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The benefits of peritoneal dialysis (PD) solution with low-glucose degradation product in residual renal function and dialysis adequacy in PD patients: A meta-analysis.

Sheng Chen[1], Jieshuang Jia[2], Huimin Guo[3] and Nan Zhu[2]

[1]Department of Nephrology, Ningbo Medical Center Lihuili Hospital, Ningbo, Zhejiang, China.

[2]Department of Nephrology, Shanghai General Hospital, Shanghai, China.

[3]Department of Nuclear Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China.

Key words: glucose degradation products; peritoneal dialysis solution; residual renal function; dialysis adequacy; meta-analysis.

Abstract. The peritoneal effects of low-glucose degradation product (GDP)-containing peritoneal dialysis (PD) solutions have been extensively described. To systematically evaluate the efficacy and safety of low GDP solution for PD patients, specifically the effect on residual renal function (RRF) and dialysis adequacy, we conducted a meta-analysis of the published randomized controlled trials (RCTs). Different databases were searched for RCTs that compared low GDP-PD solutions with conventional PD solutions in the treatment of PD patients with continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). The outcomes of RCTs should include RRF and may include small solute clearance, peritoneal transport status, nutritional status, and all-cause mortality. Seven studies (632 patients) were included. Compared with the conventional solution, low-GDP solution preserved RRF in PD patients over time (MD 0.66 mL/min, 95% CI 0.34 to 0.99; $p<0.0001$), particularly in one year of treatment ($p<0.01$), and improved weekly Kt/V (MD 0.11, 95% CI 0.05 to 0.17; $p=0.0007$) without an increased 4-hour D/Pcr (MD 0.00, 95% CI -0.02 to 0.02; $p=1.00$). Notably, the MD of RRF and urine volume between the two groups tended to decrease as time on PD progressed up to 24 months. Patients using low GDP PD solutions did not have an increased risk of all-cause mortality (MD 0.97, 95% CI 0.50 to 1.88; $p=0.93$). Our meta-analysis confirms that the low GDP PD solution preserves RRF, improves the dialysis adequacy without increasing the peritoneal solute transport rate and all-cause mortality. Further trials are needed to determine whether this beneficial effect can affect long-term clinical outcomes.

Corresponding author: Huimin Guo, Department of Nuclear Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No. 324, Jingwu Road, Huaiyin District, Jinan, Shandong, China. Tel.: 86-0531-68776577. Email: guohuiminmail@126.com

Beneficios de la solución de diálisis peritoneal (DP), con producto de degradación bajo en glucosa, en la función renal residual y la adecuación de la diálisis en pacientes en DP: un metanálisis.

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Palabras clave: productos de degradación de glucosa; solución de diálisis peritoneal; función renal residual; adecuación de diálisis; metanálisis.

Resumen. Los efectos peritoneales de las soluciones de diálisis peritoneal (DP) que contienen productos de degradación bajos en glucosa (PIB) se han descrito ampliamente. Para evaluar sistemáticamente la eficacia y la seguridad de la solución de PIB bajo para pacientes en DP, específicamente el efecto sobre la función renal residual (RRF) y la adecuación de la diálisis, realizamos un metanálisis de los ensayos controlados aleatorios (ECA) publicados. Se realizaron búsquedas en diferentes bases de datos de ECA que compararan la solución de DP de bajo PIB con la solución de DP convencional en el tratamiento de pacientes con EP con CAPD y APD. Los resultados de los ECA deben incluir la RRF y pueden incluir la depuración de solutos pequeños, el estado nutricional, el estado del transporte peritoneal y la mortalidad por todas las causas. Se incluyeron siete estudios (632 pacientes). En comparación con la solución convencional, la solución de bajo PIB preservó la FRR en pacientes con EP a lo largo del tiempo (DM 0,66 mL/min, IC del 95%: 0,34 a 0,99; p<0,0001), particularmente en un año de tratamiento (p<0,01), y mejoró el Kt/V semanal (DM 0,11, IC del 95%: 0,05 a 0,17; p = 0,0007), sin un aumento de D/Pcr a las 4 horas (DM 0,00, IC del 95%: -0,02 a 0,02; p = 1,00). Los pacientes que usaron una solución para DP con bajo contenido de GDP no tuvieron un mayor riesgo de mortalidad por todas las causas (DM 0,97; IC del 95%: 0,50 a 1,88; p = 0,93). Nuestro metanálisis confirma que la solución de DP de bajo PIB preserva la FRR, mejora la adecuación de la diálisis sin aumentar la tasa de transporte peritoneal de solutos y la mortalidad por todas las causas. Se necesitan más ensayos para determinar si este efecto beneficioso puede afectar los resultados clínicos a largo plazo.

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INTRODUCTION

Peritoneal dialysis (PD) has become an established form of renal replacement therapy for patients with end-stage renal disease (ESRD) in the past thirty years [1]. In 2008, there were approximately 196,000 PD patients worldwide, representing 11% of the dialysis population [2] and the number is increasing by at least 6% per annum [3].

Conventional peritoneal dialysis solutions (CS) are acidic and contain high levels of glucose degradation products (GDPs) as a result of the heat sterilization process [9]. GDPs as a major factor in the bioincompatibility of peritoneal solutions[10], exert poten-

tially negative effects on both the structural and functional deterioration of peritoneum and systemic metabolic disturbance, leading to treatment failure and an increase in cardiovascular morbidity and mortality [11]. Residual renal function (RRF) plays a vital role in the prognosis of patients on dialysis4, which evaluates the excretion of small solute and middle-molecular uremic toxins [5], salt and water homeostasis, acid-base balance, nutritional status and associated survival[6-8]. Accumulating evidence from epidemiological and experimental researches [10,12-14] reveals that low-GDP peritoneal dialysis solutions (LS) may play a role in retarding RRF loss in PD patients [14]. However, not all clinical trials show encouraging results of the perceived advantages that LSs have on RRF [15,16]. The impact of the low GDP in RRF protection and other beneficial effects remain insufficiently described, even though there has been interest in evaluating the systemic biocompatibility of these solutions [17]. Therefore, we conducted a meta-analysis to examine the effect of LS on RRF and other related factors known to affect PD in PD patients compared with CS.

SUBJECTS AND METHODS

Study Inclusion and Exclusion Criteria

Studies that met all the following basic criteria were included in our meta-analysis: (1) a randomized controlled trial (RCT) for patients on continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) as the treatment of ESRD; (2) LS was compared with CS. The crossover randomized trials or RCTs that did not assess RRF were excluded.

