Vasopressin release is enhanced by the Hemocontrol biofeedback system and could contribute to better haemodynamic stability during haemodialysis

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Abstract

Background. Haemodialysis with the Hemocontrol biofeedback system (HHD) is associated with improved haemodynamic stability compared with standard haemodialysis (HD) (SHD). Although the beneficial effect of HHD on haemodynamic stability is generally explained by its effect on blood volume, we questioned whether additional factors could play a role. Since HHD is associated with higher initial dialysate sodium concentrations and ultrafiltration (UF) rate, we studied whether the
beneficial effect of HHD on haemodynamic stability may be explained by an increased release of the vasoconstrictor arginine vasopressin (AVP).

**Methods.** Fifteen chronic dialysis patients underwent SHD and HHD in random order. All other treatment factors were identical and patients served as their own control. Plasma levels of AVP were measured pre-dialysis, at 30 and 60 min intra-dialysis and, next, hourly until completion of the dialysis session.

**Results.** Plasma AVP levels did not change significantly during SHD, whereas AVP levels rose significantly within 30 min after the start of HHD (P < 0.01). AVP levels were significantly higher at 30 and 60 min of HHD in comparison with SHD (P < 0.05). Dialysis hypotension occurred significantly less frequent during HHD than during SHD (P < 0.05).

**Conclusions.** HHD is associated with higher initial AVP levels compared with SHD. The enhanced release of the vasoconstrictor AVP with HHD could contribute to the lower frequency of dialysis hypotension by facilitating fluid removal during the first part of the dialysis session, permitting lower UF rates during the second half of the dialysis session.

**Keywords:** haemodialysis; Hemocontrol; hypotension; vasopressin

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**Introduction**

Intra-dialytic hypotension occurs in ~20% of haemodialysis (HD) treatments [1]. Consequences range from transient symptoms such as nausea, dizziness and muscle cramps to permanent vascular damage like cerebral infarction and cardiac ischaemia [2]. Intra-dialytic hypotension is associated with an increased mortality in HD patients [3]. The combination of a decrease in blood volume and an inadequate cardiovascular response to the hypovolaemia plays a crucial role in the development of intra-dialytic hypotension [4–6].

The Hemocontrol biofeedback system is designed to preserve blood volume by continuously adjusting the dialysate conductivity and the ultrafiltration (UF) rate in response to blood volume changes. Various studies have shown that this system improves intra-dialytic haemodynamic stability [4, 5, 7–11]. The beneficial effect of Hemocontrol HD (HHD) on haemodynamic stability is generally explained by its effect on blood volume [9, 10]. However, we and others have previously shown that the actual blood volume levels in the second half of HHD did not differ significantly between HHD and standard HD (SHD) [4, 7, 9]. Therefore, other factors than blood volume must play a role.

Adequate and rapid modifications of the peripheral resistance are crucial for the maintenance of haemodynamic stability during HD with UF [12]. The peripheral resistance is mainly regulated by the renin–angiotensin system, the sympathetic nervous system and by the release of vasoconstrictors like arginine vasopressin (AVP). The most potent stimuli to AVP release are increased plasma osmolality and hypovolaemia [13, 14]. Since HHD is associated with higher initial dialysate sodium concentrations and a higher initial UF rate, we questioned whether the beneficial effect of HHD on haemodynamic stability may (at least in part) be explained by an increased release of AVP. In this study, we therefore tested the hypotheses that HHD is associated with higher plasma AVP levels than SHD with constant dialysate conductivity and UF rate and that higher plasma AVP levels are associated with improved haemodynamic stability during HD.

**Materials and methods**

**Patients**

Patients from the University Medical Center Groningen and the Dialysis Center Groningen were eligible for inclusion when they were 18 years or older, were on a three times a week 4 h HD schedule and had frequent (in >20% of HD sessions in the previous 4 weeks) episodes of dialysis hypotension.

