Influence of low-glucose peritoneal dialysis on serum lipids and apolipoproteins in the IMPENDIA/EDEN trials

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BACKGROUND: Glucose, the conventional osmotic agent in peritoneal dialysis (PD) solutions, may contribute to atherogenic dyslipoproteinemia and increased cardiovascular risk.

OBJECTIVE: To determine whether a low-glucose PD regimen may improve the serum lipid and lipoprotein profile in patients with diabetes.

METHODS: A prospective, open-label, parallel group, multinational, randomized, controlled trial with a 6-month follow-up, comprising 251 patients with diabetes receiving PD. Patients were randomized to a low-glucose PD regimen (dextrose-based PD solution plus icodextrin, a starch polymer, and amino acids) or a conventional PD regimen (dextrose PD solutions). Serum lipid and apolipoprotein profiles were determined at baseline and 3 and 6 months.

RESULTS: Serum triglycerides, very low-density-lipoprotein cholesterol, and apolipoprotein B (apoB) decreased significantly in the intervention group at both 3 and 6 months compared with baseline (serum triglycerides: median change at 3 months −2.0 mmol/L, \( P < .001 \), at 6 months −0.3 mmol/L, \( P < .001 \); very low-density-lipoprotein cholesterol: −0.3 mg/dL, \( P < .001 \); −0.3 mg/dL, \( P < .001 \); and apoB: −8.5 mg/dL, \( P < .001 \); −3.6 mg/dL, \( P = .043 \), respectively) and also compared with the control group. In contrast, apoB levels increased significantly in the control group at 3 and 6 months compared with baseline (5.3 mg/dL, \( P = .041 \); 5.2 mg/dL, \( P = .007 \), respectively). Percentage of patients on lipid-lowering medications at baseline and intensity of therapy was equivalent in each group. The apoB decrease was not affected by lipid-lowering medications in the intervention group.

CONCLUSION: A low glucose-PD regimen significantly improved the atherogenic lipoprotein phenotype compared with PD patients treated with a conventional glucose regimen.

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Patients on peritoneal dialysis (PD), particularly those with diabetes,¹ may have a greater risk of myocardial infarction² and atherosclerotic death³ than those on hemodialysis (HD). In both PD and HD patients, hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C) are common. However, apolipoprotein B (apoB) levels are higher in PD than in HD patients and characteristically apoB is disproportionately elevated compared with low-density lipoprotein cholesterol (LDL-C), pointing to

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increased numbers of smaller, cholesterol-depleted LDL particles. This raises the possibility that this atherogenic dyslipoproteinemia might be responsible, at least in part, for the increased coronary artery event rate in PD compared with HD patients.

Glucose, used as an osmotic agent in PD, may contribute to the pathogenesis of this atherogenic dyslipoproteinemia. Depending on the glucose concentration and the membrane transport status, PD patients can absorb up to 200 g of glucose from the dialysis fluid per day. The increased glucose load can increase hepatic fatty acid synthesis and consequently increase hepatic triglyceride (TG) synthesis and secretion resulting in increased very LDL (VLDL) and LDL particle numbers. Because each VLDL and LDL particle contains 1 molecule of apoB, plasma apoB levels increase in parallel.

Accordingly, limiting the amount of glucose in the PD prescription might improve the atherogenic lipoprotein profile in PD patients, as suggested by previous work. IMPENDIA (Improved Metabolic control of Physioneal, Extraneal, and Nutrineal [P-E-N] vs Dianeal-only treatment in DIAbetic PD patients) and EDEN (Evaluation of Dianeal, Extraneal, and Nutrineal [D-E-N] in diabetic PD patients) were trials primarily designed to determine if low-glucose dialysate (icodextrin, a starch polymer, plus amino acids substituted for dextrose-based PD solutions for part of the PD prescription) improved metabolic status in diabetic patients treated with PD. Diabetic control, as estimated by HbA1c, was the primary end point. These results have been reported and demonstrated significant improvement. This analysis details the effect of low-glucose PD on plasma lipid, lipoprotein, and apolipoprotein levels.

Methods

The study design, methodology, and initial results of the IMPENDIA and EDEN randomized, controlled trials have been described previously. IMPENDIA (Clinicaltrials.gov registration NCT00567398 Canada, Australia, and New Zealand; NCT00567489 in Europe and Asia) is a prospective, open-label, parallel group, multinational randomized, controlled trial, which determines whether a glucose-sparing PD prescription would improve metabolic control in diabetic PD patients compared with a glucose-only prescription that was substituted for the pH-neutral Physioneal because of the unavailability of Physioneal solutions in Colombia. Because Dianeal and Physioneal have identical glucose concentrations, the results of IMPENDIA and EDEN were combined based on an a priori analytical plan. Study protocols were approved by ethics committees at participating centers. All patients provided written informed consent before participation.

