EFFECTS OF PERITONEAL DIALYSIS WITH AN OVERNIGHT ICODEXTRIN DWELL ON PARAMETERS OF GLUCOSE AND LIPID METABOLISM

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Objective: To examine whether a reduced daily glucose load by overnight application of the less-absorbed glucose polymer icodextrin would have favorable effects on lipid profiles of continuous ambulatory peritoneal dialysis (CAPD) patients.

Study Design: Randomized crossover study with two subsequent periods of 6 weeks.

Setting: Home PD unit of a secondary-care hospital.

Patients: Twenty-one nondiabetic CAPD patients (15 male, 6 female; mean age 50.3 ± 11.8 years).

Intervention: Participants were randomly assigned to receive an overnight dwell with either standard glucose solution or with a 7.5% icodextrin-containing solution.

Main Outcome Measures: Relation between reduction in the total amount of intraperitoneal infused glucose and parameters of glucose (plasma glucose, insulin, and HbA1C) and lipid metabolism [free fatty acids, plasma lipids, lipoproteins, and low density lipoprotein (LDL) subfraction profile].

Results: After the icodextrin dwells, a reduction of plasma total cholesterol (from 5.43 ± 0.85 to 4.86 ± 0.70 mmol/L, p < 0.001) and LDL cholesterol (from 3.38 ± 0.87 to 2.93 ± 0.73 mmol/L, p = 0.001) was observed. Also, high density lipoprotein (HDL) cholesterol (from 0.95 ± 0.27 to 0.90 ± 0.24 mmol/L, p = 0.029) was reduced, but the plasma total cholesterol-to-HDL ratio remained similar. Plasma free fatty acids and triglyceride levels tended to decrease (from 0.16 ± 0.10 to 0.13 ± 0.08 mmol/L, p = 0.06, and from 2.14 ± 1.96 to 1.92 ± 1.03 mmol/L, respectively). Evaluation of LDL subfraction profiles after ultracentrifugation showed a more buoyant LDL subfraction profile with fewer dense LDL particles in 6 patients and no changes in 14 patients after icodextrin. The effects on lipids were not accompanied by a decrease in fasting plasma glucose (from 5.76 ± 1.29 to 5.86 ± 0.80 mmol/L) or insulin levels (from 19.5 ± 14.4 to 20.3 ± 13.0 mU/L).

Conclusion: These results suggest a beneficial effect on lipid profiles of CAPD patients with the use of an overnight dwell with icodextrin.

KEY WORDS: Atherogenic lipoprotein profile; icodextrin; glucose; lipoproteins; metabolism.

Continuous ambulatory peritoneal dialysis (CAPD) has become established as an alternative to hemodialysis in a growing portion of the dialysis population (1). Based on recent prospective studies, it is reasonable to conclude that hemodialysis and CAPD have an equal technique survival (1). A recent study reported a 5-year survival of 50% – 70% for CAPD, irrespective of the underlying disease (2). Since the majority of dialysis patients die from cardiovascular complications (3–5), risk factors for these events may become increasingly important as the possibility of longer survival on renal replacement therapy increases. Among the different cardiovascular risk factors, lipid abnormalities dominate the high mortality in CAPD patients (1,6). Prospective studies have shown that even small changes in lipid concentrations, persisting over a longer time, affect the incidence of cardiovascular events in the general population (7).

In general, abnormalities in lipid metabolism are common in uremic patients, on dialysis or not (6,8,9). Also, an accelerated general atherosclerosis in end-stage renal disease is frequently observed (9,10). Furthermore, progressive renal vascular insufficiency due to lipid abnormalities may aggravate renal dysfunction (9). The exact mechanism of uremic dyslipidemia has not been fully elucidated, but it seems to be caused by a decreased catabolism of apoprotein-B–containing lipoproteins, due to decreased activity of lipolytic enzymes and altered lipoprotein composition (10). Additionally, the excessive peritoneal glucose absorption from highly concentrated glucose-containing CAPD solutions may enhance metabolic disturbances, revealing an impaired glucose tolerance and hyperinsulinemia (11,12). Hyperinsulinemia itself has been directly...
associated with increased cardiovascular disease (13). Furthermore, CAPD-induced hyperinsulinemia is associated with a suppressed efflux of free fatty acids from adipocytes and higher adiposity. Gain of abdominal fat results in a higher overall plasma concentration of free (nonesterified) fatty acids, which is associated with increased hepatic production of triglyceride-containing, very low density lipoproteins (VLDL) (14). These VLDL particles are easily metabolized into low density lipoproteins (LDL). Recent studies show a relation between elevated triglyceride levels and a more atherogenic lipoprotein profile, consisting of a decreased high density lipoprotein (HDL) cholesterol level (15,16) and a LDL cholesterol with predominantly unfavorable dense particles more prone to oxidative modification (17). Modified LDL and a decreased HDL level are determinants of increased cardiovascular mortality (18). On the other hand, reduction of the triglyceride level increases HDL cholesterol levels and decreases the amount of small dense LDL particles (19). Therefore, a reduction in peritoneal glucose uptake may improve the atherogenic lipid profile by a reduction of hepatic triglyceride production.

