Nocturnal but not Short Hours Quotidian Hemodialysis Requires an Elevated Dialysate Calcium Concentration

FAYEZ AL-HEJAILI, CLAUDE KORTAS, ROSEMARY LEITCH, A. PAUL HEIDENHEIM, LAURIE CLEMENT, GHIAD NESRALLAH, and ROBERT M. LINDSAY
Optimal Dialysis Research Unit, London Health Sciences Centre and The University of Western Ontario, London, Ontario, Canada.

Abstract. Interest in quotidian (daily) hemodialysis (HD) is growing. Some advocate short-hours high-efficiency daily HD (SDH) and others long-hours slow-flow nocturnal HD (NH) while the patient is asleep, both being used 5 to 7 d/week. The London Daily/Nocturnal Hemodialysis Study was the first attempt to obtain data of SDH and NH that may be compared with conventional thrice weekly HD (CH). This was a 4-yr observational study designed to enter and follow 40 patients: 10 receiving SDH, 10 receiving NH, and 20 receiving CH. The CH patients were cohort control subjects matched for each SDH and NH patient by age, gender, comorbidity, and original dialysis modality (in-center, home, self-care, or satellite HD). All SDH and NH treatments were at home. Data collection to December 2001 was analyzed. Then enrollment had been completed and all patients had been followed for 15 mo, eight SDH plus six NH for 18 mo, seven SDH plus six NH for 21 mo, and seven SDH and five NH for 24 mo. This report gives data on calcium and phosphorus metabolism in these patients. All patients were initially dialyzed against a 1.25-mmol/L calcium bath. Predialysis serum calcium levels became lower in NH versus SDH patients by the first month and at 9 mo were 2.67 ± 0.25 mmol/L (M ± SD) in SDH, 2.40 ± 0.16 mmol/L in NH, and 2.52 ± 0.21 mmol/L in CH (SDH versus NH, P = 0.038; SDH versus CH versus NH, NS). Predialysis phosphorus levels were better controlled by NH than by SDH or CH, and with NH, all phosphate binders were discontinued. By 12 mo, a rise in bone alkaline phosphatase was seen in NH patients (but not in SDH or CH patients), which peaked at 15 to 18 mo (NH 191 IU/L ± 70; SDH 82 ± 34; CH 80 ± 36; P < 0.002) and similarly with intact parathyroid hormone (iPTH) levels (NH 159 pmol/L ± 75; SDH 13.1 ± 10; CH 18 ± 18; P < 0.00001). Because of these changes, the dialysate calcium concentration was increased to 1.75 mmol/L for the NH patients. Postdialysis calcium then rose to 2.57 ± 0.21, and alkaline phosphatase and iPTH normalized completely by 21 mo. These observations prompted mass balance studies that showed that a 1.25-mmol/L calcium dialysate was associated with a mean net calcium loss of 2.1 mmol/h of dialysis time, whereas 1.75-mmol/L calcium dialysate provides a net gain of 3.7 mmol/h. In addition, the mass balance studies showed that phosphate removal by NH (43.5 ± 20.7 mmol) was significantly (P < 0.05) higher than by SHD (24.2 ± 13.9 mmol) but not by CH (34.0 ± 8.7 mmol) on a per-treatment basis. With the increased frequency of treatments provided by quotidian dialysis, the weekly phosphorus removal (261.2 ± 124.2 mmol) by NH was significantly higher than by SDH (P = 0.014) and CH (P = 0.03). This allowed the discontinuation of P binders in the NH group, which in turn eliminated approximately 8 g elemental Ca/wk oral intake. This, together with a 4 g elemental Ca/wk dialysate loss induced by a 1.25-mmol/L Ca bath, explains the changes in Ca, alkaline phosphatase, and iPTH seen in the NH patients. The SDH patients have weekly dialysis times similar to CH and still require P binders and do not become Ca deficient using 1.25-mmol/L Ca dialysate. With NH but not SDH, an elevated dialysate Ca concentration is required.

