The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration—The Pan Thames Renal Audit

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Abstract
Background and Objectives. Hyperphosphataemia is a primary risk factor for patients with end-stage kidney failure. Phosphate clearance by traditional thrice-weekly standard haemodialysis is inadequate for patients achieving recommended dietary protein goals. We investigated whether phosphate control was improved by adding convective clearance with haemodiafiltration.

Methods. We audited pre-midweek session calcium and phosphate levels in 5366 adult patients, 4515 treated by haemodialysis and 851 by on-line haemodiafiltration.

Results. The cohorts were similar for age, sex and dialysis vintage. Serum phosphate was lower in the haemodiafiltration cohort (1.42 ± 0.61 mmol/l) compared to the haemodialysis cohort (1.53 ± 0.53 mmol/l; \( P < 0.001 \)), as was the calcium-phosphate product (3.31 ± 1.53 vs 3.5 ± 1.33 mmol\(^2\)/l\(^2\), respectively; \( P < 0.001 \)) despite a shorter treatment session time (3.68 ± 0.44 vs 3.92 ± 0.49 h; \( P < 0.001 \)). Parathyroid hormone levels were similar.

Conclusions. The results of this audit suggest that haemodiafiltration offers improved phosphate control compared to standard intermittent haemodialysis.

Keywords: calcium; guidelines; haemodiafiltration; haemodialysis; phosphate

Introduction
Traditionally, the dose of haemodialysis delivered to a patient with chronic kidney disease stage 5 (CKD5) has been based on urea clearance using the Kt/V model, although patient outcomes do not appear to be improved with increasing urea clearance [1]. However, there are several paradoxes between CKD5 patient survival and the general population. For example, morbid obesity (body mass index > 35) and male sex are increased risk factors for shorter survival in the general population, but have positive survival advantage in American CKD5 haemodialysis patients [2]. This has led to the concept of non-traditional risk factors for mortality in CKD5 patients. As patients develop progressive kidney disease and lose kidney function, renal phosphate clearance declines, resulting in phosphate retention. Recently, hyperphosphataemia secondary to phosphate retention has been shown to be an independent risk factor for CKD5 dialysis patient survival [3].

If patients achieve the nutritional guidelines recommended for CKD5 patients, then their dietary phosphate intake will be ~1000–1500 mg/day (32–48 mmol/day), with some 600–1000 mg (19–32 mmol) expected to be absorbed from the gastrointestinal tract. As the phosphate pool is mainly intracellular rather than intravascular, phosphate is not effectively removed by conventional thrice-weekly dialysis [4]. Thus, to maintain phosphate within the Kidney Disease Outcomes Quality Initiative (KDOQI) and UK Renal Association guidelines [5,6], the majority of patients require the additional combination of dietary advice to avoid foodstuffs rich in phosphate and prescription of phosphate-binding drugs.

During standard haemodialysis, phosphate is primarily removed by diffusion and is therefore dependent upon the plasma concentration. Attempts to improve phosphate clearances by increasing dialyser surface area, switching dialyser from low to high flux, using higher blood flow and dialysate flows and changing dialysate bicarbonate and glucose concentrations have either been reported to have no effect or a variable effect [7–9].

The failure to adequately clear phosphate during intermittent haemodialysis is well established. The rate-limiting step to phosphate removal is slow or inadequate refilling of the plasma from the intracellular stores [10]. On the other hand, hypophosphataemia is a relatively common complication of continuous renal replacement therapies in the intensive care setting [11], and studies from daily nocturnal dialysis show that, given enough session time on dialysis, serum phosphate concentrations can become normalized or even necessitate phosphate supplementation [12,13].

Unfortunately, lengthening dialysis session time or increasing dialysis frequency is not available to the majority of CKD5 patients. One other possibility to potentially in-
crease phosphate clearance would be adding an additional convective element to standard diffusion, with post-dilutional haemodiafiltration. Some studies have reported that haemodiafiltration improved phosphate losses [14], but others have shown no difference [7,15]. In view of the discrepancy in the reports of haemodiafiltration on phosphate control, we decided to prospectively audit serum calcium and phosphate values in CKD5 patients treated by haemodialysis or haemodiafiltration in the Pan Thames area.

Methods

The project was initiated by the London Renal Modernisation Audit Group and implemented by the Audit, Information and Analysis Unit. Participation approval was obtained from each centre’s trust, and data protection policies were followed. Data were prospectively collected prior to a midweek dialysis session during April and May, 2008. Data on patient demographics, dialysis schedule and prescription and pre- and post-blood biochemical measurements were collected on specific audit sheets and returned to the audit unit for analysis. Data were returned on all patients from the 14 main hospital and associated satellite dialysis units, located in the greater London area and South East England, who were registered as established on chronic regular outpatient dialysis for more than 90 days with the national UK renal registry. Patients who had been admitted to hospital with intercurrent illnesses were excluded.

