European Geriatric Medicine 3 (2012) 277–280

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Research paper

Increased ferritin levels could reflect ongoing aging-associated inflammation and may obscure underlying iron deficiency in the geriatric population

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ARTICLE INFO

Article history:
Received 29 March 2012
Accepted 10 June 2012
Available online 12 July 2012

Keywords:
Inflammaging
Acute-phase response
Ferritin
Iron deficiency
Inflammation

ABSTRACT

Background and aim: Ferritin level is decreased in iron deficiency (ID) and increased in inflammation as an acute-phase reacting protein. In the case of inflammation ferritin, level may not decrease even if ID is present. Inflammation is regarded as one of the mechanisms of aging. This subclinical systemic inflammatory state is named as "inflammaging". The aim of this study is to assess whether serum ferritin levels could indicate aging-associated inflammation rather than ID in older adults.
Methods: Consecutive 1310 patients admitted to the geriatric medicine outpatient clinic were enrolled. The clinical conditions, which could alter acute-phase reactants, were excluded. ID diagnosis was made by transferrin saturation (< 15%), MCV and serum iron. Patients with increased levels of either one of Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC), or decreased level of albumin were diagnosed as having subclinical inflammatory state. The correlations of ferritin with those groups were analyzed.
Results: Mean age was 71.8 ± 6.9 years and 827 (63.1%) were female. Ferritin levels were significantly higher in patients with subclinical inflammatory state and significantly lower in patients with ID. The interrelationships of the ferritin with acute-phase reactants were stronger than its relationship with the ID.
Conclusion: The results of this study suggested that the ferritin level can increase with aging as a part of the ongoing asymptomatic chronic systemic inflammatory state called inflammaging. Inflammaging can result with increased ferritin levels, even if there is ID. Normal or elevated levels of ferritin in the geriatric population should not exclude ID in clinical practice.

1. Introduction and aim

Ferritin is the major protein associated with stored intracellular iron, both in the cytoplasm and mitochondria, and low level of ferritin confirms iron deficiency (ID) [1]. On the other hand, ferritin is also an acute-phase reactant and a typical marker of inflammation. The level of ferritin increases during active inflammation and other acute-phase reactions [2–4]. In the case of inflammatory state or existing acute-phase reaction, the level of ferritin may not be decreased even if the state of ID is present at the same patient.

Aging is associated with chronic ongoing subclinical inflammatory status [5]. Inflammation is regarded as a mechanism of aging and it is known that some inflammatory cytokines especially IL-6 and TNF-α increase with aging regardless of the inflammation or infection [6]. Activation of the inflammatory pathways appears to be linked to many aging systems, so the term "inflammaging" has come up to indicate the physiological and molecular changes consistent with the aging process that are known to be associated with chronic activation of the inflammatory pathways and chronic inflammation [6]. This term "inflammaging" indicates that healthy aging is accompanied by a low-grade chronic inflammatory status [5–9].

The aim of this study is to assess whether ferritin levels are a part of the inflammatory process that is usually seen in the normal healthy aging, and whether ferritin can be a marker of aging-associated inflammation. Patients with ID and the patients with altered acute-phase reactants were compared in terms of ferritin levels to test, which one of them is significantly marked by the ferritin level. The hypothesis of the study was that ferritin is a better indicator of aging-associated inflammation rather than ID in older adults.

2. Patients and methods

Consecutive 1310 patients aged 65 years and over admitted to geriatric medicine outpatient clinic were enrolled in the study. Comprehensive geriatric assessment, nutritional assessment,

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1878-7649/$ – see front matter
http://dx.doi.org/10.1016/j.eurger.2012.06.005