The interest in high-efficiency short-hours daily hemodialysis (SDH) and slow long-hours nocturnal hemodialysis (NH) has experienced a resurgence in recent years. The effects of these dialysis modalities on calcium and phosphorus metabolism have been described to some extent (1,2), but direct comparisons between SDH and NH have not yet been made in this regard. Before the advent of calcium-based phosphorus binders, patients were dialyzed against a 1.5- to 1.75-mmol/L calcium bath to prevent calcium depletion. With the widespread use of calcium-containing phosphorus binders, this practice changed, and a 1.25-mmol/L bath became the standard. In this article, we describe the effect of this latter bath calcium concentration on calcium balance in SDH and NH, as well as the influence of dialysate composition and dialysis time on net calcium shift and on intact parathyroid hormone (iPTH) levels.

Materials and Methods
The Daily/Nocturnal HD Study
This was a 4-yr observational study to follow 40 patients: 10 receiving SDH, 10 receiving NH, and 20 receiving conventional thrice weekly hemodialysis (CH). The CH patients were cohort control...
subjects matched for each SDH and NH patient by age, gender, comorbidity, and original dialysis modality (in-center, home, self-care, or satellite hemodialysis [HD]). The study aim was to follow all patients for a minimum of 18 mo. The treatments were at home. Outcome measures such as anemia, BP, volume control, nutrition, adequacy, hospitalization, quality of life, and bone disease have been studied. This report gives data on calcium metabolism in these patients. The Ministry of Health and Long Term Care, the Government of Ontario, Canada, funded this study.

**Patient Recruitment**

Patients in the Southwestern Ontario renal program were provided with information regarding the Daily/Nocturnal study early in 1998. Patients were asked to apply for the program specifying whether they preferred SDH or NH dialysis or had no preference. Thereafter, patients were selected by ballot. Informed consent was then obtained. The Ethics Committee of The University of Western Ontario approved the study.

**Hypothesis**

Because of the different dialysis prescriptions used in the two treatment groups, calcium and phosphorus clearances may differ to the extent that changes in bath Ca composition and oral phosphorus binder use are necessary.

**Study Design**

This was an observational, prospective study—patients were not randomized. This was done deliberately to allow for patient preference and to avoid the many potential complications that might arise by interfering with lifestyle and personal schedules. These may have had an adverse impact on patient adherence and on quality-of-life study results. A cohort control subject was selected for each study patient and was matched as closely as possible for age, gender, initial dialysis modality, comorbidities (particularly diabetes and cardiovascular disease), and, if possible, vascular access. All patients were older than 18 yr, were able to give informed consent, had been on HD for at least 3 mo before enrollment, and had to have a reasonable expectation of surviving 1 yr regardless of the comorbidities that were present. In December 2001, enrollment was complete and all patients had gone 15 mo; eight SDH and six NH had completed 18 mo, seven SDH and six NH had completed 21 mo, and seven SDH and five NH had completed 24 mo. For this article, data up to 24 mo are used. The HD prescription is summarized in Table 1. All patients consumed their usual diet and were initially dialyzed against a 1.25-mmol/L calcium bath.

**Routine Measurement over Study Time**

Plasma concentrations of total calcium (mmol/L; normal range, 2.12 to 2.65), albumin (g/L) (35 to 40), inorganic phosphorus (mmol/L; 0.8 to 1.45), bone alkaline phosphatase (IU/L; 20 to 111), intact parathyroid hormone (iPTH; pmol/L; 1 to 6), and doses of active vitamin D analogues (μg/wk) and calcium carbonate (mg/d) given were measured at 1 mo and then every 3 mo throughout the study. The vitamin D analogue used was one-alpha (Leo Pharma, Ballerup, Denmark) and was given orally in daily doses.