Search Strategy

We identified eligible RCTs by searching the PubMed, Embase, Wiley, Scopus, Ovid databases and abstracts presented at the annual meetings of the American Society of Nephrology (ASN), the National Kidney Foundation (NKF), and the European Renal Association (ERA), from inception to July 2014, using appropriate Medical Subject Headings (MeSH) and text words: peritoneal dialysis, glucose degradation products, biocompatible solution, low-GDP, APD, CAPD in combination with "residual renal function". Further, the reference lists of retrieved articles were then searched for additional relevant studies. No language restrictions were imposed.

Study Selection

We included RCTs examining the effect of LSs on RRF in PD patients >18 years old compared with CSs. PD modality was restricted as either CAPD or APD. The outcomes of RCTs should include the RRF value, which is measured as the arithmetic means of residual renal clearances of urea and creatinine by collecting 24-hour urine volume. Other endpoints for the evaluation may include small solute clearance, peritoneal solute transport rate (PSTR), nutritional status, and all-cause mortality of PD patients. The study had at least 12 months of duration of follow-up without restriction on sample size. Two investigators (NZ and JW), independently, screened titles and abstracts of all electronic citations to select studies that met the inclusion criteria for further analysis. All articles identified by the investigators were retained.

Study Validity Assessment

We used the Cochrane Collaboration's bias tool and Jadad score for assessing the risk of bias for the included studies. The first approach incorporates assessment of randomization (sequence generation and allocation sequence concealment), blinding (participants, personnel, and outcome assessors), completeness of outcome data, selection of outcomes reported, and other sources of bias. The items were scored with "yes," "no," and "unclear" [18]. The Jadad scale score ranged from 0 to 5 points about the randomization, double-blinding, and withdrawals and dropouts [19].

Data Extraction

Two investigators extracted the useful data independently and reached a consensus on all eligible data. Relevant information was obtained by contacting the corresponding authors of the respective studies.

Study characteristics were extracted from all included trials with respect to year of publication, the study sample, baseline characteristics of the trials, follow-up, and the following reported outcomes of different follow-up months (baseline, 6, 12, and 24 months): (1) RRF (mL/min) (2) total weekly urea clearance (total Kt/V) and peritoneal urea clearance (peritoneal Kt/V), (3) total creatinine clearance (total CrCl) (L/week/1.73m^2), and peritoneal creatinine clearance (peritoneal CrCl) (L/week/1.73m^2), (4) daily urine volume (UV) (mL), daily peritoneal ultrafiltration (UF) (mL) and daily glucose exposure (g), (5) dialysate-to-plasma ratio of creatinine at 4 hours of peritoneal equilibration test (PET) (D/Pcr) and D/D0 glucose at 4 hours (D/D0 glucose), (6) blood pressure (mmHg) including systolic blood pressure (SBP) and diastolic blood pressure (DBP), (7) nutritional data, including serum albumin (g/dL), subjective global assessment (SGA) and normalized protein nitrogen appearance (nPNA) (g/kg/day), (8) all-cause mortality.

Data Synthesis and Analysis

Continuous outcomes results were presented as the mean difference (MD) and its 95% confidence intervals (CIs). Dichotomous outcomes were reported as the risk ratio (RR) and 95% CIs. Statistical pooling was performed with a random-effect model, *via* generic inverse variance weighting. All the statistical analyses in this meta-analysis were performed using Review Manager 5 software (RevMan 2012) for the meta-analysis.

Hypothesis testing was set at the two-tailed and results were considered statistically significant at 0.05 level. The I^2 statistic was calculated as a measure of statistical heterogeneity, and I^2 values of 25%, 50%, and 75% corresponded to low, medium, and high levels of heterogeneity. When heterogeneity was found (I^2>25%), sensitivity analysis was performed in an attempt to explain the findings. When doing a pool for some outcome assessment, we excluded the study which has the significant difference at baseline to keep two groups in all studies have the consistent outcome at the baseline. For each parameter estimate, an integrated analysis was given, finally.

The meta-analysis was performed in accordance with the recommendations by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) workgroup [20].

RESULTS

Study Characteristics

A total of 223 potentially relevant citations were identified and screened, of which 197 were selectively excluded from the study because they were not clinical RCTs or did not expose the outcome of interest. Twenty-six articles were retrieved for detailed evaluation. Overall, seven RCTs were included with a combined total of 632 patients [3,15,17,21-24] (Fig. 1).

The details of the characteristics and the demographic data of the RCTs included in our analysis were summarized in Table 1. These studies varied in sample size, and follow-up duration differed from 12 to 24 months, spanning nearly 10 years. The mean age of the populations ranged from 51~62 years and the mean of body mass index (BMI) ranged from 23~28.4 kg/m^2. The prevalence of diabetes in the patients was from 11%~56%. More than half of the patients in both groups used angiotensin converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and half of the patients in both groups used diuretics in two studies [3,23]. All trials evaluated the LS (Balance: Fresenius Medical Care) compared with a CS (Stay•Safe: Fresenius Medical Care). Almost all studies included incident CAPD patients except the Choi *et*

