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DIALYSIS – TRANSPLANTATION

Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration

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Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration.

Background. Daily dialysis has shown excellent clinical results because a higher frequency of dialysis is more physiologic. On-line hemodiafiltration (OL-HDF) is a HDF technique that combines diffusion with high convection in which the dialysis fluid itself is used as a reinfusion solution. The aim of this study was to demonstrate the beneficial effect of the more effective dialysis schedule (daily dialysis) with the dialysis modality that offers the highest uremic toxin removal (on-line HDF).

Methods. Eight patients, six males and two females, on standard 4 to 5 hours three times a week OL-HDF (S-OL-HDF) were switched to daily OL-HDF (D-OL-HDF) 2 to 2½ hours six times per week. Dialysis parameters were identical during both periods and only frequency and dialysis time of each session were changed. Tolerance, uremic toxin removal, urea kinetics, biochemical and anemia profiles, blood pressure, and left ventricular hypertrophy were evaluated.

Results. D-OL-HDF was well accepted and tolerated. The disappearance of postdialysis fatigue was rapidly reported by patients. Patients mantained the same [time average concentration (TAC) and weekly single-pool Kt/V (spKt/V)] throughout the study. However, equivalent renal urea clearance (EKR), standard Kt/V and weekly urea reduction ratio (URR) were increased during D-OL-HDF. Weekly urea, creatinine, osteocalcin, β_2-microglobulin, myoglobin, and prolactin reduction ratios were improved with D-OL-HDF. There was a significant decrease in predialysis plasma levels of urea, creatinine, acid uric, β_2-microglobulin and homocysteine over 6 months. Phosphate binders were reduced and antihypertensive drugs were stopped. A 30% regression of left ventricular mass was observed.

Conclusion. The change from S-OL-HDF to D-OL-HDF was well tolerated. Disappearance of postdialysis fatigue, better dialysis adequacy, a higher removal of middle and large molecules, a reduction of phosphate binders, improvement of status nutritional, and an important reduction of cardiovascular risk factors were observed.

Key words: dialysis adequacy, daily hemodialysis, nutrition, on-line hemodiafiltration, solute removal.

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The frequency of hemodialysis was established as thrice weekly in the 1960s and it has been mainly accepted and maintained for logistical, pragmatic, and economic reasons. However, there is a growing interest in the use of more frequent dialysis schedules since long-term experiences using higher frequencies have shown good results [1–5]. The first experiences with daily dialysis were reported in 1967 [6] and two predominant treatment schedules have been established. Short daily dialysis [1, 2, 4] has been used for more than 20 years and slow nightly dialysis [5, 7, 8] has been used since 1995. Although there are only a few studies and the number of patients is limited, they show excellent clinical results because a higher frequency of dialysis is more physiologic and it decreases fluctuations in fluid volume, solutes, and electrolytes. Improvements in comfort during and between dialysis sessions, clinical and biochemical parameters, anemia correction, hypertension control, nutrition status, and quality of life have been reported.

On-line hemodiafiltration (OL-HDF) could offer an optimal form of extracorporeal treatment for dialysis patients. This technique, which combines diffusion with high convection [infusion flux (Qi) 50 to 200 mL/minute or 3–12 L/hour], provides the highest clearances per unit of surface area for small, medium, and large-sized molecules. The same dialysis fluid, free of toxins and pyrogens, is used as substitution solution. It is a safe, well-tolerated technique, and good clinical results have been observed [9–11].

In this study, we sought to combine the more physiologic and effective dialysis schedule (daily dialysis) with the dialysis modality that offers higher solute and uremic toxine removal (OL-HDF). The aim of this study was to change patients from standard 4 to 5 hours three times a week OL-HDF to 2 to 2½ hours six times a week OL-HDF, and evaluate the impact of higher frequency therapy on solute removal capacity and on biochemical and clinical outcomes.

METHODS

This was a single-center, prospective, and nonrandomized study. Eight patients, six males and two females,

with a mean age of 65.9 ± 14 years (range, 41 to 80 years), stable on hemodialysis over a period of 68.4 ± 43 months and on standard 4 to 5 hours three times a week OL-HDF (S-OL-HDF) during the last 36.3 ± 21 months (range, 8 to 68 months) were switched to daily OL-HDF (D-OL-HDF) 2 to 2½ hours six times per week. The underlying renal diseases were chronic glomerulonephritis in two patients, nephroangiosclerosis in two patients, polycystic kidney disease in one patient, chronic tubulointerstitial nephritis in one patient, diabetic nephropathy in one patient, and undiagnosed nephropathy in one patient. All patients signed consent forms approved by the Hospital Research Committee.

The S-OL-HDF parameters were as follows: dialysis buffer with bicarbonate, 1.8 m^2 high-flux polysulfone filter (HF80, Fresenius, Bad Homburg, Germany), blood flow (Qb) 445 ± 54 mL/min (range, 350 to 560 mL/min), dialysate flow (Qd) 800 mL/min minus the infusion flow (Qi), which ranged from 80 to 150 mL/min and a Fresenius 4008 dialysis monitor. Reinfusion was always performed in a postdilutional mode. On D-OL-HDF, these parameters were the same and only the frequency and dialysis duration of each session were changed. All patients had native arteriovenous fistulas. The dialysers were not reused. Residual renal function was negligible in all patients. Before the study period, six patients used 15-gauge needles and two used 14-gauge needles. All patients used 15-gauge needles while on D-OL-HDF (Qb was limited to 500 mL/min).