Subjects were randomized to intervention (low-glucose PD) or control (high-glucose PD) using a centralized randomization scheme. The eligible study population included incident and prevalent patients with type 1 and type 2 diabetes, aged ≥18 years performing continuous ambulatory PD or automated PD for ≥30 days. Eligibility criteria included HbA1c level >6.0% and ≤12.0%, blood hemoglobin concentration of ≥8.0 g/dL and ≤13.0 g/dL, and total Kt/Vurea ≥1.7. Kt/Vurea is an arithmetic formula expressing total urea clearance (K) per minutes per week (t) adjusted to the patient’s urea volume of distribution (Vurea). A value of >1.7 is considered adequate dialysis by international standards. Patients entering the study were expected to remain on PD for the study duration period (at least 6 months). A full list of exclusion criteria and study methodology detail is available online in the primary publication supplemental file.

Lipids and apolipoproteins were assayed in serum samples drawn at screening, baseline, 3-month (for the majority of subjects), and 6-month end-of-study visits. Total cholesterol (TC), LDL-C, HDL-C, and serum TG were measured directly in serum. Very LDL cholesterol (VLDL-C) was calculated as TC – LDL-C and HDL-C. Apolipoproteins measured were: apolipoprotein (a) (Lp(a)), apolipoprotein A1 (apoA1), and apoB.

Patients fasted and had no dwelling PD solution for 10 hours before blood samples were collected. Samples were assayed at a central laboratory (Baxter’s Clinical Laboratory Services, Round Lake, IL, USA) using validated techniques. TC was determined using Trinder’s colorimetric absorption spectrophotometry after enzymatic digestion and oxidation. LDL-C and HDL-C levels were directly measured in a similar fashion using a 2-reagent elimination/catalase technique (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). TG levels were measured by colorimetric absorption after a 3-step enzymatic reaction.

ApoA1 and apoB were measured by immunonephelometry on a Siemens BN-ProSpec analyzer (Siemens Healthcare Diagnostics). Lp(a) was measured using polystyrene particle-enhanced immunonephelometry and N-Latex-Lp(a) Reagent. Medications were administered as determined by the treating physician. This included both hypoglycemic and hypolipidemic medications. Information regarding prescription of any lipid-lowering medications, including statins, fibrates, bile sequestration agents, and/or ezetimibe, was specifically requested from patients at baseline and the 3- and 6-month visits. Changes in these medications in relation to changes in lipid and apolipoprotein levels were identified and evaluated. Changes in insulin or other hypoglycemic agents during the trial were also determined.

Statistical methods

The statistical plan, which was developed before completion of either clinical trial or database lock, combined both trials (IMPENDIA/EDEN) to achieve the desired sample
size for the primary end point (ΔHbA₁c). A repeated measures analysis of variance (RM-ANOVA) was performed in the analysis to examine change in lipids/lipoproteins. RM-ANOVA incorporated time (corresponding to visits when the endpoint of interest was measured), treatment group (Dianeal only vs P-E-N/D-E-N), and their interaction (time × treatment group) as primary independent class variables.

The relationship between treatment groups and quartiles of change in apoB from baseline was also analyzed. All data were expressed as mean ± standard deviation with exception of TGs. Given the nonparametric distribution of TGs, values were expressed as median with range.

Results

In total, 251 patients were randomized to either intervention (n = 124) or control groups (n = 127). The baseline characteristics of enrolled randomized patients are shown in Table 1. Time on dialysis was similar between groups at 1.7 ± 2.0 years in the control group and 1.5 ± 1.8 years in the intervention group. Baseline values of all lipids, lipoprotein lipids, and apolipoproteins are shown in Table 2. Baseline levels of VLDL-C and lipoprotein levels were not obtained in a few patients from both control and intervention arms. Lipid and apoB measurements were performed in 110 control and 91 intervention patients at 3 months, and 120 control and 106 intervention patients at 6 months. One patient in the intervention arm had lipid level measurements without accompanying lipoprotein level measurements. No significant differences were demonstrated between groups at baseline, indicating balanced randomization.

Changes in lipids and apolipoproteins during the study period are shown in Table 3. In the control group, there were no statistically significant decreases in any measurements during the study period. On the other hand, significant increases from baseline in apoB levels were observed in the control group at both 3 and 6 months (5.3 ± 24.2 mg/dL, P = .041; 5.2 ± 25.4 mg/dL, P = .007, respectively). In the low-glucose group, there were significant decreases from baseline at both 3- and 6-month follow-up assessments in TG (median change −0.5 mmol/L [range: 12–2.7], P < .001; −0.3 mmol/L [range: 13–3.8], P < .001); VLDL-C (−0.3 mg/dL ± 0.8, P = .001; −0.3 mg/dL ± 0.9, P < .001), and apoB (−8.5 mg/dL ± 18.4, P < .001; −3.6 mg/dL ± 23.9, P = .043). In the low-glucose group, TG, VLDL-C, and apoB were significantly lower compared with values observed in the control group at both 3 and 6 months (Table 3).

