Randomized, Controlled Trial of Glucose-Sparing Peritoneal Dialysis in Diabetic Patients

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ABSTRACT

Glucose-containing peritoneal dialysis solutions may exacerbate metabolic abnormalities and increase cardiovascular risk in diabetic patients. Here, we examined whether a low-glucose regimen improves metabolic control in diabetic patients undergoing peritoneal dialysis. Eligible patients were randomly assigned in a 1:1 manner to the control group (dextrose solutions only) or to the low-glucose intervention group (IMPENDIA trial: combination of dextrose-based solution, icodextrin and amino acids; EDEN trial: a different dextrose-based solution, icodextrin and amino acids) and followed for 6 months. Combining both studies, 251 patients were allocated to control (*n*=127) or intervention (*n*=124) across 11 countries. The primary endpoint was change in glycated hemoglobin from baseline. Mean glycated hemoglobin at baseline was similar in both groups. In the intention-to-treat population, the mean glycated hemoglobin profile improved in the intervention group but remained unchanged in the control group (0.5% difference between groups; 95% confidence interval, 0.1% to 0.8%; *P*=0.006). Serum triglyceride, very-low-density lipoprotein, and apolipoprotein B levels also improved in the intervention group. Deaths and serious adverse events, including several related to extracellular fluid volume expansion, increased in the intervention group, however. These data suggest that a low-glucose dialysis regimen improves metabolic indices in diabetic patients receiving peritoneal dialysis but may be associated with an increased risk of extracellular fluid volume expansion. Thus, use of glucose-sparing regimens in peritoneal dialysis patients should be accompanied by close monitoring of fluid volume status.

Peritoneal dialysis (PD) is a well established treatment for renal replacement therapy that provides clinical outcomes similar to those with hemodialysis (HD)[1] and similar and possibly better quality of life.[2–4] However, registry data from Australia/New Zealand, Europe, and the United States show that dialysis patients continue to have a high risk of cardiovascular (CV) mortality compared with the general population of the same age.[5] Although overall survival appears no different between patients treated with PD or HD,[1,6,7] features unique to both modalities may contribute to differences in the underlying mechanisms leading to morbidity and

death. PD populations have multiple modifiable CV risk factors, including dyslipidemia, hypertension, smoking, obesity, and factors that are associated with uremia (such as vascular calcification,

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inflammation, endothelial dysfunction, and oxidative stress).[8] Fluid overload and glucose exposure are postulated to contribute significantly to CV mortality in PD patients.[8,9]

Unique to PD therapy is the exposure of the patient to large amounts of glucose contained in the dialysis fluids. Glucose serves as the osmotic agent for the PD-based solutions, and patients can absorb up to 200 g per day, depending on the glucose concentration in the PD fluid used and the patient's peritoneal membrane transport status.[10,11] Patients treated with PD experience a heightened exposure to metabolic risk factors, including dyslipidemia (elevated triglycerides and very-low-density lipoprotein [VLDL]) and hyperglycemia. This group of risk factors (including hypertension) composes the metabolic syndrome, a disorder estimated to occur in about 50% of patients undergoing PD.[12,13] For patients with diabetes, the glucose loading can aggravate glycemic control and potentially require increased doses of insulin or other hypoglycemic agents.

Poor glycemic control is associated with increased mortality in PD patients.[14] Adjusted all-cause mortality hazard ratio for time-averaged hemoglobin A_{1c} (HbA$_{1c}$) values of 7.0%–7.9% and 8.0%–8.9% were 1.10 and 1.28, respectively, compared with 6.0%–6.9% as reference.[14] In addition, higher HbA$_{1c}$ is associated with increased CV mortality in nondiabetic patients undergoing PD.[15]

A recent randomized, controlled trial performed in Mexico demonstrated improved control of multiple metabolic variables with an icodextrin-based intervention in diabetic PD patients with high average peritoneal transport status.[16] In addition, amino acid–containing solutions, such as Nutrineal, have been shown to improve glucose and lipid metabolism.[17]

The Improved Metabolic Control of Physioneal, Extraneal, Nutrineal (P-E-N) versus Dianeal Only in DIAbetic continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) Patients (IMPENDIA) trial was designed with these considerations in mind. IMPENDIA was a prospective, randomized, controlled, open-label, parallel-group, multicenter, multinational trial designed to investigate whether a glucose-sparing PD prescription (P-E-N) improves metabolic control in diabetic PD patients compared with a glucose-only prescription (Dianeal only) regimen over 6 months. The Evaluation of Dianeal, Extraneal and Nutrineal (D-E-N) versus Dianeal only in Diabetic CAPD Patients (EDEN) study was a separate study of patients from Colombia in which Dianeal was substituted for Physioneal as part of an otherwise identical trial design. The EDEN trial was added as a result of insufficient enrollment into the IMPENDIA study. However, because of the unavailability of the Physioneal solutions in Colombia, Dianeal was used instead. Given that both Dianeal and Physioneal have a similar glucose concentration, the analysis of the combined results of both studies provides a legitimate evaluation of the safety and efficacy of glucose-sparing PD regimens compared with conventional PD regimens in diabetic PD patients. It was decided a priori, before

the statistical plan was completed and the databases were locked, to pool the data from both studies into a combined analysis.

RESULTS

Patient Characteristics at Baseline

Between February 2008 and January 2011, 251 patients (180 in IMPENDIA and 71 in EDEN) were enrolled and randomly assigned to the intervention (n=124) or the control (n=127) group. Complete follow-up was achieved for all participants (Figure 1). Significantly more patients withdrew from the intervention group than the control group before study completion. The difference between groups in the withdrawal rate was driven by an increased number of deaths, renal transplants, and voluntary withdrawals by the investigators and the patients, as shown in Figure 1.

Patient baseline characteristics are shown in Table 1. The two groups were well balanced with respect to other baseline characteristics.

