Comparative analysis of lipid and glucose metabolism biomarkers in non-diabetic hemodialysis and peritoneal dialysis patients

Análise comparativa de biomarcadores do metabolismo de glicose e lipídeos em pacientes não diabéticos em hemodiálise e diálise peritoneal

Authors

Thyago Proença de Moraes[1]
Paulo Cesar Nunes Fortes[2]
Silvia Carreira Ribeiro[3]
Miguel Carlos Riella[3]
Roberto Pecoits-Filho[4]

[1] *Fundação Pró-Renal, Hospital Evangélico de Curitiba* and *Hospital Cajuru*; International Society for Peritoneal Dialysis (ISPD).
[2] *Hospital Universitário Cajuru.*
[3] *Fundação Pró-Renal; Hospital Evangélico de Curitiba.*
[4] *Centro de Ciências Biológicas e da Saúde of Pontifícia Universidade Católica do Paraná (PUC/PR).*

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Corresponding author:
Thyago Proença de Moraes
Rua Aristides Athayde Junior, 560, complemento 92, Bigorrilho –
Curitiba (PR), Brazil
Zip code: 80730-370
E-mail: thyagomoraes@hotmail.com

ABSTRACT

Objective: To investigate and compare glucose and lipid metabolism biomarkers in non-diabetic peritoneal dialysis and hemodialysis patients. **Methods:** The study followed a prospective and cross-sectional design Participants: participants included all prevalent end-stage renal disease patients under renal replacement therapy treated in a university-based clinic. Interventions: there were no interventions. Main outcomes measures: blood samples were taken after 8 hours of fasting. Insulin serum levels were determined by chemiluminescence. Insulin resistance were assessed by the insulin sensitivity check index (QUICKI) determined as follow: 1/[log(Io) + log(Go)], where Io is the fasting insulin, and Go is the fasting glucose. HOMA index was also measured: (FPG × FPI)/22.5; FPG = fasting plasma glucose (mmol/L); FPI = fasting plasma insulin (mU/mL). The others biochemical exams were measured utilizing the routine tests. **Results:** We screened 154 patients (80 on hemodialysis and 74 on peritoneal dialysis). Seventy-four diabetic patients were excluded. Of the remaining 80 patients (55% males, mean age 52 ± 15 years), 35 were on peritoneal dialysis and 45 on hemodialysis. Fasting glucose of peritoneal dialysis patients compared to hemodialysis patients were 5.0 ± 0.14 versus 4,58 ± 0.14 mmol/L, p<0.05; glycated hemoglobin 5.9 ± 0.1 versus 5.5 ± 0.1%, p < 0.05; total cholesterol 5.06 ± 0.19 versus 3.39 ± 0.20 mmol/L, p < 0.01; LDL-c 2.93 ± 0.17 versus 1.60 ± 0.17 mmol/L, p < 0.01; and index HOMA 3.27 versus 1,68, p < 0,05. Importantly, all variables were adjusted for age, gender, dialysis vintage, calcium-phosphorus product,

RESUMO

Objetivo: O presente estudo foi desenhado pra investigar e comparar biomarcadores do metabolismo de glicose e lipídeos em pacientes não diabéticos em diálise peritoneal e hemodiálise. **Métodos:** O estudo possui um desenho prospectivo e transversal. Participantes: foram incluídos todos os pacientes prevalentes em terapia de substituição renal tratados em uma clínica universitária. Intervenções: não houve intervenções. Medida das variáveis principais: as amostras de sangue foram coletadas com jejum oral de 8 horas. Os níveis séricos de insulina foram determinados por quimioluminescência. Resistência insulínica foi avaliada pelo index QUICKI como se segue: 1/[log(Io) + log(Go)], onde Io é a insulina de jejum, e Go a glicemia de jejum. Índice HOMA também foi medido: (FPG × FPI)/22,5; FPG = glicemia de jejum (mmol/L); FPI = insulina de jejum (mU/mL). Os demais exames bioquímicos foram analisados utilizando métodos de rotina. **Resultados:** Foram avaliados 154 pacientes (80 em hemodiálise e 74 em diálise peritoneal). Setenta e quatro pacientes diabéticos foram excluídos. Dos 80 pacientes restantes (55% homens, idade média de 52 ± 15 anos), 35 estavam em diálise peritoneal e 45 em hemodiálise. A glicemia em jejum dos pacientes em diálise peritoneal em relação à hemodiálise foi 5,0 ± 0,14 versus 4,58 ± 0,14 mmol/L, p < 0,05; para hemoglobina glicada (HbA1c) de 5,9 ± 0,1 versus 5,5 ± 0,1%, p<0,05; colesterol total de 5,06 ± 0,19 versus 3,39 ± 0,20 mmol/L, p < 0,01; LDL-c de 2,93 ± 0,17 versus 1,60 ± 0,17 mmol/L, p < 0,01; e índice HOMA de 3,27 versus 1,68, p < 0,05. Todas as variáveis foram ajustadas para idade, sexo, tempo em diálise, produto cálcio-fósforo, albumina e proteína