**Mass Balance Studies**

Mass balance studies were carried out to examine the influence of dialysate composition and dialysate time on net calcium and phosphorus shift. A total of 31 studies were conducted using four different calcium baths of 1, 1.25, 1.5, and 1.75 mmol/L and dialysis times of 120, 240, and 360 min. These 31 studies were done on 14 of the study patients (eight SH, six NH) who came to the research center for them; 13 patients were studied twice, and one was studied five times. These balance studies used direct dialysate quantification of the total amount of calcium in the spent dialysate plus volume of ultrafiltration. The ultrafiltration rate was standardized at 500 ml/h for these studies. From this amount of calcium was subtracted the product of dialysate volume (directly measured) and initial dialysate calcium concentration used (directly measured from a predialysis sample). There being no phosphorus in the initial dialysate, the amount of phosphorus removed was easily measured in the spent dialysate. The influence of dialysate composition on pre- and postdialysis serum calcium and iPTH levels was also examined at the same time. In all cases, serum or dialysate calcium and phosphorus levels were measured using a Beckman Coulter Synchron CX7 instrument (Fullerton, CA) with standard reagents. iPTH was measured using the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA). Albumin was measured by bromcresol green. Total serum calcium was adjusted for albumin using the widely accepted correction factor (3): corrected calcium (mmol/L) = measured calcium (mmol/L) + (40 – serum albumin g/L)* 0.02.

**Statistical Analyses**

Data are presented as mean ± 1 SD. Repeated measurement ANOVA was used to make multiple comparisons over time and to make between-group comparisons at each time point. One-way ANOVA was used simply for between-group comparisons. Paired t tests were used to compare data from follow-up points with baseline.

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**Table 1. Hemodialysis prescriptions**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>SDH</th>
<th>NH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dialyzer</strong></td>
<td>F80*</td>
<td>F80*</td>
<td>F80*</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>3.5–4.5 hr</td>
<td>1.5–2.5 hr</td>
<td>6–8 hr</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>×3/wk</td>
<td>×6–7/wk</td>
<td>×6–7/wk</td>
</tr>
<tr>
<td><strong>Qb</strong></td>
<td>450 ml/min</td>
<td>450 ml/min</td>
<td>150–300 ml/min</td>
</tr>
<tr>
<td><strong>Qd</strong></td>
<td>500 ml/min</td>
<td>800 ml/min</td>
<td>300 ml/min</td>
</tr>
<tr>
<td><strong>Dialysate Ca</strong></td>
<td>1.25 mmol/L</td>
<td>1.25 mmol/L</td>
<td>1.25 → 1.75 mmol/L</td>
</tr>
<tr>
<td><strong>Dialysate P</strong></td>
<td>0 mmol/L</td>
<td>0 mmol/L</td>
<td>0 → 0.7 mmol/L</td>
</tr>
</tbody>
</table>

* Fresenius North America (Lexington, MA).
Results

Routine Measurements over Study Time

All patients were initially dialyzed against a 1.25-mmol/L calcium bath. Both total serum calcium and albumin-adjusted predialysis calcium values were significantly lower ($P < 0.05$) in the NH versus the SDH patients from 1 to 9 mo of study. The adjusted values over time are shown in Figure 1. At 9 mo, the adjusted serum calcium values were $2.67 \pm 0.25$ (SDH), $2.40 \pm 0.16$ (NH), and $2.52 \pm 0.21$ (CH) (SDH versus NH, $P = 0.038$; SDH versus CH versus NH, NS). Predialysis phosphorus levels were slightly better controlled by SDH and NH than by CH and significantly so at 6 mo ($P < 0.05$). Pre- and postdialysis phosphorus values are shown in Figure 2, which also indicates that a phosphorus addition was made to the dialysate in two NH patients (final concentration of phosphorus, 0.7 mmol/L). With NH, all P binders were discontinued (Figure 3). By 12 mo, a rise in bone alkaline phosphatase was seen in NH patients, which peaked at 15 to 18 mo (NH, 191 IU/L $\pm$ 70; SDH, 82 $\pm$ 34; CH, 80 $\pm$ 36; $P < 0.002$; Figure 4) and similarly with iPTH levels (NH, 159 pmol/L $\pm$ 75; SDH, 13.1 $\pm$ 10; CH, 18 $\pm$ 18; $P < 0.0001$; Figure 5) and requirement of higher doses of vitamin D (Figure 6). After 18 mo into the study, the realization of rising iPTH levels in NH patients led to a change in dialysate calcium concentration to 1.75 mmol/L. This change was made at one time (November 2000) and to all NH patients. This corresponded to the 15 to 18 mo for the first few patients and earlier for subsequent patients as they entered the study in a serial manner. The median time for dialysate calcium change was at 9 mo of study (Figures 1, 4, and 5). The dialysate calcium concentration remained at 1.25 mmol/L for SDH and CH patients throughout. In the NH patients, the mean predialysis serum-adjusted calcium then rose to $2.74 \pm 0.48$ and alkaline phosphatase and iPTH values normalized completely by 21 mo and vitamin D requirements reduced.

