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Impact of serum albumin levels on the body fluid response to tolvaptan in chronic kidney disease patients

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Abstract

Purpose Tolvaptan exerts an aquaretic effect by blocking vasopressin V2 receptor. Although tolvaptan ameliorates body fluid retention even in patients with chronic kidney disease (CKD), predictors of body fluid reduction induced by tolvaptan remain unclear. We, therefore, examined the clinical parameters associated with the effect of tolvaptan on fluid volume in CKD patients.

Methods Twelve CKD patients (stage 3–5) with fluid retention were treated with tolvaptan in addition to conventional diuretic treatment. Patients were divided into low and high responders by the median change in total body water (TBW) for 1 week measured by a bioimpedance analysis (BIA) device, and clinical parameters were compared between the groups.

Results The body weight significantly decreased by 2.0 ± 2.3 kg ($p = 0.005$), but the estimated glomerular filtration rate (eGFR) was not significantly changed (16.9 ± 11.9 vs. 17.4 ± 12.4 mL/min/1.73 m^2, $p = 0.139$) after 1 week. The BIA showed that the intracellular water (ICW) decreased by 6.0% ± 4.7% ($p < 0.001$), the extracellular water (ECW) decreased by 6.7% ± 5.4% ($p = 0.001$), and the TBW decreased by 6.3% ± 4.9% (median value − 6.02%, $p < 0.001$). The serum albumin level in the high responders was significantly lower than in the low responders (2.3 ± 0.5 vs. 3.3 ± 0.8 g/dL, $p = 0.013$). Significant partial correlations adjusted for the eGFR were observed between the baseline serum albumin level and changes in the ICW ($r = 0.440$, $p = 0.048$), ECW ($r = 0.593$, $p = 0.009$) and TBW ($r = 0.520$, $p = 0.020$).

Conclusions Serum albumin levels predict the body fluid response to tolvaptan in CKD patients. Tolvaptan may be a promising therapeutic option for ameliorating body fluid retention, especially in patients with hypoalbuminemia.

Keywords Tolvaptan · Hypoalbuminemia · Bioimpedance analysis · Volume overload · Fluid retention · Responder

Introduction

Body fluid retention is frequent among chronic kidney disease (CKD) patients and an independent risk factor for end-stage renal disease, cardiovascular disease and mortality [1, 2]. Traditionally, loop diuretics like furosemide have been used to treat fluid retention. However, these agents have some major drawbacks, such as a worsening the renal function, inducing resistance to diuretic action in hypoalbuminemia and a dose-dependent increase in mortality [3, 4].

Tolvaptan selectively binds to the vasopressin V2 receptor that is located in the renal collecting duct, and it inhibits fluid reabsorption as an antagonist [5]. Tolvaptan has been used to treat hyponatremia [6] and fluid retention due to congestive heart failure, CKD and liver cirrhosis [3, 7, 8]. We recently reported that tolvaptan equally decreases the extracellular water (ECW) and intracellular water (ICW) without exacerbating the renal function in CKD patients; whereas, loop diuretic furosemide predominantly lowers the ECW [7, 9, 10], which may result in excessive plasma volume reduction and a subsequent worsened renal function.

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Several predictors of the diuretic response to tolvaptan, such as the pretreatment urine volume and urinary osmolality, have been recently proposed in CKD patients [11]. However, predictors of the fluid response to tolvaptan, not just the diuretic response, remain unclear. Furthermore, effective serum predictors of tolvaptan also have not yet been evaluated. We, therefore, examined the association between the serum parameters and the changes in body fluid volume in CKD patients with fluid retention.

