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Serum Selenium Levels in Hemodialysis Patients Are Significantly Lower than Those in Healthy Controls

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Key Words
Hemodialysis · Selenium · Risk factors · End-stage renal disease

Abstract
Serum selenium levels have been thought to be decreased in hemodialysis patients; however, results of previous studies have been inconsistent. Population-based hemodialysis patients (n = 1,041) and randomly recruited healthy controls (n = 384) were enrolled. Serum selenium levels were determined by inductively coupled plasma mass spectrometry and compared in hemodialysis patients and controls using analysis of covariance after adjustment for confounding factors with $p < 0.1$ as the result of the multiple regression analysis. Age, serum albumin levels, hsCRP levels, LDLC levels, HDLC levels, regular drinking habit and hemodialysis treatment were significantly associated with serum selenium levels in multiple regression analysis. Multivariate-adjusted means (95% CIs) of serum selenium levels were 103 μg/l (101–105) in hemodialysis patients and 117 μg/l (114–121) in controls. Selenium levels in hemodialysis patients were decreased. Whether decreased serum selenium levels contribute to increased risks for morbidity and mortality in hemodialysis patients should be examined.

Introduction

Selenium deficiency contributes to an increased risk for the development of malignant neoplasms [1–3], viral infectious diseases [4–7] and cardiovascular diseases [3, 8, 9] in general populations. On the other hand, several studies have shown that serum levels of selenium in hemodialysis patients were lower than those in normal controls [10–14]. These findings suggest that decreased selenium levels in hemodialysis patients may contribute to increases in risks for morbidities from various diseases and that a decreased selenium level may be one of the unknown strong risk factors for death in hemodialysis patients.

However, there were inconsistent results and considerable wide variations of serum selenium levels in previous

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studies. The inconsistent results and wide variations were mainly due to small sample analysis and due to relatively inaccurate measurements by old equipment [15]. It is necessary to determine whether serum selenium levels are in fact decreased in hemodialysis patients compared to those in normal controls based on representative samples and a highly sensitive assay of selenium.

Subjects and Methods

Subjects

Eligible participants were adult hemodialysis patients who participated in the KAREN Study [16]. Data for 1,041 participants (663 men aged 22–91 years with a mean age of 61.2 ± 13.4 years, 378 women aged 25–88 years with a mean age of 61.1 ± 12.7 years) were analyzed in this study. Control subjects (193 men aged 40–78 years with a mean age of 57.6 ± 10.1 years, 191 women aged 41–77 years with a mean age of 56.9 ± 9.8 years) were recruited from two towns in the KAREN study area by stratified random sampling methods [17].

All participants gave written informed consent. This study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

Data Collection

The examinations in hemodialysis patients and controls consisted of a questionnaire, measurements of blood pressure and anthropometric data and blood tests. Predialysis blood sampling was carried out in hemodialysis patients [16] and overnight fasting samples were obtained from healthy controls [17]. Biochemical tests and blood counts were performed on the same day [16, 17]. The methods used for biochemical tests and blood counts have been previously reported in detail [16]. Residual sera were stored at −80°C in our laboratory until determination of selenium.

Selenium Determination

Frozen serum samples were unfrozen and each serum specimen (1 ml) was pipetted into a Teflon tube; then 3.0 ml of high-purity nitric acid was added. The tube was heated to 120°C for 12 h to completely decompose organic matter in the serum sample. The resultant solution was cooled and transferred into a Teflon beaker. The beaker was heated to 100°C until dryness. 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 within-run and total imprecision were determined according to the NCCLS Approved Guideline [18]. Two replicates of selenium measurements in mixed sera per day were carried out. The method produced a within-run standard deviation (SD) 3.9 μg/l at 139.8 μg/l. Total precision gave a SD of 6.2 μg/l at 139.8 μg/l.

Statistical Analysis

Mean ages (SDs) of hemodialysis patients and controls were compared by Student's t test. Sex- and age-adjusted means of continuous variables were compared between hemodialysis patients and controls using analysis of covariance (ANCOVA). The χ^2 test was used to compare frequencies among categories. Multiple regression analysis was performed for predicting serum selenium level using age, sex, serum albumin level, high-sensitivity C-reactive protein (hsCRP) level, low-density lipoprotein cholesterol (LDLC) level, high-density lipoprotein cholesterol (HDLC) level, regular drinking habit and hemodialysis treatment as explanatory variables. We calculated crude and adjusted mean levels of serum selenium in both hemodialysis patients and controls using ANCOVA separately by sex after adjusting for confounding factors with $p < 0.1$ as the result of multiple regression analysis (except for hemodialysis treatment). All p values were based on two-sided tests and p values <0.05 were considered to be statistically significant. The Statistical Package for Social Sciences (SPSS Japan Inc., version 15.0, Tokyo) was used for the analyses.

Results

Table 1 shows characteristics of hemodialysis patients and controls. Sex- and age-adjusted means of body mass index (BMI), serum albumin, total cholesterol levels, HDLC levels and LDLC levels in hemodialysis patients were significantly lower than those in controls. Adjusted geometric means of hsCRP levels in hemodialysis patients were significantly higher than those in controls. The proportion of patients having a regular drinking habit was significantly lower in hemodialysis patients than in controls.

Table 2 shows the results of multiple linear regression analysis for predicting serum selenium levels. Age, serum albumin levels, hsCRP levels, LDLC levels, HDLC levels, regular drinking habit and hemodialysis treatment were significantly associated with serum selenium levels. Collinearity between the explanatory variables was not found. Therefore, we used these variables except for hemodialysis treatment as explanatory variables in ANCOVA in order to calculate multivariate-adjusted means of serum selenium in hemodialysis patients and controls.

Table 3 shows crude and adjusted serum selenium levels both in hemodialysis patients and healthy controls. Crude means (SD) of serum selenium level (measured in micrograms per liter) were 100 (23) and 100 (21) in male and female hemodialysis patients, respectively, and they were 132 (23) and 125 (19) in male and female controls, respectively. Age-adjusted means (95% CI) of serum selenium level were 101 (99–103) and 101 (98–103) in male and female hemodialysis patients, respectively, and they were 131 (128–134) and 124 (121–127) in male and female controls, respectively. Multivariate-adjusted means (95%

Table 1. Baseline characteristics of hemodialysis patients and controls

Groups, n	Hemodialysis (1,041)	Controls (384)	p value
Serum selenium range, μg/l	18.41–226.22	56.12–215.62	
Mean age (SD), years	61.1 (13.1)	57.2 (9.9)	<0.001
Men, n (%)	663 (63.7)	193 (48.9)	<0.001
Sex- and age-adjusted means (95% CI)			
BMI	20.8 (20.6–21.0)	24.1 (23.8–24.4)	<0.001
Serum albumin, g/dl	3.8 (3.7–3.8)	4.4 (4.3–4.4	<0.001
hsCRP, mg/l	3.920 (3.46–4.38)	0.970 (0.13–1.80)	<0.001
Total cholesterol, mg/dl	155.4 (153.5–157.4)	197.8 (194.4–201.3)	<0.001
LDLC, mg/dl	85.2 (83.6–86.7)	122.4 (119.7–125.2)	<0.001
HDLC, mg/dl	47.2 (46.4–48.1)	53.0 (51.5–54.5)	<0.001
Current smoker, n (%)	278 (26.7)	100 (25.3)	0.3
Regular drinker, n (%)	74 (7.1)	131 (33.2)	<0.001

p values were calculated by Student's t test, χ^2 test or ANCOVA between hemodialysis patients and controls.
BMI = Body mass index; hsCRP = high-sensitivity C-reactive protein; LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol.

CI) of serum selenium level were 103 (102–105) and 103 (100–105) in male and female hemodialysis patients, respectively, and they were 119 (114–123) and 117 (112–122) in male and female controls, respectively. Serum selenium levels in hemodialysis patients were significantly lower than those in controls for both males and females even after adjustment for confounding factors ($p < 0.05$).

Table 2. Standardized regression coefficients by multiple linear regression analysis predicting serum selenium concentrations

	Standardized coefficients	p value	Variance inflation factor
Age	−0.123	<0.001	1.219
Men	0.027	0.309	1.309
BMI	0.027	0.313	1.360
Serum albumin	0.187	<0.001	2.044
hsCRP	−0.053	0.027	1.084
LDLC	0.097	<0.001	1.445
HDLC	0.077	0.006	1.464
Regular drinker	0.061	0.025	1.406
Hemodialysis	−0.234	<0.001	2.349

For abbreviations, see table 1.

Discussion

In this study, we estimated crude and adjusted means of serum selenium levels in both hemodialysis patients and controls. We revealed that serum selenium levels in hemodialysis patients were significantly lower than those in controls for both males and females. The results were robust even after adjustment for confounding factors.

