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EFFECT OF BIOCOMPATIBLE PERITONEAL DIALYSIS SOLUTION ON RESIDUAL RENAL FUNCTION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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♦ ***Introduction:*** **Residual renal function (RRF) plays an important role in outcome of peritoneal dialysis (PD) including mortality. It is, therefore, important to provide a strategy for the preservation of RRF. The objective of this study was to evaluate relative protective effects of new glucose-based multicompartmental PD solution (PDS), which is well known to be more biocompatible than glucose-based conventional PDS, on RRF compared to conventional PDS by performing a systematic review (SR) of randomized controlled trials.**

♦ ***Methods:*** **We searched studies presented up to January 2014 in MEDLINE, EMBASE, the COCHRANE library, and local databases. Three independent reviewers reviewed and extracted prespecified data from each study. The random effects model, a more conservative analysis model, was used to combine trials and to perform stratified analyses based on the duration of follow-up. Study quality was assessed using the Cochrane Handbook for risk of bias. Eleven articles with 1,034 patients were identified for the SR.**

♦ ***Results:*** **The heterogeneity of the studies under 12 months was very high, and the heterogeneity decreased substantially when we stratified studies by the duration of follow-up. The mean difference of the studies after 12 months was 0.46 mL/min/1.73 m^2 (95% confidence interval = 0.25 to + 0.67).**

♦ ***Conclusion:*** **New PDS showed the effect to preserve and improve RRF for long-term use compared to conventional PDS, even though it did not show a significant difference to preserve RRF for short-term use.**

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KEY WORDS: Residual renal function; peritoneal dialysis solutions; randomized controlled trials; systematic review.

Residual renal function (RRF) has a major impact on the outcome of peritoneal dialysis (PD) (1,2), and is directly correlated with patient survival (3,4). The declining rate of RRF was also positively associated with all-cause mortality and technique failure in patients on long-term PD (5–7). It is, therefore, important to search a strategy for preserving RRF in PD.

Glucose degradation products (GDP) generated during heat sterilization of glucose-based conventional PD solutions (PDS) have been suggested to impair not only local peritoneal membrane function but also systemic remnant kidney function directly and indirectly via the formation of advanced glycation end product (AGE). Both GDP and AGE cause apoptosis, inflammation, and fibrosis in a context-dependent manner (8–10). In this connection, 3-deoxyglucosone (3-DG) was detected in the blood during dialysis with conventional PDS (11), suggesting that GDP in the PDS can be diffused into systemic circulation. Consistent with cytotoxic effect of GDP in various cells and tissues (12–15), renal tubular epithelial cells underwent apoptosis in response to 3,4-dideoxyglucosone-3-ene (3,4-DGE) (16), the most cytotoxic GDP in PDS (17).

With this background and the advance of technology, a new glucose-based biocompatible PDS, which contains a lower level of GDP and neutral pH than glucose-based conventional PDS, has been developed. Three major products, Balance (Fresenius Medical Care North America, Waltham, MA, USA), Physioneal (Baxter Healthcare Corporation, Deerfield, IL, USA), and Gambrosol trio

(Gambro Lundia AB, Lund, Sweden) of new biocompatible PDS are available commercially.

The application of new PDS with less GDP results in a significantly lower peritoneal thickness *in vivo* (18) and may help to preserve peritoneal and vascular function compared to the conventional PDS (19). Consistent with this, the use of a new PDS increases cancer antigen 125 (CA125) and procollagen I peptide (PICP) and decreases hyaluronic acid (HA) in peritoneal effluent compared to a conventional PDS, confirming the protective effect on the peritoneal membrane as a dialyzing organ (20–22).

The systemic effect of the new PDS on RRF, cardiovascular effect, and survival has been also actively studied by comparing the preservative effect to conventional PDS (21–32). Consequently, it is important to synthesize relevant results of clinical studies involving chronic PD patients. We aimed to evaluate the preservative effect of the new biocompatible PDS on RRF compared to conventional PDS by conducting a systematic review (SR) of randomized controlled trials (RCTs) which will give us rationale for the selection of PDS.

METHODS

STUDIES ELIGIBLE FOR REVIEW

Studies were eligible if they were RCTs comparing the effect of new PDS on RRF with that of conventional PDS in chronic PD patients. Studies with PD patients using mainly amino acid and icodextrin solutions were excluded. Eligible patients included continuous ambulatory PD and automated PD patients.