albumin and C-reactive protein levels. **Conclusion:** We observed a worst profile of lipid and glucose metabolism biomarkers in peritoneal dialysis patients (lower insulin sensitivity and higher fasting glucose, HbA1c, total cholesterol and LDL-c) when compared to hemodialysis, potentially due to the glucose-based dialysis solutions utilized in the peritoneal dialysis population.
Keywords: peritoneal dialysis, glucose, insulin resistance, dyslipidemias.

C-reativa. **Conclusão:** Nós observamos um pior perfil no metabolismo de glicose e lipídeos em pacientes em diálise peritoneal (menor sensibilidade insulínica e valores mais elevados de glicemia em jejum, HbA1c, colesterol total e LDL-c) quando comparados a pacientes em hemodiálise, potencialmente devido à utilização de glicose nas soluções de diálise peritoneal.
Palavras-chave: diálise peritoneal, glucose, resistência à insulina, dislipidemias.

Introduction

Carbohydrate metabolism disturbances are known factors potentially associated with cardiovascular complications in patients with chronic kidney disease (CKD). Disorders of lipids and glucose metabolism are commonly found in the early stages of CKD and aggravate with the progression of kidney dysfunction. Recent reports suggest that the relationship between hyperglycemia and cardiovascular disease (CVD) may extend below the limits currently defined as diabetes, since higher levels of glycosylated hemoglobin (HbA1c) are independent predictors of mortality in general population and non-diabetic CKD patients.[1-3] Insulin resistance was also identified as an independent predictor of cardiovascular events and mortality in general and CKD patients.[4,5]

The initiation of peritoneal dialysis (PD) represents an additional risk to glucose metabolism, due to the absorption of dextrose contained in the dialysate, which potentially intensifies carbohydrate disturbances[6]. In fact, patients with no previous history of glucose intolerance are more likely to develop hyperglycemia and *de novo* diabetes after the initiation of PD therapy, as described in previous studies[7,8]. Such high glucose load offered during PD therapy can also contribute to insulin resistance and worsening of dyslipidemia. However, specific factors are also introduced when hemodialysis (HD) is initiated. Information comparing the prevalence of these metabolic disturbances in unselected PD and HD patients is important to provide substrate for future actions. Thus, the aim of this study was to compare biomarkers of carbohydrate and lipid metabolism in non-diabetic PD and HD patients.

Materials and methods

This cross-sectional study included all prevalent adult patients with end-stage renal disease treated with HD or PD (on therapy for more than 90 days) in a university-based clinic. All diabetic patients (fasting serum glucose > 126mg/dL or use of hypoglycemiants drugs) were excluded. All PD patients were dialysed with glucose-based solutions.

A blood sample was taken from all patients in the morning after 8 hours of fasting. Serum concentrations of insulin, glucose, fructosamine, triglycerides, total cholesterol, HDL, LDL, albumin, intact PTH, calcium, phosphorous, hemoglobin, C-reactive protein (CRP) and fibrinogen were measured. Insulin was determined by chemiluminescence. Levels of total cholesterol, HDL and triglycerides were measured enzymatically while LDL was calculated.

The homeostasis model assessment (HOMA) index was then calculated using the baseline insulin and glucose serum concentrations: HOMA = (FPG × FPI)/22.5; FPG = fasting plasma glucose (mmol/L); FPI = fasting plasma insulin (mU/mL).[7]An additional validated quantitative insulin sensitivity check index (QUICKI) was determined as follow: 1/[log(Io) + log(Go)], where Io is the fasting insulin, and Go is the fasting glucose[9].

Blood pressure was measured with a standard mercury sphygmomanometer by the auscultator method and after a 20-minute rest period in supine position. Pulse pressure was calculated as the difference between sistolic blood pressure (SBP) and diastolic blood pressure (DBP). Abdominal waist circumference was assessed in PD patients after a complete drainage of dialysis solution from the peritoneal cavity.

