Prospective evaluation of an in-centre conversion from conventional haemodialysis to an intensified nocturnal strategy

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Abstract

Introduction. Under physiological conditions kidneys work continuously, 168 h/week. In contrast, patients with end-stage renal disease are usually dialyzed only 12–15 h/week. This unphysiological dialysis dose, even if considered adequate by current Kt/V-based dose estimates, is just capable to maintain the alterations of multiple metabolic parameters at a level that permits an unacceptable annual mortality rate of 10–20%, mainly due to cardiovascular events, protein energy wasting and infections.

Patients and Methods. Thirteen haemodialysis patients were converted from conventional (3 × 4 h/week) to an intensified nocturnal (3 × 8 h/week) dialysis and were longitudinally followed up for 12 months. Different parameters were evaluated before treatment conversion and quarterly during the follow-up period [i.e. dialysis efficacy
(eKt/V), mean arterial pressure (MAP), antihypertensive drug score, extra-cellular volume (ECV), haemoglobin, transferrin saturation, ferritin, dose of erythropoiesis-stimulating agents (ESA), iron requirement, parameters of nutrition (body weight (BW), albumin, protein, normalized protein catabolic rate (nPCR), bioelectrical impedance analysis (BIA)), C-reactive protein, calcium–phosphate product, alkaline phosphatase (AP), intact parathyroid hormone (iPTH) and amount of phosphate-binding pharmacotherapy.

**Results.** The calculated dialysis efficacy rose after switching the treatment mode (eKt/V 1.87 versus 2.7, \( P < 0.0001 \)). Further, a significantly decreased MAP in the pre- (100 versus 89 mmHg) and postdialytic period (97 versus 83 mmHg), and a decreased ECV (13.8 versus 13.2 L; \( P = 0.03 \)) even though antihypertensive pharmacotherapy could be substantially reduced (\( P < 0.0001 \)), was found. Concomitant with a reduction of ESA (66.5 versus 45.2 IU/kg/week; \( P = 0.006 \)), the haemoglobin level rose significantly (11.4 versus 12.5 g/dL, \( P = 0.01 \)). Nutritional status assessed by BW (70.9 ± 20.2 versus 72.1 ± 19.8 kg, \( P = 0.02 \)), nPCR (1.39 versus 2.25 g/kg/day, \( P = 0.02 \)) and BIA (phase angle: 6.2 versus 6.9°, \( P < 0.001 \)) improved. The calcium–phosphate product slightly declined, without changes in the dose of any phosphate binders. Surprisingly, iPTH of those patients with intact parathyroid glands (\( n = 7 \)) increased ~3-fold (27.9 versus 59.35 pmol/L, \( P = 0.009 \)), while the AP was found stable.

**Conclusion.** This study demonstrates improvements in numerous dialysis-associated metabolic variables after intensification of HD time. Of note, an increase of iPTH was detected in those patients with intact parathyroid glands.

**Keywords:** anaemia; blood pressure; calcium × phosphate product; hyperparathyroidism; nocturnal haemodialysis

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**Introduction**

The number of end-stage renal disease (ESRD) patients is steadily increasing while financial resources to treat these patients are limited. Economical factors and increased dialysis intensity, due to an increased membrane surface and better material, have led to a sharp reduction in weekly dialysis time as compared to the first two decades of chronic dialysis treatment. The short brisk dialysis sessions, felt to be endorsed by adequate Kt/V, are accompanied by 5-year survival rates as low as 35% [1]. Consequently, there is a critical need to improve renal replacement therapies resulting in a renewed interest in longer and more frequent sessions. In three times weekly long (e.g. 8 h) haemodialysis (HD) both dialysis time and dose are significantly increased [2,3]. These coordinates of an intense dialysis regime have been employed for over three decades in Tassin, France, resulting in a better 5-year survival as compared to general registers [4]. Nocturnal haemodialysis uses nightly sleep, an otherwise idle time, giving patients the opportunity to pursue their daily duties without major limitations. Several smaller clinical studies have shown that this form of dialysis provides excellent urea, and phosphate removal as well as an improved control of blood pressure [5]. Although many studies investigated the effect of frequent (6 per week) nocturnal dialysis [6] on nutritional status and anaemia, data in the less intense regime, i.e. 3 × 8 h/week, are lacking or are cross-sectional in nature, comparing conventional HD and (nocturnal) prolonged/intensified HD regimen. Therefore, we aimed to prospectively investigate the influence of nocturnal (3 × 8 h) HD over 12 months in quarterly examinations evaluating dialysis efficacy, clinical parameters, indicators of anaemia, bone metabolism, nutritional/hydration status, inflammation and pharmacotherapeutical parameters. This treatment strategy seems to be most realistic in terms of patience acceptance as well as economical considerations, i.e. dialysis reimbursed at a weekly flat rate [7].

