High Ferritin Level and Malnutrition Predict High Risk of Infection-Related Hospitalization in Incident Dialysis Patients: A Japanese Prospective Cohort Study

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Abstract

Aims: To clarify the relationship between serum ferritin and infectious risks.

Methods: We evaluated all hospital admissions due to infections, clinical biomarkers and nutrition status in 129 incident Japanese dialysis patients during a median follow-up of 38 months.

Results: Kaplan-Meier analysis revealed that the period without infections requiring hospitalization was significantly shorter in ferritin > median (82.0 ng/mL) group than in the ferritin < median group (log-rank test = 4.44, P = 0.035). High ferritin was associated with significantly increased relative risk (RR) of hospitalization for infection (Cox hazard model = 1.52, 95% CI = 1.06–2.17). The number of hospitalization days was gradually longer in patients with high ferritin levels and malnutrition.

Conclusion: Although serum ferritin levels were low, and doses of iron administered to dialysis patients in Japan are generally lower than in Western countries, an elevated ferritin level associated with increased risk of infection, particularly in patients with poor nutritional status.

Introduction

Patients with chronic kidney disease (CKD) show increased premature mortality compared to the general population. Infection is a frequent cause of hospitalization in patients with end-stage renal disease (ESRD) and the second leading cause of death after cardiovascular disease (CVD) [1]. Various factors including altered immune dysfunction, protein-energy wasting (PEW), and co-morbidities are thought to contribute to increased infection risk in this patient group [2]. Indeed, the risk of infection was inversely proportional to kidney function [3], and in dialysis patients up to 35% of all hospitalizations were related to a primary diagnosis of infection [4].

Even though the introduction of erythropoiesis-stimulating agents (ESAs) into clinical practice was a major breakthrough in the treatment of renal anemia [5], management of anemia in this patient group is still a challenging task [6], and often yields conflicting outcomes, including mortality in patients with ESRD [7]. While the treatment of renal anemia is achieved primarily with ESA, iron supplementation is necessary in patients who also have iron deficiency anemia [8]. However, with iron supplementation, particularly in the case of intravenous (IV) iron, it is necessary to monitor iron status carefully to avoid the adverse effects of iron, including iron overload, toxicity from oxidative stress, and increased infection risk [9].

Although ferritin is a widespread biomarker of iron status, it has the limitation that it is also affected by liver disease, malignancy, infection, and

inflammation, due to its acute-phase protein characteristics and, therefore, it is not entirely specific for body iron stores [10]. Inflammation is a common complication in ESRD patients and associates with the uremic milieu [11,12]. Thus, ferritin levels are influenced by the inflammatory status and are not reliable to detect true iron deficiency [13]. In Japan, the doses of IV iron administered to ESRD patients have historically been considerably lower than doses used in Western counties. Indeed, lower ferritin levels were observed in Japanese dialysis patients in an international large-scale cohort study [14]. Moreover, inflammation in Japanese CKD patients is suggested to be less extensive than in patients from other countries; C-reactive protein (CRP) levels reported in Japanese studies are much lower than those in Western CKD patients [15,16]. Nonetheless, one study reported that elevated serum ferritin level was associated with increased mortality in Japanese ESRD patients [17]. To the best of our knowledge, studies evaluating the relations between risk of infection, serum ferritin and nutritional status are lacking. The present study therefore aimed to examine whether serum ferritin level at baseline predicts infection-related hospitalization and whether poor nutritional status may influence this relation in Japanese incident dialysis patients.

Subjects and Methods

Study design and patients

Incident dialysis patients were enrolled in the study between June 2007 and February 2013 at the Masuko Memorial Hospital and the Meiyo Clinic in Aichi prefecture, Japan. This study was part of an ongoing prospective cohort study approved by the Ethics Committee of the Nagoya University Graduate School of Medicine (No 2012-0241). Informed consent was obtained from all patients before participating in this study. Exclusion criteria were as follows: age older than 75 years, acute severe infectious disease, severe liver dysfunction, and administration of steroids and/or immunosuppressants. The study included a total of 129 patients (84 men and 45 women), with a mean age of 59 ± 11 years. Administration of ESA and oral or IV iron supplementation was carried out in line with the guidelines released by the Japanese Society for Dialysis Therapy [18]. In practically all patients, the IV iron preparations used were iron saccharate and oral iron supplementation was with sodium ferrous citrate. Baseline demographic and clinical characteristics, such as age, gender, primary cause of renal disease, current medications and blood access were extracted from the patients' medical records. Smoking habits and history of CVD, which was defined as cardiac, cerebrovascular, or peripheral vascular disease, were assessed during patient interviews. The primary causes of renal disease were glomerulonephritis (n = 33), nephrosclerosis (n = 12), diabetic nephropathy (n = 63) due to diabetes mellitus type 1 (n = 6) and type 2 (n = 57), polycystic kidney