A meta-analysis (consisting of 46 studies, n = 2,939; Europe: 47%, Asia: 30%, North America: 14%) showed results of comparisons of serum selenium levels between hemodialysis patients and controls [15]. Sample sizes of hemodialysis patients and controls ranged from 6 to 456 (median: 24) for hemodialysis patients and 5 to 490 (median: 28) for controls in this meta-analysis. There were 37 studies that showed lower selenium levels in hemodialysis patients, 8 studies that showed no differences between selenium levels in hemodialysis patients and controls, and one study that showed higher selenium levels in hemodialysis patients than in controls. Briefly, the results of the meta-analysis indicated that hemodialysis patients appeared to have lower levels of selenium than general populations. However, there were inconsistent results and considerable wide variations of serum selenium levels in those studies. The inconsistent results and wide variations were mainly due to small sample analysis and due to relatively inaccurate measurements by old equipment. Moreover, there have been no studies in which consideration was given to important confounders such as environmental selenium concentration (i.e. regional dif-

Table 3. Crude and adjusted serum selenium levels in hemodialysis patients and controls

Group	n	Serum selenium level, μg/l		
		crude mean ± SD	age-adjusted mean (95% CI)	multivariate-adjusted mean (95% CI)
HD				
Male	663	100 ± 23	101 (99–103)	103 (102–105)
Female	378	100 ± 21	101 (98–103)	103 (100–105)
Total	1,041	100 ± 22	101 (99–102)	103 (101–105)
Control				
Male	193	132 ± 23	131 (128–134)	119 (114–123)
Female	191	125 ± 19	124 (121–127)	117 (112–122)
Total	384	128 ± 21	128 (125–130)	117 (114–121)

Multivariate-adjusted means of serum selenium were estimated by analysis of covariance using age, serum albumin levels, hsCRP levels, HDLC levels, LDLC levels, and regular drinking habit as explanatory variables. For abbreviations, see table 1.

ference), sex-based differences and generation-based differences. Therefore, our study is the first study showing lower selenium levels in hemodialysis patients than in controls based on representative samples and a highly sensitive assay of selenium.

We determined serum selenium levels in this study. Generally, selenium levels in hair and nails are measured to determine past excessive exposure to selenium [19]. However, measurement of selenium levels in serum is useful for determining recent excessive exposure to selenium and detecting selenium insufficiency/deficiency [20]. Measurement of serum levels of selenium was therefore considered to be an ideal method for detecting selenium deficiency in hemodialysis patients in this study, and the serum selenium level is thought to be an ideal marker for determining selenium insufficiency/deficiency.

Conclusions

Serum levels of selenium in hemodialysis patients were significantly lower than those in healthy controls. Decreased selenium levels in hemodialysis patients may contribute to increases in risks for morbidities and mortalities from various diseases. We should examine in prospective longitudinal studies why serum selenium levels in hemodialysis patients are decreased and we should confirm whether decreased serum selenium levels in hemodialysis patients contribute to an increased risk for morbidity and mortality due to malignant, infectious and cardiovascular diseases.

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Disclosure Statement

None.

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Serum C-Reactive Protein Levels and Death and Cardiovascular Events in Mild to Moderate Chronic Kidney Disease

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SUMMARY

Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular (CV) disease. Elevated circulating levels of high sensitivity C-reactive protein (hsCRP) have been suggested to be associated with high risk of CV disease. It is uncertain whether the CV risk in CKD can be stratified by hsCRP levels in the Japanese population. Baseline data including serum hsCRP and creatinine levels were determined in the general population. Estimated glomerular filtration rate (eGFR) was calculated using a modified MDRD equation, and CKD was defined as eGFR below 60 mL/minute/1.73m^2. We analyzed 1,074 male subjects with mild to moderate CKD (mean age, 70.4 years). CV events (stroke and myocardial infarction) and all-cause death were surveyed prospectively. The CKD subjects were followed for 5.1 years, and 72 CV events and 115 all-cause deaths were found (composite endpoint). After adjustment for established CV risk factors, hazard ratios (HRs) for the endpoint were significantly increased according to the hsCRP quintile ($P < 0.001$), and HR for the highest (versus the lowest) quintile was 2.77 (95% CI; 1.61-4.77). These results suggest that serum hsCRP measurement is a useful tool for the risk stratification of CV events and death in CKD male subjects selected from the general population. (Int Heart J 2011; 52: 180-184)

Key words: Risk, Prediction, Stroke, Myocardial infarction, Mortality

Chronic kidney disease (CKD) is defined by a decreased glomerular filtration rate (GFR) and/or proteinuria.[1)] Several recent reports have shown that the risk for death is increased independently in subjects with mild renal dysfunction, compared with those who have preserved kidney function.[2,3)] The incidence of cardiovascular (CV) events in patients with CKD is higher than in those with normal kidney function,[2)] and it has been reported that CKD is an independent risk factor for CV events and CV death.[2,4)] Indeed, the incidence of CV events and death in Japanese patients with CKD is higher than that for individuals without CKD according to longitudinal studies.[5,6)]

On the other hand, serum high sensitivity CRP (hsCRP) has been reported to be related to the incidence of CV events in European and US general populations.[7-9)] The mean value of serum hsCRP in the Japanese general population tends to be lower than in other ethnic groups.[7-13)] Recently, the Hisayama cohort study has reported that elevated hsCRP in the Japanese adult population is a risk factor for ischemic stroke and coronary heart disease.[12,13)]

However, it remains unknown whether serum hsCRP levels increase the risk for CV events in individuals with CKD. Moreover, as the prevalence of CKD in the Japanese general population is greater than 10%[14)] and is higher than in the US population,[15,16)] it is uncertain whether the CV risk in CKD could be stratified by hsCRP levels in the Japanese population. The present longitudinal cohort study has therefore sought to ascertain whether increased serum hsCRP levels elevate the risk for CV events and all-cause death in CKD subjects selected from the general Japanese male population.

METHODS

Study subjects: We conducted a prospective community based cohort study of cardiovascular disease in Iwate Prefecture, which is located in the northern part of Honshu, Japan (Iwate-KENCO study). A total of 26,469 residents consented to participate in the study. The following participants were excluded from analysis: under 40 years of age (n = 1,100), female subjects (n = 16,508) (since females have a lower incidence of CV events), a history of myocardial infarction and stroke (n = 478), or missing data relating to blood sampling (n = 192), body mass index (BMI) (n = 13), or systemic blood pressure (n = 2).

The eGFR was calculated using an equation [eGFR (mL/

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minute/1.73 m^2) = 194 x $Cr^{-1.094}$ × $age^{-0.287}$] from the Modification Diet in Renal Disease Study (MDRD) for the Japanese population.[17] CKD was defined in the present study as eGFR < 60 mL/minute/1.73 m^2. Subjects with severe renal dysfunction (eGFR < 30 mL/minute/1.73 m^2) were excluded (n = 16). The final statistical analysis included 1,074 male subjects with CKD (mean age = 70.4 years). The study protocol was approved by the university ethics committee and the local hospital review committee. All participants provided written informed consent.

Measurements: All subjects used a self-report questionnaire to confirm their medical history, including the use (yes/no) of prescribed drugs for hypertension, diabetes, or hypercholesterolemia. Smoking status (current, past smoker, or nonsmoker) was also ascertained by questionnaire.

Systemic blood pressure in a sitting position after at least 5 minutes rest was measured by experienced research staff using an automatic digital device (BP-103i II, model 513000, Nippon Colin). Measurement was performed twice, with the mean value used for statistical analysis. Peripheral venous blood samples were taken from the upper arm with the subjects in a seated position to measure lipids, blood sugar, hemoglobin A1c, creatinine (Cr), and hsCRP. Serum Cr levels were measured by an enzymatic method (Hitachi 7700, Hitachi, Tokyo), and serum hsCRP levels were determined by turbidimetric immunoassay using a Nephelometer Analyzer II (Dade Behring).

Diabetes was defined as a nonfasting glucose concentration ≧ 200 mg/dL and/or HbA1c value ≧ 6.5% and/or use of antidiabetic agents including insulin. Hypertension was defined as systolic blood pressure ≧ 140 mmHg and/or diastolic blood pressure ≧ 90 mmHg and/or the use of antihypertensive medication. Hypercholesterolemia was defined as a total cholesterol concentration ≧ 240 mg/dL and/or use of lipid-lowering agents. BMI was calculated as weight (kg) divided by the square of height (m^2).

Endpoints: We defined the endpoint as the composite of CV event (stroke and myocardial infarction) and all-cause death. Incidents of hospitalized myocardial infarction were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. The registration of myocardial infarction was based on the criteria of the MONICA study.[18] Stroke events were identified by accessing the Iwate Prefecture Stroke Registration Program, which included the entire area where the subjects lived; the details have been described previously.[19] Since 1991, the stroke registration program has been coordinated by the Iwate prefecture government and the Iwate Medical Association; the medical records of all medical facilities within the survey area are verified to ensure complete capture of all data. To verify the accuracy of the data, a physician or trained research nurse visited and checked the medical records of the referral hospitals.

The follow-up survey for acute myocardial infarction and stroke was carried out after the baseline study and between 2002 and 2004. Follow-up for stroke and myocardial infarction continued until March 2009. All-cause deaths and migrations were confirmed by official resident registration data issued by the local government offices (October, 2009).

Statistical analysis: Continuous variables are shown as the mean or median. CKD subjects were divided into quintiles according to their baseline serum hsCRP levels. To compare results among the hsCRP quintiles, one-way analysis of variance, Kruskal-Wallis test, and Pearson's chi-square test were used as appropriate. The event-free rate from entry into the study was estimated using the Kaplan-Meier method, followed by a trend test (log rank). The association between baseline serum hsCRP levels and the endpoint was evaluated. The hazard ratios (HR) of the hsCRP quintile for the endpoint were assessed using a Cox proportional hazards regression model. In this multivariable proportional-hazards regression model, adjustments were made in the analysis for age, hypertension, diabetes, hypercholesterolemia, BMI, and current smoking. We also used the Cox proportional hazards regression model for analysis of the linear trend among the hsCRP quintile as an ordinal variable. For analyses of CV incidence, person-years were censored at the date of CV events, the date of emigration from the study area, the date of death, or the end of the follow-up period, whichever came first. All statistical analyses were performed using SPSS software (Chicago, IL, USA). A significant difference was defined as $P < 0.05$.

