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Influential factors on serum albumin concentration in hospitalized chronic kidney disease patients

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Abstract : Background : Serum albumin concentration (SAC) is a prognostic factor that is affected by many factors such as postural change, liver function and food intake. Chronic kidney disease (CKD) patients excrete proteinuria, have low-protein diet, and receive glucocorticoid therapy. No one has evaluated the most influential factors on SAC in CKD patients. Methods : A retrospective study. Hospitalized CKD patients with less than 1 g/gCreatinine proteinuria receiving glucocorticoid therapy (n=28), with 1 or more g/gCreatinine proteinuria not receiving glucocorticoid therapy (n=36), and with 1 or more g/gCreatinine proteinuria receiving glucocorticoid therapy (n=39) were enrolled. SAC, hemoglobin, proteinuria and blood pressure at the last outpatient check-up before hospitalization, on the second day of hospitalization, at the last laboratory examination before discharge, as well as at the first outpatient follow-up after discharge were analyzed. Results : SAC decreased on the second day of hospitalization and increased at the first outpatient follow-up significantly in all groups. Unexpectedly, the change of SAC was irrelevant to the amount of proteinuria. Conclusions : SAC was affected by not only proteinuria, but also postural change, physical activity, and food in CKD patients. SAC should be analyzed by standardizing a patient's condition during phlebotomy. J. Med. Invest. 64 : 146-152, February, 2017

Keywords **:** *Serum albumin concentration, Proteinuria, Chronic kidney disease, Postural change, Hospitalization*

INTRODUCTION

Serum albumin concentration (SAC) is a classical representative marker of nutritional status, generating oncotic pressure and working as antioxidants (1). Decreased serum albumin is associated with rapid loss of kidney function in patients with chronic kidney disease (CKD) all over the world (2, 3). Therefore, the increase of SAC is one of the therapeutic goals in the management of CKD patients (4).

SAC is affected by many factors. One of these factors includes postural change (5). SAC is significantly modified by postural change-induced plasma volume distribution and the relative gap of gravitational force. Statistically significant differences of SAC from supine to sitting or standing posture were found, and SAC taken in a standing posture is approximately 10% higher than that in a supine position. In addition, changes in SAC are caused by health condition and comorbidities. Organ dysfunction has a direct relationship with SAC, because albumin is produced in the liver and abnormally excreted in urine or feces only when the kidney or bowel is damaged. Thus, liver function, proteinuria, and protein-losing gastrointestinal disorders can govern albumin concentration. Moreover, food intake can influence on SAC (6). However, to our knowledge, no one has evaluated the primary determinants for SAC in CKD patients around hospitalization, who take low-protein diet and receive glucocorticoid administration.

Therefore, in this study, we investigated the time course of SAC in hospitalized CKD patients to determine whether it can serve as an indicator to decide the discharge of hospitalized patients. We also focus on the amount of proteinuria around hospitalization, which is a unique and influential factor on SAC in CKD patients to investigate how critical the amount of proteinuria is for SAC.

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PATIENTS AND METHODS

Ethics statement

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the Research Ethics Committee of Tokushima University.

Study design and subjects

This study is a retrospective study. Study flow diagram is shown in Figure 1. The subjects initially enrolled in this study met the following criteria ; 1) hospitalization for ten or more days in Tokushima University Hospital from 2012 to 2015 ; 2) eating more than 90% of served hospital foods ; 3) without significant infection, organ failure, gastrointestinal bleeding or malignancy. Next, CKD patients who took all of the blood and urine examination of SAC, hemoglobin, urine protein, urine creatinine at the last outpatient check-up before hospitalization (A point), on the second day of hospitalization (B point), at the last laboratory examination before discharge from the hospital (C point), as well as at the first outpatient follow-up after discharge (D point) were selected. Finally, patients were divided into groups based on those who had less than 1 g/gCreatinine proteinuria (low proteinuria) with glucocorticoid only/and immunosuppressant treatment during hospitalization (LPG group), those who had 1 or more g/gCreatinine proteinuria