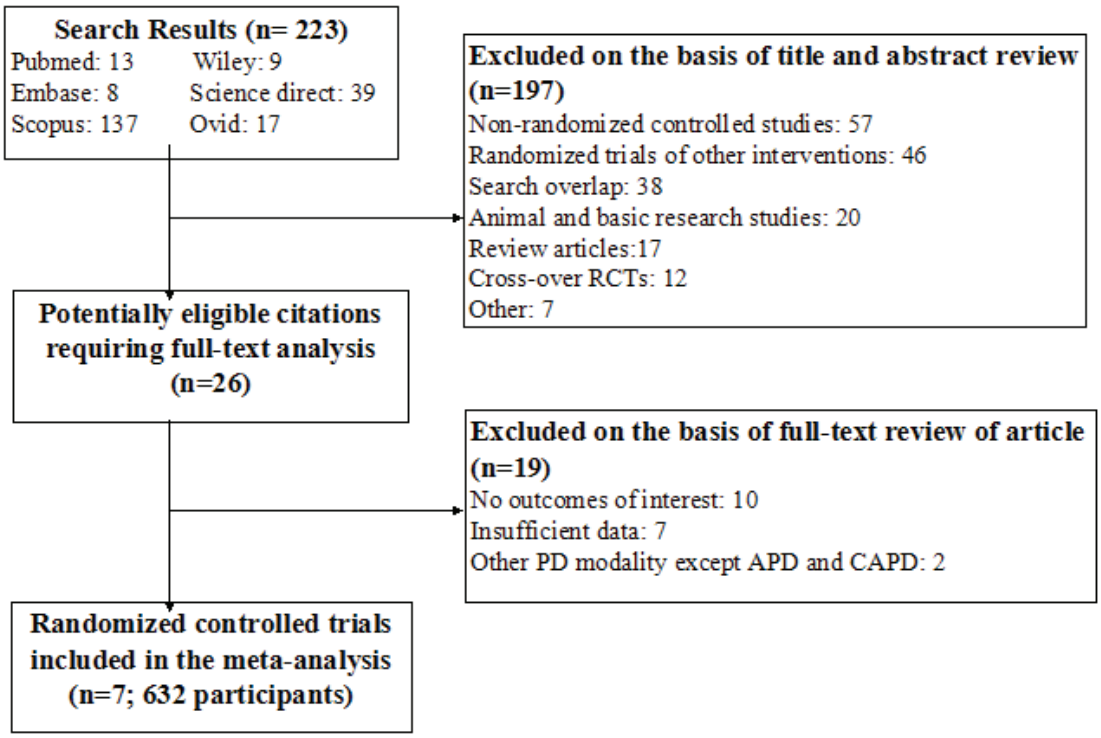

Fig 1. Flow chart showing the number of citations retrieved by individual searches and the number of trials included in the review.

al.[21] study, and patients with CAPD modality except the balANZ Trial [3].

Baseline of outcomes in these included studies were shown in Table 2. Kim *et al.*[22] demonstrated that there were no significant differences of all outcomes between the two groups except CrCl (LS group, 95.5±5.0 vs. CS group, 78.6±11.8 L/week/1.73m^2, $p<0.05$) and nPNA (LS group, 0.85±0.07 vs. CS group, 1.06±0.11 g/kg/day, $p<0.05$). The D/Per at the baseline was higher in the LS group than in the CS group in the two trials studied by Kim *et al.* [23] and Park *et al.*[17]. Moreover in the study by Park *et al.* [17] peritoneal CrCl and was higher in the LS group, peritoneal UF volume was lower in the LS group at baseline in keeping with higher peritoneal transport characteristics in this group. Szeto *et al.*[15] showed that at baseline, the CS group had a better nutritional status than the LS group (serum albumin, $p=0.004$ and SGA, $p=0.023$), but the difference disappeared in 12 months.

Quality Assessment

Two investigators assessed the quality of the included studies independently. All RCTs were considered fair to good quality (Fig. 2). Allocation methods and concealment were generally, incompletely reported and therefore difficult to assess. Allocation concealment was adequate in four studies (43%). Six studies (86%) were classified as low risk of performance bias and only one study was unclearly reported. However, no information about the blinding of outcome assessment (detection bias) of the studies was provided. Completeness of outcome reporting and intention-to-treat analysis methodology was applied in 29% of included studies. Selective reporting was observed in six studies (86%). No other significant biases were identified in these seven studies, except an unclear description of participant details in four studies. The Jadad score was 3 or higher (Table 1), even though the method of random se-

Table 1
Characteristics of the included RCTs in this analysis.

Study or Author Year	Country	Peritoneal dialysis (PD)	PD solution (L/C)	Modality	Sample size, n (L/C)	Mean age, year (L/C)	Male, n(L/C)	Follow-up duration, mouth	DM, % (L/C)	BMI(kg/m^2) (L/C)	Charlson's Index score (L/C)	Use of ACEI/ARB, (%) (L/C)	Use of diuretics, (%) (L/C)	Sum of Jadad Score
Bajo *et al.* 2011	Spain	Incident CAPD	Balance versus Stay-safe	CAPD	13/20	62/59	10/9	24	11/38	NA	NA	NA	NA	3
balANZ Trial	New Zealand, Australia, Singapore	Incident CAPD	Balance versus Stay-safe	CAPD / APD	91/91	59.3/57.9	52/48	24	33/34	27.7/28.4	NA	44.0/45.1	44/50.5	4
Choi *et al.* 2008	Korea	Prevalent CAPD	Balance versus Stay-safe	CAPD	51/53	52.6/55.4	20/27	12	18/19	24.5/24.3	NA	NA	NA	3
Kim *et al.* 2003	South Korea	Incident CAPD	Balance versus Stay-safe	CAPD	16//10	51.6/56.1	NA	12	38/30	NA	NA	NA	NA	3
Kim *et al.* 2008	Korea	Incident CAPD	Balance versus Stay-safe	CAPD	48/43	55.3/52.8	31/24	12	56/42	22.7/23.5	NA	64.6/58.1	52.1/55.8	3
Park *et al.* 2012	Korea	Incident CAPD	Balance versus Stay-safe	CAPD	79/67	52.2/52.6	37/30	12	52/55	22.9/22.6	4.06/3.99	65.8/78.1	NA	4
Szeto *et al.* 2007	Hongkong	Incident CAPD	Balance versus Stay-safe	CAPD	25/25	60.9/55.0	16/14	12	40/32	23.0/23.3	5.4/4.68	NA	NA	4

Note: data are presented as mean or median (range). NA, not available. L/C, neutral pH and low-GDP PDSs/conventional PDSs; DM, diabetes mellitus; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2
The baseline of outcomes in the included RCTs.