All patients used bicarbonate dialysate, and apart from two centres which used modified cellulose acetate dialysates, patients were dialysed with polysulfone membranes. On-line haemodiafiltration was typically performed in the post-dilution mode, although one centre also used mid-dilution haemodiafiltration. The calcium concentration of the dialysate for the haemodialysis cohort was 1.28 ± 0.14 mmol/l (median 1.25 [1.25–1.35]) and that for the dialysate/haemodiafiltration replacement solution was 1.26 ± 0.07 mmol/l (median 1.25 [1.25–1.25]). The volume of fluid exchanged during haemodiafiltration sessions varied between 15 and 20 l per treatment. Unfractionated heparin was the most common anticoagulant. All participating centres had unrestricted access to both calcium-containing (calcium carbonate and calcium acetate) and non-calcium-based phosphate binders (Renagel, lanthanum carbonate and aluminium-containing medications). However, we did not collect data on individual patient phosphate binder prescriptions. Dietetic review varied between the centres; however, all patients received appropriate dietetic advice to restrict phosphate intake and when to take their phosphate binders in relation to meals. Unfortunately, we were unable to make any systematic estimation of dietary phosphate intake.

Routine biochemistry was measured prior to the midweek treatment by standard methods, and urea clearance was calculated by single-pool Kr/V.

Statistical analysis was by Student’s t-test or Mann–Whitney U-test for parametric and non-parametric data, respectively, and additionally the chi-square test, with Yate’s correction, where appropriate, was also used. Data are expressed as mean ± standard deviation or median and interquartile range. Statistical significance was taken at a ≤ 5% level.

### Table 1. Haemodialysis and haemodiafiltration groups

<table>
<thead>
<tr>
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<th>Haemodialysis</th>
<th>Haemodiafiltration</th>
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<tbody>
<tr>
<td>Number</td>
<td>4515</td>
<td>851</td>
</tr>
<tr>
<td>Sex male, %</td>
<td>59.9</td>
<td>61.6</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.1 ± 15.5</td>
<td>61.6 ± 15.9</td>
</tr>
<tr>
<td>Dialysis vintage, months</td>
<td>29 (14–59.2)</td>
<td>29 (13–52)</td>
</tr>
<tr>
<td>Dialysis session, h</td>
<td>3.92 ± 0.49</td>
<td>3.68 ± 0.44*</td>
</tr>
<tr>
<td>Kr/V</td>
<td>1.59 ± 0.39</td>
<td>1.36 ± 0.26*</td>
</tr>
<tr>
<td>Urea reduction ratio, %</td>
<td>71.6 ± 7.9</td>
<td>71.0 ± 12.0</td>
</tr>
<tr>
<td>Ultrafiltration volume, l</td>
<td>1.96 ± 1.05</td>
<td>1.90 ± 0.96</td>
</tr>
<tr>
<td>Dialysate calcium, mmol/l</td>
<td>1.28 ± 0.14</td>
<td>1.26 ± 0.07*</td>
</tr>
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</table>

Data presented as mean ± SD or median and quartiles. *P < 0.001.

### Results

Data were collected on 5366 adult patients, 4515 (84%) treated by regular haemodialysis and 851 (16%) by haemodiafiltration. There were no differences in sex, age or dialysis vintage between the groups (Table 1). The haemodialysis group had longer dialysis treatment session duration and greater small solute clearance, as assessed by Kr/V, but similar ultrafiltration losses (Table 1).

Although the corrected serum calcium was only marginally lower in the haemodiafiltration group, this difference was highly significant (Table 2). The dialysate calcium concentration was lower in the haemodiafiltration group. When only the units practising haemodiafiltration were reviewed, the dialysate calcium for their haemodialysis cohorts was 1.3 ± 0.17 mmol/l (median 1.25 [1.25–1.35]), which was significantly greater than that for their haemodiafiltration patients (Table 1; P < 0.001). Serum phosphate was significantly lower in the haemodiafiltration group (Figure 1), as was the calcium–phosphate product.