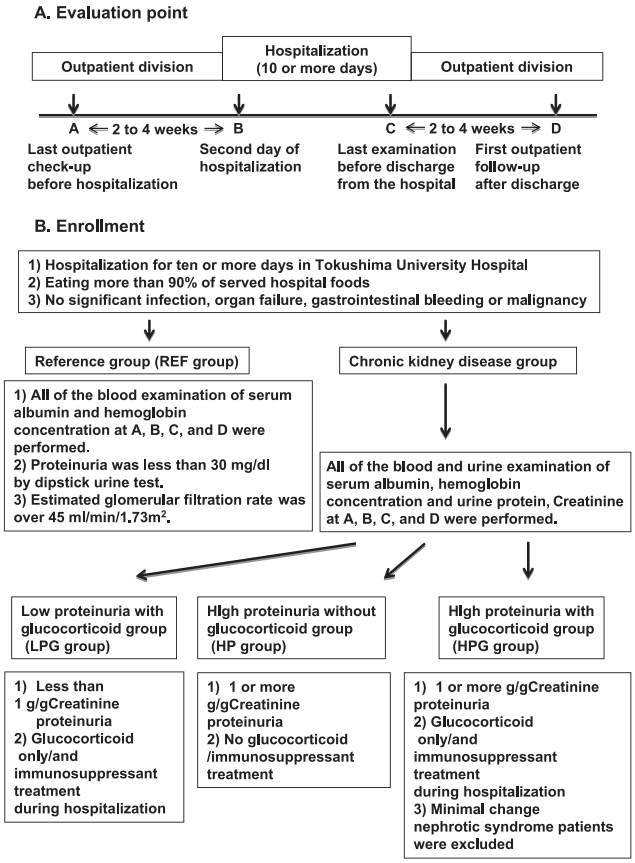

Figure 1. Evaluation point and enrollment of subjects analyzed in this study
(A, B) The subjects initially enrolled in this study met the following criteria ; 1) hospitalization for ten or more days in Tokushima University Hospital ; 2) eating more than 90% of served hospital foods ; 3) without significant infection, organ failure, gastrointestinal bleeding or malignancy. Next, CKD patients who took all of the blood and urine examination at the last outpatient check-up before hospitalization (A point), on the second day of hospitalization (B point), at the last laboratory examination before discharge from the hospital (C point), at the first outpatient follow-up after discharge (D point) were selected. Finally, patients were divided into groups based on those who had less than 1 g/gCreatinine proteinuria (low proteinuria) with glucocorticoid only/and immunosuppressant treatment during hospitalization (LPG group), those who had 1 or more g/gCreatinine proteinuria (high proteinuria) without glucocorticoid/immunosuppressant treatment during hospitalization (HP group), and those who had 1 or more g/gCreatinine proteinuria (high proteinuria) with glucocorticoid only/and immunosuppressant treatment during hospitalization (HPG group). The patients with biopsy-proven minimal change nephrotic syndrome were excluded.
The reference group (REF group) consists of patients who took all of the blood examination at A, B, C, and D and whose proteinuria was less than 30 mg/dl by dipstick urine test with an estimated glomerular filtration rate over 45 ml/min/1.73 m^2.

(high proteinuria) without glucocorticoid/immunosuppressant treatment during hospitalization (HP group), and those who had 1 or more g/gCreatinine proteinuria (high proteinuria) with glucocorticoid only/and immunosuppressant treatment during hospitalization (HPG group). Of note, we excluded the patients with biopsy-proven minimal change nephrotic syndrome from HPG group, because it is common to have complete remission of proteinuria and rapid increase of SAC in this condition. All patients involved ate hospital food, which included 1600 to 2000 kcal with 0.6 to 1.0 g of protein/kg of idealistic body weight and less than 5 g of salt.

The reference group (REF group) to the registered CKD patients consisted of patients who took all of the blood examinations of SAC and hemoglobin at A, B, C, and D points and whose proteinuria was less than 30 mg/dl by dipstick urine test with an estimated glomerular filtration rate over 45 ml/min/1.73 m^2 (7). Their meal included 1600 to 2200 kcal with 1.2 to 1.4 g of protein/kg of idealistic body weight protein and less than 10 g of salt.

