Serum selenium levels are inversely associated with death risk among hemodialysis patients

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Abstract

Background. Previous studies have indicated that serum selenium levels are decreased in hemodialysis patients. Selenium deficiency may contribute to an increased risk for death among hemodialysis patients.

Methods. A population-based prospective cohort study in adult hemodialysis patients was conducted. A total of 1041 patients were enrolled. Patients were divided into quartile groups according to serum selenium levels. Mortality rates between the groups were compared by the log-rank test. Associations between serum selenium levels and cause-specific mortality risks in hemodialysis patients were examined by Cox’s regression model.

Results. A total of 382 patients died during the 5-year follow-up period (median follow-up period, 4.9 years). Crude mortality rates in quartile groups according to serum selenium levels were 134.5, 99.9, 85.9 and 55.2 (per 1000 patient-years), respectively. The lowest quartile group had significantly higher mortality rates from all-cause and infectious disease-related death than the rates in the other three groups (P < 0.001, by log-rank test). Mortality rates from cardiovascular and malignant disease-related death were similar between the groups. A strong inverse relationship between selenium levels and infectious disease-related death was observed even after multivariate adjustment (trend P = 0.024).

Conclusions. Serum selenium levels were inversely associated with death risk, especially death risk due to infectious disease, among hemodialysis patients. Decreased serum selenium level may contribute to immunity dysfunction and may increase the risk of death from infectious disease in hemodialysis patients.

Keywords: hemodialysis; mortality; prospective study; risk factors; selenium

Introduction

Selenium is an essential component of the antioxidant enzyme and is needed for proper functioning of the immune system [1]. In the general population, selenium deficiency
has been observed in patients with cardiovascular disease (CVD) [2], patients with cancer [3] and patients with viral infection [4], and the effects of selenium supplementation on prevention of several diseases such as cancer [5, 6] and CVD [2] have been reported on the basis of results of clinical trials and epidemiological studies.

Several studies have shown that serum levels of selenium in hemodialysis patients were lower than those in normal controls [7–12]. Insufficient dietary intake of selenium and/or loss of selenium through hemodialysis membranes may contribute to the low serum levels of selenium in hemodialysis patients [7]. These findings suggest that hemodialysis patients have low levels of serum selenium and that a considerable number of hemodialysis patients suffer from significant selenium deficiency.

Hemodialysis is associated with considerable morbidity and mortality due to accelerated CVD and general infectious disease [13, 14]. Hemodialysis-related risk factors for CVD mortality, including low body mass index (BMI), low serum cholesterol and low blood pressure, have been reported [15]. Moreover, the presence of ‘malnutrition-inflammation complex syndrome’ (MICS) [16] and ‘malnutrition-inflammation-atherosclerosis syndrome’ (MIAS) [17] in hemodialysis patients strongly contribute to poor prognosis.

However, much remains to be learned about other factors that contribute to the risk for death in hemodialysis patients. Selenium deficiency in hemodialysis patients may contribute to an increased risk for death from various diseases, and selenium deficiency may be one of the unknown strong risk factors for death in hemodialysis patients.

The aim of this study was to determine whether low serum selenium levels contribute to increased mortality in hemodialysis patients.

Materials and methods

Subjects

We have been conducting the ‘Kaleidoscopic Approaches to patients with end-stage RENal disease Study’ (the KAREN Study) since 2003 in the northern part of Japan. The KAREN Study is a population-based prospective study designed to determine the effects of risk factors on cardiovascular morbidity and mortality in hemodialysis patients. The study subjects were prevalent cases of adult hemodialysis patients.

Initial registration was completed in 1214 patients. Serum selenium tests were not done in 173 patients. Therefore, data for 1041 participants (663 men aged 22–91 years with a mean age of 61.2 ± 13.4 years and 378 women aged 25–88 years with a mean age of 61.1 ± 12.7 years) were analyzed in this study (see Figure 1) [18, 19]. Written informed consent for participation in the study was obtained from all subjects. The study was approved by the Medical Ethics Committee of Iwate Medical University and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurements

Initial investigations in the KAREN Study were conducted from June 2003 to March 2004 and the examinations consisted of a questionnaire, review of medical records, measurements of blood pressure and anthropometric data and blood tests. The data gathering methodology was previously described [18]. The blood samples were transported to a laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Morioka branch office) and analyzed the same day. Residual sera were stored at −80°C in our laboratory until determination of selenium.