FINDING RELEVANT STUDIES

We searched the relevant studies presented up to January 2014 (last search: January 9th) in the international and local databases. For searching MEDLINE, EMBASE, and the COCHRANE databases, the search terms, 'peritoneal dialysis and (residual renal function or RRF) and (RCT or randomized controlled trial* or randomised controlled trial*)' were utilized. We searched local databases of KMBase and KoreaMed with the search terms, 'peritoneal dialysis and residual renal function.' The search was restricted to the English language.

ASSESSMENT OF STUDY QUALITY

Three reviewers (E-Y Seo, SH An, and JH Cho) independently assessed methodological qualities of the final 16 RCTs. One reviewer assessed 12 studies and each study was assessed by 2 reviewers. If 2 reviewers had disagreements even after a thorough discussion, another reviewer joined the discussion to break the deadlock. The studies were assessed for validity using the Cochrane Handbook for risk of bias on RCT (33). The Cochrane's tool has 7 domains which include the following: random sequence generation for selection bias, allocation concealment for selection bias, blinding of participants and personnel for performance bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias, and others. The risk level of each study in regard to its bias was graded as 'low risk of bias,' 'unclear risk of bias,' or 'high risk of bias.'

COLLECTING DATA

Data were extracted in duplicate using a data extraction form. The form was developed by the 3 reviewers and was supplemented and revised by YL Kim. Two studies (25,34) were seen to employ the same patients. The study by Kim *et al.* (25) was published after reinterpreting the previous results (34) with adjustments for age, gender, and the Davies score. We included the study by Kim *et al.* (25) for conducting a SR based on statistical rationale. Most studies evaluated the RRF with a mean value of creatinine clearance and urea clearance and standard deviation (SD) as described (35). The study by le Poole *et al.* (36) was excluded because the RRF was evaluated only by creatinine clearance. The Euro-Balance Trial (22) showed the result with median value and interquartile range (IQR). We, thus, converted the median value and IQR to mean and SD value. The study by Haag-Weber *et al.* (24) expressed a result as monthly change percentage and confidence interval (CI) instead of each value at the time point. We, therefore, converted them to mean and SD value of final value using the Cochrane's tool (33). As the RRF unit, mL/min, mL/min/1.73 m^2, L/week/1.73 m^2, and L/day were used and we standardized the RRF unit of all studies to mL/min/1.73 m^2. After standardizing the method of measurement and unit, we applied all values to Review Manager. Data standardization was performed by E-Y Seo and HS Suh in duplicate. The potential for publication bias was addressed by drawing a funnel plot and visual assessment.

RESULTS

The combined search identified a total of 238 citations, 218 of which were judged ineligible after the title and abstract review (Figure 1). The major reasons for exclusion were study population, duplicates, and PDS used not meeting the inclusion criteria. Full text analysis of the remaining 20 articles led to 12 studies which met the inclusion criteria (i.e. glucose-based multi

compartmental PDS). Among 20 articles, we found 2 protocols (37,38) without results and excluded them. We additionally excluded 2 correspondence articles (39,40) because they were not the original articles. We excluded 1 study in which the biocompatible solutions did not divide into icodextrin, amino acid, and low GDP-lactate solution (41). One study showed mixed results of cross-over design, so we could not include the data (42). At the stage of collecting data, we excluded 2 studies due to duplication (34) or inconsistent measurement method of the RRF (36). Two among the final 12 studies were performed by Kim *et al*. One showed the result at 12 months and the more recent study showed the result at 24 months with the same patients (28). Therefore, we applied the result only at 24 months, and the SR was conducted on the final 11 studies (1,034 patients) (21–30,43,44) (Figure 1).

The study quality was assessed by the Cochrane Handbook for risk of bias on RCTs and scored (33). The risk of bias graphs are presented in Figure 2 and the risk of bias summary is shown in Supplementary Figure 1.

The characteristics of studies included in the final SR are listed in Table 1. The detailed characteristics of each study are presented in Supplementary Table 1. Data were extracted using an internally developed data extraction form, and the Review Manager software (Revman 2011; Version 5.1, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for statistical analyses after standardizing the method of measurement and the unit of the RRF.

We found no major asymmetrical appearance in the funnel plot to address a publication bias (Figure 3).