Complications due to the nonphysiological composition of dialysis solutions, such as failure in ultrafiltration and the occurrence of peritoneal fibrosis syndrome, have led to the introduction of alternative CAPD solutions. Among these newer solutions, the starch-based glucose polymer icodextrin was found to increase ultrafiltration compared to glucose solutions (20). Furthermore, a low peritoneal absorption of icodextrin, which is catabolized into maltose, considerably reduces caloric uptake. Therefore, icodextrin may have an additional favorable effect on the lipid profile by reducing hyperinsulinemia.

So far, no data about the consequences for lipid metabolism related to a reduced peritoneal glucose uptake in CAPD patients are available. However, a post hoc evaluation after the Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis (MIDAS) study on lipids after icodextrin, showed a reduction of cholesterol, triglycerides, and LDL cholesterol of 6% – 10% over 6 months (20). To further elucidate the possible favorable effects of icodextrin on defined cardiovascular risk factors, we performed a prospective randomized crossover study comparing the effects on parameters of both glucose and lipid metabolism in CAPD patients receiving either standard CAPD or CAPD with an overnight icodextrin dwell.

**PATIENTS AND METHODS**

**PATIENTS**

For this study, 22 patients, established on CAPD for at least 3 months and using standard 3 – 4 exchanges per 24 hours, were recruited from the nephrology department of the Rijnstate Hospital of Arnhem. None of the included patients was known for diabetes mellitus or familial dyslipidemia. The patients were also free of peritonitis and mechanical drainage complications for at least 3 months prior to their inclusion. Approval for this study was obtained from the local ethical committee and each patient gave written informed consent.

**STUDY DESIGN**

In a prospective randomized crossover study, the application of a CAPD method with standard glucose-containing solutions (1.36%, 2.27%, and 3.86%) was compared with a CAPD regime with the overnight glucose dwell replaced by a dwell of 7.5% icodextrin-containing solution (icodextrin 7.5%, Extraneal; Baxter Healthcare SA, Castlebar, Ireland) (Figure 1). Patients using their standard CAPD method were included (week 0) after notification of a stable clinical condition for at least 4 weeks (week –4 to week 0). They were randomized into a group (n = 11) that continued their initial standard CAPD method with glucose-containing dialysis solutions for 6 weeks (week 0 to week 6), followed by a 6-week experimental CAPD regime with overnight icodextrin dwells (weeks 6 to 12). The other group (n = 11) started directly with the experimental regime for 6 weeks, followed by a 6-week period on standard CAPD.

**OBSERVATIONS AND ANALYTIC METHODS**

After inclusion at week –4, patients visited the outpatient department for monitoring at weeks 0, 3, 6, 9, and 12 in a fasting state. At week 0, a standardized oral 75-g glucose tolerance test was performed. At each visit, measurements of body weight and blood pressure were performed and blood was drawn for routine determinations. Further, urine and dialysate fluid, collected for 24 hours, were delivered for determination of creatinine, urea, and glucose concentrations. At weeks 0, 6, and 12, an extended lipoprotein analysis, including determination of LDL subfraction
profiles and the concentration of free fatty acid, was performed.

Glucose concentrations were measured using an enzymatic hydrolysis method with colorimetric determination of glycerol (Hitachi 717, Reagentia Boehringer; Almere, The Netherlands). Plasma insulin concentrations were determined using a commercially-available radioimmunoassay (Pharmacia, Woerden, The Netherlands). Hemoglobin A1c (HbA1c) was determined with a turbidimetric inhibition immunoassay (1488457, Boehringer; Almere, The Netherlands). The concentration of free fatty acids was determined using a commercially-available enzymatic ACS-ACOD method (Waco Chemicals GmbH cat. no. 994-75409; Neuss, Germany). Total plasma cholesterol, triglyceride, and HDL concentrations were determined by enzymatic method on a Hitachi 747 analyzer. VLDL was isolated from whole plasma by ultracentrifugation at density 1.019 g/mL for 16 hours at 36 000 rpm in a fixed-angle rotor (TFT 45.6 rotor, Kontron, Zürich, Switzerland) in a Beckman L7-55 ultracentrifuge (Beckman, Palo Alto, CA, U.S.A.).

