Clin Exp Nephrol (2010) 14:349–355
DOI 10.1007/s10157-010-0288-x

ORIGINAL ARTICLE

Serum ferritin predicts prognosis in hemodialysis patients: the Nishinomiya study

Yukiko Hasuike · Hiroshi Nonoguchi · Masanori Tokuyama · Mai Ohue · Takanori Nagai · Mana Yahiro · Masayoshi Nanami · Yoshinaga Otaki · Takeshi Nakanishi

Received: 17 March 2010 / Accepted: 18 April 2010 / Published online: 14 May 2010

Abstract
Background The mortality in end-stage renal disease patients with dialysis remains high. Serum ferritin is a useful surrogated marker of iron storage. It has not been elucidated whether the ferritin level can predict the prognosis of patients with dialysis but without obvious inflammation. To clarify whether the ferritin level is involved in the prognosis in dialyzed patients, we investigated the relation between ferritin level and mortality in hemodialyzed patients during long-term follow-up.
Methods Ninety stable hemodialyzed patients were enrolled and followed for 107 months. Serum ferritin and related factors (dialysis, nutrition, iron metabolism, inflammation and oxidative stress) were measured and used for statistical analysis. Survival analysis of death for ferritin as a predictive variable was performed.
Results A relatively high level of serum ferritin ($\geq$100 ng/ml) was associated with poor prognosis after adjustment for basic factors and C reactive protein (hazard ratio, 4.18). Hemoglobin-stratified Kaplan-Meier analysis showed that the prognosis for the high ferritin-low hemoglobin group was significantly poor.
Conclusion This study suggests that the ferritin level is closely associated with high mortality in hemodialyzed patients. Further studies investigating the pathological role of iron storage on survival of hemodialyzed patients with large populations are needed.

Keywords Dialysis · End-stage renal disease · Ferritin · Iron · Prognosis

Y. Hasuike (✉) · H. Nonoguchi · M. Tokuyama · M. Yahiro · M. Nanami · Y. Otaki · T. Nakanishi
Division of Kidney and Dialysis, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: cherry39@hyo-med.ac.jp

M. Ohue · T. Nagai
Division of Kidney and Dialysis, Meiwa Hospital, Hyogo, Japan

Introduction

The mortality in end-stage renal disease (ESRD) patients with dialysis remains high despite marked improvement in dialysis technology and patient care, such as anemia management with the administration of erythropoietin-stimulating agents and iron. Among the high mortality-related factors, the contribution of inflammation to low survival rates in ESRD patients has been reported by many investigations. Serum ferritin is a clinical marker of iron storage and influenced by inflammation. Several reports showed that ferritin is associated with poor prognosis in patients on hemodialysis (HD) [1]. Interestingly, the ferritin level of HD patients in Japan differs from other reports after the publication of the guidelines to start of iron supplementation (serum ferritin <100 ng/ml) [2].

To clarify whether serum ferritin itself predicts the prognosis in ESRD patients, we investigated the association of hyperferritinemia with all-cause death during long-term follow-up in HD patients.

Methods

Participants

This study was a prospective observational cohort study initially enrolling 94 maintenance HD patients in the seven

