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【 ORIGINAL ARTICLE 】

A Slight Decrease in the Serum Albumin Level Is Associated with the Rapid Progression of Kidney Dysfunction, Even within the Normal Range

Hoichi Amano[1,2], Kazunobu Yoshimura[3], Ryutaro Iijima[3], Kaito Waki[3], Keisei Matsumoto[3], Hitomi Ueda[3], Yasuko Ito[3], Kimihiko Akimoto[4], Takashi Yokoo[2], Kazuo Inoue[5] and Hiroyuki Terawaki[3]

Abstract:

Objective A low-normal albumin level is associated with a high risk of cardiovascular disease and mortality in the general population. However, the relationship between the serum albumin level and the future decline in the kidney function is unclear. We evaluated the effect of the serum albumin level on the decline in the kidney function in the general population.

Methods The data used were from 11,000 participants in a voluntary health checkup program conducted between 1998 and 2006 in Japan. The primary outcome for the kidney function was a difference in the estimated glomerular filtration rate (ΔeGFR) of ≥3 mL/min/1.73 m^2/year. The association of the risk of a decreased kidney function with the albumin level was determined using a logistic regression analysis. We fit separate multivariable logistic regressions for the serum albumin levels (g/dL) as a continuous variable and as categorical data, classified as ≤4.3 (n=2,530), 4.4-4.6 (n=5,427), and ≥4.7 (n=3,043).

Results Of the 11,000 participants, 346 had a ΔeGFR/year of ≥3. Compared with the participants with albumin levels of ≥4.7 g/dL, the risk of a decline in the kidney function was higher not only in those with albumin levels of ≤4.3 g/dL [adjusted odds ratio (OR)=2.10, 95% confidence interval (CI): 1.20-2.93] but also in those with levels of 4.4-4.6 g/dL (adjusted OR=1.53, 95% CI: 1.14-2.05).

Conclusion A decreased albumin level is an independent risk factor for a rapid decline in the kidney function, even within the normal range.

Key words: chronic kidney disease, kidney dysfunction, general population, albumin

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Introduction

The number of patients with chronic kidney disease (CKD) has been increasing in most parts of the world, and the disease is estimated to affect 200 million individuals worldwide (1). Furthermore, the increase in the number of patients with CKD is expected to accelerate. CKD creates a large burden and is recognized as an important problem for both individuals and society as a whole. First, CKD is a risk factor for not only end-stage kidney disease (ESKD) but also cardiovascular disease (CVD), which is the main cause of death worldwide (2-5). Second, the worldwide medical expenses associated with hemodialysis due to ESKD is estimated to increase to 1 trillion USD within the next 10 years (6). For these reasons, the establishment of an effective measure for CKD prevention is vital; in fact, this is one of the most important issues in public and national health.

[1]Graduate School of Public Health, Teikyo University, Japan, [2]Division of Nephrology and Hypertension, The Jikei University School of Medicine, Japan, [3]Department of Internal Medicine, Nephrology, Teikyo University Chiba Medical Center, Japan, [4]Akimoto Occupational Health Consultant Office, Japan and [5]Department of Community Medicine, Teikyo University Chiba Medical Center, Japan
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Correspondence to Dr. Hiroyuki Terawaki, terawaki@med.teikyo-u.ac.jp

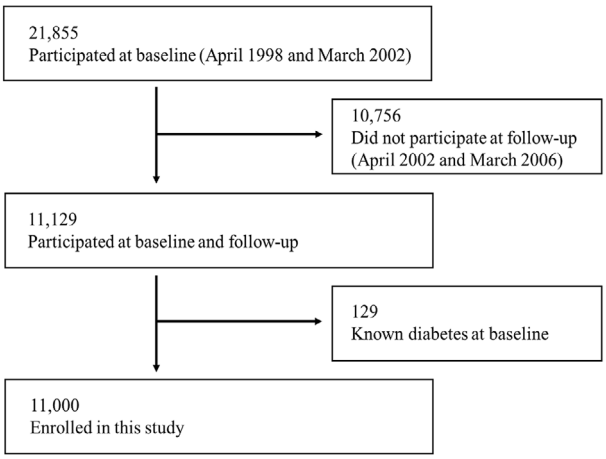

Figure 1. Flowchart of the study population.