There were no significant changes in LDL-C, HDL-C, apoA1, or Lp(a) in either the intervention or control groups. Mean differences ± 95% confidence interval (CI) in change in all lipids and apolipoproteins from baseline to both 3 months and the end of the study between the treatment groups were calculated. This difference was significant, favoring the low-glucose PD regimen, at both 3- and (as shown in Fig. 1) 6-month intervals (Δ TG: 0.8 mmol/L [95% CI: 0.4–0.3], P < .001; 0.7 mmol/L [95% CI: 0.3–1.1], P = .002; Δ VLDL-C: 0.4 mg/dL [95% CI: 0.2–0.6], P < .001; 0.3 mg/dL [95% CI: 0.1–0.5], P = .003; Δ apoB: 11.4 mg/dL [95% CI: 3.6–19.2], P = .004; 8.4 mg/dL [95% CI: 0.8–15.9], P = .030). We next examined whether differences in lipid-lowering medications could have accounted for these findings. Statins accounted for approximately 80% of the total lipid-lowering medications used. There were no significant differences in administration of statins (Fig. 2) or other lipid-lowering medications (data not shown, but mirrors changes for statins in Fig. 2) during the course of the study between the 2 groups. In the control group, 39.4%, and in the intervention group, 36.3% of patients were not on lipid-lowering medications at any

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<tr>
<td></td>
<td>(Dextrose)</td>
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<td>Time on dialysis, years</td>
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BMI, body mass index; D-E-N, Dianeal, Extraneal, and Nutrineal; P-E-N, Physioneal, Extraneal, and Nutrineal.

*Mean and standard deviation are shown for continuous variables.
time during the study. In addition, of those taking lipid-lowering medications, 40.2% and 35.5% of control and intervention patients, respectively, had no change in dose during the study. Therefore lipid-lowering medications were unlikely contributors to changes in lipid parameters. An increase in lipid-lowering medications during the course of study was recorded in 10.2% of control patients and 6.5% of intervention patients; conversely, a decrease in lipid-lowering medications was seen in 10.2% of control and 21.8% of intervention patients.

Further analyses were performed, restricted to patients who either were not receiving any lipid-lowering medications during the study period or whose lipid-lowering medication dose remained unchanged throughout the study (79.6% and 71.8% of control and intervention patients, respectively). ApoB either increased or changed minimally in the control group (Fig. 3). In contrast, decreases in apoB levels, similar in magnitude to those observed in the overall group, occurred in the subset of patients in the intervention group who were not receiving any lipid-lowering medications or whose dose of lipid-lowering medications did not change. The magnitude of change from baseline quartile of apoB was examined (Fig. 4). In the intervention group, the greatest apoB reductions occurred in patients in the highest baseline quartile of apoB in which mean apoB levels were reduced by 21.1 mg/dL at 6 months vs baseline. In contrast, apoB levels increased in most patients in the control group during the study period, with the largest changes occurring in those within the third baseline quartile of apoB. Negligible changes were observed in the highest baseline quartile of the control group.

Over the course of the trial, the HbA1c was 0.5% (95% CI: 0.1-0.8; \( P = .006 \) lower in the intervention compared with the control group. This decrease could not be explained...
by a difference in the administration of insulin or hypoglycemic agents between the 2 groups.

Discussion

This study compares plasma-lipid and apolipoprotein profiles in diabetic PD patients treated with glucose-sparing dialysate with those receiving conventional glucose-based dialysate. Plasma TG, VLDL-C, and plasma apoB all decreased significantly in the glucose-sparing arm. By contrast, there were no significant differences in the other lipoprotein markers—TC, LDL-C, HDL-C, Lp(a), and apoA1—in either group during the course of study.

We examined in detail whether the differences observed could be due to differences in the use of lipid-lowering medication therapy between the 2 groups. There was no evidence that this was the case. The pattern of use, doses, and changes in doses of lipid-lowering medications were similar in both groups. Moreover, the same pattern and extent of change in lipoprotein indices were evident in patients not taking lipid-lowering medications or in whom no change in dose occurred during the course of study. Additionally, the observation that apoB levels in the highest baseline apoB quartile of the control group changed minimally suggests that substantial decreases seen in the intervention group in response to glucose-sparing dialysate did not simply reflect regression to the mean. Accordingly, it seems reasonable to conclude that the changes documented were the consequences of the low-glucose PD regimen.