Measurements of serum selenium concentrations

Frozen serum samples were unfrozen and each serum specimen (1 mL) was pipetted into a Teflon tube and then 3.0 mL of high-purity nitric acid was added. The solution was allowed to sit for 2 h at room temperature. Then, the tube was heated to 120°C for 12 h to completely degrade the organic matter in the sample serum. The resultant solution was cooled to room temperature and then transferred into a Teflon beaker. The beaker was heated to 100°C until desiccated. Dried samples were dissolved with 5 mL of 10% nitric acid and used for measurements. Selenium levels in sample solutions were determined using inductively coupled plasma-mass spectrometry (Elan 6000; PerkinElmer Co Ltd.). The with-run and total imprecision were determined according to the National Committee for Clinical Laboratory Standards Approved Guideline [20]. Two replicates of selenium measurements in mixed sera per day were carried out. The method produced a within-run standard deviation of 3.9 μg/L to 139.8 μg/L. Total precision gave a standard deviation of 6.2 μg/L to 139.8 μg/L.

Definitions of comorbid conditions and risk factors

We determined the causes of renal failure and comorbid conditions based on medical records according to the KAREN study criteria [18]. Hyper-tension was defined as systolic blood pressure of 140 mmHg or higher and diastolic blood pressure of 90 mmHg or higher or use of antihypertension medication. Diabetes mellitus was defined as casual plasma glucose of 200 mg/dL or higher and Hb A1C of 6.5% or higher or past or current use of hyperglycemic agents. Dyslipidemia was defined as serum total cholesterol (TC) of 220 mg/dL or higher or high-density lipoprotein (HDL-C) of <40 mg/dL or use of anti-hyperlipidemic agents. Smoking status was classified into non-smoker, current smoker and past smoker. Regular alcohol drinking was defined as drinking ≥ 5 days/week.

Follow-up surveys and determination of causes of deaths

Follow-up studies were performed annually at each center. Members of the KAREN Study team reviewed all the medical records of study participants. The medical records of deceased patients were summarized. The cause of death was independently determined, based on the summaries, by KAREN Outcome Review Committee physicians who were blinded to the patient’s characteristics including serum selenium levels. Discordant cases were discussed and final determination was reached by consensus.

In this study, we determined three major causes of death (CVD death), infectious disease-related death and malignant disease-related death) after coding according to the ICD10th revision (see Table 1). CVD includes cardiac death (I20–I25), death from pulmonary embolism (I26), stroke death (I60–I69), vascular death (I70–177) and sudden cardiac death (I46, 149 and R96). Infectious disease-related death includes death from certain infectious and parasitic diseases (A00–B99), death from infectious diseases in the nervous system (G00 and G04.2), death from infectious diseases in the respiratory tract (J10–J18, J20, J69 and J86), death from infectious diseases in the gastrointestinal tract and digestive organs (K65, K80.3, K81) and death from infectious diseases in skin and subcutaneous tissue (L03 and L89). Malignant disease-related death is death from neoplasms (C82, C15, C16, C18, C20, C22, C34, C45, C55, C61, C64, C67, C72, C76 and D45).

Statistical analysis

Hemodialysis patients were divided into quartile groups according to serum selenium levels. Continuous variables are expressed as means (standard deviations) or sex- and age-adjusted means [95% confidence intervals (CIs)] estimated by analysis of covariance (ANCOVA) in quartile groups. Multiple comparisons were performed using the Bonferroni method. Sex- and age-adjusted proportions were determined by logistic regression analysis.

Cumulative probability of death was estimated by the Kaplan–Meier method, and mortalities were compared between the groups by the log-rank test. Crude mortality rates and direct age-adjusted mortality rates (per 1000 patient-years) stratified by quartile groups were calculated. Age-adjusted mortality rate was calculated by the direct method using the WHO standard population of 2000–25. Sex- and age-adjusted hazard ratios (HRs) and multivariate-adjusted HRs and their 95% CIs for total death, infection disease death, CVD death and malignant disease death were estimated in the upper three quartile groups compared with those for patients in the Q1 group serving as a reference after adjustment for risk factors [age, male gender, underweight (BMI < 18.5), overweight (BMI ≥ 27.5), hypertension (systolic blood pressure > 140 or diastolic blood pressure > 90 or medication), dyslipidemia (TC ≥ 220 mg/dL or HDLC < 40 mg/dL), diabetes mellitus, serum albumin levels, high-sensitivity CRP (hsCRP) levels, history of myocardial infarction, history of stroke, history of malignant disease, smoking status and regular drinking habit] using Cox’s regression model. All
Selenium and death risk in hemodialysis patients