Table. Baseline Data

	Total	hsCRP quintile and range					P*****
		Quintile 1 ≦ 0.2 mg/L	Quintile 2 0.3-0.4 mg/L	Quintile 3 0.5-0.7 mg/L	Quintile 4 0.8-1.5 mg/L	Quintlie 5 ≧ 1.6 mg/L	
n	1,074	173	227	224	233	217	
hsCRP* (mg/L)	0.6	0.2	0.3	0.6	1.0	2.8	
Age (years)	70.4	69.9	69.0	69.8	70.9	72.1	< 0.001
BMI (kg/m^2)	24.2	22.8	24.0	24.6	24.5	25.0	< 0.001
eGFR (mL/minute/1.73m^2)	53.3	53.8	53.7	53.7	53.2	52.8	0.359
Diabetes mellitus**	8.6%	6.4%	7.1%	7.6%	8.6%	13.8%	0.079
Hypertension***	56.6%	51.5%	51.5%	60.3%	60.1%	61.3%	< 0.05
(medication)	38.4%	32.9%	33.0%	37.1%	39.5%	48.4%	< 0.01
Hyperlipidemia****	11.9%	9.3%	11.9%	10.3%	11.6%	16.1%	0.219
(medication)	4.7%	5.2%	4.4%	2.7%	5.2%	6.0%	0.510
Smoking habits	21.7%	20.2%	20.3%	19.6%	22.8%	25.4%	0.439

*Median, **HbA1c ≥ 6.5% or BS ≥ 200 mg/dL and/or medications; ***BP ≥ 140 or 90 mmHg and/or medications; ****TC ≥ 240 mg/dL and/or medications; *****Differences among the CRP quintile.

Results

The prevalence of male CKD in the original cohort (Iwate- KENCO) study was 13.3%. As shown in the Table, in the CKD cohort, the percentage of cases of diabetes, hypertension, hypercholesterolemia, and current smoking were 8.6%, 56.6%, 11.9% and 21.7%, respectively. The mean eGFR was 53.3 mL/minute/1.73 m^2. Among the hsCRP quintiles, mean age and percentage use of antihypertensive agent were higher in the highest quintile compared to the lower quintiles. The percentage use of lipid-lowering agents did not differ significantly among the quintiles.

During the mean follow-up period of 5.1 years for the CKD cohort, 72 CV events (stroke = 55, myocardial infarction = 19) and 115 all-cause deaths were recorded. Kaplan-Meier curves for the event-free rate according to hsCRP quintiles in the CKD cohort are shown in Figure 1. The event-free rate was significantly lower in the 4th and 5th quintiles for hsCRP ($P <$ 0.0001 by log-rank test).

Cox regression analysis was performed to analyze the relationship between serum hsCRP and the outcome after adjustment for age, diabetes, hypertension, hypercholesterolemia, current smoking, and BMI (Figure 2). The HR for CV event and all-cause death obtained from the Cox proportional model for the 4th and 5th quintile for hsCRP was 1.78 (95% CI; 1.02-3.12) and 2.77 (95% CI; 1.61-4.77), respectively. The linear trend was significant ($P < 0.001$).

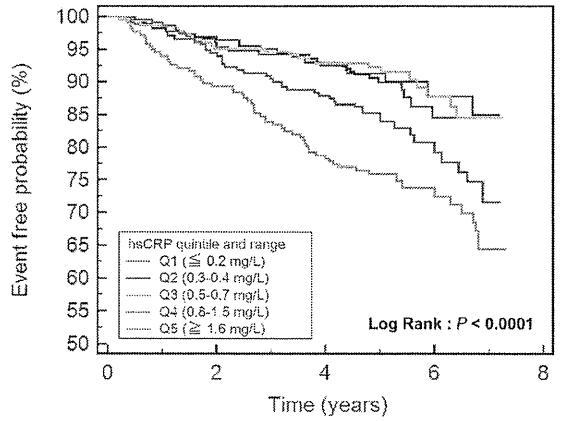

Figure 1. Kaplan-Meier curves of event-free probability according to the quintile of hsCRP value for cardiovascular events and all-cause death.

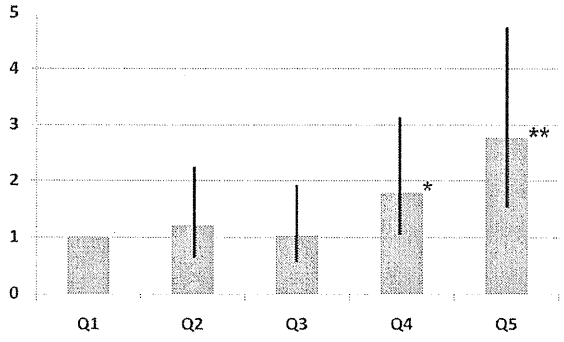

Figure 2. Hazard ratio and 95% CI for cardiovascular events and all-cause death adjusted by established risk factors. Cox's proportional hazard model after adjustment for classical cardiovascular risk factors (such as age, hypertension, hypercholesterolemia, diabetes mellitus, smoking habits and BMI). $^{*}P < 0.05$ (versus Q1). $^{**}P < 0.001$ (versus Q1).

Discussion

The present study demonstrates for the first time that in a CKD cohort defined by eGFR < 60 mL/minute/1.73 m^2 selected from a community based population, the subgroups with the higher hsCRP levels had a significantly greater risk of CV events (ie, myocardial infarction, stroke) and death compared to the low hsCRP subgroup. This relationship was robust even after adjustment for established CV risk factors such as age, hypertension, diabetes, hypercholestolemia, BMI, and current smoking. Our observations suggest that serum hsCRP levels are a useful tool for stratifying the risk of CV events and death within a CKD cohort selected from a general male population.

Go, *et al* reported that eGFR measured in subjects who underwent a health checkup was inversely correlated with mortality and incidence of CV events including stroke and heart failure, over a longitudinal follow-up for 3 years.[2] Similarly, the NIPPON DATA 90 study (a general population study with subjects recruited from various regions of Japan), reported that a decrease in eGFR (< 30 mL/minute/1.73 m^2) elevated the risk of all-cause death and CV death.[6]

The prevalence of CKD in the US population is about 8%, and has recently increased.[16] In contrast, the prevalence of CKD in Japanese is very high at about 20%, according to data on 52,759 subjects recruited from 7 regions around the country.[14] Particularly in men, the prevalence of CKD rises with aging in association with increased prevalence of hypertension and diabetes.[20] In order to prevent CV disease, it is therefore important that effective interventions be developed for the increasing number of individuals with CKD. It is also desirable that markers be developed to facilitate identification of the subgroup of those with CKD who are at increased risk of experiencing CV events.

On the other hand, it is known that inflammation is implicated in the progression of atherosclerosis, and that hsCRP is a useful biomarker for prediction of the risk of CV events such as coronary heart disease and stroke.[7-9] According to the results of a longitudinal follow-up for more than 10 years in a Japanese general population, men with high hsCRP levels (5th quintile versus 1st quintile) had a 6-fold higher risk of ischemic stroke.[13] It was also reported that the relative risk of coronary heart disease in the 3rd quintile of hsCRP was 3 times that in the 1st quintile.[12] We have previously reported that in men attending a multiphasic checkup, a positive relationship was observed between serum hsCRP levels and atherosclerotic plaque score in the carotid artery,[21] and the high hsCRP subgroup in the general population had a 2-fold higher risk of ischemic stroke and death.[19]

On the basis of these backgrounds, we established a hypothesis that among individuals with CKD, the risk of CV events is higher in the high hsCRP subgroup than the lower hsCRP subgroup. We have therefore sought to determine whether CV risk and death in subjects with mild to moderate

CKD (stage 3) could be stratified by serum hsCRP. As a result, we observed that the CKD subgroup with high hsCRP levels had a greater risk of CV events and all-cause death even after adjustment for confounding factors. Our findings suggest that inflammation may play a role in the progression of arteriosclerosis in CKD subjects.

A few reports have shown an association between CKD and serum hsCRP levels. According to a study of the relationship between serum hsCRP and CKD in African Americans, a positive correlation was seen between the presence of albuminuria and serum hsCRP levels in CKD subjects.[22] Menon, *et al* reported that high hsCRP levels (> 6.0 mg/L) are independently associated with onset of CV events in patients with predominantly nondiabetic kidney disease.[23] Soriano, *et al* also reported in a small number of CKD patients (n = 90) that the high hsCRP subgroup (> 10.5 mg/L) had significantly higher CV risk and mortality than the low hsCRP subgroup (< 8 mg/L).[24] However, no studies have yet explored whether serum hsCRP levels may be effective for stratifying CV risk within a large number of CKD subjects selected from a Japanese general population.

In the present study, all-cause death and CV events such as myocardial infarction and stroke were clearly prevalent in the higher hsCRP subgroups. These findings suggest that inflammation is associated with progression of atherosclerosis, and that hsCRP levels are a useful tool for stratifying the risk of CV events within a male CKD cohort selected from a general population. In the present study, the mechanisms by which inflammation increases CV events and death are not clear. However, there are several possible explanations for the fact that elevated serum hsCRP levels are associated with a high risk of CV events. A deterioration in renal function may accelerate inflammation activators such as homocysteine, oxidative stress, thrombogenic factors, apolipoprotein, and anemia.[25-28] In addition, it has been reported that inflammation is itself associated with progression of renal dysfunction and atherosclerosis.[29-31] Because renal dysfunction causes activation of macrophages and inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha,[30-33] renal dysfunction and inflammation may conspire in a vicious cycle, injuring cerebral and coronary blood vessels and thus causing stroke and myocardial infarction.

