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COMMENTARIES

IS THE EFFECT OF LOW-GDP SOLUTIONS ON RESIDUAL RENAL FUNCTION MEDIATED BY FLUID STATE? AN ENIGMATIC QUESTION WHICH STILL NEEDS TO BE SOLVED

Fluid overload is still a problem in peritoneal dialysis (PD). In a recent international multicenter study of 639 patients on PD, approximately 25% were classified with severe fluid overload according to bioimpedance indices reflecting extracellular hypervolemia, whereas only 40% were classified as normovolemic (1). Two recent studies found that the mean degree of fluid overload in PD was comparable to pre-dialysis values in hemodialysis (HD) patients (2,3). This is of clinical importance, given the relation between fluid overload with hypertension and cardiac congestion, although there is no evidence for an inferiority of PD as compared to HD regarding the effect on blood pressure regulation or cardiac structure (3,4). Recently, a relation between fluid overload and mortality was also observed in PD patients, confirming previous findings in HD patients (5,6).

Regulation of fluid balance during PD treatment is dependent upon 3 basic factors: salt and water intake, peritoneal ultrafiltration (or reabsorption), and residual diuresis (6–9). Peritoneal ultrafiltration was inversely related to the extracellular:total body water (ECW:TBW) ratio, assessed by bioimpedance (8). Importantly, both total and peritoneal fluid and sodium removal were related to outcome (9). Due to alterations in the peritoneal membrane based on long-term exposure to unphysiologic concentrations of glucose and glucose degradation products, higher glucose concentrations are often needed to maintain adequate peritoneal ultrafiltration during long-term treatment but at the risk of initiating a vicious cycle leading to further peritoneal membrane damage (10).

The relevance of diuresis and residual renal function (RRF) for PD treatment is evident from its relation to survival in prospective observational studies (11). The extent to which the relation between RRF and outcome is mediated by the effect on fluid overload or uremic toxins removal is not completely clear. Residual renal function was found to be inversely associated with the presence of fluid overload (12), although this has not been a uniform finding (1). Still, a recent study subdivided patients according to the median value of the RRF decline during the first year of PD. Whereas left ventricular diameter and mass improved in the subgroup experiencing a slower decline in RRF, these parameters remained stable in the subgroup with the faster decline in RRF (13).

As preservation of both peritoneal membrane function and RRF are both of major importance for the success of long-term PD, it would be a great asset if both the decline in RRF and peritoneal membrane function could be positively influenced by modification of the PD strategy. By improving biocompatibility, the use of PD solutions with lower concentrations of glucose degradation products (GDP) and more physiological pH levels (to be called "low-GDP solutions" in this review) may be a further step towards achieving this goal.

Despite the variety of low-GDP solutions on the market, common mechanisms behind the beneficial effects of low-GDP solutions on peritoneal membrane function are, amongst others, a lesser peritoneal and systemic toxicity of glyoxidation and advanced glycation end-products (14). Where there is ample evidence for a beneficial effect of low-GDP fluids on cell viability, as well as on peritoneal membrane structure and function from experimental trials, long-term data in humans are more scarce (15,16). In the largest randomized controlled study on this subject, after an increase in the D/P creatinine ratio in the short term, low-GDP solutions were associated with a stabilization of peritoneal membrane function as compared to standard solutions (17,18). Importantly, peritoneal ultrafiltration volume is generally found to be higher with conventional as compared to low-GDP solutions of the same glucose concentrations (17,19). Although the underlying mechanisms have not been fully elucidated, more pronounced vasodilation and peritoneal capillary recruitment with conventional solutions may be implicated (20).