disease (n = 5), and other (n = 5) or unknown causes (n = 11). In the 121 patients who were on hemodialysis (HD), blood access was provided by arteriovenous fistula in most cases (n = 93), or by a graft (n = 7), or a double lumen catheter into the jugular vein (n = 16); none of these 121 patients showed signs of infection. The remaining eight patients, who were on peritoneal dialysis (PD), all received a peritoneal catheter before initiating PD. Subjective global nutritional assessment (SGA) was used to evaluate the patient's nutritional status [11]. Briefly, each patient was given a score based on the clinical judgment of four subscales representing their recent weight change, dietary intake, and gastrointestinal symptoms, loss of subcutaneous fat, and signs of muscle wasting. We classified the patients into three groups using SGA scores: A, well nourished; B, mild/moderately malnourished; and C, severely malnourished.

Blood sampling and laboratory analysis

Blood samples were collected from each subject within one month of the first dialysis session. Sample collections from the HD patients were performed at the start of a dialysis session at the outpatient clinic. Full blood cell count, serum albumin, total cholesterol, high-density lipoprotein cholesterol, uric acid, creatinine, intact parathyroid hormone, ferritin, and CRP levels were determined by the clinical laboratory at each clinic using standard protocols and automated analyzers. Serum interleukin (IL)-6 levels were measured from

samples stored at −30°C using a commercially available enzyme linked immunosorbent assay kit (R & D systems, Inc., Minneapolis, MN).

Statistical analysis

Continuous variables are shown as mean ± standard deviation (SD) and/or median and interquartile range (25th to 75th percentiles). Comparisons of the baseline characteristics and laboratory biomarkers for the continuous variables between the high-ferritin group (i.e. serum ferritin > median) and the low-ferritin group (i.e. serum ferritin < median) were performed with Wilcoxon singed-rank test. Between group comparisons for the categorical variables were performed using the chi-square test. The duration of the period between initiating dialysis and the first hospitalization due to infection was analyzed with the Kaplan-Meier method, and comparisons were performed with the log-rank test. The Cox proportional hazards model was used to calculate relative risk (RR) of hospitalization due to infection after dialysis was initiated. Data are shown as RR with 95% confidence intervals (CI), and analyses were adjusted for age, gender, log ferritin, log CRP, and log IL-6. The proportionality of hazards was examined graphically using log-minus-log survival plots. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 10.0.2 (SAS Campus Drive, Cary, NC, USA 27513).

Results

Patient characteristics and laboratory biomarkers

Baseline clinical characteristics and selected laboratory biomarkers for well-established mortality risk factors among the 129 ESRD patients (84 men, 65.1%) enrolled in this study are presented in Table 1 and Table 2, respectively. Patients were placed into two groups according to their serum ferritin level in relation to the median ferritin value of 82 ng/mL: high-ferritin group with levels above the median and the low-ferritin group with levels below the median. The mean age was 59 ± 11 years and there were more smokers in the high-ferritin group. Although 16 patients had CV catheter as a blood access at the baseline, no patients needed a permanent CV catheter during the observation period. Total cholesterol was significantly lower (P = 0.046), and inflammatory markers including serum CRP (P = 0.0035) and IL-6 (P = 0.047) were significantly higher, in the high-ferritin group than in the low-ferritin group. Other biomarkers did not differ between the groups.

Hospitalization due to infection

Patients were followed up for at least 1 month or until death, transfer to another clinic, or renal transplantation. The median duration of follow-up was for 38.1 months (range, 1–74.0 months). During the follow-up period, 13 patients died from infectious disease (sepsis) (n = 3), sudden death (n = 5), myocardial infarction (n = 1), cancer (n = 1), liver failure (n = 1), stroke (n = 1), or unknown

cause related to a tsunami (n = 1). Thirteen patients were lost to follow-up because they received a transplant (n = 2) or were transferred to another clinic (n=11). A total of 65 infection-related hospitalizations were recorded, including 22 cases of pneumonia, 11 cases of infectious gangrene, 6 cases of peritonitis, 4 cases of sepsis, 3 cases of vascular access infection, 2 cases of urinary tract infection, 1 case of infection at the exit-site for the PD catheter, and 16 cases of other infections.