**Patients and methods**

**Study design**

The study was approved by the local Ethics Committee of Hanover Medical School, Germany (protocol no. 5076) and was performed as a prospective, longitudinal, single-centre study. Out of 70 patients on maintenance HD, 25 remained available after adjustment for exclusion criteria (secondary hyperparathyroidism with need of a calcium-sensitizing therapy, central venous catheter, need of erythrocyte transfusion, severe arterial hypertension (HTP) and severe comorbidities).

Twenty-five remained available after adjustment for inclusion/exclusion criteria. Finally, 13 stable HD (11♂, 2♀) patients were included. All of them had been dialysed at least 1 year prior to the study using a native (Cimino-Brescia) AV-fistula with a standard dialysis regimen of 4 h three times weekly.

Both dialysis regimens (standard versus intensified) were performed as in-centre high-flux bicarbonate haemodialysis and did not differ in terms of ultrapure water quality, dialysis modality, dialysis machines (5008, Fresenius Medical Care, Bad Homburg, Germany), heparin use (400 IU/h), vascular access (native AV-fistula), high-flux dialysis filter (Polyflux-140-H, Gambro) and surface (1.4 m²). After initiating the study, all participants were dialyzed with the same blood (Qb 200 mL/min) and dialysate flow (Qd 500 mL/min).

Initially, multiple surrogate parameters of known dialysis-associated morbidities were assessed. It concerned the following scopes:

- dialysis efficacy (eKt/V, creatinine)
- blood pressure (pre- and postdialytic MAP, antihypertensive drug score, extra-cellular volume (ECV))
- erythropoiesis (Hb, transferrin saturation, ferritin, need of ESA/kg body weight, need of iron substitution)
- nutrition and inflammation (total protein, albumin, CRP, dry body weight (BW), body mass index (BMI), normalized protein catabolic rate (nPCR) and BIA)
- bone metabolism (Ca × Phos product, 25-(OH) vitamin D, alkaline phosphatase (AP), phosphate-binding pharmacotherapy). Intact PTH was measured using the Elecsys assay (Roche Diagnostics, Mannheim, Germany).

All participants were switched from their conventional (cHD, 3 × 4 h/week) to the intensified nocturnal haemodialysis regimen (nHD, 3 × 8 h/week). During the following 12 months, quarterly follow-up visits with evaluation of all above-mentioned parameters were performed. Blood pressure (BP) was measured pre- and postdialytic using an automated system (Dinamap® Pro 1000, GE Healthcare, Munich, Germany) in a supine position. Predialytic mean arterial pressure (MAP) after the long interdialytic interval was calculated as the mean value of the four previous long interval sessions. Antihypertensive medication was recorded and standardized according to an antihypertensive drug index (Table 1) [8].

ESA units were divided per body weight. Due to different treatment regimens an erythropoietin equivalent dose (EPO ED) was defined according to published recommendations [9]. The weekly dose of epoetin alpha (Erypo®) was defined as EPO ED. For darbepoetin alpha (Aranesp®), factor 176 was used in order to calculate the weekly EPO ED.
the voltage drop was detected at the proximal electrodes. Values of the µcitation current of 800
were performed at 5, 50 and 100 kHz using separate generators. An ex-
one electrode on the hand opposite from the A V -shunt and the other one
performed with the patient in a supine position for at least 15 min, placing
(Nutriguard-M, data input, Darmstadt, Germany). Measurements were
multi-frequency bioelectrical impedance analysis (BIA) at baseline, af-

Bioelectrical impedance analysis (BIA)
We assessed nutritional parameters such as extra-cellular mass (ECM),
body cell mass (BCM) and the phase angle (PA) in all patients using
multi-frequency bioelectrical impedance analysis (BIA) at baseline, af-
ter 6 and 12 months. We used a multi-frequency impedance analysers
(Nutriguard-M, data input, Darmstadt, Germany). Measurements were
performed with the patient in a supine position for at least 15 min, placing
one electrode on the hand opposite from the AV-shunt and the other one
on the corresponding foot. Ultra-specific multi-frequency measurements
were performed at 5, 50 and 100 kHz using separate generators. An ex-
citation current of 800 μA was introduced at both distal electrodes and
the voltage drop was detected at the proximal electrodes. Values of the
total resistance (Rt), the reactance (Xt) and resistance of upper and lower
extremities (Ri, Ri) were obtained and body composition was calculated
using specially designed software (Nutriflex 5.1©, Darmstadt, Germany).
Nutritional parameters (ECM, BCM and PA) were evaluated. Measuring at
different frequencies permitted additional determination of extra-
cellular and intracellular volumes (ECV, ICV). The BIA technique has
been validated previously [14–17]. The relevance of the ECV in fluid state
has been assessed.

Antihypertensive drug index (DI)/drug score (DS)
We used an antihypertensive DI according to the following formula, as de-
scribed previously [8]. The DI has been defined as (10 × [daily dose/max.
recommended dose]). Due to different antihypertensive treatment strate-
gies, we used the sum of the daily DI of all antihypertensives as so-called
drug score (DS), DS = Sum of the DI per day. Table 1 shows the antihy-
tensive drugs of the study participants and the maximum recommended
daily doses.