Demographic and clinical characteristics of enrolled patients at A were acquired. The values of hemoglobin, SAC, serum creatinine, urine protein, urine creatinine and clinic blood pressure (8) at A, B, C, and D were collected. At A and D in outpatient division, blood was collected in a sitting position, while at B and C, in sitting or supine positions. Blood samples were taken between six and seven o'clock in the morning before breakfast during hospitalization. SAC was measured by a modified BCP method (9). Urine creatinine was determined by an enzymatic method (10). Urine protein was measured by a dye-binding colorimetric method utilizing pyrogallol red-molybdate complex (11).

Statistical analysis

All values are expressed as mean±SD. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA). Baseline characteristics between CKD and REF patients were compared using student's t-test or Welch's t-test, if data were normally distributed. Non-normal data were analyzed by Man-Whitney's U test. F-test was used for comparing the factors of total deviation. Prevalence data were analyzed by means of chi-square or Fisher's exact probability test. The changes of serological and clinical parameters in the observation period were analyzed using paired t-test or Wilcoxon signed-ranks test, as appropriate. Significance was defined by P less than 0.05.

RESULTS

Demographic and clinical characteristics

Basic characteristics were shown in Tables 1 and 2. Most of the patients in the REF group were hospitalized due to a cerebrovascular disease with mild motor and/or sensory disturbance or neuritis. They had relatively normal kidney function and no anemia. The majority of the LPG group patients suffered from biopsy-proven IgA nephropathy receiving three-week serial steroid pulse therapy (12). These patients were the youngest and had the lowest blood pressure among groups. The HP group consisted of educational hospitalization patients to manage hypertension, blood sugar control, or edema (13). These subjects were the oldest and had the highest blood pressure and the worst kidney function among all groups. The HPG group patients needed steroid and/or immunosuppressant therapy because of biopsy-proven kidney diseases, such as membranous nephropathy and lupus nephritis. They had the longest duration of hospitalization among groups. Of note, basically, A/G ratios were inversely related to SAC while A/G ratios in the HP and HPG groups were significantly lower than those in the REF and LPG groups probably because of proteinuria. These results suggested that general conditions including inflammation and nutrition were similar between the REF and LPG groups or between the HP and HPG groups.

SAC in the REF group

Figure 2 shows the change of SAC and hemoglobin in the REF group. SAC decreased significantly at B compared to A (when hospitalized) and increased significantly at D compared to C (after hospital discharge). The time course of SAC was similar as that of hemoglobin. The decrease of SAC mean value at B (3.60 g/dl) was 8.6% compared to A (3.94 g/dL). The increase of SAC mean value at D (4.03 g/dL) was 15.3% compared to C (3.49 g/dL).

Table 1. Principal disease, comorbidity and drug profile of the patients enrolled.

	REF (1)	LPG (2)	HP (3)	HPG (4)
Principal Disease	CVD 13 Neuritis 5 Epilepsy 3 DM 3 Basedow 2 Spondylosis 2 MG 1	IgAN 19 ANCA 3 Lupus 2 IN 1 MPGN 1 IgG4 1 CholE 1	NSCL 14 DM 9 MN 5 IgAN 3 Cryo 2 MPGN 2 ANCA 1	MN 15 IgAN 7 Lupus 6 Purpura 3 ANCA 3 MPGN 3 IN 3
Comorbidity				
DM (%)	8 (27.6%)[2,4]	2 (7.1%)[1,3]	16 (44.4%)[2,4]	1 (2.5%)[1,3]
HT (%)	14 (48.3%)[3]	12 (42.9%)[3]	36 (100%)[1,2,4]	24 (60.0%)[3]
Treatment				
GC start (%)	5 (17.2%)[2,3,4]	25 (89.3%)[1,3]	0 (0.0%)[1,2,4]	35(87.5%)[1,3]
GC inc. (%)	1 (3.4%)	1 (3.6%)	0 (0.0%)[4]	5 (12.5%)[3]
GC user (%)	9 (31.0%)[2,3,4]	28 (100%)[1,3]	0 (0.0%)[1,2,4]	40 (100%)[1,3]
Drug				
DM (%)	4 (13.8%)	1 (3.6%)[3]	12 (33.3%)[2,4]	2 (5.0%)[3]
Anti-HT (%)	8 (27.6%)[3,4]	12 (42.9%)[3]	32 (88.9%)[1,2,4]	22(55.0%)[1,3]
Statin (%)	5 (17.2%)	4 (14.3%)	10 (27.8%)	8 (20.0%)
Anti-UA (%)	1 (3.4%)[3]	5 (17.9%)	12 (33.3%)[1]	6 (15.0%)
GC (%)	4 (13.8%)[3]	3 (10.7%)	0 (0.0%)[1,4]	5 (12.5%)[3]
IS (%)	1 (3.4%)	1 (3.6%)	1 (2.8%)	3 (7.5%)
ESA (%)	0 (0.0%)[3]	2 (7.1%)	5 (13.9%)[1]	3 (7.5%)