Materials and methods

Patients

This study prospectively enrolled 12 CKD patients treated at Jichi Medical University ($n=8$, Shimotsuke, Tochigi, Japan) and Nasu Minami Hospital ($n=4$, Nasukarasuyama, Tochigi, Japan) between December 2013 and December 2018. Hospitalized patients with high extracellular water (ECW)/total body water (TBW) values (see below details), generalized edema and/or pleural effusion were included. The exclusion criteria were a history of prior renal replacement, current dialysis or active malignancy. Tolvaptan (3.75 or 7.5 mg/day, average 6.9 ± 3.3 mg/day) was administrated in addition to the baseline medication.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol and amendments were approved by the independent ethics committees of Jichi Medical University (approval number: A17-014) and Nasu Minami Hospital (approval number: 2016-03). All patients provided their written informed consent to participate in this study. The study was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) Clinical Trial (UMIN registration number: 000029863).

Blood and urine sample collection

Blood samples and body weight data were collected before dosing on days 0 and 7 after the administration of tolvaptan. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation coefficients modified for Japanese patients [12]. The stages of CKD were based on the NKF K/DOQI clinical practice guidelines [13].

Measurement of the fluid volume using a bioimpedance analysis

The body fluid volume was measured using a bioimpedance analysis (BIA) device with eight tactile electrodes (InBody S10; InBody Japan Inc., Tokyo, Japan) before dosing on day 0 and 1 week after tolvaptan administration (3 h or later), similar to our previous studies [7, 9, 10, 14]. Intracellular water (ICW), ECW, TBW (ICW+ECW), and ECW/TBW were calculated from the sum of each segment, using the equations in the BIA software program. High ECW/TBW values were defined as those over 0.39, based on the user manual provided by the manufacturer [15].

Statistical analyses

The data were expressed as the mean ± standard deviation. Patients were divided into low and high responders based on the median change in the TBW for 1 week. Unpaired *t*-tests were used to compare two variables. The correlations among clinical parameters were analyzed using Pearson's correlation and partial correlation. p values of <0.05 were considered to indicate statistical significance. The statistical analyses were performed using the JMP Pro 14.0 software program (SAS Institute, Inc., Cary, NC, USA).

Results

The baseline characteristics of the 12 enrolled CKD patients were as follows: age 72.4 ± 11.3 years; male gender 8 (66.7%); body mass index 27.3 ± 4.4 kg/m^2; eGFR 16.9 ± 11.9 mL/min/1.73 m^2; serum albumin 2.8 ± 0.8 g/dL; serum Na 139 ± 5 mEq/L; serum Cl 105 ± 8 mEq/L; serum K 4.0 ± 0.7 mEq/L; ICW 23.1 ± 6.0 L; ECW 16.8 ± 4.5 L; TBW 39.8 ± 10.2 L and ECW/TBW 0.420 ± 0.017. Primary diseases included diabetic nephropathy ($n=5$), liver cirrhosis ($n=3$), glomerulonephropathy ($n=2$), nephrosclerosis ($n=1$) and amyloidosis ($n=1$). All patients used some form of diuretic (loop diuretic $n=12$, thiazide $n=1$, mineralocorticoid receptor blocker $n=4$). The body weight significantly decreased by 2.0 ± 2.3 kg from baseline (70.9 ± 15.9 vs. 68.8 ± 15.2 kg, $p=0.005$), but the eGFR (16.9 ± 11.9 vs. 17.4 ± 12.4 mL/min/1.73 m^2, $p=0.139$), serum Na (139 ± 6 vs. 140 ± 3 mEq/L, $p=0.358$), serum albumin (2.8 ± 0.8 vs. 2.8 ± 0.9 g/dL, $p=0.142$) and systolic blood pressure (130 ± 19 vs. 128 ± 16 mmHg, $p=0.346$) were not significantly changed after 1 week. The addition of tolvaptan numerically decreased the urine osmolality (277 ± 48 vs. 253 ± 65 mOsm/kg, $p=0.236$). The BIA showed that the ICW decreased by 6.0% ± 4.7% (23.1 ± 6.0 vs. 21.6 ± 1.6 L, $p<0.001$), the ECW decreased by 6.7% ± 5.4% (16.8 ± 4.5 vs. 15.6 ± 3.9 L, $p=0.001$), and the TBW decreased by 6.3% ± 4.9% (39.8 ± 3.0 vs. 37.2 ± 9.4 L, $p<0.001$). The ECW/TBW was not significantly changed after the administration of tolvaptan (− 0.3% ± 1.0%; 0.420 ± 0.017 vs. 0.418 ± 0.017, $p=0.223$).