The following urea kinetic parameters were calculated: single-pool second-generation Daugirdas Kt/V (spKt/V) [12], equilibrated Kt/V (eKt/V) [13], urea reduction ratio (URR), time average concentration (TAC), and normalized protein catabolic rate (nPCR). Moreover, different yardsticks proposed to measure the dialysis dose delivered by the different dialysis regimens have also been included: weekly spKt/V, weekly eKt/V, the equivalent renal urea clearance (EKR) introduced by Casino and Lopez [14], the standard Kt/V described by Gotch [15] and, finally, we calculated the weekly URR and the time average deviation (TAD) introduced by Lopot and Vàlek [16].

To evaluate removal capacity between both treatments modes, "in vivo" removal of a wide spectrum of solutes was studied. Pre- and postdialysis concentrations of urea (60 D), creatinine (113 D), osteocalcin (5800 D), β_2-microglobulin (11,800 D), myoglobin (17,000 D), and prolactin (23,000 D) were measured. Pretreatment blood samples were drawn immediately after access needle insertion. Posttreatment samples were drawn from the arterial blood line 60 seconds after decreasing the blood flow rate to 50 mL/min. Osteocalcin concentrations were measured by a commercial immunometric assay, Immulite (DPC Diagnostics, Los Angeles, CA, USA) osteocalcin. The normal range of osteocalcin values is 3.1 to 13.7 ng/mL in our laboratory. Serum β_2-microglobulin was measured using the Quantex β_2-microglobulin commercial immunoturbidimetry, which has a normal range of 1.1 to 2.4 mg/L. Myoglobin concentrations were measured by a commercial immunoenzymatic "sandwich" assay (Access; Beckman, Fullerton, CA, USA), which has a normal range of 0 to 70 ng/mL. Prolactin concentrations were measured by a commercial immunometric assay, Immulite 2000 DPC, which has a normal range of 3 to 30 ng/mL. The pre- to posttreatment reduction ratios in plasma for osteocalcin, β_2-microglobulin, myoglobin, and prolactin were determined after correcting postdialysis concentrations using the method of Bergström and Wehle [17].

The second part of study was designed to evaluate biochemical and clinical outcomes. The last 6 months on S-OL-HDF, during which conditions of treatment were not varied, were taken as the baseline period, before switching the patients to D-OL-HDF. Treatment was carried out over 6 months. Each month at mid-week, predialysis plasma analyses for hemoglobin, hematocrit, ferritin, transferrin saturation, fibrinogen, urea, creatinine, sodium, potassium, uric acid, bicarbonate, calcium, phosphorus, intact parathyroid hormone (iPTH), serum protein, albumin, prealbumin, transferrin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, β_2-microglobulin, myoglobin, and C-reactive protein were carried out, as well as a quarterly analysis of homocysteine. Homocysteine was determined by the IMx method (IMX System; Abbott, Wiesbaden, Germany), using fluorescence polarization immunoassay technology.

At baseline and each month, each patient completed a fatigue index questionnaire concerning the intensity and duration of frequency of postdialysis fatigue [18]. Fatigue intensity was scored as follows: 0, none; 1, mild (noticeable but without effect); 2, moderate (felt sluggish); 3, severe (required rest); or 4, overwhelming (slept). Fatigue duration was scored as follows: 0, none; 1, mild (one to 4 hours); 2, moderate (6 to 12 hours); 3, severe (12 to 24 hours); or 4, overwhelming (more than 24 hours).

Predialysis blood pressure was measured immediately before treatment with an automatic blood pressure monitor (BPM). Left ventricular hypertrophy (LVH) was evaluated by magnetic resonance imaging (MRI). Measurements included left ventricular internal diameter at end-diastole (LVIDD) and left ventricular internal diameter at end-systole (LVISD), interventricular septal thickness (IVS), anterior wall thickness at end-diastole (AWT), posterior wall thickness at end-diastole (PWT), lateral wall thickness at end-diastole (LWT), inferior wall thickness at end-diastole (IWT), left atrium dimension (LA) and aortic root dimension (AO). Left ventricular wall mass (LVM) was calculated by outlining endo- and epicardial contours on a stack of image sections of a specific

Table 1. Change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF): Comparison of urea kinetics during the two study periods

	Baseline	Month 3	Month 6
spKt/V	2.30 ± 0.20	1.13 ± 0.15[b]	1.11 ± 0.11[b]
eKt/V	1.96 ± 0.17	0.90 ± 0.12[b]	0.88 ± 0.08[b]
URR %	84.3 ± 2.5	64.2 ± 5.3[b]	63.3 ± 4.2[b]
Weekly spKt/V	6.90 ± 0.59	6.78 ± 0.91	6.67 ± 0.64
Weekly eKt/V	5.88 ± 0.52	5.39 ± 0.75[a]	5.30 ± 0.50[a]
EKR *mL/min*	19.2 ± 0.5	24.2 ± 2.6[b]	23.8 ± 1.9[b]
stdKt/V	2.62 ± 0.1	3.87 ± 0.3[b]	3.86 ± 0.2[b]
Weekly URR %	253 ± 7.5	385 ± 32[b]	380 ± 25[b]
TAC_{BUN} *mg/dL*	27.3 ± 7.1	26.7 ± 8.6	27.7 ± 6.1
TAD_{BUN} *mg/dL*	9.69 ± 2.3	6.24 ± 2.1[b]	6.26 ± 1.3[b]

Abbreviations are: URR, urea reduction ratio; spKt/V, single-pool Kt/V; eKt/V, equilibrated Kt/V; stdKt/V, standard Kt/V; TAC, time average concentration; TAD, time average deviation; ERK, equivalent renal urea clearance.

