Scientific Research

Do We Have a Biocompatible Peritoneal Dialysis Fluid?

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ABSTRACT

Objective: Cardiovascular disease remains the leading cause of morbidity and mortality in patients on maintenance dialysis. Diabetes mellitus, dyslipidemia, hypertension, inflammation and hyperhomocyteinemia are major cardiovascular risk factors. **Aim:** To evaluate the effects of Icodextrin and amino acid peritoneal dialysis fluid (AAPDF) on these major cardiovascular risk factors looking for a more biocompatible PDF formula. **Methods:** 20 adult stable peritoneal dialysis patients were included in the study. 10 patients received 2 L Icodextrin and other 10 patients received 2 L AAPDF in their dialysis prescription for 8 weeks. **Results:** Icodextrin decreased fasting plasma glucose ($p < 0.001$), LDL-C ($p = 0.03$), SBP ($p < 0.01$), DBP ($p < 0.05$) and plasma homocysteine ($p = 0.002$), and increased HDL-C ($p = 0.009$), CRP ($p = 0.035$) and fibrinogen ($p = 0.009$). AAPDF did not affect fasting plasma glucose, LDL-C, HDL-C, CRP and fibrinogen but increased serum albumin ($p = 0.03$), SBP ($p < 0.01$), DBP ($p < 0.05$) and P_{Hcy} ($p = 0.03$). **Conclusions:** A biocompatible PDF should provide not only adequate dialysis and ultrafiltration but should also improve nutritional and metabolic status, blood pressure control and reduce inflammation and plasma homocyteine.

Keywords: Icodextrin; Amino Acids PDF; Homocyteine; Carbohydrates; Lipids; Inflammation

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in end-stage renal disease patients on maintenance dialysis [1]. Diabetes mellitus, dyslipidemia, hypertension, inflammation and hyperhomocyteinemia are major cardiovascular risk factors. Recent studies have suggested that novel risk factors, uremia or dialysis-related, are of great importance, as they act synergistically with the highly prevalent traditional risk factors for CVD in chronic kidney disease (CKD) patients [2]. Glucose based peritoneal dialysis fluids (PDFs) are usually associated with progressive loss of the osmotic gradient, concomitant reduction in ultrafiltration (UF) and to the development of hyperglycemia and dyslipidemia. Dyslipidemia increases the risk of CVD and becomes worse in peritoneal dialysis (PD) patients [3]. Up to 80% of peritoneal dialysis patients are hypertensive [4]. Hypertension plays an important role in the development of CVD in this population [4]. Elevated plasma inflammation markers associated with increased risk for CVD [5]. Almost all (97% - 98%) PD and hemodialysis patients have hyperhomocyteinemia that known to be associated with an increased risk of cardiovascular, cerebrovascular and venous thromboembolic diseases

[6-8]. Icodextrin and Amino acid PDF (AAPDF) considered more biocompatible PDFs. Icodextrin PDF is targeted to have more sustained oncotic effect, to reduce plasma glucose and glucose-induced lipid abnormalities, and to avoid the production of glucose degradation products (GDPs) [9,10]. Generally, there is some concern that Icodextrin treatment may induce a subclinical inflammatory response, both intraperitoneally and systemically [10-12]. AAPDF was designed to correct nutriational status by supplying extra nitrogen through the intraperitoneal route [13]. Although the effects of Icodextrin and AAPDF on metabolic status, blood pressure control, inflammation and plasma homocyteine were studied but some issues still controversial. Aim of this study was to evaluate the effects of Icodextrin and AAPDF on these major cardiovascular risk factors.

2. Patients and Methods

Randomly, 20 adult stable PD patients on continuous ambulatory peritoneal dialysis (CAPD) or automated Peritoneal Dialysis (APD) for at least 3 months and with Kt/V > 1.8 were included in the study. Demographic and clinical characteristics of the enrolled subjects are listed in **Table 1**. The study protocol was approved by the local