While accumulating evidence shows that some metabolic and lifestyle risk factors of CKD, such as hypertension, dyslipidemia, and diabetes mellitus, have been addressed (7-13), effective measures for CKD prevention have not yet been established. Therefore, risk factors other than the "conventional" risk factors of CKD should be considered.

Previous studies have suggested that a low albumin level, even that within the clinical normal range, is associated with a high risk of CVD and mortality in the general population (14, 15). Other studies have suggested that hypoalbuminemia (albumin level below the normal range) is associated with a high risk of CKD progression (16-19). However, studies investigating the relationship between an albumin level within the normal range and a decline in the kidney function are lacking.

The present study evaluated the effect of the serum albumin level on the decline in the kidney function in the general population using a large retrospective cohort data set of the Japanese population.

Materials and Methods

Study design and study population

This was a retrospective cohort study, and we used a dataset derived from the health screening program performed by the Yuport Medical Checkup Center in Tokyo. In this study, we set the 4-year baseline period to be between April 1998 and March 2002 and the 4-year follow-up period to be between April 2002 and March 2006. During the baseline period, 21,885 people underwent checkups at least once, with a total of 47,995 checkups performed (Fig. 1). If the subjects underwent more than one checkup during the baseline period, the initial checkup data were used. During the follow-up period, 23,547 people underwent checkups at least once for 49,390 checkups. If the subjects underwent more than one checkup during the follow-up period, all of the data were used to identify incident diabetes. The follow-up data were merged with the baseline data, yielding 11,129 people who had been examined during both time periods. Of these subjects, 129 with known diabetes at baseline were excluded, leaving 11,000 people. Subjects who were found to have a history of chronic kidney disease were not included among these 11,000.

In accordance with the Private Information Protection Law, information that might identify subjects was kept private by the center. Informed consent for anonymous participation in epidemiological research was obtained at every checkup.

Measurements

The serum albumin level was determined using the bromocresol green method (reagents supplied by Denka Seiken, Tokyo, Japan) (20). Other laboratory values were measured using the standard laboratory technique. All of the checkup procedures were performed in the same manner, both during the baseline and follow-up periods, including blood measurements. Height and weight were measured to calculate the body mass index (BMI), which was defined as the weight divided by the height squared (kg/m^2). Blood pressure was measured by trained nurses using a sphygmomanometer.

The kidney function

The kidney function was expressed as an estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) modified for Japanese (21). The GFR estimated by the coefficient-modified CKD-EPI equation was more closely related to the CVD incidence than that estimated by the Japanese GFR equation (22). The coefficient-modified CKD-EPI equation is as follows:

Estimated GFR (mL/min/1.73 mL^2)=141× min (Cr/κ, 1)$^{\alpha}$× max (Cr/κ, 1)$^{-1.209}$×0.993^{Age}×1.018 (if a woman)×0.813 (Japanese coefficient)

(κ: 0.7 in women and 0.9 in men, α: -0.329 in women and -0.411 in men)

In general, the kidney function decreases with age: A previous study showed that the rate of GFR decline was 0.36 mL/min/1.73 m^2/year on average among 120,727 individuals ≥40 years old (23). Therefore, the clinical kidney disease outcome in this study was assessed as an abnormal annual decline in the kidney function in each participant.

In the present study, an abnormal annual decline in the kidney function was defined as a difference in the eGFR (ΔeGFR) of ≥3 mL/min/1.73 m^2/year. This cut-off value for an "abnormal decline," represents a magnitude of change that is >3 times the rate previously described in studies of normal aging, and this change is known to be associated with clinically deleterious outcomes (24, 25). To ensure the accuracy of the evaluated trend, we also performed a sensitivity analysis in which a ΔeGFR of ≥5 mL/min/1.73 m^2/year was regarded as an abnormal decline (26).