[a] $P < 0.05$; [b] $P < 0.01$ with respect to baseline value (ANOVA repeated measures)

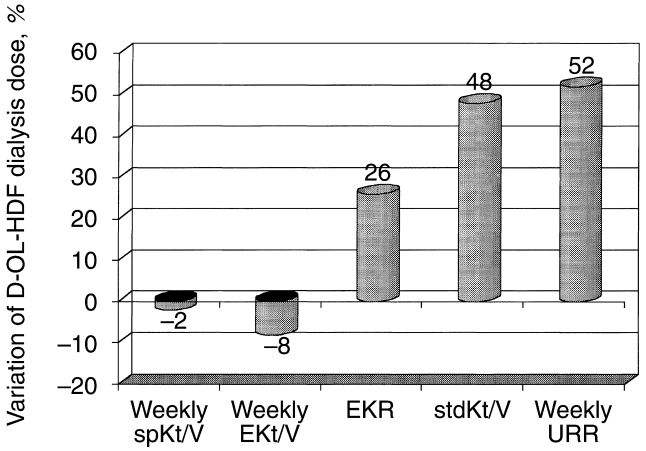

Fig. 1. Percentage variation of different dialysis dose evaluations with change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodialfilitration (D-OL-HDF). Abbreviations are: spKt/V, single-pool Kt/V; eKt/V, equilibrated Kt/V; ERK, equivalent renal urea clearance; stdKt/V, standard Kt/V; URR, urea reduction ratio.

time frame encompassing the ventricle, using Simpson's rule algorithm [19]. LVM index (LVMI) was calculated by dividing LVM by body surface area. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (EF) were also calculated. All studies were performed and analyzed by the same experienced cardiologist, who was blinded to the patients' data. Studies were performed on a mid-week nondialysis day in S-OL-HDF and on a mid-week day before dialysis in D-OL-HDF. Specific criteria were used to determine the presence of LVH (men, LVM >158 g or LVMI >83 g/m^2; women, LVM >123 g or LVMI >73 g/m^2) [19].

The results were expressed as the arithmetic mean ± standard deviation. Each patient served as his/her own control. The Student *t* test (paired data) and analysis of variance (ANOVA) test (repetitive data) were used in the analysis of differences in quantitative variables. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The duration per dialysis session changed from 274 ± 25 minutes (range, 240 to 300 minutes) in S-OL-HDF to 133 ± 12 minutes (range, 120 to 150 minutes) in D-OL-HDF ($P < 0.01$) but weekly dialysis time was similar, 822 minutes versus 798 minutes (NS), respectively. Qb was 445 ± 59 mL/min in S-OL-HDF versus 438 ± 38 mL/min in D-OL-HDF (NS). Mean session value for reinfusion volume in S-OL-HDF was 30.7 ± 6 L and 14.6 ± 2 L in D-OL-HDF ($P < 0.01$), and weekly reinfusion volume was 95.8 ± 21 L and 88.1 ± 9 L (NS), respectively.

Daily OL-HDF was well accepted and tolerated by all patients. No local infections, thromboses, or bleeding of the vascular access occurred. The number of nausea, dizziness, cramps, and hypotensive episodes did not change between the two treatment schedules. In the first 4 weeks, the patients reported a rapid improvement in the following symptoms: headaches in three patients, sleep disorders in three patients, sexual disorders in two patients, thoracic pain in one patient, increased appetite in five patients, and decreased thirst in two patients. The most significant benefit was the disappearance of postdialysis fatigue. Fatigue intensity scores diminished from 1.88 ± 1.2 in S-OL-HDF to 0.38 ± 0.7 in S-OL-HDF ($P < 0.01$), and fatigue duration scores decreased from 1.75 ± 1.4 in S-OL-HDF to 0.25 ± 0.5 in S-OL-HDF ($P < 0.01$).

Urea kinetics

Throughout the study, patients mantained the same TAC, weekly spKt/V, and weekly eKt/V (Table 1). However, EKR, standard Kt/V, and weekly URR were significantly increased in D-OL-HDF. The percentage variation of D-OL-HDF dialysis dose, measured by different methods, is shown in Figure 1. The outcome of pre- and postdialysis blood urea nitrogen (BUN), TAC_{BUN}, and TAD_{BUN} is shown in Figure 2.

Solute removal

Mean session values for urea, creatinine, osteocalcin, β_2-microglobulin, myoglobin, and prolactin reduction ratios were lower on D-OL-HDF; however, the weekly reduction ratios were significantly increased on D-OL-HDF (Table 2). Figure 3 shows the weekly percentage increase in the efficacy of D-OL-HDF over a broad spectrum of solutes in comparison with S-OL-HDF.

There was a significant decrease in predialysis levels of urea, creatinine, uric acid (Table 3), and large molecules (β_2-microglobulin and myoglobin) over 6 months (Fig. 4). The biochemical outcomes for predialysis so-

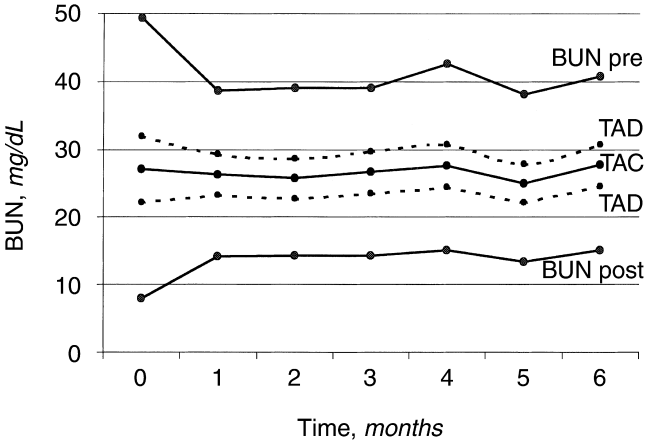

Fig. 2. Evolution of pre and postdialysis blood urea nitrogen (BUN), time average concentration $(TAC)_{BUN}$ and time average deviation $(TAD)_{BUN}$ switching from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF).