The baseline characteristics are compared between low and high responders in Table 1. The low responders were

Table 1 A comparison of the baseline characteristics between low and high responders

Characteristics	Low responders	High responders	*p* value
Number	6	6	
Age (years)	72.1 ± 21.8	72.0 ± 13.1	0.453
Male gender (%)	83.3	50.0	0.213
Body weight (kg)	72.1 ± 21.8	69.7 ± 8.6	0.401
Body mass index (kg/m^2)	26.9 ± 3.8	27.7 ± 5.3	0.384
Diabetes mellitus (%)	33.3	66.7	0.244
Systolic BP (mmHg)	136 ± 20	126 ± 19	0.219
eGFR (mL/min/1.73 m^2)	12.4 ± 5.2	21.5 ± 15.4	0.101
CKD stage III/IV/V (*n*)	0/1/5	1/2/3	
Serum albumin (g/dL)	3.3 ± 0.8	2.3 ± 0.5	0.013
Serum Na (mEq/L)	141 ± 6	138 ± 5	0.198
Serum Cl (mEq/L)	107 ± 9	103 ± 8	0.187
Serum K (mEq/L)	4.0 ± 0.9	4.0 ± 0.6	0.485
ICW (L)	23.6 ± 6.5	22.5 ± 6.0	0.383
ECW (L)	16.8 ± 4.0	16.8 ± 4.5	0.481
TBW (L)	40.4 ± 10.3	39.2 ± 11.1	0.420
ECW/TBW	0.418 ± 0.023	0.422 ± 0.011	0.326
Concomitant diuretics (%)			
Loop diuretics	100	100	1.00
MR antagonist	33.3	33.3	1.00
Thiazide diuretics	0	16.7	0.224

The low responders were those whose change in the TBW for 1 week was greater than or equal to the median value (− 6.02%), while high responders were those whose values were less than the median value [please check this carefully]. Variables are presented as the mean ± standard deviation

BP blood pressure, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *ICW* intracellular water, *ECW* extracellular water, *TBW* total body water, *MR* mineralocorticoid receptor

those whose change in the TBW for 1 week was greater than or equal to the median value (− 6.02%), while high responders were those whose values were less than the median value. The serum albumin level in the high responders was significantly lower than in the low responders (Table 1, Fig. 1). Other parameters, including the age, body mass index, systolic blood pressure, eGFR and body fluid status (ICW, ECW, TBW and ECW/TBW), were similar between the groups (Table 1).

Next, we examined the correlation between the serum albumin level and the change in body fluid status (ICW, ECW and TBW). The baseline serum albumin level was positively and significantly correlated with the changes in the ICW ($r = 0.580$, $p = 0.048$), ECW ($r = 0.715$, $p = 0.009$) and TBW ($r = 0.657$, $p = 0.020$) (Fig. 2). Significant partial correlations adjusted by the eGFR were also observed between the baseline serum albumin level and the changes in the ICW ($r = 0.440$, $p = 0.048$), ECW ($r = 0.593$, $p = 0.009$)