The final value of the RRF in each of 11 studies was compared for evaluating preservation of the RRF. Heterogeneity and overall effect was evaluated using random effects model. Since heterogeneity was very high (84%) from all studies (Figure 4A), we categorized studies depending on the duration of observation: short-term studies (3 months to 6 months, Figure 4B) vs long-term studies (12 months to around 45 months, Figure 4C) in order to find the cause of high heterogeneity. Where a study showed both short-term and long-term results, we analyzed both results. While heterogeneity of the short-term studies remained very high (85%), that of the long-term studies was relatively low (49%). We conducted analyses with the long-term studies accordingly. The overall preservative effect on RRF in patients who were treated by the new PDS for more than 12 months was more effective compared to patients on conventional PDS. The mean difference of final RRF value between the conventional PDS and the new PDS groups of long-term study was 0.46 mL/min/1.73 m^2 (95% confidence interval = +0.25 to +0.67) showing improvement of RRF. The *p*-value for the overall effect was below 0.0001.

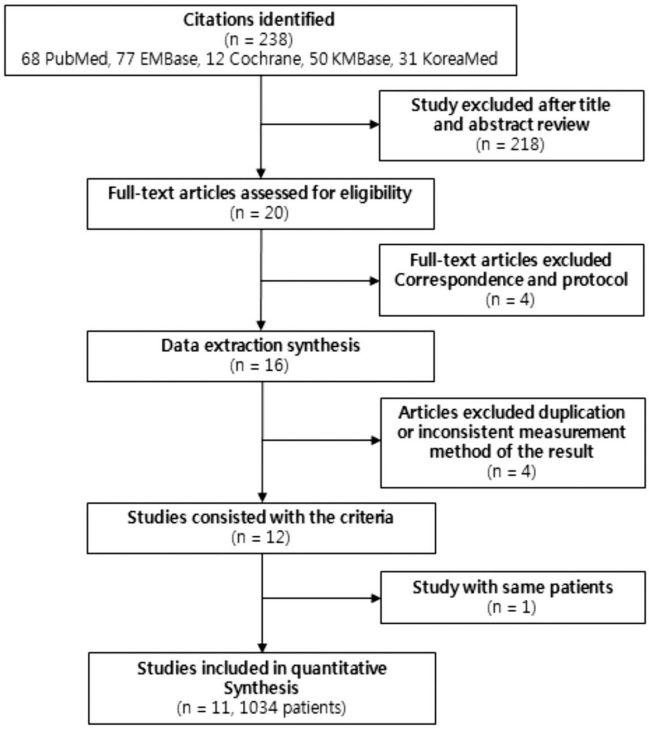


Figure 1 — Selection of studies.

DISCUSSION

This SR utilizing random effects model suggests that long-term use of the new glucose-based biocompatible PDS may have a preservative effect on the RRF compared to the glucose-based conventional PDS.

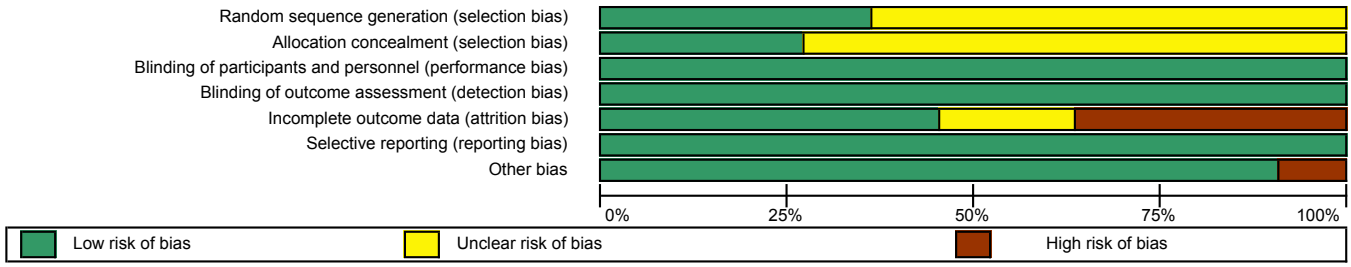


Figure 2 — Risk of bias graph of included trials.