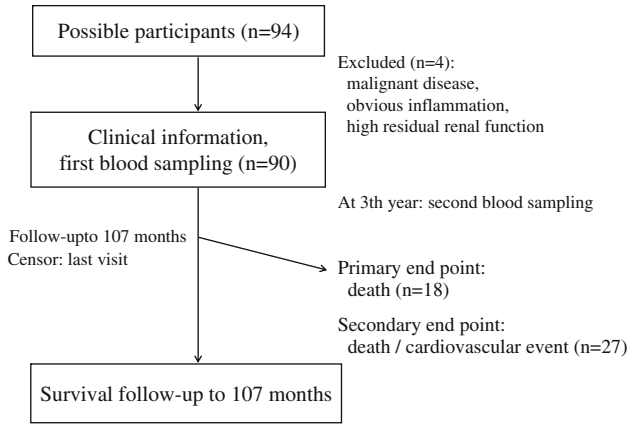

Fig. 1 Patients' flow

dialysis units (Fig. 1). After four patients who had malignant disease, obvious inflammation and high residual renal function were excluded from the study; stable HD patients ($n = 90$) were enrolled and followed. Baseline cross-sectional analysis of the relationship between ferritin and related factors (dialysis, nutrition, the metabolism of calcium/phosphorus and iron, inflammation and oxidative stress) was performed. Primary and secondary survival analyses were performed. The primary endpoint was all-cause death for ferritin as a predictive variable; the secondary endpoint was death and/or onset of cardiovascular disease (myocardial infarction, stroke and peripheral artery disease). Baseline demographic and clinical data and laboratory parameters were measured prior to the first dialysis session of the week. Anemia treatment during the follow-up period was decided by each physician according to the Japanese guidelines: the start of anemia treatment (Hb <10 g/dl), the upper-limit of ESAs (9000 IU/week as recombinant human erythropoietin) and the start of iron supplementation [serum ferritin <100 ng/ml, transferrin saturation rate (TSAT) <20%]. All patients provided informed consent. To examine whether the elevation of ferritin continued, a second sampling was performed at the 3rd year. The protocol of the study was approved by the

Table 1 Baseline characteristics of all, high ferritin and low ferritin patients (mean ± SE)

	All patients 90 (46)	High Frt group 30 (13)	Low Frt group 60 (33)	*p* value
Serum ferritin (ng/ml)	60.2 (32.2–132.4)	161.9 (131.7–240.1)	37.0 (26.1–58.2)*	<0.0001
Demographic characteristics				
Age (years)	55.3 ± 13.6	58.7 ± 12.9	53.6 ± 13.7	0.091
Dialysis vintage (months)	105.1 ± 76.9	83.3 ± 78.9	116.0 ± 73.6	0.056
Body mass index (kg/m^2)	20.7 ± 2.7	21.1 ± 2.4	20.5 ± 2.8	0.429
Blood pressure, systolic (mmHg)	143.9 ± 24.6	149.7 ± 28.0	140.3 ± 21.7	0.142
Kt/V (single pool)	1.39 ± 0.24	1.32 ± 0.23	1.41 ± 0.24	0.160
Comorbid condition at start				
Diabetes mellitus (%)	13.3	20.0	10.0	0.191
Cardiovascular disease (%)	42.5	42.3	42.6	0.981
Medication at start				
ACEI and/or ARB (%)	28.6	40.7	22.8	0.091
Iron administration and/or blood transfusion (%)	32.4	28.6	34.0	0.658
Laboratory data				
Creatinine (μmol/l)	1087 ± 274	955 ± 248	1149 ± 256*	0.001
Urea nitrogen (mmol/l)	26.8 ± 5.3	26.3 ± 5.5	27.0 ± 5.2	0.605
Calcium, corrected (mmol/l)	2.38 ± 0.18	2.33 ± 0.18	2.43 ± 0.15*	0.006
Phosphorus (mmol/l)	1.91 ± 0.48	1.71 ± 0.42	2.00 ± 0.48*	0.006
Albumin (g/l)	40.0 ± 3.6	39.6 ± 3.7	40.2 ± 3.5	0.457
Hemoglobin (g/l)	99.5 ± 11.4	98.1 ± 10.7	100.3 ± 11.8	0.392
Total cholesterol (mmol/l)	4.61 ± 1.00	4.34 ± 0.95	4.75 ± 1.00	0.064
Iron (μmol/l)	11.5 ± 4.0	11.6 ± 3.6	11.5 ± 4.3	0.914
TSAT (%)	24.9 ± 9.8	28.6 ± 8.9	23.2 ± 9.8*	0.019
C reactive protein (mg/dl)	0.10 (0.10–0.20)	0.10 (0.10–0.30)	0.10 (0.10–0.20)	0.165
Malondialdehyde (nmol/ml)	0.99 (0.74–1.27)	1.11 (0.81–1.33)	0.95 (0.69–1.21)	0.100

Frt Ferritin, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *TSAT* transferrin saturation rate