Table 1. Maximum daily dose of the study participants’ antihypertensive
drug regimens for the calculation of the drug index (DI = 10 × [daily
dose/max. recommended dose]); of the drug score (DS) results from the
sum of the daily DI (DS = sum of the DI per day)

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Maximum daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>200</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>40</td>
</tr>
<tr>
<td>Enalapril</td>
<td>40</td>
</tr>
<tr>
<td>Ramipril</td>
<td>10</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>10</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>270</td>
</tr>
<tr>
<td>Nebilet</td>
<td>5</td>
</tr>
<tr>
<td>Cardivilol</td>
<td>25</td>
</tr>
<tr>
<td>Lercapindip</td>
<td>20</td>
</tr>
<tr>
<td>Cansecurity</td>
<td>32</td>
</tr>
<tr>
<td>Losartan</td>
<td>100</td>
</tr>
<tr>
<td>Moxonidin</td>
<td>0.6</td>
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</tbody>
</table>

Measurement of equilibrated Kt/V (eKt/V)
For the present study, we used the eKt/V, calculated according to the Dau-
girdas formula [10]. Our practice is to slow the blood pump to 100 mL/
min and then obtain the blood sample BUN 15 s later. This procedure is
consistent with the 2006 National Kidney Foundation Dialysis Outcomes
Quality Initiative (K/DOQI) and the European and Canadian haemodial-
ysis guidelines [11–13]. Compared to later sampling times, this earlier
measurement is thought to be the most accurate method to support formal
kinetic modelling. To ensure consistent values, all measurement of the
postdialysis BUN were performed exactly the same way each time it has
been assessed.

Dialysis efficacy increased 3 months after intensifying
dialysis dose
According to the current guidelines [11–13], HD efficacy
was assessed by measurement of the eKt/V and showed a
significant increase after dialysis intensification [baseline
(BL): 1.9 ± 0.3, 3 months: 2.6 ± 0.8 and after 12 months:
2.7 ± 0.5, P < 0.0001, Table 2]. Residual renal function
(RRF) did not differ significantly over the study period
(baseline 327 ± 588 mL/day versus after 12 months 261 ±
457 mL/day, P = 0.21).

Improvement in blood pressure control despite a reduction
in antihypertensive pharmacotherapy
The predialytic MAP significantly declined during the
study period (BL: 100.1 ± 15.3, after 12 months: 89.2 ±
11.3 mmHg, P = 0.002, Figure 1A). Similarly, postdia-
lytic MAP significantly declined (BL: 97.3 ± 15.8, after
12 months: 83.4 ± 9.3, P = 0.005), while concomitantly
the amount and doses of antihypertensive drugs could be
reduced (drug score BL: 11.6 ± 9.1, after 12 months: 3.5 ±
4.5, P < 0.0001, Figure 1B). Blood pressure reduction
is paralleled by a slight decline in ECV (BL 13.8 ±
4.0 L versus 13.22 ± 3.8 L after 12 months, P = 0.03,
Table 2).