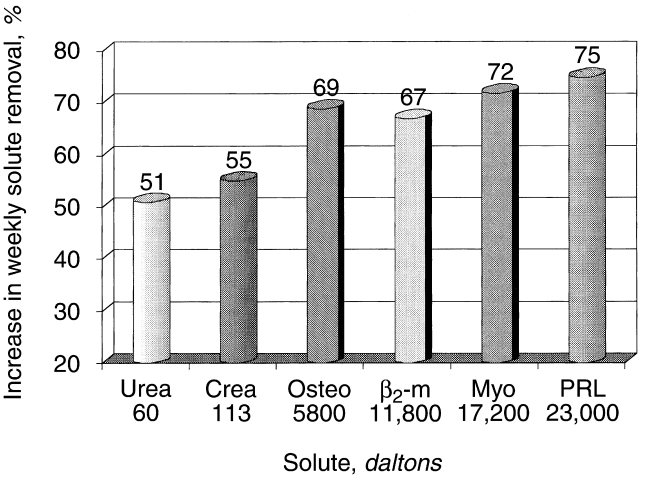

Fig. 3. Increase in the weekly percentage removal of a broad spectrum of solutes with short daily on-line hemodiafiltration (D-OL-HDF) in comparison with three times a week on-line hemodiafiltration (OL-HDF). Abbreviations are: Crea, creatinine; Osteo, osteopontin; β_2-m, microglobulin; Myo, myoglobin; PRL, prolactin.

Table 2. Comparison of urea, creatinine, osteocalcin, β_2-microglobulin, myoglobin, and prolactin reduction ratios between three times a week standard on-line hemodiafiltration (S-OL-HDF) and short daily on-line hemodiafiltration (D-OL-HDF)

Reduction ratio	S-OL-HDF	D-OL-HDF	*P* value
Session			
Urea %	84.3 ± 3	64.2 ± 5	<0.001
Creatinine %	73.1 ± 2	56.7 ± 3	<0.001
Osteocalcin %	71.3 ± 7	60.6 ± 7	<0.001
β_2-microglobulin %	79.8 ± 4	66.3 ± 11	<0.05
Myoglobin %	65.7 ± 5	56.5 ± 10	<0.05
Prolactin %	65.6 ± 4	57.1 ± 9	<0.05
Weekly			
Urea %	253 ± 8	385 ± 32	<0.001
Creatinine %	219 ± 5	340 ± 15	<0.001
Osteocalcin %	214 ± 21	363 ± 39	<0.001
β_2-microglobulin %	239 ± 11	398 ± 66	<0.001
Myoglobin %	197 ± 14	339 ± 62	<0.001
Prolactin %	196 ± 13	343 ± 55	<0.001

dium, potassium, bicarbonate, calcium, phosphorus, and iPTH are shown in Table 3. Althought serum phosphate did not change, phosphate binders (calcium carbonate in seven patients and calcium acetate plus aluminium hydroxide in one patient) were reduced from 7.3 ± 3 tablets/day on S-OL-HDF to 2.9 ± 3 tablets/day after 3 months and 2.85 ± 4 after 6 months ($P < 0.001$) on D-OL-HDF. The mean baseline value for β_2-microglobulin (29.5 ± 2 mg/L) was 15 times higher than normal range and myoglobin (214 ± 75 mg/L) was three times higher than maximal normal range. The mean baseline predialysis level of osteocalcin (18.4 ± 19 mg/L) was slightly higher than maximal normal range, and the baseline predialysis levels of prolactin (16.4 ± 10 ng/mL) were within the normal range and remained constant during the 6-month study period (Table 3). In the diabetic patient, the insulin dose was reduced from 24 IU/day at baseline to 12 IU/day after 2 months on D-OL-HDF.

Hematologic monitoring

Most hematologic parameters in our study did not show any significant changes (Table 4). Only the predialysis ferritin decreased from 473 ± 263 ng/mL at baseline to 312 ± 147 ng/mL after 3 months ($P < 0.01$) and to 290 ± 177 ng/mL after 6 months ($P < 0.01$). Erythropoietin doses (3250 ± 2052 IU/week) were not varied during the study and intravenous iron was increased from 24 to 46 mg/week (sodium ferric gluconate complex) during the study period.

Nutrition and inflammation parameters

Interdialytic weight gain per session decreased from 2.17 ± 1.5 kg to 1.25 ± 0.5 kg, but weekly interdialytic weight gain rose from 7.62 ± 1.5 kg on S-OL-HDF to 8.48 ± 2.5 kg on D-OL-HDF ($P < 0.001$) (Table 5). Mean nPCR increased from 0.93 ± 0.2 g/kg/day on S-OL-HDF to 1.18 ± 0.3 g/kg/day after 3 months ($P < 0.05$) and 1.13 ± 0.2 g/kg/day after 6 months on D-OL-HDF. There were no significant changes in serum protein, albumin, prealbumin, transferrin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fibrinogen and C-reactive protein. Body weight (measured as dry weight after dialysis) increased from 67.8 ± 8 kg on S-OL-HDF to 68.3 ± 8 kg after 3 months and 69.4 ± 8 kg after 6 months (NS) on D-OL-HDF.