* Significantly different versus high Frt group

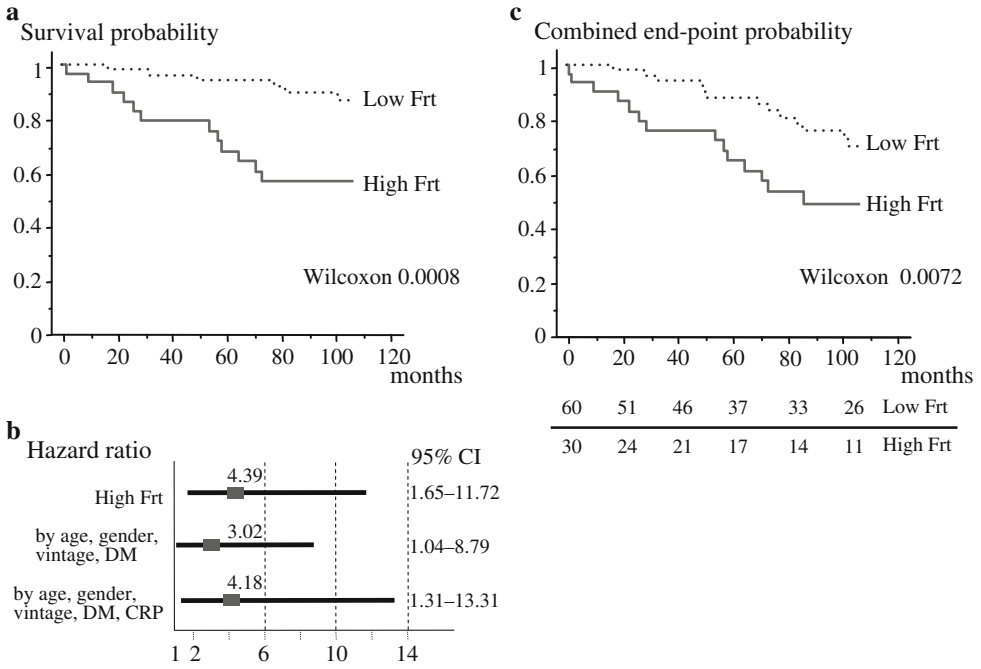

Fig. 2 Estimated cumulative incidence of all-cause death in the high/low ferritin groups. **a** Kaplan-Meier analysis indicates time to all-cause death in the high/low ferritin groups. The *solid line* represents patients with ferritin ≥100 ng/ml (the high ferritin group) and the *dotted line* represents those with <100 ng/ml (the low ferritin group). **b** Cox proportional hazard model of high ferritin levels for death. **c** Kaplan-Meier analysis indicates time to death and/or cardiovascular disease in the high/low ferritin groups. The *solid line* represents patients with ferritin ≥100 ng/ml (the high ferritin group), and the *dotted line* represents those with <100 ng/ml (the low ferritin group). *Frt* Ferritin, *CI* confidence interval, *DM* diabetes mellitus, *CRP* C reactive protein, *CVD* cardiovascular disease

ethics committee of the Hyogo College of Medicine (no. 125) and was registered at the University Hospital Medication Information Network (UMIN, no. C000000362).

Laboratory evaluation

Blood samples were taken at the first dialysis of the week. The specimens for malondialdehyde (MDA) were divided into aliquots and were frozen at −80°C. Plasma levels of MDA were measured as a marker of lipid peroxidation by the method developed by Yagi [3]. The single pool Kt/V was used to represent the weekly dialysis dose. The covariates used in this study included sociodemographic variables (age, gender), comorbidity (adjudicated presence of diabetes, HD vintage) and physical and biological parameters, including body mass index (BMI, weight in kilograms divided by height in meters squared), Hb, serum concentration of iron, total iron-binding capacity (TIBC), ferritin and albumin. TSAT was calculated as [(serum iron/TIBC) × 100].

Statistical analysis

Since the distribution of ferritin, CRP and MDA was skewed, logarithmically transformed values were used for statistical analysis. Differences in proportions and means of covariates across persons with and without diabetes mellitus, cardiovascular disease and administration of angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) at entry were assessed by Mann-Whitney *U* test or Student's *t* test. Because the levels of ferritin, markers of inflammation and oxidative stress were not normally distributed, median values with interquartile ranges were reported, and probability values were based on Mann-Whitney *U* test. The cumulative probabilities of survival from entry in the study to the terminal event (stated as all-cause death and cardiovascular death) were estimated by the product limit (Kaplan-Meier) method. The Wilcoxon test was used to compare the homogeneity of survival functions across strata defined by binary transformation of prognostic variables. To assess the relative risk for all-cause death, Cox proportional hazard analyses were performed.

