Abstract

Introduction
It has been documented that preservation of residual renal function (RRF) in peritoneal dialysis (PD) patients could improve the quality of life as well as survival. To preserve RRF, different protective methods have been put into practice, such as sodium restriction, avoidance of nephrotoxic agents, use of renin-angiotensin-aldosterone system (RAAS) inhibition, and use of biocompatible solutions and so on. And well-protected RRF will contribute to a better control of fluid status. Fluid status of PD patients has been proved to play a role in the protection of RRF. Some clinicians proposed to keep PD patients overhydration in order to slow down the decline of RRF, while others hold different opinions. This article will review the evidence linking RRF and fluid status in PD patients, and discuss which kind of fluid status is more profitable to the preservation of RRF.

Conclusion
Optimal fluid status may lead to a better protection of RRF and achieve appropriate hydration management in return. Also the preserved RRF is helpful to maintain the optimal fluid status.

Introduction
Residual renal function (RRF) means the function of residual healthy nephrons, which includes the clearance of molecular-solute, regulation of water-electrolyte and acid-base balance and iatrogenic substitution of endogenous hormones. Just as in chronic kidney disease (CKD) patients, preservation of RRF is one of the primary goals in the management of peritoneal dialysis (PD) patients. RRF was associated with survival in PD patients. Loss of RRF in PD patients has been linked with overhydration\(^1\), left ventricular hypertrophy\(^2\), increased arterial stiffness\(^3\), cardiovascular comorbidity in general\(^4\), and mortality\(^5\).

Careful volume control to prevent dehydration has been used to minimize loss of RRF in PD patients. Dehydration is known to lead to a loss in RRF\(^6\). This phenomenon of volume depletion has led some clinicians to run their patients to ‘overhydration’. On the other hand, Overhydration is associated with hypertension, left ventricular hypertrophy\(^7\) and excess mortality, and hypertension has been reported to lead to the loss of RRF\(^8\). Based on this evidence, some clinicians run their patients to ‘dehydration’. It is necessary to highlight the relationship between RRF and fluid status in PD patients, which does not simply indicate causality. However it leads to a hypothesis that RRF and fluid status could interact as both cause and effect. Our paper intends to discuss the interaction of fluid status and RRF in peritoneal dialysis patients.

Fluid status of PD patients
Hydration status is usually assessed by clinical parameters, such as extremities oedema, changes in body weight, blood pressure and so on\(^9\). This method is simple and useful. However, multi-frequency bio-electrical impedance analysis (BIA) is a much more accurate technique in estimation of hydration status. Extracellular water (ECW), intracellular water (ICW), total body water (TBW) and excess body fluid could be estimated by BIA\(^10\).

It is indicated that overhydration is a common complication in PD patients\(^11\). Likewise, in a large cohort of PD patients\(^11\), overhydration is a prevalent finding compared to a normal reference population using Body Composition Monitor. An epidemiological analysis manifested that 66.8% in 307 continuous ambulatory peritoneal dialysis (CAPD) patients was attached by overhydration, defined by ECW/TBW of more than 0.4\(^1\). The first step to maintaining normal hydration in PD patients is dietary salt restriction. Moreover, the use of loop diuretics\(^12,13\), icodextrin or hypertonic glucose peritoneal dialysis solutions\(^14\) may also contribute to maintain volume homeostasis.

Residual renal function (RRF) in PD patients
As RRF is such a strong predictor of outcome in PD patients, it is significant to preserve RRF in PD patients. Here are some methods for protection of RRF.

Sodium restriction
Dietary salt restriction, as mentioned before, is an effective strategy to preserve volume homeostasis in PD patients.

Besides, it has potential benefits on protection of RRF as well. Ying et al. testified that high glomerular sodium exposure will induce the up-regulation of TGF-β, and TGF-β has a positive correlation with glomerulosclerosis, and thus leads to the deterioration of RRF\(^15\).

Avoid peritonitis
Better preservation of RRF may lead to a reduced rate of peritonitis. On the other hand, Liao et al.\(^16\) indicated that increased episodes of peritonitis may result in declining RRF. This might be explained by peritonitis’ association...
with hypotension, systemic inflammation, and the use of nephrotoxic antibiotics, as these factors do harm the preservation of RRF. Avoid nephrotoxic agents The avoidance of nephrotoxic drugs, such as nonsteroidal anti-inflammatory agents and aminoglycosides, and radiographic agents, is beneficial in preserving RRF. Therefore, Baker et al.7 proved that once-daily dosing, avoiding the use of concomitant nephrotoxins, monitoring of drug concentration and using the least nephrotoxic aminoglycosides can reduce the nephrotoxic effect of aminoglycoside.