Ethics Committee and all patients gave written informed consent before participating in the study. The patients randomly assigned to receive Icodextrin or AAPDF. Ten patients received 2 L Icodextrin in their dialysis prescription for 8 weeks, the night dwells in CAPD subjects were substituted with 2 L Icodextrin and in APD subjects 2 L from their regular regimen were substituted with 2 L Icodextrin given as last fill. Ten patients received 2 L AAPDF in their dialysis prescription for 8 weeks, the second dwells in CAPD subjects were substituted with 2 L AAPDF and in APD subjects 2 L from their regular regimen were substituted with 2 L AAPDF given at noon. The residual renal function (RRF) was estimated by mean urea and creatinine clearance (C_{UC}) and by the Modification of Diet in Renal Disease (MDRD) equation study [14]. At baseline the standard peritoneal equilibration test (PET) [15], and estimation of Kt/V were performed using PD-Adequest 2.0 for Windows program (Baxter Healthcare Co., Deerfield, IL) [16]. Blood, urine and dialysate analysis were performed in both groups at baseline and 8 weeks. Blood analysis included complete blood count (CBC), glucose, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, albumin, CRP, fibrinogen, plasma homocysteine (P_{Hcy}), folic acid, vitamin B12, and PTH. Urine analysis included 24-hour urinary collections for creatinine (mg/dl) (U_{Cr}) and urea (mg/dl) (U_{Urea}). Dialysate analysis included creatinine (mg/dl) (D_{Cr}) and glucose (mg/dl) (D_{Glu}). Daily urinary output (ml/day) (DUO), PET and Kt/V were also evaluated at baseline and 8 weeks. P_{Hcy} was determined using AxSYM Homocysteine assay (Produced by Axis-Shied, Dundee, UK for Abbott laboratories, Abbott park, IL 60064, USA). Statistical methods: Qualitative variables were described as incidences and percentages. Quantitative variables were described as means and standard deviations. Repeated Measures tests were used to evaluate the effects of Icodextrin and AAPDF on RRF, DUO, UF, D/P_{Cr}, D_{Glu}, D_{Cr}, fasting glucose, plasma lipids, plasma inflammation markers, body weight, blood pressure and P_{Hcy}. Repeated Measures tests were also used to evaluate the effects of PD modality, peritoneal membrane characteristics, Kt/V, gender, cause of CKD and hemoglobin on P_{Hcy}. Linear regression was used to evaluate the correlation between P_{Hcy} and RRF, DUO, PD duration, age, body weight, PTH and hemoglobin levels. Linear regression was also used to evaluate the correlation between degree of increment in UF (ΔNet UF) and the degree of reduction in P_{Hcy} (ΔP_{Hcy}) as well as between the degree of increment in D/P_{Cr} ($\Delta D/P_{Cr}$) and ΔP_{Hcy}.

3. Results

Repeated measures analysis revealed that Icodextrin and AAPDF did not affect the RRF or DUO (**Table 2**). No linear correlation was found between the RRF and P_{Hcy}. Icodextrin increased UF (p = 0.003) and D/P_{Cr} (p < 0.001) (**Table 2**). Icodextrin, as well AAPDF decreased D_{Glu} (p = 0.02) (**Table 2**).

Table 2. Effects of Icodextrin and AAPDF on RRF, DUO, UF, D/P_{Cr} and D_{Glu}.

	Icodextrin group		
	Baseline	8 Weeks	p
P_{Hcy} (μmol/L)	29.1 ± 21.8	14.8 ± 5.3	0.002
C_{UC} (ml/min/1.73m²)	10.1 ± 2.3	9.5 ± 2.9	n.s.
eGFR$_{MDRD}$ (ml/min/1.73m²)	8.3 ± 2.4	8.1 ± 2.0	n.s.
DUO (L/day)	0.8 ± 0.4	0.75 ± 0.3	n.s.
UF (L/day)	0.98 ± 0.1	1.22 ± 1.3	0.003
D/P_{Cr}	0.54 ± 0.1	0.79 ± 0.1	<0.001
D_{Glu} (mg/dl)	1035.8 ± 438.1	901.8 ± 354.9	0.016
	AAPDF group		
	Baseline	8 weeks	p
P_{Hcy}[a] (μmol/L)	26.6 ± 17.0	36.4 ± 15.6	0.03
C_{UC}[b] (ml/min/1.73m²)	10.2 ± 3.7	9.7 ± 3.3	n.s.
eGFR$_{MDRD}$[c] (ml/min/1.73m²)	8.1 ± 2.3	8.0 ± 2.0	n.s.
DUO[d] (L/day)	0.7 ± 0.3	0.6 ± 0.4	n.s.
UF[e] (L/day)	0.99 ± 0.2	0.97 ± 0.2	n.s.
D/P_{Cr}[f]	0.64 ± 0.1	0.61 ± 0.2	n.s.
D_{Glu}[g] (mg/dl)	981.4 ± 446.8	854.5 ± 435.5	0.02

a: Plasma homocysteine; b: Mean urea and creatinine clearance; c: estimated GFR using the Modification of Diet in Renal Disease equation study; d: Daily Urinary Output; e: Ultrafiltration, f: Dialysate creatinine/plasma creatinine; g: Dialysate glucose level.