Increase of haemoglobin despite a reduction in ESAs and
iron substitution
The HD dose increase led to a significant haemoglobin
improvement. During this study, all patients were within
the K/DOQI recommended reference range [19] >11 g/dL
(BL: 11.4 ± 0.9, after 12 months: 12.6 ± 0.9 g/dL, P <
0.0001, Figure 1A). Additionally, the need for ESAs fell
slightly under intensified nHD (BL: 66.5 ± 36, after 12
months: 45.2 ± 32 µg/kg/week, P = 0.006, Figure 2B).
However, transferrin saturation remained unchanged (BL
24%, after 12 months: 29%, P = 0.2), in spite of significant
reduction in intravenous iron substitution (BL: 58.7 ± 42,
after 12 months 16.9 ± 25.6 mg/week, P = 0.003, Figure
2C). Ferritin levels were stable over the whole study period
(P = 0.75, Table 2).
Table 2. Evaluation of clinical, biochemical and pharmacotherapeutical changes at baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>P-value</th>
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<tr>
<td><strong>Dialysis efficacy</strong></td>
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<tr>
<td>Creatinine</td>
<td>11.43 ± 3.1</td>
<td>11 ± 2.9</td>
<td>11 ± 3.7</td>
<td>10.9 ± 3.1</td>
<td>11.6 ± 4.7</td>
<td>ns</td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.87 ± 0.3</td>
<td>2.44 ± 0.43**</td>
<td>2.56 ± 0.54**</td>
<td>2.64 ± 0.48**</td>
<td>2.7 ± 0.53**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MAP predialytic (mmHg)</td>
<td>100 ± 15</td>
<td>99 ± 11</td>
<td>97 ± 11</td>
<td>94 ± 14*</td>
<td>89 ± 12**</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP postdialytic (mmHg)</td>
<td>97 ± 16</td>
<td>88 ± 11*</td>
<td>85 ± 9*</td>
<td>85 ± 11**</td>
<td>82 ± 9**</td>
<td>0.005</td>
</tr>
<tr>
<td>Drug score</td>
<td>11.6 ± 9.1</td>
<td>10.0 ± 8.7*</td>
<td>6.7 ± 5.8*</td>
<td>4.9 ± 5.4**</td>
<td>3.8 ± 4.5**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECV (L)</td>
<td>13.8 ± 4.0</td>
<td></td>
<td>13.38 ± 4.1</td>
<td></td>
<td>13.22 ± 3.9*</td>
<td>ns</td>
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<tr>
<td><strong>Erythropoiesis</strong></td>
<td></td>
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<tr>
<td>Hb (g/dL)</td>
<td>11.42 ± 0.92</td>
<td>12.16 ± 0.87</td>
<td>12.31 ± 0.99*</td>
<td>12.53 ± 1.1*</td>
<td>12.53 ± 0.84**</td>
<td>0.02</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>643 ± 323</td>
<td>666 ± 340</td>
<td>736 ± 341</td>
<td>680 ± 174</td>
<td>553 ± 262</td>
<td>ns</td>
</tr>
<tr>
<td>EPO (U/kg/week)</td>
<td>66.5 ± 36</td>
<td>45 ± 32.8</td>
<td>42.3 ± 21.5*</td>
<td>53.5 ± 38.5</td>
<td>45.2 ± 32**</td>
<td>0.003</td>
</tr>
<tr>
<td>Iron substitution (mg/week)</td>
<td>58.6 ± 42</td>
<td>73.3 ± 40.3</td>
<td>41.5 ± 38.6</td>
<td>16.9 ± 25.6*</td>
<td>18.3 ± 26.2*</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Malnutrition/inflammation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Dry body weight (kg)</td>
<td>70.9 ± 20.2</td>
<td>71.0 ± 21</td>
<td>71.2 ± 20.5</td>
<td>71.6 ± 19.5*</td>
<td>72.1 ± 19.8*</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.8 ± 5.1</td>
<td>22.9 ± 5.1</td>
<td>23.2 ± 5.2</td>
<td>23.4 ± 5.0*</td>
<td>23.6 ± 4.9*</td>
<td>0.009</td>
</tr>
<tr>
<td>Total protein (mg/dL)</td>
<td>68.6 ± 6.2</td>
<td>68.9 ± 5.5</td>
<td>70.7 ± 4.3</td>
<td>69 ± 4.1</td>
<td>70.4 ± 5.4</td>
<td>ns</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>42.8 ± 2.6</td>
<td>43.3 ± 1.6</td>
<td>43.6 ± 2.6</td>
<td>43.2 ± 3.1</td>
<td>44.4 ± 2.5</td>
<td>ns</td>
</tr>
<tr>
<td>nPCR (g/kg per day)</td>
<td>1.39 ± 0.29</td>
<td>1.71 ± 0.23*</td>
<td>1.55 ± 0.38</td>
<td>1.78 ± 0.37*</td>
<td>2.25 ± 1.5*</td>
<td>ns</td>
</tr>
<tr>
<td>ECM / BCM</td>
<td>0.91 ± 0.16</td>
<td></td>
<td>0.78 ± 0.09*</td>
<td></td>
<td>0.78 ± 0.1**</td>
<td>0.002</td>
</tr>
<tr>
<td>Phase angle</td>
<td>6.2 ± 1.1</td>
<td></td>
<td>6.91 ± 0.73*</td>
<td></td>
<td>6.88 ± 0.72**</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Bone metabolism</strong></td>
<td></td>
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</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.23 ± 0.3</td>
<td>2.19 ± 0.2</td>
<td>2.28 ± 0.21</td>
<td>2.28 ± 0.24</td>
<td>2.19 ± 0.27</td>
<td>ns</td>
</tr>
<tr>
<td>Phosphat (mmol/L)</td>
<td>1.94 ± 0.65</td>
<td>1.73 ± 0.52</td>
<td>1.7 ± 0.53</td>
<td>1.79 ± 0.36</td>
<td>1.71 ± 0.4</td>
<td>ns</td>
</tr>
<tr>
<td>Ca × Ph product (mmol²/L²)</td>
<td>4.39 ± 1.58</td>
<td>3.82 ± 1.31</td>
<td>3.88 ± 1.31</td>
<td>4.09 ± 1.1</td>
<td>3.73 ± 0.96</td>
<td>ns</td>
</tr>
<tr>
<td>25(OH) vitamin D (µg/L)</td>
<td>28.5 ± 11.7</td>
<td>37.54 ± 13.3</td>
<td>38.9 ± 15.1*</td>
<td>39.38 ± 33.6*</td>
<td>39.25 ± 26.6*</td>
<td>0.01</td>
</tr>
<tr>
<td>iPTH (pmol/L) TOTAL</td>
<td>27.03 ± 25.32</td>
<td>40.41 ± 18.9</td>
<td>35.59 ± 32.8</td>
<td>39.38 ± 9.6</td>
<td>31.1 ± 26.9</td>
<td>ns</td>
</tr>
<tr>
<td>iPTH intact gland</td>
<td>27.9 ± 24.2</td>
<td>40.1 ± 18.9</td>
<td>55.8 ± 33.0*</td>
<td>62.5 ± 46.9*</td>
<td>59.0 ± 25.7*</td>
<td>0.009</td>
</tr>
<tr>
<td>Alkaline phosphate (IU/L)</td>
<td>101.5 ± 63</td>
<td>96.8 ± 41</td>
<td>100.8 ± 42</td>
<td>117.5 ± 66</td>
<td>106.9 ± 50</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Phosphat binders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calciumacetat (mg/week)</td>
<td>3735 ± 2245</td>
<td>3735 ± 2245</td>
<td>4725 ± 1886</td>
<td>3960 ± 1400</td>
<td>4480 ± 572</td>
<td>ns</td>
</tr>
<tr>
<td>Lanthanum carbonate (mg/week)</td>
<td>562 ± 562</td>
<td>1125 ± 650</td>
<td>563 ± 563</td>
<td>563 ± 563</td>
<td>1125 ± 650</td>
<td>ns</td>
</tr>
<tr>
<td>Sevelamer (mg/week)</td>
<td>600 ± 600</td>
<td>1800 ± 1149</td>
<td>1200 ± 693</td>
<td>3000 ± 1449</td>
<td>3000 ± 1149</td>
<td>ns</td>
</tr>
</tbody>
</table>