Results

At the beginning of the study, clinical information and the first blood sampling were obtained as baseline data in 90 HD outpatients (Table 1, the left column). During the 107-month follow-up period, 18 (20.0%) patients died, and 13 (14.4%) patients had new cardiovascular diseases (Fig. 1).

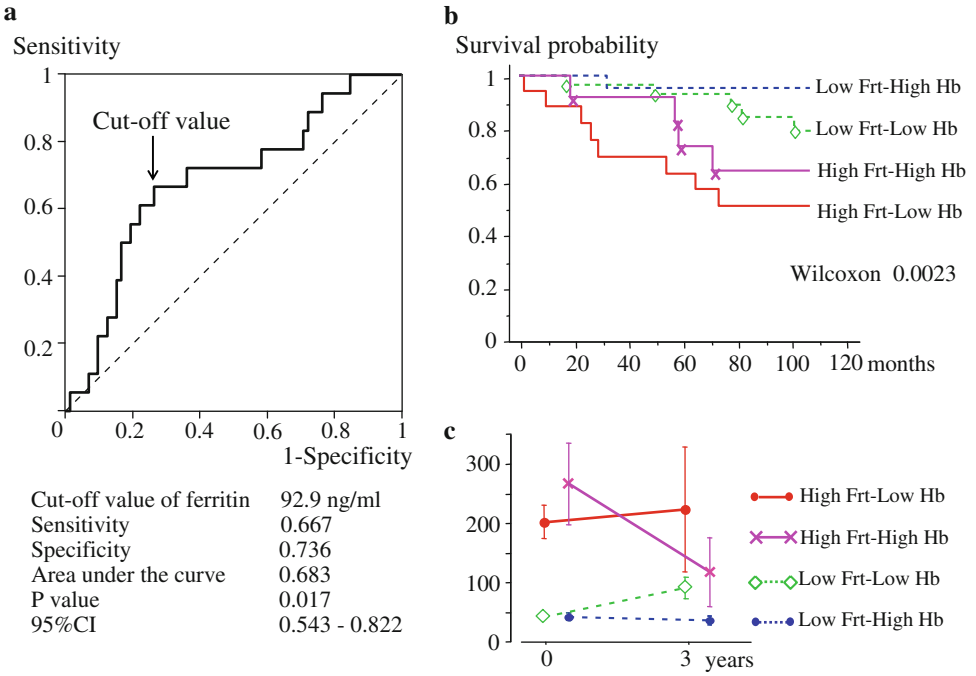

Fig. 3 The usefulness of ferritin measurement. **a** Diagnostic accuracy of ferritin with regard to death as expressed by the ROC curve. **b** Estimated cumulative incidence of all-cause mortality and the changes in ferritin values for 3 years in the four stratified groups. Kaplan-Meier analysis indicates time to all-cause death in the four stratified groups. **c** The changes in ferritin values for 36 months in the four stratified groups. The ferritin levels at entry and at 36 months in the four groups. The *solid line* represents patients with ferritin ≥100 ng/ml and hemoglobin <100 g/l (high Frt-low Hb group); the *solid line* with *cross symbols* represents those with ferritin ≥100 ng/ml and hemoglobin ≥100 g/l (high Frt-high Hb group); the *dotted line with diamond symbols* represents patients with ferritin <100 ng/ml and hemoglobin <100 g/l (low Frt-low Hb group); the *dotted line* represents patients with ferritin <100 ng/ml and hemoglobin ≥100 g/l (low Frt-high Hb group). *ROC* Receiver-operating characteristic curve, *CI* confidence interval, *Frt* ferritin, *Hb* hemoglobin

Table 2 The rates of iron administration or blood transfusion in the high and low ferritin groups at the start and for 3 years

	All patients	High Frt group	Low Frt group	*p* value
At start (%)	39.8	42.9	38.2	0.683
During 3 years (%)	70.8	61.5	76.1	0.195

p value of comparison between the high and low groups using Mann-Whitney *U* test

