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Effect of low-GDP bicarbonate–lactate-buffered peritoneal dialysis solutions on plasma levels of adipokines and gut appetite-regulatory peptides: a randomized crossover study

Ana Rodríguez-Carmona[1], Miguel Pérez-Fontán[1,4], Ana Guitián[1], Javier Peteiro[2], Teresa García-Falcón[1],Andrés López-Muñiz[1], Jesús García-Buela[2] and Fernando Cordido[4,3]

[1] Division of Nephrology, University Hospital a Coruña, A Coruña, Spain, [2] Division of Laboratory, University Hospital a Coruña, A Coruña, Spain, [3] Division of Endocrinology, University Hospital a Coruña, A Coruña, Spain and [4] Department of Medicine, Health Sciences Faculty, University of a Coruña, A Coruña, Spain

Abstract

Background. Malnutrition is common in patients treated with peritoneal dialysis (PD). Previous studies have disclosed disturbances in the hormonal axes regulating appetite in these patients. The effect of newer biocompatible PD solutions on these disorders is undetermined.

Methods. Using a crossover randomized design, 21 patients stable on PD underwent 5 weeks of therapy with each of classic glucose degradation product (GDP)-rich lactate-buffered PD solutions (L) and newer low-GDP bicarbonate–lactate-buffered PD solutions (BL). At the end of each phase, we scrutinized patients for adequacy markers, peritoneal transport (peritoneal equilibration test with 3.86% glucose-based solutions), general biochemical markers and, more specifically, cytokines, adipokines (leptin and adiponectin) and selected gastrointestinal peptides which regulate appetite in the short term [ghrelin, peptide YY, cholecystokinin, glucagon-like peptide 1 (GLP1)]. For plasma GLP1 levels, we analysed a group of healthy, sex-, age- and body mass index-matched controls.

Results. Use of BL solutions was associated with higher plasma levels of acylated (but not total) ghrelin (median 243 BL versus 141 pg/mL L, P = 0.05), adiponectin (median 20.2 BL versus 17.6 mcg/mL L, P = 0.008) and growth hormone (median 1.8 BL versus 1.0 ng/mL L, P = 0.013), without significant differences for the other cytokines, leptin or gut peptides scrutinized. We did not observe significant differences between L and BL solutions concerning estimations of adequacy, peritoneal transport or general biochemical markers.

Conclusions. Use of GDP-free, neutral-pH, bicarbonate–lactate-buffered PD solutions is associated with higher plasma levels of acylated ghrelin and adiponectin than classic solutions. These findings may contribute to explaining improved appetite scores and overall survival rates reported with the use of so-called biocompatible PD solutions.

Keywords

Peritoneal dialysis, Biocompatible solutions, Adipokines, Gut peptides, Appetite, Malnutrition

Introduction

During the last decade, traditional glucose-based, lactate-buffered, glucose degradation product (GDP)-rich peritoneal dialysis (PD) solutions have been progressively, yet not completely substituted by newer, seemingly more biocompatible solutions, with a low content in GDP and in which lactate has been totally or partially replaced by bicarbonate as a buffer. Many *in vitro* and *ex vivo* studies have shown the beneficial effects of these solutions for the preservation of the integrity of the peritoneal membrane [1 , 2 , 3] and peritoneal membrane defense mechanisms [4]. On the other side, evidence linking these solutions to systemic benefits and better clinical outcomes, including preservation of residual renal function (RRF) [5 , 6 , 7], peritonitis rates [2 , 5], improved peritoneal membrane longevity [5] or patient survival [8], are encouraging, but more controversial.

Malnutrition is frequent in patients undergoing renal replacement therapy, bearing a significant impact on their outcomes. The genesis of malnutrition in this setting is complex, but anorexia is undoubtedly a main pathogenic factor [9]. It has been suggested that patients treated with PD may be particularly prone to anorexia [10], due both to the caloric contribution of glucose-infused intraperitoneally and to abdominal fullness favoured by an elevated intraperitoneal pressure.