Table 1. Criteria for determining causes of death in the KAREN Study (based on ICD-10)

<table>
<thead>
<tr>
<th>Category: Cardiovascular death</th>
<th>Cause: 101–199</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death: I20–I25, I29, I27, I30–I52</td>
<td></td>
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<tr>
<td>I20–I25 Coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>I33 Acute and subacute endocarditis</td>
<td></td>
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<tr>
<td>I50 Heart failure</td>
<td></td>
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</tbody>
</table>

Cardiac arrest: 146
I46.0 Cardiac arrest with successful resuscitation
I46.1 Sudden cardiac death, so described
I46.9 Cardiac arrest, unspecified

Ventricular fibrillation and flutter: I49
I49.0 Ventricular fibrillation and flutter

Other sudden death, cause unknown R96
R96.0 Instantaneous death
R96.1 Death occurring less than 24 h from onset of symptoms, not otherwise explained

Infectious disease-related death
A: bacterial infection: A00–A09, A15–A19, A40–A41
B: viral infection, fungal and other microorganism infection G: infectious diseases in nervous system
G00 Bacterial meningitis, not elsewhere classified
G04.2 Bacterial meningocerebritis and meningoencephalitis, not elsewhere classified

K: infectious diseases in gastrointestinal tract and digestive organ
K65 Peritonitis
K80.3 Calculus of bile duct with cholangitis
K81 Cholecystitis

L: infectious diseases in skin and subcutaneous tissue
L03 Cellulites
L89 Decubitus ulcer

Table 2 shows baseline characteristics of patients stratified by quartile groups according to serum selenium levels. Ranges of serum levels of the quartile groups were 18.4–85.3 (µg/L) in the Q1 group, 85.4–99.9 in the Q2 group, 100.0–114.0 in the Q3 group and 114.2–226.2 in the Q4 group. Mean age in the Q1 group was significantly higher than mean ages in the other groups (Q1 versus Q2, P = 0.006; Q1 versus Q3, P < 0.001; Q1 versus Q4, P < 0.001, by analysis of variance), and an inverse relationship between serum selenium levels and age was observed (trend P < 0.05). Proportions of male patients and mean vintage of hemodialysis were not different between the groups.

Both sex- and age-adjusted means of BMI in the Q3 and Q4 groups were significantly higher than that in the Q1 group (Q1 versus Q2, P = 0.450; Q1 versus Q3, P = 0.020; Q1 versus Q4, P = 0.043, by ANCOVA). Adjusted means of serum albumin in the Q3 and Q4 groups were significantly higher than that in the Q1 group (Q1 versus Q2, P = 0.292; Q1 versus Q3, P = 0.004; Q1 versus Q4, P < 0.001, by ANCOVA). Adjusted geometric means of hsCRP levels in the Q2, Q3 and Q4 groups were significantly lower than that in the Q1 group (Q1 versus Q2, P = 0.001; Q1 versus Q3, P = 0.002; Q1 versus Q4, P < 0.001, by ANCOVA). The proportion of patients with hypertension in the Q4 group was significantly higher than that in the Q1 group (Q1 versus Q2, P = 0.819; Q1 versus Q3, P = 0.777; Q1 versus Q4, P = 0.024, by logistic regression). The proportion of patients having a current smoking habit in the Q2 group was significantly higher than that in the Q1 group (Q1 versus Q2, P = 0.029; Q1 versus Q3, P = 0.901; Q1 versus Q4, P = 0.113, by logistic
After completion of 5-year follow-up studies, the observed patient-years were 4152. Mean and median follow-up periods were 4.0 and 4.9 years, respectively. A total of 382 patients died during the 5-year observation period. Figure 2 shows Kaplan–Meier estimated cumulative probability of death for the groups. The Q1 group had a significantly higher mortality rate from all causes of death than the rates in the other three groups (Q1 versus Q2, P = 0.024; Q1 versus Q3, P < 0.001; Q1 versus Q4, P < 0.001, by log-rank test, Figure A). The Q1 group also had a significantly higher mortality rate from infectious disease than the rates in the other three groups (Q1 versus Q2, P < 0.001; Q1 versus Q3, P < 0.001; Q1 versus Q4, P < 0.001, Figure A). No significant differences in mortality rate between the groups were observed for CVD-related death and malignant disease-related death.