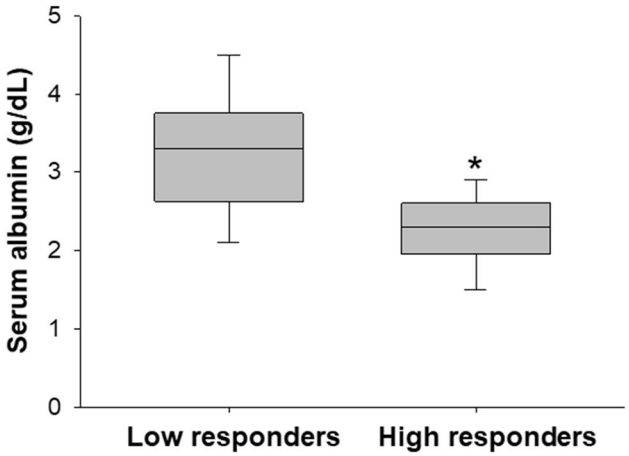

Fig. 1 Serum albumin levels in the high responders ($n = 6$) were significantly lower than those ($n = 6$) in the low responders. The low responders were those whose change in the TBW for 1 week was greater than or equal to the median value (− 6.02%), while high responders were those whose values were less than the median value. *$p < 0.05$ vs. Low responders

and TBW ($r = 0.520$, $p = 0.020$). The baseline serum albumin level was negatively correlated with the baseline ECW/TBW ($r = -0.521$, p = 0.083) and the baseline TBW/body weight ($r = -0.496$, $p = 0.101$).

Discussion

The novelty of this study is that serum albumin levels predict the fluid response to tolvaptan in CKD patients with fluid retention. To our knowledge, this is the first study in which a diuretic drug had a great reduction effect on the body fluid volume in a state of hypoalbuminemia.

Recent studies, including our own, have shown that tolvaptan exerts a diuretic effect even in patients with low serum albumin levels [8, 10, 16, 17]. Furthermore, it has been reported that the serum albumin levels were similar between responders (body weight loss exceeding 1.5–2.0 kg/week) and non-responders to tolvaptan among liver cirrhosis patients [18, 19]. However, these studies failed to demonstrate the superior fluid reduction effect of hypoalbuminemia in response to tolvaptan. One possible reason for these results may be the narrow range of serum albumin levels in those previously enrolled patients (25th–75th percentile ranges: 2.4–2.9 g/dL) [19], as the serum albumin levels in our study had a relatively wide range (1.5–4.5 g/dL), which helped to reveal the clear impact of different albumin values on the body fluid volume. Interestingly and surprisingly, Okabe et al. reported that a low serum albumin level was associated with an increased urine volume after tolvaptan administration in hospitalized heart failure patients [20]. Although that study focused on the urine volume but not

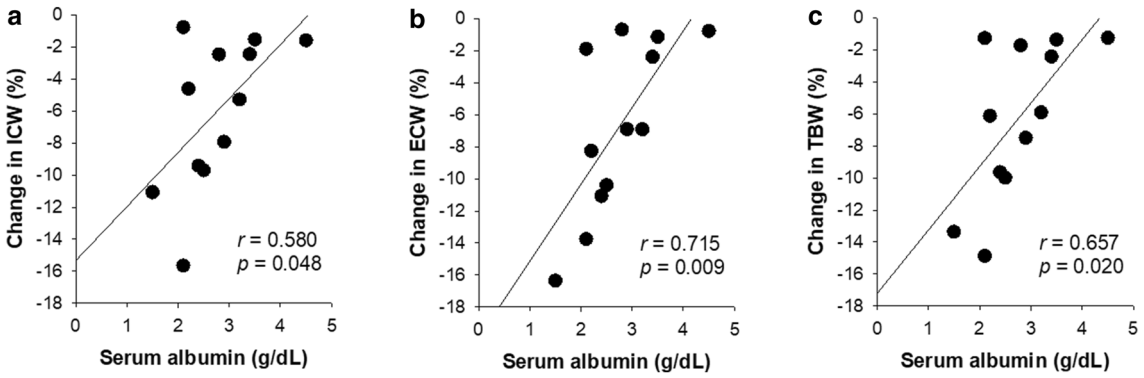

Fig. 2 The serum albumin level was positively and significantly correlated with the changes in the ICW (**a**), ECW (**b**) and TBW (**c**). ICW: intracellular water, ECW: extracellular water, TBW: total body water

body fluid volume, the results are essentially similar to our own.