Dialysis hypotension was defined as a decrease in systolic blood pressure ≥30 mmHg in combination with hypotensive symptoms (e.g. nausea, dizziness, light-headedness, muscle cramps, sweating) or a treatment intervention by the dialysis nurse. Treatment interventions were defined as temporary interruption of UF, need for Trendelenburg position, and/or administration of intravenous fluids.

All patients gave written informed consent to the study protocol and the study was performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the local Medical Ethical Committee.

**Study protocol**

Each participating patient underwent one SHD and one HHD in randomised order. The maximum time interval between the two treatments was 2 weeks. Patients served as their own control. Treatment conditions were identical during both treatments except for the dialysate sodium concentration that is the major difference between SHD and HHD (vide infra). Medication use was similar at both treatments as well as the posture (half-supine) and food intake (light meal) during HD. The measurements took place at the first HD treatment of the week because the UF volume and the blood volume decreases are most pronounced after the longest inter-dialytic interval [15].

Blood samples for AVP, sodium, potassium, urea, glucose and osmolality were collected from the arterial line at the initiation of HD, at 30 and 60 min of HD and, thereafter, every hour until completion of the treatment. Blood sampling for AVP at 240 min of dialysis was performed before blood re-entry to the patient excluding the possibility of a haemodilution effect on post-dialysis AVP levels. At the same time points of blood sampling, systolic and diastolic blood pressure, heart rate, the change in blood volume and the cumulative UF volume were registered. The blood volume change normalized for UF volume (ABV/UF ratio) was calculated as a surrogate marker of the plasma refill rate. Blood pressure and heart rate were measured by an automatic oscillometric monitor that is incorporated in the HD apparatus. Changes in blood volume were measured by Hemoscan (Gambro-Hospal, Lyon, France). All patients’ complaints and treatment interventions were registered by the dialysis nurse.

**HD treatment**

HD was conducted with a low-flux polysulphon dialyzer on an Integra Physio HD apparatus (Gambro-Hospal). The UF volume was set to achieve dry weight at the completion of the HD session. Prescriptions regarding dry weight were made by the nephrologists during their weekly visit to the participating patients. Dry weight was evaluated clinically (peripheral oedema, signs of pulmonary congestion, intra-dialytic and inter-dialytic blood pressure course and muscle cramps) in combination with the cardio-thoracic ratio on chest radiography. For patients who were not previously on Hemocontrol, the ideal relative blood volume trajectory for HHD was derived in the week before the start of the study by analysing the spontaneous relative blood volume curves in relation to intra-dialytic blood pressure behaviour, cumulative UF volume and complaints as described previously [7, 8, 10].

Blood flow and dialysate flow rates were 250–380 mL/min and 500–700 mL/min, respectively, and for the individual patient identical for
SHD and HHD. Dialysate temperature was 36.0 or 36.5°C and for the individual patient identical for both treatments. Dialysate composition for SHD was: sodium 138 mmol/L, magnesium 0.5 mmol/L, chloride 109 mmol/L, bicarbonate 32 mmol/L, acetate 3.0 mmol/L and glucose 1.0 g/dL. Potassium and calcium varied between 1 and 3 mmol/L and between 1.25 and 1.50 mmol/L, respectively. Dialysate conductivity in SHD was 13.9 mS/cm. In HHD, the dialysate composition was identical, except for the dialysate sodium concentration, which was variable according to the concept of HHD. The equivalent conductivity during HHD was set at 13.8 mS/cm with lower and upper tolerance limits of 13.6 and 14.0 mS/cm, respectively. We chose these settings since it is our experience that, in most patients, the actual equivalent conductivity upon completion of HHD is ~0.1 mS/cm higher than the set equivalent conductivity. In this way, the actually achieved equivalent conductivity during HHD was expected to equal the dialysate conductivity in SHD.