Statistical analysis

All data are expressed as mean ± standard deviation (SD), median and range, or percentage depending on variable characteristics. Between-group comparisons of continuous numeric variables with equal variances and normal distribution were performed using unpaired *t*-tests. MannWhitney-U rank sum test were

utilized for nonparametric variables or when unequal variances between groups were present. Normality was analyzed through Kolmogorov-Smirnov test and homogeneity of variances, when required, by Levene's test. To evaluate the effect of dialysis modality on the main outcomes analysis of covariance was performed to avoid possible confounding factors. All variables related to metabolic profile were adjusted for age, gender, dialysis vintage, albumin, calcium-phosphorus product and CRP serum levels. Adjusted results are presented as estimated marginal means with standard errors (SE). The null hypothesis was refused for all tests if two-tailed alpha values were lower than 0.05. The software Statistical Package for the Social Sciences (SPSS) 11.0.1 was used for statistical analysis.

Results

Characteristics of study population

One hundred fifty-four patients (80 on HD and 74 on PD) were screened. Seventy-four diabetic patients were excluded. Of the remaining 80 patients (55% males, mean age 52 ± 15 years), 35 were on PD and 45 on HD. PD patients were older (58 ± 16 *versus* 46 ± 11 years; $p < 0.01$) and HD patients were on dialysis for longer periods (51.4 ± 50 *versus* 33.9 ± 31years; $p = 0.075$). There was a trend to PD patients to have higher abdominal waist circumference (93.3 ± 12.8 *versus* 87.5 ± 12.1 cm; $p = 0.06$), which was taken after a complete drainage of dialysis solution from the peritoneal cavity, while body mass index (BMI) was slightly, but with no statistical difference, lower in HD patients (23.6 ± 4.2 *versus* 25 ± 5.1 kg/m^2; $p = 0.22$). There was no significant difference regarding underlying renal disease. Although there was no statistical difference in diastolic blood pressure, the significant higher systolic blood pressure observed in HD patients (148 ± 17 *versus* 133 ± 30 mmHg; $p < 0.01$) lead to a higher pulse pressure in these patients (65.5 ± 11.8 *versus* 51.6 ± 15.1 mmHg; $p < 0.01$). Demographic and clinical variables of the study population are shown in Table 1.

General biochemical characteristics

Hemoglobin levels were very similar between groups (118 ± 16 *versus* 119 ± 20 g/L; $p = 0.82$) although at expenses of high EPO dose in HD group (10,344 ± 5,821 *versus* 3,428 ± 3,508u; $p < 0.01$). Albumin levels were significant higher in HD group (40 ± 4.6 *versus* 36 ± 5.0 g/L; $p < 0.01$). HD patients presented higher levels of serum phosphorus (1.97 ± 0.65 *versus* 1.42 ± 0.32 mmol/L; $p < 0.01$) and a tendency to more elevated iPTH levels (471 ± 584 *versus* 281 ± 348 ng/L; $p = 0.07$). There was no difference in total calcium serum levels (2.3 ± 0.3 *versus* 2.3 ± 0.17 mmol/L; $p = 0.98$).

Table 1 Demographic and clinical variables by dialysis modality

	All patients (n=80)	HD patients (n=45)	PD patients (n=35)	p-value
Age (years)	51±15	46±11	58±16	<0.01
Gender (% male)	54%	62%	43%	0.09
Underling renal disease				NS
Glomerulonephritis (%)	37.5%	49%	23%	
Hypertension (%)	40%	31%	51%	
PKD (%)	7.5%	7%	9%	
Others (%)	15%	13%	17%	
Dialysis vintag e (months)	43.8±43	51.4±50	33.9±31	0.075
Metabolic syndrome*	67%	69%	63%	NS
BMI	24.0±4.6	23.6±4.2	25±5.1	NS (0.22)
Abdominal waist (cm)	89.9±12.6	87.5±12.1	93.3±12.8	0.06
Pulse pressure (mmHg)	59.5±14.9	65.5±11.8	51.6±15.1	< 0.01
SBP (mmHg)	141.8±24.3	148.4±16.7	133.3±29.7	0.01
DBP (mmHg)	82.4±15.9	82.9±11.8	81.7±20.3	NS (0.75)

Values mentioned are expressed by mean±standard deviation.
*** American Heart Association/National Heart, Lung, and Blood Institute.**
HD: hemodialysis; PD: peritoneal dialysis; PKD: Polycystic Kidney Disease; BMI: body mas index; SBP: Sistolic Blood Pressure; DBP: Diastolic Blood Pressure; NS: Non significant.

