PREDICTIVE VALUE OF LOW FERRITIN IN OLDER PERSONS WITH ANEMIA WITH AND WITHOUT INFLAMMATION: THE LEIDEN 85-PLUS STUDY

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To the Editor: Iron deficiency is a common cause of anemia, being found in more than 15% of older persons with anemia.[1,2] Serum ferritin levels strongly correlate with body iron stores[3] and are considered the best noninvasive test for the diagnosis of iron deficiency.[2,4] Ferritin therefore plays a central role in diagnostic and therapeutic algorithms for iron deficiency anemia in clinical practice,[5] although ferritin is also an acute-phase protein and may be high with acute and chronic inflammatory conditions such as infections, rheumatoid arthritis, and cancer.[2] Because the prevalence of inflammatory conditions is very high in old age,[6] it is not clear whether low ferritin can be used as a marker of low iron status in old age. Therefore, the association between low ferritin levels and anemia in old age in the presence and absence of inflammation was investigated.

METHODS

The present study is embedded in the Leiden 85-plus Study, a population-based prospective follow-up study of 512 85-year-old inhabitants of Leiden, the Netherlands.[7] Participants who used iron supplements were excluded from the present study. At age 85, ferritin levels were determined using an immunological assay (E170, Roche, Almere, the Netherlands). Low serum ferritin was defined as ferritin less than 20 μg/L for men and less than 15 μg/L for women.[8] C-reactive protein (CRP) levels were measured using a Hitachi 747 automated analyzer (Hitachi, Tokyo, Japan). High CRP was defined as CRP greater than 5 mg/L. Hemoglobin levels and mean corpuscular volume (MCV) were determined annually (aged 85–90) using an automated analysis system (Coulter Counter, Coulter Electronics, Hialeah, FL). Anemia was defined according to criteria of the World Health Organization (hemoglobin <130 g/L for men and <120 g/L for women).[9]

RESULTS

One hundred seventy-eight participants (34.8%) were male. The prevalence of anemia was 23.8% (n = 122); 35 participants (6.8%) had low ferritin levels. Participants with low ferritin levels had more than twice the risk of having anemia than participants with normal ferritin levels (odds ratio (OR) = 2.2, 95% CI = 1.1–4.5). In participants with high CRP levels (n = 171), low ferritin was associated with a risk of anemia that was 7 times as great (OR 7.0, 95% CI = 1.4–34.9). No significant association was found between low ferritin and anemia in participants with normal CRP levels (n = 341, OR 1.7, 95% CI = 0.7–4.2).

The lowest hemoglobin levels were found in participants with low ferritin and high CRP levels (mean (SE) hemoglobin level 99 g/L (11 g/L) in men and 112 g/L (8 g/L) in women, Figure 1). Similar results were found for MCV (data not shown). Low ferritin was also associated with an additional decline in hemoglobin level (additional annual change in hemoglobin -2 g/L, 95% CI = -4.0 to -0.3 g/L) and MCV (additional annual change in MCV -0.78 fL, 95% CI = -1.3 to -0.22 fL) in the years thereafter. Again, these associations were most apparent in participants with high CRP levels. In this subgroup, low ferritin was associated with an additional annual decline in hemoglobin level of 5 g/L (additional annual change in hemoglobin level -5 g/L, 95% CI = -10 to -0.4 g/L) and an additional annual decline in MCV of 2.2 fL (additional annual change in MCV -2.2 fL, 95% CI = -3.6 to -0.71 fL).

DISCUSSION

The present study shows that low ferritin is associated with anemia in old age. This association is most prominent in older individuals with signs of an inflammatory host response in the plasma.

The diagnostic value of serum ferritin levels to detect iron deficiency in patients with anemia, infection, and inflammation has been questioned because of ferritin's "acute phase" properties. The findings presented here show the significance of measuring ferritin levels in older individuals, especially in those with infection or inflammation. In these patients, a low level of ferritin is a specific marker of iron status because of its "acute phase" properties; iron status must be poor when low ferritin levels are found in the presence of systemic inflammation.