Primary Outcome: Change in HbA$_{1c}$

Ninety-seven percent (n=244) of patients were included in the intention-to-treat (ITT) primary efficacy analysis. During the 6 months of therapy, in the ITT population the mean HbA$_{1c}$ profile improved in the intervention group but remained unchanged in the control group (0.5% difference between groups; 95% confidence interval [CI], 0.1% to 0.8%; P=0.006) (Figure 2). In the per-protocol analysis, a similar difference of 0.5% (95% CI, 0.1% to 0.8%; P=0.009) in the mean change in HbA$_{1c}$ profile between groups was observed. In both the ITT and per-protocol populations, the separation between treatment groups was observed as early as 3 months and continued until the end of study assessment. In a post hoc analysis, no relationship between these treatment differences for HbA$_{1c}$ and the use of insulin or oral hypoglycemic agents was found.

Secondary Outcomes

Significant treatment differences between the two groups were observed for several lipids and lipoproteins (**Table 2**). Notably, treatment differences between groups were detected for serum triglyceride, VLDL cholesterol, and apolipoprotein B levels. In a post hoc analysis, no relationship between these treatment differences and the use of lipid-lowering agents was found.

No differences between treatment groups were observed for most of the remaining secondary endpoints, with the exception of change in serum albumin. In the control group, mean serum albumin increased by 0.6 g/L, while in the intervention group mean serum albumin decreased by 0.5 g/L. Through use of ANOVA with repeated measures, the difference between groups for the change from the baseline profile of serum albumin was 1.3 g/L (95% CI, 0.1 to 2.5 g/L; P=0.03).
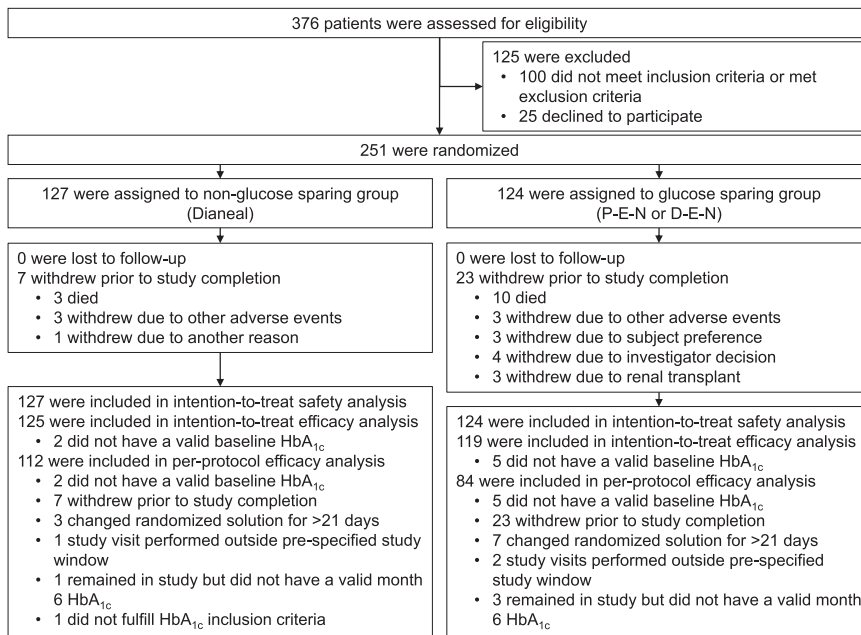
Figure 1. Enrollment, randomization, and follow-up of study participants. D-E-N, Dianeal, Extraneal and Nutrineal; HbA1c, hemoglobin A_{1c}; P-E-N, Physioneal, Extraneal, Nutrineal.

Results for the primary and secondary endpoint analyses for the individual IMPENDIA and EDEN trials are provided in the Supplemental Material.

Safety

Adverse events were actively solicited during the conduct of both studies, and the relatedness to the PD solutions was judged by the clinical trial site investigator. Seventy-nine percent ($n=199$) of the participants experienced at least one adverse event. The number of patients who experienced an adverse event and the overall number of adverse events was similar between the two groups. However, the total number of adverse events judged to be related to the PD solutions was higher in the intervention group (34 related adverse events) compared with the control group (14 related adverse events). As shown in Table 3, more patients in the control group experienced related CV adverse events, while more patients in the intervention group experienced related adverse events that were gastrointestinal, endocrine, or neurologic/musculoskeletal in origin.

Of all the adverse events, 78 events (in 41 patients) in the control group and 105 events (in 58 patients) in the intervention group were considered serious (life-threatening and/or resulted in hospitalization or death). More patients in the intervention group also experienced at least one serious adverse event (47% versus 32%; $P=0.02$). Most of these serious adverse events were CV or infectious in origin.

Five patients in the control group and 11 in the intervention group died. None of these deaths were judged by the investigators to be related to the study solutions. The causes of these deaths are outlined in Table 4.

Results of the safety analyses for the individual IMPENDIA and EDEN trials are provided in the Supplemental Material.

DISCUSSION

This is the largest multinational, multicenter, randomized, controlled study investigating the effect of low-glucose PD solutions on metabolic control in diabetic patients.