Calcium Balance Studies

These studies were stimulated by the changes in calcium, phosphorus, alkaline phosphatase, and iPTH levels in the observational study (above). The results of the 31 balance studies are shown in Table 2. They were carried out with dialysate bath calcium levels ranging from 1 to 1.75 mmol/L and with dialysis times ranging from 120 to 360 min as would be found in SH, NH, and CH. The calcium shift (i.e., gain or loss to the patient) is presented in mmol. The number in parentheses is the
phosphorus removal (mmol) per dialysis treatment were 24.2 ± 13.9 (SDH, n = 13), 43.5 ± 20.7 (NH, n = 10), and 34.0 ± 17.2 (CH, n = 8; NH > SDH, P < 0.05; NH versus CH, NS; SDH versus CH, NS). The extrapolation of these treatment losses to a weekly loss is depicted in Figure 8, which shows the improvement in NH and SDH versus CH afforded by the increased frequency of dialysis. The weekly phosphorus removal by NH is significantly higher than by SDH (P = 0.014) and CH (P = 0.003).

**Intradialysis Changes in Serum Calcium and iPTH**

With a 1.25-mmol/L calcium bath, there was a significant fall in albumin-adjusted serum calcium from 2.54 ± 0.12 predialysis to 2.46 ± 0.08 postdialysis (P < 0.001, n = 13). Overall, the iPTH values did not show any significant change. Five of the 13 patients had predialysis iPTH levels higher than the clinically acceptable range of 10 to 30 pmol/L (normal range for a nonuremic patient is 3 to 6 pmol/L). The eight patients with predialysis iPTH levels <30 pmol/L did show a slight but significant increase in the level over the dialysis (P = 0.017). These data are shown in Figure 9.

With the 1.5-mmol/L calcium bath, the adjusted serum calcium showed an increment across dialysis in 10 of 13 patients. The overall change was of borderline statistical significance (P = 0.051) from 2.54 ± 0.13 pre- to 2.61 ± 0.08 postdialysis. Again, the overall iPTH level change is insignificant, but among patients within the clinically acceptable range, levels showed a slight but significant decrease from 12.7 ± 10.3 to 6.1 ± 4.9 (P = 0.011). These data are shown in Figure 10.

In the four runs with 1.75-mmol/L calcium bath, there was a sharp rise in adjusted serum calcium over dialysis and an associated fall in iPTH (precalcium 2.47 ± 0.06, postcalcium 2.75 ± 0.08, P < 0.001; pre-iPTH 31.0 ± 50.2, post-iPTH 8.9 ± 15.7, NS). These data are shown in Figure 11.

**Discussion**

Hyperparathyroidism is the most common cause of renal bone disease despite the improvement achieved in its treatment and prevention. Certain disturbances in mineral metabolism, such as hypocalcemia, hyperphosphatemia, and impaired renal 1,25-hydroxyvitamin D synthesis, are crucial determinants of excess PTH secretion in patients with chronic renal failure. It is important to stress that hypocalcemia is the most powerful stimulus of PTH secretion as it may result in an increase more than twice that induced by hyperphosphatemia (4). Therefore, calcium balance and regulation are very important when treating hyperparathyroidism (5).