Statistical analyses

Continuous data were expressed as the mean ± standard

deviation or median within the 25th and 75th percentiles, and categorical data were expressed as percentages. Baseline characteristics were compared between those who met the criteria for an abnormal decline in the kidney function and those who did not, and independent variables were assessed using the chi-square test in the case of categorical variables and the *t*-test or Mann-Whitney U test in the case of continuous variables. The analysis for trend was evaluated using the Cochran-Armitage test and Jonckheere-Terpstra test. To assess the relationship between two values, Pearson's correlation coefficient was employed.

The abnormal decline in the kidney function and odds ratios (ORs) were estimated from the logistic regression model. Multivariable logistic analyses were used to calculate the OR for an abnormal decline in the kidney function after adjusting for the age, sex, BMI, systolic blood pressure (SBP), eGFR at baseline, serum alanine aminotransferase level, serum uric acid level, high-density lipoprotein (HDL) level, HbA1c level, C-reactive protein level, and history of cardiovascular disease (stroke or ischemic heart disease, or both). The inclusion of variables in the models was based on our existing knowledge regarding the risk factors of a kidney function decline. We fit separate multivariable logistic regressions for both the serum albumin level as a continuous variable and categorical data, which were classified as ≤4.3, 4.4-4.6, and ≥4.7 g/dL.

Differences with a p value of <0.05 were considered statistically significant. All statistical analyses were performed using EZR Version 1.33 (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander, which is designed to add statistical functions frequently used in biostatistics (27).

Ethics issues

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the review board of Teikyo University (approval No. 15-205). The participants' written informed consent for anonymous participation in epidemiological research was obtained at every evaluation.

Results

The baseline characteristics of the participants according to abnormal decline in the kidney function status are shown in Table 1. Of the participants, 346 had an abnormal decline in the kidney function. Among the patients with an abnormal decline in the kidney function, higher SBP values and lower levels of albumin and HDL-C were observed. The relationship between the baseline serum albumin levels and the change in the eGFR is shown in Fig. 2.

Next, we evaluated the unadjusted and adjusted ORs and 95% confidence intervals (CIs) for an abnormal decline in the kidney function according to the albumin level (Table 2, 3). In the continuous variable evaluation, the albumin levels (per 0.1 g/dL) were negatively associated with the risk of abnormal decline in the kidney function in both the crude (OR=0.89, 95% CI: 0.84-0.93) and adjusted models (OR=0.86, 95% CI: 0.82-0.91). The same trends were also observed in the sensitivity analysis in both the crude (OR=0.88, 95% CI: 0.81-0.97) and adjusted models (OR=0.85, 95% CI: 0.77-0.94).

In the categorical variable evaluation, compared with the participants with albumin levels of ≥4.7 g/dL, the risk of an abnormal decline in the kidney function was significantly higher not only in those with albumin levels of ≤4.3 g/dL but also in those with levels of 4.4-4.6 g/dL (Fig. 3A). This result means that a low serum albumin level, even one still within the normal range, is related to a rapid kidney function decline. The results of the sensitivity analysis, in which a ΔeGFR of ≥5 mL/min/1.73 m^2/year was regarded as an abnormal decline in the kidney function, are shown in Fig. 3B. Similar trends were observed.

Discussion

In this retrospective, population-based, cohort study, the relationship between albumin level and decline in the kidney function over time was investigated. A decrease in the albumin level was found to be the primary risk factor for an abnormal decline in the kidney function. More importantly, our study suggests that even when levels were still within the normal range, those with albumin levels of ≤4.6 g/dL had a risk of a decline in the kidney function.

Our study could not clarify why a relatively low but still-within-the-normal-limit level of albumin led to an early decline in the kidney function. A slight decline in serum albumin might reflect some confounding risk factors, such as slight undernutrition (28), slight albuminuria, or profound liver dysfunction. Alternatively, a relatively low level of serum albumin *per se* caused a rapid decline in the kidney function. A serum albumin, which has the epithet "multifunctional protein" (29), has various functions, including the maintenance of osmotic pressure, buffering of the acid-base balance, supply of amino acid to tissues, binding and transporting of numerous compounds, elastase activity, and antioxidative activity. In fact, the serum albumin level is the most abundant, and thus the most important, antioxidant of the extracellular space (30). We previously reported that the decrease in the serum albumin fraction, which has an antioxidative property, was correlated with kidney dysfunction (31, 32) and that this decrease in the serum albumin fraction was directly related to cardiovascular incidence in the population with advanced CKD (33, 34). Therefore, in theory and in actuality, a low serum albumin level can induce undesirable outcomes, such as mortality (14), cardiovascular incidence (15), and a rapid decline in the kidney function, as shown in the present study.