DM : Diabetes mellitus. HT : Hypertension. GC start/inc. : Glucocorticoid was started/increased during hospitalization. UA : Uric acid. IS : Immunosuppressant. ESA : Erythropoiesis-stimulating agent. CVD : Cerebrovascular disease. MG : Myasthenia Gravis. IgAN : IgA nephropathy. ANCA : ANCA-related nephritis. Lupus : Lupus nephritis. IN : Interstitial nephritis. MPGN : Membranoproliferative glomerulonephritis. IgG4 : IgG4-related kidney disease. CholE : Cholesterol embolism. NSCL : Nephrosclerosis. MN : Membranous nephropathy. Cryo : Cryoglobulin nephropathy. Superscript[1,2,3,4] : Significantly different from 1, 2, 3, 4.

Table 2. Demographic and clinical characteristics of the patients enrolled.

	REF (1)	LPG (2)	HP (3)	HPG (4)
Patients (n)	29	28	36	40
Age (years)	54.3±17.6[2,3]	40.8±20.2[1,3,4]	66.8±14.5[1,2,4]	56.2±18.5[2,3]
Female (%)	8 (27.6%)	13 (46.4%)	14 (38.9%)	15 (37.5%)
BMI (kg/m^2)	22.4±3.6	21.4±3.4	22.6±4.3	22.4±3.4
DurHos (day)	25.9±20.5[4]	29.9±21.7[4]	24.8±14.9[4]	48.5±24.7[1,2,3]
SBP (mmHg)	130±22[2,3]	119±14[1,3,4]	152±25[1,2,4]	131±17[2,3]
DBP (mmHg)	76.1±15.7	71.3±8.9[4]	79.3±18.4	78.3±11.9[2]
WBC (10^3/μl)	7.51±2.60	6.41±2.12	6.70±2.43	7.35±3.58
Hb (g/dL)	14.5±1.5[2,3,4]	12.7±2.1[1,3]	11.3±2.1[1,2,4]	12.6±2.9[1,3]
Plt (10^4/μl)	24.9±6.2	25.8±6.1	24.3±8.5	26.2±7.2
GOT (U/L)	23.9±8.4[2]	16.4±4.1[1,4]	19.6±8.8	21.5±7.6[2]
GPT (U/L)	21.1±11.4[2,3,4]	13.5±7.2[1]	12.5±6.2[1]	14.9±6.0[1]
LDH (U/L)	218±75[2,3]	173±33[1,3,4]	252±70[1,2,4]	208±37[2,3]
ALP (U/L)	246±96[2]	190±60[1,3]	240±84[2]	211±70
TP (g/dL)	7.08±0.62[3,4]	7.20±0.53[3,4]	6.17±0.77[1,2]	5.91±1.19[1,2]
Alb (g/dL)	3.94±0.25[3,4]	3.91±0.35[3,4]	2.87±0.62[1,2]	2.61±0.68[1,2]
A/G ratio	1.26±0.22[3,4]	1.15±0.28[3,4]	0.87±0.20[1,2]	0.79±0.21[1,2]
BUN (mg/dL)	13.4±5.6[3,4]	19.4±13.9[3]	38.6±24.6[1,2,4]	24.1±15.6[1,3]
Cre (mg/dL)	0.74±0.21[2,3,4]	1.37±1.32[1,3]	2.70±2.00[1,2,4]	1.61±1.19[1,3]
UA (mg/dL)	Not available	5.70±1.67[3,4]	7.45±2.09[2]	6.81±2.08[2]
Na (mEq/L)	140.1±2.5[3,4]	141.0±2.6	141.7±3.8[1]	141.6±2.3[1]
K (mEq/L)	4.17±0.46	4.29±0.32	4.13±0.64	4.32±0.64
Cl (mEq/L)	103.5±2.7[2,3,4]	104.9±2.4[1]	105.6±5.8[1]	106.1±3.1[1]
Tcho (mg/dL)	195±29[4]	180±29[3,4]	210±57[2]	245±92[1,2]
TG (mg/dL)	178±152[2]	110±55[1,3,4]	178±117[2]	191±179[2]
HDL (mg/dL)	61.2±17.1	57.1±17.7	55.0±13.5	59.8±21.1
UP (g/gCr)	Not available	0.52±0.28[3,4]	6.41±3.74[2]	5.31±3.83[2]