LDL cholesterol was calculated by subtraction of VLDL and HDL cholesterol from plasma total cholesterol. LDL subfractions were detected by single spin density gradient ultracentrifugation, according to a previously described method (17). Accurate documentation of the different LDL subfraction patterns was obtained by determination of the cholesterol content of each visible LDL subfraction to calculate a continuous variable, K (–1 < K < 1) (21). This K value reflects the intraindividual varying contribution of distinct LDL subfractions, as described elsewhere (21). In summary, a negative K value (–1 < K < 0) reflects a LDL subfraction profile more or less predominated by small dense subfractions. A profile with a predominance of buoyant LDL subfractions reveals a positive K value (0 ≤ K < 1) (21,22).

STATISTICAL ANALYSIS

For analysis, the results of both groups after each treatment period in the crossover set-up were combined. Parameters are given as mean ± standard deviation. Differences from baseline characteristics were tested by the nonparametric two-sample Wilcoxon signed rank test. All statistical analyses were performed using the SPSS program, version 9.0 (SPSS Inc, Chicago, IL, U.S.A.).

RESULTS

Twenty-one of 22 recruited CAPD patients finished the protocol (Figure 1). One patient who started with standard CAPD withdrew from the study for private reasons not related to the study protocol. Her results were excluded from further analysis. Baseline characteristics of the study population are shown in Table 1. At the beginning of the run-in period (week –4), 4 patients treated for hypertension with a beta-blocker were prescribed a beta-blocker with intrinsic sympathomimetic activity, which is known for only marginal effects on LDL cholesterol composition. All other medication was continued during the study period. Overall, icodextrin was well tolerated and none of the patients developed peritonitis during the study. Some patients felt comfortable using weaker glucose-containing CAPD solutions during the day after they started with overnight icodextrin solutions, possibly due to an increased overnight ultrafiltration due to icodextrin. However, in these patients this effect appeared not to be consistent during the entire study period because they all reported a return to their regular CAPD regimen.

EFFECTS ON GLUCOSE METABOLISM

The results of the oral 75-g glucose tolerance test in 21 CAPD patients are shown in Figure 2. At baseline, 1 patient showed a fasting glucose level of 8.6 mmol/L, and 12.1 mmol/L 2 hours after glucose intake, meeting the criteria for diabetes mellitus. Inclusion of this individual patient did not affect the overall results. Furthermore, the mean glucose response was within the normal range for this test. Compared to age and body mass index-matched controls, a diminished glucose clearance was observed in these CAPD patients (data not shown). During the standard CAPD period and after 6 weeks of overnight icodextrin, no detectable alterations in glucose, HbA1c, or insulin levels were observed (Table 2).

EFFECTS ON LIPID METABOLISM

Table 2 shows the effects of 6 weeks’ CAPD with overnight icodextrin on parameters of lipid metabolism. At baseline, only 1 patient showed fasting total plasma cholesterol above 6.5 mmol/L. A fasting hypertriglyceridemia (plasma triglyceride concentration > 2.0 mmol/L) was observed in 9 of 21 patients. Furthermore, the LDL subfraction profiles consisted of an equal amount of buoyant and dense

### TABLE 1
Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
</tr>
<tr>
<td>Male:female</td>
<td>15:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.3±11.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.7±2.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>141.3±18.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89.3±8.9</td>
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</table>
LDL subfractions, resulting in a mean intermediate profile.