Table 1. Characteristics of the study population.

	Icodextrin group	AAPDF[a] group
Number	10	10
Age (years)	61.3 ± 11.9	59.6 ± 20.0
Male/female	5/5	5/5
CAPD[b]/APD[c]	5/5	5/5
Dialysis duration (months)	29.2 ± 33.6	28.8 ± 17.3
PET[d]: HATs[e]/LATs[f]	5/5	5/5
Kt/V	2.41 ± 0.4	2.39 ± 0.4
Vitamin B12 (pg/ml) (Normal:160 - 680)	598.3 ± 280.3	610.9 ± 330.5
Folic acid (ng/mL) (Normal:150 - 700)	760.0 ± 385.0	771.2 ± 318.1
PTH (pg/ml) (normal:10 - 60)	313 ± 185	301 ± 158
Underlying cause:		
Diabetes mellitus	5	5
Primary hyperoxaluria type 1	2	2
APKD[g]	1	1
Unknown	2	2

a: Amino Acid Peritoneal Dialysis Fluid; b: Continuous ambulatory peritoneal dialysis; c: Automated peritoneal dialysis; d: Peritoneal equilibration test; e: High average transporters; f: Low average transporters; g: Adult Polycystic Kidney Disease.

The basal levels of HbA_{1C} in the two study groups were similar (4.9% ± 0.7% in Icodextrin group and 5.1% ± 1.5% in AAPDF group). Icodextrin decreased fasting glucose (p < 0.001), LDL-C (p = 0.03) and triglycerides (p = 0.04), and increased HDL-C levels (p = 0.009) (**Table 3**). AAPDF did not affect glucose and lipid metabolism (**Table 3**).

Basal levels of inflammation markers were similar in both study groups. Basal serum CRP and fibrinogen levels were elevated in both study groups. Compared to AAPDF, Icodextrin increased serum CRP (p = 0.035) and fibrinogen levels (p = 0.009) (**Table 3**). AAPDF, in contrast to Icodextrin, increased serum albumin (p = 0.03) (**Table 3**). Icodextrin decreased body weight (p=0.002), SBP (p < 0.01) and DBP (p < 0.05) while AAPDF increased body weight (p = 0.002), SBP (p < 0.01) and DBP (p < 0.05) (**Table 3**).

Table 3. Effects of Icodextrin and AAPDF on carbohydrates, lipids, inflammation and blood pressure.

	Icodextrin group		
	Baseline	8 weeks	p
Fasting glucose (mg/dl)	141.1 ± 39.9	119.3 ± 29.1	<0.001
LDL-C (mg/dl)	102.3 ± 33.3	89.6 ± 22.0	0.03
HDL-C (mg/dl)	35.6 ± 10.1	40.7 ± 11.8	0.009
TG (mg/dl)	272.4 ± 67.0	221.4 ± 74.8	0.04
Albumin(gr/dl)	3.6 ± 0.4	3.6 ± 0.3	n.s.
CRP (0 - 5 mg/L)	9.5 ± 6.5	22.4 ± 16.5	0.035
Fibrinogen (200 - 400 mg/dl)	835.1 ± 126.5	1066.1 ± 199.8	0.009
Body weight (kg)	80.4 ± 14.1	78.5 ± 14.7	0.002
SBP (mmHg)	149.5 ± 35.5	131.4 ± 21.9	<0.01
DBP (mmHg)	79.0 ± 14.5	72.8 ± 9.9	<0.05

|	AAPDF group		
	Baseline	8 weeks	p
Fasting glucose (mg/dl)	138.4 ± 76.2	142.2 ± 86.6	n.s.
LDL-C[a] (mg/dl)	117.6 ± 25.9	112.97 ± 21.1	n.s.
HDL-C[b] (mg/dl)	42.0 ± 9.4	45.0 ± 11.6	n.s.
TG[c] (mg/dl)	186.4 ± 96.6	176.3 ± 62.7	n.s.
Albumin (gr/dl)	3.5 ± 0.4	4.3 ± 0.5	0.03
CRP (0 - 5 mg/L)	12.6 ± 26.0	10.4 ± 18.3	n.s.
Fibrinogen (200 - 400 mg/dl)	999.6 ± 189.6	973.0 ± 231.4	n.s.
Body weight (kg)	71.6 ± 15.0	72.5 ± 15.0	0.002
SBP[d] (mmHg)	138.7 ± 28.4	146.6 ± 26.4	<0.01
DBP[e] (mmHg)	75.4 ± 12.3	80.1 ± 11.8	<0.05

a: Low density lipoprotein cholesterol; b: High density lipoprotein cholesterol; c: Triglycerides; d: Systolic blood pressure; e: Diastolic blood pressure.