The present study has several limitations. First, more than 35% of CKD subjects were receiving antihypertensive medications at baseline. Several types of antihypertensive drugs such as angiotensin-converting enzyme-inhibitors and angiotensin II receptor blockers reduce the onset of CV events. The present study could not examine what kind of antihypertensive drugs they take, and could not evaluate the effects of these drugs on the incidence of CV events. However, the percentage of subjects receiving antihypertensive drugs increased with quintiles of serum hsCRP (Table), which suggests that CKD subjects with higher serum hsCRP levels were more likely to receive these medications. This limitation may have underestimated the true association between serum hsCRP levels and CV events. Second, about 5% of the CKD subjects were receiving lipid-lowering agents. Statins have been reported to decrease serum hsCRP levels.[34] In the present study, however, there were no significant differences in the percentage of subjects receiving lipid-lowering agents among the quintiles. Third, in this CKD cohort, levels of hsCRP were obviously low compared to previously reported levels in other ethnic populations.[5,6,10,22-24] There were some reports that serum hsCRP levels in the Japanese population are clearly lower than in other races.[10,11] It is therefore uncertain whether the results found in the present study would be observed in other CKD populations with higher serum hsCRP levels. Fourth, although CKD in the present study was defined by reduced eGFR only, several studies have suggested that proteinuria or albuminuria is another diagnostic component for CKD.[35,36] In view of this, the prevalence of CKD and the relationship between the event risk and serum hsCRP might be varied according to the definition of CKD. Finally, this study clarified that Japanese adult men with CKD and high hsCRP levels had a greater risk of CV events and death than lower hsCRP subgroups. However, it is uncertain whether intervention to reduce serum hsCRP levels would decrease the incidence of CV events and death in CKD. One recent study has shown that statins lower CV events with a reduction in serum hsCRP levels in CKD subjects.[37] Further studies may be necessary to determine whether interventions to reduce serum hsCRP levels will decrease the prevalence of CV events and death in CKD subjects.

Conclusions: Serum hsCRP levels provide predictive information about CV events and all-cause death in men with CKD. This result implies that serum hsCRP measurement is a useful tool for the risk stratification of CV events and death in CKD male subjects.

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原著

透析患者の血清中ヒ素濃度の検討―健常対照との比較、血清ヒ素濃度が心筋梗塞ならびに虚血性脳卒中罹患リスクに与える影響

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要　約　【背景】高濃度のヒ素に曝露された地域住民の冠動脈疾患有病リスク・脳卒中有病リスクが高いことが報告されている。一方有機ヒ素を含む魚介類を多く摂取する日本人慢性維持透析患者では、有機ヒ素が排泄されずに体内に残存している可能性がある。本研究では、透析患者と無作為抽出された健常対照で血清中ヒ素濃度を比較した。次に血清中のヒ素濃度の高さが透析患者の心筋梗塞罹患リスク、脳卒中罹患リスクと関連しているのかを検討した。【方法】対象は平成15年に岩手県で開始した成人血液透析患者地域悉皆的コホート研究参加者1,214名中、登録調査時に血清中ヒ素濃度を測定した1,041名（男663名、女378名、平均年齢61.1歳）。健常対照は岩手県内の二つの町に居住する40-79歳の住民から年齢層化抽出法により選定した384人。血清ヒ素濃度はICP-MS（Elan 6000, Perkin Elmer Co Ltd.）を用いて測定し、透析患者と健常対照でそれぞれ年齢調整平均値を算出して比較した。透析患者の追跡調査は毎年透析施設を直接訪問して全ての透析患者診療記録を閲覧して死亡と心筋梗塞・脳卒中罹患を前向きに調査した。血清中ヒ素濃度で対象者を4分位に分けて粗死亡率、心筋梗塞と脳卒中の粗罹患率（/1000人年）を求めた。ヒ素濃度と死亡リスクならびに心筋梗塞罹患・脳卒中罹患との関係を多変量調整（性別・年齢・血圧・BMI・脂質異常・糖尿病・心筋梗塞既往・脳卒中既往・悪性新生物既往・CRP高値・アルブミン低値）トレンド検定で検証した。【結果】血清ヒ素濃度の性・年齢調整平均値（95%信頼区間）は、透析患者では42.4（40.1-44.6）μg/L、健常対照では11.6（7.82-15.4）μg/Lで透析患者の血清ヒ素濃度は有意に高かった。5年間の追跡調査（追跡調査総計4152人年、平均追跡期間3.9年）で382名の死亡、48名の急性心筋梗塞罹患、112名の虚血性脳卒中を確認した。4群の総死亡率（Q1/Q2/Q3/Q4（/1000人年））は93.3/89.7/79.5/106.0、心筋梗塞罹患率は4.0/10.6/15.6/15.0、虚血性脳卒中罹患率は、28.3/27.6/39.0/18.3であった。血清中ヒ素濃度が高いほど、急性心筋梗塞罹患リスクが有意に高くなっていた（多変量調整トレンド $p = 0.014$ ）。ヒ素濃度と総死亡リスク・虚血性脳卒中罹患リスクとの間に関係性はみられなかった。心筋梗塞既往例を除外した解析では、ヒ素濃度が高くなるほど心筋梗塞罹患リスクが高くなる関係はより明確になった（多変量調整トレンド $p = 0.009$）。【結論】透析患者は一般住民と比較して血清ヒ素濃度が高く、血清中ヒ素濃度が高くなるほど透析患者の心筋梗塞罹患リスクが高かった。日本人透析患者では体内にヒ素が過剰に蓄積している可能性があり、しかも過剰に蓄積したヒ素が心筋梗塞罹患リスクを上げている可能性がある。その因果関係について更なる検討が必要であるとともに、予防対策を講じる必要があると考えられた。

キーワード：透析患者，ヒ素，悉皆的コホート研究，心筋梗塞，虚血性脳卒中，カレン研究
（日循予防誌　46：●―●，2011）

I. 緒　　言

透析患者は循環器疾患のハイリスク集団であり、一般住民に比べその循環器疾患有病リスク、発症リスク、循環器病死亡リスクはいずれも非常に高い[1]。しかし、一般住民で確立した循環器疾患の古典的危険因子の一部は（高血圧、高コレステロール血症、肥満）は、透析患者では予後に悪影響をもたらさないばかりか、一部の報告ではむしろ予後を改善する方向に働くことが観察されている[2]。また、上記の危険因子以外の古典的危険因子（年齢、男性、喫煙など）も、一般人に比べて予後への影響度は強くないことが示されており、透析患者では、古典的危険因子以外のリスク要因が死亡や循環器疾患発症に強く影響していることが示唆されている[3~5]。透析患者における特殊な状況は、古典的危険因子以外のリスク要因の確定を我々に求めているといえる。

一方高濃度のヒ素に慢性的に曝露された集団では、皮膚疾患、神経疾患、呼吸器疾患、一部の悪性新生物（皮膚がん、肺がん、膀胱がん）[6]の発症リスクが上がることが示唆されている。また高濃度ヒ素に慢性的に曝露された集団では、上記疾患発症リスク上昇とともに、冠動脈疾患[7~11]、下肢末梢動脈疾患[12]、脳卒中[13]などの心血管疾患発症リスクが高まることが指摘されている。透析患者は、心血管疾患発症リスクが非常に高い集団であり、危険因子として古典的な危険因子以外の要因が強く影響していることが示唆されていることから、高濃度ヒ素暴露地域で観察された循環器疾患危険因子としてのヒ素が、透析患者の循環器疾患罹患リスクに関係しているかどうかを検討する価値があると思われる。

健常人と比較して透析患者の生体内ヒ素が過剰に蓄積されているかどうかは欧米の報告では一定の見解が得られていない14)。しかし、有機ヒ素を多く含む魚介類を好んで食べる東アジア人はヒ素の食事による摂取量が多いことが知られ[15,16]、有機ヒ素が殆ど尿排泄されることを考慮すると[17]、腎機能が廃絶している日本人透析患者の体内にはヒ素が過剰に蓄積している可能性がある。また慢性的に過剰に蓄積したヒ素が透析患者の死亡リスクや疾患発症リスク（がんや循環器疾患）に影響を与えていることが判明した場合には、日本人の透析患者ではヒ素含有率の高い魚介類などの食事制限などを勧告し、透析患者の予後改善に寄与することを目指すべきである。

本研究では、従来明らかにされていなかった二つの点について焦点を当てて検討を行う。一つは、日本人透析患者の生体内ヒ素が過剰に蓄積しているのかを調べる目的で、多数の透析患者と代表性のある一般住民の血清のヒ素濃度を、精度の高い測定法を用いて測定してその違いを検討することである。もう一つは、すでに行われている地域悉皆的末期腎不全患者コホート研究データベースを用いて、コホート研究開始時の血清のヒ素濃度の高さが透析患者の予後に影響しているのかを前向き調査で明らかにすることである。今回の検討では、環境の高濃度ヒ素に曝露された台湾住民で観察された冠動脈疾患有病率と脳卒中有病率の高さに注目して、血清ヒ素濃度が総死亡に与える影響をみるとともに心筋梗塞症と虚血性脳卒中の罹患リスクに影響しているのかを検討した。