Kt/V, dialysis efficacy; MAP, mean arterial pressure; EVC, extra-cellular volume; Hb, haemoglobin; EPO, erythropoietin; CRP, C-reactive protein; ECM, extra-cellular mass; BCM, body cellular mass; BMI, body mass index; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; AP, alkaline phosphatase; ns, not significant. 
*P < 0.01 compared to baseline; **P < 0.0001 compared to baseline.

Fig. 1. Improvement in blood pressure control was accompanied by a reduction in antihypertensive pharmacotherapy. (A) Predialytic mean arterial pressure (MAP) at baseline and quarterly during the follow-up period. Data are visualized as mean ± standard error of the mean (SEM). (B) Antihypertensive) Drug score at baseline and quarterly during the follow-up period. Data are visualized as box and whisker plots; *P < 0.05, **P < 0.0001 compared to baseline.
Micro-inflammation and severity of malnutrition decreased after intensifying dialysis dose

CRP, as a surrogate marker of micro-inflammation tended to decline after dialysis intensification (BL: 10.2 ± 13.7, after 12 months: 3.3 ± 4.0 mg/L, P = 0.18).

First, the presence of malnutrition has been assessed by chemical markers such as albumin (BL: 42.7 ± 2.6, after 12 months: 44.3 ± 2.4 g/L, P = 0.54) and total serum protein (BL: 68.2 ± 6.7, after 12 months: 70.2 ± 5.3 mg/dL, P = 0.63). Second, clinical data such as ‘dry’ body weight (BW) and body mass index (BMI) indicated an increase in nutritional state (BL: BW 70.9 ± 20.2 kg, BMI 22.8 ± 5.1 kg/m²; after 12 months: BW 72.1 ± 19.8 kg, BMI 23.6 ± 4.9 kg/m²; P = 0.02, P = 0.008, respectively). Third, the nPCR did show a rapid, significant increase after switching the dialysis regimen (BL nPCR 1.39 ± 0.29, after 3 months: 1.71 ± 0.23, P = 0.02; after 12 months: 2.25 ± 1.5 g/kg per day, P = 0.02). Fourth, serial bioelectrical impedance analyses (BIA) have been performed. The BIA method served as an objective feature to evaluate our patients’ nutritional (and hydration) status. Therefore, ECM and BCM have been measured and accordingly their ratio (ECM/BCM) calculated in order to best reflect patients’ nutritional status. The lower this ratio, the better the current nutritional situation (ECM/BCM: BL: 0.91 ± 0.16, after 12 months: 0.78 ± 0.1, P = 0.002). Consistent with the decline in ECM/BCM, we detected an increase in the phase angle (PA) (BL 6.2 ± 1.1°, after 12 months: 6.88 ± 0.72°, P = 0.001, Figure 3). Serum albumin and protein were negatively correlated with the ECM/BCM ratio (Spearman’s coefficients of correlation $r = -0.823$, $P = 0.006$; and $r = -0.713$, $P = 0.03$; respectively). All data are summarized in Table 2.