Hyperhomocysteinemia was identified in 84% of the study subjects at baseline. Icodextrin decreased P_{Hcy} (p = 0.002) (**Table 2**). AAPDF increased P_{Hcy} (p = 0.03) (**Table 2**). Furthermore, in Icodextrin group, a linear correlation was found between the degree of increment in UF (ΔUF) and the degree of reduction in P_{Hcy} (ΔP_{Hcy}) (p < 0.001, R^2 = 0.962) (**Figure 1**), and between the degree of increment in D/P_{Cr} ($\Delta D/P_{Cr}$) and ΔP_{Hcy} (p < 0.001, R^2 = 0.836) (**Figure 2**).

Icodextrin decreased P_{Hcy} in both CAPD and APD patients (p = 0.033), in low average transporter patients (LATs) (p = 0.006), in PD patients with Kt/V > 2 (p = 0.04) or Kt/V ≤ 2 (p = 0.003) and in non diabetic patients (p = 0.039) (**Table 4**). LATs had a higher basal P_{Hcy} compared with high-average transporter patients (HATs) (p = 0.015) (**Table 4**). HATs had lower P_{Hcy} which were in the upper normal limits (**Table 4**).
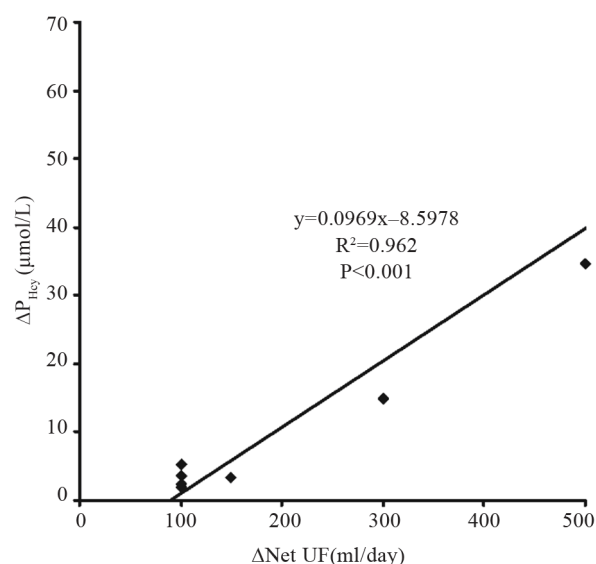
Figure 1. The correlation between ΔP_{Hcy} and ΔNet UF in the extraneal group.
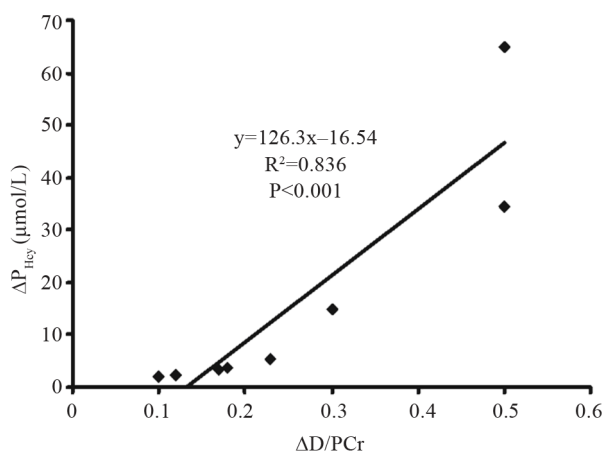
Figure 2. The correlation between ΔP_{Hcy} and $\Delta D/P_{Cr}$ in the extraneal group.

Table 4. Effects of PD[a] modality, peritoneal membrane characteristics, Kt/V, gender and diabetes mellitus on P_{Hcy}.