Blood pressure monitoring

During the baseline period, three patients had hypertension (predialysis mean blood pressure >110 mm Hg)

Table 3. Change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF). Predialysis levels of sodium, potassium, bicarbonate, urea, creatinine, uric acid, calcium, phosphorus, intact PTH (iPTH), osteocalcin and prolactin

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Sodium *mmol/L*	139 ± 1	140 ± 4	140 ± 4	139 ± 4	140 ± 5	141 ± 1	139 ± 4
Potassium *mmol/L*	5.1 ± 0.5	4.5 ± 0.4	4.6 ± 0.7	4.7 ± 0.5	4.6 ± 0.7	4.7 ± 0.8	4.8 ± 0.5
Bicarbonate *mmol/L*	22.0 ± 2	23.6 ± 3	23.3 ± 2	24.4 ± 3[a]	23.5 ± 3	25.6 ± 3[b]	24.5 ± 3[a]
Uric acid *mg/dL*	6.08 ± 1	5.12 ± 1[b]	4.73 ± 1[b]	5.03 ± 1[b]	4.80 ± 1[b]	4.64 ± 1[b]	4.71 ± 1[b]
Urea *mg/dL*	105 ± 20	83 ± 18[b]	83 ± 17[b]	83 ± 24[b]	91 ± 10[a]	82 ± 15[b]	87 ± 15[b]
Creatinine *mg/dL*	7.38 ± 1	6.19 ± 1[b]	5.76 ± 1[b]	6.03 ± 1[b]	5.96 ± 1[b]	6.23 ± 1[b]	6.34 ± 1[b]
Calcium *mg/dL*	9.8 ± 0.3	9.7 ± 0.7	9.6 ± 0.7	9.6 ± 0.6	9.6 ± 0.4	9.5 ± 0.5	9.8 ± 0.6
Phosphorus *mg/dL*	4.29 ± 1	4.54 ± 1	4.68 ± 1	4.11 ± 1	4.81 ± 1	4.46 ± 1	4.65 ± 1
iPTH *pg/mL*	136 ± 111	275 ± 288	176 ± 156	171 ± 157	189 ± 171	161 ± 141	117 ± 90
Osteocalcin *mg/L*	18.4 ± 19	19.6 ± 19	19.0 ± 20	23.0 ± 18	22.1 ± 17	19.8 ± 16	17.4 ± 14
Prolactin *ng/mL*	16.4 ± 10	17.3 ± 11	19.4 ± 14	18.9 ± 12	17.8 ± 12	19.8 ± 13	17.0 ± 12

[a] $P < 0.05$. [b] $P < 0.01$ with respect to baseline value (ANOVA repeated measures)

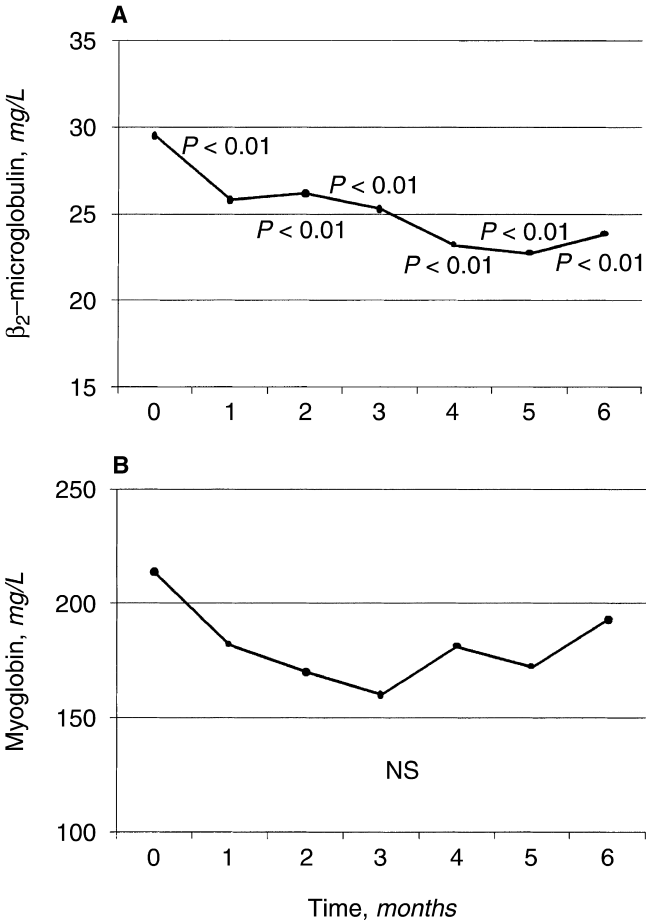

Fig. 4. Change from three times a week on-line hemodiafilitration (HDF) to short daily on-line hemodiafiltration (D-OL-HDF). (*A*) Predialysis serum β_2-microglobulin (11,800 D) over 6 months. (*B*) Myoglobin (17,200 D) levels over 6 months. $P < 0.01$, analysis of variance (ANOVA) repeated measures.

and two were receiving antihypertensive medication. Average baseline values were systolic blood pressure 144.5 ± 24 mm Hg; diastolic blood pressure 79.3 ± 11 mm Hg; and mean blood pressure 101.0 ± 15 mm Hg. During the first month on D-OL-HDF, antihypertensive medication was withdrawn and only one patient had high blood pressure. Reductions in blood pressure were observed although without achieving statistical significance (Table 4).

