levels of hemoglobin concentration, we estimated the predicted probability of being frail. Results are presented in Figure 2. Results indicate that a higher proportion of older adults with low levels of hemoglobin were frail. At 12 g/dL, probability of being frail is about 30% for men and 25% for women. At 14g/dL, probability of frailty is reduced to 10% for men and to less than 10% for women. Finally, results from the Poisson regression indicate that lower levels of hemoglobin were associated to higher number of frailty criteria. The effects were significant in all models.

Figure 2

Raw and fitted probability of being frail according to blood hemoglobin concentration, by gender



Discussion

In our study, anemia was found in 7.7% of the older adults, and the prevalence was higher in frail older adults. According to WHO, levels of anemia above 5.0% should be considered a public health problem (19). Therefore, levels found in our sample should be classified as a mild public health problem.

There are very few studies that examined the relationship between anemia and frailty. Previous studies have been focused in women and to our knowledge, this is the first paper addressing this association among men and women. We used four approaches which allowed us not only to analyze the relationship between hemoglobin and frailty when anemia is defined by WHO criteria, but also to explore whether hemoglobin concentration was associated with frailty status and the number of frailty components. None of the previous studies have explored the association between hemoglobin concentration and the number of frailty characteristics. We demonstrate that anemia and lower levels of hemoglobin concentrations are strongly associated to frailty, even after many controls are included in the analyses.

There are some mechanisms that can explain the role of anemia in the development of frailty syndrome. Anemia reduces the oxygen-carrying capacity, which can lead to tissue hypoxia, which in turn can result in a number of problems, including reduced submaximal and maximal aerobic capacity, sarcopenia, osteoporosis, cardiac dysfunction, and progression of renal disorders (5, 23). In this scenario, anemia could potentially contribute to the clinical manifestations of

Table 3
Results from the logistic regression for each frailty criterion, anemia and hemoglobin concentration in older adults (≥ 60 years old), adjusted by age and gender. SABE Study. São Paulo, Brazil, 2010

Frailty Criterion	Anemia	Hemoglobin Concentration	
		Male	Female
	OR [95% CI]	OR [95% CI]	OR [95% CI]
Low physical activity level	2.74*[1.75,4.37]	0.93 [0.77,1.12]	0.77*[0.69,0.87]
Weakness	1.91*[1.19,3.06]	0.96 [0.79,1.18]	0.72*[0.62,0.83]
Slowness	1.98*[1.22,3.20]	0.82 [0.65,1.04]	0.81*[0.70,0.94]
Weight loss	1.24 [0.56,2.78]	0.69**[0.48,0.99]	1.10 [0.83,1.47]
Exhaustion	1.59 [0.92,2.76]	0.82 [0.57,1.18]	0.80**[0.66,0.97]

§ Adjusted by age and gender for anemia, and age for hemoglobin concentration; * p<0.01; ** p<0.05

Table 4
Results of logistic and Poisson regression models for frailty status in older adults (≥ 60 years old). SABE Study. São Paulo, Brazil, 2010

	Model 1†	Model 2‡	Model 3§
Logistic regression	OR [95% CI]	OR [95% CI]	OR [95% CI]
Anemia	3.14*[1.92,5.15]	2.97*[1.74,5.07]	3.27*[1.89,5.65]
Hemoglobin concentration			
Male	0.63*[0.49,0.80]	0.69*[0.55,0.87]	0.70*[0.55,0.88]
Female	0.72*[0.58,0.89]	0.71*[0.57,0.89]	0.68*[0.54,0.85]
Poisson regression			
Hemoglobin concentration			
Male	0.92*[0.87,0.97]	0.94**[0.89,0.99]	0.94**[0.90,0.99]
Female	0.88*[0.83,0.93]	0.88*[0.83,0.92]	0.87*[0.83,0.92]

† Model 1: Adjusted by age and gender for anemia, and age for hemoglobin concentration; ‡ Model 2: Adjusted by age and gender for anemia, and age for hemoglobin concentration, number of chronic conditions and obesity; § Model 3: Adjusted by age and gender for anemia, and age for hemoglobin concentration, number of chronic conditions, obesity and cognitive impairment; * p<0.01; ** p<0.05

weakness, such as the occurrence of symptoms of exercise tolerance (24), as well as a reduction in physical activity, strength, and walking speed, all part of frailty phenotype.

This pathway can be confirmed with our results that show that anemia was associated to low physical activity, weakness and slowness. Xue and colleagues (25) had already demonstrated that the occurrence of weakness, slowness, and low physical activity preceded exhaustion and weight loss in 76% of the women who were nonfrail at baseline. Thus, anemia could be playing an important role in the initial manifestations of frailty. However, when we stratified the analysis using the hemoglobin concentration, this pathway can be confirmed among women but not among men. In men, lower hemoglobin levels seem to be associated to weight loss, which would be one of the latest manifestations of frailty according to Xue and colleagues (25). However, our results should be analyzed with caution given that the number of frail men who had lower levels of hemoglobin was small. These differences can also result from men having different pathways in the development of frailty in anemic older adults. To our knowledge, this is the first paper that analyzed this relationship among men, which limits our ability to contrast with previous studies.

The association between anemia and frailty may also indirectly reflect in part the effect of low-grade inflammation, which has long been accepted to play a major role in the development of chronic anemia in older adults (23, 26) and is also related to frailty through anemia-independent effects on other systems (27, 28)

The findings explored in Figure 2 also show some important results. After all adjustments of Model 3, the probability of being frail declines sharply for higher levels of hemoglobin. It is important to observe that when the WHO cutoffs are considered (12g/dL for women and 13g/dL for men) the probability of being frail is high (about 20%). This indicates that, regardless of other health conditions, the clinical diagnosis of anemia among older adults is associated with a high

susceptibility of being frail.

This study has some limitations. First, this study is cross-sectional; therefore, it cannot determine the direction of the association between anemia and frailty. But as discussed, oxygen transportation is one of the bases for the dysregulation of homeostasis that can lead to frailty. So, it would seem unlikely that frailty could cause anemia. Another limitation is that we do not have good measures of inflammation markers, such as interleukin-6, that could allow us to clarify all those associations described here. However, our study is based on a large population based cohort, with a representative sample of community-living older adults of both genders of the largest city in Brazil. Besides, this is first study based on a sample from Latin America, where demographic, epidemiological, and nutritional transitions are occurring at very rapid pace. Like other developing countries, Brazil does not have a sufficiently organized healthcare structure or policies to cope with these rapid transitional processes, which have a considerable impact on healthcare services and consequently the quality of life of older adults.

Conclusion

In conclusion, anemia was found in 7.7% of the older adults, and the prevalence was higher in frail older adults. We also found important associations between anemia, hemoglobin concentration and frailty; and these associations were independent from other important health conditions. Given the current cutoffs for anemia, when it is clinically detected, the probability of frailty is already around 20%. Therefore, health care professionals caring for older adults should be aware of the associations between lower levels of hemoglobin and frailty. This way, early treatment and strategies can be employed for avoiding, delaying or even reverting frailty syndrome.

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