How can the occurrence of low ferritin levels in the presence of inflammation be explained? Older patients with gastrointestinal tumors or chronic inflammatory diseases will have low iron stores because of gastrointestinal blood loss, malnutrition, or malabsorption of food-bound iron. In these individuals, iron stores may have become too low to facilitate a rise in ferritin in response to inflammation. Upregulation of hepcidin—the main regulator of iron homeostasis—is an alternative molecular pathway to explain these findings. Proinflammatory cytokines, particularly interleukin 6, induce the production and secretion of hepcidin by hepatocytes. Hepcidin binds to the membrane protein ferroprotein and induces its internalization and degradation in lysosomes, blocking the export of iron from cells.[10] Although a preliminary analysis in the Invecchiare in Chianti Study could not demonstrate higher urinary hepcidin levels

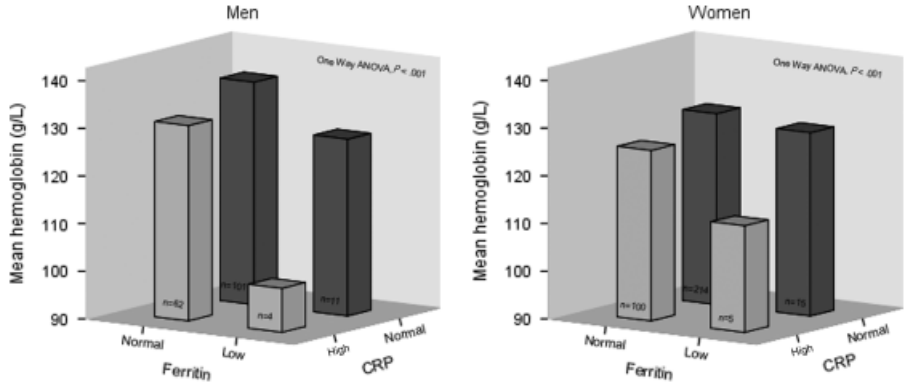

Figure 1. Mean hemoglobin levels according to ferritin status and C-reactive protein (CRP) status for men and women at age 85. Low ferritin was defined as ferritin <20 μg/L for men and <15 μg/L for women. High CRP was defined as CRP >5 mg/L. ANOVA = analysis of variance.

in older individuals with anemia of inflammation,[11] the hypothesis should be tested in other population-based studies, preferably using serum hepcidin assays, which have recently become available.[12]

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ACKNOWLEDGMENTS

Conflicts of interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

The Leiden 85-plus Study was partly funded by an unrestricted grant from the Dutch Ministry of Health, Welfare and Sports. The Leiden 85-plus Study is a collaborative project of the Department of Gerontology and Geriatrics (RGJ Westendorp) and the Department of Public Health and Primary Care (J Gussekloo) of the Leiden University Medical Center, Leiden, the Netherlands.

Author Contributions: Professor Westendorp had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J. Gussekloo and R.G.J. Westendorp. Acquisition of data: J. Gussekloo, A.J.M. de Craen, G.J. Blauw, and R.G.J. Westendorp. Analysis and interpretation of data: W.P.J. den Elzen, J. Gussekloo, J.M. Willems, A.J.M. de Craen, G.J. Blauw, W.J.J. Assendelft, and R.G.J. Westendorp. Drafting of the manuscript: W.P.J. den Elzen, J. Gussekloo, and R.G.J. Westendorp. Critical revision of the manuscript for important intellectual content: W.P.J. den Elzen, J. Gussekloo, J.M. Willems, A.J.M. de Craen, G.J. Blauw, W.J.J. Assendelft, and R.G.J. Westendorp. Statistical analysis: W.P.J. den Elzen., J. Gussekloo, A.J.M. de Craen, and R.G.J. Westendorp. Obtained funding: J. Gussekloo and R.G.J. Westendorp. Administrative, technical, or material support: W.P.J. den Elzen, J. Gussekloo, A.J.M. de Craen, and G.J. Blauw. Study supervision: J. Gussekloo, A.J.M. de Craen, W.J.J. Assendelft, and R.G.J. Westendorp.

Sponsor's Role: The sponsor had no role in the design, methods, subject recruitment, data collections, analysis, or preparation of the letter.