Time between initiating dialysis and first hospitalization due to infection

Thirty-four patients were hospitalized due to infectious diseases. The infection-related hospitalization free time period was calculated from the initiation of dialysis therapy. Kaplan-Meier analysis revealed that the period between initiating dialysis therapy and the first hospital admission due to infection was significantly shorter in the high-ferritin group than in the low-ferritin group (log-rank test = 4.44, P = 0.035; Figure 1). The RR for first infection-related hospitalization, calculated with the Cox proportional hazards model, is shown in Table 3. Unadjusted analysis indicated that patients with a high serum ferritin had an increased risk of infection-related hospitalization (RR = 1.51, 95% CI = 1.06–2.17; *unadjusted model*). This effect remained after adjusting for age and gender (RR = 1.47, 95% CI = 1.00-2.13; *model 1 adjusted for age, gender and log ferritin*). To compare the predictive value of serum ferritin relative to other clinical biomarkers for inflammation, we also determined the RR

after adjusting for ferritin, CRP, and IL-6 levels, in addition to age and gender; the respective RRs for log ferritin, log CRP, and log IL-6 were 1.57 (1.04–2.38), 0.92 (0.73–1.15), and 1.10 (0.76–1.61) (*adjusted model 2*). Moreover, to evaluate the predictive value of serum ferritin and nutritional status, we calculated the RR after adjusting for SGA category in addition to parameters of model 2; the respective RRs for log ferritin and SGA Category B & C were 1.60 (1.07 to 2.40) and 2.74 (0.92 to 12.0) (adjusted model 3).

Cumulative hospitalization days due to infection during the entire study period

Thirty-four patients were hospitalized due to infection during the observation period: 1 patient was admitted 6 times, 2 patients were admitted 5 times, 5 patients were admitted 3 times, 8 patients were admitted twice, and 18 patients were admitted once. The total length of hospitalization was 2320 days. Then, cumulative hospitalization days due to infectious disease during the observation period were calculated. The median length of individual patients´ cumulative hospitalization periods was 31 (interquartile range: 8-71) days. Patients who were more frequently hospitalized spent longer mean time in the hospital, 309, 276 ± 275, 91 ± 87, 95 ± 93 and 14 ±17 days respectively, in patients admitted 6 times, 5 times, 3 times, twice and once. In patients with infection-related hospitalization, the prevalence of diabetes was higher (66.7 % vs 42.7 % in patients without infection-related hospitalization, P = 0.02), and

nutritional status by SGA category was poorer (SGA Category C and B: 29.0 % and 61.3 % vs 10.8 % and 62.4 % respectively in patients without infection-related hospitalization, P = 0.02), whereas no statistically significant differences were found in age and gender. The rates of hospital admission due to infection were 0.23 (with on average 10.9 hospital days) per patient year in the high-ferritin group, and 0.09 (with on average 1.57 hospital days) per patient year in the low-ferritin group. Moreover, the average length of hospital stay for patients divided according to the SGA categories C, B and A, were 27.7, 10.1 and 2.5 days per patient year in the high-ferritin group, and 6.4, 1.4 and 0.2 days in the low-ferritin group, respectively (Figure 2).

Discussion

Our study, in Japanese incident dialysis patients, demonstrated the prognostic value of increased serum ferritin levels for infection-related hospitalization. The main finding from this study was that patients with elevated ferritin levels at the start of dialysis therapy showed an increased risk of infection-related hospitalization, with shorter hospitalization-free periods and longer hospital stays. Furthermore, patients with high serum ferritin and poor nutrition status were more likely to have longer hospital stays.

CKD patients are predisposed to iron deficiency with increased iron losses due to gastrointestinal bleeding, blood losses during dialysis, frequent blood tests and other [6]. However, iron supplementation, particularly with IV iron, may be associated with bacterial infection because iron is an essential nutrient for growth in microorganisms. Findings from an *in vitro* study using serum samples collected from hemodialysis patients, suggest that non-transferrin-bound iron, observed in serum after IV iron, was positively associated with bacterial growth [19]. Moreover, in a challenge test with healthy subjects, iron supplementation suppressed the phagocytic function of leukocytes against both gram-negative and gram-positive bacteria and induced cell apoptosis [20]. Recently, it was reported that a high serum ferritin level was associated with increased mortality in Japanese hemodialysis patients [17]. In the US, IV iron has been shown to be associated with an increased risk of infection-related hospitalizations in dialysis patients [21]. The study presented

here is the first report showing that high serum ferritin is also associated with hospitalization due to infection in Japanese incident dialysis patients.