Changes in bone metabolism

After intensifying the HD dose, both serum calcium level (BL: 2.23 ± 0.3, 12 months: 2.19 ± 0.3 mmol/L) and serum phosphate level slightly declined (BL: 1.94 ± 0.65, 12 months: 1.71 ± 0.4 mmol/L), albeit not on a statistically
significant level ($P = 0.1$, $P = 0.38$, respectively). Regarding patients with an intact parathyroid gland, when analysed separately, these patients exhibited a trend towards phosphate reduction, which, however, did still not reach statistical significance (BL: $2.03 \pm 0.56$ versus 12 months: $1.75 \pm 0.42$ mmol/L).

Likewise, the amount of phosphate binding pharmaceutical therapy did not change significantly (calciumacetat BL: $3375 \pm 2240$ versus 12 months $4480 \pm 572$ mg/week, $P = 0.136$; lanthanum carbonate BL: $562 \pm 562$ versus 12 months: $1125 \pm 650$ mg/week, $P = 0.285$; sevelamer BL: $600 \pm 600$ versus 12 months: $3000 \pm 1149$ mg, $P = 0.066$).

However, these mild changes in calcium–phosphate balance were coexisting with a significant elevation of the 25-(OH) vitamin D serum level (baseline: $28.5 \pm 11.7$, after 12 months: $39.4 \pm 11.7$ µg/L, $P = 0.01$) despite stable doses of vitamin D substitution (20000 IU colecalciferol every other week).

The overall iPTH levels did not change significantly. However, six of the patients had a previous medical history of surgical subtotal parathyroidectomy due to secondary hyperparathyroidism (sHPT). Regarding the remaining patients with intact parathyroid glands separately ($n = 7$), one disadvantageous aspect could be detected. Surprisingly, these patients showed significant and unexpected iPTH alterations after intensifying the HD regimen (reference range according to the K/DOQI guidelines: 16.5–33 pmol/L). Parallel to the increased dialysis dose, a marked increase in circulating iPTH levels was observed (baseline: $19 \pm 6.2$ pmol/L, after 3 months: $35.5 \pm 16$ pmol/L, after 6 months: $45.5 \pm 19.9$ pmol/L, after 12 months: $59.3 \pm 19.6$ pmol/L, $P = 0.009$). The longitudinal courses of iPTH in those patients with intact parathyroid glands are visualized in Figure 4. Due to this aggravation of sHPT, one of our patients needed parathyroidectomy during the study period (after 10 months, iPTH at this time point was 129.7 pmol/L). In contrast, AP was found stable (baseline $101.5 \pm 63$ versus 12 months $106.9 \pm 50$ IU/L), even when evaluated separately for those patients with intact parathyroid glands (baseline $82 \pm 33$ versus 12 months $94 \pm 29$ IU/L, $P = 0.345$). All study participants have been dialysed with a standard calcium bath concentration of 1.25 mmol/L. All data are summarized in Table 2.

**Discussion**

This is the first comprehensive prospective, longitudinal study investigating the effect of increasing the haemodialysis (HD) time from $3 \times 4$ to $3 \times 8$ h on clinical, biochemical and pharmacotherapeutic parameters. The pertinent findings are (1) doubling HD time was associated with an improvement of multiple known dialysis-associated alterations. Of note, these advances were accompanied by a simultaneous reduction of the according substitution drug (e.g. anaemia – EPO and iron; blood pressure – antihypertensives). (2) Individual patients’ nutritional status improved significantly as demonstrated by BW, BMI, nPCR and serial bioelectrical impedance analyses. (3) As a probable negative effect of the dialysis time increase we observed a marked elevation in serum iPTH.

Optimal dialysis would be characterized by the combination of at least five factors: sufficient removal of (i) small and (ii) middle molecules, (iii) adequate nutrition for proteins and calories, (iv) satisfactory ECV control and (v) BP control [20]. Many studies could show that frequent (6 times/week) nocturnal dialysis improves all of the five afore-mentioned factors [21–24]. In contrast, outside Tassin, three times weekly 8-h dialysis has only been scarcely evaluated [5] and benefit of this intermediate form between conventional $3 \times 4$ h and frequent (6 times/week) 8 h dialysis remained largely unclear.