PD solutions are able to modify the secretion patterns and plasma levels of adipokines and gastrointestinal peptides which regulate cycles of hunger and satiety [11 , 12 , 13]. However, there is a remarkable paucity of information about the specific effects of so-called biocompatible PD solutions on the secretion patterns and plasma levels of appetite-regulatory hormones. We have undertaken a randomized crossover study, with the main objective of comparing the effect of classic lactate-based and new, neutral-pH, bicarbonate–lactate-based GDP-free PD solutions on plasma levels of adipokines and selected gastrointestinal appetite-regulatory peptides.

Population and methods

General design

Following a prospective crossover design, patients stable on chronic PD therapy underwent two consecutive periods of 5 weeks using either classic, lactate-buffered, GDP-rich (thereafter designed as L) or bicarbonate–lactate-buffered, neutral-pH, low-GDP PD solutions (designed as BL) in a randomized order. The PD prescription was otherwise kept essentially invariable during the whole study span. At the end of each period, we scrutinized patients for adequacy markers, peritoneal transport (standard Peritoneal Equilibration Test PET using 3,86% glucose-based dialysate) and selected appetite-regulatory hormones, including adipokines (leptin, adiponectin) and gut peptides: ghrelin, peptide YY, cholecystokinin and glucagon-like peptide 1 (GLP-1).

The study protocol fulfilled the requirements of the ethical committee of our centre, and written informed consent was obtained from all patients.

Subjects

Patients were selected from our population undergoing chronic PD therapy, after applying the following exclusion criteria: age <18 or >85 years, chronic PD for <2 months, significant clinical events (including peritonitis) during the previous 3 months and unwillingness or inability to cooperate. Twenty-nine patients were eligible, but we excluded five due to refusal to participate ($n = 1$) or nonmedical reasons ($n = 4$). Thus, 24 patients were randomized, but 3 could not complete the study due to renal transplantation ($n = 2$) or adverse event ($n = 1$, pulmonary infection). The study flow diagramme is depicted in Figure 1 . The main characteristics of the final study group are presented in Table 1 .

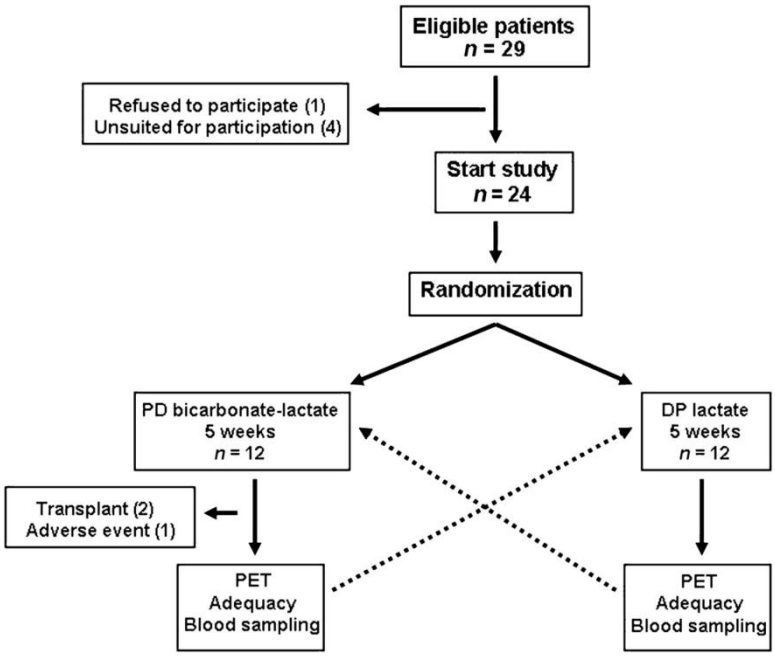


Fig. 1. Study flow chart.

Table 1. Main characteristics of patients in the study

Age (years)	57 (21–84)
Sex (males/females) (%)	16/5 (76.2/23.8)
Kidney disease	
Glomerular	3
Interstitial	3
Vascular	4
Cystic	3
Diabetic nephropathy	5
Other/unknown	3
Diabetes (%)	7 (33.3%)
Modality of PD (CAPD/automated PD) (%)	10/11 (47.6/52.4)
Icodextrin (%)	15 (71.4)
Aminoacid-based solutions (%)	9 (42.9)
Body mass index (kg/m ^{2})	26.1 (19.8–36.4)
Obese patients (>30 kg/m ^{2}) (%)	3 (14.3)
Time on PD at the start of the study (months)	26 (5–74)
Patients with previous peritonitis (%)	10 (47.6)
Main drug therapies (%)	
Furosemide	10 (47.6)
Calcium antagonists	9 (42.9)
ACEI-ARA	13 (61.9)
Statins	13 (61.9)
Antiplatelet drugs	6 (28.6)
Insulin	5 (23.8)