Carbohydrate metabolism biomarkers

PD patients presented higher fasting glucose levels (5.0 ± 0.14 *versus* 4.58 ± 0.14 mmol/L; $p < 0.05$) and HbA1c (5.9 ± 0.1 *versus* 5.5 ± 0.1%; $p < 0.05$). There was a trend to higher fasting insulin levels in PD patients (97.9 ± 12.8 *versus* 57.9 ± 12.3 pmol/L; $p = 0.055$). Importantly, PD patients presented significant lower insulin sensitivity: HOMA index was almost twice higher (3.27 *versus* 1.68; $p < 0.05$) and the QUICKI index 7% lower (the lower the worst) (0.338 *versus* 0.363; $p < 0.05$) as shown in Figure 1. Metabolic syndrome, defined according to the National Cholesterol Education Program/Adult Treatment Panel III, was identified in 44% of PD patients and 38% of HD patients (p = NS). Adjusted carbohydrates metabolism biomarkers comparison between groups are shown in Figure 1.

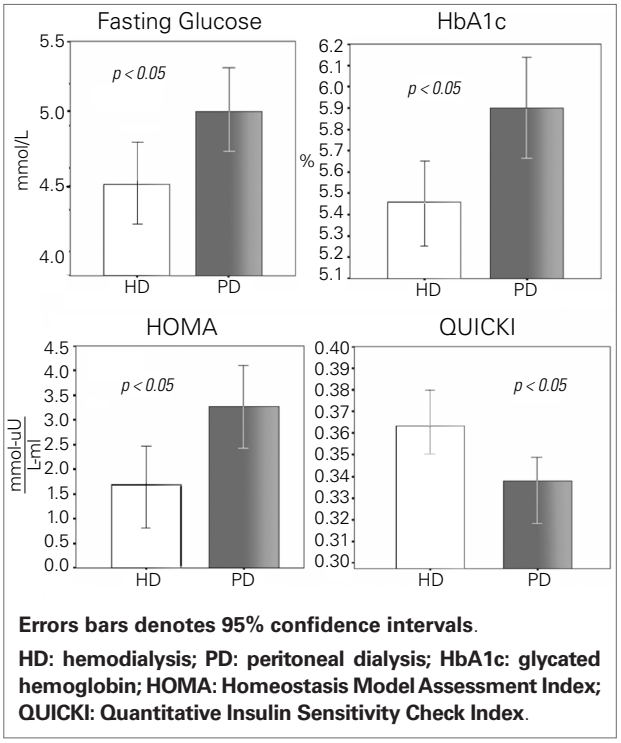
Lipid metabolism biomarkers

All measurements were adjusted for possible covariates, expressed as estimated marginal means ± SE and are shown in Figure 2. Total cholesterol (5.06 ± 0.19 *versus* 3.39 ± 0.20 mmol/L; $p < 0.01$) and LDL-c (2.93 ± 0.17 *versus* 1.60 ± 0.17 mmol/L; $p < 0.01$) were significant higher in PD patients. Higher HDL levels initially observed in PD patients (1.29 ± 0.39 SD *versus* 1.09 ± 0.31 SD mmol/L; $p < 0.05$) disappeared after adjustments for covariates (1.22 ± 0.07 *versus* 1.18 ± 0.07 mmol/L; NS). Hypertriglyceridemia (>1.695 mmol/L) was present in 40% of all patients of which 48% in PD and 33% of HD patients. These triglycerides levels were non-significantly higher in PD patients (1.96 ± 0.21 *versus* 1.32 ± 0.22 mmol/L; $p = 0.07$). Lipid ratios calculated were TC/HDL and LDL/HDL. These ratios were significant higher in PD patients (TC/HDL 4.39 ± 0.23SE *versus* 3.00 ± 0.24; $p < 0.01$) – LDL/HDL 2.54 ± 0.17 *versus* 1.43 ± 0.17; $p < 0.01$).

In the present study, insulin sensitivity tests were moderately correlated to BMI (r = 0.48; $p < 0.01$), abdominal waist circumference (r = 0.51; $p < 0.01$), total cholesterol (r = 0.33; $p < 0.05$) and triglycerides (r =0.59; $p < 0.01$). Significant correlations were observed with insulin resistance (for age and pulse pressure but disappeared after adjustments for confounders.