Cardiac parameters

Six patients had LVH assessments performed while on S-OL-HDF, just before the beginning of the study. A considerable reduction of LVH was observed when patients were switched to D-OL-HDF. LVM decreased from 167 ± 76 g at baseline to 124 ± 47 g after 3 months ($P < 0.01$) and 118 ± 37 g after 6 months ($P < 0.01$). LVMI decreased from 98 ± 45 g/m^2 at baseline to 72 ± 28 g/m^2 after 3 months ($P < 0.01$) and 69 ± 22 g/m^2 after 6 months ($P < 0.01$). LVH was present in only one patient at the end of the 6-month study period. A significant reduction in IVS, AWT, PWT, LWT, and IWT was also observed. There were no changes in in LVIDD, LVISD, LA, AO, LVEDV, LVESV, and EF (Table 6)

Finally, predialysis homocysteine levels decreased from 21.8 ± 3 μmol/L on S-OL-HDF to 12.5 ± 2 μmol/L after 3 months ($P < 0.01$) and 14.1 ± 5 kg after 6 months ($P < 0.01$) on D-OL-HDF.

DISCUSSION

Several groups [1–8] have reported excellent clinical results with higher frequency or daily dialysis because it is more physiologic and decreases the fluctuations in volume, solutes, and electrolytes. Improvement in comfort during and between dialysis sessions, clinical and biochemical parameters, anemia correction, hypertension control, nutrition status, and quality of life have been reported. OL-HDF is a safe technique that allows a considerable increase in convection, a high dialysis dose for both small and large molecules, and good control of anemia, nutrition, and blood pressure. In a previous paper [20], we reported that OL-HDF is the best technique for large molecule removal. The present study is the first experience reported in literature with D-OL-HDF and shows that the switch from standard three times a week

Table 4. Change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF). Hematologic parameters and blood pressure findings

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Hemoglobin *g/dL*	12.3 ± 1	12.7 ± 1	12.5 ± 1	12.8 ± 1	12.6 ± 1	12.8 ± 1	12.8 ± 1
Hematocrit %	36.8 ± 5	37.8 ± 5	36.9 ± 5	38.2 ± 4	37.2 ± 3	38.0 ± 4	38.1 ± 4
Leucocytes $\times 10^3/\mu L$	6.91 ± 1	6.91 ± 1	6.93 ± 2	6.33 ± 1	6.83 ± 1	6.85 ± 2	6.14 ± 1
Lymphocyte $\times 10^3/\mu L$	1.93 ± 0.3	1.78 ± 0.5	1.71 ± 0.3	1.92 ± 0.4	1.87 ± 0.4	1.88 ± 0.3	1.84 ± 0.4
TS %	31.9 ± 12	31.2 ± 12	24.5 ± 7	31.7 ± 11	28.3 ± 10	28.4 ± 14	27.5 ± 11
Ferritin *ng/mL*	473 ± 263	360 ± 152[a]	375 ± 160[a]	312 ± 147[b]	277 ± 151[b]	273 ± 165[b]	290 ± 177[b]
Iron doses *mg/week*	24 ± 8	27 ± 14	28 ± 18	28 ± 18	37 ± 32	43 ± 33[a]	46 ± 31[b]
EPO doses *IU/kg/week*	48.0 ± 28	47.5 ± 28	47.4 ± 28	47.3 ± 28	47.0 ± 28	46.8 ± 28	46.8 ± 28
ERI	4.01 ± 2	3.83 ± 2	3.71 ± 2	3.68 ± 2[a]	3.75 ± 2	3.76 ± 2	3.75 ± 2
SBP *mm Hg*	144 ± 24	140 ± 23	130 ± 29	131 ± 25	130 ± 17	131 ± 22	135 ± 18
DBP *mm Hg*	79.3 ± 11	78.3 ± 13	71.4 ± 14	70.1 ± 16	72.4 ± 11	75.2 ± 10	75.5 ± 12
MBP *mm Hg*	101 ± 15	98.9 ± 16	90.8 ± 18	90.4 ± 18	91.4 ± 12	93.8 ± 13	95.6 ± 14

Abbreviations are: TS, transferrin saturation; EPO, erythropoietin; ERI, EPO resistivity index (EPO doses/hemoglobin); SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.

[a]$P < 0.05$; [b]$P < 0.01$ with to respect baseline value (ANOVA repeated measures); [c]iron dose was endovenous sodium ferric gluconate complex

Table 5. Change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF). Nutrition and inflammation findings

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
nPCR *g/kg/day*	0.931 ± 0.2	1.123 ± 0.3	1.075 ± 0.3	1.178 ± 0.3[a]	1.160 ± 0.1[a]	1.064 ± 0.3	1.129 ± 0.2
Body weight *kg*	67.8 ± 8	68.1 ± 8	68.1 ± 8	68.4 ± 8	68.8 ± 8	69.2 ± 8	69.4 ± 8
Weight gain *kg*	2.17 ± 0.5	1.28 ± 0.7[b]	1.13 ± 0.4[b]	1.24 ± 0.7[b]	1.26 ± 0.4[b]	1.26 ± 0.6[b]	1.15 ± 0.6[b]
Total protein *mg/dL*	7.0 ± 0.3	7.3 ± 0.6	6.8 ± 0.5	6.9 ± 0.3	7.0 ± 0.4	6.9 ± 0.4	7.0 ± 0.5
Albumin *mg/dL*	3.73 ± 0.2	3.74 ± 0.2	3.62 ± 0.3	3.77 ± 0.4	3.76 ± 0.2	3.65 ± 0.2	3.77 ± 0.2
Prealbumin *mg/dL*	33.1 ± 5	35.0 ± 6	32.3 ± 7	32.2 ± 7	33.8 ± 5	30.2 ± 5	32.3 ± 4
Transferrin *mg/dL*	169 ± 17	176 ± 26	162 ± 22	179 ± 15	184 ± 21	186 ± 20	195 ± 17
T cholesterol *mg/dL*	186 ± 44	200 ± 53	190 ± 59	203 ± 60	205 ± 66	203 ± 72	201 ± 58
HDL-c *mg/dL*	49.5 ± 8	57.0 ± 9	51.1 ± 16	58.9 ± 6	54.9 ± 7	56.3 ± 6	57.1 ± 11
LDL-c *mg/dL*	102 ± 33	113 ± 42	108 ± 38	115 ± 52	118 ± 56	135 ± 82	125 ± 45
Triglycerides *mg/dL*	165 ± 64	149 ± 96	152 ± 69	146 ± 82	157 ± 92	154 ± 62	162 ± 92
Fibrinogen *mg/dL*	428 ± 136	445 ± 35	486 ± 77	392 ± 24	420 ± 64	343 ± 38	353 ± 52
CRP *mg/L*	6.7 ± 7	8.4 ± 12	20.9 ± 36	3.8 ± 4	4.9 ± 7	5.4 ± 10	3.4 ± 4