Study or Author Year	Bajo *et al*. 2011		balANZ Trial		Choi *et al*. 2008		Kim *et al*. 2003		Kim *et al*. 2008		Park *et al*. 2012		Szeto *et al*. 2007	
Groups	LS	CS	LS	CS	LS	CS	LS	CS	LS	CS	LS	CS	LS	CS
sample size (n)	13	20	91	91	51	53	16	10	48	43	79	67	25	25
RRF (mL/min)	7.0±4.3	5.8±3.9	7.0±6.0	7.0±6.0	7.9±17.7	8.9±22.9	4.3±0.4	3.2±1.2	6.84±6.69	5.71±3.76	3.9±3.1	3.7±2.6	3.91±2.09	3.67±2.27
Kt/V	NA	NA	NA	NA	1.9±0.4	1.9±0.4	2.83±0.17	2.52±0.29	2.41±1.01	2.08±0.59	2.4±0.6	2.3±0.6	2.28±0.35	2.23±0.62
peritoneal Kt/V	NA	NA	NA	NA	1.8±0.3	1.7±0.3	NA	NA	1.63±0.4	1.46±0.4	1.7±0.4	1.7±0.5	NA	NA
CrCl (L/week/1.73m2)	NA	NA	NA	NA	55.2±15.2	55.9±22.8	95.5±5.0*	78.6±11.8	90±47.7	78±27.7	84.1±30.9	77.5±27.9	NA	NA
peritoneal CrCl (L/week/1.73m2)	NA	NA	38.3±9.0	36.3±11.9	49.2±7.0	48.3±6.3	NA	NA	44.6±10.1	39.6±10.7	41.4±7.3*	37.9±6.9	NA	NA
urine volume (mL/d)	NA	NA	1556.0±691.0	1501.0±682.0	385.5±330.7	447.1±278.4	NA	NA	783.0±630.0	698.0±430.0	880.0±732.0	717.0±536.0	870.0±620.0	900.0±710.0
peritoneal UF (mL/d)	NA	NA	700 (2700 to 3500)	1090 (2400 to 2800)	1110.8±555.2	921.2±498.0	NA	NA	865.0±338.0	923.0±430.0	621.0±520.0*	962.0±527.0	560.0±600.0	560.0±690.0
glucose load (g/d)	NA	NA	121.5±35.3	123.6±36.3	145.1±38.3	155. ±44.3	NA	NA	121.0±21.1	121.0±48.7	100.8±11.1*	109.1±10.3	100.7±14.6	100.9±17.7
D/Pcr	NA	NA	0.67±0.1	0.62±0.1	NA	NA	0.69±0.02	0.66±0.03	0.72±0.1*	0.67±0.1	0.74±0.12*	0.69±0.12	NA	NA
D/P0 glucose	NA	NA	NA	NA	NA	NA	0.28 ±0.02	0.3± 0.03	0.32 ±0.14	0.35 ±0.14	NA	NA	NA	NA
SBP (mmHg)	NA	NA	139.8±21.4	138.9±21.8	NA	NA	NA	NA	NA	NA	131.6±19.3	131.4±20.8	NA	NA
DBP (mmHg)	NA	NA	76.6±11.3	78.1±11.0	NA	NA	NA	NA	NA	NA	82.2±11.9	81.3±12.1	NA	NA
Serum alb (g/dL)	NA	NA	3.8±0.5	3.7±0.6	3.6±0.3	3.5±0.4	3.4±0.1	3.7±0.2	3.39±0.56	3.51±0.51	3.6±0.6	3.6±0.5	3.28±0.44*	3.65±0.41
SGA	NA	NA	NA	NA	6.0±0.7	6.1±0.9	NA	NA	NA	NA	5.9±1.2	5.7±1.1	4.83±0.87*	5.24±0.78
nPNA (g/kg/d)	NA	NA	1.05±0.25	1.06±0.26	0.9±0.2	0.9±0.2	0.85±0.07*	1.06±0.11	0.92±0.23	0.89±0.19	0.91±0.18	0.9±0.25	1.07±0.19	1.18±0.19

Note: data are presented as mean±SD or median (range). NA, not available. Bold indicates the parameters have significant differences between the two groups and asterisk (*) indicates $p<0.05$ versus CS group. RRF, mean of creatinine clearance (Ccr) and urea clearance (Curea); Kt/V, total weekly urea clearance; peritoneal Kt/V, weekly peritoneal urea clearance; CrCl, total creatinine clearance; peritoneal CCr, peritoneal creatinine clearance; peritoneal UF, peritoneal ultrafiltration; D/Pcr, dialyzate-to-plasma creatinine ratio at 4 hours of peritoneal equilibration test (PET); D/D0 glucose, D/D0 glucose at 4 hours of PET; SBP, systolic blood pressure; DBP, diastolic blood pressure; SGA, subjective global assessment; nPNA, normalized protein nitrogen appearance.

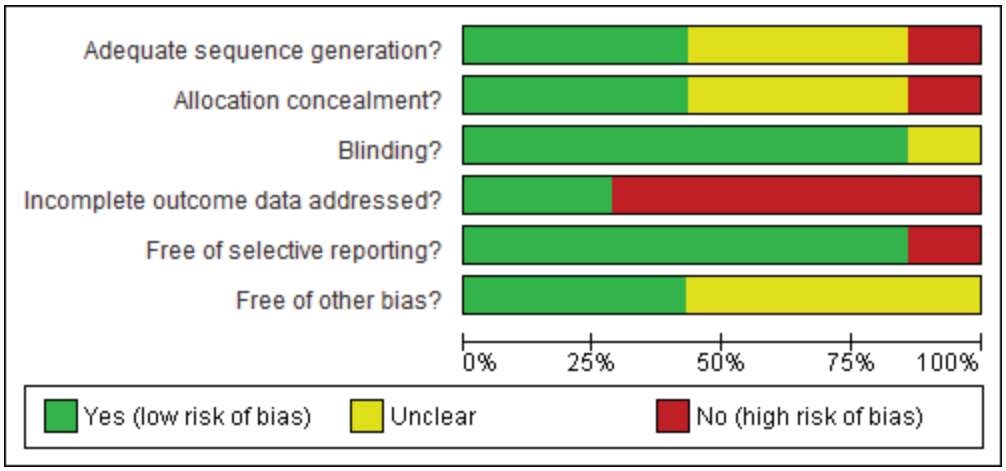

Fig 2. Risk of bias graph: each risk of bias item is presented as percentages across all included studies.

quence generation, blinding of participants and allocation concealment were not mentioned in most studies.

Outcome Measurement

PD patients in these different studies were followed up for different periods, which may have influenced the effectiveness of the outcomes of this analysis. Therefore, subgroup analysis was used to decrease clinical heterogeneity according to the follow-up periods.

Residual Renal Function

Two studies [17,23] of seven RCTs were undertaken to calculate the RRF of 226 patients after 6 months of follow-up, and indicated that LS group was beneficial for preserving RRF compared with the control group (MD 1.28 mL/min, 95% CI 0.52 to 2.03, p=0.0009; I^2=0%). Similar results were obtained after 12 months of follow-up in all studies including 520 patients (MD 0.60 mL/min, 95% CI 0.18 to 1.02, p=0.005; I^2=11%). The balANZ Trial [3] followed up 24 months and RRF was measured at baseline, 12 and 24 months, as well as the study by Bajo *et al.*[24], and the pooled data indicated no difference between the two groups (p=0.76). As the studies duration continued from 6 to 24 months, the difference of RRF between the two groups was reduced gradually. This should be commented in the abstract and/or conclusions. Considering the heterogeneity, exclusion of the study [24] with a small sample size did not materially change the results of the meta-analysis or the subgroup analyses Overall, the use of LS induced a reduction in RRF decline compared with the control group (MD 0.66 mL/min, 95% CI 0.34 to 0.99; p<0.0001; I^2=4%; Fig. 3).