Next to the effects on peritoneal membrane, there are data in the literature suggesting a better preservation of RRF with the use of low-GDP solutions. In the balANZ trial, the slope of the decline in RRF was not significantly different between the low-GDP and the conventional group, but the time to anuria was longer in the group treated with low-GDP solutions (17). In a subsequent meta-analysis, RRF and urine volume 12 months after the start of PD were significantly higher in patients treated with low-GDP as compared to conventional solutions (21,22). Whereas the beneficial effect of low-GDP solutions on peritoneal membrane function has strong theoretical underpinnings, the effects on RRF and/or diuresis are more enigmatic, although it has been proposed that the

lesser systemic glyoxidation toxicity may play a role, as e.g. 3,4-dideoxyglucosone-3-ene (3,4-DGE) was shown to induce apoptosis in renal epithelial cells (23,24). However, given the lower peritoneal ultrafiltration observed with the use of low-GDP fluids, it has also been suggested that differences in fluid status might be partly responsible for the better preservation of RRF and diuresis with the use of low-GDP solutions (25). However, there are no studies comparing fluid status using objective techniques, between patients treated with conventional and low-GDP solutions. In order to shed more light on this question, a single-center study by Lichodziejewska-Niemierko *et al.*, of which the results are published in this volume of PDI, allocated 18 patients to either conventional or low-GDP solutions and followed for 24 months. The main outcome of the study is that, in the 14 remaining patients who were eligible for assessment, the peritoneal ultrafiltration volume declined in the low-GDP group while the "overhydration index" assessed by multifrequency bioimpedance, reflecting the percentual expansion of the extracellular compartment, was higher at the end of follow-up (26).

The first question is whether this study adds support to the hypothesis that the better preservation of RRF associated with the use of low-GDP solutions may be related to differences in fluid status. Despite the difference in fluid status, no significant differences in urine volume were observed between both groups, so the present study does not provide direct evidence for the hypothesis. An important limitation of the study is the lack of randomization. It should be noted that the limited statistical power of the study can have affected the interpretation of these results, given the fact that urine volume declined by 30% in the low-GDP group and by 40% in the group treated with conventional solutions. Despite this decline in urine volume, patients were continued on 4-times daily exchanges with 1.5% solutions during the follow-up. Therefore, the absence of a significant change in fluid status observed with the conventional glucose solutions remains somewhat unexplained in the absence of detailed data on fluid intake. However, from the data presented, it appears likely that the increase in fluid overload with low-GDP solutions is at least partly related to the lower ultrafiltration as compared to conventional glucose solutions. It is also clear that the present study does not provide direct evidence for a causal relation between differences in fluid state and the better preservation of RRF with low-GDP as compared to conventional solutions. However, the next question is whether the study supports a possible association between mild fluid overload and the better preservation of RRF and/or residual diuresis with the use of low-GDP solutions observed in previous literature.

Available evidence suggests that fluid state may affect RRF, as forceful fluid removal may lead to a decline in RRF in PD patients (27). Also, a subanalysis of a randomized trial comparing icodextrin with glucose solutions showed that fluid-depleted patients, according to ECW measurements by bromide dilution, experienced a more rapid decline in RRF (28). In the NECOSAD cohort, the decline in RRF was faster in patients who experienced episodes of dehydration, assessed according to clinical criteria (29). However, whereas fluid depletion likely affects RRF and diuresis in a negative way, the more pertinent reciprocal question is whether the latter are positively influenced by (mild) fluid overload (30). Although a relation between urine volume and fluid overload appears likely from the Guytonian mechanism of pressure natriuresis, there are not yet hard data to support this assumption in dialysis patients. A recent observational study in 237 patients showed no differences in the change in RRF between different tertiles of the ECW:TBW ratio assessed by bioimpedance in incident PD patients, nor a relation between changes in the ECW:TBW ratio and the change in RRF during 12 months of follow-up (31). However, the different ECW:TBW tertiles may not fully correspond with the physiologic classifications of fluid depletion, normovolemia, and fluid overload. In addition, the ECW:TBW ratio, which is also a predictor of outcome in PD patients, can be influenced by other factors, such as differences in muscle mass or fat tissue mass between patients (30,32). Notably, the relation between the ECW:TBW ratio and the overhydration index which was used both in the present study and in previous cohorts (1,20) is weak ($r = 0.31$), suggesting that these parameters partly reflect different entities (6). The discussion on the best normalization procedure for mulltifrequency bioimpedance parameters is not fully closed, given the fact that the overhydration index is also influenced by a certain assumption regarding the hydration of lean tissue and fat mass (32,33).