When dialysis was first initiated, a dialysate calcium concentration of 1.25 mmol/L was frequently used. It soon became clear that this dialysate calcium concentration could decrease ionized serum calcium and lead to secondary hyperparathyroidism (6–10). This led to increasing the dialysate calcium concentration to 1.75 mmol/L, which remained the standard for many years (11). The recognition of the toxic effects of chronic administration of aluminum-based phosphorus binders (12,13) led to the use of calcium salts as the main phosphorus binders (14). This, as well as the widespread use of oral and intrave-

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**Phosphorus Balance Studies**

The net phosphorus removed per treatment was different among the three different modalities. The mean values for number of studies carried out with given bath calcium concentrations and times. Note that only one study was carried out at bath concentrations of 1.0 and 1.75 mmol/L when dialysis time was 120 min. The results show mean calcium losses to the patients with dialysate calcium concentrations of 1.5 mmol/L or less but net gains with the 1.75-mmol/L calcium bath. The mean gain or loss of calcium is related both to dialysate calcium concentration and to duration of dialysis. The rates of calcium gain or loss (mmol/h), therefore, are given as well in Table 2. There was no change of statistical significance in the rate of loss (mmol/h) over dialysis time (e.g., first versus last hour). The total data in Table 2 are also shown in Figure 7 as a plot of rate of net calcium change (mmol/h; gain or loss) against the dialysate calcium concentrations (mmol/L). The 95% confidence intervals are also shown to the extent that data observations allow. This figure clearly shows that to remain in positive calcium balance, a patient requires the dialysate calcium to be in excess of 1.5 mmol/L. Most patients who dialyze against a 1.25 mmol/L bath are going to have net calcium loss, the extent of which will depend on the duration of the dialysis treatment.

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*Figure 5. Intact parathyroid hormone level (pmol/L) over time of study.*

*Figure 6. Vitamin D dose (µg/wk) over time of study.*
nous active vitamin D analogues, frequently led to the development of hypercalcemia (15). To counteract this while continuing to benefit from the use of calcium carbonate as a phosphorus-binding agent, a trend to reduce the calcium concentration in the dialysate from 1.75 to 1.25 mmol/L occurred (16–18). However, there are concerns that low dialysate calcium concentrations expose patients to the risks of negative calcium balance with increases in PTH concentration and worsening of secondary hyperparathyroidism, particularly if they are noncompliant with the intake of calcium-containing phosphorus binders (10,19). The appropriate dialysate calcium concentration in SDH or NH has not been studied, and most nephrologists have used the same low-dialysate calcium as used with conventional dialysis. The literature suggests that SDH is no better than CH with regard to phosphorus control (20–22). However, the situation in NH is different. Mucsi et al. (23) reported a reduction in serum phosphorus levels from 2.1 ± 0.5 to 1.3 ± 0.2 mmol/L (P < 0.001) in the setting of a 50% increase in dietary phosphorus intake and total discontinuation of phosphorus binders in seven patients within 4 mo of starting NH. This finding has been confirmed by several additional reports (1,2,24–26). Some patients on NH even require phosphorus supplements to maintain normal serum phosphorus concentrations (26,27).

In this study, we demonstrated that calcium and phosphorus balance during NH is different than with SDH or CH. Our observational study shows that by 12 mo, a rise in bone alkaline phosphatase occurred in NH patients, which peaked at 15 to 18 mo (NH, 191 ± 70 IU/L; SDH, 82 ± 34 IU/L; CH, 80 ± 36 IU/L; P < 0.002), and similarly there were changes in

### Table 2. Calcium balance with varying dialysate calcium concentration

<table>
<thead>
<tr>
<th>Dialysate Ca Concentration (mmol/L)</th>
<th>Total Ca Shift Across HD Membrane (mmol) with Dialysis of Varying Time (min)</th>
<th>Ca - Gain/Loss (mmol/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120 Min</td>
<td>240 Min</td>
</tr>
<tr>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>−6.35 ± 6.37 (6)</td>
<td>−0.14 ± 6.06 (4)</td>
</tr>
<tr>
<td>1.50</td>
<td>−0.89 ± 4.56 (6)</td>
<td>−1.14 ± 1.87 (3)</td>
</tr>
<tr>
<td>1.75</td>
<td>10.85 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses = number of studies performed.