Most previous studies considered abnormally low albumin levels as an indicator of malnutrition status for their re-

Table 1. Participants' Characteristics at Baseline according to Decline in Kidney Function.

	All	ΔeGFR/year<3 mL/min/1.73 m^2 (n=10,654)	ΔeGFR/year ≥ 3 mL/min/1.73 m^2 (n=346)	p value
Age (years)	53.2 (11.6)	53.2 (11.6)	52.2 (13.4)	0.104
Sex (male), n (%)	5,248 (48)	5,101 (48)	147 (43)	0.049
Body mass index (kg/m^2)	23.0 (3.0)	23.0 (3.0)	23.1 (3.2)	0.387
Systolic blood pressure (mmHg)	124.1 (17.9)	124.0 (17.9)	126.5 (18.7)	0.011
Diastolic blood pressure (mmHg)	75.0 (11.0)	74.9 (11.0)	77.5 (11.4)	<0.001
Laboratory data				
Hemoglobin (g/dL)	13.9 (1.4)	13.9 (1.4)	13.9 (1.6)	0.460
Serum albumin (g/dL)	4.52 (0.23)	4.52 (0.23)	4.46 (0.23)	<0.001
Aspartate aminotransferase (U/L)	22.9 (16.7)	22.8 (16.7)	22.2 (16.1)	0.476
Alanine aminotransferase (U/L)	22.7 (9.3)	22.69 (9.35)	22.25 (8.70)	0.393
Lactate dehydrogenase (U/L)	298.2 (55.3)	298.1 (55.2)	299.29 (57.5)	0.701
Blood urea nitrogen (mg/dL)	14.9 (3.5)	14.9 (3.5)	14.9 (3.8)	0.989
Serum creatinine (mg/dL)	0.7 (0.2)	0.72 (0.16)	0.73 (0.2)	0.191
Estimated glomerular filtration rate (mL/min/1.73 m^2)	82.9 (10.3)	82.4 (10.2)	83.8 (13.3)	0.090
Serum uric acid (mg/dL)	5.4 (1.4)	5.4 (1.4)	5.4 (1.5)	0.951
Total cholesterol (mg/dL)	203.3 (35.0)	203.4 (34.9)	201.0 (36.8)	0.206
High-density lipoprotein cholesterol (mg/dL)	58.5 (15.2)	58.6 (15.2)	55.7 (14.2)	<0.001
Triglyceride (mg/dL)	97.0 [70.0, 140.0]	97.0 [69.0, 140.0]	97.5 [73.0, 143.0]	0.308
HbA1c (%, NGSP)	5.1 (0.7)	5.1 (0.7)	5.1 (1.0)	0.770
C-reactive protein (mg/dL)	0.10 [0.01, 0.10]	0.10 [0.01, 0.10]	0.10 [0.01, 0.10]	0.092
History of complications				
Stroke (+, %)	20 (0.2)	19 (0.2)	1 (0.3)	0.473
Angina pectoris (+, %)	36 (1.2)	32 (0.3)	4 (1.2)	0.026
Myocardial infarction (+, %)	10 (0.1)	10 (0.1)	0 (0)	0.999
Observation period (years)	5.4 (1.6)	5.5 (1.6)	3.2 (1.8)	<0.001

Data are expressed as mean and standard deviation, or percentage and number or median with 25th and 75th percentiles.
NGSP: National Glycohemoglobin Standardization Program