As a consequence of the dialysis time increase, virtually all patients showed a significant rise in their eKt/V. This is not surprising and well in line with previous reports, however, absolutely relevant for our patients long-term survival. Our colleagues from Tassin subdivided 445 dialysis patients regarding their Kt/V (higher or lower than 1.60). During an exceedingly long follow-up period of 20 years they found a significantly superior survival in those patients with higher Kt/V (57 versus 33%, $P < 0.005$) [4]. These results impressively illustrate the impact of an improved dialysis efficacy. In our study, eKt/V was much higher than the cut-off value of 1.6 in Tassin (Hanover eKt/V $2.7 \pm 0.5$). It is unclear whether this would result in an increased survival. In 1998, Laurent and Charra published their experience on three times weekly nocturnal dialysis [25]. Interestingly, these patients had much lower Kt/V values ($1.85 \pm 0.41$) than our patients. According to a very recent paper from Elloot et al. [26], care must be taken when using Kt/V as the only parameter to quantify dialysis adequacy. As we did not use the GENIUS batch dialysis ( Fresenius Medical Care, Bad Homburg, Germany) system for this study, we were not able to measure dialysis efficacy by quantifying the absolute amount of solutes in the dialysate as done previously in the acute renal failure setting [27].
The conversion from conventional to three times 8 h dialysis was associated with a significant amelioration of the high blood pressure. In contrast to the data from France, our patients were not completely free of antihypertensive drugs [25]. We attribute this difference to two components. First of all, this finding might be related to the lack of an active increase in fluid removal after switching the treatment regimen in our study protocol. Second, definition of ‘normotension’, especially in patients with chronic kidney disease, did significantly change in the last decade(s). After conversion from short to long dialysis the population from Tassin had a predialysis MAP of 100 mmHg without any pharmacological therapy while the predialysis MAP in our population was 89 mmHg, i.e. 11 mmHg lower than in Tassin but still with some residual antihypertensive medication. The 40% reduction of the antihypertensive pharmacotherapy, with a concomitant decrease in predialytic MAP is in line with the data by Haag-Weber et al. [5].

Again, the reduced need for ESA of ~40% in our study is in line with the study by Haag-Weber and colleagues who could decrease the ESA dose by ~30% after the switch from 3 × 5 to 3 × 8 h/week. Also Laurent and Charra found that three times weekly 8-h dialysis led to an increase in haemocrit while the ESA dose could be reduced [25]. Interestingly, Culleton et al. could not reproduce this difference in the need for ESA between conventional and frequent nocturnal haemodialysis [21]. It is also of interest that the need for i.v. iron supplementation decreased by almost 30%. To our knowledge this has never been evaluated before. Despite a decrease in iron supplementation and a reduced dose of ESA, the mean haemoglobin increased significantly by > 1 g/dL, an effect that had not been seen by Culleton et al. in frequent nocturnal dialysis. Haag-Weber et al. did not report any haemoglobin data in her study [5].

The calcium–phosphate product is a challenging issue in the development of accelerated atherosclerosis in CKD patients. In the past, multiple ‘novel’ uraemic toxins have been suspected to aggravate atherosclerotic burden of the dialysis population. However, most of them failed to prove their uniqueness and an elevated calcium–phosphate product still seems to be a major player of the accelerated pathogenesis of atherosclerosis in ESRD. For CKD patients, serum phosphate is suggested as the dominant dynamic factor that determines the Ca × Phos product. In the present study, intensifying the dialysis regimen led to a slight decrease in Ca × Phos product of ~15% while the amount of phosphate binders were found stable, probably at least partially due to an increased nutritional intake. The decrease of the Ca × Phos product was less compared to the study by Haag-Weber who found a reduction of almost 50%. However, these data were obtained in only nine patients [5]. Culleton et al. found a 20% reduction in Ca × Phos product in frequent nocturnal dialysis suggesting that 3 × 8 h is not inferior [21]. In our view, the lack of a significant reduction in the dose of phosphate binders might be explained by an increased nutritional intake that also included phosphate. This is reflected in the improved nutritional status, the increased nPCR and the increase in dry body weight. A second theory giving an explanation for our disappointing phosphate findings is a more methodical one. As we took our blood samples after the long interdialytic interval, we probably measured inaccurate high serum phosphate levels.

The loss of amino acids during dialysis can be as high as 13 g per dialysis session and thereby eliminates 3–12% of the weekly intake [28,29]. The increase in dialysis time might indeed lead to a significant increase of amino acid loss. Although we did not quantify the amino acid removal, the nutritional parameters suggest that the increase in nutritional intake at least outweigh the possible increased removal of amino acids. The absent increase in albumin might, however, be attributed to the increased loss of amino acids.

Further, we found a marked increase in iPTH in non-parathyroidectomized patients. This finding is in contrast to other studies that found a decrease in PTH by 20–30% [5]. However, there are some articles that report the same findings of an iPTH increase and its relation to the calcium bath concentration [30–33].

We cannot exclude a negative calcium balance in our study population. If present, the negative calcium balance might be related to the prolonged contact of nHD patient blood with standard calcium bath concentration (i.e. 1.25 mmol/L), and secondly, the poor oral calcium supply by calcium acetate might have led to an intra-dialytic decrease in serum calcium (during the HD session) and a consecutive increased excretion of parathyroid hormone.

These data make the general recommendation of routine measurements of iPTH in several guidelines even more relevant.

Another theory of an iPTH increase should be discussed. Due to the fact that the AP was stable during the whole study period, there might not be a relevant ‘bone turnover-activation’. Is this the case, the elevated iPTH probably reflects a change in bone metabolism that is not strictly pathologic but represents a change from functional ‘low-turn over bone disease’ (despite normal initial values, i.e. K/DOQI range 16.5–33 pmol/L) to a more ‘vital’ bone.