BMI : Body mass index. DurHos : Duration of hospitalization. SBP : Systolic blood pressure. DBP : Diastolic blood pressure. UP : Urine proteinuria.
Superscript[1,2,3,4] : Significantly different from 1, 2, 3, 4.

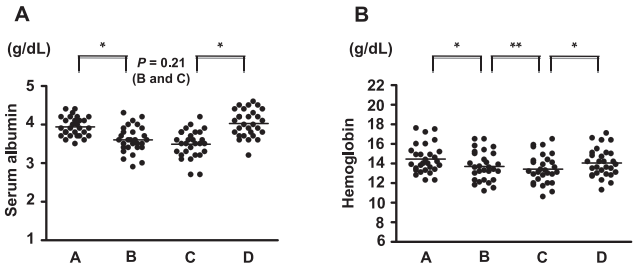

Figure 2. Serum albumin and hemoglobin concentration in the reference group
(A) Serum albumin concentration decreased significantly at B compared to A and increased significantly at D compared to C. (B) The time course of hemoglobin concentration was similar as that of serum albumin concentration. Dots are the values of patients. Horizontal bar shows mean value. *$P < 0.01$. **$P < 0.05$.

SAC and proteinuria in the LPG group

SAC and proteinuria in CKD patients with low proteinuria receiving steroid/immunosuppressant therapy (LPG group) were investigated. SAC decreased significantly and continuously from A to C, but increased at D significantly. The movement of SAC was similar from A to B and C to D with that of hemoglobin. In this group, SAC became lower significantly from B to C and it was different from the REF group. Meanwhile, proteinuria decreased significantly and continuously from A to C. At D, proteinuria became lower, but not reaching statistical significance (Figure 3).

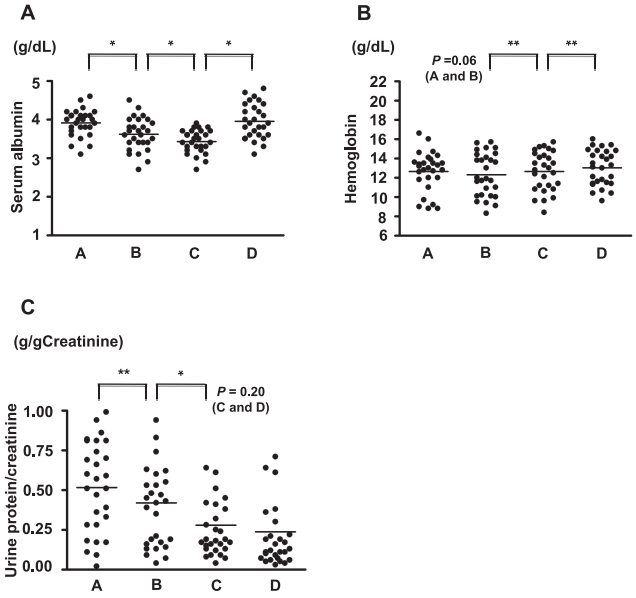

Figure 3. Serum albumin, hemoglobin concentration and proteinuria in chronic kidney disease patients with low proteinuria (LPG group)
(A) Serum albumin concentration decreased significantly and continuously from A to C, but increased at D point significantly. (B) The movement of hemoglobin concentration was similar from A to B and C to D with that of serum albumin concentration. (C) Proteinuria decreased significantly and continuously from A to C. Dots are the values of patients. Horizontal bar shows mean value. *$P < 0.01$. **$P < 0.05$.