Daily Urine Volume

Three studies [3,17,23] with a total of 377 patients and five studies [3,15,17,21,23] with a total of 462 patients showed the 24h urine volume separately at 6 and 12 months. The 24h urine volume in the LS group was higher than that in the CS group (MD 155.42 mL/d, 95% CI 37.84 to 273.00; p=0.01) at 6 months. A total of 238 patients were followed up in the LS groups and 224 patients were followed up in the CS groups after 1 year's study. Patients with the LS had more daily urine volume than the CS group (MD 158.93 mL/d, 95% CI 83.22 to 234.64; p<0.0001). Only the balANZ Trial [3] reported the urine volume at 24 months follow-up, and there was no significant difference between the two groups. As the study duration continued from 12 to 24 months, the MD of the residual urine volume decreased from

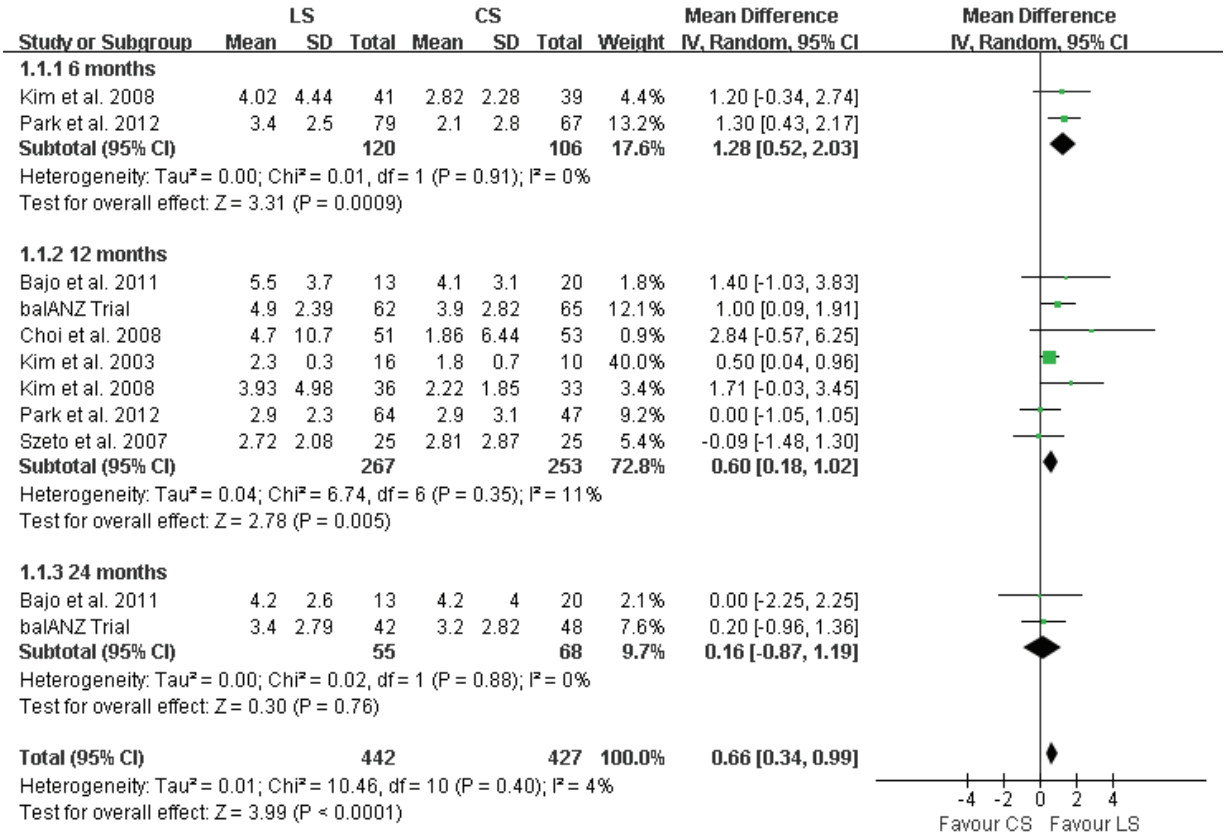

Fig 3. Effect of low-GDP PD solution on RRF (mL/min).

158.93 mL/d to 115.00 mL/d. The pooled urine volume in patients using LS was greater than using CS (MD 153.15 mL/d, 95% CI 96.62 to 209.68; p<0.00001; I^2=0%; Table 2). Overall, our meta-analysis indicated that the LS had a significant effect on RRF with an increase in daily urine output compared with the CS group.

Small solute clearance

At 6 months, Kim *et al.* [23] and Park *et al.*[17] published the data of total Kt/V and peritoneal Kt/V showing that there was no statistical difference between the two groups (p=0.99; p=0.18). After one year follow up, five studies involving 360 patients reported the effect of LS on total Kt/V in PD patients [15,17,21-23]. Compared to the CS group, the LS group showed significantly increased Kt/V (MD 0.13, 95% CI 0.06 to 0.20; p=0.0002). Overall, we found that patients with LS had higher total Kt/V than with CS (MD 0.11, 95% CI 0.05 to 0.17; p=0.0007; I^2=0%) (Fig. 4) and the CS group had a higher peritoneal Kt/V than the LS group (MD -0.10, 95% CI -0.20 to -0.01; p=0.03; I^2=0%) (Table 2).

Our subgroup analyses showed no statistical differences of total CrCl and peritoneal CrCl between the LS and CS groups at 6 and 12 months (Table 2). We excluded the total CrCl data of the follow-up period from the study performed by Kim *et al.*[22] who reported the significant difference between the two groups at baseline but no statistical difference observed at 12 months. The study by Park *et al.*[17] was excluded because this study published that peritoneal CrCl was higher in the LS group at baseline and there was no significant difference after 6 months.