Table 3 shows numbers of deaths and crude or age-adjusted mortality rates (per 1000 patient-years) by the quartile groups according to serum selenium levels in the hemodialysis patients. Crude (age-adjusted) mortality rates in the quartile groups (Q1, Q2, Q3 and Q4) were 134.5 (53.3), 57.7 (22.7), 42.9 (16.8) and 36.8 (14.8), respectively, for all-cause death and 52.7 (14.4), 20.2 (6.6), 17.9 (4.8), and 8.9 (3.6), respectively, for infectious disease-related death. These data suggested that lower selenium levels in hemodialysis patients contributed to increased risks for all-cause and infectious disease-related deaths. On the other hand, relationships of serum selenium levels with CVD-related death and malignant disease-related death were not observed. Results were similar when the general Japanese population was used for age-standardization (data not shown).

Figure 3 shows adjusted HRs for all-cause death, CVD-related death, infectious disease-related death and malignant disease-related death in the upper three groups compared with those for patients in the Q1 group. An inverse relationship between serum selenium levels and all-cause mortality was observed after adjustment for sex and age (trend P = 0.007), and an inverse relationship between serum selenium and infectious disease-related mortality was observed after adjustment for sex and age (trend P < 0.001). Risks for infectious disease-related mortality in the Q2, Q3 and Q4 groups were significantly lower than that in the Q1 group (each P < 0.001) after adjustment for sex and age. Risks for infectious disease-related death in the Q2 and Q4 groups were significantly lower than that in the Q1 group (Q1 versus Q2, P = 0.038; Q1 versus Q4, P = 0.032), and the risk for infectious disease-related death in the Q3 group was lower but not significantly lower (P = 0.121) after multivariate adjustment. An evident inverse relationship between serum selenium levels and infectious disease-related mortality was observed even after multivariate adjustment (trend P = 0.024). On the other hand,
relationships between serum selenium levels and all-cause, cardiovascular and malignant disease-related mortality rates were not observed after multivariate adjustment.

Discussion

We showed that low levels of serum selenium increased the risk for death, especially infectious disease-related death, in hemodialysis patients. Previous studies showed that lower levels of serum selenium were associated with the development of cardiovascular diseases [2, 21, 22], malignant neoplasms [5, 6, 22] and viral infectious diseases [4, 23] in the general population. However, to our knowledge, there has been no investigation of whether low serum selenium levels contribute to an increase in mortality either in the general population or hemodialysis patients.

It is known that hemodialysis patients have disturbances of the immune system and subsequent susceptibility to infections. Rate of mortality caused by sepsis was shown to be 50 times higher in hemodialysis patients than in the general population after adjustments for risk factors [24]. Current data suggest that acquired immunity disturbances in hemodialysis patients are attributed mainly to dysfunction of T-lymphocytes and activation of antigen-presenting cells.
Since T-lymphocyte-dependent immune response is impaired in hemodialysis patients, hemodialysis patients tend to develop infectious diseases. In addition, MIAS activates APCs and also exacerbates T-lymphocyte function [25]. The influence of selenium on immunity function has been shown [23]. An appropriate selenium intake is necessary for maintenance of cell-mediated immunity and humoral immunity [26, 27]. Selenium-deficient lymphocytes have less capability for proliferation in response to mitogen [28]. Selenium inhibits activation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells, which regulates genes that encode inflammatory cytokines. Reduction of selenium contributes to activated inflammation [29, 30]. These studies suggested that selenium deficiency exacerbates immune function and activates inflammation. Selenium deficiency also exacerbates hemodialysis-related immune dysfunction and may contribute to an increase in risks for severe infection and infectious disease-related death.

It was not definitely determined in this observational study whether decreased selenium directly contributes to increased risks for death due to infection and there remains the possibility that selenium deficiency is one of the common phenomena just secondarily derived from a systemic deconditioning status. In our previous study, cross-sectional analysis indicated that decreased selenium levels were associated with malnutrition and activated inflammation status [31]. However, we also revealed that low levels of serum selenium increased the risk for infectious disease-related death independently of MIAS and that decreased selenium level is not only a subsequent event secondary to systemic deconditioning but also an independent predictive risk factor for infectious disease-related death.