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EVALUATION OF SHORT-TERM EFFECTIVENESS OF THE DISEASE MANAGEMENT PROGRAM "DI.PRO.DI." ON CONTINUITY OF CARE OF PATIENTS WITH CONGESTIVE HEART FAILURE

To the Editor: This study aimed to assess the early effectiveness of a disease management program (DMP), called "Dimissione Protetta Difficile" (Di.Pro.Di) conducted by personnel from the intensive care unit (ICU) of Public Hospital S. Paolo, Naples, Italy. This hospital serves an area of 31 km^2 with 211,000 inhabitants (20.6% aged $\geq$ 65). This controlled nonrandomized trial aimed to stabilize patients fully with three home visits in the 3 months after discharge. Rehospitalizations and hospital length of stay of elderly patients suffering from congestive heart failure (CHF) after discharge from the ICU were focused on, because reducing these outcomes is a crucial challenge for developed countries because of their increasing elderly population. The literature shows that DMPs improve care.[1–3] Comparing these outcomes in treatment and control groups, using conventional statistic tests, it was observed, albeit in small numbers, that Di.Pro.Di significantly reduces the number and risk of rehospitalizations and total hospital length of stay.

METHODS

Multidisciplinary teams evaluate patients and educate their families. Patients receive up to three domiciliary visits in the 3 months after discharge. Telephone communication integrates these visits. A physician evaluates the patient's condition and, if there is mild deterioration, modulates the therapy or orders further investigations. If there is major deterioration, the patient is rehospitalized. If the patient's health condition is stable, the patient is fully discharged.[4] The group of patients enrolled in the program (treatment group, TG) were benchmarked with a group of patients hospitalized in the same structure but not enrolled in the program (control group, CG). The outcomes of a subset of patients enrolled in the TG were retrospectively analyzed. A *t*-test and a chi-square test with Yates's correction were performed to assess the statistical significance of the results and the homogeneity between groups.

Protocol

Two hundred fifty patients were involved in the Di.Pro.Di, approximately 20 at any one time. Sixteen patients met the inclusion criteria: aged 65 and older, New York Heart Association classification II or III, high risk of rehospitalization, and adequate family support.

The hospital provides the required predosed drugs. During each visit, a gerontologist or cardiologist and a nurse, supported by a car driver or orderly, perform and electrocardiogram, oximetry, blood-gas analysis, capillary blood glucose, and urinalysis.

Oxygen therapy or pulmonary ventilation might also be required. After the third visit, the patient is discharged from the Di.Pro.Di and, according to the stability criteria, rehospitalized or transferred to local health services.

RESULTS

The results of this study are summarized in Table 1.

Outcomes

TG After Di.Pro.Di

The TG included 16 patients with a mean age of 81.0 $\pm$ 8.8. Four patients (25%) were rehospitalized, for a total of four rehospitalizations, (mean 0.3, maximum of one per patient). The total hospital length of stay was 17 days (mean total 1.1 $\pm$ 2.1 days per patient).

TG Before Di.Pro.Di

Six patients in the TG were investigated retrospectively for the year before the Di.Pro.Di. Five of them (83%) were rehospitalized, for a total of 11 rehospitalizations (mean 1.8 hospitalizations; maximum 4 per patient). Total hospital length of stay for these patients was 69 days (mean total 11.5 $\pm$ 7.2 days per patient).

Control Group

The CG included 18 patients with a mean age of 79.5 $\pm$ 9.6. Eleven (61.1%) were rehospitalized, for a total of 17 rehospitalizations (mean 0.9, maximum 3 per patient). Total hospital length of stay was 234 days (mean total 13.0 $\pm$ 7.7 days per patient).

Homogeneity of TG and CG

No statistically significant difference was observed between the CG and TG before Di.Pro.Di in terms of mean age, number of rehospitalizations, and hospital length of stay. In both groups, the number of rehospitalizations and hospital lengths of stay were slightly higher than reported in previous studies,[5,6] possibly because the mean age was slightly higher.

Table 1. Rehospitalizations and Hospital Length of Stay According to Group in the 3 Months After Discharge

Outcome	Control Group (n = 18)	Treatment Group	
		Before Di.Pro.Di* (n = 6)	After Di.Pro.Di (n = 16)
Rehospitalizations, n			
Patients rehospitalized	11	5	4
Rehospitalizations	17	11	4
Length of hospital stay			
Days per group, n	234	69	17
Days per patient, mean $\pm$ standard deviation	13.0 $\pm$ 7.7	11.5 $\pm$ 7.2	1.1 $\pm$ 2.1

*Disease management program "Dimissione Protetta Difficile" (Di.Pro.Di).