Study protocol

Before the start of the study, all patients were treated with conventional L solutions (Dianeal; Baxter, Deerfield, IL). We randomized them to either 5 weeks on the same regime under tight prescription control or switch to BL solutions (Physioneal Clear Flex; Baxter). At the end of this period, blood and dialysate samples were collected for adequacy (Kt/V, creatinine clearance, RRF) and for the scrutiny of the selected biochemical, inflammation and hormonal variables (see below). All blood samples were retrieved after an overnight fast; the usual PD prescription was maintained during this overnight period. A standard 4-h 3.86% PET was also performed, using the type of solution (either BL or L) of the corresponding study period. Patients were then switched to the alternative PD solution, keeping the remaining prescription parameters as constant as possible. Five weeks later, adequacy, blood sample collection and a 3.86% PET were repeated. During both study periods, patients recorded daily at home their blood pressure, body weight and ultrafiltration rates (difference between infusion and drainage bags for manual exchanges), as also any changes to the PD regime.

Blood biochemical estimations included urea, creatinine, glucose, sodium, potassium, calcium, phosphate, venous pH, bicarbonate, albumin, cholesterol and triglycerides. Markers of inflammation and endothelial dysfunction included C-reactive protein (CRP), interleukin 6 (IL-6) and 10 (IL-10), Intercellullar adhesion molecule-1, total homocysteine, transforming growth factor β1 (TGF-β1) and vascular endothelial growth factor (VEGF). We also scrutinized adipokines, hormones and appetite-regulatory peptides, including leptin, adiponectin, insulin, GLP1(7–36), growth hormone (GH), ghrelin (total and acylated), PYY $_{(1–36 \text{ and } 3–36)}$ and cholecystokinin. Given the paucity of previous information on this hormone, in the case of GLP-1, we also present values estimated in a group of age 48, sex and BMI-matched controls, recruited from a pool of healthy individuals available to the Endocrinology Unit of our center.

Total Kt/V creatinine clearance and normalized protein nitrogen appearance were estimated with the Adequest® software (Baxter). Twenty-four- hour peritoneal glucose absorption was calculated by simple mass balance. Ultrafiltration during 3.86% PET was estimated from the difference of weight of the dialysate bag before infusion and after final drainage. RRF (Glomerular filtration rate (GFR)] was estimated as the mean of urea and creatinine clearances, after 24-h urine collections.

Sample management and laboratory methods

Blood samples for biochemical determinations were processed immediately. Those destinated to estimations of hormones, gut peptides, adipokines and inflammatory markers were immediately centrifuged, separated and frozen at −80°C. Samples for determination of plasma ghrelin levels were specifically retrieved to chilled tubes containing aprotinin and EDTA-Na and then immediately centrifuged at 4°C, separated to aliquots and frozen at −80°C.

We used an autoanalyser for all standard biochemical determinations. CRP was estimated using a high-sensitivity immunoturbidimetric assay (Roche, Mannheim, Germany). IL-6, IL-10, TGF-β1 and VEGF were estimated using ELISA assays (R&D Systems, Minneapolis, MN). Total homocysteine levels were estimated by fluorescence polarization immunoanalysis (Imx; Abbott Lab., Abbott Park, IL). For estimation of the scrutinized hormones, we used the following specific commercial radioimmunoassays: PYY $_{(1–36)}$ and PYY $_{(3–36)}$ (Linco, St. Charles, MO), total ghrelin (Phoenix Pharmaceuticals, Belmont, CA), acylated ghrelin (Linco), cholecystokinin (Alpro, Windham, NH), GH (Nichols Inst. Diagnostics, San Juan Capistrano), leptin (Mediagnost, Tübingen, Germany), adiponectin (Millipore, Billerica, MA), GLP-1 (Millipore) and insulin (CIS Bio International, Cedex, France).

