Sodium removal in peritoneal dialysis: is there room for a new parameter in dialysis adequacy?

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Résumé
En dialyse péritonéale (DP), ainsi qu’en hémodialyse (HD), une faible clairance du soluté mesurée par le Kt/V urée a longtemps été utilisée comme représentant l’adéquation de la dialyse. On pensait initialement que l’amélioration de la clairance de l’urée augmentait la survie des patients dialysés (comme le montrait l’essai CANUSA) (1), mais la réanalyse des données a montré une contribution supérieure de la fonction rénale résiduelle en tant que facteur prédicatif de la survie du patient. Deux essais contrôlés randomisés (ECR) (2, 3) ont confirmé cette observation, ne montrant aucun bénéfice en termes de survie chez les patients présentant un Kt/V supérieur. Ensuite, les recommandations ont été révisées et un Kt/V minimum de 1,7/ semaine a été recommandé, mais peu d’attention a été accordée aux paramètres supplémentaires de l’adéquation de la dialyse. En tant que telles, la surcharge volumique et l’élimination du sodium ont retenu l’attention, leur optimisation étant associée à une diminution de la mortalité chez les patients en DP(4, 5). Une élimination inadéquate du sodium est associée à une surcharge liquidienne qui conduit à une hypertrophie ventriculaire et à une mortalité cardiovasculaire accrue(6). La prescription individualisée est essentielle pour une élimination optimale du sodium car il existe des différences entre les techniques de DP, dialyse péritonéale continue ambulatoire et dialyse péritonéale automatisée (DPCA et DPA), et de nouvelles stratégies d’élimination du sodium ont émergé (solutions à faible teneur en sodium et DP adaptée). En conclusion, les futures recommandations devraient traiter des paramètres associés à des résultats de survie améliorés (l’élimination du sodium jouant un rôle important) et abandonner le modèle actuel de prescription unique.

Summary
In peritoneal dialysis (PD) (as well as in hemodialysis) small solute clearance measured as Kt/v urea has long been used as a surrogate of dialysis adequacy. A better urea clearance was initially thought to increase survival in dialysis patients (as shown in the CANUSA trial)(1), but reanalysis of the data showed a superior contribution of residual renal function as a predictor of patient survival. Two randomized controlled trials (RCT)(2, 3) supported this observation, demonstrating no survival benefit in patients with higher achieved Kt/v. Then guidelines were revised and a minimum Kt/v of 1,7/ week was recommended but little emphasis was given to additional parameters of dialysis adequacy. As such, volume overload and sodium removal have gained major attention, since their optimization has been associated with decreased mortality in PD patients(4, 5). Inadequate sodium removal is associated with fluid overload which leads to ventricular hypertrophy and increased cardiovascular mortality(6). Individualized prescription is key for optimal sodium removal as there are differences between PD techniques (CAPD versus APD) and new strategies for sodium removal have emerged (low sodium solutions and adapted PD). In conclusion, future guidelines should address parameters associated with increased survival outcomes (sodium removal playing an important role) and abandon the current one fit all prescription model

Mots clés : Dialyse péritonéale, dialyse adéquate, soustraction sodium

Keywords : peritoneal dialysis,dialysis adequacy sodium removal

Note : ce texte a été soumis initialement en anglais sa traduction française est disponible à l'url : https://doi.org/10.25796/ddd.v2i3.21343
Introduction

Chronic kidney disease (CKD) is an emerging global problem and the number of individuals requiring renal replacement therapy (RRT) is increasing worldwide. Since introduction of peritoneal dialysis as an option of RRT in patients with end stage kidney disease (ESKD) there have been many changes that allowed better treatment quality (lower glucose degradation products concentration, better connectivity systems) as well as clinical procedures aiming for reducing PD related infection rates (technique training, antibiotic prophylaxis) (7, 8). These factors, associated with rising life expectancy, as well as increased evidence of PD as a technique associated with comparable clinical outcomes and quality of life as hemodialysis have led to an increase in its use.