Studies performed to date support the hypothesis that glucose-sparing regimens can improve glycemic control in patients with diabetes undergoing PD. In a study involving eight diabetic PD patients, replacement of a glucose-based regimen with a P-E-N regimen was associated with a reduction in the 24-hour variability of glucose concentrations as measured by a subcutaneous probe in the interstitial fluid of the abdominal wall.[18] In another small study, HbA_{1c} decreased significantly among PD patients with diabetes ($n=12$) when icodextrin was introduced into the dialysis regimen.[19] Several other small, nonrandomized studies have reported that nondiabetic PD patients treated with icodextrin exhibited significantly lower serum insulin levels and significantly higher insulin sensitivity than those treated with glucose-based solutions.[20–23] Although these preliminary studies suggest that use of biocompatible and glucose-sparing solutions may improve metabolic control in PD patients with diabetes, most of these studies involved only small numbers of patients or lacked adequate controls.[16,17,24]

The present study has now demonstrated that, in diabetic PD patients, a glucose-sparing prescription using icodextrin and amino acid–based dialysate for two of the daily PD exchanges improves HbA_{1c} compared with a prescription of all glucose-based solutions. HbA_{1c} is the most widely used measure of long-term glycemic control in diabetic patients.[25] Laboratory assays for measuring HbA_{1c} levels are well established, and screening has been standardized by international consensus.[25] Although some studies have indicated that HbA_{1c} only loosely correlates with glycemic control, especially in patients with CKD,[26–28] many other studies do support the hypothesis that HbA_{1c} is a reliable indicator of glycemic control and morbidity outcomes in dialysis patients.

Wu *et al.* studied 137 HD patients with type 2 diabetes and reported that the cumulative survival was lower in the group with poor glycemic control.[29] Similarly, it has been shown that higher HbA_{1c} is associated with increased death risk in patients treated with HD.[30] Recently, Williams *et al.* reported a higher risk for death only in patients with type 2 diabetes undergoing HD with HbA_{1c} levels >11%.[31] Adoption of HbA_{1c} as the primary efficacy variable in IMPENDIA/EDEN is

Table 1. Baseline characteristics (IMPENDIA and EDEN studies combined)

Variable	Control Group (Dianeal Only) ($n=127$)	Intervention Group (P-E-N or D-E-N) ($n=124$)
Age (yr)	58 ± 13	57 ± 12
Women, n (%)	59 (46)	64 (52)
Men, n (%)	68 (54)	60 (48)
Race, n (%)		
Asian	41 (32)	42 (34)
Caucasian	41 (32)	41 (33)
Hispanic	32 (25)	31 (25)
Other	13 (10)	10 (8)
Country, n (%)		
Australia	8 (6)	9 (7)
Canada	6 (5)	3 (2)
Colombia	36 (28)	35 (28)
France	1 (1)	0 (0)
Hong Kong	21 (17)	19 (15)
Korea	13 (10)	12 (10)
New Zealand	9 (7)	8 (6)
Portugal	1 (1)	0 (0)
Russia	29 (23)	30 (24)
Singapore	1 (1)	2 (2)
Taiwan	2 (2)	6 (5)
BMI (kg/m^2)	27 ± 5	27 ± 4
CAPD, n (%)	118 (93)	122 (98)
Diabetes, n (%)		
Type 1	21 (17)	27 (22)
Type 2	106 (83)	97 (78)
Dialysis vintage (yr)	1.7 ± 2.0	1.5 ± 1.8
SGA classification, n (%)		
Well nourished	96 (80)	84 (81)
Mild to moderate malnutrition	24 (20)	20 (19)
Severe malnutrition	0 (0)	0 (0)
BP (mmHg)		
Systolic	138 ± 19	142 ± 18
Diastolic	77 ± 12	79 ± 11
HbA$_{1c}$ (%)	7.6 ± 1.1	7.7 ± 1.3
Hemoglobin (g/L)	108 ± 14	110 ± 13
BUN (mmol/L)	21 ± 6	21 ± 7

Data are presented as n (%) or mean ± SD. IMPENDIA, Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dianeal Only in DIAbetic continuous ambulatory peritoneal dialysis and automated peritoneal dialysis Patients; EDEN, Evaluation of Dianeal, Extraneal and Nutrineal versus Dianeal only in Diabetic CAPD Patients; P-E-N, Physioneal, Extraneal, Nutrineal; D-E-N, Dianeal, Extraneal and Nutrineal; (BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; SGA, Subjective Global Assessment.

further supported by a recent study that found patients receiving HD with HbA$_{1c}$ levels >8% had a greater than two-fold increase in the risk of sudden death compared with patients with HbA$_{1c}$ levels ≤6%.[32]

A previous study on the relationship between glycemic control and outcome in 101 PD patients found poor glycemic control to be associated with a higher death risk.[33] Poor glycemic control, as measured by the change in HbA$_{1c}$ level, was also associated with higher mortality in PD patients with diabetes in another recent study.[14] The researchers demonstrated that in a cohort of 2798 diabetic PD patients, the adjusted all-cause death hazard ratio for time-averaged HbA$_{1c}$ increments of 7.0%–7.9%, 8.0%–8.9%, 9.0%–9.9%, and >10%, compared with 6.0%–6.9% as reference, were 1.10, 1.28, 1.34, and 1.81, respectively.[14] However, HbA$_{1c}$ has not always been associated with outcomes, as shown in a recent retrospective analysis of 91 diabetic patients undergoing PD.[34] Time-averaged follow-up HbA$_{1c}$ in increments of <6.5%, ≥6.5%–8%, and >8% showed no significant survival difference among groups in this smaller PD cohort.[34]

The present study also demonstrated modest but significant improvements in several lipid measures, including triglycerides, VLDL, and apolipoprotein B, in the glucose-sparing group. The prominent features of uremic dyslipidemia are an increase in serum triglyceride levels (due to elevated VLDL remnants and intermediate-density lipoprotein) and low HDL cholesterol.[35] Hyperapobetalipoproteinemia appears to be a prevalent dyslipoproteinemia in PD patients and, as such, might be another factor that places patients undergoing CAPD at particularly increased risk of atherosclerosis.[36] In a large, prospective study in the general population of >7500 patients in the United States, apolipoprotein B measurements significantly predicted coronary heart disease death, independent of conventional lipids and other CV risk factors.[37] Impaired clearance of TG-rich lipoproteins and accumulation of their oxidation-prone, atherogenic remnants in patients with advanced CKD is associated with major adverse consequences. Accumulation of oxidation-prone intermediate-density lipoprotein, chylomicron remnants, and TG-containing small dense LDL promotes accelerated atherosclerosis.[38] Also, increased triglyceride levels are associated with chronic low-grade inflammation,[39,40] which may lead to the accelerated mortality observed in these patients.