Additional analysis

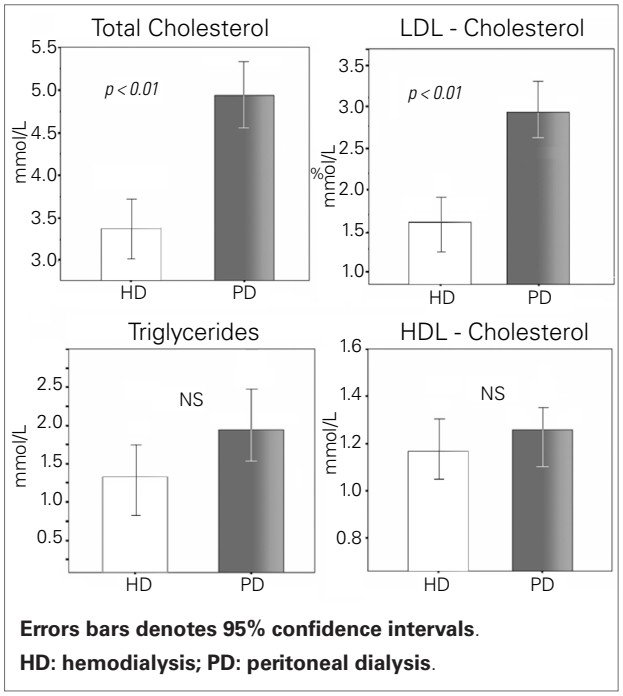
CRP and fibrinogen levels were analyzed as inflammatory markers and there was significant correlation between them (r = 0.575, $p < 0.01$). Fibrinogen levels were higher in PD when compared to HD group (17.29 ± 5.61SD *versus* 13.32 ± 5.52 SD µmol/L; $p < 0.05$) but no statistical difference was seen for CRP levels (PD 1.3 ± 2.6 SD *versus* HD 3.3 ± 10.0 SD; $p = 0.27$).



Errors bars denotes 95% confidence intervals.

HD: hemodialysis; PD: peritoneal dialysis; HbA1c: glycated hemoglobin; HOMA: Homeostasis Model Assessment Index; QUICKI: Quantitative Insulin Sensitivity Check Index.

Figure 1. Estimated marginal means adjusted for age, dialysis vintage, gender, albumin, product Ca-P and C-reactive protein.



Errors bars denotes 95% confidence intervals.

HD: hemodialysis; PD: peritoneal dialysis.

Figure 2. Estimated marginal means adjusted for age, dialysis vintage, gender, albumin, product Ca-P and C-reactive protein.

Discussion

Carbohydrate disturbances are common findings in CKD even in the early stages. The progressive decline of renal function intensifies CKD-related risk factors such as mineral metabolism disturbances, fluid overload, anemia, uremic toxicity and worsening of insulin resistance, dislipidemia and increased signs of oxidative stress and inflammation.[10,11] Its known that initiation of dialysis therapy partially revert those disturbances.[12] However, initiation of PD adds potential harm related to the great glucose absorption from PD fluids that lead to worsening of insulin resistance, dyslipidemia and higher levels of HbA1c. In the present study we confirm that the glucose and lipid metabolism profile in PD patients is worse than the observed in their HD counterparts.

A fasting state condition is difficult to achieve in most PD patients in consequence of the continuous glucose absorption from dialysate. Szeto *et al*. in 405 consecutive incident PD patients found new-onset hyperglycemia to be common in non-diabetic PD patients and worst patient survival was associated even with mild hyperglycemia[7]. In this study, PD patients presented significant higher levels of oral fasting glucose compared to HD patients. This elevation was confirmed with a higher HbA1c levels observed in the PD group: 6.5% higher than HD patients' levels. This may represent potential harm to PD patients, since HbA1c has been strongly associated with a high risk for diabetes, CV disease and all cause mortality in general non-diabetic patients and CKD patients.[1-3,13] Although HbA1c it's not considered the ideal method to evaluate glycaemic control in the uremic setting,[14,15] it is still widely available and can be an useful tool to compare groups and stratify those at high risk. Its ideal levels are still not established.