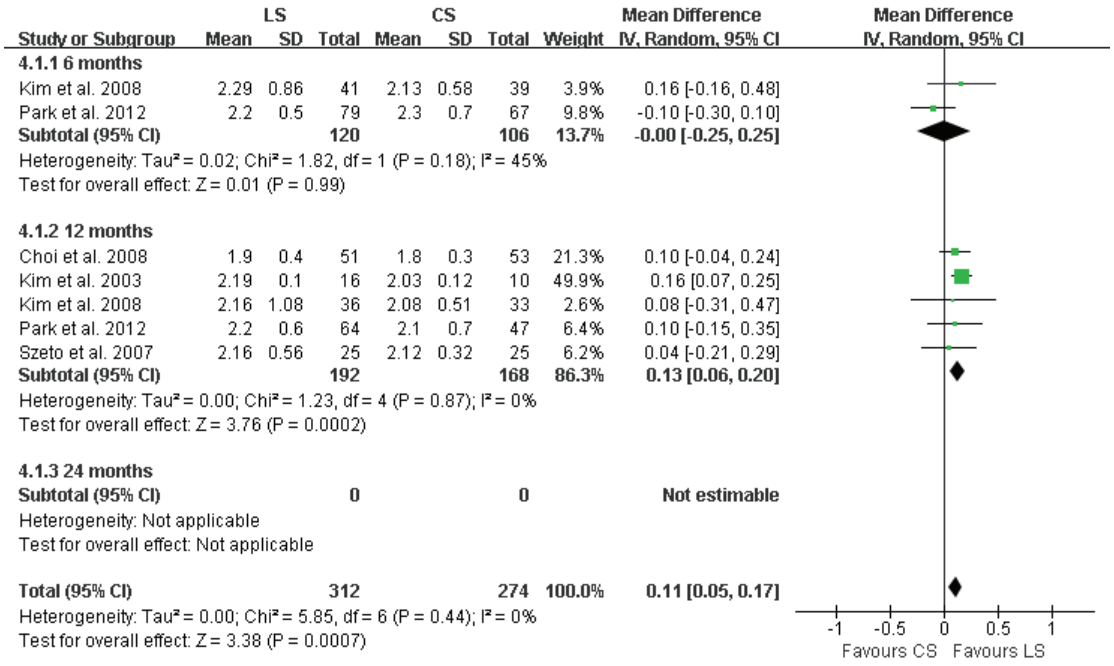

Fig. 4. Effect of low-GDP PD solution on total Kt/V.

Peritoneal Ultrafiltration and Glucose Load

Five studies [3,15,17,21,23] published the daily peritoneal UF volume in the follow-up period. Park *et al.*[17] indicated that the CS group had higher UF than the LS group at baseline and 6 months. After exclusion of this study, we pooled the data at 6 months, showing the higher UF in the CS group (MD -261.97 mL/d, 95% CI -427.73 to -96.21; p=0.002). In the subgroup analyses of 12 months, Choi *et al.*[21] who included all prevalent PD patients with more than half number of anuric, revealed the outcome that UF was significantly higher in the LS group than in the CS group at all follow-up visits. The exclusion of this study did materially change the results of the meta-analysis or the subgroup analyses. Table 3 showed that patients with the LS had less daily peritoneal UF volume than the CS (MD -193.45 mL/d, 95% CI -315.36 to -71.54; p=0.002; I^2=36%). The subgroup analyses of glucose load suggested that there was no statistically significant difference between patients using the LS and CS at 6 and 12 months.

Blood Pressure

The balANZ Trial [3] and the study by Park *et al.* [17] followed up the blood pressure of the two groups. There was no significant difference between the two -groups in controlling blood pressure during 1 year of follow-up (SBP, p=0.91; DBP, p=0.59) (Table 3).

Peritoneal Solute Transport Rate

Five studies [3,17,21-23] published the D/Pcr. In the study by Kim *et al.* [23], the D/Pcr was higher in the LS group than in the CS group, and this difference persisted throughout the treatment period. Similar results were obtained from Park *et al.* [17], but after 6 months, the D/Pcr showed no difference between the two groups. The patients of two groups in these three included stud-

Table 3
Comparison of low glucose degradation products (GDP) versus standard glucose dialysate.

Outcome or subgroup title	No. of studies	No. of patients (LS/CS)	Statistical method	Effect size	p	Heterogeneity
Residual renal function						
6 months	2	120/106	Mean Difference (IV, Random, 95% CI)	1.28 [0.52, 2.03]	0.0009	I2=0%
12 months	7	267/253	Mean Difference (IV, Random, 95% CI)	0.60 [0.18, 1.02]	0.005	I2=11%
24 months	2	55/68	Mean Difference (IV, Random, 95% CI)	0.16 [-0.87, 1.19]	0.76	I2=0%
Total		442/427	Mean Difference (IV, Random, 95% CI)	0.66 [0.34, 0.99]	<0.0001	I2=4%
Daily Urine Volume						
6 months	3	196/181	Mean Difference (IV, Random, 95% CI)	155.42 [37.84, 273.00]	0.01	I2=0%
12 months	5	238/224	Mean Difference (IV, Random, 95% CI)	158.93 [83.22, 234.64]	<0.0001	I2=7%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	115.00 [-146.33, 376.33]	0.39	
Total		476/453	Mean Difference (IV, Random, 95% CI)	153.15 [96.62, 209.68]	<0.00001	I2=0%
Peritoneal Ultrafiltration						
6 months	2	117/114	Mean Difference (IV, Random, 95% CI)	-261.97 [-427.73, -96.21]	0.002	I2=0%
12 months	3	123/124	Mean Difference (IV, Random, 95% CI)	-200.57 [-389.25, -11.88]	0.04	I2=48%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	65.00 [-234.81, 364.81]	0.67	
Total		282/286	Mean Difference (IV, Random, 95% CI)	-193.45 [-315.36, -71.54]	0.002	I2=36%
glucose load						
6 months	3	203/185	Mean Difference (IV, Random, 95% CI)	1.35 [-1.76, 4.47]	0.40	I2=0%
12 months	5	250/234	Mean Difference (IV, Random, 95% CI)	0.25 [-3.25, 3.74]	0.89	I2=0%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	4.30 [-17.76, 26.36]	0.70	
Total		495/467	Mean Difference (IV, Random, 95% CI)	0.90 [-1.41, 3.21]	0.45	I2=0%
Small solute clearance						
total Kt/V						
6 months	2	120/104	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.25, 0.25]	0.99	I2=45%
12 months	5	192/168	Mean Difference (IV, Random, 95% CI)	0.13 [0.06, 0.20]	0.0002	I2=0%
24 months	0					

Table 3. Continuación

Outcome or subgroup title	No. of studies	No. of patients (LS/CS)	Statistical method	Effect size	p	Heterogeneity
Total		312/274	Mean Difference (IV, Random, 95% CI)	0.11 [0.05, 0.17]	0.0007	I2=0%
Peritoneal Kt/V						
6 months	2	120/106	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.19, 0.04]	0.18	I2=0%
12 months	2	100/80	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.33, 0.01]	0.06	I2=0%
24 months	0					
Total		220/186	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.20, -0.01]	0.03	I2=0%
total CrCl						
6 months	2	120/106	Mean Difference (IV, Random, 95% CI)	4.82 [-6.96, 16.61]	0.42	I2=45%
12 months	3	151/133	Mean Difference (IV, Random, 95% CI)	3.60 [-2.48, 9.67]	0.25	I2=34%
24 months	0					
Total		271/239	Mean Difference (IV, Random, 95% CI)	3.39 [-0.75, 7.53]	0.11	I2=17%
Peritoneal CrCl						
6 months	1	48/43	Mean Difference (IV, Random, 95% CI)	1.50 [-2.91, 5.91]	0.05	
12 months	2	99/96	Mean Difference (IV, Random, 95% CI)	-0.08 [-2.09, 1.93]	0.94	I2=0%
24 months	1	91/91	Mean Difference (IV, Random, 95% CI)	2.00 [-1.07, 5.07]	0.20	
Total		238/230	Mean Difference (IV, Random, 95% CI)	0.67 [-0.90, 2.24]	0.40	I2=0%
Peritoneal Solute Transport Rate						
D/Pcr						
6 months	0					
12 months	2	54/40	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]	1	I2=0%
24 months	1	37/47	Mean Difference (IV, Random, 95% CI)	0.00 [-0.04, 0.04]	1	
Total		91/87	Mean Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.02]	1	I2=0%
D/D0 glucose						
6 months	1	41/39	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.11, 0.01]	0.09	
12 months	2	52/43	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.06, 0.00]	0.08	I2=40%