The total cholesterol and LDL cholesterol concentrations showed a significant decrease of 11% and 13%, respectively (a decrease in 19 of 21 patients for both parameters). The mean total triglyceride (~10%), VLDL cholesterol (~23%), and VLDL triglyceride (~28%) levels were not reduced significantly. HDL cholesterol decreased significantly (~5%) (a reduction in 12 patients, an increase in 6, and no change in 2). The ratio of total cholesterol to HDL cholesterol remained equal after icodextrin and there was no detectable relation between a reduction in triglycerides and an increase in HDL cholesterol. A reduction (~19%) in 13 of 21 patients in the mean concentration of free fatty acids almost reached the level of significance ($p = 0.062$). Evaluation of visualized LDL subfraction profiles after ultracentrifugation showed a more buoyant LDL subfraction profile, with fewer dense LDL particles in 6 patients after icodextrin. In 14 patients no changes after icodextrin were observed, and in 1 patient a LDL subfraction profile with more dense LDL particles was observed. Figure 3 shows the mean cholesterol content of four distinct LDL subfractions isolated by ultracentrifugation. Although there is some loss of cholesterol due to the method of determination, which is comparable for either treatment, a decrease of the more dense LDL subfractions LDL-2, LDL-3, and LDL-4, seems to be responsible for the observed significant reduction of total LDL cholesterol. However, the calculated K value, reflecting the intraindividual varying contribution of the distinct LDL subfraction, showed no significant change toward a more buoyant LDL subfraction profile.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 6 weeks of standard CAPD</th>
<th>After 6 weeks of CAPD with overnight icodextrin</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.76±1.29</td>
<td>5.59±0.47</td>
<td>5.86±0.80</td>
<td></td>
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<tr>
<td>HbA1c (%)</td>
<td>5.54±0.38</td>
<td>5.57±0.37</td>
<td>5.59±0.36</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>19.5±14.4</td>
<td>18.4±10.4</td>
<td>20.3±13.0</td>
<td></td>
</tr>
<tr>
<td>Free fatty acids (mmol/L)</td>
<td>0.16±0.10</td>
<td>0.17±0.13</td>
<td>0.13±0.08</td>
<td>$p=0.062^a$</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.43±0.85</td>
<td>5.26±0.70</td>
<td>4.86±0.70</td>
<td>$p&lt;0.001^a$</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.14±1.96</td>
<td>2.06±1.15</td>
<td>1.92±1.03</td>
<td></td>
</tr>
<tr>
<td>VLDL cholesterol (mmol/L)</td>
<td>1.43±1.35</td>
<td>1.37±0.94</td>
<td>1.10±0.70</td>
<td></td>
</tr>
<tr>
<td>VLDL triglycerides (mmol/L)</td>
<td>2.08±2.39</td>
<td>1.83±1.25</td>
<td>1.50±1.00</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.95±0.27</td>
<td>0.94±0.28</td>
<td>0.90±0.24</td>
<td>$p=0.029^a$</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.38±0.87</td>
<td>3.19±0.75</td>
<td>2.93±0.73</td>
<td>$p=0.001^a$</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>6.13±1.69</td>
<td>6.07±1.83</td>
<td>6.01±1.30</td>
<td></td>
</tr>
</tbody>
</table>

VLDL = very low density lipoprotein; HDL = high density lipoprotein; LDL = low density lipoprotein.

* Compared with baseline.
EFFECTS ON CAPD DIALYSATE VOLUME AND COMPOSITION

During the study period, no changes in body weight were observed. Table 3 shows the concentrations of urea, creatinine, and glucose in 24-hour dialysate collected the day before patients returned to the outpatient clinic. Although not significant, a small increase in total 24-hour effluent volume, in combination with a decrease in its glucose content and an increase in creatinine content, was observed after the use of icodextrin.

DISCUSSION

Because of reported changes in glucose and lipid metabolism involving the high cardiovascular morbidity and mortality in CAPD, we investigated the possible favorable effects of icodextrin on defined cardiovascular risk factors. It appeared that an overnight dwell replacement with icodextrin indeed improved the lipid profiles of CAPD patients. These results were observed in a prospective study and, because of the crossover design, possible confounding environmental effects, such as dietary changes, could be reduced to a minimum.

The recent MIDAS study on efficacy and safety of icodextrin in CAPD demonstrated an overall overnight ultrafiltration achieved by icodextrin equal to a 3.86% glucose solution (20). Also, long-term use of icodextrin had no detrimental influence on peritoneal ultrafiltration capacity (20), and the routine use of icodextrin did not deteriorate the peritoneal defense mechanism (23). Due to a dynamic equilibrium, absorbed icodextrin and breakdown products reach steady-state levels; no adverse effects of these products have been observed so far during long-term follow-up (20). Because of its demonstrated efficacy and safety, icodextrin has been increasingly used for objectives other than improved ultrafiltration.