Although iron supplementation is indicated for treatment of iron deficiency anemia, functional iron deficiency – characterized by impaired iron release from body stores – is common in this patient group and should be treated differently from absolute' iron deficiency, which is characterized by both low circulating iron levels and low body iron stores [22]. Nonetheless, it has been reported that iron supplementation therapy can be successful in raising hemoglobin levels, even in patients with functional iron deficiency [23]. However, the serum ferritin range to consider cessation of iron supplementation should be defined in guidelines for dialysis patients since much higher than the target for absolute iron deficiency anemia, or these patients may end up falling into a vicious cycle, where functional iron deficiency is exacerbated and leads to iron overload [22]. In our study, we treated renal anemia using ESAs and iron deficiency anemia with IV iron for the vast majority, or with oral iron, according to the Japanese guidelines [18]. Even though the Japanese guidelines for iron supplementation in dialysis patients are more conservative than in other countries, the recommendation is for iron supplementation to be used only if serum ferritin < 100 ng/mL [18]. In our study, high serum ferritin was still associated with infection risk. We consider that using serum ferritin alone to reflect body iron stores in CKD patients is limited and possibly needs to be combined with other markers for the accurate evaluation of body iron stores and

iron dynamics and to distinguish between ‘functional’ and ‘absolute’ iron deficiency in these patients.

Serum ferritin is a biomarker of iron status but is also an inflammatory marker because it responds to inflammation in dialysis patients [13]. Indeed, in our study, patients with high ferritin levels showed increased inflammatory markers, namely CRP and IL-6. While iron treatment has been shown to induce oxidative stress in lymphocytes [24], it also appears to induce inflammation via activated monocytes releasing cytokines such as IL-6 [25]. This may result in a vicious cycle whereby the immune system alteration induced by uremia, contributes to susceptibility to infection and, in turn, this results in chronic inflammation and general health deterioration in uremic patients [2]. As for infectious risks, we speculate that patients with serum high ferritin levels may be at higher risk than those with inflammation without iron overload.

Protein-energy wasting (PEW), a well-known and serious condition characterized by a decrease in both body protein and energy stores, is highly prevalent in CKD patients and may be caused not only by low caloric intake but also by increased catabolism [26]. SGA is a reliable tool for evaluating PEW in dialysis patients according to the guidelines released by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 2000 [27]. In the current study, the combination of PEW with high ferritin levels associated with prolonged infection-related hospitalization. Hyporesponsiveness to ESAs is a common problem in CKD patients with PEW and inflammation [28]. Because

hematopoietic tissue requires a high nutrient supply, nutritional protein and caloric deficiencies may alter bone marrow function [29]. In such situations, iron supplementation, especially when used routinely, should be administered more cautiously to avoid iron overload and aggravated inflammation; iron supplementation may be associated with more severe immune dysfunction and, in turn, increased susceptibility to infections and related hospitalization.

We wish to note some limitations of our study. First, although we administered oral or IV iron according to the guidelines of the Japanese Society for Dialysis Therapy, the dosage was left at the doctor's discretion and was not monitored. Second, serum ferritin levels were measured only once near the start of dialysis therapy; serial measurements throughout the study period would have been more informative. Finally, this study included both HD and PD patients as we tried to ascertain the usefulness of serum ferritin for predicting infection risk in the entire patient group with ESRD. However, we acknowledge that the causes of infection may have differed between the different dialysis modalities.

In conclusion, albeit the serum ferritin levels and the doses of iron administered to dialysis patients are in general lower in Japan than in Western counties, in our study, higher ferritin levels were still associated with increased risk of infection-related hospitalization, particularly in patients with poor nutritional status.

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Declaration of conflicts of interest

Bengt Lindholm is an employee of Baxter Healthcare Corporation. All other authors declare no conflict of interest.

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Figure Legends

Figure 1

Kaplan-Meier analysis of the time between dialysis initiation and first hospitalization due to infection. The infection-free period was significantly shorter in the high-ferritin group than in the low-ferritin group (P = 0.0351).

Figure 2

Duration of the infection-related hospital stay. The total number of hospitalization days due to infection during the entire observation period was higher in patients with high ferritin levels and poor nutrition status.