II. 方　　法

研究対象地域

今回の研究対象である透析患者はカレン研究（末期腎不全患者に対する多面的な取り組みにより循環器疾患発症リスクを割り出す研究：Kaleidoscopic Approaches to patients with end-stage RENnal disease, KAREN研究）に参加した成人血液透析患者である。カレン研究の対象地域は岩手県北部から県中央部で、平成14年当時の域内には38市町村が含まれ、総人口は939,448人である。図1の左側はカレン研究を実施した市町村（白塗りの区域）と参加した透析施設の存在地（白抜き番号表示）を示す。右側の図は健常対照を募っ

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*3 三愛病院泌尿器科
*4 結核予防会　第一健康相談所
*5 岩手医科大学医学部救急医学講座
*6 岩手医科大学医学部内科学講座、心血管・腎・内分泌内科分野
*7 岩手大学教育学部
受付日2010年●月●日・受理日　2010年●月●日

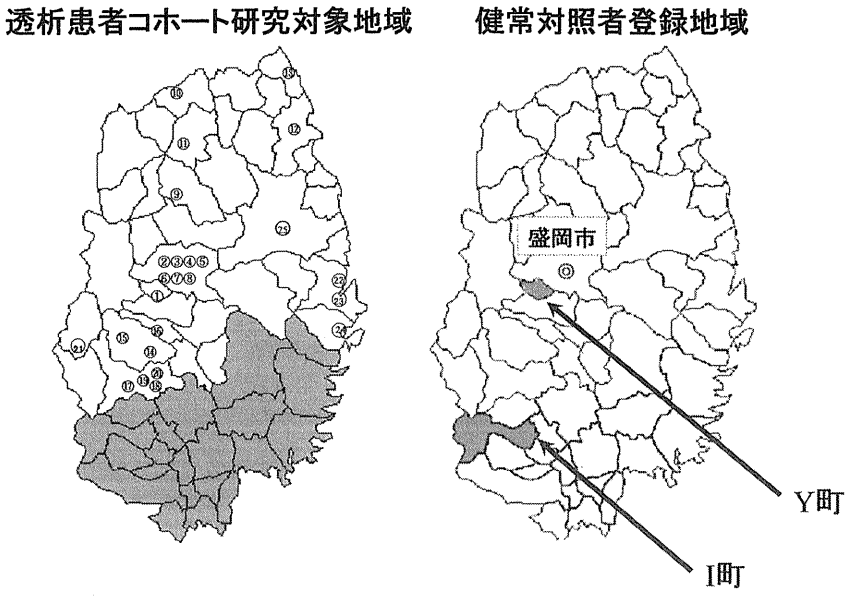

図1　カレン研究対象地域と参加施設ならびに健常対照参加者募集地域

図1は岩手県地図を示している。カレン研究は、左側の岩手県地図の中で、白く塗りつぶされた地域に存在する全ての透析施設(26施設)に研究参加を呼びかけ、25施設の協力を得て開始した。右側は健常対照参加者を募った二つの町の位置を示している。

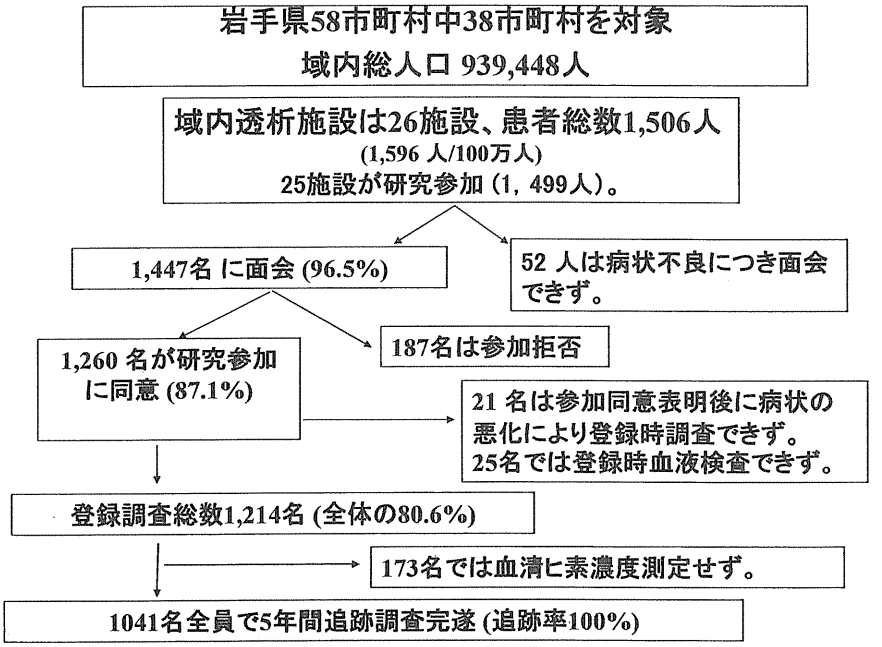

図2　カレン研究参加者選択手法と追跡調査内容の樹枝状図

岩手県中央部から北部にかけての総人口は2003年時点で94万人で、成人血液透析患者数は1,506名であった。インフォームドコンセントを実施できたのは1,447名で、最終的に1,214名の透析患者の登録が行われた。1214名中1041名で凍結保存された血清を用いて血清ヒ素濃度の測定を行った。5年間の追跡調査で1041名全員の生存状況・死亡年月日・死因・循環器疾患発症年月日を確認した。

た岩手県内に存在する二つの町の位置（灰色で示したY町とI町）を示している。

研究参加者

カレン研究参加者の選択手法と内訳を図2に示す。25施設1,499名の透析患者の内、全身状態不良などにより27名は面会できなかった。残りの1,447名に面会し、1,260名から書面による同意を得た(同意受容率87.0%)。同意が得られた1,260名中21名は病状の悪化や転院により登録調査ができなかった。25名の患者では血液検査がなされなかった。最終的に1,214名がコホート研究に参加した[18,19]。1,214名中173名では血清ヒ素濃度測定が行われなかった。本研究では1,041名を解析対象とした。更に、再発例を除いた新規罹患リスクの定量的評価を行うために、心筋梗塞の既往を有する45名を除外した970名で心筋梗塞新規罹患リスク評価を行った。同様に脳卒中既往を有する165名をのぞいた876名で虚血性脳卒中新規罹患リスク評価も行った。

健常対照は、岩手県Y町（平成15年当時の人口26,566人）と岩手県I町（人口17,500人）に居住する40-79歳の住民から年齢層化抽出法により対象者を選定し、インフォームドコンセントを必要人数が得られるまで繰り返して最終的に397人を集めた[20]。血清ヒ素濃度は397人中384人で測定した。尚、上記二つの研究は、岩手医科大学倫理審査委員会の承認を得て、ヘルシンキ宣言に従って実施された[18～20]。

研究参加者情報収集

研究参加者の情報収集には、調査員の面談による生活問診、血圧測定、身長測定、血液検査が含まれる。透析患者では、患者医療記録による患者医療情報収集が加わる。健常対照の採血検査は午前中の空腹時採血を行い、透析患者では透析施行直前の採血（非空腹時）を行った。参加者情報収集（透析患者ならびに一般健常対照）の詳細については、すでに公表している論文を参照されたい[18～21]。

血清ヒ素濃度測定

登録調査時に採取された透析患者血液と一般住民血液検体は、採血当日に測定検査機関（三菱化学メディエンス盛岡支社）に送付され同日中に血球数測定と血液生化学検査を実施した。血液検査に関しての詳細な方法はすでに公表している論文を参照されたい[18～21]。残存した血清は我々の研究室に運ばれ、-80℃に凍結されて保管された。

血清中ヒ素濃度の測定は以下の手順で行った。まず凍結血清検体を解凍して直接テフロン試験管に血清1mlを分取して高純度硝酸3mlを加えて2時間室温で放置した。その後ブロックバスを用いて120℃で12時間加熱分解した。ブロックバスよりテフロン試験管を取り出して冷却し、これに高純度の過酸化水素水を1ml加える行程を随時2回行った。テフロンジャーに移し変えて、100℃のホットプレート上で蒸発乾固させ、10%の硝酸溶液5mlに溶解させて測定用試料溶液とした。試料溶液中ヒ素濃度をアルゴンプラズマ質量分析法（ICP-MS Perkin Elmer社製Elan 6000）を用いて測定した。

ヒ素濃度測定に当たって実施した精度管理は1999年に改定されたNCLLSの精度管理のガイドラインにそって行われた[22]。精度管理の目的で、毎回の測定においてプール血清中のヒ素濃度を測定した。一回当たり5例のプール血清を36回測定したヒ素濃度の平均値は11.1ng/mlであった。一回測定当たりの精度（標準偏差）は平均値11.1ng/mlに対して1.37ng/ml、全測定における精度（標準偏差）は平均値11.1ng/mlに対して1.22ng/ml、であった。

追跡調査

研究者と研究看護師は、直接透析施設を毎年訪問して、患者診療記録ならびに死亡診断書を閲覧して、死亡、循環器疾患発症（急性心筋梗塞、心不全、脳血管疾患）の有無、悪性新生物発症の有無について追跡調査を行った。カレン研究開始時に研究チームで協議して一定の基準を設けた[19]。疾患定義は表1に示したとおりである。尚、脳卒中の診断基準において、脳出血、脳梗塞、くも膜下出血の診断は、画像診断で確認したものとした。転院した症例に関しては、転院先を訪問し、患者診療記録を閲覧して情報収集した。