The improvements in the lipid profiles of the glucose-sparing group shown in our study could conceivably reduce atherosclerotic risk in the longer term. However, this potential benefit requires an outcome study. Certainly it is clear from studies to date with conventional lipid-lowering strategies in dialysis patients that the effect is absent or more difficult to demonstrate.

Subjective Global Assessment, quality of life, and abdominal magnetic resonance imaging (MRI) results did not significantly differ between the two groups. A glucose-sparing regimen may not lead to measureable differences in these particular outcomes, or this finding may be related to the short duration of the study.

An unexpected finding was the imbalance between groups on serum albumin. This imbalance remains unexplained, but several hypotheses are possible. First, it is unlikely that this is a dilutional effect due to icodextrin and its metabolites. Although icodextrin and its metabolites can theoretically expand plasma volume through a colloidal effect, peritoneal ultrafiltration from icodextrin typically outweighs any colloid-related
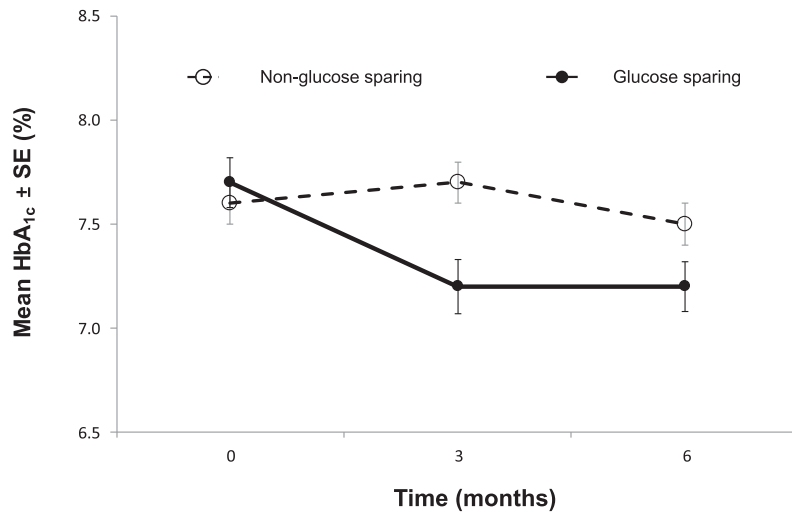
Figure 2. Mean hemoglobin A$_{1c}$ (±SEM) at baseline, month 3, and end of study by treatment group in the intention-to-treat population. HbA1c, hemoglobin A$_{1c}$.

plasma volume increase. Prior randomized controlled trials have also not demonstrated any effect of icodextrin on serum albumin.[41,42] Second, we have also been unable to find any reports of icodextrin or amino acids interfering with the methods used for serum albumin determination. Third, a different cause of dilution, independent of icodextrin, could lead to an imbalance between groups for serum albumin. This could occur if the vigorous pursuit of lowering exposure to glucose was done at the expense of extracellular fluid volume control. In other words, if higher-dextrose solutions needed for adequate ultrafiltration were purposely avoided to optimize metabolic endpoints, progressively volume overload could occur. In the combined analyses, no difference between groups was observed for weight gain, physician assessments of edema or euvolemia, or end-diastolic volume as measured by CV MRI in a subgroup of IMPENDIA participants. We also did not observe strong correlations between change in serum albumin and change in other markers of dilution, including serum sodium and hemoglobin. Furthermore, adverse events that could be related to volume expansion (Table 3) were actually more common in the control group. A fourth explanation for the imbalance in serum albumin between groups is related to the difference between groups in serious adverse events (hospitalizations, for example). Serum albumin is an acute phase reactant and is known to decrease abruptly with acute medical illnesses, such as infection-related events. Insofar as more patients in the intervention group experienced more serious adverse events, the lower serum albumin may reflect this imbalance of events. Finally, the use of nonconventional PD solutions has been associated with the development of a more rapid transmembrane transport status.[43,44] The

change in membrane transport could lead to increased flux of albumin into the peritoneal cavity with consequent reduction in serum albumin.

Another unexpected finding was the greater number of adverse events, related adverse events, serious adverse events and deaths in the treatment group. Given that the intervention consisted of three "drugs" versus one "drug" in the control group, some of this imbalance in number and relatedness of adverse events could be explained by known drug-specific adverse effects. For example, skin rash and other skin disorders, adverse effects known to occur with icodextrin, were more frequently observed in the intervention group. Nausea, vomiting, and decreased appetite, reported adverse effects with intraperitoneal amino acids, were also more likely to occur in the intervention group. However, a surprising number of hypertensive crises and episodes of heart failure occurred in the intervention group. We found no association between these events and use of erythropoietin or increase in hemoglobin. Given that the intervention group received icodextrin as part of the glucose-sparing regimen, this result is even more surprising. Although the purpose of using icodextrin in this trial was to spare glucose exposure, it usually produces good ultrafiltration and is commonly used to maintain normal volume status when there is insufficient ultrafiltration with dextrose-based solutions. In addition, as a result of the continuous ultrafiltration with PD, compared with intermittent HD and perhaps other reasons, BP tends to be well controlled in patients receiving this modality, and episodes of malignant-range hypertension are uncommon. Again, a possible explanation is that in the pursuit of better metabolic values, investigators used lower concentrations of dextrose-based dialysis fluid, when more hypertonic dialysate was indicated to optimize ultrafiltration. If this were the case, the investigators may not have recognized the association between reduced ultrafiltration and these adverse events. It follows, then, that a preference for less hypertonic dialysate could have contributed to the improved metabolic results seen in the intervention group. If this were the case, it points out that fluid balance control should not be compromised in pursuit of better metabolic endpoints.