Table 3. Continuación

Outcome or subgroup title	No. of studies	No. of patients (LS/CS)	Statistical method	Effect size	p	Heterogeneity
24 months	0					
Total		93/82	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.05, -0.01]	0.01	I2=17%
Blood Pressure						
systolic blood pressure						
6 months	2	155/142	Mean Difference (IV, Random, 95% CI)	0.96 [-3.67, 5.60]	0.68	I2=0%
12 months	2	126/113	Mean Difference (IV, Random, 95% CI)	2.89 [-2.41, 8.18]	0.29	I2=0%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	-10.80 [-19.24, -2.36]	0.01	
Total		323/303	Mean Difference (IV, Random, 95% CI)	-0.29 [-5.04, 4.46]	0.91	I2=53%
diastolic blood pressure						
6 months	2	155/142	Mean Difference (IV, Random, 95% CI)	1.01 [-1.84, 3.85]	0.49	I2=0%
12 months	2	126/113	Mean Difference (IV, Random, 95% CI)	1.10 [-1.88, 4.07]	0.47	I2=0%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	-3.10 [-8.51, 2.31]	0.26	
Total		323/303	Mean Difference (IV, Random, 95% CI)	0.53 [-1.40, 2.45]	0.59	I2=0%
Nutritional Status						
Serum albumin						
6 months	3	203/185	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.28, 0.10]	0.35	I2=59%
12 months	5	225/209	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.28, -0.05]	0.005	I2=45%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.41, 0.01]	0.06	
Total		470/442	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.23, -0.05]	0.002	I2=45%
nPNA						
6 months	3	203/185	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.07, 0.02]	0.29	I2=0%
12 months	5	250/234	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.07, 0.01]	0.18	I2=0%
24 months	1	42/48	Mean Difference (IV, Random, 95% CI)	0.00 [-0.12, 0.12]	1	
Total		495/467	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.05, 0.00]	0.10	I2=0%
SGA score						
6 months	1	79/67	Mean Difference (IV, Random, 95% CI)	0.20 [-0.19, 0.59]	0.31	

Table 3. Continuación

Outcome or subgroup title	No. of studies	No. of patients (LS/CS)	Statistical method	Effect size	p	Heterogeneity
12 months	2	115/100	Mean Difference (IV, Random, 95% CI)	0.36 [-0.02, 0.73]	0.06	I2=45%
24 months	0	0	Mean Difference (IV, Random, 95% CI)			
Total		194/167	Mean Difference (IV, Random, 95% CI)	0.33 [0.08, 0.57]	0.009	I2=21%
all-cause mortality		Total events (LS/CS)				
6 months	0					I2=0%
12 months	5	9/10	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.03]	0.64	I2=0%
24 months	2	10/9	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.46, 3.03]	0.73	
Total		19/19	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.50, 1.88]	0.93	I2=0%

ies [3,21,22] had high average transport status. Overall, there was no statistically significant difference in the D/Pcr between the two groups (MD 0.00, 95% CI -0.02 to 0.02; p=1.00; I^2=0%) (Table 3).

However, two studies [22,23] with a difference on D/D0 glucose were small sample trials. The pooled analysis suggested that the CS had a higher D/D0 than the LS (MD -0.03, 95% CI -0.05 to -0.01; p=0.01; I^2=17%) (Table 3).

Overall, the D/Pcr and D/D0 glucose of all patients included in this subgroup analysis indicated that both the LS group and the CS group had high-average transport characteristics of peritoneal membrane [6].

Nutritional Status

Our meta-analysis indicated that patients using the LS had lower serum albumin than the CS (MD -0.14 g/dL, 95% CI -0.23 to -0.05; p=0.002; I^2=45%) (Table 3).

In the meta-analysis of five studies [3,15,17,21,23], we found there was no significant difference in nPNA between the two groups (MD -0.02 g/kg/d, 95% CI -0.05 to 0.00; p=0.10;I^2=0%) (Table 3).

Only two studies [17,21], publishing the data of SGA were small sample trials. We found that the LS group had a better SGA score than the CS group (MD 0.33, 95% CI 0.08 to 0.57; p=0.009; I^2=21%) (Table 3).

All-cause Mortality

All seven studies [3,15,17,21-24] published the effect of LS on patients' survival. No patient died in the two groups at 6-month follow-up. At 12 months five studies [15,17,21-23] involving 417 patients and at 24 months two studies involving 215 patients were included in the subgroup analysis, suggesting that there was no significant difference between the two groups, respectively (Table 3).

DISCUSSION

Our study suggests that low GDP solution preserves RRF in PD patients over time,

particularly in one year of treatment, and improves the dialysis adequacy especially the urea clearance without increasing the peritoneal solute transport rate. In addition, low-GDP solution was found to have no benefits on blood pressure, nutritional status and all-cause mortality.

The low GDP solution preserves more RRF as they may cause less intraperitoneal inflammation, thereby reducing peritoneal ultrafiltration and fluid losses. It is supported by a crossover designed RCT by EURO-BALANCE [14], which showed more urine volume and better clearance of both urinary urea and creatinine with the neutral pH low GDP glucose containing dialysates alongside lower serum concentrations of AGE markers. In addition, these findings were also confirmed by several clinical trials, suggesting better preservation of RRF compared with the conventional PD solutions [3,23]. The improved preservation of RRF with low GDP solution was observed at all study time points [40]. Kim *et al.* [23] firstly declared the beneficial effect of low GDP solution on RRF with more urine volume in a prospective RCT. The balANZ trial [3], as the largest RCT, observed that the rate of decline of renal function did not reach statistical significance in the first and the second year, but there was a significant delay in time to anuria. However, these beneficial effects on RRF were not substantiated by other studies [15,17,21,22,24]. Szeto *et al.* [15] failed to show any difference in RRF and urine output between the two groups because the small sample size was not adequately powered to elucidate the effect on RRF. Similarly, Fan *et al.* [16] reported negative results from a larger number of patients, which was due to the lack of homogeneity for the patients in each study group. Therefore, meta-analysis, differing from included single study, can exert statistical power and result in a highly reliability outcome. The benefits of low-GDP solution are biologically plausible, as GDPs have been demonstrated to exert nephrotoxic effects directly on renal tubular cells [11]. One potential and underpinning mechanism is that low-GDP solution better preserves RRF in PD patients *via* reduction of GDP and the AGE in the systemic circulation [27]. The other possible reason for the beneficial effect of low GDP solution on RRF could be that decreased peritoneal UF results in more urine output and higher residual renal clearance [28,29].