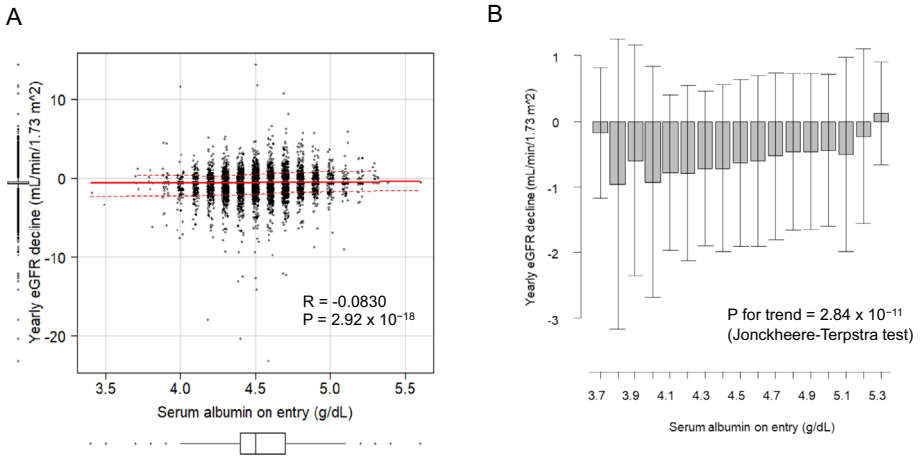

Figure 2. The relationship between the baseline serum albumin level and the yearly decline in the kidney function. A lower serum albumin level was related to a greater decline in the estimated glomerular filtration rate. (A) A weak but significant relationship was observed between the baseline serum albumin level and the yearly decline in the kidney function. (B) The same trend was noted on a trend test (Jonckheere-Terpstra test).

Table 2. Association between Albumin Level at Baseline and Renal Outcome (ΔeGFR/year ≥3 or Not).

		Unadjusted			Adjusted		
	N	OR	95%CI	p value	OR	95%CI	p value
Albumin (per 0.1 g/dL)		0.88	0.81-0.96	0.006	0.84	0.75-0.93	<0.001
Albumin levels (g/dL, Categorical variables)							
≤4.3	2,530	1.87	1.37-2.54	<0.001	2.10	1.20-2.93	<0.001
4.4-4.6	5,427	1.41	1.06-1.87	<0.001	1.53	1.14-2.05	<0.001
4.7≤	3,043	ref			ref		

Adjusted for age, sex, body mass index, systolic blood pressure, eGFR at baseline, serum alanine aminotransferase level, serum uric acid, high-density lipoprotein cholesterol, HbA1c, C reactive protein history of stroke and history of heart disease.

CI: confidence interval, eGFR: estimated glomerular filtration, ref: reference, OR: odds ratio

Table 3. Sensitivity Analysis: Association between Albumin Level at Baseline and Renal Outcome (ΔeGFR/year ≥5 or Not).

		Unadjusted			Adjusted		
	N	OR	95%CI	p value	OR	95%CI	p value
Albumin (per 0.1 g/dL)		0.89	0.84-0.93	<0.001	0.85	0.81-0.90	<0.001
Albumin levels (g/dL, Categorical variables)							
≤4.3	2,530	1.95	1.08-3.52	0.026	2.37	1.25-4.42	0.002
4.4-4.6	5,427	1.47	0.85-2.53	0.23	1.65	0.94-2.90	0.06
4.7≤	3,043	ref			ref		

Adjusted for age, sex, body mass index, systolic blood pressure, eGFR at baseline, serum alanine aminotransferase level, serum uric acid, high-density lipoprotein cholesterol, HbA1c, C reactive protein history of stroke and history of heart disease.

CI: confidence interval, eGFR: estimated glomerular filtration, ref: reference, OR: odds ratio

search (15, 35). However, our study showed that, even within the normal range, albumin levels of ≤4.6 g/dL are associated with a risk of a reduced kidney function. Only a few studies showed that lower albumin levels that were still within the normal range affect the kidney function. Multivariable analyses in 2,535 subjects 40-69 years old showed that the CKD hazard ratios (95% CI) for the highest and lowest quartiles of serum albumin levels were 0.69 (0.40-1.17) for men and 0.42 (0.28-0.64) for women (36). While these results were similar to ours, the number of subjects was relatively small. To overcome this limitation, in our study, we included almost five times as many subjects as that previous study.