physical examination, comprehensive clinical file examination, and appropriate laboratory tests were performed to determine all chronic diseases, infectious or inflammatory events or diseases, and all comorbidities of every patient. Patients with the conditions which can cause acute-phase reaction, were excluded. Exclusion criteria included all acute and chronic infections, chronic inflammatory diseases, rheumatologic diseases, malignancies, acute trauma, and acute hemorrhage. Furthermore, patients with malnutrition (determined by the WHO criteria and Mini Nutritional Assessment Score) were also excluded.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC), serum albumin, serum iron, iron binding capacity, and ferritin levels were determined. Patients with transferrin saturation lower than 15% were considered as having ID. ID diagnosis was supported with low mean corpuscular volume (MCV) and serum iron levels. Patients who had increased levels of either one of ESR, CRP, WBC, or decreased level of albumin were classified as patients with subclinical inflammatory state. Abnormal lab parameter levels were determined according to the reference ranges of the laboratory, which were 0 to 0.8 mg/dl for CRP, counts/μl for WBC, 3.2 to 4.8 g/dl for albumin, 0 to 40 mm/h for ESR in women and 0 to 45 mm/h ESR for men. Normal MCV levels were taken as 81 to 99 fL and normal ferritin range in the laboratory was 13 to 150 ng/mL. Data of patients having both ID and subclinical inflammatory state were also analyzed. Relationships of the ferritin with these groups were analyzed.

Categorical variables are presented as percentages, normally distributed continuous variables as mean ± SD, and skew distributed variables as median (minimum-maximum). Categorical variables were compared by Chi^2 test and continuous variables were compared with Mann Whitney U test or *t*-test, where appropriate. Correlation analysis of ferritin and other continuous variables were performed by Spearman analysis. Linear regression analysis was performed to test correlations of ferritin levels. Patients with ID, subclinical inflammatory state and both were put into equation. The significant results are given with beta, *t*, *P* values and 95% confidence interval. For conducting the statistical analysis SPSS 15.0 for Windows was used and a *P* value below 0.05 was considered as statistically significant.

3. Results

Mean age of the study population was 71.8 ± 6.9 years and 827 (63.1%) were female. Number of patients in the subclinical inflammatory state group was 366 (27.9%) and 75 (5.7%) of the total population had ID. General characteristics and laboratory results of the study population are given in Table 1. Gender distribution was similar in all groups. Mean age was similar between patients with ID and without. However, patients with subclinical inflammatory state were significantly older than the patients without ($P = 0.025$).

Ferritin levels were significantly higher in patients with subclinical inflammatory state when compared to patients without (75.5 [2.1–789], vs. 60.7 [3.2–680], respectively; $P = 0.001$) (Fig. 1). Ferritin levels were significantly lower in patients with ID when compared to the patients without (27.4 [3.9–504], vs. 66.7 [2.1–789], respectively; $P < 0.001$) (Fig. 2). Correlation analyses showed that ferritin levels had a weak but significant correlation with serum iron ($r = 0.086$, $P = 0.002$), iron binding capacity ($r = -0.164$, $P < 0.001$), transferrin saturation ($r = 0.111$, $P < 0.001$), MCV ($r = 0.123$, $P < 0.001$), WBC count ($r = 0.086$, $P = 0.002$), ESR ($r = 0.129$, $P < 0.001$), CRP ($r = 0.187$, $P < 0.001$), and albumin ($r = -0.063$, $P = 0.023$).

Results of linear regression analysis revealed that the relationship of ferritin with acute-phase reactants was stronger than its relationship with ID (for subclinical inflammatory state beta: 0.16, *t*: 5.71, %95 CI: 19.72; 40.35, $P < 0.001$; for ID beta: –0.05, *t*: –1.35, %95 CI:–43.84; 8.04, $P = 0.176$; for ID and subclinical inflammatory state existing together beta: –0.09, *t*: –2.24, %95 CI: –82.69; –5.56, $P = 0.025$).

4. Discussion

The results of this study revealed that the association of ferritin levels with inflammatory state is stronger than its association with ID in older adults free from documented infection, inflammation, malignancy, hemorrhage, trauma, and malnutrition. Ferritin level can increase with aging as a part of the low-grade chronic inflammatory state, which occurs, with aging, so called inflammaging.

Aging is associated with low-grade chronic inflammation [5]. Inflammation is regarded as one of the mechanisms of aging and it has been indicated that activation of inflammatory pathways is linked to many aging systems [6]. In older adults, a chronic subclinical inflammatory status is a common finding and in recent years a strong relationship between serum inflammatory markers and adverse health outcomes have been identified [5,6]. This chronic inflammatory state has been referred to as inflammaging [10,11]. Inflammaging is a low-grade, asymptomatic, controlled, nonpathological, systemic inflammatory state [7] and has been demonstrated in healthy elderly individuals by the increasing circulating levels of inflammatory substances and cytokines which in turn triggers the acute-phase response and triggers release of inflammatory proteins [7,9,12–15]. It is important to remember that increases of inflammatory markers are two to four fold and thus far from the increases of acute inflammation [16]. Inflammaging results from

Table 1
General characteristics and the laboratory results of the study population.