Abbreviations are: nPCR, normalized protein catabolic rate; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a]$P < 0.05$; [b]$P < 0.01$ with respect to baseline value (ANOVA repeated measures)

Table 6. Change from three times a week on-line hemodiafiltration (OL-HDF) to short daily on-line hemodiafiltration (D-OL-HDF). Cardiac magnetic resonance imaging data

	Baseline	Month 3	Month 6
LVIDD *mm*	45.6 ± 2	47.1 ± 3	46.9 ± 4
LVISD *mm*	29.0 ± 3	29.2 ± 4	28.7 ± 3
IVS *mm*	15.0 ± 3.9	12.9 ± 3.2[a]	12.7 ± 1.8[a]
AWT *mm*	11.9 ± 4.6	8.3 ± 1.7[a]	9.4 ± 1.4[a]
PWT *mm*	11.9 ± 2.2	9.9 ± 2.6[b]	9.8 ± 2.3[b]
LWT *mm*	11.5 ± 2.9	9.7 ± 1.7	9.5 ± 2.0
IWT *mm*	12.6 ± 3.1	9.6 ± 2.7[b]	10.1 ± 2.1[b]
LA *mm*	34.7 ± 4.2	36.5 ± 5.0	37.6 ± 6.0
AO *mm*	33.8 ± 4.0	33.8 ± 2.6	33.8 ± 2.8
LVEDV *mL*	127.9 ± 18	116.4 ± 18	113.4 ± 13
LVESV *mL*	53.3 ± 9	39.7 ± 12	44.7 ± 11
EF %	60.7 ± 5	66.4 ± 10	62.3 ± 8
LVM *g*	166.9 ± 76	123.7 ± 47[b]	118.1 ± 37[b]
LVMI g/m^2	97.9 ± 45	72.4 ± 28[b]	68.9 ± 22[b]

Abbreviations are: LVIDD, left ventricular internal diameter at end-diastole; LVISD, left ventricular internal end-systole diameter; IVS, interventricular septal thickness; AWT, anterior wall thickness; PWT, posterior wall thickness; LWT, lateral wall thickness; IWT, inferior wall thickness; LA, left atrium dimension; AO, aortic root dimension; LVEDV, left ventricular end diastole volume; LVESV, left ventricular end systole volume; EF, ejection fraction; LVM, left ventricular wall mass; LVMI, LVM index.

[a]$P < 0.05$; [b]$P < 0.01$ with respect to baseline value (ANOVA repeated measures)

OL-HDF to short D-OL-HDF has been satisfactory with excellent clinical tolerance and patient acceptance. It should be pointed out that, during the baseline period, the patients received a high dialysis dose and mantained a good control of anemia, nutrition, and blood pressure.

Although dialysis time was similar during both treatment schedules, an increase in the dialysis dose was obtained with D-OL-HDF, which confirms the beneficial effect of higher frequency. Although weekly spKt/V or weekly eKt/V were similar between both study periods, the EKR and standard Kt/V, proposed to measure the dialysis dose in dialysis regimens with different frequency, were 26% and 48% higher on D-OL-HDF, respectively. Weekly URR also was 52% higher in the daily schedule; this is a simple method that is able to show differences between regimens with different frequencies and the weekly reduction ratio can be used for any solute as well as urea.

Solute and fluid removal are the major goals of dialysis. Reduction of elevated predialysis uremic toxins levels may prevent or postpone the onset of dialysis-related complica-

tions. The difficulty in reducing large molecule plasma levels can be explained by the low distribution volume (approximately 20% of the body weight) or by a multicompartimental model [21, 22]. In β_2-microglobulin, the best results have been reported by Raj et al [23] with daily 8-hour nocturnal dialysis. They noted that the predialysis β_2-microglobulin levels progressively declined from 27.2 to 13.7 mg/dL by 9 months. In the present paper, we observed a 21% reduction in predialysis plasma β_2-microglobulin levels over a 6-month period.

Resistance to diffusion within tissues and organs creates solute disequilibrium gradients. The resistance to diffusion can be quantitated as the intercompartment mass-transfer coefficient (Kc) and is molecular size–sensitive. It is known that to obtain the same TAC in patients treated intermittently, the dialysis dose must be greater than during daily or continuous treatment. This phenomenon is magnified in solutes that have a lower Kc than urea [24, 25]. Our study supports this argument since we observed an increase in solute removal with higher frequency and this effect was more significant in solutes with greater molecular size or lower Kc (Fig. 3).