	P_{Hcy}[b] (µmol/L) in Icodextrin group		
	Baseline	8 weeks	p
CAPD[c]	33.0 ± 26.3	14.7 ± 6.2	0.033
APD[d]	24.3 ± 17.0	14.8 ± 5.0	0.033
p	n.s.		
LATs[e]	46.4 ± 23.2	17.2 ± 5.3	0.006
HATs[f]	15.3 ± 3.0	12.8 ± 5.1	n.s.
P	0.015		
Kt/V ≤ 2	46.9 ± 32.5	19.5 ± 2.7	0.003
Kt/V > 2	20.2 ± 7.3	15.9 ± 6.2	0.04
p	0.05		
DM[g]	24.5 ± 7.9	17.0 ± 7.4	n.s.
Non DM	31.4 ± 6.7	13.7 ± 4.4	0.039
p	n.s.		

	P_{Hcy} (µmol/L) in AAPDF group		
	Baseline	8 weeks	p
CAPD	26.72 ± 7.2	33.6 ± 15.7	n.s.
APD	26.52 ± 24.5	31.12 ± 34.9	n.s.
p	n.s.		
LATs	37.5 ± 18.8	48.5 ± 28.5	n.s.
HATs	15.8 ± 2.1	16.2 ± 3.1	n.s.
p	0.015		
Kt/V ≤ 2	32.3 ± 25.5	38.5 ± 36.6	n.s.
Kt/V > 2	22.8 ± 9.4	28.3 ± 17.9	n.s.
p	0.05		
DM	28.7 ± 5.1	37.0 ± 3.9	n.s.
Non DM	30.0 ± 19.5	38.9 ± 28.4	n.s.
p	n.s.		

a: Peritoneal dialysis; b: Plasma homocysteine; c: Continuous ambulatory peritoneal dialysis; d: Automated peritoneal dialysis, HATs = High average transporters; e: Low average transporters; f: High average transporters; g: Diabetes mellitus.

AAPDF increased P_{Hcy} (p = 0.03) (**Table 2**).

Linear regression analysis did not show any correlation between P_{Hcy} and age, gender, body weight, duration of PD, DUO, hemoglobin and PTH levels in both Icodextrin and AAPDF groups.

4. Discussion

Long-term systemic exposure of glucose caused by conventional PD solutions has been well recognized to cause metabolic and cardiovascular abnormalities, which contribute to the morbidities seen in PD patients. Several studies have shown that conventional solutions damage mesothelial cells and peritoneal blood vessels leading to functional impairment [17,18]. Besides its effects on the peritoneal membrane, rapid absorption of glucose during a dwell leads to loss of osmotic gradient and diminished

ultrafiltration as well as to the development of hyperglycemia and associated hyperinsulinemia in both diabetic as well as nondiabetic patients [19]. The high levels of dextrose and the lactate acidic buffer make the conventional solutions nonphysiologic and nonbiocompatible. Introducing the newer solutions that designed to be more biocompatible by either, containing physiologic buffer bicarbonate, or having lower GDP concentration, and/or substituting glucose with alternative osmotic agents, like polyglucose or amino acids were targeted to ameliorate the complications of conventional dextrose solutions [20-22]. It is postulated that newer PD solutions containing lower levels of GDPs are less nephrotoxic, and hence may preserve RRF longer. Additionally, the effect of fluid status on preservation of RRF cannot be ignored.

In the present study, Icodextrin and AAPDF did not affect RRF (**Table 2**). Icodextrin improved glucose control and lipid profile including significant decrease in LDL-C and triglyceride levels as well as significant increase in HDL-C (**Table 3**). Similar results were reported by Bredie *et al*. [23].

It is well known that the major reason for the elevation of blood pressure in PD patients is volume overload. Icodextrin improved blood pressure control by improving UF and decreasing body weight (**Tables 2** and **3**).

The effects of Icodextrin on inflammation status in PD patients are controversial [11,12]. Martikainen *et al*. showed that Icodextrin use was resulted in subclinical inflammatory response [11]. In contrast, Lin *et al*. reported that Icodextrin decreased CRP [12]. In this study the basal serum CRP and fibrinogen levels were similar and elevated in both study groups (**Table 3**). Icodextrin use was accompanied by a rise in plasma CRP and fibrinogen levels (**Table 3**). There is a concern that Icodextrin use may induce a subclinical inflammatory response, both intraperitoneally and systemically. Accordingly, Icodextrin that lowered GDPs levels and designed to preserve the peritoneal membrane and to improve glucose and lipid control, seems to intensify systemic inflammation.