The pattern of change seen here is likely related to the reduced mass of glucose absorbed from the dialysate and delivered to the liver. That the HbA1c was significantly lower without significant difference between the groups in terms of insulin or hypoglycemic agents is evidence in favor of this conclusion. Dialysate glucose, which is designed to be an osmole for ultrafiltration (fluid removal), unfortunately is itself absorbed across the peritoneal cavity and so constitutes a metabolic load. The extent of this load depends on the overall amount of glucose administered and the membrane transport capacity for glucose. Glucose absorbed and delivered to the liver stimulates hepatic fatty acid synthesis and therefore triglyceride synthesis and secretion. Increased VLDL apoB secretion and LDL apoB production therefore ensues. In addition, excess glucose loading can provoke insulin resistance, which can also contribute to increased hepatic lipid synthesis and VLDL secretion. Hypertriglyceridemia also stoichiometrically accelerates cholesterol ester transfer protein-mediated exchange of the 2 core lipids—cholesterol ester and TG—between LDL and VLDL particles. This creates greater numbers of LDL particles that are relatively TG-enriched and cholesterol ester-depleted. TG in these particles is hydrolyzed by hepatic lipase producing the smaller, denser, cholesterol-depleted particles characteristic of hypertriglyceridemia.

The combination of increased plasma TG, VLDL-C, and apoB, but unchanged LDL-C in the PD patients is consistent with the metabolic consequences of increased glucose delivery to the liver. It follows that reduction of glucose delivery in PD might improve these abnormalities. Specifically, reduced VLDL secretion would lead to lower TG, VLDL-C, and apoB. Lower TG will reduce cholesterol ester transfer protein-mediated core lipid exchange and, therefore, the cholesterol mass per LDL particle will not be reduced. Accordingly, the observation that LDL-C did not change although apoB decreased is exactly what would be predicted to happen. An alternative and perhaps complementary explanation for the decrease in apoB is that the increased amino acid content of dialysate in the low-glucose PD regimen may itself be beneficial, because in vitro studies have demonstrated that increased delivery of amino acids can reduce apoB secretion by HepG2 cells.

Whether apoB is a better marker of cardiovascular risk than cholesterol indices has been controversial. However, a series of recent studies based on discordance analysis have consistently shown that apoB and LDL particle number are more closely associated with cardiovascular risk than LDL-C and non-HDL-C. Moreover, there is no dispute that higher levels of apoB are associated with greater...
cardiovascular risk and lower levels associated with less. Therefore, the reductions in apoB documented in this study reflect metabolic improvement. Of interest, the average apoB of 93–95 mg/dL in PD patients before glucose-sparing dialysis therapy corresponds to the 55th percentile of the American population, a level that is well above a target level of 80 mg/dL for apoB as identified by the recent Canadian and European Guidelines. Based on our meta-analysis of the prospective association of apoB with cardiovascular risk, a reduction of 8.4 mg/dL in apoB in the general population would result in an 8.1% reduction in cardiovascular events. The greatest decreases in apoB, approximately 20 mg/dL from baseline, which were observed in the group with the highest baseline levels, would be predicted to reduce cardiovascular events by approximately 19%. Obviously, predictions based on a general population cannot be extrapolated to a particular group such as PD patients. However, a directionally beneficial change in levels of apoB, particularly observed in diabetics, the subgroup in whom an excess cardiovascular risk with PD has been identified, is a promising finding.

A limitation of our study was that total daily-prescribed glucose was not monitored. Systemic underprescribing of glucose-based PD solutions in the intervention arm or overprescribing in the control arm could have occurred. Irrespective of this possibility, demonstration of the principle that attenuating the glucose content of the PD prescription has salutary effects on the lipid profile is shown. As well, because of local licensing issues, the control dialysates were not the same in the IMPENDIA and EDEN arms. However, the glucose concentrations were identical in both these studies, and both data sets exhibited the same trends with the same extent of change in all parameters.

In summary, a glucose-sparing dialysis regimen resulted in a less atherogenic lipoprotein profile as evidenced by decreases in plasma TG, VLDL-C, and apoB, a result that is consistent with the known adverse effects of glucose on apoB lipoprotein metabolism. This randomized controlled study demonstrates that the composition of fluid instilled in the peritoneal cavity can have significant effects on metabolic indices. This finding may have important implications for minimizing cardiovascular risk in PD patients.

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Figure 3 Change in apolipoprotein B in patients (A) not prescribed lipid-lowering medications (P = .023 at 3 months and P = .010 at 6 months) or (B) without a change in dose of lipid-lowering medication (P = .25 at 3 months and P = .24 at 6 months) during the course of the study. apoB, apolipoprotein (B); black bars, low glucose; white bars, control.

Figure 4 Mean change in apolipoprotein B at 3 months and 6 months according to the baseline quartile. Shading shows quartiles of apoB range. apoB, apolipoprotein (B); white, Q1 and Q2 (39–<89 mg/dL); gray, Q3 (89–<110 mg/dL); black, Q4 (110–182 mg/dL).
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