Statistics

Numerical variables are presented as median values (range), unless otherwise stated. For comparisons between the study periods, we used Student's *t* -test (paired) and Wilcoxon's test. Comparisons between subgroups of patients were based on Fisher's (categorical) and Mann–Whitney *U*- (numerical) tests. Numerical correlations were analysed using the Spearman's correlation test. Unless otherwise stated, the results reported for secondary correlations correspond to the BL period. P-values ≤0.05 were considered to be significant. We used the SPSS 17.0 software for statistical analysis.

Results

All patients were able to maintain stable PD regimes during the whole study period. There were no differences in the general biochemical profile during the study period, except for a nonsignificant trend to higher blood bicarbonate levels during the BL phase (Table 2). We also did not observe any significant differences in the adequacy or PET-related estimations between the study periods (Table 3).

Table 2. Main laboratory variables [a]

	Bicarbonate–lactate	Lactate	P
Urea (mg/dL)	149 (101–251)	152 (108–274)	NS
Creatinine (mg/dL)	7.1 (3.7–14.9)	7.3 (3.6–16.8)	NS
Sodium (mM/L)	139 (131–143)	137 (133–144)	NS
Potassium (mM/L)	4.8 (3.7–6.0)	4.9 (3.7–6.2)	NS
Blood pH (venous)	7.32 (7.23–7.38)	7.31 (7.25–7.41)	NS
Bicarbonate (mM/L)	22.2 (16.1–25.4)	21.7 (17.1–30.7)	0.07
Calcium (mg/dL)	9.1 (8.1–10.4)	9.1 (8.2–10.3)	NS
Phosphate (mg/dL)	5.1 (3.2–6.7)	5.2 (3.7–7.1)	NS
Glycemia (mg/dL)	93 (80–221)	91 (73–250)	NS
Albumin (g/L)	37 (32–47)	38 (32–44)	NS
Cholesterol (mg/dL)	161 (93–234)	176 (90–216)	NS
Triglycerides (mg/dL)	117 (53–269)	123 (51–455)	NS
Homocysteine (μM/L)	26 (15–173)	26 (16–139)	NS
ICAM-1 (ng/mL)	330 (99–513)	313 (140–544)	NS
Interleukin 6 (pg/mL)	7 (3–21)	6 (3–16)	NS
Interleukin 10 (pg/mL)	0.8 (0.1–7.2)	1.5 (0.1–11.2)	NS
CRP (mg/dL)	4.1 (1.0–41)	3.0 (1.0–11.2)	NS
TGF-β1 (ng/mL)	7 (0.15)	7 (0.12)	NS
VEGF (pg/mL)	107 (22–400)	100 (5–455)	NS

Figures denote median values (range). Comparisons by Student's *t* -test (paired) and Wilcoxon's test.

[a] ICAM, Intercellular adhesion molecule-1.

Table 3. Peritoneal transport and adequacy markers [a]

	Bicarbonate–lactate	Lactate	P
Body weight (kg)	71.5 (48–105.5)	71.5 (49–105)	NS
Diuresis (mL/day)	1100 (0–3500)	1400 (0–2700)	NS
GFR (mL/min)	5.0 (0–11.5)	6.4 (0–10.8)	0.07
Peritoneal Kt/V	1.14 (0.97–2.20)	1.06 (0.91–2.60)	NS
Peritoneal creatinine clearance (L/week/1.73 m^2)	38.9 (22.1–84.3)	42.0 (22.4–85.4)	NS
Peritoneal glucose load (g/day)	79.6 (27.2–178.8)	79.6 (27.2–178.8)	NS
Peritoneal glucose absorption (g/day)	35.4 (14.4–66.7)	36.4 (12.2–71.1)	NS
nPNA (g/kg/day)	1.12 (0.68–1.91)	1.11 (0.64–1.70)	NS
Peritoneal protein excretion (g/day)	5.0 (2.7–10.4)	4.6 (2.6–9.1)	NS
Daily ultrafiltration (L)	720 (200–2350)	720 (200–2400)	NS
Peritoneal sodium removal (mM/day)	54 [(−37) to 184]	64 [(−36) to 184]	NS
Systolic blood pressure (mmHg)	131 (99–160)	130 (86–155)	NS
Diastolic blood pressure (mmHg)	79 (61–101)	77 (45–103)	NS
D/P 240′ creatinine (PET)	0.71 (0.49–1.02)	0.71 (0.45–0.93)	NS
Ultrafiltration during PET (mL)	550 (50–900)	650 (0–1450)	NS
Sodium dip 60’ (mM/L) (PET)	3 [(−1) to 14]	6 (2–13)	0.09