Hyperhomocysteinemia was identified in 84% of our study subjects compared to the 97% - 98% reported by Van Guldener [24]. The significant rise in D/P_{Cr} and UF as well as the linear correlations between ΔP_{Hcy} and ΔNetUF, and between ΔP_{Hcy} and ΔD/P_{Cr} in the Icodextrin group, suggest better peritoneal clearances of Hcy compared to standard glucose-based fluids and AAPDF (**Table 2**, **Figures 1** and **2**). Similar results were reported by Czupryniak *et al*. [25].

It is well known that AAPDF improve nutritional status in malnourished PD patients. Although increased serum albumin levels and did not affect UF, glucose and lipid metabolism, and inflammation status, AAPDF increased body weight, SBP, DBP and P_{Hcy} levels (p =

0.002, p < 0.01, p < 0.05, p = 0.03—respectively) (**Tables 2** and **3**). The increase in P_{Hcy} in the AAPDF group is, most likely, related to methionine, a precursor of Hcy, absorption as well as to the decrease in D/P_{Cr} and UF in the AAPDF group (**Table 2**). Then, AAPDF that introduced to improve nutritional status and survival may contribute to the unfavorable rise of P_{Hcy}. The rise in P_{Hcy} in PD patients treated with AAPDF described also in previous studies [26,27].

End stage renal disease patients are unable to excrete the daily acid load. The standard PDFs, Icodextrin and AAPDF use lactate as a buffer that, by its acidic pH, causes harmful effects on the peritoneal cells [17]. In contrast, bicarbonate-based PDFs include a physiologic buffer with neutral pH, cause less peritoneal damage [28].

The relationships between the PD modality, the peritoneal membrane characteristics and Kt/V, and P_{Hcy} remain a controversial issue [29,30]. Basal P_{Hcy} was elevated and not different in the two study groups and all subgroups apart from HATs (**Table 4**). In the Icodextrin group P_{Hcy} decreased in both PD modalities (p = 0.033) (**Table 3**). On the other hand, AAPDF increase P_{Hcy} (p = 0.033) (**Table 2**). This may be due to its low osmotic drive and as a result of the absorption of methionine through the peritoneal membrane. These results suggest that the peritoneal membrane characteristics and the composition of the PDF have an important role in the peritoneal elimination of Hcy.

Basal P_{Hcy} in HATs were near normal in both study groups (**Table 4**). It may be related to the higher solute clearances across the peritoneal membrane in HATs.

Basal P_{Hcy} was marginally lower in subjects with Kt/V > 2 compared to those with Kt/V ≤ 2 (p = 0.05) (**Table 4**). Icodextrin, but not AAPDF, significantly decreased P_{Hcy} in PD patients with Kt/V > 2, in those with Kt/V ≤ 2 and in non diabetic patients (**Table 4**). Therefore, Icodextrin may influence the atherosclerotic outcomes through Hcy-lowering effects, as it was stated previously by Docloux et al [29].

No associations between age, gender, body weight, duration of PD, hemoglobin, PTH, RRF and DUO and P_{Hcy} were found.

In summary: Higher UF, higher D/P_{Cr}, HATs, Kt/V > 2, non diabetic patients and Icodextrin use were associated with decline in P_{Hcy}. Conversely, lower UF, lower D/P_{Cr}, LATs, Kt/V ≤ 2, diabetic patients and AAPDF use were associated with rise in P_{Hcy}.

Although it exhibited favorable effects on metabolic status, blood pressure control and P_{Hcy} levels, Icodextrin seems to intensify systemic inflammation. On the other hand, although it did not seem to affect adversely the metabolic status and systemic inflammation, AAPDF increased P_{Hcy} and blood pressure.

The results of the present study suggested that the use of Icodextrin and AAPDF was associated with beneficial effects as well as with considerable harmful consequences that may adversely affect the prognosis and survival of PD patients.

5. Conclusion

A new PDF containing a mixture of a biocompatible substance, amino acids without methionine, lower glucose and GDPs content, and neutral pH will provide sustained oncotic effect, adequate dialysis and ultrafiltration as well as will improve nutritional status and metabolic profile, reduce inflammation, plasma homocyteine and blood pressure. A PDF with those properties will preserve the peritoneal membrane and improve the prognosis and survival of peritoneal dialysis patients.

6. Acknowledgements

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