As with any regimen that strives to improve glycemic control, there may be an increased risk of hypoglycemic events. Four serious hypoglycemic events (in three patients) developed in the treatment group, compared with none in the control group.

The IMPENDIA and EDEN trials were multicenter, randomized, and controlled, and therefore free from the biases and limitations inherent in observational studies and small,

Table 2. Secondary outcomes (IMPENDIA and EDEN studies combined)

Endpoint[a]	Control Group (Dianeal Only)			Intervention Group (P-E-N or D-E-N)			Treatment Difference between Groups[b]	
	Baseline (n=127)	Month 3 (n=110)	Month 6 (n=120)	Baseline (n=124)	Month 3 (n=91)	Month 6 (n=107)	Control–Intervention (95% CI)	P Value
Metabolic control								
Total cholesterol (mmol/L)	5.1±1.5	5.2±1.6	5.1±1.6	5.2±1.4	4.8±1.3	4.8±1.3	0.3 (0.0 to 0.7)	0.07
LDL cholesterol (mmol/L)	2.8±1.1	2.9±1.3	2.9±1.3	3.0±1.2	2.7±1.1	2.8±1.1	0.1 (−0.2 to 0.4)	0.59
HDL cholesterol (mmol/L)	1.1±0.4	1.1±0.3	1.0±0.4	1.1±0.3	1.1±0.4	1.1±0.3	0.0 (−0.1 to 0.1)	0.30
VLDL cholesterol (mmol/L)	1.0 (0.2–12.6)	0.9 (0.3–6.0)	0.9 (0.1–7.7)	0.9 (0.3–6.8)	0.8 (0.2–2.7)	0.8 (0.2–3.3)	0.3 (0.1 to 0.5)	0.003
Serum TG (mmol/L)	2.1 (0.4–27.7)	2.1 (0.6–13.2)	2.2 (0.5–16.9)	1.9 (0.6–15.0)	1.8 (0.4–6.0)	1.7 (0.7–7.3)	0.7 (0.3 to 1.1)	0.002
Apolipoprotein A1 (mg/dl)	134±26	133±26	130±25	135±25	127±26	125±26	5.0 (−1.5 to 11.5)	0.13
Apolipoprotein B (mg/dl)	94±28	99±34	99±33	96±27	88±25	90±28	8.4 (0.8 to 15.9)	0.03
Lipoprotein(a) (mg/dl)	14 (2–125)	14 (2–150)	17 (2–171)	13 (2–102)	18 (2–113)	18 (2–140)	−1.9 (−8.2 to 4.4)	0.56
Proinsulin (pmol/L)	17 (3–1187)	17 (3–193)	15 (3–1475)	16 (3–240)	18 (3–752)	19 (3–285)	13.5 (−9.4 to 36.4)	0.25
Insulin (pg/ml)	485 (70–3674)	462 (137–3873)	471 (137–6190)	416 (87–7354)	462 (131–4592)	478 (137–8155)	−29.2 (−269 to 211)	0.81
C-peptide (pg/ml)	3745 (69–20058)	3756 (69–20743)	3725 (69–19581)	2744 (69–17287)	3635 (69–22325)	3903 (69–23126)	121 (−928 to 1171)	0.82
Glycemic control medications								
Daily insulin use (units)	20 (0–156)	22 (0–244)	25 (0–286)	24 (0–168)	22 (0–168)	24 (0–258)	4.7 (−5 to 14.4)	0.34
Severe hypoglycemia								
Number of events	0		0	0		4	NA	NA
Nutritional status[c]								
Serum albumin (g/L)	34.8±4.4	34.5±5.1	35.4±4.7	34.7±4.2	34.3±4.6	34.2±4.5	1.3 (0.1 to 2.5)	0.03
Total protein (g/L)	64.2±6.7	63.7±7.1	64.9±6.3	64.1±6.3	64.3±5.8	63.7±5.8	1.4 (−0.2 to 2.9)	0.09
Body mass index (kg/m^2)	26.6±4.8	26.5±4.8	26.7±4.8	26.7±4.2	26.7±4.5	26.7±4.5	0.3 (−0.8 to 1.5)	0.58
Drained body weight (kg)	70.6±15.4	70.3±15.0	70.8±15.2	70.8±13.6	71.1±14.7	70.9±14.9	0.7 (−3.0 to 4.3)	0.64
Quality of life								
EuroQOL-5D Health Status	63.6±25.5	60.8±25.6	61.2±26.5	61.5±26.7	59.8±26.9	61.4±27.6	0.02 (−6.79 to 6.83)	0.99
EuroQOL-5D Index	0.81±0.16	0.80±0.18	0.77±0.19	0.82±0.17	0.78±0.22	0.80±0.21	−0.02 (−0.07 to 0.03)	0.49
Abdominal fat composition[d]								
Visceral fat volume (ml)	234 (71–885)		197 (42–906)	227 (77–858)		150 (33–510)	55 (−7 to 118)	0.08
Subcutaneous fat volume (ml)	307 (107–693)		326 (115–664)	245 (99–828)		270 (85–664)	25 (−47 to 96)	0.50
LV mass and function[d]								
LV mass (g)	128±37		132±60	128±45		124±39	2.3 (−18.9 to 23.4)	0.83
Ejection fraction (%)	59±14		58±17	57±14		58±14	−0.2 (−5.3 to 7.7)	0.72

IMPENDIA, Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dianeal Only in DIAbetic continuous ambulatory peritoneal dialysis and automated peritoneal dialysis Patients; EDEN, Evaluation of Dianeal, Extraneal and Nutrineal versus Dianeal only in Diabetic CAPD Patients; D-E-N, Dianeal, Extraneal and Nutrineal; P-E-N, Physioneal, Extraneal, Nutrineal; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; TG, triglycerides; EuroQOL-5D, European Quality of Life 5 Dimensions; LV, left ventricular.