In contrast to intraperitoneal glucose solutions, maltose and related metabolites of icodextrin do not affect glucose metabolism or lead to hyperinsulinemia (24). The observed prolonged hyperglycemic response to the oral glucose tolerance test in this study may indicate a degree of insulin resistance in these CAPD patients, conforming to other reports (11,25). Since the ratio of plasma glucose to insulin remained equal after icodextrin, no arguments for a reduction of insulin resistance after icodextrin treatment were ascertained. Furthermore, the use of a reference method for plasma glucose determination prevented overestimation due to measurement of other polysaccharides derived from icodextrin (26). The inclusion of normoglycemic patients apparently limited the effects on plasma glucose and insulin. However, the observed decrease in plasma free fatty acids of 19% ($p = 0.062$) after icodextrin might be a result of a decreased efflux of fatty acids from adipocytes, due to a more sufficient insulin action at this site (27). Perhaps multiple non glucose-containing exchanges per day may enhance this proposed effect.

The observed effects after 6 weeks of icodextrin on lipid and lipoproteins showed a very consistent reduction in total plasma cholesterol and LDL cholesterol. The hypothesis that this results from decreased hepatic VLDL production due to reduced peritoneal glucose absorption and free fatty acid delivery to the liver could partly be confirmed by our other results. Although not significantly, the concentrations of both plasma free fatty acids and triglyceride-rich particles tended to decrease. Possibly, the relatively large intraindividual differences in relation to group size were responsible for the lack of significance of the

| TABLE 3 |
| Alterations in Body Weight and Dialysate Volume and Composition After Standard CAPD Method with Glucose-Containing Solutions, and After CAPD with an Overnight Icodextrin Dwell |
| [Results presented as mean±standard deviation and median (25th – 75th percentile)] |

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 6 weeks of standard CAPD</th>
<th>After 6 weeks of CAPD with overnight icodextrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>77.5±10.7</td>
<td>77.5±10.7</td>
<td>77.6±10.7</td>
</tr>
<tr>
<td></td>
<td>77.3 (71.0–85.4)</td>
<td>79.0 (71.0–85.0)</td>
<td>78.5 (70.5–86.8)</td>
</tr>
<tr>
<td>Total effluent dialysate volume after 24 hours (mL)</td>
<td>9357±1169</td>
<td>9540±821</td>
<td>9718±866</td>
</tr>
<tr>
<td></td>
<td>9500 (9000–10 000)</td>
<td>9750 (8925–10 000)</td>
<td>10 000 (9400–10 150)</td>
</tr>
<tr>
<td>Urea content of 24-hour dialysate (mmol/L)</td>
<td>215±47</td>
<td>219±42</td>
<td>211±40</td>
</tr>
<tr>
<td>Creatinine content of 24-hour dialysate (µmol/L)</td>
<td>6917±2376</td>
<td>6938±1955</td>
<td>7023±2279</td>
</tr>
<tr>
<td></td>
<td>6690 (4965–8165)</td>
<td>6700 (5298–7649)</td>
<td>6915 (4880–8276)</td>
</tr>
<tr>
<td>Glucose content of 24-hour dialysate (mmol/L)</td>
<td>354±94</td>
<td>358±85</td>
<td>336±94</td>
</tr>
<tr>
<td></td>
<td>357 (266–414)</td>
<td>363 (292–404)</td>
<td>324 (301–366)</td>
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</tbody>
</table>
observed effect. Furthermore, an increased calorie intake to compensate diminished peritoneal glucose absorption may theoretically reduce the triglyceride-lowering effect of icodextrin.

On the other hand, our results confirm the analysis performed in the MIDAS population in which, in the icodextrin group, the cholesterol, triglyceride, and LDL levels fell by 6% – 10% (20). In a later presented subgroup analysis in normolipidemic subjects, a significant reduction of total plasma cholesterol (±6%) and LDL cholesterol (±12%) was observed after a 6-month period with overnight icodextrin (28). These reductions were more pronounced (±12% and ±16%, respectively) in hypercholesterolemic (total plasma cholesterol > 6.5 mmol/L) patients (28). Comparable to our results, there were no significant changes in cholesterol > 6.5 mmol/L) patients (28). Comparable reductions were more pronounced (±12% and ±16%, respectively) in hypercholesterolemic (total plasma cholesterol > 6.5 mmol/L) patients (28). Comparable to our results, there were no significant changes in plasma triglycerides and VLDL cholesterol (28). In their study, an unexplained reduction in total plasma triglycerides and VLDL cholesterol (28). In conclusion, this prospective study showed substantial favorable effects on total plasma cholesterol and LDL cholesterol after replacement of glucose by icodextrin during the overnight dwell in CAPD patients. The hypothesized mechanism involved in the lipid-lowering effect has not been fully elucidated. However, some evidence for a reduced substrate delivery to the liver, and reduced hepatic VLDL production, both due to diminished total peritoneal glucose uptake, is provided.

ACKNOWLEDGMENT

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