In a randomized trial of 160 PD patients comparing the effects of routine versus technique-assisted assessment of fluid state, no differences in changes in urine volume were observed between both groups, despite a significant difference in fluid status of about 0.8 L at the end of 3 months follow-up (34). However, in this study, even with the use of technique-assisted prescription of fluid state, patients still remained generally fluid overloaded both in the control and intervention group. A last argument from physiology is that an effect of fluid overload on RRF (including the removal of uremic toxins) is less likely than a possible effect on residual diuresis, for which there is a sound physiologic explanation through pressure natriuresis. However, in the literature, both entities, which likely only partly overlap, are not always strictly distinguished.

Interestingly, differences in fluid state between conventional and low-GDP solutions in the present study were only detected by bioimpedance, whereas no changes in biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiographic parameters were observed. Also in a recent study, agreement between different techniques, such as bioimpedance, NT-proBNP, and vena cava echography used to assess fluid state in dialysis patients was relatively weak (35). The data from the present study suggest that bioimpedance may be more sensitive in detecting small changes in fluid state as compared to the other parameters, although in the absence of gold standard techniques, this cannot be proven.

In conclusion, the results of the study of Lichodziejewska-Niemierko *et al.* do not directly support the hypothesis that differences in the preservation of RRF between low-GDP and

conventional solutions may be partly related to differences in fluid state due to reduced peritoneal ultrafiltration. Still, it does not negate the presence of such a relation, as it provides preliminary evidence for potential differences in fluid status between low-GDP and conventional solutions of the same tonicity. The study may aid in the design of future trials in which the effect of conventional and low-GDP solutions, carefully distinguishing between RRF and residual diuresis, are compared while fluid state is prescribed to a preset target, using technique-assisted monitoring, e.g. by bioimpedance. Such a trial could also provide more definite evidence for the presence or absence of a relation between peritoneal ultrafiltration, fluid status, and preservation of RRF in PD patients.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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REFERENCES