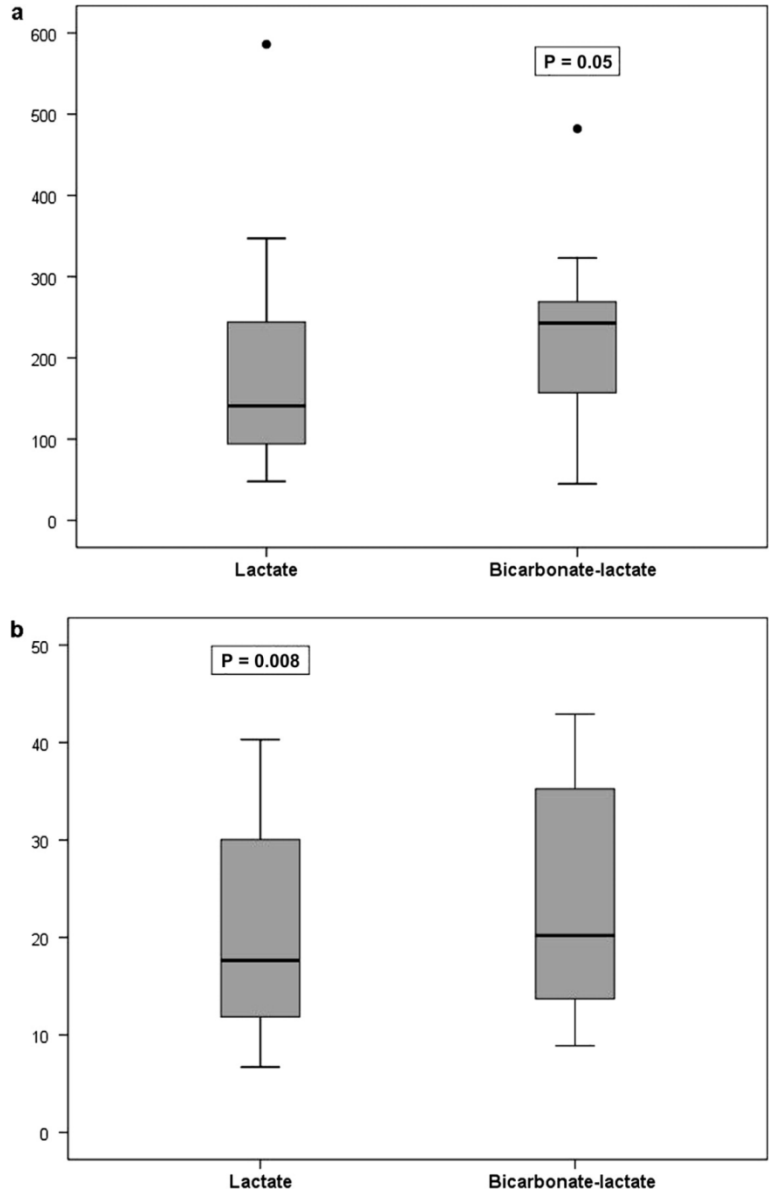
Figures denote median values (range). Comparisons by Student’s *t* -test (paired) and Wilcoxon’s test.
[a] nPNA, Normalized protein nitrogen appearance.

Table 4 shows the main comparisons between the levels of the selected adipokines, hormones and appetite-regulatory peptides. Interestingly, levels of GH (mean difference 1.32 ng/mL, *i* 0.51, P = 0.01), acylated (but not total) ghrelin (mean difference 64.5 pg/mL, SEM 29.7, P = 0.05) (Figure 2a) and adiponectin (mean difference 1.90 mcg/mL, SEM 1.06, P = 0.008) (Figure 2b) were significantly higher after 5 weeks of treatment with BL solutions. Plasma levels of $GLP1_{7–36}$ did not differ between the study phases (Table 4) and were not significantly different from those observed in normal controls (median 13.2 pM/L, range 1.1–38.6).