Similarly to hemodialysis, the principles that originally guided PD prescription were based on small solute clearance, with the major guidelines (ISPD and KDOQI in 2006(9, 10)) defending the use of Kt/v of urea as a surrogate marker of dialysis adequacy. In addition, in patients in automatic peritoneal dialysis (APD), attention should also be given to creatinine clearance (CrCl), as creatinine removal is more time dependent than urea removal because of its higher molecular weight. Consequently, a dissociation between urea Kt/v and CrCl in APD patients is not unexpected and may explain clinical presence of inadequate dialysis despite “adequate” Kt/v. Initially, a better urea clearance was thought to increase survival in dialysis patients, as shown in the CANUSA trial,(1) whose data showed an increased relative risk of death with a decrease in Kt/v and creatinine clearance(1). The results obtained in this study were interpreted in the idea that peritoneal and renal clearances are equivalent and therefore additive. Posterior reanalysis of the CANUSA data concluded that residual renal function (RRF) showed a superior contribution as a predictor of patient survival(11). These data were supported by two randomized controlled trials (RCT)(2, 3) which demonstrated that aiming at a higher Kt/V did not improve survival. The first was a study performed in Mexico with prevalent PD patients and assessed patient survival outcomes comparing two groups: one that continued standard PD prescription (four 2L daily exchanges) versus a group in which prescription was modified to achieve a creatinine clearance (CrCl) target of 60L/week per 1.37m2. Creatinine clearance values and Kt/v were higher in the latter group (with statistical significance) but this did not translate in a mortality difference between them(2). Similarly, a study performed in Hong Kong followed incident PD patients and divided them in three groups according to Kt/v target: <1.7, 1.7-2.0 and >2.0. The results of this study also failed to demonstrate the association of Kt/v and better survival outcomes. Nonetheless, patients in the Kt/v <1.7 group had significantly more clinical problems and severe anemia.

The latest guidelines from ISPD and KDOQI already date from 2006 and, although they adjusted the Kt/v target to a lower level after the studies mentioned above, they did not contemplate other potential goals for dialysis adequacy(9, 10). Hemodialysis also struggles with the absence of better markers for dialysis adequacy other than Kt/v, that in the present date, is considered rather obsolete (12).

As a consequence of a too strict interpretation of this flawed marker of adequacy, many patients have transitioned to different PD modalities or to hemodialysis in consequence of failure to achieve the target. Nowadays, dialysis adequacy is perceived by the nephrology community as being not only dependent on an isolated numeric concept such as Kt/v but should be seen as a holistic perception of the patient in terms of well-being, control of symptoms and comorbidities associated with CKD (anemia, mineral bone disease) and a perspective to the future (for instance possibility of renal transplantation). This perspective urges for revision of current guidelines and their adoption to include more suitable targets for dialysis adequacy that relate to patient outcomes and survival.

Is sodium removal an important target to achieve?

Cardiovascular (CV) mortality is, next to infection, the major cause of death in CKD patients, and that remains truth for ESKD (hemodialysis and peritoneal dialysis) (13-15). This association between CV mortality in CKD is influenced by many factors: presence of uremic toxins, chronic inflammation, atherosclerosis and fluid overload. Besides those factors, excessive sodium intake also plays a role as it has been associated with volume expansion, hypertension and left ventricular hypertrophy, the latter being a predictor of mortality in ESKD(16, 17). A study published in 2001 evaluated the effect of sodium and fluid removal on mortality in PD patients and concluded that, as opposed to Kt/v and CrCl, sodium removal is a predictor of mortality in peritoneal dialysis patients(4). This was a major finding and strengthened the importance of considering sodium removal optimi-
zation as a target for dialysis adequacy (4). Besides an effect in mortality and cardiovascular outcomes, sodium seems to play a role in morbidity related to other scopes of CKD (18): available data support the finding that excessive sodium can have deleterious effects in a variety of organs and systems such as blood vessels, heart, the brain and an association with auto-immune diseases has also been described(19-23).

Many other substances have been proposed as markers of inflammation with possible association with mortality. For instance, β2-microglobulin levels seems to be associated with clinical outcomes in PD patients as well as in HD (24, 25). Higher β2-microglobulin levels are associated with increased mortality and even as risk factor for transition from PD to HD (26). However, this is probably indicative of worsening RRF and, to date, despite some data that shows better β2-microglobulin clearance with convective techniques such as hemodiafiltration or nocturnal HD (27, 28), RRF preservation and renal transplantation remain the only effective means to lower β2-microglobulin concentration with better clinical outcomes (25).