Potential mechanisms regarding why a low serum albumin level had a great reduction effect of tolvaptan on the fluid volume include the following: (1) tolvaptan acts without binding to albumin, (2) hypoalbuminemia may lead to a larger increase in the intravascular colloid osmotic pressure by tolvaptan, (3) a high interstitial fluid hydrostatic pressure in hypoalbuminemia may accelerate the fluid shift into the intravascular space and (4) the change in vascular endothelial permeability associated with hypoalbuminemia may accelerate the fluid shift into the intravascular space. First, unlike loop diuretic furosemide, hypoalbuminemia does not cause diuretic resistance during tolvaptan treatment, as tolvaptan exerts diuretic action without binding to albumin [3]. Thus, tolvaptan can still exert its activity even under conditions of hypoalbuminemia, and the water diuretic action induced by daily tolvaptan intake may provide a sustained driving force to increase the serum albumin level. Second, a lower serum albumin level, which is linked to a low colloid osmotic pressure and, thus, a low intravascular fluid level [21], is more concentrated after plasma volume reduction by tolvaptan; whereas, a higher serum albumin level is less concentrated in the same setting. For example, if tolvaptan reduces 0.3 L of plasma volume (from 2.5 L to 2.2 L) in a patient with low albumin (2.0 g/dL), the concentration rate of serum albumin is 13.5% (total serum albumin 50 g/post plasma volume 22 dL = post serum albumin level 2.27 g/dL). On the other hand, if tolvaptan reduces 0.3L of plasma volume (from 3 L to 2.7 L) in a patient with normal albumin (4.0 g/dL), the concentration rate of serum albumin is 11.0% (total serum albumin 120 g/post plasma volume 27 dL = post serum albumin level 4.44 g/dL), which is less than in a patient with low albumin. Therefore, for a similar diuretic effect of tolvaptan, a lower baseline serum albumin level will induce a higher increase rate of colloid osmotic pressure than a higher baseline serum albumin, which in turn becomes a more substantial driving force for shifting fluid from the extravascular to the intravascular space [21]. Third, an increase in interstitial fluid hydrostatic pressure in patients with hypoalbuminemia may accelerate the fluid shift into the intravascular space. In our study, the baseline serum albumin level was negatively correlated with the baseline ECW/TBW, a marker of the extracellular fluid status [22]. The result indicates that patients with a low serum albumin level exhibit extracellular fluid retention, which may induce an increase in interstitial fluid hydrostatic pressure. The magnitude of the increase in interstitial fluid hydrostatic pressure exceeding the increase in capillary pressure causes a negative transcapillary pressure gradient, which in turn induces a fluid shift from the extravascular to the intravascular compartment [23]. Forth, the vascular endothelial hyperpermeability associated with hypoalbuminemia may accelerate the fluid shift into the vascular space. Vascular endothelial permeability, which is mainly controlled by the sugar–protein glycocalyx [24], has been reported to increase in chronic conditions such as diabetes [25]. Further examination is needed to determine whether or not glycocalyx contributes to the dominant fluid reduction effect associated with hypoalbuminemia. The unique pharmacological property of tolvaptan, which can still work as a diuretic in cases of hypoalbuminemia, and the sustained driving force of the fluid shift from the extravascular to the intravascular space may be promising mechanisms explaining why patients with a low serum albumin level showed a greater decrease in body fluid volume than those with a high serum albumin level.