SAC and proteinuria in the HP group

SAC and proteinuria in CKD patients with high proteinuria but who were not using steroid/immunosuppressant therapy (HP group) were evaluated. SAC and hemoglobin decreased from A to B and increased from C to D significantly, as well as those in the REF and LPG groups. Conversely, a moderate but statistically significant increase of SAC from B to C (during hospitalization) was observed. SAC at D became significantly higher than that at A. As for proteinuria, a significant decrease was detected from A to C, as well as that in the LPG group. However, at D, proteinuria increased significantly compared with that at C. The time course of proteinuria was irrelevant with that of SAC (Figure 4).

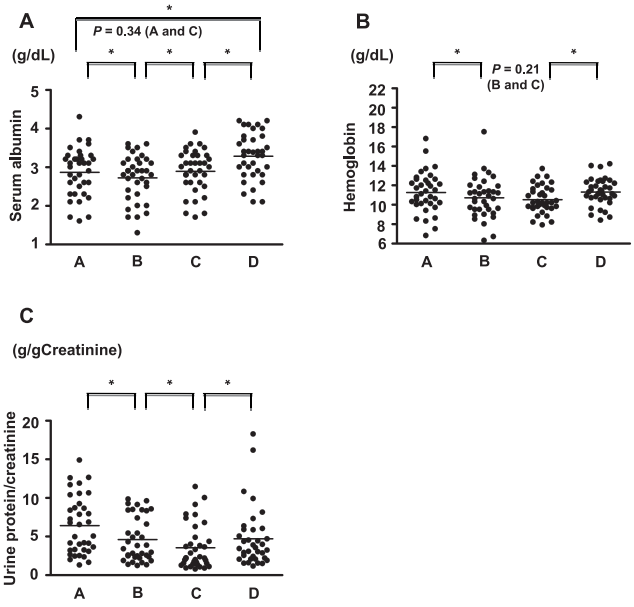

Figure 4. Serum albumin, hemoglobin concentration and proteinuria in chronic kidney disease patients with high proteinuria without glucocorticoid therapy (HP group)
(A) Serum albumin concentration decreased from A to B and increased from C to D significantly. Significant increase of serum albumin concentration from B to C was also observed. Serum albumin concentration at D became significantly higher than that at A. (B) Hemoglobin concentration decreased from A to B and increased from C to D significantly. (C) Significant decrease of proteinuria was detected at B compared to A. Proteinuria continue to decrease from B to C, but it increased significantly from C to D. Dots are the values of patients. Horizontal bar shows mean value. *$P < 0.01$.

SAC and proteinuria in the HPG group

SAC and proteinuria in CKD patients with high proteinuria using steroid/immunosuppressant therapy (HPG group) were analyzed. The movements of SAC and proteinuria were basically similar with those in the HP group. However, at D, proteinuria was not significantly lower than that at C, even with glucocorticoid treatment. It was similar with that in the LPG group (Figure 5).

Time course of systolic blood pressure

Proteinuria decreased significantly at B in CKD patients (Figure 3, 4, 5) and increased significantly at D in the HP group (Figure 4). In order to clarify the reason why proteinuria decreased during hos-