Frt Ferritin

To investigate the association of ferritin level and survival in HD patients, all subjects were divided into two groups according to the value of serum ferritin, 100 ng/ml, based on the Japanese guidelines for treating renal anemia management. A comparison of the characteristics and laboratory data of the two groups, a high and low ferritin group, is shown in Table 1 (the middle and right columns). The all-cause mortality rate was significantly higher in the high ferritin group (40.0%) compared with the low ferritin group (10%, $p = 0.0009$). There was a difference rate of combined endpoints (death and/or cardiovascular disease) between the high (46.7%) and low ferritin groups (21.7%, $p = 0.0153$). In addition to the mortality, a significant elevation of TSAT was evident in the high compared with the low ferritin group. Serum creatinine, calcium and phosphorus levels were lower in the high compared with those in the low ferritin group. No statistically significant differences were found in the age, dialysis vintage, comorbid condition, ACEI and/or ARB administration, albumin, Hb, iron, and markers of inflammation and oxidative stress at the time of enrollment between the two groups.

The role of the value of ferritin 100 ng/ml in predicting death during an 107-month prospective follow-up period was examined. The mean follow-up period was 75.6 months: 70.7 and 78.1 months in the high and low ferritin groups, respectively. Kaplan-Meier analysis using a proportional Cox hazard model revealed that death in the high ferritin group occurred more frequently than in the low ferritin group (Fig. 2a). Figure 2b indicates that a higher ferritin level of more than 100 ng/ml was significantly associated with high mortality (hazard ratio, 4.39; 95% confidence intervals, 1.65–11.72). After adjusting by basic factors (age, gender, dialysis vintage, diabetes mellitus), a higher level of ferritin was associated with death

Table 3 Baseline patients characteristics in dialyzed patients with low/high ferritin and low/high hemoglobin levels (mean ± SE)

Frt (ng/ml):	High (≥100)		Low (<100)	
Hb (g/l):	Low (<100) 17 (8)	High (≥100) 13 (5)	Low (<100) 32 (23)	High (≥100) 28 (10)
Age (years)	57.8 ± 10.7	60.0 ± 15.7	54.1 ± 13.8	53.1 ± 13.8
Dialysis vintage (months)	98.2 ± 88.4	63.9 ± 62.6	124.8 ± 78.5	106.0 ± 67.7
Body mass index (kg/m^2)	20.6 ± 2.0	21.7 ± 2.8	20.3 ± 2.4	21.0 ± 3.3
Kt/V (single pool)	1.36 ± 0.25	1.26 ± 0.20	1.42 ± 0.23	1.40 ± 0.25
Creatinine (μmol/l)	972 ± 212	928 ± 292	1105 ± 274	1202 ± 239*
Urea nitrogen (mmol/l)	26.1 ± 6.3	26.6 ± 4.6	26.6 ± 4.7	27.5 ± 5.8
Calcium, corrected (mmol/l)	2.34 ± 0.16	2.28 ± 0.20	2.42 ± 0.16	2.41 ± 0.15
Phosphorus (mmol/l)	1.76 ± 0.43	1.63 ± 0.45	1.92 ± 0.46	2.10 ± 0.50*
Albumin (g/l)	38.9 ± 4.2	40.6 ± 2.8	39.3 ± 3.4	41.3 ± 3.4
Total cholesterol (mmol/l)	4.11 ± 1.03	4.65 ± 0.76	4.72 ± 1.06	4.79 ± 0.95
Iron (μmol/l)	10.3 ± 3.5	13.2 ± 3.2	11.9 ± 4.1	11.0 ± 4.5
TSAT (%)	24.6 ± 5.5	34.0 ± 10.1	23.6 ± 8.3*	22.8 ± 11.5
C reactive protein (mg/dl)	0.10 (0.10–0.43)	0.10 (0.10–0.20)	0.10 (0.10–0.10)	0.10 (0.10–0.26)
Malondialdehyde (nmol/ml)	0.92 (0.78–1.20)	1.12 (1.05–1.90)	0.87 (0.69–1.04)	1.00 (0.69–1.39)

Frt Ferritin, *Hb* hemoglobin, *TSAT* transferrin saturation rate

* Significantly different versus high Frt-high Hb group

(hazard ratio, 3.02). Moreover, after adjusting by the basic factor and CRP, a higher level of ferritin was also associated with death (hazard ratio 4.18). Using the secondary endpoint (combined with death and cardiovascular disease), Kaplan-Meier analysis using a Cox proportional hazard model revealed that death and/or cardiovascular disease in the high ferritin group occurred more frequently than in the low ferritin group (Fig. 2c).