TABLE 1
Characteristics of 11 Studies Included in the Systematic Review

Study (reference)	Country	Study period	Patients number		PD solutions used		Follow-up period (months)	RRF	
			New PDS group	Conventional PDS group	New PDS group	Conventional PDS group		Method of measurement	Unit
Bajo *et al.*, 2011 (43)	Spain	—	13	20	Balance (Fresenius)	Stay safe (Fresenius)	24	Mean of C_{cr} and C_{urea}	mL/min
Cho *et al.*, 2013 (44)	Republic of Korea	2001–2003	32	28	Balance (Fresenius)	Stay safe (Fresenius)	12	Mean of C_{cr} and C_{urea}	mL/min/1.73 m^2
Choi *et al.*, 2008 (26)	Republic of Korea	—	51	53	Balance (Fresenius)	Stay safe (Fresenius), Dianeal (Baxter) Perisis (Boryung)	12	C_{cr} and C_{urea}	mL/min
Fan *et al.*, 2008 (27)	UK	2004–2005	57	61	Balance (Fresenius), Physioneal (Baxter)	Stay safe (Fresenius), Dianeal (Baxter)	12	Mean of C_{cr} and C_{urea}	L/week/1.73 m^2
Haag-Weber *et al.*, 2010 (24)	Germany, France, Austria	1999–2005	43	26	Gambrosol trio (Gambro AB, Sweden)	Gambrosol (Gambro), Stay safe (Fresenius), Dianeal (Baxter)	18	Mean of C_{cr} and C_{urea}	mL/min/1.73 m^2
Johnson *et al.*, 2012 (30)	Australia, Singapore, New Zealand	—	85	82	Balance (Fresenius)	Stay safe (Fresenius)	24	Mean of C_{cr} and C_{urea}	mL/min/1.73 m^2
Kim *et al.*, 2012 (28), 2009 (25)	Republic of Korea	2004–2006	48	43	Balance (Fresenius)	Stay safe (Fresenius)	24 12	Mean of C_{cr} and C_{urea}	L/week/1.73 m^2
Lai *et al.*, 2012 (29)	Hong Kong	—	58	67	Balance (Fresenius), (Baxter) Gambrosol trio (Gambro AB)	Dianeal (Baxter) ANDY-Disc (Fresenius)	45	Mean of C_{cr} and C_{urea}	mL/min/1.73 m^2
Park *et al.*, 2012 (23)	Republic of Korea	2005–2007	79	67	Balance (Fresenius)	Stay safe (Fresenius)	12	Mean of C_{cr} and C_{urea}	mL/min
Szeto *et al.*, 2007 (21)	Hong Kong	—	25	25	Balance (Fresenius)	Stay safe (Fresenius)	12	Mean of C_{cr} and C_{urea}	mL/min/1.73 m^2
Williams *et al.*, 2004 (22)	11 countries in Europe	—	36	35	Balance (Fresenius)	Stay safe (Fresenius, Germany)	3 (cross-over design*)	Median of C_{cr} and C_{urea}	L/day

PD = peritoneal dialysis; RRF = residual renal function; PDS = PD solution; C_{cr} = total creatinine clearance; C_{urea} = urea clearance.
* We extracted data at the end of treatment phase I considering residual initial PDS effect, because this study has cross-over design.

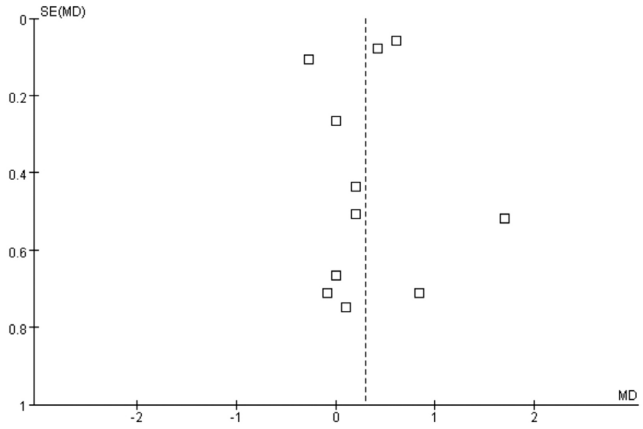
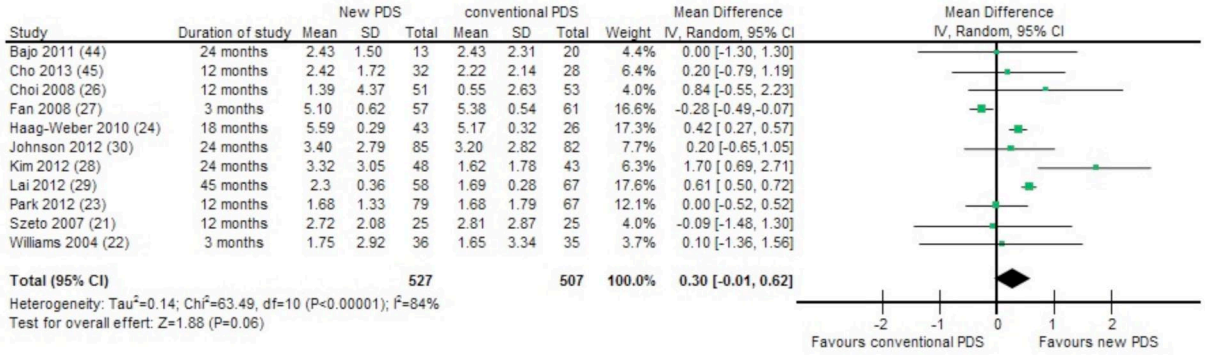