Moreover, hyperlipidemia, a well-known risk factor for CVD in general population, is very common in CKD and can be found in up to 50% of ESRD patients.[16] The causes of these lipid disorders are multifactorial and have been already associated with genetic factors, diet, obesity, CKD itself, dialysis solution, insulin resistance and inflammation. Recently, a randomized clinical trial with more than 9,000 CKD patients, of which 3,000 on dialysis, showed better outcomes after treatment of dyslipidemia.[17] PD patients presents a high prevalence of dyslipidemia probably related to the high glucose load absorbed from peritoneal cavity every day. In this study, PD patients presented significant higher levels of TC, LDL-c and HDL-C. TG was also higher but with no statistical significance. Except for the non significant higher HDL levels in PD patients, our data are similar of those found by Siamopoulos *et al*. in which PD patients presents a worsened lipid profiles.[18] Unfortunately we don't have measured HDL fractions AI, AII and CIII, the last two fractions associated with proatherogenic profile.[19] Insulin resistance is an additional risk factor involved with disorders of HDL metabolism in CKD patients, an issue recently reviewed and discussed below.[20]

Hypertriglyceridemia is the most common lipid disorder in PD patients[21] and was found in almost 50% of our PD patients. It has been related to IR in non-diabetic, non-obese patients undergoing CAPD almost 10 years ago.[22] The mechanisms postulated to be involved with dyslipidemia and IR in PD patients are increased hepatic synthesis of VLDL due the hyperinsulinemia caused by the high glucose absorption from peritoneal cavity, decreased removal of TG in consequence of a impaired regulation of lipoprotein lipase activity by insulin, peritoneal protein loss and weight gain.

A new approach based on lipid ratios has been recently associated with clinical indicators.[23,24] In a large prospective cohort study of 15,632 women aged 45 or older, the total cholesterol/HDL-C ratio has been suggested as a predictor as good or better than apolipoproteins fractions for prediction future cardiovascular events[23] while McLaughlin *et al*. reported triglycerides/HDL-C ratio as a reliable indicator of insulin resistance[24]. Although not yet validated in CKD patients, we compared these lipid ratios between PD and HD patients controlling them for covariates and a significant increase was found in PD patients in line with the mentioned studies. The ratio was almost 50% higher when TC/HDL ratio was considered and hover 75% with LDL/HDL ratio. Insulin resistance, which is also considered a risk factor for CVD, was recently associated with all-cause mortality even in a large cohort of 5511 non-diabetic patients[4] and is commonly found in CKD patients, even during their early stages.[10] Insulin sensitivity was lower in our PD patients in all three indirect methods we performed: HOMA index, QUICKI and triglycerides/HDL-c ratio. The mechanism involved is probably related to the higher glucose load daily offered to PD patients, which leads to a high fasting glucose and a compensatory hyperinsulinemia.

As a surrogate of systemic inflammation, we found no significant difference in CRP levels between groups. This is important since inflammation is often associated with decreased insulin sensitivity. Differently, fibrinogen levels were approximately 30% higher in

our PD patients. Since fibrinogen has been also described as a marker of inflammation, such contrasting results can be explained by a recent meta-analysis in which fibrinogen levels were identified to be markedly greater in PD than HD patients,[25] although the subjacent mechanism are still incompletely understood.

The use of glucose sparing solutions is an interesting approach aiming to reduce glucose load and by consequence IR. Amici *et al.* [26], in a cross-sectional study of non-diabetic CAPD patients treated with either icodextrina 7.5% during the long dwell or the traditional prescription with glucose, firstly described a metabolic advantage in the former, with a reduction in hyperinsulinism and IR measured by HOMA index. Similar results were found in non-diabetic CAPD patients in two studies, by Gursu and Canbakan.[27,28] In addition to the reduction in glucose load Takeguchi *et al.* described an increase in adiponectin serum levels with icodextrin in 25 prevalent CAPD patients,[29] an important factor for increasing insulin sensitivity.

Limitations of this study includes the issues of an observational study with no interventions, absent data regarding residual renal function and the small sample size. On the other hand, an in depth analysis of the metabolic profile of non-diabetic patients, who are usually not screened for glucose metabolism disorders, are strengths of the study.

In summary, we observed a worst profile of lipid and glucose metabolism in PD patients, when compared to HD, potentially due to the glucose-based dialysis solutions utilized in the PD population. These disturbances are potentially harmful to the patients and represent an important area for interventions. Therapeutic strategies, such as pharmacological interventions and/or the reduction in glucose load including the use of glucose sparing solutions should be tested aiming to reduce morbidity and mortality in the PD population.

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