Serum albumin as a predictor for the fluid response to tolvaptan may be very useful in the clinical setting. Several predictors of the response to tolvaptan, such as urinary osmolality (before and after the administration of tolvaptan), urinary Na excretion, urine Na/K ratio, and urine aquaporin-2 have recently been advocated [26–29]. Some of these predictors cannot be measured at all institutes, and it

sometimes takes time to get results. In contrast, the measurement of serum albumin is easier and less time-consuming in most cases. With the pre-treatment measurement of serum albumin, several diseases characterized by hypoalbuminemia and body fluid retention, such as diabetic nephropathy, nephrotic syndrome and liver cirrhosis, may become suitable targets for tolvaptan. Furthermore, importantly, loop diuretics such as furosemide may not exert sufficient diuretic action in hypoalbuminemia [3] and carry an increased risk for renal dysfunction. In this regard, tolvaptan, which exhibits its diuretic properties even under conditions of hypoalbuminemia and carries a low risk of renal dysfunction [3, 30], is a promising therapeutic option for patients with hypoalbuminemia and extracellular fluid retention.

The similar rates of reduction in ICW and ECW are a unique characteristic of tolvaptan, which differs from the loop diuretic furosemide [9]. Notably, a decrease in intracellular volume is thought to occur due to an increase in extracellular tonicity. Thus, the serum sodium concentration, one of the main determinants of tonicity, is expected to increase after the initiation of tolvaptan treatment. Unfortunately, in our study, the serum sodium concentrations at baseline and 1 week after the initiation of tolvaptan treatment were similar. On the other hand, a study of CKD patients showed that tolvaptan increased the serum sodium concentration within 12 h [31], which might facilitate the shifting of fluid from the intracellular space to the extracellular space over the short term.

Older studies have shown that vasopressin resistance appears in CKD and diabetes, at least in part, due to the selective downregulation of the V2 receptor [32, 33]. Interestingly, however, tolvaptan (a vasopressin V2 receptor antagonist) exerts diuretic action, even in CKD patients. Because tolvaptan blocks the vasopressin V2 receptor from the basolateral side of the tubules, its diuretic action does not depend on the glomerular filtration rate [3]. Indeed, previous studies showed that tolvaptan decreases urine osmolality with an increased urine volume in CKD patients [11, 34, 35]. Similarly, in our study, tolvaptan numerically decreased urine osmolality after 1 week of treatment. The beneficial effect of tolvaptan in the treatment of hyponatremia has also been reported [3, 6]. In conditions associated with hypervolemic hyponatremia with a low effective intravascular volume, such as congestive heart failure and hepatic cirrhosis, water excretion by the kidneys is impaired, partially due to the high serum vasopressin levels released in circulation due to volume stimuli [36]. In these conditions with CKD, tolvaptan may sufficiently improve hyponatremia by inhibiting high serum vasopressin with no resistance to its water diuretic action.

The present study includes several limitations. First, this study had a small sample size; so larger size studies are necessary to confirm our findings. Second, the impact of the serum albumin levels on the efficacy of tolvaptan in non-CKD patients remains unclear, as all patients enrolled in this study had CKD. Third, BIA measurements obtained in overhydrated individuals, such as dialysis patients, lack both accuracy and precision in the determination of TBW and the volume of its two major compartments [26, 27]. Our study population consisted of non-dialyzed CKD patients and we mainly focused on the relative changes in fluid volume and not absolute fluid volume; however, careful interpretation of our findings is necessary. Fourth, the effects of tolvaptan alone without concomitant diuretics are unclear, as all patients were taking other diuretics at baseline due to the regulation of their use in Japan.

Conclusions

This study shows that the serum albumin levels predict a fluid response to tolvaptan in CKD patients. Tolvaptan may be a promising therapeutic option for ameliorating body fluid retention, especially in patients with hypoalbuminemia.

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Author contributions TMa conceived and designed the study. TMa, KOh, IN, TMu, SN, KOk, MA, YI and YF performed the data collection. TMa and KOh conducted the data analysis. TMa drafted the manuscript. TMa, IN, and RM interpreted results of the analysis. YM, AM, TA, OS and DN approved the final version of manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The study was approved by the Ethics Committees of Jichi Medical University (Shimotsuke, Japan) and Nasu Minami Hospital (Nasukarasuyama, Japan).

Informed consent Informed consent was obtained from all individual participants included in the study.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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