**Sodium removal in PD: back to basics**

Water and solute transport across the peritoneal membrane can be explained by the established and validated three-pore-model (29, 30). This model defines the existence of different sized pores, whose number also vary inversely with their size: ultra-small pores (aquaporin-1 (AQ1), mainly responsible for water transport, small-pores (responsible for water and small solute transport) and large-pores (involved in macromolecule transport). When the dialysis solution gets in contact with the peritoneal membrane, because of the osmotic gradient present, free-water transport occurs across the membrane primarily across AQ1 channels. This free water transport is responsible for sodium dilution in the dialysate, the so-called sodium sieving, and this in turn is the drive for sodium transport across the membrane by the small-pore channels. Sodium transport in this case is made mainly by convection – solvent drag that occurs in conjunction with ultrafiltration. Because sodium concentration in the dialysate is very similar to serum sodium concentration, the diffusive driving force for sodium transport is rather small. Another process to take into account is absorption of water and solutes (by either back filtration or absorption through the lymphatics). In summary sodium transport is a time-dependent process that is driven by diffusion and convection (solvent drag that occurs with ultrafiltration) across the peritoneal membrane (29, 30).

The physiology of sodium transport in PD is very important in the daily clinical practice. Because of the sodium sieving, depending on the dialysis schedule and rate of small solute transport, the ability to remove sodium may be compromised. As exposed above, sodium removal is optimized in the end of the cycle with sodium removal correlated with the UF, but, since it is shorter in automatic peritoneal dialysis (APD), this exposes the patients to a higher risk of hypernatremia, with dissociation between water and sodium removal. Many studies have demonstrated superiority of CAPD in sodium and water removal, especially in patients with slower membrane transport (31-34). Indeed, sodium removal in APD is lower when compared with CAPD for any degree of ultrafiltration (UF). This is followed by a tendency for better hypertension control in CADP (33) although these differences seem to not have an effect in cardiovascular outcomes (31).

**What can we optimize?**

Fortunately, there are many options to optimize sodium removal and homeostasis. First, general measures include dietary sodium and water restriction. International guidelines (KDIGO and WHO (35, 36)) recommend lowering sodium daily intake to <90mmol (<2g) of sodium (corresponding to 5g of sodium chloride). Although evident, this measure might be difficult to attain in daily practice, especially in countries that are known to traditionally have high sodium diets (37). Preserving RRF also adds up to optimizing sodium removal. This is achieved by, for instance, eviction of nephrotoxic agents and renal hypoperfusion. An extensive review of this topic is beyond the scope of this article.

In the past focus was given to the use of lower sodium concentration dialysates in the belief that it could optimize sodium removal by increasing the diffusion gradient. In peritoneal dialysis, lowering sodium concentration poses an important implication: lower solution osmolarity and consequently lower osmotic gradient for UF (38). To overcome this catch 22 a higher glucose concentration could be added to the solution, but this, as well, may have negative consequences due to membrane exposition to glucose degradation products and putative metabolic adverse effects and increased cardiovascular risk (39-43).
Nonetheless, studies with low-sodium PD solutions were performed and presented interesting results (44). Davies and colleagues (38) compared compensated low-sodium solutions (with higher glucose concentration, sodium concentration 115mEq/L) versus non-compensated low-sodium solutions (sodium concentration 102mEq/L) and demonstrated that the latter is accompanied by decreased UF despite increasing sodium removal. This was accompanied by inability to decrease blood pressure and extracellular fluid volume as opposed to the compensated low-sodium group. The authors thus concluded that, to observe clinical effects by using low-sodium solutions, osmolarity compensation had to be endorsed (38).

Another study used solutions with only mildly reduced sodium concentration (125mEq/L) not compensated by higher glucose concentration. Their results were very promising, demonstrating that even with a small reduction in sodium concentration it was possible to achieve increased sodium removal, UF, and better blood pressure control (45). This difference in comparison with the previous study could be explained by the fact that in this, all the dwells were performed with a low-sodium solution (as opposed by only one daily low-sodium dwell in the first study).

Another possible approach is to maintain the solution osmolarity by adding another osmotically active substance other than glucose, for instance icodextrin. A study performed by Freida and colleagues evaluated sodium removal, UF and blood pressure control variation using a bimodal dialysis solution (combining glucose and icodextrin) with encouraging results (46). They also demonstrated increased sodium removal and UF but no difference in blood pressure control.