The present study showed that a decreased albumin level was significantly associated with an abnormal decline in the kidney function, and patients with albumin levels of ≤4.6 g/dL had a risk of a decline in the kidney function. This indicated that a slight decrease within the normal range of albumin level might carry a risk of kidney function deterioration. This is consistent with the results of a previous study that reported that a lower albumin level that was still within the normal range was predictive of CKD in women (36). These present and previous findings suggest that the risk of a kidney function decline might increase with decreasing albumin levels, even within the normal range. These findings might support a new therapeutic target from the viewpoint of public health.

Several limitations associated with the present study warrant mention. First, the findings cannot be generalized to other ethnic or age groups, as the study participants might be healthier than the general population with a lower risk of developing medical complications, as the study subjects were participants in a health checkup program. Second, the albumin levels were measured only at baseline; changes in the levels during the follow-up period that might have had an independent effect on the kidney outcome were not evaluated. Third, the eGFR was evaluated only twice; this parameter is known to show day-to-day variations. Fourth, this study did not consider other profound confounders, such as the use of diuretics, smoking history, serum calcium/phosphate levels, cystatin C, brain natriuretic peptide, C-reactive protein, cardio-thoracic ratio on chest X-ray, data regarding muscle and fluid volume, and especially data regarding the urinary finding (urinary albumin and protein lev-

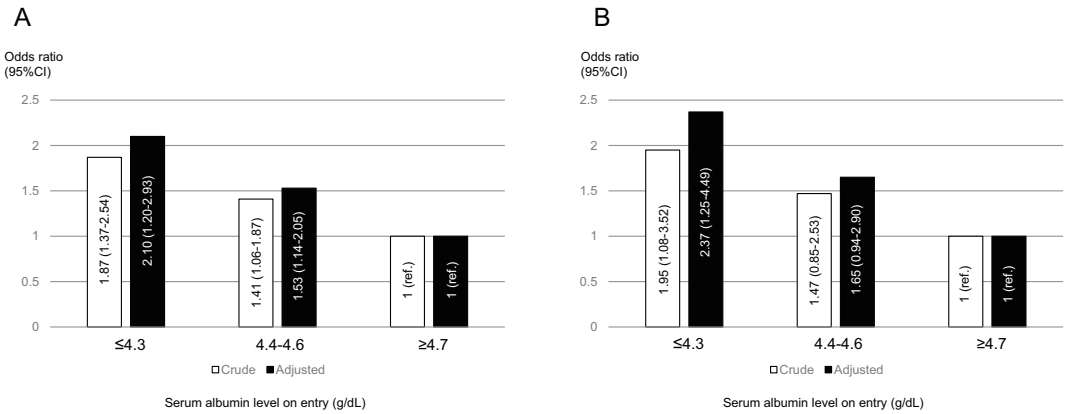

Figure 3. The relationship between the baseline serum albumin level and the renal outcome. A: The main analysis in which the renal outcome was ΔeGFR/year ≥3 mL/min/1.73 m^2, B: a sensitivity analysis in which the renal outcome was ΔeGFR/year ≥5 mL/min/1.73 m^2. In both analyses, similar trends were observed: Namely, the risk of kidney impairment increased as the serum albumin level decreased, even within the normal range (p value; <0.0001 in A and=0.0249 in B, Cochran-Armitage test). After adjusting for the age, sex, body mass index, systolic blood pressure, eGFR at baseline, serum alanine aminotransferase level, serum uric acid, high-density lipoprotein cholesterol, HbA1c level, C-reactive protein level, and history of cardiovascular disease. CI: confidence interval, eGFR: estimated glomerular filtration

els), all which might affect the kidney function and serum albumin level. To overcome such limitations, future prospective studies on these relationships should be conducted to provide more insight.

In conclusion, our study showed that a decreased serum albumin level is an independent risk factor of an abnormal decline in the kidney function in the general population and that a slight decrease in the albumin level, even within the normal range, may be a risk factor of a decline in the kidney function.

The authors state that they have no Conflict of Interest (COI).

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