**Laboratory procedures**

Blood samples for the determination of AVP were collected in ethylenediaminetetraacetic acid tubes and immediately put on ice. Next, the samples were centrifuged and stored at -20°C until processing. AVP was measured by radioimmunoassay following an extraction using octadecylsilyl-silica (DiaSorin, Stillwater, MN) in the General Clinical Laboratory of the IJsselland Hospital (Capelle aan de IJssel, The Netherlands). The assay range was between 0.20 and 4.7 pg/mL with a sensitivity of 0.17 pg/mL. Blood samples for the determination of sodium, potassium, urea and osmolality were collected in heparin-coated tubes. Plasma sodium and potassium levels were measured with the indirect method of ion-selective electrode on a Roche Modular (Hitachi, Tokyo, Japan). Urea was measured with the colorimetric method on a Roche Modular analyser. Coefficients of variation for plasma levels of sodium, potassium and urea were 0.8, 1.1 and 2.6%, respectively. Blood glucose levels were measured with the Precision Xceed (Abbott Diabetes Care, Witney, UK) with a drop of blood from the arterial line. Plasma osmolality was measured by freezing-point depression on the Ostosmat Osmometer (Arkray, Kyoto, Japan). The coefficient of variation was 1.0%. Plasma osmolality was also calculated as 2 x plasma [Na+] + plasma glucose + plasma urea. Urea is considered an ineffective osmole since it can freely cross cell membranes [16]. Consequently, changes in plasma urea levels will not affect AVP release [17]. Therefore, we also calculated the effective osmolality as 2 x plasma [Na+] + plasma glucose [17].

**Statistical analysis**

Analyses were performed with GraphPad Prism version 5.0 and SPSS version 16.0. Normally distributed variables are represented as mean ± SD, variables with a skewed distribution are represented as median and interquartile range. Normality was tested with the Shapiro–Wilk test. Comparisons were made with a paired Student’s t-test, Wilcoxon Signed-Rank Test or Fisher’s exact test when appropriate. The difference in the course of the UF rate over time between SHD and HHD was tested by comparing the hourly average UF volumes by analysis of variance. P-values of <0.05 (two-tailed) were considered statistically significant.

**Results**

**Patients**

The patient characteristics are shown in Table 1. The causes of renal failure were pyelonephritis (n = 1), diabetes mellitus (n = 2), hypertension (n = 1), microscopic polyangiitis (n = 1), anti-glomerular basement membrane glomerulonephritis (n = 1), urologic cause (n = 2) and focal segmental glomerulosclerosis (n = 3). In four patients, the cause of renal failure was unknown.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.0 ± 15.5</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>29.0 ± 20.6</td>
</tr>
<tr>
<td>Number of males (%)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Number of diabetics (%)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Diastolic dysfunction, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Aortic stenosis, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Coronary artery stenosis, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Medication used</td>
<td></td>
</tr>
<tr>
<td>Beta blocker, n (%)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Nitrate, n (%)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>CCB, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>ACE-I, n (%)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>SSRI/TCA, n (%)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

*Continuous variables are represented as mean ± SD. ACE-I, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; CVA, cerebrovascular accident; SSRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant.*

**Total weight loss, UF volume, blood pressure, heart rate and hypotensive episodes**

As shown in Table 2, the total weight loss and UF volume were comparable for the two treatments. Systolic and diastolic blood pressure and mean arterial pressure decreased significantly during both treatments (P < 0.05) (Table 2).

Heart rate did not change significantly during SHD, whereas it increased modestly but significantly (P = 0.049) during HHD (Table 2).

Pre-dialysis systolic and diastolic blood pressure as well as heart rate did not differ between SHD and HHD (Table 2). Figure 1 shows the percentage change in blood pressure and heart rate during dialysis. There were no significant differences between SHD and HHD although there was a trend towards a more stable blood pressure with HHD compared with SHD at 180 and 240 min of dialysis (P = 0.14 and P = 0.12 at 180 and 240 min, respectively).