All these experiments brought interesting results but unfortunately, there are still no options of low-sodium solutions in the market (commercially available solutions have a sodium concentration ranging from 132 to 134mmol/L). Probably bigger studies (RCT for instance) must confirm these results and demonstrate their safety in clinical practice. Nonetheless, this seems a promising upgrade in dialysis prescription and management.

But, what can we do now? Although low-sodium solutions are not yet available on the market, there are other possibilities for optimizing sodium removal. Simple approaches include prescription skills. Individualized increased infusion volume will increase recruitment of peritoneal surface area leading to greater contact between capillaries and dialysis solution which favours water and solute exchange (47) (in comparison with haemodialysis - this would translate to an upgrade in the filter area). Nevertheless, potential increase in intraperitoneal pressure and consequent backfiltration should be taken into account, so caution is advised. Increasing dwell time, adjusted to the small solute rate, also permits a greater solute dialysis (surpassing the initial sodium sieving effect) (47). Icodextrin use by exerting a colloid osmotic grading promotes UF via small pores and thus enhances sodium convective removal (48).

For patients in APD, who by definition have a lower sodium removal with short dwells, a prescription adaptation recently proposed by Fischbach and colleagues aids in promoting efficient sodium removal (49). It is called adapted APD (A-APD) and involves two mechanisms. First shorter and low volume initial dwells are performed – this promotes UF by AQP1 channels and thus free water transport. It is followed by incomplete drainage and subsequent larger volume and longer dwells. By incompletely draining the peritoneal cavity, the remaining solute will dilute the subsequent dialysis solution infused and decrease its sodium concentration. By this means, increased diffusion gradient is enhanced. Subsequently, longer and larger dwells stimulate water-coupled sodium transport (membrane recruitment and longer convection time). A small multicentre RCT performed initially with 25 patients (6 withdrawals) demonstrated that sodium dialytic removal was higher with A-APD (50) but a recent computer simulation for A-APD showed conflicting results (51) - minor improvement of sodium dialytic removal by A-APD. Future investigations are needed to further clarify the role of A-APD in promoting better sodium removal in APD patients.

As depicted above, sodium overload is associated with volume overload and its negative consequences. Besides applying the strategies depicted, a clinical tool aiding in volume overload assessment in daily practice is a major coadjuvant in PD patient management. For instance, many centers use bioelectrical impedance analysis (BIA) for estimation of overhydration. BIA, by the passage of an electric current through the body, estimates extracellular water (ECW) and intracellular water (ICW). A recent systematic review concluded that bioimpedance defined overhydration is an independent predictor of mortality in end stage kidney disease (52). Nonetheless this analysis had some limitations - for instance methodological heterogeneity between the data collection in the studies analysed. Also, BIA is not the Holy Grail of overhydration evaluation: the inability to categorize ECW in its components of intravascular and extravas-
cular water, as well as the existence of wide ranges of normality in body composition pose some limitations in its use (53). Despite this, serial measurements of BIA in the particular patient setting seems to provide important information and aid in clinical assessment of changes in hydration or nutrition over time (53). Herein BIA use in PD patients may be a useful adjuvant in clinical assessment of hyperhydration that often occurs in states of excessive sodium overload.

**Conclusion**

Although current guidelines consider evaluation of dialysis adequacy in terms of an isolate numeric concept (Kt/V urea), the nephrology community has long assimilated adequacy as a multi-targeted approach (patient well-being in all CKD dimensions). Nonetheless, the existence of a numeric target is not an aim to avoid. However, it is imperative to guide dialysis prescription and adequacy by variables that are related to mortality and morbidity. The data currently available have proved that sodium removal and water balance are key determinants in better patient control and appear to be related with outcomes in dialysis patients. Thus, determinants of sodium removal should be used alongside with variables as residual renal function (and its preservation), volume status and optimized control of CKD complications (anemia and mineral bone disease). In conclusion, an update on dialysis adequacy guidelines is long needed to translate into clinical practice what the nephrology community has already endorsed as better markers for life quality and factors that are likely to affect outcomes in CKD patients undergoing dialytic treatment.

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Reçu le 2019/08/10, accepté après révision le 2019/08/30, publié le 2019/09/1