Table 4. Hormones, adipokines and appetite-regulatory peptides

	Bicarbonate–lactate	Lactate	P
Insulin (mcU/mL)	27.3 (8.7–71.9)	28.8 (12.2–87.8)	NS
$GLP1_{7–36}$ (pM/L)	11.8 (0.9–22.4)	10.5 (1.1–20.1)	NS
GH (ng/mL)	1.8 (0.1–7.6)	1.0 (0.1–5.7)	0.013
Adiponectin (mcg/mL)	20.2 (8.9–42.9)	17.6 (6.7–40.3)	0.008
Leptin (ng/mL)	13.6 (2.8–297.0)	18.7 (3.7–349.0)	NS
Ghrelin, total (pg/mL)	1895 (656–4264)	2010 (745–4447)	NS
Ghrelin, acylated (pg/mL)	243 (45–482)	141 (48–586)	0.05
Ratio acylated/total ghrelin	0.12 (0.03–0.42)	0.08 (0.02–0.29)	0.09
$PYY_{1,36}$ (pg/mL)	461 (307–1024)	482 (245–949)	NS
$PYY_{3,36}$ (pg/mL)	178 (104–454)	170 (77–401)	NS
Cholecystokinin (pM/L)	0.29 (0.09–4.60)	0.34 (0.08–4.55)	NS

Figures denote median values (range). Comparisons by Student’s t (paired) and Wilcoxon’s tests.



(**a**) Plasma levels of acylated ghrelin (pg/mL) after 5 weeks of therapy with GDP-rich lactate-buffered solutions and low-GDP bicarbonate–lactate-buffered solutions. (**b**) Plasma levels of adiponectin (mcg/mL) after 5 weeks of therapy with GDP-rich lactate-buffered solutions and low-GDP bicarbonate–lactate-buffered solutions.

In general, observed blood levels of cytokines, adipokines and gut peptides were tightly correlated in both periods (Spearman's correlation coefficients > 0.80), with the remarkable exceptions of insulin (r = 0.36, P = 0.10) and GLP-1 (r = 0.35, P = 0.23). Plasma levels of PYY $_{1–36}$ and PYY $_{3–36}$ ran tightly correlated (r = 0.81, P = 0.002), while plasma levels of total and acylated ghrelin did not (r = 0.27, Not significant). Plasma GH levels were correlated with adiponectin (r = 0.61, P = 0.007) and acylated ghrelin (r = 0.46, P = 0,04). As refers to other variables, age correlated inversely with blood levels of total ghrelin (r = −0.62, P = 0.003), PYY $_{1–36}$ (r = −0.49, P = 0.04) and PYY $_{3–36}$ (r = −0.56, P = 0.008) and directly with IL-6 (r = 0.51, P = 0.02). On the other hand, GFR showed an inverse correlation with blood levels of PYY $_{1–36}$ (r = −0.58, P = 0.006), PYY $_{3–36}$ (r = −0.52, P = 0.015) and IL-6 (r = −0.65, P = 0.009) and directly with GH (r = 0.58, P = 0.008) and IL-10 (r = 0.77, P = 0.002). As expected, leptin levels

correlated with body mass index ($R = 0.65$, $P = 0.002$) and tended to be higher in women (median 21.1 versus 14.8 ng/mL, $P = 0.07$).

Discussion

The general results of our study agree for the most part with previous short- and mid-term reports comparing L and BL solutions. Both types of solution yielded similar results as refers to adequacy, general biochemical and PET-related markers (Tables 2 and 3). PET results disclosed a nonsignificant trend to lower Ultrafiltration (UF) and less sodium dip at 60 min with BL than with L solutions (Table 3). The compared UF rates yielded by L and BL solutions are a matter of controversy. The current view suggests that, for reasons which are not totally clear, BL solutions may yield marginally lower UF in the short-term [5 , 7 , 13 , 14 , 15], while a better preservation of peritoneal integrity could favour better long-term UF rates [14 , 16]. Our results also support previous reports indicating no apparent impact of the type of solution on plasma cytokine levels [17 , 18] (Table 2).