	Total sample ($n = 1310$)	Subclinical inflammatory state (+) ($n = 366$)	Subclinical inflammatory state (–) ($n = 944$)	ID (+) ($n = 75$)	ID (–) ($n = 1235$)	Patients with both ID and subclinical inflammatory state ($n = 35$)
Age[a]	71.8 ± 6.9	72.5 ± 7.2	71.6 ± 6.8	72.6 ± 5.9	71.8 ± 6.9	73 ± 5.3
Gender (F)	827 (63.1%)	245 (66.9%)	582 (61.7%)	48 (64%)	779 (63.1%)	23 (65.7%)
Ferritin[b] (ng/mL)	64.4 (2.1–789.0)	75.5 (2.1–789)	60.7 (3.2–680)	27.4 (3.9–504)	66.7 (2.1–789.0)	25.6 (6.2–303.0)
WBC (count/μl)	6500 (2800–18,000)	7200 (2800–18,000)	6300 (2900–11,200)	7200 (2800–18,000)	6500 (2900–17,900)	7600 (2800–18,000)
ESR (mm/h)	15 (2–95)	28 (2–95)	12 (2–45)	23.0 (2–75)	15 (2–95)	28 (2–75)
CRP (mg/dl)	0.35 (0.01–20.5)	1.01 (0.10–20.5)	0.32 (0.01–0.80)	0.51 (0.10–7.20)	0.35 (0.01–20.5)	1.07 (0.10–7.20)
Albumin (g/dl)	4.3 (2.8–9.2)	4.1 (2.9–7.0)	4.3 (3.2–9.2)	4.2 (3.5–4.8)	4.3 (2.9–9.2)	4.1 (3.5–4.7)
MCV[c] (fl)	86.9 ± 7.1	86.6 ± 5.8	87.1 ± 7.5	74.6 ± 4.4	88.1 ± 4.5	82.6 ± 7.2
Serum iron	114.6 ± 60.2	110.3 ± 69.3	116.3 ± 56.2	39.0 ± 13.9	119.2 ± 58.9	37.9 ± 9.9

ID: iron deficiency; F: Female; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MCV: mean corpuscular volume.
[a] Patients with subclinical inflammatory state were significantly older than the patients without ($P = 0.025$).
[b] Ferritin level was significantly lower in iron deficiency ($P < 0.001$) and significantly higher in subclinical inflammatory status group ($P = 0.001$).
[c] MCV was significantly lower in iron deficiency group than the patients without iron deficiency.

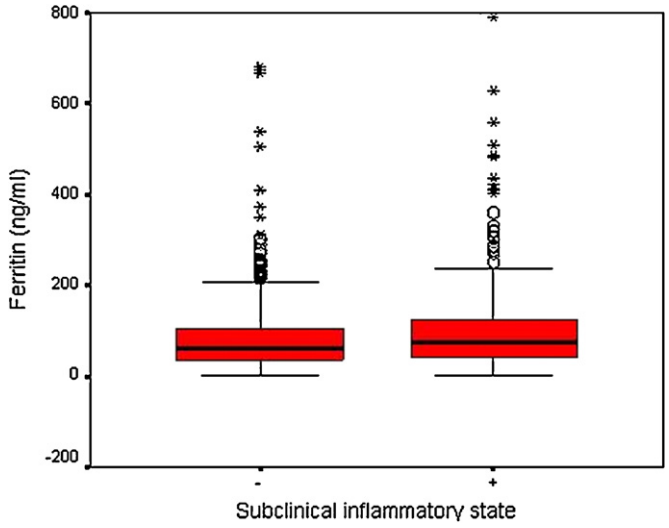

Fig. 1. Distribution of ferritin levels in patients with and without subclinical inflammatory state in the studied geriatric population (75.5 [2.1–789], vs. 60.7 [3.2–680], respectively; $P = 0.001$).