1. van Biesen W, Williams JD, Covic AC, Fan S, Claes K, Lichodziejewska-Niemierko M, *et al.*; EuroBCM Study Group. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. *PLOS ONE* 2011; 6:e17148.
2. van Biesen W, Claes K, Covic A, Fan S, Lichodziejewska-Niemierko M, Schoder V, *et al.* A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. *Nephrol Dial Transplant* 2013; 28:2620–8.
3. Yao YH, Fu CH, Ho SJ, Tsai SH, Ng YY, Chuang CL, *et al.* Peritoneal dialysis as compared with hemodialysis is associated with higher overhydration but non-inferior blood pressure control and heart function. *Blood Purif* 2012; 34:40–7.
4. Konings CJ, Kooman JP, Schonck M, Dammers R, Cheriex E, Palmans Meulemans AP, *et al.* Fluid status, blood pressure, and cardiovascular abnormalities in patients on peritoneal dialysis. *Perit Dial Int* 2002; 22:477–87.
5. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, *et al.* The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24:1574–9.
6. O'Lone EL, Visser A, Finney H, Fan SL. Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival. *Nephrol Dial Transplant* 2014; 29:1430–7.
7. Quan L, Xu Y, Luo SP, Wang L, LeBlanc D, Wang T. Negotiated care improves fluid status in diabetic peritoneal dialysis patients. *Perit Dial Int* 2006; 26:95–100.
8. Avila-Díaz M, Ventura MD, Valle D, Vicenté-Martínez M, García-González Z, Cisneros A, *et al.* Inflammation and extracellular volume expansion are related to sodium and water removal in patients on peritoneal dialysis. *Perit Dial Int* 2006; 26:574–80.
9. Ateş K, Nergizoğlu G, Keven K, Sen A, Kutlay S, Ertürk S, *et al.* Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 2001; 60:767–76.
10. Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol* 2001; 12:1046–51.
11. Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001; 12:2158–62.
12. Konings CJ, Kooman JP, Schonck M, Struijk DG, Gladziwa U, Hoorntje SJ, *et al.* Fluid status in CAPD patients is related to peritoneal transport and residual renal function: evidence from a longitudinal study. *Nephrol Dial Transplant* 2003; 18:797–803.
13. Koo HM, Doh FM, Kim CH, Lee MJ, Kim EJ, Han JH, *et al.* Changes in echocardiographic parameters according to the rate of residual renal function decline in incident peritoneal dialysis patients. *Medicine (Baltimore)* 2015; 94:e427.
14. Johnson DW, Cho Y, Brown FG. Trials (and tribulations) of biocompatible peritoneal dialysis fluids. *Perit Dial Int* 2012; 32:247–51.
15. Chan TM, Yung S. Studying the effects of new peritoneal dialysis solutions on the peritoneum. *Perit Dial Int* 2007; 27 (Suppl 2):S87–93.
16. Kawanishi K, Honda K, Tsukada M, Oda H, Nitta K. Neutral solution low in glucose degradation products is associated with less peritoneal fibrosis and vascular sclerosis in patients receiving peritoneal dialysis. *Perit Dial Int* 2013; 33:242–51.
17. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, *et al.*; balANZ Trial Investigators. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *J Am Soc Nephrol* 2012; 23:1097–107.
18. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, *et al.*; balANZ Trial Investigators. The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial. *Nephrol Dial Transplant* 2012; 27:4445–53.
19. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, *et al.*; The Euro-Balance Trial Group. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. *Kidney Int* 2004; 66:408–18.
20. Mortier S, De Vriese AS, Van de Voorde J, Schaub TP, Passlick-Deetjen J, Lameire NH. Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. *J Am Soc Nephrol* 2002; 13:480–9.
21. Cho Y, Johnson DW, Badve SV, Craig JC, Strippoli GF, Wiggins KJ. The impact of neutral-pH peritoneal dialysates with reduced glucose degradation products on clinical outcomes in peritoneal dialysis patients. *Kidney Int* 2013; 84:969–79.
22. Seo EY, An SH, Cho JH, Suh HS, Park SH, Gwak H, *et al.* Effect of biocompatible peritoneal dialysis solution on residual renal function: a systematic review of randomized controlled trials. *Perit Dial Int* 2014; 34:724–31.
23. Haag-Weber M, Krämer R, Haake R, Islam MS, Prischl F, Haug U, *et al.*; behalf of the DIUREST Study Group. Low-GDP fluid (Gambrosol trio) attenuates decline of residual renal function in PD patients: a prospective randomized study. *Nephrol Dial Transplant* 2010; 25:2288–96.
24. Ortiz A, Wieslander A, Linden T, Santamaria B, Sanz A, Justo P, *et al.* 3,4-DGE is important for side effects in peritoneal dialysis what about its role in diabetes. *Curr Med Chem* 2006; 13:2695–702.
25. Davies SJ. Preserving residual renal function in peritoneal dialysis: volume or biocompatibility? *Nephrol Dial Transplant* 2009; 24:2620–2.
26. Lichodziejewska-Niemierko M, Chmielewski M, Dudziak M, Ryta A, Rutkowski B. Hydration status of patients dialyzed with biocompatible peritoneal dialysis fluids. *Perit Dial Int* 2016; 36:257–61.
27. Günal AI, Duman S, Ozkahya M, Töz H, Asçi G, Akçiçek F, *et al.* Strict volume control normalizes hypertension in peritoneal dialysis patients. *Am J Kidney Dis* 2001; 37:588–93.
28. Konings CJ, Kooman JP, Gladziwa U, van der Sande FM, Leunissen KM. A decline in residual glomerular filtration during the use of icodextrin may be due to underhydration. *Kidney Int* 2005; 67:1190–1.
29. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT;

NECOSAD Study Group. Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 2002; 62:1046–53.
30. Van Biesen W, Jörres A. Fluid overload and residual renal function in peritoneal dialysis: the proof of the pudding is in the eating. *Kidney Int* 2014; 85:15–7.
31. McCafferty K, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. *Kidney Int* 2014; 85:151–7.
32. Lindley EJ, Lopot F. The use of bioimpedance to aid volume assessment in dialysis patients. *Kidney Int* 2015; 87:240.
33. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, *et al*. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006; 27:921–33.
34. Luo YJ, Lu XH, Woods F, Wang T. Volume control in peritoneal dialysis patients guided by bioimpedance spectroscopy assessment. *Blood Purif* 2011; 31:296–302.
35. Basso F, Milan Manani S, Cruz DN, Teixeira C, Brendolan A, Nalesso F, *et al*. Comparison and reproducibility of techniques for fluid status assessment in chronic hemodialysis patients. *Cardiorenal Med* 2013; 3:104–12.
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