[a]Data are presented as mean ± SD or median (range).
[b]Difference between groups calculated using ANOVA with repeated measures and represents the comparison of change from baseline between groups.
[c]Subjective Global Assessment was also a secondary endpoint within the nutritional status category. Results are not shown in this table because of the ordered ordinal nature of the data. Using a proportional odds logistic regression model with a working independence correlation structure, no difference was observed between treatment groups for Subjective Global Assessment.
[d]Abdominal fat composition and left ventricular mass and function were measured at baseline and end of study in a subset of IMPENDIA patients (n=82).

Table 3. Adverse events and serious adverse events by treatment group (IMPENDIA and EDEN studies combined)

Variable	All Adverse Events, n (Related Adverse Events, n)[a]		Serious Adverse Events, n (Related Serious Adverse Events, n)[a]	
	Control Group (n=127)	Intervention Group (n=124)	Control Group (n=127)	Intervention Group (n=124)
Cardiovascular				
Ischemic heart disease	9 (1)	2	5	2
Edema/fluid overload	38 (7)	19 (3)	7 (2)	8 (1)
Hypertension	14 (1)	8	1 (1)	1
Hypotension/dehydration	8	8 (3)	3	1 (1)
Peripheral vascular	8	5	5	3
Hypertensive crisis/urgency/ encephalopathy	1	7	1	7
Heart failure	1	6	1	6
Cardiac arrest/sudden death	1	3	1	3
Other	5 (2)	5	0	0
Subtotal	85 (11)	63 (6)	24 (3)	31 (2)
Infectious				
Peritonitis	29	27	11	17
Respiratory	10	18	4	6
Abscess/cellulitis	4	10	3	8
Catheter site/exit site infection	6	7	0	0
Other	22	20	10	7
Subtotal	71 (0)	82 (0)	28 (0)	38 (0)
Gastrointestinal and hepatobiliary				
Pain and discomfort	13	26 (3)	3	4
Nausea, vomiting, or decreased appetite	14	20 (3)	0	0
Malnutrition	5	7	0	0
Other	11	11	0	2
Subtotal	43 (0)	64 (6)	3 (0)	6 (0)
Endocrine				
Hypoglycemia	4 (1)	15 (5)	0	4 (2)
Hyperglycemia	4 (1)	5 (2)	2 (1)	1
Hyperparathyroidism or increased PTH	5	1	0	0
Other	9 (1)	5	2	1
Subtotal	22 (3)	26 (7)	4 (1)	6 (2)
Neuromuscular/musculoskeletal				
Pain	12	12 (3)	2	1
Peripheral neuropathy	7	7	1	1
Cerebrovascular	4	1	4	1
Dizziness	3	2	1	0
Seizures	0	3	0	3
Headache	0	3 (1)	0	0
Other	7	8	1	2
Subtotal	33 (0)	36 (4)	9 (0)	8 (0)
Respiratory				
Cough	8	4	0	0
Other	5	6	0	1
Subtotal	13 (0)	10 (0)	0 (0)	1 (0)
Nonspecific skin rash and other skin disorders	6	12 (3)	0	2
Allergic/immune system disorders	0	5 (1)	0	2 (1)
Abnormal blood test results, not otherwise specified	19	20	2	1
Noninfectious catheter or exit site complications	10	10	2	3
Eye, ear, and throat disorders	12	9	1	2
Blood and lymphatic system disorders	8	9	2	2
Other	23	27 (7)	3	3

Table 3. Continued

Variable	All Adverse Events, n (Related Adverse Events, n)[a]		Serious Adverse Events, n (Related Serious Adverse Events, n)[a]	
	Control Group (n=127)	Intervention Group (n=124)	Control Group (n=127)	Intervention Group (n=124)
Total	345[b] (14)	373[b] (34)	78[c] (4)	105[c] (5)
Number of patients with any adverse event or serious adverse event (% of total group sample)	101[b] (80)	98[b] (79)	41[c] (32)	58[c] (47)

IMPENDIA, Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dianeal Only in DIAbetic continuous ambulatory peritoneal dialysis and automated peritoneal dialysis Patients; EDEN, Evaluation of Dianeal, Extraneal and Nutrineal versus Dianeal only in Diabetic CAPD Patients; PTH, parathyroid hormone.
[a]Relatedness was judged by the clinical trial site investigator. The numbers of related events are shown in brackets.
[b]$P=0.15$ for difference between groups in adverse event rate; $P=0.92$ for difference between groups in the number of patients with an adverse event.
[c]$P=0.06$ for difference between groups in serious adverse event rate; $P=0.02$ for difference between groups in number of patients with a serious adverse event.

Table 4. Deaths by treatment group (IMPENDIA and EDEN studies combined)

Cause of Death	Treatment Group	Days on Randomized PD Solutions before Death	Age (yr)	Sex	Country	Association with Study PD Solutions[a]
Cardiorespiratory arrest	D-E-N	165	70	Female	Colombia	No
Pneumonia	D-E-N	29	64	Male	Colombia	No
Hypertensive encephalopathy	D-E-N	98	38	Male	Colombia	No
Hypertensive encephalopathy	D-E-N	83	54	Female	Colombia	No
Sepsis/peritonitis	D-E-N	16	54	Female	Colombia	No
Coronary artery disease	P-E-N	126	84	Male	New Zealand	No
Cardiac arrest	P-E-N	147	58	Female	Hong Kong	No
Gastrointestinal bleeding	P-E-N	72	30	Male	Russia	No
Acute heart failure	P-E-N	72	43	Male	Russia	No
Acute heart failure	P-E-N	33	43	Male	Russia	No
Bacterial peritonitis[b]	P-E-N	179	50	Female	Russia	No
Intracerebral hemorrhage	Dianeal only	75	61	Female	New Zealand	No
Multisystem organ failure	Dianeal only	46	55	Male	Russia	No
Sudden death	Dianeal only	42	54	Male	Colombia	No
Cerebrovascular accident[c]	Dianeal only	173	74	Female	Canada	No
Acute heart failure[d]	Dianeal only	200	76	Male	Russia	No