As shown in Table 2, the maximum decrease in systolic blood pressure compared with the pre-dialysis value was greater during SHD than during HHD but the difference was not statistically significant (P = 0.082). Dialysis hypotension occurred in five patients during SHD and in none of the patients during HHD (P = 0.042). All episodes of dialysis hypotension occurred in the third and fourth hour of HD.

**Plasma sodium and osmolality**

As shown in Figure 2, pre-dialysis plasma sodium levels and effective osmolality were identical. During the first 2 h of HHD, plasma levels of sodium and effective osmolality were significantly higher than during SHD. The post-dialysis plasma sodium concentration and the effective plasma osmolality were comparable for SHD and
HHD. Results for measured and calculated osmolality were comparable with the results of effective osmolality (data not shown). The course of osmolality was comparable with or without urea in the calculation of osmolality. The main determinants of plasma osmolality are plasma concentrations of sodium, glucose and urea. Pre-dialysis and intra-dialysis plasma levels of potassium, urea and glucose were comparable for the two treatments (data not shown). The difference in effective plasma osmolality between SHD and HHD was solely caused by the difference in plasma sodium concentration.

The average UF volume in the first hour of HD was significantly higher with HHD compared with SHD (1.20 ± 0.22 versus 0.95 ± 0.23 L/h; P < 0.01) and did not differ significantly between HHD and SHD from the second hour onwards (Figure 3). The total UF volume during the complete HD session was comparable for both treatments (Table 2).

The initially higher UF rate with HHD coincided with a more pronounced fall in the relative blood volume at 30 min of HHD compared with SHD (P < 0.01). From 60 min onwards until the end of the HD session, the relative blood volume did not differ significantly between both treatments (Figure 3). The course of the ΔBV/UF ratio did not differ between SHD and HHD (Figure 3).

**Vasopressin**

As shown in Table 3, pre-dialysis AVP levels did not differ between HHD and SHD. During SHD, almost no change in plasma AVP levels was observed (Figure 4). During HHD, however, plasma AVP levels rose significantly and almost doubled within the first 30 min of the HD session. At 30 min and at 60 min of dialysis with HHD, plasma AVP levels were significantly higher in comparison with SHD (P < 0.01).

**Discussion**

This study shows that HHD is associated with higher plasma AVP levels in comparison with SHD. The divergence occurred early during treatment: plasma AVP levels rose significantly within 30 min after the start of HHD, whereas AVP levels did not rise significantly during SHD. Our findings of significantly less intra-dialytic hypotension with HHD [4, 5, 7–11, 18] and our observation that AVP did not increase during SHD [19–25] match previous findings. The observation that HHD is associated with an increase in plasma AVP levels during HD has not been reported before.

Hyperosmolality and hypovolaemia are powerful stimuli for AVP release [13, 14]. It follows that the increase in AVP levels during HHD could be related to the higher plasma osmolality and the more pronounced hypovolaemia with HHD compared with SHD. The peak of the AVP response during HHD coincided with the peak of the effective plasma osmolality and with the most prominent change in blood volume. The response of AVP on hypovolaemia and hyperosmolality occurs within minutes [16] and, therefore, the coincident dynamics of AVP levels with plasma osmolality and blood volume changes are compatible with the expected physiology of AVP release. Another major physiological stimulus for AVP release is hypotension [13, 14]. However, the intra-dialytic blood pressure reduction during the first half of the dialysis did not differ significantly between the two treatment modalities and,
therefore, the early divergence in AVP levels between SHD and HHD cannot be explained by differences in blood pressure reduction.

Hyperosmolality as a stimulus for AVP release can also be induced during SHD by modification of the dialysate sodium concentration using sodium profiles [26]. However, sodium profiling during SHD carries the risk of sodium retention resulting in increased thirst, increased inter-dialytic weight gain and hypertension [27], whereas Hemocontrol uses controlled sodium modifications to prevent intra-dialytic sodium loading [4, 5, 7, 9–11, 18].