To examine the diagnostic efficiency of ferritin measurement for death, receiver-operating characteristic (ROC) curves were used (Fig. 3a). The area under the curve for ferritin was 0.683 (95% CI 0.543–0.822, $p = 0.017$). Therefore, high mortality was closely associated with a high ferritin level. In the ROC report, the cutoff value for measured ferritin corresponding to the highest accuracy (minimal false-negative and false-positive results) was indicated. The ROC curve determined a cutoff value of 92.9 ng/ml with a sensitivity of 66.7% and specificity of 73.6%. The rate of iron administration including blood transfusion was examined (Table 2). There was no difference in the rate of iron administration between the high and low ferritin group.

In addition to serum ferritin levels, Hb was also included in the analysis of mortality in this study, since Hb levels could be the important predictors. Both the high and low Frt groups were divided into two subgroups according to the value of Hb (100 g/l), based on the Japanese guidelines for treating renal management (Table 3). The four subgroups were high Frt-low Hb ($n = 17$), high Frt-high Hb ($n = 13$), low Frt-low Hb ($n = 32$) and low Frt-high Hb ($n = 28$). Consequently, ferritin- and Hb-stratified Kaplan-Meier analysis showed that the prognosis of the high Frt-low Hb group was significantly poor compared with the high Frt-high Hb group, as shown in Fig. 3b. To examine whether the elevation of ferritin was maintained during the 3-year period, serum ferritin values were examined both at the start and the 3rd year in each Frt- and Hb-stratified group. There were no significant changes between years 0 and 3 in each subgroup (Fig. 3c).

To identify significant baseline predictors of the ferritin level, correlations among age, factors related to dialysis, nutrition, and anemia, iron metabolism, several markers of inflammation and oxidative stress were examined. There were significant negative correlations between the logarithm (log) of ferritin and serum creatinine, calcium and phosphorus, and a positive correlation between log ferritin and TSAT (Table 4a). To determine the independent predictors for ferritin level, stepwise regression analysis was performed. On stepwise multiple regression analyses, TSAT and corrected calcium were selected as independent predictors for ferritin (Table 4b; Fig. 4).

Discussion

This study showed that a relatively high level of ferritin was associated with poor prognosis during long-term follow-up. Moreover, a fatal risk of hyperferritinemia was independent from age, gender, dialysis vintage, diabetes mellitus and CRP level. Our results suggest that ferritin can

Table 4 Results of simple and multiple stepwise regression analyses in dialysis patients

Variables	*R*	*P*
(a)		
Age	0.188	0.0752
Dialysis vintage	0.178	0.0933
Body mass index	0.028	0.8193
Kt/V	0.112	0.3776
Creatinine	−0.265	0.012
Urea nitrogen	0.048	0.6583
Albumin	0.022	0.8352
Total cholesterol	−0.118	0.2683
Hemoglobin	−0.180	0.0887
Calcium, corrected	−0.329	0.0016
Phosphorus	−0.268	0.0108
Iron	0.137	0.1971
TSAT	0.427	<0.0001
C reactive protein[a]	0.174	0.103
Malondialdehyde	−0.042	0.7249

	β	*F*	R^2	*P*
(b)				
TSAT	0.409	16.256	0.167	0.0001
Calcium, corrected	−0.272	7.152	0.235	<0.0001

(a) Simple regression analyses for log ferritin using the surrogate factor of the category: demographic, related to dialysis, nutrition, metabolism of calcium and iron, inflammation and oxidative stress

(b) Multiple regression analyses for log ferritin using the independent variables used for simple analysis were selected

TSAT Transferrin saturation rate

[a] Log-transformed values were used

predict survival in HD patients, which is compatible with the results of other studies [1]. The cutoff value of ferritin in the present study, 100 ng/ml, was lower than that described by others (500 ng/ml according to Kalantar-Zadeh et al. [1] and 700 ng/ml according to Jenq et al. [4]).