IMPENDIA, Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dianeal Only in DIAbetic continuous ambulatory peritoneal dialysis and automated peritoneal dialysis Patients; EDEN, Evaluation of Dianeal, Extraneal and Nutrineal versus Dianeal only in Diabetic CAPD Patients; D-E-N, Dianeal, Extraneal and Nutrineal; P-E-N, Physioneal, Extraneal, Nutrineal.
[a]Relatedness to the study PD solutions was judged by the clinical trial site investigator.
[b]Patient died 30 days after completing all clinical trial visits.
[c]Patient died 12 days after completing all clinical trial visits.
[d]Patient died 12 days after completing all clinical trial visits.

single-centered randomized trials. However, the statistical blending together of two different treatment regimens into a single analysis presents challenges. Given that the two solutions have the same glucose concentration, it was decided before the inception of the EDEN trial that the results of the two trials could be combined. In this way, the patient numbers afforded sufficient statistical power to detect a clinically meaningful difference in the primary outcome measure of HbA_{1c}. HbA_{1c} is an unvalidated surrogate outcome measure, such that the improvement in HbA_{1c} demonstrated in this study may not necessarily translate into improved clinical outcomes. Another limitation of the trial was the lack of collection of data on peritoneal ultrafiltration and peritoneal glucose exposure, which made it difficult to assess the effect of glucose-sparing regimens on overall fluid management in PD patients. Likewise, methods to accurately measure residual kidney function or volume overload were not used, thus limiting the assessment of adverse events associated with hypertension or heart failure. The trial was open label which also potentially introduced observer and performance biases. The assessment by investigators of related adverse events was subjective and open to potential bias. There was also a significant difference in withdrawal of patients from the intervention and control groups before study completion (19% versus 6%), raising the possibility of informative censoring bias.

In conclusion, in diabetic PD patients, a glucose-sparing prescription improves metabolic control, as evidenced by reductions in HbA_{1c}, serum VLDL cholesterol, serum triglycerides, and apolipoprotein B. This benefit was counterbalanced

by a significant reduction in serum albumin and increases in related adverse events. The numbers of serious adverse events and deaths were also higher in the group given glucose-sparing solutions. Use of glucose-sparing regimens in PD patients should be accompanied by close monitoring of fluid volume status.

CONCISE METHODS

Trial Design
The low glucose clinical study program consisted of the IMPENDIA (Improved Metabolic control of Physioneal, Extraneal, and Nutrineal [P-E-N] *versus* Dianeal-only treatment in DIAbetic peritoneal dialysis patients) and EDEN (Evaluation of Dianeal, Extraneal, and Nutrineal [D-E-N] in diabetic PD patients) clinical trials. IMPENDIA was a phase III protocol in Canada, Australia, and New Zealand (Clinicaltrials.gov registration NCT00567398) and a phase IV protocol in Europe and Asia (NCT00567489). The EDEN trial was a phase III protocol performed in Colombia (NCT01219959). The EDEN trial was added as a result of insufficient enrollment into the IMPENDIA study. However, because of the unavailability of the Physioneal solution in Colombia, Dianeal was used instead. The phase III nature of the trials in Canada, Australia, New Zealand, and Colombia was due to country-specific regulatory requirements for the use of Nutrineal. Both IMPENDIA and EDEN were randomized, controlled, open-label, parallel-group, multicenter trials that compared the effects of a P-E-N or D-E-N PD regimen to a Dianeal-only regimen in diabetic CAPD and APD patients during a 6-month study period.

Patients were randomly assigned to the intervention group (P-E-N or D-E-N) or the control group (Dianeal only) using a centralized randomization scheme implemented locally using a web-based automated randomization system. Patients were assigned the next available patient number at the time of randomization. A 1:1 stratified randomization scheme was carried out in which randomization was stratified by informed consent status (*i.e.*, informed consent to participate in the MRI subgroup evaluation, yes or no). Blocks of size 4 were used, so that in each block two patients were randomly assigned to the intervention group and two to the control group.

The primary efficacy endpoint of the glucose-sparing clinical trial program was change in HbA$_{1c}$ from baseline to 6 months. Secondary efficacy endpoints included the following:

- Change from baseline value in metabolic control measures, including total cholesterol, LDL cholesterol, HDL cholesterol, VLDL, serum triglycerides, lipoprotein(a), apolipoprotein A1, apolipoprotein B, pro-insulin, insulin and C-peptide.

- Change in glycemic control medication use, as defined by change in medication dose and use.

- Change in the number of severe hypoglycemic events requiring medical intervention.

- Change from baseline value in nutritional status, as measured by the Subjective Global Assessment test, total protein, serum albumin, body mass index, and drained body weight.

- Quality of life as measured by the Diabetes Symptom Checklist and the European Quality of Life 5 Dimensions (EuroQol-5D) score.

- Change in composition and distribution of abdominal fat and in left ventricular structure and function, as measured by abdominal and cardiac MRI, respectively. This secondary endpoint was assessed only in a prespecified subgroup of IMPENDIA study participants.

Primary and secondary outcome measures were assessed at screening and baseline visits, a 3-month visit (for most patients), and an end-of-study visit 6 months after the start of study solutions. HbA$_{1c}$ and other biochemical secondary endpoint measures were collected with patients fasting (*nil per os* and no dwelling PD solution) for 10 hours and were measured at a central laboratory (Baxter's Clinical Laboratory Services, Round Lake, IL) using validated techniques. For the HbA$_{1c}$ measurement, a Tina-quant immunologic assay (Roche Diagnostic) suitable for samples from dialysis patients, including patients with icodextrin metabolites, was used.