There was no significant difference between the haemodialysis and haemodiafiltration groups in terms of achieving KDOQI-corrected serum calcium target (Table 3). More haemodialysis patients achieved the serum phosphate target range (χ² = 28.1, P < 0.01), and as a consequence more patients also achieved all three targets (χ² = 5.2, P = 0.022). However, more patients failed to achieve the phosphate target range due to a low phosphate in the haemodiafiltration group rather than a high phosphate (54.4% vs 45.6%; Figure 2), whereas in the haemodialysis group, more patients failed...
Phosphate control with haemodiafiltration

Table 3. Percentage of patients achieving KDOQI standards of corrected serum calcium of 2.1–2.37 mmol/l (8.4–9.5 mg/dl), phosphate 1.13–1.78 mmol/l (3.5–5.5 mg/dl) and calcium–phosphate product of <4.3 mmol²/l² (<55 mg²/dl²)

<table>
<thead>
<tr>
<th>Target</th>
<th>Haemodialysis</th>
<th>Haemodiafiltration</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>51.9%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Phosphate</td>
<td>51.1%</td>
<td>41.1%*</td>
</tr>
<tr>
<td>Calcium × phosphate</td>
<td>81.0%</td>
<td>81.4%</td>
</tr>
<tr>
<td>All of the above three targets</td>
<td>26%</td>
<td>22.3%**</td>
</tr>
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Chi-square analysis, *P < 0.001, **P < 0.05.

Fig. 2. Frequency distribution curves of the pre-dialysis midweek serum phosphate concentrations in the haemodialysis patients (black bars) and haemodiafiltration patients (white bars).

Discussion

Over the last few years, an increasing number of cases of calcific uraemic arteriolopathy or calciphylaxis has been reported in chronic haemodialysis patients not only in North America and Europe but also Australia and New Zealand, with a prevalence as high as 4.1% reported in one study [17]. Although relatively uncommon, calciphylaxis is a serious life-threatening complication of dialysis, and the increasing incidence has led to research into soft tissue calcification. Vascular calcification, in particular medial calcification, is common in dialysis patients, but vascular calcification is more than just a simple calcium–phosphate deposition or precipitation in vessel walls. Although hyperphosphataemia and increased calcium–phosphate product are important, other factors such as local inflammation and inhibitors of ossification including fetuin and matrix GLA proteins and pyrophosphates also play a regulatory role. However, extracellular phosphate availability plays a key role in regulating bone mineralisation [18].

Retrospective and observational studies have reported that control of serum phosphate, calcium and parathyroid hormone (PTH) have been associated with improved survival of CKD5 patients treated by regular haemodialysis [19,20]. As such, all participating centres in the audit were trying to maintain patients’ blood biochemistries within the target ranges set out by the KDOQI and UK Renal Association clinical guidelines [5,6].

As with many previous reports, the number of patients achieving these targets was somewhat disappointing, with ~50% of patients achieving the calcium (2.1–2.37 mmol/l or 8.4–9.5 mg/dl) and phosphate (1.13–1.78 mmol/l or 3.5–5.5 mg/dl) targets, and although the majority, some 80% had a calcium–phosphate product of <4.3 mmol²/l² or 55 mg²/dl², less than a quarter of all patients achieved all three of these clinical guideline targets.

As there has been debate as to whether adding a convective element to standard diffusion-based haemodialysis improves phosphate control [14–16], we analysed phosphate levels in the haemodialysis and haemodiafiltration cohorts, and phosphate levels were statistically significantly lower in the haemodiafiltration cohort. This was despite the haemodialysis cohort having longer session times and a higher urea clearance as assessed by Kt/V. We did not measure residual renal function. However, as cohorts were of similar dialysis vintage, and some centres reserved haemodiafiltration only for anuric patients, it is unlikely that residual renal function differed between cohorts, and if anything residual renal function was more likely to be less in the haemodiafiltration cohort.

Phosphate control can be affected by dietary intake, and as such, previous studies have suggested that both age and sex distribution of the population can affect phosphate control [21]. However, the haemodialysis and haemodiafiltration cohorts were well matched and there were no differences in age and/or sex. Although we did not record the absolute number of phosphate binders prescribed to individual patients, all centres had equal access to the currently available phosphate binders and were trying to adhere to UK Renal Association clinical guideline targets for phosphate control. We cannot exclude the fact that the differences in phosphate levels could have potentially been due to a major difference in phosphate binder prescription and increased patient compliance. However, increased phosphate binder prescription in the haemodiafiltration group compared to the haemodialysis cohort is somewhat unlikely, in view of the increased proportion with low phosphate values, below the lower target threshold in the haemodiafiltration group, and the corresponding higher number of patients in the haemodialysis cohort having higher phosphate value, above the higher threshold target.