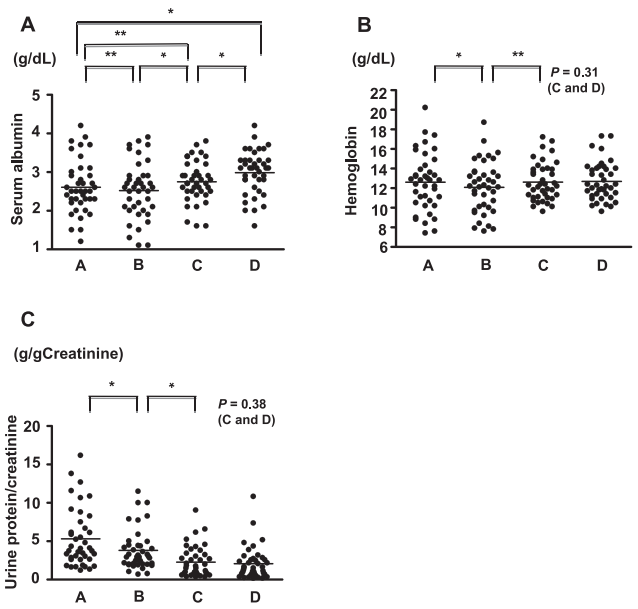

Figure 5. Serum albumin, hemoglobin concentration and proteinuria in chronic kidney disease patients with high proteinuria with glucocorticoid therapy (HPG group)
(A) Serum albumin concentration decreased from A to B and increased from C to D significantly. Significant increase of serum albumin concentration from B to C was also observed. Serum albumin concentration at C and D became significantly higher than that at A. (B) Hemoglobin concentration decreased from A to B significantly. It increased from C to D, but not reaching significant difference. (C) Significant decrease of proteinuria was detected continuously from A to C. Dots are the values of patients. Horizontal bar shows mean value. $*P < 0.01$. $**P < 0.05$.

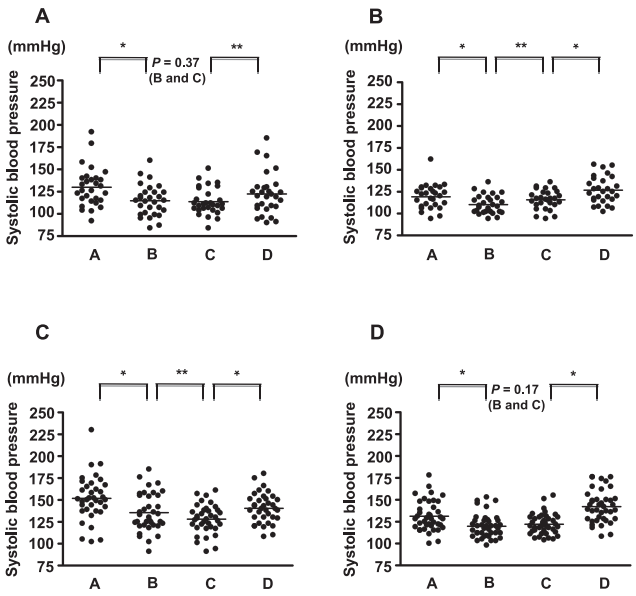

Figure 6. Time course of systolic blood pressure
(A) Reference group ; (B) LPG group ; (C) HP group ; (D) HPG group. Systolic blood pressure improved from A to B and increased from C to D significantly in all groups. Dots are the values of patients. Horizontal bar shows mean value. $*P < 0.01$. $**P < 0.05$.

pitalization, we investigated the change of systolic blood pressure. In all groups, systolic blood pressure improved at B and increased at D significantly (Figure 6).

DISCUSSION

In this study, we investigated the influential factors of SAC in CKD patients during and immediately after hospitalization. Unexpectedly, the time course of SAC was not consistent with that of proteinuria, even in patients with high proteinuria. The improvement of SAC during hospitalization in CKD patients with high proteinuria was significant, but similar with that after discharge from the hospital. Thus, SAC was affected by many factors such as postural change, activity, treatment, meals, as well as proteinuria. SAC is a classical prognostic factor in general, so it should be analyzed while standardizing a patient's condition during phlebotomy. Proteinuria was affected partly by blood pressure, even with educational and therapeutic intervention.