Weekly Kt/V is an important parameter for evaluating PD treatment adequacy. Our data indicate that although the use of the low GDP dialysates was not associated with increasing creatinine clearance (either total CrCl or peritoneal CrCl) or decreasing blood pressure (either SBP or DBP), it exhibited significant benefit in weekly Kt/V in 12 months of treatment. While patients using conventional PD solutions had a small advantage in the peritoneal Kt/V ($p=0.03$) which was consistent with the analysis of peritoneal UF ($p=0.002$) despite similar glucose load ($p=0.73$) (Supplementary Figure S3 and S6). Our study analyzed the nutritional status including serum albumin, nPNA and SGA score, which is important to evaluate the adequacy of peritoneal dialysis and CAPD patients survival [36]. However, serum albumin suffered from a moderate level of statistical heterogeneity, which could not be satisfactorily explained [37]. Improved nutritional status with low GDP PD solution was confirmed by the increase of SGA in the LS group. Inconsistency of these parameters for evaluating nutritional status may be due to heterogeneity among studies [27].

Most of the clinical studies find that low GDP solution reduces peritoneal UF accompanied by high average PSTR, whereas our review revealed that low GDP solution improved the dialysis adequacy with no expense of PSTR represented by D/Pcr and D/D0 glucose at 4 hours. Two studies by Choi *et al.*[21] and Tranaeus *et al.*[30] showed similar findings but with a high level of clinical heterogeneity. McDonald *et al.*[31] thought that the reduction of peritoneal UF was an important

cause of technique failure. However, excessive peritoneal UF may also play a causal role in the decline of RRF by provoking intravascular volume depletion [32,33]. Thus, it is difficult to delimit UF volume as a clinical outcome, which is affected by many other variables such as fluid status, UV, PSTR and glucose load [34].

PSTR has been recognized as an important factor for the assessment of clinical outcomes, including technical failure and patient survival [35]. Although the study by Kim *et al.* [23] was excluded for analyzing the effect of low GDP PD solution on PSTR because of a difference at baseline, the significant difference still existed at 6 and 12 months. It also supported our outcome that low GDP solution contributed to the lower UF without the difference of PSTR. Taken together, our results highlighted that the assessment for PSTR should be focused on process carefully rather than just an absolute value at the end of the study [34].

Concerning the survival advantage with low GDP PD solution, retrospective studies from Korea [38,39] suggested that the biocompatible solution improved the survival in patients with PD and reduced mortality risk by 39%. However, our data showed that low GDPs in PD solution have no statistical impact on the survival of PD patients at 1 year or even longer follow-up period.

Several limitations of this study should be considered. First, most of the studies included patients who were receiving RAS (renin-angiotensin system) blockers that might be effective in slowing the decrease in RRF in PD patients. In addition, the primary endpoints of the studies and the dose of peritoneal dialysis in patients were different. Furthermore, RCTs investigating the effects of neutral pH, low GDP PD solution on RRF and adequacy were limited in number and publication bias. The Balance® (Fresenius Medical Care, Bad Homburg, Germany), the only one particular solution analyzed in our meta-analysis, may not enough to represent the neutral pH, low GDP PD solutions. At last, PD treatment adequacy should be interpreted clinically rather than be evaluated by solute and fluid removal [28].

CONCLUSIONS

This meta-analysis suggests that low GDP PD solution significantly preserved residual renal function and improved dialysis adequacy without increasing the peritoneal solute transport rate (Table 4). Future randomized trials with adequate statistical power are needed to determine whether low GDP PD solution affects long-term clinical outcomes.

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Ethics approval and consent to participate

The ethic approval was obtained from the Ethic Committee of Ningbo Medical Center Lihuili Hospital.

Consent to publish

All of the authors have consented to publish this research.

Competing interests

All authors declare no conflict of interest.

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Authors' contributions

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.

Table 4
Summary of findings for the main comparison

Low-glucose degradation product versus standard glucose dialysate

Patient or population: PD patients

Setting: community

Intervention: low GDP dialysate

Comparison: standard glucose dialysate

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (Grade)	Comments
Residual renal function	MD 0.66 (0.34, 0.99)	442 (11)	high	Benefits reached significance as the study duration continued from 6 to 12 months
Daily Urine Volume	MD 153.15 (96.62, 209.68)	476 (9)	high	Benefits reached significance as the study duration continued from 6 to 12 months
Small solute clearance				
total Kt/V	MD 0.11 (0.05, 0.17)	312 (7)	high	Benefit reached significance after one year followed up
Peritoneal Kt/V	MD -0.10 (-0.20, -0.01)	220 (4)	moderate	Benefit reached significance after one year followed up
total CrCl	MD 3.39 (-0.75, 7.53)	271 (5)	Very low	
Peritoneal CrCl	MD 0.67 (-0.90, 2.24)	238 (4)	Very low	Benefit reached significance at 6 months followed up
Peritoneal Ultrafiltration	MD -193.45 (-315.36, -71.54)	282 (6)	high	Benefits reached significance as the study duration continued from 6 to 12 months
glucose load	MD 0.90 (-1.41, 3.21)	495 (9)	Very low	
Blood Pressure				
systolic blood pressure	MD -0.29 (-5.04, 4.46)	323 (5)	Very low	

Table 4. CONTINUACIÓN

Low-glucose degradation product versus standard glucose dialysate

Patient or population: PD patients

Setting: community

Intervention: low GDP dialysate

Comparison: standard glucose dialysate

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (Grade)	Comments
diastolic blood p ressure	MD 0.53 (-1.40, 2.45)	323 (5)	Very low	
Peritoneal Solute Transport Rate				
D/Pcr	MD 0.00 (-0.02, 0.02)	91 (3)	Very low	
D/D0 glucose	MD -0.03 (-0.05, -0.01)	91 (3)	high	
Nutritional Status				
Serum albumin	MD -0.14 (-0.23, -0.05)	470 (9)	high	Benefit reached significance after one year followed up
nPNA	MD -0.02 (-0.05, 0.00)	495 (9)	Very low	
SGA score	MD 0.33 (0.08, 0.57)	194 (3)	high	
All-cause mortality	OR 0.97 (0.50, 1.88)	19 (7)	Very low	

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