Since it was shown that severe selenium deficiency caused endemic cardiomyopathy [32], relationships between selenium deficiency and cardiac diseases have been investigated in several studies. Salonen et al. [21] showed that the adjusted relative risk for cardiovascular death due to low serum selenium level (Se < 45 µg/L) was 2.2 (95% CI: 1.20–4.00, P < 0.01) in a case–control study in Finland, where selenium level in the soil is very low. A meta-analysis (including 14 prospective cohort studies and 11 case–control studies) indicated that the pooled relative risk for coronary events in a comparison of the highest to lowest categories of selenium level was 0.85 in cohort studies (95% CI: 0.74–0.99) and 0.43 in case–control studies (95% CI: 0.29–0.66) [2]. This meta-analysis showed that high levels of serum selenium contribute to decreased risk of coronary events.

An inverse relationship was not observed between serum selenium levels and cardiovascular mortality among hemodialysis patients in our study. There are several possible reasons for this. Although serum selenium levels in hemodialysis patients in our study were lower than those in the Japanese general population [33], the levels of serum selenium in our study samples were not greatly decreased compared to those in the study in Finland [21]. The small number of subjects with severe selenium deficiency in our study may have attenuated the inverse relationship between selenium levels and cardiovascular death. In

<table>
<thead>
<tr>
<th>Serum selenium quartile group</th>
<th>Events / years</th>
<th>Person-years</th>
<th>Sex and age-adjusted</th>
<th>Multivariate-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q1</td>
<td>125/16812.5</td>
<td></td>
<td>0.85 (0.65-1.10)</td>
<td>0.98 (0.74-1.30)</td>
</tr>
<tr>
<td>Q2</td>
<td>104/10389.6</td>
<td></td>
<td>0.78 (0.59-1.03)</td>
<td>1.00 (0.74-1.33)</td>
</tr>
<tr>
<td>Q3</td>
<td>91/7816.9</td>
<td></td>
<td>0.66 (0.48-0.90)</td>
<td>0.92 (0.66-1.29)</td>
</tr>
<tr>
<td>Q4</td>
<td>62/3422.4</td>
<td></td>
<td>Trend p = 0.007</td>
<td>Trend p = 0.705</td>
</tr>
<tr>
<td>Cardiovascular disease-related death</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q1</td>
<td>41/672.5</td>
<td></td>
<td>1.46 (0.81-2.28)</td>
<td>1.48 (0.98-2.25)</td>
</tr>
<tr>
<td>Q2</td>
<td>60/1111.8</td>
<td></td>
<td>0.90 (0.50-1.60)</td>
<td>1.38 (0.89-2.14)</td>
</tr>
<tr>
<td>Q3</td>
<td>52/457.6</td>
<td></td>
<td>0.80 (0.42-1.51)</td>
<td>1.01 (0.61-1.69)</td>
</tr>
<tr>
<td>Q4</td>
<td>30/256.7</td>
<td></td>
<td>Trend p = 0.286</td>
<td>Trend p = 0.913</td>
</tr>
<tr>
<td>Infectious disease-related death</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q1</td>
<td>49/2582.3</td>
<td></td>
<td>0.45 (0.27-0.75)</td>
<td>0.55 (0.33-0.97)</td>
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<tr>
<td>Q2</td>
<td>21/424.2</td>
<td></td>
<td>0.43 (0.25-0.74)</td>
<td>0.64 (0.36-1.13)</td>
</tr>
<tr>
<td>Q3</td>
<td>19/340.1</td>
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<td>0.29 (0.15-0.58)</td>
<td>0.45 (0.22-0.93)</td>
</tr>
<tr>
<td>Q4</td>
<td>10/89.0</td>
<td></td>
<td>Trend p &lt; 0.001</td>
<td>Trend p &lt; 0.024</td>
</tr>
<tr>
<td>Malignant disease-related death</td>
<td></td>
<td></td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q1</td>
<td>4/17.2</td>
<td></td>
<td>1.18 (0.32-4.43)</td>
<td>2.41 (0.54-10.84)</td>
</tr>
<tr>
<td>Q2</td>
<td>5/24.0</td>
<td></td>
<td>0.78 (0.17-3.53)</td>
<td>1.62 (0.31-6.62)</td>
</tr>
<tr>
<td>Q3</td>
<td>3/8.4</td>
<td></td>
<td>1.61 (0.41-6.25)</td>
<td>2.98 (0.62-14.35)</td>
</tr>
<tr>
<td>Q4</td>
<td>5/22.5</td>
<td></td>
<td>Trend p = 0.637</td>
<td>Trend p = 0.262</td>
</tr>
</tbody>
</table>