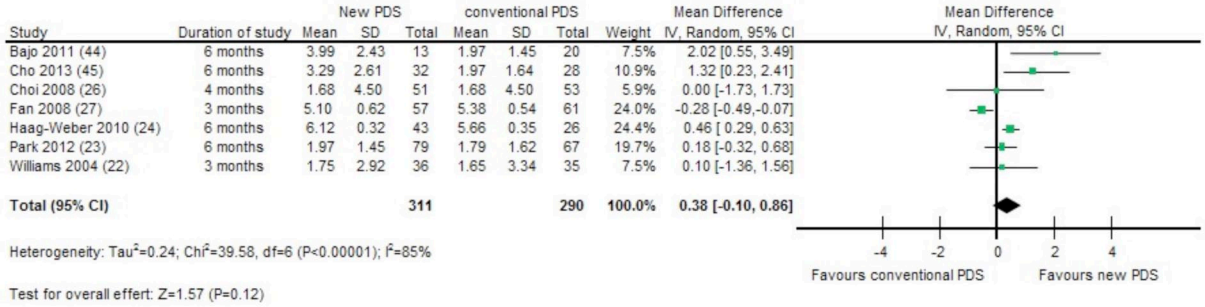
Figure 3 — Funnel plot analysis to detect publication bias.

The 11 RCTs which were included in this SR were estimated to be of a fairly good methodological quality. We classified 7 domains, which are either random sequence generation or allocation concealment for selection bias, blinding of participants and personnel for performance bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias, and other bias according to the Cochrane Handbook (33). Among these 7, 3 domains including performance bias, detection bias, and reporting bias, were assessed as "low risk of bias" in all studies. There are, however, some biases in the other 4 domains. The most common bias was "attrition bias." Four of the 11 studies had "high risk of bias" because they each showed

A. Total data from all 11 studies



B. Short-term data from 7 studies



C. Long-term data from 9 studies

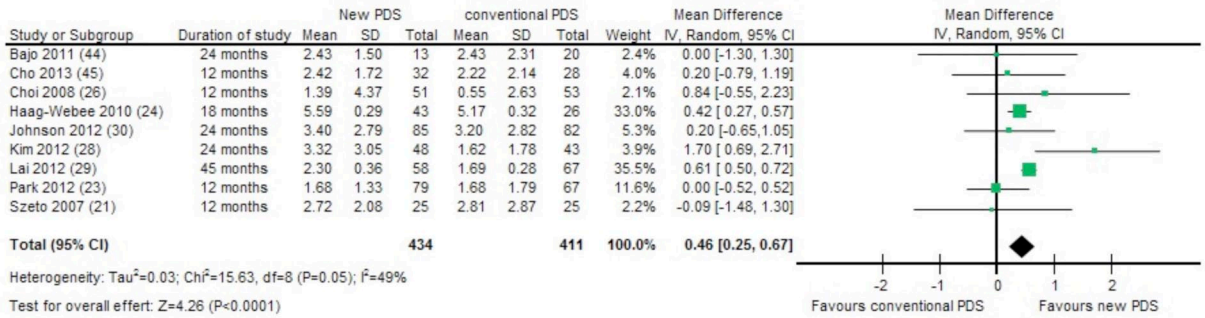


Figure 4 — Effect of biocompatible and conventional peritoneal dialysis solution on residual renal function: A) total data, B) short-term data, and C) long-term data.

only the per-protocol analysis without intention-to-treat analysis. Two of 11 studies had "unclear risk of bias" as they did not state the method of analysis. The other 5 studies had "low risk of bias". The second common bias was "selection bias". Seven or 8 studies among 11 had "unclear risk of bias". They did not state the method for random sequence generation and allocation concealment.