統計ならびに解析手法

透析患者と健常対照の血清中ヒ素濃度のヒストグラムを示し、平均値、中央値（25-75パーセン

表1 KAREN研究腎不全原因疾患診断基準ならびに合併疾患、新規発症疾患診断基準

表1. KAREN研究腎不全原因疾患診断基準ならびに合併疾患、新規発症疾患診断基準

腎不全原因疾患診断基準

慢性糸球体腎炎

1 血尿
2 蛋白尿(2＋、3＋)
3 長期にわたる腎機能低下

上記臨床症状1～3を満たすもの、または腎生検診断されたものを慢性糸球体腎炎と定義する。

糖尿病性腎症

1 糖尿病と診断されている
2 蛋白尿(**300mg**/日以上)・浮腫・高血圧・腎機能低下(一つ以上)

上記の1と2を満たすもの、あるいは腎生検診断されたものを糖尿病性腎症と定義する。

腎硬化症

1 蛋白尿(±、＋)
2 高血圧
3 長期にわたる腎機能低下

上記1～3を満たすもの、または腎生検診断されたものを腎硬化症と定義する。

多発性嚢胞腎

腹部**US・CT**にて両側に多発性嚢胞を認めるものを
多発性嚢胞腎と定義する。

膠原病に起因する腎炎

膠原病と診断された上で腎機能低下を認め、かつ腎生検診断されたものと定義する。

その他

上記以外の原疾患(薬剤性腎炎、先天性、感染性等)

合併疾患、新規発症疾患診断基準

心不全

1 肺水腫または胸水貯留(心機能障害の有無、uremic lungかどうかは問わず)を持って所見ありとする。
2 その他の心不全徴候に関しては、心不全に影響を及ぼす左室機能障害または弁膜症の存在の確認を必要とする。

心エコー図による左駆出率50%未満、大動脈弁または僧帽弁の狭窄または逆流が中等度以上をもって心機能異常ありとする。

心筋梗塞症

1 心電図で最低二つの誘導で異常Q波の出現
2 心筋逸脱酵素の2倍以上の上昇
3 30分以上持続する胸痛

上記の1～3のうちいずれか2項目を含むもので、循環器専門医師の診断をうけているものを心筋梗塞の既往ありとする。

脳卒中

1 突然生じた神経症状(巣症状)が医師により確認され、24時間以上持続
2 神経症状が脳血管疾患以外の病気であることが否定されている
3 CTまたはMRIによる脳梗塞巣または脳出血巣の確認

上記の1、2の両者を同時にみたすもの、または3があるものを脳卒中と診断する。

閉塞性動脈硬化症

1 血管バイパス手術、血管形成術の存在
2 Ankle-arm systolic ratio ≦ 0.8
3 間歇性跛行・大腿部痛

上記の1～3のうちいずれか1項目を含むものを閉塞性動脈硬化症と診断する。

糖尿病

1 糖尿病治療中である
2 随時血糖 ≧ 200mg/dl
3 HbA1c ≧ 6.5%以上

上記の1～3のうちいずれか1項目を含むものを糖尿病と診断する。

高血圧

1 高血圧治療中である
2 収縮期血圧 ≧140mmHg以上
3 拡張期血圧 ≧ 90mmHg以上

上記の1～3のうちいずれか1項目を含むものを高血圧と診断する。

脂質異常

1 高脂血症治療中である
2 高コレステロール血症 ≧220mg/dl
3 高LDL-コレステロール血症 ≧140mg/dl
4 低HDL-コレステロール血症 ＜ 40mg/dl

上記の1～4のうちいずれか1項目を含むものを脂質異常と診断する。

タイル値）を算出した。両群の性年齢調整平均値と95%信頼区間を共分散分析で求め、両側で5%の有意水準で差があるのかを検定した。尚、一般健常対照では診療記録閲覧による既往歴の調査は行っていないが、自記式問診の既往歴（心臓病や脳卒中と言われたことがある）の項目で、あると答えた者が34名存在した。この34名を除外して同様に2群間で調整平均値の比較も行った。

透析患者のコホート研究開始時の患者属性を見るに当たり、透析患者を血清ヒ素濃度で4分位に分け、4群で年齢、男性割合、body mass index (BMI)、血圧値、血清脂質値、血清総蛋白値、アルブミン値、クレアチニン値、ヘモグロビン値、血小板数、高感度C反応性蛋白値を比較した。また4群間で、腎不全原因割合、合併疾患ならびに既往症、喫煙割合、常用飲酒割合を比較した。年齢の比較には一元配置分散分析を用いて多重比較にはボンフェローニの修正式を用いた。年齢以外の連続変数は性・年齢で調整した推定平均値を共分散分析で求め、同じく一元配置の多重比較においてはボンフェローニ法による修正を行った。高感度CRPの比較においては、性年齢調整した幾何平均値を求めて同様の比較を行った。

縦断解析では、まずヒ素4分位グループ別に総死亡数、心筋梗塞罹患数、虚血性脳卒中罹患数を求め、1000人年あたりの粗死亡率と粗罹患率を算出した。累積死亡率と心筋梗塞ならびに脳卒中の累積罹患率曲線をカプランマイヤー法により求め、群間の累積死亡率と累積罹患率の差はログランク法により有意差検定を行った。

ヒ素4分位グループにおいて、最低4分位グループを基準として、上位3群の総死亡、心筋梗塞罹患、虚血性脳卒中罹患の相対危険度を算出した。相対危険度の算出に当たっては、コックス回帰分析を用いて多変量調整ハザード比と95%信頼区間を求めて相対危険度に代用した。調整ハザード比を求めるに当たり、性年齢調整ハザード比と多変量調整ハザード比を求めた。多変量調整では、説明変数として、古典的な危険因子（年齢、男性、body mass index (BMI) 高値（≥27.5 kg/m^2）、血圧高値、糖尿病合併、脂質異常合併、既往症あり（心筋梗塞、脳卒中、悪性新生物）、現在喫煙、常用飲酒）と透析患者特有の生命予後危険因子（BMI低値（< 18.5 kg/m^2）、血圧低値、B型肝炎抗原陽性、C型肝炎抗体陽性、CRP高値、アルブミン低値）を説明変数に用いた。

説明変数に投入する変数は以下の手順で定義または編集した。BMIの算出にあたり、体重はdry weightを用いた。収縮期血圧の4分位で対象者を分け、最低位カテゴリを血圧低値者群、最高位カテゴリを血圧高値者群と定義して、血圧低値（< 140 mmHg）と血圧高値（≥ 169 mmHg)）をそれぞれ説明変数とした。脂質異常は、血清総コレステロール値が220 mg/dL以上、またはHDLコレステロール値が40 mg/dL未満、または抗高脂血症薬服用者と定義した。空腹時採血ではなかったため、中性脂肪値は定義基準に取り上げなかった。現在喫煙者を喫煙ありとした。週5日以上飲酒している者を常用飲酒者と定義した。血清アルブミンの4分位最低位グループ（< 3.5mg/dL）をアルブミン低値群と定義した。血清CRP値4分位の最高位グループ(≥3.6 mg/L)をCRP高値群と定義した。以上の説明変数を多変量調整分析の際に説明変数として用いた。

血清ヒ素濃度が高くなるほど死亡リスクや疾患罹患リスクが高くなるのかを検討する目的で線形トレンド検定を行った。解析では、強制投入法を用いて、有意性の有無に関わらず、全ての項目を説明変数として投入した。P値は両側で5%未満を有意とした。統計解析にはSPSS. Version 14を用いた。

III. 結　　果

図3は透析患者と健常対照群の血清ヒ素濃度のヒストグラムを示している。上段が透析患者で下段が健常対照である。透析患者の血清ヒ素濃度の平均値・中央値・最小値 - 最大値は33.4・42.7・3.76-573.6 μg/Lであり、健常対照はそれぞれ9.47・10.7・1.25-124.5 μg/Lであった。分布を見ると健常対照では10 μg/L付近に分布の鋭いピークを持ち、狭い範囲に多くの対象者が含まれるのに対し、透析患者では10 μg/L付近に分布のピークを有し、右側になだらかに分布の幅が広がっていた。健常対照では、25 μg/L未満に対象者の

95％が含まれていたが、透析患者では、25μg/Lを超えていた患者が全体の75％以上であった。性・年齢調整をした平均値（95％信頼区間）を比較すると透析患者では42.4（40.1-44.6）μg/L、健常対照では11.6（7.82-15.4）μg/Lで明らかに透析患者の血清ヒ素濃度は高かった。対象者群で心臓病や脳卒中と言われたことがあると答えた34名を除いた解析では、性・年齢調整平均値（95％信頼区間）は透析患者で42.4（40.1-44.6）μg/L、健常対照で11.8（7.79-15.7）μg/Lであった。この結果は既往歴を有する者を除外する前と大きな違いはみられなかった。