The beneficial effect of HHD on haemodynamic stability is generally explained by its effect on blood volume [9, 10]. Although this and other studies have shown that the actual blood volume at the end of the HD session is comparable between HHD and SHD [4, 7, 9], HHD may well favour haemodynamic stability by preventing sudden blood volume reductions as has been suggested by Santoro et al. [9]. In the present study, we have identified a possible additional explanation for the positive effect of HHD on haemodynamic stability, e.g. an enhanced release of AVP. The higher plasma levels of the vasoconstrictor AVP early during HHD may favour haemodynamic stability and, thus, facilitate relatively high UF rates early during HD, permitting lower UF rates during the second half of the dialysis session.

In this study, we found no evidence for a higher plasma refill rate with HHD compared with SHD. Santoro et al. reported that the ΔBV normalized for total weight loss at the end of the dialysis session did not differ significantly between SHD and HHD [5]. However, it should be realised that the ΔBV/UF ratio provides only a rough estimation of refill. With the use of a bioimpedance-based estimation of the plasma refill rate, Basile et al. observed higher refill rates with Hemocontrol compared with SHD in five hypotension-prone patients [7].

Although the final change in blood volume was comparable between SHD and HHD [4, 7, 9], the blood volume course differed between SHD and HHD.

**Fig. 1.** Percentage change in systolic (upper panel) and diastolic blood pressure (middle panel) and heart rate (lower panel) compared with the pre-dialysis values. Mean ± SD.

**Fig. 2.** Course of plasma sodium (left panel) and effective plasma osmolality (right panel). Mean ± SD. *Denotes a significant difference (P < 0.05) between SHD and HHD.
throughout the dialysis session. In accordance with previous studies, HHD was associated with a more rapid reduction in blood volume within the first hour of dialysis compared with SHD [4, 9, 28]. This may be related to the relatively high cumulative UF volume and/or the use of a lower equivalent conductivity for HHD in the present study.

From this study, it can be concluded that modifying the dialysis prescription can increase the AVP release in dialysis patients. At the same time, it should be realised that the extent of the increase of AVP levels with HHD is still rather small given the combination of stimuli for AVP secretion, i.e. the fall in blood volume and blood pressure and the increase in effective osmolality [13].

The question why AVP levels do not increase substantially during SHD, as shown in the present and previous studies [19–25] still exists. Several groups have suggested that autonomic dysfunction may play a role [19, 21, 29]. Since AVP secretion is under baroreflex control, it follows that autonomic dysfunction could impair AVP release. Alternatively, increased nitric oxide (NO) synthesis induced by HD [30] may inhibit the release of AVP [19, 31, 32]. Finally, endogenous AVP release during HD may be underestimated as a result of the removal of AVP (molecular size 1 kDa) by dialysis, as has been suggested previously [33]. Further research is needed to investigate whether this is indeed the case.

The small number of patients and dialysis sessions studied are limitations of the present study. Therefore, our results should be confirmed in a larger cohort of dialysis patients before a definite conclusion can be drawn. Although the dialysis settings, medication use, food and beverage intake and posture during HD were all standardised in this study, we cannot exclude variations in inter-dialytic sodium and/or water intake with associated differences in extracellular and blood volume between SHD and HHD. However, the randomised cross-over design and the observation that pre-dialysis weight, plasma sodium levels, plasma osmolality and AVP levels were comparable between SHD and HHD make it unlikely that this has affected our results. We did not measure detailed haemodynamic data like peripheral vascular resistance and cardiac index. Future studies should preferably assess the change in AVP levels in relation to the change of these haemodynamic parameters. A strength of the present study is the within-subject design where patients served as their own control.