A decrease in erythropoietin dose has been reported by Vos, Zilch, and Kooistra [26], Galland et al [27], and Pierratos [28], amounting to 20%, 63%, and 40%, respectively. Buoncristiani et al [1] initially reported an increase in hemoglobin from 8.1 ± 2 g/dL to 13.8 ± 3.8 g/dL, although the erythropoietin dose was not mentioned. We did not observe any changes in hemoglobin levels or erythropoietin dose in this study. Compared with these papers our patients received a higher dialysis dose with OL-HDF and baseline hemoglobin levels were higher with a low erythropoietin dose (<50 UI/kg/week). Ferritin was significantly reduced during the study and iron supplements were raised gradually to improve functional iron deficiency. The use of intravenous iron in daily dialysis experiencies has not been clearly specified in the literature but it is possible that iron needs in daily dialysis may be higher. Kooistra et al [7] and Pierratos et al [5] did not observe any changes in erythropoietin dose and anemia control in initial reports but, in later papers, reported a decrease in erythropoietin dose related to changes in iron use [26, 28].

An increase in body weight (1.5 kg after 6 months) has been observed in this study as a marker of improvement in nutritional status. A rapid improvement in appetite was reported and an increase of nPCR was observed. Improvement of certain causes of anorexia such as postdialysis fatigue, reduction in fluid overload, uremic milieu, medium and large-sized molecule removal was observed with the change to D-OL-HDF. Accumulation of substances <5000 D isolated from uremic plasma [29] and leptin [30, 31], 16,000 D have been related with anorexia and nutrition. Improvement in insulin resistance, growth hormone and insulin-like growth factor-1 (IGF-1) resistance, and metabolic acidosis could be also involved [32]. Galland et al [27] reported similar data and found that short daily hemodialysis rapidly improves nutritional status, reporting an increase in body weight of 1.8 kg after 6 months without any changes in weekly Kt/V.

An improvement in phosphate control has been observed in this study and it has also been reported by most authors in daily dialysis treatment. Although we did not observe significant differences from predialysis phospate levels, this could be due to the existence of confounding factors such as a reduction in phosphate binders (60% in our patients) and an increase in phosphate intake.

Cardiovascular disease is the most common cause of mortality in chronic hemodialysis patients, being the attributed cause of death in approximately 50% of the cases. In this study, the change to D-OL-HDF improved several cardiovascular risk factors such as arterial hypertension, hyperuricemia, LVH, and hyperhomocysteinemia. Hypertension is strongly associated with mortality and is very prevalent in dialysis patients ranging from 75% to 100%. Although our patients were relatively well controlled at baseline (only three patients were hypertensive and two were receiving drugs), better blood pressure control was achieved with D-OL-HDF without antihypertensive medications.

LVH is an independent cardiovascular risk factor and is strongly associated with mortality in dialysis patients [33]. LVH is present in 70% to 80% of the dialysis population [34]. Hypertension, poor extracelular fluid volume control, anemia, and uremia (accumulation of uremic toxins and circulatory vasoconstrictors) have been implicated in the pathophysiology of LVH. In the present study, we observed a marked regression of LVH. The LVMI was reduced by 30% after 6 months, after patients on S-OL-HDF were switched to D-OL-HDF. MRI has been validated for measurements of LV and RV wall mass [35]. Because of its high accuracy and superior reproducibility, MRI may be considered the gold standard for the assessment of ventricular dimensions, functional parameters and left and right ventricular mass [36]. Other authors have reported regression of cardiac hypertrophy measured with echocardiography. Fagugli et al [37] and Galland et al [27] reported a LVMI reduction of 18% and 31%, respectively, in patients receiving short daily dialysis. Recently, Chan et al [38] reported a LVMI reduction of 22% in 28 patients receiving slow nocturnal daily dialysis.

Hyperhomocysteinemia has been identified as an independent risk factor for cardiovascular disease [39]. The moderate elevation of total homocysteine concentrations in plasma, which is observed in at least 85% of hemodialysis patients, can be lowered by appropriate cofactor supplementation (folic acid, vitamin B_6, and B_{12}). However, administration of folic acid at pharmacologic doses,

either alone or combined with vitamin B_6 and B_{12}, is only partially effective in reducing plasma homocysteine and few dialysis patients normalize their homocysteine concentrations entirely [40]. This elevation of homocysteine concentrations is mainly due to the reduction of plasma homocysteine clearance, although the cause of this decrease is still unkown [41]. It is possible that the reduction of clearance is due to multiple abnormalities of the remethylation pathway that are not related to folate [42]. Therefore, the inhibition by uremic toxins of enzymes involved in the extrarenal homocysteine removal has been suggested as an alternative explanation for the elevated homocysteine levels in end-stage renal disease (ESRD) [43]. The effect of dialysis itself on plasma homocysteine concentration has been investigated in only a small number of studies. Interestingly, the reduction in homocysteine was not markedly different between high- and low-flux devices [44]. In the present study, plasma homocysteine levels decreased near normality without any changes in medical therapy, but only a higher frequency of dialysis. Similar data have been reported by Floridi et al [45], where homocysteine levels in 16 patients switched from standard hemodialysis to daily short hemodialysis diminished from 27.5 ± 11 μmol/L to 17.2 ± 7 μmol/L.

CONCLUSION

The change from three times a week S-OL-HDF to short D-OL-HDF has been satisfactory. The main benefits observed in this study were the excellent clinical tolerance and patient acceptance, disappearance of postdialysis fatigue, better dialysis adequacy (EKR, Kt/Vstd, weekly URR and TAD), a higher removal of medium and large-sized molecules, a reduction of phosphate binders, an improvement in nutritional status and, finally, a marked reduction of cardiovascular risk factors: better control of blood pressure without antihypertensive medication, reduction of ferritin and uric acid levels, regression of LVH and normalization of homocysteinemia levels.

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