Concerning the association of ferritin increment with death, several possible mechanisms could be involved. First, iron excess that promotes ferritin generation can contribute to a poor prognosis. Ferritin is the intracellular protein responsible for iron storage. Iron excess with ferritin generation can contribute to the generation of reactive oxygen species via the Fenton and Haber-Weiss reaction resulting in cellular dysfunction and oxidative damage [5, 6]. Furthermore, ferritin protein plays an important role in iron sequestering and release; circulating ferritin releases ferrous iron in some conditions [7], and released iron from ferritin can also contribute to oxidative stress. Our study in vitro indicated that human circulating ferritin could release labile iron with aminolevulinate, one of uremic toxin, and induced oxidative stress [8]. These results are consistent with the idea that the existence of iron with a ferritin increment is associated with higher mortality in HD patients.

The serum ferritin level is affected by several factors other than the amount of iron, including inflammation and tissue damage [9]. Since inflammation can cause an elevation of ferritin, it is possible that inflammation accompanied with hyperferritinemia can be involved in several complications such as cardiovascular disease, resulting in a poor prognosis. Moreover, tissue damage and malignant disease induce an elevation of the serum ferritin level. Ferritin may enter the circulation both via secretion of ferritin by cells and via leakage from the damaged cells [10]. In the present study, the maximum value of CRP (3.6 mg/dl) was not too high compared with other reports, and the mean value of serum albumin was within the normal range (40.0 g/l). Furthermore, no significant difference of CRP or albumin levels existed between the high and low ferritin groups. These results indicate that both inflammation and tissue damage scarcely influenced the ferritin level in our study.

The change of ferritin level after 3 years was examined in each of the four subgroups as a middle evaluation since it is difficult to predict prognosis using data only at the start of the study. There was no significant difference between the ferritin levels at the start and after 3 years in each subgroup. Our findings indicated that maintaining a higher ferritin level for at least 3 years, which could be associated

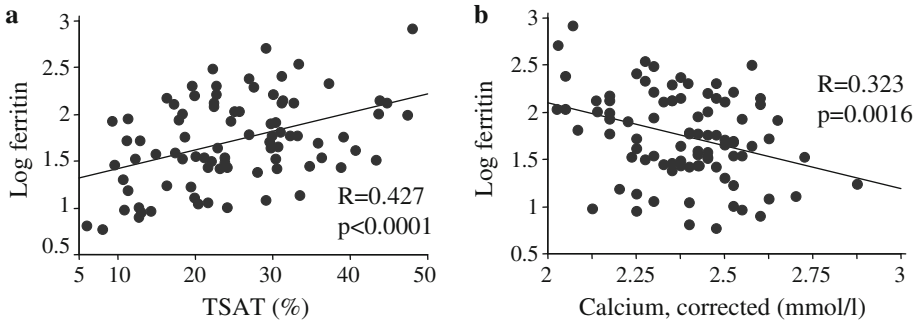

Fig. 4 The correlations between log ferritin and TSAT or calcium in dialysis patients. **a** Log ferritin and TSAT; **b** log ferritin and calcium. *TSAT* Transferrin saturation rate

with high iron storage, might influence the long-term outcome in HD patients.

This report provides the remarkable finding that anemic hyperferritinemia could predict poor prognosis in a long-term follow-up study. Although the mechanism of this evidence has not been elucidated, a possible mechanism is the pathological status, namely iron dysregulation in ESRD. We investigated the change of iron transporters and iron dysregulation in the leukocytes of ESRD patients [5]. Moreover, the mechanism of inflammatory cytokine-induced iron dysregulation was reported in human umbilical endothelial cells [6]. Iron dysregulation causes a relative insufficiency of iron for erythropoiesis and an excess of intracellular iron in other cells. Iron dysregulation can occur without an excess supplementation of iron, since most of the iron is reutilized from the erythrocyte breakdown for erythropoiesis [11].