The ‘malnutrition–inflammation–atherosclerosis (MIA) syndrome’ describes the complexity of metabolic alterations CKD patients regularly suffer from [34]. Atherosclerotic burden is already present long before the initiation of renal replacement therapy; thus, the majority of patients starting dialysis already have signs of advanced atherosclerosis [35]. Cardiovascular disease (CVD) in patients with CKD stage V is enhanced by sustained inflammation. A pivotal role in inflammatory processes in this population is generated in response to fluid overload [36], chronic infections and pro-inflammatory cytokines [37]. Bedsides muscle wasting, hypoalbuminuria and anorexia, chronic inflammation directly causes atherosclerotic disease. Additionally, malnutrition further aggravates existing inflammation [38], accelerates atherosclerosis and increases susceptibility to infection.

In the present study, surrogate parameters for different components of the MIA syndrome have been found to be modulated. Both laboratory parameters reflecting nutritional status and BIA improved after dialysis intensification. Further, a trend in CRP reduction (a surrogate parameter for inflammation) was detected.

Although the current investigation provides comprehensive and new information on the clinical, biochemical and
pharmacotherapeutical benefits of conversion from standard to intensified three times weekly dialysis, we wish to point out important limitations of our study. First, the sample size was small and the duration of the follow-up was limited to 12 months. The sample size allows only the evaluation of surrogate end-points instead of cardiovascular events. As more than 5000 patients would be needed to detect a 30% difference in 1-year mortality between nocturnal and conventional HD patients [39] evaluation of cardiovascular end-points would have been futile. Secondly, we did not randomize patients to different treatment modalities for ethical reasons, an approach that might reflect the strategy of many dialysis centres making the conversion from standard to intensified three times weekly dialysis.

In summary, this study demonstrates multiple clinical, biochemical and pharmacotherapeutical benefits of conversion from standard to intensified three times weekly dialysis. It is conceivable to assume that this approach might be a practical compromise between standard in-centre HD and daily nocturnal home HD that precludes widespread application. Besides the improvement in anaemia, blood pressure, Ca × Phos product and nutritional control, a negative effect on the intact parathyroid gland has been found. This aspect should be kept in mind when dealing with patients on intensified dialysis regimens developing secondary hyperparathyroidism.

Conflict of interest statement. None declared.

References
Fluctuating parathyroid hormone values

Background. Fluctuating parathyroid hormone values (PTH) are common in patients undergoing haemodialysis. Widely varying PTH results in an 82-year-old haemodialysis (HD) patient could not be explained. When PTH in the same blood sample was no longer detectable 24 h after blood draw, it was hypothesized that contamination with the catheter lock solution containing tissue plasminogen activator (tPA, alteplase) caused degradation of PTH in vitro.

Methods. Leftover samples from 21 patients on maintenance HD as well as control samples from healthy volunteers (n = 3) were incubated at 4°C with small amounts of tPA (25 and 50 µL). In addition, pooled samples from HD patients with various PTH levels were incubated with 6.5, 12.5 and 25 µL of tPA and analysed with two different PTH assays with incubation times up to 48 h.

Results. A rapid decline of PTH values to 2.5–33.5% of the original baseline was observed after 24 h with a further decrease to <1–15% after 48 h. The two different assays gave very similar results when the samples were incubated with tPA.

Conclusion. Minimal contamination of a blood sample with tPA results in degradation of PTH in a time-dependent manner. The tPA is therefore unique as a contaminant since its enzymatic activity means that even tiny amounts of contamination will lead to major errors in PTH results by digestion of the protein. This phenomenon was independent of the assay used. Strict attention to the technique when drawing a blood sample from a catheter is mandatory to prevent contamination and avoid spurious test results.

Keywords: haemodialysis; haemodialysis access; parathyroid hormone (PTH); tissue plasminogen activator (tPA)

Introduction

An 82-year-old Caucasian female with end-stage renal disease secondary to diabetes mellitus and hypertension had undergone maintenance haemodialysis for 6 years. Quarterly parathyroid hormone (PTH) results had ranged between 230 and 480 pg/mL. When PTH increased to 834 pg/mL, 30 mg oral cinacalcet was added to her thrice weekly IV vitamin D and oral phosphate binder regimen. Three months later, PTH had decreased to 142 pg/mL, a surprisingly dramatic decrease of >80%, higher than the usual decrease of 30–40% following the administration of a calcimimetic [1]. Over the next 7 months, PTH values ranged between 48 and 471 pg/mL. Inconsistency of calcimimetic intake including non-adherence to the recommended 12-h dose interval prior to blood draw was suspected [2]. However, a PTH value of 17 pg/mL made this assumption questionable. Laboratory quality control on precision and accuracy were validated.

Fortuitously, at this time a stability study of PTH measurements was being performed in our laboratory in order to assess any effect of the delay in specimen receipt with centralized laboratory services common in dialysis practice. Left-over plasma samples from the routine monthly blood draw in a nearby dialysis unit were measured...