Use of renin-angiotensin-aldosterone system (RAAS) inhibition Inhibitors of the RAAS have been well described to be associated with preservation of RRF by a number of studies. In a prospective study by Li et al., the RRF deterioration rate of PD patients prescribed with ramipril was slower than the control group. In another study by Suzuki et al., there’s no significant difference in blood pressure between the valsartan group and control group, but it is clear that valsartan can slow the deterioration of RRF.

Use of loop diuretics In a study by van Olden et al., they observed that the use of loop diuretics in PD patients would increase the renal excretion of water and sodium without impact on RRF. Medcalf et al.13 proved that using loop diuretics for 12 months resulted in higher level of RRF compared with a placebo group, however no significant changes was found in preservation of RRF.

Use of biocompatible solutions The Euro-Balance Trial19 provides positive expectations on the protective effect of new biocompatible solutions on RRF using a neutral pH and low glucose degradation product (GDP) fluid. However, in a randomized controlled trial by Fan et al., no difference was found in the decline of RRF between high-GDP and low-GDP solutions. The variable findings of these studies is probably due to the difference in the study period, baseline RRF, baseline fluid status and so on, but no clear association pattern was identified.

Automated peritoneal dialysis (APD) versus continuous ambulatory peritoneal dialysis (CAPD) In some preliminary reports, a faster decline of RRF was associated with APD. This faster decline might be explained by the increase of total glucose exposure and the intermittent nature of APD. Therefore, some recent surveys, such as a study by Michels et al., began to report the worse preservation of RRF in those starting on APD than CAPD. Although we haven’t got a definitive conclusion yet, it is still important to take their different features in consideration when choosing and observing modality options.

Use of medication The effect of fluid status to RRF In an attempt to maintain RRF, some authors suggested keeping patients overhydrated. So far, there is a lack of evidence from intervention trials that hypervolemia compared with euvoolemia or hypovolemia may lead to better protection of RRF.

Substantial fluid overload is a common problem for PD patients, but early observational studies did not find a determinate association between overhydration and preservation of RRF. From the study of Davenport et al., a close relationship was observed between fluid status and RRF based on analysis relating 24-hour urine output to ratio of ECW/TBW. They suggested that ECW volume expansion may result in better preservation of RRF in PD patients. In a recent study in PD patients in which fluid status was assessed by multi-frequency bio-impedance, McCafferty et al.24 found that overhydration, as identified by increased ECW/TBW, was not linked to the improvement of RRF.

On the other hand, overhydration may result in hypertension, left ventricular hypertrophy and cardiac disease, and intradialytic hypertension. In a cross-sectional study, Jansen et al. 25 found that these complications induced by overhydration could lead to a steeper decline of RRF. Moreover, in the study by Hidaka and Nakao, hypertension and a high level of atrial natriuretic peptide (ANP), as a marker of overhydration were found as independent negative predictors for decline in RRF. Rodriguez-Camona et al. 27 found that automated peritoneal dialysis (APD) had lower levels of sodium and water removal compared with continuous ambulatory peritoneal dialysis (CAPD), and thus bringing about the result of hypertension.

In addition to overhydration, decline of RRF was faster in the APD group. This also brings the suspicion that there may be a relationship between overhydration and decline of RRF.

Overhydration influences the loss of GDP from some other approaches as well. Van Biesen et al.28 demonstrated that overhydrated patients were more likely to be diabetic and had worse glycaemic control. And of note is that worse glycaemic control intensifies microvascular damage, especially in the kidney. In other words, diabetic changes induced by overhydration will accelerate the damage of residual nephrons and result in loss of RRF. Sato et al.29 observed that hypervolemia induces inflammation, and Chung et al. 30 demonstrated that inflammation is associated with an accelerated deterioration of preserved RRF.

Dehydration can cause acute kidney injury (AKI) and loss of RRF. This may be attributed to the functional reduction of aquaporins, renal vasoconstriction and structural changes in the tubular system in the condition of hypovolemia. Jansen et al. 25 and Liao et al. 30 demonstrated that intravascular volume insufficiency and hypotension may play important roles in the decline of RRF. Volume depletion may induce...
ischemic injury of nephridial tissue and thus lead to the decrease of glomerular filtration rate (GFR). Gural et al.31 reported that strict volume control with restriction of sodium and water and/or elevated ultrafiltration resulted in a 2.8kg weight loss and a 10% reduction in weekly Kt/V urea.

**The effect of RRF to fluid status**

Preservation of RRF contributes to an improved fluid balance32. Menon et al.33 demonstrated that the blood pressure of PD patients increased notably with the decrease of RRF, and this may be associated with the decline of volume removal. In a study by Konings et al.34, PD patients with GFR <2ml/min were certified to have increased volume of extracellular fluid compared with those who had better preserved RRF. This effect of RRF to fluid status may be realized by the following pathology and physiology mechanism. Volume homeostasis is one of the fundamental roles of kidneys and it plays an important role in PD patients’ clinical management.