Hormonal disturbances of appetite regulation in PD patients have been a subject of attention in the last years. Reported abnormalities include hyperleptinaemia [19] and hyperadiponectinaemia [20 , 21], high plasma levels of total, but not the active acylated fraction of ghrelin [22], YY peptide [23] and cholecystokinin [24], as also more or less markedly disturbed patterns of secretion of gut peptides following meals [11 , 23 , 25 , 26 , 27]. The compared effects of different PD solutions on the secretion patterns and plasma levels of these hormones have been insufficiently studied. Plasma leptin levels are significantly higher in PD than in haemodialysis patients, a difference that persists after controlling for fat mass [28]. This phenomenon has been attributed to the capacity of glucose to stimulate directly secretion of leptin by peritoneal adipocytes [29]. In the clinical setting, the short-term effect of glucose-based dialysate on plasma leptin levels is a matter of controversy [11 , 29]. Partial substitution of glucose-based by icodextrin-based PD solutions results in lower plasma levels of leptin and insulin and higher plasma levels of adiponectin [12]. On the other hand, hypertonic (3.86%) glucose-based dialysate is able to inhibit partially acute ghrelin [11], but not PYY secretion [23]. Finally, PD is able to dialyze adipokines and gut peptides [30 , 31], but it is unclear if this factor has any significant influence on the plasma levels or the physiology of these hormones.

There is a remarkable paucity of information about the potential effects of so-called biocompatible PD solutions on the secretion patterns and plasma levels of adipokines and gut appetite-regulatory peptides. These solutions appear to induce leptin secretion by cultured adipocytes to a higher extent than classic lactate-based solutions [32], but the clinical significance of this finding is unknown. Trials comparing classic and new solutions in the clinical setting have not addressed this question, and only some controversial results on selected cytokine levels have been reported [17 , 18].

Our results show no apparent effect of BL solutions over L solutions for the majority of the hormones scrutinized (Table 4). Interestingly, we observed significantly higher plasma levels of acyl ghrelin during treatment with BL solutions. This pattern, combined with similar plasma levels of anorexigenic peptides, could configurate a more orexigenic scenery than L solutions, contributing to explain the results of previous reports, suggesting that biocompatible solutions may bear a less negative effect on appetite than L solutions [33 , 34]. Acyl ghrelin may also stimulate GH secretion [35], which may help to understand the higher plasma levels of GH observed during the BL phase (Table 4). We do not have a clear explanation for the different levels of acyl-ghrelin observed during the study phases, mainly because there is a remarkable lack of information on the factors that regulate the physiology of this hormone in patients with chronic kidney disease. The particular conditions favoured by BL over L solutions (acid–base status, less GDP content, lower lactate load) could potentially modify the secretion patterns of this hormone. The presence of similar levels of total ghrelin in both phases, with a close to significant increase in the acyl-ghrelin/total ghrelin ratio (Table 4), could also be consistent with a longer half-life of acylated ghrelin under BL solutions. On the other hand, we found moderately, but significantly, higher plasma levels of adiponectin during treatment with BL solutions than with L solutions. This

phenomenon could follow an improvement of the acid–base status brought by BL solutions because metabolic acidosis has been shown to lower circulating adiponectin levels through inhibition of adiponectin gene transcription in adipocytes [36]. However, the clinical significance of this finding is unclear because the differences observed were small. Moreover, adiponectinemia does not have a clear clinical interpretation in patients with chronic kidney disease. This adipokine appears to have antiinflammatory and antiatherogenic properties [20], but some studies have even observed an inverse correlation between plasma levels of adiponectin and survival, in these patients [21].

The main strength of this study is a rigorous and comprehensive design, permitting clear comparisons between phases. The relatively short follow-up may have limited the significance of the findings but permitted stable conditions (prescription, clinical events …), which are difficult to sustain in long-term PD. A second limitation is the lack of dynamic studies, including meal provocation tests, which could have contributed to clarify the potential effects of PD solutions on the physiology of these hormones. More importantly, we did not search for potential variations in appetite scores. The latter could have disclosed clinical correlates of the differences between the hormonal patterns observed during the study phases.

In summary, this short-term randomized crossover study, performed under strictly controlled conditions, shows that, when compared with classic L solutions, newer BL solutions associate higher plasma levels of acyl-ghrelin, adiponectin and growth hormone. The potential contribution of these differences to the improved appetite scores and survival rates reported after the use of these solutions will need to be assessed in future studies.

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