Serum calcium was lower in haemodiafiltration group, as was the calcium concentration of the dialysate and replacement solution. Calcium losses during treatment would be expected to be greater with post-dilutional haemodiafiltration [22]. As such, the combination of lower calcium-containing dialysates and infusion fluids for haemodiafiltration could potentially result in a negative calcium balance in the longer term. However, there was no difference in PTH levels between the groups.

The combination of lower phosphate and calcium resulted in a lower calcium–phosphate product in the haemo-
diafiltration group. This could potentially reduce both the requirement for the more expensive non-calcium-based binders [23] and also the risk of iatrogenic hypercalcaemia [24].

Hyperphosphataemia has been shown to be an independent factor of all-cause mortality in the CKD stage 5 populations [25]. During standard haemodialysis, phosphate is primarily removed by diffusion and is therefore dependent upon the plasma concentration. The rate-limiting step to phosphate removal is adequate refilling of the plasma from the intracellular stores during intermittent haemodialysis [26], and to improve phosphate removal, patients require prolonged treatment sessions such as nocturnal haemodialysis [12] or forms of continuous dialysis [27]. Unfortunately, these options are available only to a minority of patients or remain experimental. Although on superficial examination phosphate is a relatively small molecule of 95 Da, it is charged and can exist in plasma water in multiple forms, including pyrophosphates (P$_2$O$_7^-$), tri- and even decametaphosphates, and also bind to proteins, often termed phosphate moieties. As such, these forms of phosphate are of much greater molecular weight with lower diffusive capabilities, and so may be better cleared by the addition of convective. Reports of increased phosphate clearance during haemofiltration compared to haemodialysis date back to the 1970s [28], with later studies again suggesting increased clearance with biofiltration [29] and haemodiafiltration compared to conventional intermittent haemodialysis [30]. In addition, as convective clearance can increase the clearance of larger molecules, then haemodiafiltration may potentially have an additional benefit by altering key peptides and proteins involved in phosphate regulation, with some reports claiming increased clearance of PTH with haemodiafiltration [29].

Despite shorter treatment session times, the haemodiafiltration cohort not only had lower serum phosphate concentrations but also a greater proportion who had phosphate values below the UK Renal Association and KDOQI guidelines. As such, phosphate levels should be carefully reviewed in patients treated by haemodiafiltration and phosphate binder prescription amended accordingly to prevent hypophosphataemia.

Thus, for the average patient, adding a convective component to clearance with haemodiafiltration would appear to help reduce phosphate levels compared to haemodialysis.

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Conflict of interest statement. None declared.

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Visfatin is increased in chronic kidney disease patients with poor appetite and correlates negatively with fasting serum amino acids and triglyceride levels

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Abstract

Objective. Anorexia is a common complication of chronic kidney disease (CKD), while novel animal and human data suggest a role for visfatin in regulating feeding behavior. We hypothesized that increased visfatin levels in CKD patients may be involved in the regulation of appetite and nutrient homeostasis.

Methods. This is a cross-sectional study where circulating visfatin levels were analysed in 246 incident CKD stage 5 patients starting dialysis therapy. The associations between visfatin (enzyme-linked immunosorbent assay, ELISA) and anthropometric and biochemical nutritional status, self-reported appetite, fasting serum amino acids (high-performance liquid chromatography) and circulating cytokine levels (ELISAs) were assessed. We also performed genotyping (Pyrosequencing®) of two polymorphisms (rs1319501 and rs9770242) in the visfatin gene.

Results. Serum visfatin concentrations were not associated with either body mass index or serum leptin. Across groups with worsening appetite, median visfatin levels were incrementally higher (P<0.05). With increasing visfatin tertiles, patients proved to be more often anorectic (P<0.05) and to have incrementally lower serum albumin, cholesterol and triglycerides as well as lower essential and non-essential serum amino acids (P<0.05 for all). A polymorphism in the visfatin gene was associated with increased circulating visfatin levels and, at the same time, a higher prevalence of poor appetite (P<0.05 for both).

Conclusion. Our study suggests novel links between visfatin and anorexia in CKD patients. Based on recent studies, we speculate that high visfatin in CKD patients may constitute a counter-regulatory response to central visfatin resistance in uremia. Future studies should examine a putative role of visfatin as a regulator of nutrient homeostasis in uremia.

Keywords: amino acids; anorexia; NAMPT; single-nucleotide polymorphism

Introduction

Patients with chronic kidney disease (CKD) are prone to protein-energy wasting (PEW), which is associated with a poor prognosis [1,2]. The loss of the desire to eat—an-