The sample size for the glucose-sparing clinical study program was based on the goal to detect a 10% difference in the mean change from the baseline value of HbA$_{1c}$ between patients randomly assigned to the intervention and control groups. To calculate the sample size required to detect this 10% difference, the following assumptions were made: (*1*) the mean HbA$_{1c}$ would be between 7.1% and 7.9%, with an SD of 2.0, and a correlation between the baseline value and 6-month HbA$_{1c}$ of 0.50 (unpublished data from Baxter Novum, Sweden); (*2*) the control group would have a mean HbA$_{1c}$ at baseline of 7.5%, with no change anticipated during the 6 months of follow-up; (*3*) the intervention group would have a mean HbA$_{1c}$ of 7.5% at the baseline measurement and a 10% reduction (*i.e.*, an average absolute decline of 0.75 in HbA$_{1c}$) in the average HbA$_{1c}$ during the 6 months of follow-up. On the basis of a two-group repeated-measures ANOVA F-test carried out at the 5% level of significance, a sample of 100 evaluable patients per group would provide 90% power to detect a 10%, in aggregate, average difference in the mean change from baseline value for HbA$_{1c}$. It was anticipated that an annual dropout rate of approximately 30% would occur during the study. Therefore, to achieve a target of 100 evaluable patients per group, randomization of 118 patients per group would be necessary, for a desired total sample of 236 patients.

The eligible study population included patients with incident and prevalent type 1 and type 2 diabetes, aged 18 years or older, who had been receiving CAPD or APD for at least 30 days. Patients using only Dianeal and/or Physioneal solutions were included. To prevent volume depletion upon randomization to the intervention group that included icodextrin, eligible patients were also required to have at least one exchange per day of 2.5% or 4.25% dextrose (2.27% or 3.86% glucose) during screening with no prescribed dry (dialysate-free) time. Eligibility criteria also included an HbA$_{1c}$ level >6.0% but ≤12.0%, a blood hemoglobin concentration of ≥8.0 g/dl but ≤13.0 g/dl, and a total Kt/V urea ≥1.7. Patients entering into the study were expected to continue PD for at least 6 months, the duration of the study period. A full list of exclusion criteria, as well as other details on the study methods, is available in the Supplemental Material.

Patients randomly assigned to the intervention received a 24-hour combination of Physioneal (one to three exchanges daily for CAPD patients, up to 16L for APD patients), Nutrineal (1 exchange daily), and Extraneal (the long dwell exchange once daily). In the EDEN trial, patients assigned to the intervention group received Dianeal instead of Physioneal. Both Dianeal and Physioneal have similar glucose concentrations, thereby assuring that the glucose-sparing hypotheses was tested in a similar manner for IMPENDIA and EDEN patients. Patients randomly assigned to the control group continued on Dianeal for all exchanges in a 24-hour period, with three to five daily exchanges permitted for CAPD patients and up to 20 L daily for APD patients. Dry periods were not allowed in the 24-hour prescriptions of either group. PD prescriptions in both treatment groups were tailored to reach a minimum target total Kt/V urea of 1.7 throughout the study as per local standards of care.

The IMPENDIA trial commenced enrollment of eligible CAPD patients in February 2008. To address lower than anticipated recruitment, the study protocol was amended in November 2008 (see Supplemental Material for details) and the EDEN trial initiated with commencement of patient enrollment in October 2010. Enrollment was complete in January 2011 for both the IMPENDIA and EDEN trials, and the last patient finished all study-related procedures in July 2011. The IMPENDIA trial was conducted at 37 sites in Russia (7), Hong Kong (4), Korea (6), Australia (8), New Zealand (2), Canada (4), Taiwan (2), Singapore (2), France (1), and Portugal (1). The EDEN trial was conducted at 16 sites in Colombia.

All patients were required to provide informed consent after the nature of the study had been explained but before the initiation of any trial-related activities. Ethics approval for the IMPENDIA and EDEN trials was obtained from the local research ethics boards in all participating centers prior to study initiation and patient enrollment. The studies were conducted in accordance with the Declaration of Helsinki and applicable International Conference on Harmonization guidelines, and all study coordinators and investigators followed international good clinical practice guidelines.

Statistical Analyses

Before completion of either clinical trial or database lock, the statistical plan was developed to combine both clinical trials in order to achieve the desired sample size for the primary endpoint.

Two populations were identified for the primary endpoint efficacy analysis: (*1*) the ITT population included all patients who were randomly assigned and for whom, at a minimum, the baseline value of HbA_{1c} measured at screening was determined and one PD exchange using a study solution was performed, and (*2*) the per-protocol patient population, which included all ITT patients who completed the study and had, at a minimum, their 6-month HbA_{1c} value measured. A safety ITT analysis was also performed that included all patients who were randomly assigned regardless of subsequent measurement of HbA_{1c} or exposure to study solutions.

The primary efficacy analysis was carried out for both the ITT and per-protocol patient populations. A repeated-measures ANOVA compared the HbA_{1c} mean change from the baseline profile between the two groups using a generalized estimating equations approach. No confounding baseline variables were found, so no additional covariates

were added to the model. Mean change from baseline value at mid-study and 6 months was summarized for each treatment group, and comparisons between the two groups were based on the repeated-measures ANOVA model. To safeguard against model misspecification with respect to assumptions about the SD and common correlation (compound symmetry) over time, all analyses (*e.g.*, CIs, tests of hypotheses) were done using robust SEM estimates. A P value <0.05 for the treatment effect or the treatment-by-time interaction was evidence that the treatment groups were different.

For the secondary efficacy endpoints, a repeated-measures ANOVA was also carried out that is consistent with the generalized linear model and link function appropriate to the particular endpoint analyzed. In each case, the repeated-measures ANOVA incorporated time (corresponding to those visits when the endpoint of interest was measured), treatment group (Dianeal only versus P-E-N/D-E-N), and their interaction (time-by-treatment group) as the primary independent class variables.

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DISCLOSURES

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