TSAT is used as a marker of iron metabolism. In this study, a higher TSAT level in the high Frt-high Hb group compared with that in the low Frt-low Hb group was evident, and the TSAT elevation may indicate iron sufficiency. The stepwise regression analysis revealed that TSAT was an independent predictor for ferritin level, which agrees with other reports [12]. To investigate the significance of TSAT as a prognostic marker, Cox proportional hazard models for high TSAT for all-cause mortality and combined endpoints were examined. Confidential intervals were not statistically significant (0.943–1.056 and 0.944–1.036, respectively). Moreover, although ROC analyses of TSAT for all-cause mortality and combined endpoints were examined, the p values were not significant (0.850 and 0.790, respectively). Thus, the significance of TSAT as a prognostic marker was not confirmed in this study. The serum calcium was also a predictor for ferritin, but the involvement of these factors was not elucidated. Few investigations reported on the contribution of calcium to iron metabolism [13].

This study has several limitations. It was not based on a large cohort. In this respect, failure to confirm the association of the ferritin level with clinical outcomes may reflect insufficient study power. The treatment for anemia was decided by each physician, and information about the anemia treatment was not sufficiently given. The effects of statins on clinical outcome should be examined. Details about treatment including the use of not only ACEI/ARB but also vitamin D and statins on clinical outcome should be examined.

In conclusion, this study suggests that hyperferritinemia is closely associated with high mortality in HD patients. Further studies investigating the pathological role of iron dysregulation with large populations are needed.

Acknowledgments The authors acknowledge Miho Kimura for the technical assistance in preparing this paper. We thank the subjects, staff and physicians who participated in this study for their cooperation. Pacific Edit reviewed the manuscript prior to submission.

References

1. Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH. Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. Am J Kidney Dis. 2001;37:564–72.
2. Gejyo F, Saito A, Akizawa T, Akiba T, Sakai T, Suzuki M, et al. Japanese Society for Dialysis Therapy 2004. Japanese Society for Dialysis Therapy guidelines for renal anemia in chronic hemodialysis patients. Ther Apher Dial. 2004;8(6):443–59.
3. Yagi K. A simple fluorometric assay for lipoperoxide in blood plasma. Biochem Med. 1976;15(2):212–6.
4. Jenq CC, Hsu CW, Huang WH, Chen KH, Lin JL, Lin-Tan DT. Serum ferritin levels predict all-cause and infection-cause 1-year mortality in diabetic patients on maintenance hemodialysis. Am J Med Sci. 2009;337(3):188–94.
5. Otaki Y, Nakanishi T, Hasuike Y, Moriguchi R, Nanami M, Hama Y, et al. Defective regulation of iron transporters leading to iron excess in the polymorphonuclear leukocytes of patients on maintenance hemodialysis. Am J Kidney Dis. 2004;43(6):1030–9.
6. Nanami M, Ookawara T, Otaki Y, Ito K, Moriguchi R, Miyagawa K, et al. Tumor necrosis factor-alpha-induced iron sequestration and oxidative stress in human endothelial cells. Arterioscler Thromb Vasc Biol. 2005;25(12):2495–501.
7. Ford GC, Harrison PM, Rice DW, Smith JM, Treffry A, White JL, et al. Ferritin: design and formation of an iron-storage molecule. Philos Trans R Soc Lond B Biol Sci. 1984;304(1121):551–65.
8. Hasuike Y, Nonoguchi H, Tokuyama M, Hata R, Kitamura R, Hori K, et al. The pathological role of aminolevulinate in uremic patients. Ther Apher Dial. 2010 (in press).
9. Yamanishi H, Iyama S, Yamaguchi Y, Kanakura Y, Iwatani Y. Relation between iron content of serum ferritin and clinical status factors extracted by factor analysis in patients with hyperferritinemia. Clin Biochem. 2002;35(7):523–9.
10. Worwood M. Ferritin. Blood Rev. 1990;4:259–69.
11. Pietrangelo A. Physiology of iron transport and the hemochromatosis gene. Am J Physiol Gastrointest Liver Physiol. 2002;282:G403–14.
12. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol. 2005;16:3070–80.
13. Benkhedda K, L'abbé MR, Cockell KA. Effect of Ca on iron absorption in women with marginal iron status. Br J Nutr. 2009;28:1–7.