The novel finding in this study is the relationship between SAC and proteinuria in CKD patients immediately after hospitalization (from A to B) and after discharge from the hospital (from C to D). For example, minimal change disease patients usually have massive proteinuria and glucocorticoid therapy induces quick and complete remission of proteinuria, followed by an increase of SAC. Therefore, we hypothesized that the amount of proteinuria is the major determinant of SAC in CKD patients with high proteinuria (the HP and HPG groups). However, the changes of SAC and proteinuria from A to B and from C to D were not consistent with our hypothesis. Considering the REF and LPG groups, a patient's posture had a role in SAC change just after hospitalization and after hospital discharge, because SAC in a sitting position show at most a 5% increase compared with that in a supine position (5). However, the difference of SAC was greater than the value expected by postural change. We assume that the increase of physical activity and change of food at home can have an additional effect on SAC (14, 15) as hospitalized patients do not move as much as they typically do at home, and their food was restricted to hospital supply. Thus, postural change, physical activity, and food can be a more powerful factor for SAC than proteinuria at home, even in CKD patients with high proteinuria.

SAC during hospitalization (from B to C) was inversely related to proteinuria in the HP and HPG groups. The improvement of SAC was caused by the decrease of proteinuria, but the change was moderate and similar as compared to A and as was seen after hospital discharge (D). Unexpectedly, SAC decreased in the LPS group significantly during hospitalization. The REF group also experienced SAC decrease in hospitalization, but not significantly. This can be also explained by the decrease of physical activity. There is some possibility that low-protein diet and glucocorticoid therapy worsen the value of SAC in the LPG group (16). The evidence to show the effect of glucocorticoid on albumin synthesis is extremely scarce, especially when glucocorticoid is used in non-inflammatory disease patients (17). Glucocorticoid increases albumin synthesis in liver hepatocyte in vitro (18). However, to our knowledge, we do not have definitive data to clarify the glucocorticoid effect on SAC in vivo. Further investigation is needed to determine the glucocorticoid effect on liver albumin synthesis in CKD patients. Thus, our results suggest that hospitalization is not a preferable condition in terms of SAC. Taken together, we do not need to postpone hospital discharge because of relatively low SAC.

In our study, proteinuria improved just after hospitalization in CKD patients and worsened after hospital discharge in the HP group. We found that the change of systolic blood pressure was consistent with the amount of proteinuria. Ogi *et al.* reported that

a supine position induces higher blood pressure, better creatinine clearance and sodium excretion, and less renin activity and aldosterone concentration temporarily compared to a standing position in CKD patients (19). However, in reality, the effect of hospitalization to stabilize blood pressure could overcome temporal postural change and decrease proteinuria just after hospitalization. The worsening after hospital discharge can also be explained by food change and physical activity. Dietary change can influence on the amount of proteinuria (20, 21). Excessive exercise can increase proteinuria temporarily (22), while modest exercise has a preferable effect on proteinuria in patients with stable CKD (23).

Hemoglobin decreased just after hospitalization and increased after hospital discharge in all groups. This can be explained by postural change. Physical activity also played a role in the change of hemoglobin concentration (24). During hospitalization, the movement of hemoglobin concentration was variable, maybe because of a lot of influential factors including kidney function and erythropoietin usage.

A weakness of this study is its relatively small sample size. In addition, there were quite a few patients who had less than 1 g/gCreatinine proteinuria without glucocorticoid only/and immunosuppressant treatment during hospitalization. Therefore, we could not investigate the effects of hospitalization on SAC in such patients. Other limitations included the lack of optimal control subjects whose age, hospitalized duration, food, disease and therapeutic drugs were adjusted to each CKD group. Therefore, a "reference" group was established to show the effect of postural change and hospitalization on clinical parameters.

In summary, in this study, we demonstrate that SAC was affected by not only proteinuria, but also postural change and physical activity in hospitalized CKD patients. Food change and content of therapy probably played a role in SAC. Proteinuria decreased significantly just after hospitalization and the worsening of proteinuria after hospital discharge could be secondary to multiple causes, partly due to blood pressure. Thus, SAC is an important prognostic factor. However, even with educational and therapeutic intervention, the improvement of SAC during hospitalization was moderate. We can expect significantly higher SAC in the first outpatient follow-up appointment compared with that before hospitalization even in CKD patients.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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