Two common measurements were used to assess the outcome of continuous data: one is to use final value of experimental groups and the other is to use change score. Nine among 11 studies in this SR reported the final value and 2 studies showed the changes from baseline of the RRF as the primary outcome. We got the raw data of mean value and SD from the author of 1 study (30). For the other study, we converted the changes in that study to the mean and SD of final value and compared the final values of the conventional PDS group with those of the new PDS group. In fact, in this respect, the Cochrane guideline (33) advises not to focus on the changes from baseline because most studies have different numbers of participants between the baseline and the final measurement due to missed visits and study withdrawals, and RCT has the assumption that patients in each group at baseline have the same conditions through randomization.

The random effects model for the SR is more conservative, which allows for heterogeneity by assuming that underlying effects follow a normal distribution. Utilizing the random effects model for this SR, we found profound heterogeneity from all 11 studies and the heterogeneity of short-term studies was very high. Accordingly, the sensitivity analyses were performed to examine whether our overall findings are robust to individual studies. The studies by Fan *et al.* (27), Haag-Weber *et al.* (24), and Lai *et al.* (29) had a major impact on these analyses. The common features of these 3 studies were the fact that SDs were smaller than other studies. When the study of Fan *et al.* (27) was excluded from the analysis of all the studies, the result was very different from the original analysis of all studies showing the positive preservative effect ($p < 0.0001$, $I^2 = 44\%$) of the new PDS. The other 2 studies did not show any major impact on the original analysis when each study was excluded.

Systematyic review is very sensitive to the time frame for inclusion of RCTs. In this respect, our SR included RCTs published until January 2014 compared to September 2012 in the SR by Cho *et al.* (45). Our results agree with those of Cho *et al.* with updated RCTs, supporting the conclusion that new glucose-based biocompatible PDS preserve and improve the RRF for long-term use better than glucose-based conventional PDS. In addition, we have included RCTs using 'mean value of both creatinine clearance and urea clearance' and standardized the method of measurement and unit of RRF to get more precise results. In fact, the diverse RCTs showed a mixed unit of RRF like mL/min, mL/min/1.73 m^2, L/week/1.73 m^2, and L/day.

This SR is a novel evaluation which can show that the new PDS containing low GDP better protects the RRF than conventional bioincompatible PDS. However, 1 major limitation of our SR is that the RRF conditions at the baseline of the patients were diverse in all 11 studies. It has been suggested that any beneficial effect of a biocompatible PDS on RRF is expected if a PDS is introduced at an earlier stage of chronic kidney disease, that is, in patients with a relatively well-preserved RRF, rather than at a later stage when RRF is poor (46). A subgroup analysis with patients who had the RRF of 2 mL/min/1.73 m^2 or more showed that the RRF of the new PDS group was significantly higher than that of the conventional PDS group after 12 months of PD ($p = 0.004$), while intention-to-treat analysis showed that the beneficial effect of the new PDS on RRF had statistical significance ($p = 0.048$) (25). It is conceivable that any PDS has little effect on RRF at a later stage of chronic kidney disease when the RRF is extremely poor at baseline, and that the exact comparison between the conventional PDS and new PDS is difficult. The second limitation is the small sample size and relatively short duration of follow-up in studies included in the present SR, which cannot give an exact conclusion.

The overall preservative effect on RRF of the new PDS in the long-term study by random effects model showed improvement of RRF compared to the conventional PDS.

There is controversy in the literature (47,48) regarding the mechanism by which biocompatible PDS preserves the RRF. One is a direct beneficial effect of biocompatible PDS with lower level of GDP inducing apoptosis of renal tubular cell (16). The other is an indirect effect which comes from less effective ultrafiltration (UF) and consequent hypervolemia. Ten studies from 11 RCTs in this SR have showed the results of UF change. However, the results are very diverse. Among them, 2 studies (23,29) showed less effective UF with biocompatible PDS. Other studies (21,22,24,26,28,30,43,44) showed equivocal or increasing UF volume with biocompatible PDS group. The better preservation of RRF is less likely related to hypervolemia.

In conclusion, the present SR shows that the new biocompatible PDS preserves and improves RRF for long-term use compared to conventional PDS, and suggests these beneficial effects of the new PDS could be translated into a better long-term clinical outcome.

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The results presented in this paper have not been published previously in whole or in part, except in abstract form for scientific meetings.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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