表2は血清ヒ素濃度4分位別に示したコホート研究開始時の透析患者属性である。この表では各群の年齢、透析治療期間、BMI、血圧、血液検査項目の平均値（標準偏差）または性・年齢調整平均値（95％信頼区間）を示している。血清ヒ素濃度が高いほど年齢は高くなり（トレンドp＜0.05）、男性割合は高くなっていた。尿素窒素と血清クレアチニン値は、Q1群に比較してQ3群とQ4群の値が有意に高かった（p＜0.05、ANCOVA多重比較）。その他の検査項目では違いは見られなかった。表3は4群間で腎不全原因疾患、合併疾患、生活習慣を有する割合を比較したものである。Q4群では末梢動脈疾患の有病割合が有意に高かった（p＜0.05、χ^2乗検定）。またヒ素濃度が高くなるほど末梢動脈疾患有病割合が高くなる線形の関係性が認められた（トレンドp＜0.05）。4群間で腎不全原因疾患やその他の合併疾患の割合に違いはみられなかった。

5年間の追跡調査の総観察期間は4003人年、観察期間の平均は3.9年、観察期間中央値は4.9年であった。総死亡数は373人、心筋梗塞罹患者数は48人、虚血性脳卒中罹患者数は112人であった。

図4はカプランマイヤー法により求めた各群の累積死亡率曲線、心筋梗塞累積罹患率曲線、虚血性脳卒中累積罹患率曲線である。各群の死亡率

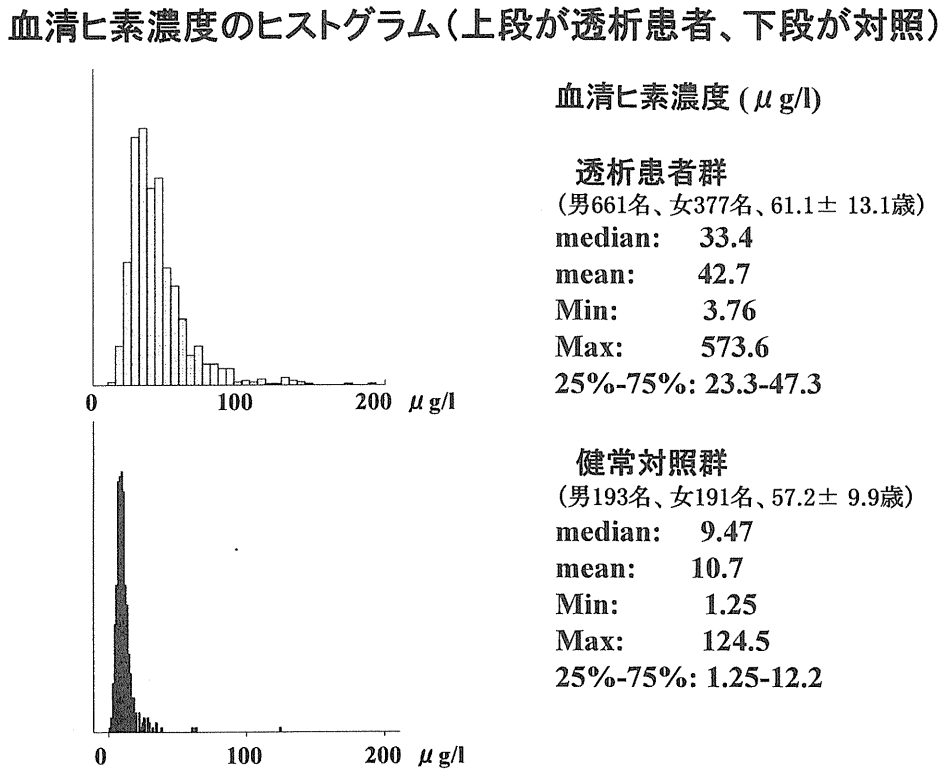

図3　血清ヒ素濃度ヒストグラム

上段が透析患者、下段が対照者のヒ素濃度ヒストグラムを示す。分布を見ると健常対照では10μg/L付近に分布の鋭いピークを持ち、狭い範囲に多くの対象者が含まれるのに対し、透析患者では40μg/L付近に分布のピークを有し、右側になだらかに分布の幅が広がっていた

表2　ヒ素4分位別に見た患者属性ー性・年齢・身体計測値と血液検査結果

subjects n		Q1 (n=260)	Q2 (n=260)	Q3 (n=261)	Q4 (n=260)
血清ヒ素濃度範囲		3.76-23.2	23.3-33.3	33.4-47.1	47.2-573.6
平均年齢 (標準偏差)	(歳)	58.8 (15.1)	60.4 (13.1)	62.6 (12.3)	62.6 (11.2)
性・年齢調整平均値(95%信頼区間)					
透析治療期間	(年)	5.8 (5.0-6.6)	6.9 (6.1-7.7)	7.1 (6.3-7.9)	6.4 (5.6-7.2)
body mass index	(kg/m²)	21.1 (20.7-21.5)	20.6 (20.2-20.9)	20.8 (20.5-21.2)	20.9 (20.6-21.3)
収縮期血圧	(mmHg)	158 (155-161)	156 (153-159)	153 (150-156)	154 (151-157)
総コレステロール	(mg/dl)	158 (153-162)	154 (150-158)	154 (149-158)	158 (154-163)
HDLコレステロール	(mg/dl)	47.4 (45.5-49.3)	47.3 (45.4-49.2)	47.9 (46.0-49.8)	46.7 (44.7-48.6)
LDLコレステロール	(mg/dl)	87.6 (84.3-90.9)	85.4 (82.1-88.7)	83.2 (79.9-86.4)	85.6 (82.3-88.8)
総タンパク	(g/dl)	6.5 (6.4-6.5)	6.5 (6.4-6.5)	6.5 (6.4-6.5)	6.5 (6.4-6.6)
アルブミン	(g/dl)	3.8 (3.7-3.8)	3.8 (3.7-3.8)	3.8 (3.7-3.8)	3.8 (3.7-3.8)
尿素窒素	(mg/dl)	64.7 (62.9-66.6)	68.7 (66.9-70.5)	74.6 (72.7-76.4)*	79.2 (77.3-81.0)*
クレアチニン	(mg/dl)	10.5 (10.2-10.8)	11.0 (10.7-11.3)	11.2 (10.9-11.5)*	11.7 (11.4-12.0)*
Hb	(g/dl)	10.0 (9.9-10.2)	10.2 (10.0-10.3)	10.2 (10.0-10.3)	10.1 (9.9-10.3)
血小板数	(/μl)	18.5 (17.8-19.3)	18.2 (17.4-18.9)	18.3 (17.6-19.1)	18.1 (17.4-18.9)
高感度CRP	(mg/l)	1.25 (1.04-1.50)	1.32 (1.10-1.58)	1.10 (0.92-1.32)	1.12 (0.93-1.34)

平均値(標準偏差)または性年齢調整平均値(95%信頼区間)で表示
*, $p < 0.05$ ANCOVA

表3　ヒ素4分位別に見た患者属性ー腎不全原因疾患、合併疾患・生活習慣割合

4分位別対象者数	Q1 (n=260)	Q2 (n=260)	Q3 (n=261)	Q4 (n=260)
血清ヒ素濃度範囲	3.76-23.2	23.3-33.3	33.4-47.1	47.2-573.6
男性 n (%)	162 (62.5%)	155 (59.6%)	166 (64.1%)	178 (68.5%)
腎不全原因 n (%)				
慢性糸球体腎炎	70 (26.9%)	82 (31.5%)	74 (28.4%)	83 (31.9%)
糖尿病性腎症	77 (29.6%)	54 (20.8%)	56 (21.5%)	66 (25.4%)
高血圧	27 (10.4%)	27 (10.4%)	27 (10.3%)	21 (8.1%)
のう胞腎	7 (2.7%)	8 (3.1%)	12 (4.6%)	12 (4.6%)
SLE	0 (0.0%)	3 (1.2%)	1 (0.4%)	0 (0.0%)
その他	64 (24.6%)	60 (23.1%)	74 (28.4%)	64 (24.6%)
不明	15 (5.8%)	26 (10.0%)	17 (6.5%)	14 (5.4%)
合併疾患 n (%)				
心筋梗塞	11 (4.2%)	9 (3.5%)	14 (5.4%)	12 (4.6%)
脳卒中	40 (15.4%)	51 (19.6%)	37 (14.2%)	37 (14.2%)
末梢動脈疾患	30 (11.5%)	33 (12.7%)	45 (17.2%)	72 (27.7%)*
悪性新生物	15 (5.8%)	20 (7.7%)	19 (7.3%)	23 (8.8%)
糖尿病	86 (33.1%)	60 (23.1%)	67 (25.7%)	74 (28.5%)
脂質異常	22 (8.5%)	32 (12.3%)	27 (10.3%)	38 (14.6%)
生活習慣				
現在喫煙	78 (30.0%)	71 (27.3%)	65 (25.0%)	64 (24.6%)
過去喫煙	58 (22.3%)	63 (24.2%)	61 (23.5%)	81 (31.2%)
常用飲酒	16 (6.2%)	13 (5.0%)	15 (5.7%)	30 (11.5%)

人数(パーセント)で表記
*, $p < 0.05$ χ^2テスト

を比較するとヒ素濃度が最も高いQ4群では生存率が一見低く見えるが、ログランクテストによる有意差検定では生存率に明らかな違いはみられなかった（p=0.18）。各群の心筋梗塞罹患率を比較すると、血清ヒ素濃度が最も低いQ1群の心筋梗塞罹患率は、Q3群（ログランクテストp=0.01）・Q4群（p=0.01）と比較して有意に低く、Q2群と比較しても低い傾向にあった（p=0.08）。虚血性脳卒中罹患率では、各群の罹患率の有意差はみられなかった。