**Conclusion**

HD with Hemocontrol is associated with an enhanced initial rise of the plasma vasopressin concentration compared with SHD. This augmented initial vasopressin release could contribute to the lower frequency of dialysis hypotension with Hemocontrol by facilitating fluid removal during the first part of the HD session, permitting lower UF rates and, consequently, improved haemodynamic stability in the second half of the HD session.
Table 3. Plasma AVP levels during SHD and HHD [median and interquartile range (IQR)]

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>AVP level (pg/mL) SHD</th>
<th>AVP level (pg/mL) HHD</th>
<th>P-value for difference between SHD &amp; HHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Min</td>
<td>0.94 (IQR 0.62–2.10)</td>
<td>1.00 (IQR 0.84–1.60)</td>
<td>0.900</td>
</tr>
<tr>
<td>30 Min</td>
<td>1.20 (IQR 0.65–1.50)</td>
<td>1.90* (IQR 1.2–2.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>60 Min</td>
<td>0.92 (IQR 0.47–1.50)</td>
<td>1.30 (IQR 0.85–2.20)</td>
<td>0.041</td>
</tr>
<tr>
<td>120 Min</td>
<td>0.85 (IQR 0.33–2.30)</td>
<td>1.30 (IQR 0.90–2.00)</td>
<td>0.776</td>
</tr>
<tr>
<td>180 Min</td>
<td>1.00 (IQR 0.59–3.00)</td>
<td>1.20 (IQR 0.65–3.2)</td>
<td>0.532</td>
</tr>
<tr>
<td>240 Min</td>
<td>1.20 (IQR 0.8–1.70)</td>
<td>1.10 (IQR 0.65–3.2)</td>
<td>0.394</td>
</tr>
</tbody>
</table>

*Denotes P < 0.01 compared with pre-dialysis value.

Fig. 4. Percentage change in plasma AVP levels compared with pre-dialysis values. The boxes represent the median values and interquartile range (IQR). The whiskers represent 1.5 × IQR. *Denotes a significant difference (P < 0.05) between SHD and HHD.

Acknowledgements. Joost van Pelt, PhD is acknowledged for his assistance in laboratory measurements.

Conflict of interest statement. None declared.

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Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study

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Abstract

Background. Optimal treatment for secondary hyperparathyroidism (SHPT) has not been defined. The IMPACT SHPT (ClinicalTrials.gov identifier: NCT00977080) study assessed whether dose-titrated paricalcitol plus supplemental cinacalcet only for hypercalcemia is superior to cinacalcet plus low-dose vitamin D in controlling intact parathyroid hormone (iPTH) levels in patients with SHPT on haemodialysis.

Methods. In this 28-week, multicentre, open-label Phase 4 study, participants were randomly selected to receive paricalcitol or cinacalcet plus low-dose vitamin D. Randomization and analyses were stratified by mode of paricalcitol administration [intravenous (IV) or oral]. The primary efficacy end point was the proportion of subjects who achieved a mean iPTH value of 150–300 pg/mL during Weeks 21–28.

Results. Of 272 subjects randomized, 268 received one or more dose of study drug; 101 in the IV and 110 in the oral stratum with two or more values during Weeks 21–28 were included in the primary analysis. In the IV stratum, 57.7% of subjects in the paricalcitol versus 32.7% in the cinacalcet group (P = 0.016) achieved the primary end point. In the oral stratum, the corresponding proportions of subjects were 54.4% for paricalcitol and 43.4% for cinacalcet (P = 0.260). Cochran–Mantel–Haenszel analysis, controlling for stratum, revealed overall superiority of paricalcitol (56.0%) over cinacalcet (38.2%; P = 0.010) in achieving iPTH 150–300 pg/mL during Weeks 21–28. Hypercalcemia occurred in 4 (7.7%) and 0 (0%) of paricalcitol-treated subjects in the IV and oral strata, respectively. Hypocalcemia occurred in 46.9% and 54.7% of cinacalcet-treated subjects in the IV and oral strata, respectively.

Conclusion. Paricalcitol versus cinacalcet plus low-dose vitamin D provided superior control of iPTH, with low incidence of hypercalcemia.

Keywords: cinacalcet hydrochloride; paricalcitol; secondary hyperparathyroidism; kidney disease; haemodialysis

Introduction

Secondary hyperparathyroidism (SHPT), a complication of chronic kidney disease (CKD), is characterized by