Kidneys regulate the circulating volume status by its excretory function. Volume overload will lead to increased clearance of sodium and water. This increase can be realized through a series of mechanisms, such as stimulating the secretion of natriuretic peptide, the generation of arachidonate metabolites, inhibiting the secretion of renin-angiotensin-aldosterone system, and sympathetic activation of kidney.

**Stimulating the secretion of natriuretic peptide**

Water-sodium retention will increase the excretion of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) by irritating atrial cells and ventricular cells. The receptors of ANP and BNP, NPRa and NPRb, distribute widely in the glomerulus, renal tubules and collecting tubules. Thus, diuretic and natriuretic effects will be realized through the combination of these natriuretic peptides with their receptors.

**Stimulating the secretion of arachidonate metabolites**

PGE2, PG12, and CYP-450 are metabolites of arachidonic acid. The combination of PEG2 and its receptor, EP3, can inhibit the reabsorption of sodium. PG12 also possess a similar effect. 5,6-EET, a metabolite of CYP-450, can inhibit transference of sodium by it effect on proximal tubule and cortical collecting tubule. Water-sodium retention will promote the anabolism of these arachidonate metabolites, and increase nephric excretion of natrium and urine.

**Inhibiting the secretion of renin-angiotensin-aldosterone**

Renin is mainly secreted by a juxtaglomerular cell in the afferent glomerular arteriolar wall. With the increase of renal blood filtration, under the circumstance of water-sodium retention, the pressure of the afferent glomerular arteriolar wall and/or the sodium concentration in the distal tubule elevated, and as the macula dense cell is stimulated, the secretion of renin by juxtaglomerular cell is suppressed, and this proceeds to the decreased generation of angiotensin II and aldosterone. Aldosterone can bind with its receptor in the distal tubule and collecting tubule to enhance water-sodium reabsorption. On the contrary, water-sodium retention will lead to decreased secretion of aldosterone and contribute to the diuretic and natriuretic effect of the kidney.

Angiotensin II can bind with the angiotensin I receptor in the glomerular arteriole, mesangial cell and proximal tubular epithelial cell, and plays a part in regulation of kidney blood flow volume, glomerular filtration rate and sodium reabsorption of the tubule.

Conversely, the reduced generation of angiotensin II will make for diuresis of the kidney.

**Inhibiting the secretion of arginine vasopressin (AVP)**

AVP, which is produced by the hypothalamus and released by the posterior pituitary, can bind to the V2 receptor in the collecting tubule to increase its water permeability, and bind to the V2 receptor in the medullary loop ascending limb to increase sodium reabsorption.

Accordingly, expansion of circulation volume caused by water-sodium retention can inhibit the secretion of AVP by negative feedback, and strengthen nephric diuretic and natriuretic effects.

**Inhibiting the secretion of sympathetic activation of the kidney**

Noradrenalin and some other neurogens released by sympathetic nerves can combine with an α-adrenoreceptor in the kidney to arouse vasoconstriction, reduce renal blood flow, enhance sodium reabsorption of the proximal tubule, and ultimately result in water-sodium retention. At the time when circulation volume is enlarged, baroreceptor will restrain sympathetic activation of kidney reflexively, and promote the nephric excretion of natrium and urine.

In a dehydration condition, nephridial tissue will exert its sodium and water-sparing function by performing the above mentioned mechanisms reversely. Therefore, RRF is extremely important with its function to regulate fluid status rather than additional solute clearance. This statement is well demonstrated by the reanalysis of the CANUSA data.

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

The relationship between RRF and fluid status in PD patients has already attracted a lot of attention, but there’s still less evidence based on randomized trials about their interaction with each other. On account of existing studies, successful management of hydration status will enhance the protection of RRF. However, what is successful...
hydration management still needs further study.

Present experiments tend to support the opinion that hypervolemia comparing with euvoolemia or hypovolemia may not lead to better preservation of RRF, and hypovolemia may also accelerate the decline of RRF. The deterioration of RRF might result in a worse control of fluid status, and thus, build up a vicious circle. This vicious circle will vulnerate the prognosis of PD patients.

Conclusion

Appropriate fluid status is important to the preservation of RRF in PD patients. The greatest challenge in hydration management might be removing the correct amount of fluid to keep PD patients away from fluid excess or fluid depletion.

The increasing cognition of the significance of optimal fluid status may lead to a better protection of RRF and achieve appropriate hydration management in return. And the preserved RRF is helpful to maintain the optimal fluid status. Appropriate fluid status and protection of RRF could form a virtuous circle and improve the final prognosis of PD patients.

References


Licensee OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)


Critical review

Competing interests: None declared.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

All authors contributed to conception and design of manuscript, read and approved the final manuscript.