表4はヒ素4分位群別にみた総死亡数、心筋梗塞罹患数ならびに虚血性脳卒中罹患と粗死亡率と粗罹患率（/1000人年）を示したものである。ヒ素血中濃度が上がるほど心筋梗塞罹患数と罹患率は高くなっていくことが示されている。しかし、総死亡率、循環器疾患死亡率、虚血性脳卒中罹患

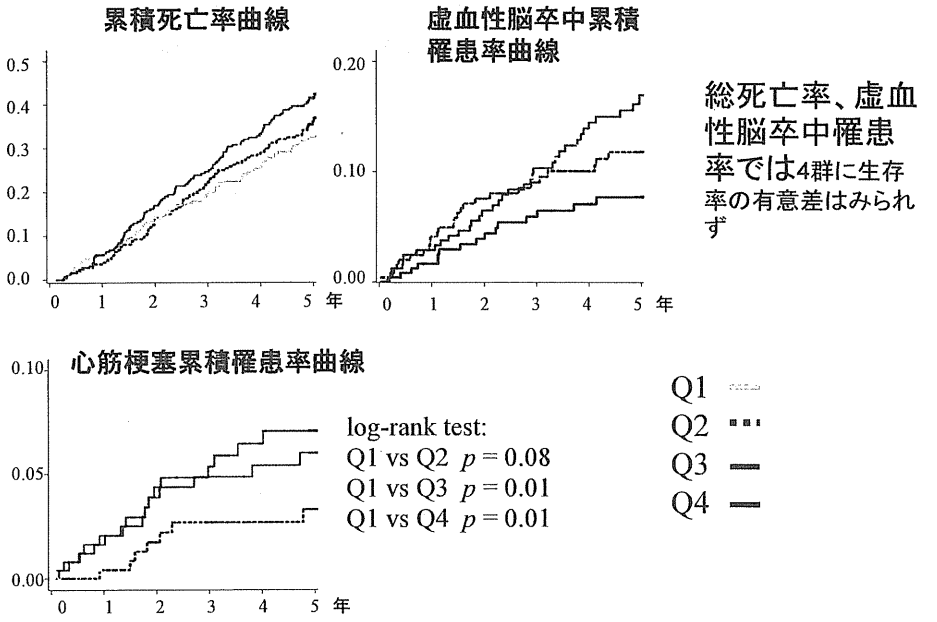

図4　カプランマイヤー累積死亡率・罹患率曲線

上段左側は累積死亡率曲線、右側は虚血性脳卒中の累積罹患率曲線である。ヒ素4分位間で総死亡率と虚血性脳卒中罹患率の差は認めなかった。

下段は心筋梗塞の累積罹患率曲線である。ヒ素濃度が最も低いQ1群はヒ素濃度が最も高いQ4群や2番目に高いQ3群と比較して死亡率は有意に低かった（p値はそれぞれ0.01）。

率と血清ヒ素濃度との間には有意な関係性は認められなかった。

図5はQ1群を基準とした上位3群の総死亡、心筋梗塞罹患ならびに虚血性脳卒中罹患の相対危険度（95%信頼区間）を示している。左側には総観察人年中のイベント数（死亡または疾患罹患）が示され、中央には多変量調整ハザード比と95%信頼区間のプロット図、右側には性・年齢調整ハザード比とその95%信頼区間の実測値が示されている。多変量解析の結果、総死亡リスク、虚血性脳卒中罹患リスクと血清ヒ素濃度との関連性は明らかではなかった。一方心筋梗塞罹患の相対危険度をみると、Q1群と比較した場合にQ3群（ハザード比と95%信頼区間：4.83（1.55-15.0））とQ4群（3.93（1.27-12.2））の心筋梗塞罹患リスクは有意に高く、多変量調整トレンド検定の結果ヒ素濃度が高くなるほど心筋梗塞罹患リスクが上がる線形の関係性が確認された（トレンドp＝0.014）。

尚、心筋梗塞の既往を有する者を除外した新規心筋梗塞罹患リスクと脳卒中既往（虚血性脳卒中または出血性脳卒中既往）を除外した解析を行うと、血清ヒ素濃度が高くなるほど心筋梗塞罹患リスクが上がる関係性はより明らかとなった（トレンドp＝0.009）。

IV. 考　　察

多数の透析患者と代表性を有すると考えられる同一地域在住の健常対照との比較検討では、透析患者の血清ヒ素濃度は平均値で4倍、中央値で3倍高く、性年齢調整した比較においても有意に差が見られた。

透析患者の生体内ヒ素については、欧米で少数の透析患者と健常対照を解析対象とした比較研究が行われており、表5は一般健常人と腎不全・透析患者での血清ヒ素濃度を測定した二つの先行研究結果と我々の研究結果の概要を示している。先行研究は1990年代に行われ、解析装置にはHGAAS (hydride-generation atomic absorption spectrometry) が用いられている。この装置は現在の主流であるICP-MSと比較して測定感度、精度、ばらつきともに遜色はない。ヒ素化合物の定量評価に関しては、現在主流となっているICP-MSと高速液体クロマトグラフィーによる解析のほうがより精度が高い。ヒ素の総量の定量解析に関して

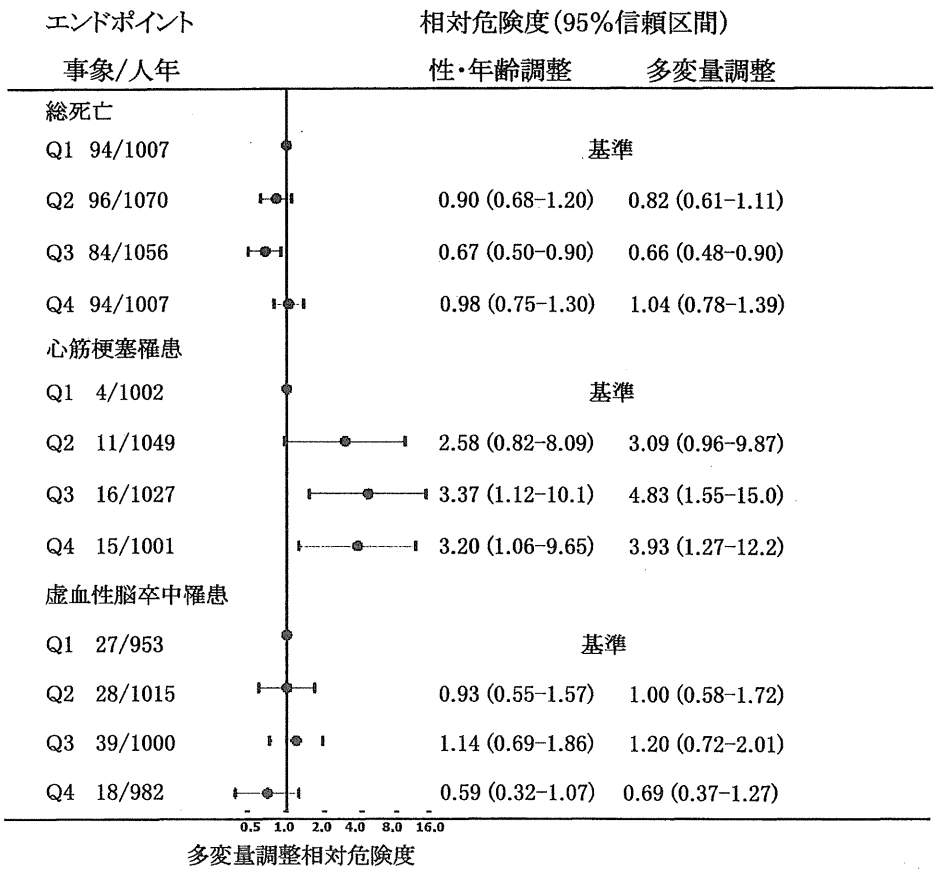

図5　血清ヒ素4分位別にみた総死亡、心筋梗塞罹患、虚血性脳卒中罹患の相対危険度

図の左端はイベント数（死亡数または罹患数）/　観察人年を示す。図の中央はQ1群を基準としたQ2-Q4群の相対危険度（多変量調整ハザード比を代用）をプロットしたものである。誤差線はハザード比の95%信頼区間を示している。図右端は性・年齢調整ハザード比と多変量調整ハザード比の実測値を示している。Q1群と比較してQ3群、Q4群の心筋梗塞罹患相対危険度はそれぞれ4.83、3.93と有意に高かった。一方総死亡リスクや虚血性脳卒中罹患リスクと血清ヒ素濃度との間に明らかな関係性は認められなかった。

表5　透析患者と対照で血清ヒ素濃度を比較検討した論文の概要

4分位グループ As (μg/L, min-max)	Q1 (n=260) 3.76-23.2	Q2 (n=260) 23.3-33.3	Q3 (n=261) 33.4-47.1	Q4 (n=260) 47.2-573.6
公表	2010	1993	1996	
研究施行地域	日本	オーストリア	ベルギー	
男女比	1.79	1.5	0.8	
透析患者年齢(歳)	61.2	64.2	62.3	
試料	凍結血清(-80℃)	凍結血清	凍結血清(-20℃)	
測定法	ICP-MS (inductively coupled plasma mass spectrometer)	hydride-generation atomic absorption spectrometry	hydride-generation atomic absorption spectrometry	
患者数(人)	1041	85	18	
対照数(人)	384	25	19	
透析患者	42.7	8.5	6.47(DMA1.93 AsB 3.42)	
健常対照	10.7	10.6	5.12(DMA0.82 AsB 3.55)	