several factors including increased numbers of dysfunctional cytokine secreting senescent cells, altered body composition (increased body fat and redistribution of fat tissue with aging, thus, increases in TNF-α and IL-6 producing adipocytes), age-related hormonal deficiency, age-related increase in free oxygen radicals, multiple chronic diseases, life exposition to various stimulators of inflammation, history/number of infections, history of trauma, chronic stress, genetic factors, and lifestyle factors [5,6,9]. Inflammaging is a predictor and yet a modulator for the development of many age-related diseases. It is accused to be a predictor of late life vulnerability, immune dysfunction, frailty, sarcopenia, anorexia, disability, falls, atherosclerosis, diabetes mellitus, osteoporosis, Alzheimer's disease, depression, anemia, sleep disturbances, and even mortality [5,6,9,17]. In this present study, individuals free from diseases or states that could trigger inflammatory response were examined. The change in the acute-phase response markers can therefore be ascribed to be due to the age-associated increases in inflammatory processes, so called inflammaging. One striking result of the study discloses that the patients in the subclinical inflammatory state group are significantly older than the patients without. As in this setting older adults who do not have any infection or inflammation were enrolled after comprehensive examination and as it was determined that the group with altered inflammation markers were older than the group without, this result can be interpreted as aging is related with inflammation, and inflammatory markers increase with aging despite the absence of any acute or chronic inflammation. The relationship between ferritin and this subclinical inflammatory state was examined and found to be linked in this study.

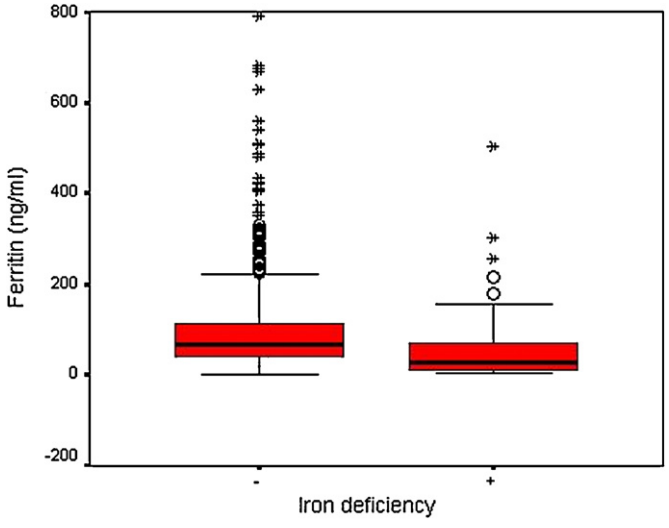

Fig. 2. Distribution of ferritin levels in patients with and without iron deficiency (27.4 [3.9–504], vs. 66.7 [2.1–789], respectively; $P < 0.001$).

Iron metabolism parameters and inflammatory state are closely linked. Iron status is influenced by inflammation [2]. The control of iron metabolism is re-organized by the primary mediators of the acute-phase response, which are TNF-α and IL-1 [2]. Augmented ferritin synthesis, thus an elevated serum ferritin level is a part of the acute-phase response [4]. Serum ferritin and transferrin saturation are regarded as the most reliable indicators of iron status and in the diagnosis of ID a low level of serum ferritin is usually expected. However, as ferritin is an acute-phase reactant, levels may be elevated in cases of inflammation and the diagnosis of ID can be difficult in diseases and states in which there is an acute-phase response [3]. Therefore, the ongoing subclinical inflammatory state occurring with aging can result with increased ferritin levels, even if there is ID.

One limitation of this study should be mentioned. Definitive diagnosis of ID could be made by determining iron stores by bone marrow aspiration, or other markers such as the serum soluble transferrin receptor, the ratio sTfR/log ferritin and hepcidin could be performed. However, bone marrow aspiration could not be performed to 1310 patients for a study because of ethical reasons. Therefore, diagnosis of ID was made according to low transferrin saturation levels and further supported by low MCV and low serum iron levels.

In conclusion, ferritin level can increase with aging as a part of the asymptomatic ongoing systemic inflammatory state called inflammaging. As ferritin levels can rise in older adults just due to advanced age, ferritin level is not a reliable marker of ID in the geriatric age group. Therefore, in the diagnosis of ID using ferritin alone can cause under-diagnosing ID in older adults. Although decreased levels of ferritin classically indicate ID, normal or elevated ferritin levels in the geriatric age group should not exclude underlying ID. This issue is clinically more important in the patients with malignancy-associated iron depletion since the sign of many cancers is the ID [18].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Ethical statement

This study protocol is consistent with the declaration of Helsinki and respects the ethical standards.

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