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Figure 7. Rate of net calcium change (mmol/h) versus dialysate calcium concentration (mmol/L). The mean values are given along with 95% confidence intervals.

Figure 8. Net phosphorus removed per week (mmol). Data are extrapolated from the single dialysis studies. Variance (±SD) is indicated for each mode of dialysis.

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Figure 9. Across dialysis serum calcium (mmol/L) and intact parathyroid hormone (iPTH; pmol/L) levels associated with the use of a 1.25-mmol/L calcium bath.
PTH levels (NH, 159 ± 75 pmol/L; SDH, 13.1 ± 10 pmol/L; CH, 18 ± 18 pmol/L; \( P < 0.00001 \)), which did not occur with SDH or CH. The observational study shows the good serum phosphorus control that occurs with NH (Figure 2) and that this occurs with virtual elimination of phosphorus binders (Figure 3). This is possible because of the much improved phosphorus removal that occurs with NH versus SDH and CH (Figure 8). Indeed, the removal of >40 mmol per treatment (>1.2 g) exceeds or balances the expected daily intake of phosphorus in these patients.

Thus, patients on NH have excellent phosphorus control, and as phosphorus binders are eliminated, this will lead to a loss of approximately 8 g of elemental calcium per week in oral intake. In addition, our calcium balance data indicate that a patient on NH when dialyzed against a 1.25-mmol/L calcium bath may lose a mean of 16 mmol per treatment (2 mmol/h × 8 h; Figure 7). Dialyzing 6 nights per week translates this to a weekly loss of 96 mmol (i.e., approximately 4 g of elemental calcium). In turn, this will likely lead to worsening of secondary hyperparathyroidism.

Our studies show that even with a single dialysis, there seems to be the expected reciprocal changes in serum calcium and iPTH levels (Figures 9, 10, and 11). Thus, one can imagine that repeated dialyses with a lower (1.25 mmol/L or less) calcium bath are constantly stimulating iPTH production, which is controlled by the overall better calcium balance with the shorter total duration of dialysis per week obtained with SH and conventional dialysis plus the oral calcium supplementation from phosphorus-binding agents. The picture with NH is different. The single dialysis studies certainly suggest that a 1.75-mmol/L calcium bath is associated with a transient rise in serum calcium and with suppression of iPTH levels (Figure 11) and at the same time a net gain of calcium to the patient (Table 2, Figure 7).

The change of the dialysate calcium concentration to 1.75 mmol/L during the course of this observational study fairly rapidly reduced the alkaline phosphatase and iPTH levels (Figures 4 and 5). The elevated levels were apparently not responding to the administration of increasing doses of active vitamin D analogues (one-Alpha). This, even more, emphasizes the importance of dialysate calcium concentrations. With the recent introduction of noncalcium phosphorus binders such as sevelamer hydrochloride and subsequent loss of calcium supplements, nephrologists must remember to watch iPTH levels and consider changes in the dialysate calcium.

We conclude that patients on NH need a higher calcium bath as compared with SDH or CH. What the ideal dialysate composition is has to be defined. Further downward adjustments are likely in this study population should the iPTH levels become markedly suppressed. The target iPTH level for which we are currently striving is one within the range of 10 to 30 pmol/L. This is higher than the normal range for a nonuremic to prevent adynamic bone disease. The hypothesis that different dialysis prescriptions (quotidian versus CH and NH versus SDH) might alter calcium and phosphorus clearances to the extent that changes in bath calcium composition and phosphorus binder use are required is confirmed.

References