Fig. 3. Adjusted HRs for death (all-cause, CVD, infectious disease and malignant disease-related death) in the upper three quartile groups with patients in the Q1 group serving as a reference. Risk for all-cause death in the Q4 group was significantly lower than that in the Q1 group (P < 0.001, by Cox’s regression), and risks for infectious disease-related death in the upper three groups were lower than that in the Q1 group after sex and age adjustment (each P < 0.001). Inverse relationships between serum selenium levels and all-cause mortality and between serum selenium levels and infectious disease-related mortality were observed even after sex and age adjustment (each trend P = 0.007, P < 0.001). An evident inverse relationship between serum selenium levels and infectious disease-related mortality was observed even after multivariate adjustment (trend P = 0.003). Relationships between serum selenium levels and all-cause, cardiovascular and malignant disease-related mortalities were not observed after multivariate adjustment.

(APCs). Since T-lymphocyte-dependent immune response is impaired in hemodialysis patients, hemodialysis patients tend to develop infectious diseases. In addition, MIAS activates APCs and also exacerbates T-lymphocyte function [25].

The influence of selenium on immunity function has been shown [23]. An appropriate selenium intake is necessary for maintenance of cell-mediated immunity and humoral immunity [26, 27]. Selenium-deficient lymphocytes have less capability for proliferation in response to mitogen [28]. Selenium inhibits activation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells, which regulates genes that encode inflammatory cytokines. Reduction of selenium contributes to activated inflammation [29, 30]. These studies suggested that selenium deficiency exacerbates immune function and activates inflammation. Selenium deficiency also exacerbates hemodialysis-related immune dysfunction and may contribute to an increase in risks for severe infection and infectious disease-related death.

It was not definitely determined in this observational study whether decreased selenium directly contributes to increased risks for death due to infection and there remains the possibility that selenium deficiency is one of the common phenomena just secondarily derived from a systemic deconditioning status. In our previous study, cross-sectional analysis indicated that decreased selenium levels were associated with malnutrition and activated inflammation status [31]. However, we also revealed that low levels of serum selenium increased the risk for infectious disease-related death independently of elevated hsCRP and low albumin level in hemodialysis patients. This suggested that low levels of serum selenium increased the risk for infectious disease-related death independently of MIAS and that decreased selenium level is not only a subsequent event secondary to systemic deconditioning but also an independent predictive risk factor for infectious disease-related death.

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An inverse relationship was not observed between serum selenium levels and cardiovascular mortality among hemodialysis patients in our study. There are several possible reasons for this. Although serum selenium levels in hemodialysis patients in our study were lower than those in the Japanese general population [33], the levels of serum selenium in our study samples were not greatly decreased compared to those in the study in Finland [21]. The small number of subjects with severe selenium deficiency in our study may have attenuated the inverse relationship between selenium levels and cardiovascular death.
addition, dialysis itself is a strong risk factor for cardiovascular disease [34], and a relatively weak inverse relationship between selenium levels and cardiovascular mortality may be negated by a strong effect of dialysis on cardiovascular risks.

An inverse relationship was also not observed between serum selenium levels and malignant disease-related mortality among hemodialysis patients in our study. Previous studies suggested associations between selenium deficiency and risks for development of several cancers [5, 6]. It was hypothesized that selenium deficiency contributes to increased risks for death due to several cancers. However, only 17 patients died of malignant disease-related death and we were not able to perform accurate risk assessment for malignant disease-related death due to the small number of subjects.

This study firstly showed that lower selenium levels in hemodialysis patients independently contributed to increased risks for infectious disease-related death. However, greatly reduced levels of selenium (<70 μg/L) [35] were found in only 80 patients, and the rather small sample size of patients with selenium deficiency probably contributed to weak statistical power for estimating risks for death after multivariate adjustment. There were 173 patients who did not provide additional serum samples to determine serum selenium levels in this study. They had rather unfavorable characteristics. Since we excluded data for these 173 patients from analysis, the results of this study were for rather healthy hemodialysis patients and the relationship between serum selenium levels and risk for death may be attenuated.

Selenium deficiency is a serious problem that commonly occurs in a very restricted area where environmental selenium is greatly depleted. However, our data indicated that selenium deficiency might occur in hemodialysis patients in non-specific areas where environmental selenium is sufficient such as in Japan [33]. Nonetheless, a strong inverse relationship between serum selenium and infectious disease-related death was clearly indicated; therefore, we should pay more attention to selenium deficiency in hemodialysis patients and should examine why serum selenium levels in hemodialysis patients are decreased.

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Conflict of interest statement. None declared.

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