Does the choice of phosphate binder affect trace element levels in chronic kidney disease patients treated by regular haemodialysis?

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Abstract

Background. Ion exchange resins have been reported to bind copper and zinc. As the phosphate binder sevelamer hydrochloride is an ion exchange resin, we audited trace element levels in our haemodialysis cohort to determine whether sevelamer prescription affected trace element levels compared with other phosphate binders.

Methods. Samples for zinc, copper and selenium were taken in special tubes and measured by atomic absorption spectroscopy or inductively coupled plasma–mass spectrometry from 211 patients attending an inner city university hospital main dialysis centre.

Results. Of the patients, 12.9% were prescribed oral or intravenous trace element supplementation. Of the remainder, 5.5% of patients had low plasma copper, 37.4% low zinc and 45.6% low selenium. There was no difference in element levels between the sevelamer group compared with other phosphate binders. Despite a high prevalence of statin prescription, total cholesterol (1.46 ± 0.1 vs 2.00 ± 0.07, P < 0.01) and total cholesterol/HDL-cholesterol ratio (2.82 ± 0.15 vs 3.52 ± 0.17, P < 0.001) and race (F 31.4, β 1.97, P < 0.001) and dialysis vintage were significantly different according to ethnicity, most likely due to differences in dietary intake.

Conclusions. Trace element and micronutrient deficiencies were relatively common in this inner city population of outpatient haemodialysis patients. However, the prescription of different phosphate binders did not have an observable effect on serum copper and zinc levels, but those prescribed sevelamer did have lower lipid profiles compared with those prescribed other phosphate binders. Trace element concentrations were more associated with albumin, a marker of general nutritional status, with some differences according to ethnicity, most likely due to differences in dietary intake.

Keywords: copper; haemodialysis; phosphate binders; selenium; zinc

Introduction

Zinc, copper and selenium are essential micronutrients, incorporated into many metallo–enzymes and proteins involved in cell metabolism and production of neurotransmitters and regulatory pathways controlling oxidative stress [1,2]. Due to its ubiquitous distribution among food sources and low daily requirement, acquired copper deficiency is rare in humans. Copper is predominantly excreted into the bile, so patients with kidney disease are not at increased risk of copper-related disorders [3]. Dietary sources of zinc are similarly widespread, including meats, whole grains, legumes and shell fish. However, binding of zinc to phytates and oxalate within the gut leads to formation of insoluble complexes which may prevent absorption [4]. Loss of zinc from the body is in faeces. Copper binds to circulating caeruloplasmin but also to albumin, and zinc is also predominantly transported by albumin. Plasma zinc levels reflect current zinc status, whereas zinc in red blood cells and hair provides an estimate of longer-term zinc status.

Selenium is found in meat, fish and cereals, although the soil in some parts of the world is deficient in selenium. Unlike zinc and copper, selenium is predominantly excreted in the urine.

There are several studies suggesting that haemodialysis patients may become zinc deficient compared with healthy controls [5]. Whether this is due to poor dietary intake [6] or related to the malnutrition and inflammation syndrome, with reduced plasma albumin, is unclear from previous published studies. This may account for the marked variability in reports, ranging from high levels of zinc deficiency in
haemodialysis patients on one hand to no deficiency on the other [3].

As zinc can form insoluble complexes, Lee and colleagues studied whether standard calcium and aluminium phosphate binders could affect zinc levels [7], but found no differences. However, ion exchange resins can bind both copper and zinc [8]. Sevelamer hydrochloride, an ion exchange resin used as a phosphate binder in clinical practice, has been reported to have greater adsorptive properties for zinc than copper [9]. We therefore decided to audit whether trace elements were lower in our haemodialysis patients prescribed sevelamer hydrochloride compared with other phosphate binders.

Materials and methods

Following the finding of a patient with copper deficiency [10], trace elements were measured prior to the midweek haemodialysis session in 210 stable adult outpatients attending a university hospital haemodialysis centre [53.3% male, median age 61 years (45–74) and dialysis vintage 30 months (13–65)]. Copper and zinc were collected in special tubes designed to minimize external contamination and measured by atomic absorption spectroscopy, and selenium by inductively coupled plasma–mass spectrometry. Patients were dialysed with polysulphone dialysers, median size 1.8 m² (1.8–2.2 m²) (Fresenius, Bad Homberg, Germany), median session time 4.0 h (4.0–4.0), designed to achieve a minimum online Kt/V clearance of >1.2 (Fresenius 4008H, Fresenius, Bad Homberg, Germany), and urea reduction ratio >75%, and patients were anticoagulated with low-molecular-weight heparin [11].

Serum biochemistry samples were analysed with a standard multichannel biochemical analyser (Roche Integra, Roche diagnostics, Lewes, UK), using the bromocresol green method for albumin determination, and haemoglobin samples by standard methodology (XE-2100 Sysmex Corporation, Kobe, Japan); interdialysis 24-h urine collections were analysed to determine urine volume.

Ethical approval was granted by the local ethical committee as audit and clinical service development.

Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Statistical analysis was by Student’s t-test for parametric and the Mann–Whitney U-test for non-parametric data (Graph Pad Prism version 3.0, Graph Pad, San Diego, CA, USA). Java stat was used for chi-square analysis, corrected for small numbers. Simple regression analysis was performed with Pearson’s rank correlation, and then, logistic linear regression analysis was undertaken with SPSS version 15.0 (SPSS, University of Chicago, IL, USA). Variables with significant or borderline univariate associations were entered into the model along with residual renal function, age, sex, racial origin, diabetic status, pre-dialysis bicarbonate, albumin, chloride, calcium, magnesium, phosphate, cholesterol, triglycerides, CRP and sevelamer hydrochloride (as we hypothesized these factors might impact on plasma levels a priori). Variables were retained in the model where the 95% confidence intervals for the estimate did not include zero or there was an improvement in model fit (as demonstrated by the −2 log likelihood). Statistical significance was taken at or below the 5% level.

Results

The mean plasma copper was 16.9 ± 0.4 μmol/L (normal range 11–24) (107.7 ± 2.8 μg/dL, normal range 76–165 μg/dL), zinc 11.6 ± 0.2 μmol/L (normal range 11–24 μmol/L) (75.8 ± 1.8 μg/dL, normal range 72–163 μg/dL), and selenium 0.83 ± 0.02 μmol/L (normal range 0.8–2.0). Of patients, 9.1% received intravenous trace element supplementation (Additrace, Fresenius Kabi, Runcorn, UK), and 3.8% oral zinc supplementation. The median weekly dose of alfalcacidol was 2.5 μg/week (0.75–5.35), and 46.7% of patients were prescribed 25-OH vitamin D3, due to previously low 25-OH vitamin D3 levels, and 5.1% cinacalcet. As for phosphate binders, 55.7% of patients were prescribed calcium-based phosphate binders, predominantly calcium carbonate (>95%), 23.7% sevelamer hydrochloride, median dose 2.4 g/day (2.4–4.8), 21.8% lanthanum carbonate, 5.7% aluminium-containing binders, and 0% magnesium-containing binders. The mean midweek pre-dialysis biochemistries were bicarbonate 23.8 ± 0.2 mmol/L, chloride 100.0 ± 0.3 mmol/L, corrected calcium 2.25 ± 0.01 mmol/L, phosphate 1.59 ± 0.04 mmol/L, magnesium 0.96 ± 0.01 mmol/L, total cholesterol 3.78 ± 0.07 mmol/L, high-density lipoprotein 1.24 ± 0.03 mmol/L, low-density lipoprotein 1.87 ± 0.06 mmol/L, triglycerides 1.56 ± 0.06 mmol/L and iron saturation 30.9 ± 1.07%, and median parathyroid hormone 23.1 pmol/L (11.7–44.9), ferritin 512 mg/L (262–916), albumin 38.9 ± 0.4 g/L and CRP 8 mg/L (3–21.5).

Excluding patients on oral or intravenous supplements, 37.4% of patients had low zinc levels, 5.5% had low copper values, 5.5% had high copper values and 45.6% had low selenium. Patients prescribed sevelamer were similar to those prescribed other phosphate binders (Table 1), although were of greater haemodialysis vintage. The lanthanum carbonate group had fewer patients from the ethnic minorities. There were no differences in trace element concentrations between the three phosphate binder groups (Table 2). Phosphate levels were greater in the lanthanum carbonate group, but there was no correlation between phosphate and trace element levels (zinc, r = 0.056; copper, r = 0.069; and selenium, P = 0.07). Despite no difference in statin prescription, the sevelamer group had lower total and LDL-cholesterol levels (Table 2).

Table 1. Patient characteristics in those prescribed calcium, sevelamer hydrochloride and lanthanum carbonate phosphate binders

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>Sevelamer</th>
<th>Lanthanum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>125</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Age, year</td>
<td>62 (46–74)</td>
<td>61.5 (46–74.5)</td>
<td>56 (34.5–70.5)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>55.2</td>
<td>47.7</td>
<td>53.7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>35.2</td>
<td>40.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Non-Caucasoid, %</td>
<td>56.8</td>
<td>61.4</td>
<td>32.4</td>
</tr>
<tr>
<td>Vintage, months</td>
<td>28 (11.5–55)*</td>
<td>49 (20.5–82)</td>
<td>26 (13.5–71)</td>
</tr>
<tr>
<td>Urine, mL/day</td>
<td>198 (0–945)</td>
<td>0 (0–380)</td>
<td>0 (0–842)</td>
</tr>
<tr>
<td>Statin, %</td>
<td>60</td>
<td>70.5</td>
<td>68.3</td>
</tr>
<tr>
<td>Cinacalcet, %</td>
<td>52</td>
<td>45.5</td>
<td>37.8</td>
</tr>
<tr>
<td>1αD3, μg/week</td>
<td>2 (0.75–6)</td>
<td>3.75 (1.25–6)</td>
<td>2 (0.75–5)</td>
</tr>
<tr>
<td>Additrace, %</td>
<td>11.3</td>
<td>4.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Oral zinc, %</td>
<td>3.2</td>
<td>3.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Four patients prescribed both sevelamer and lanthanum have been excluded. Results are expressed as mean ± SEM, median (interquartile range) or percentage of patients. Patients prescribed HMGCoA3 reductase inhibitors (statin prescription), percentage of patients prescribed 25-OH vitamin D3 (25 D), and weekly alfalcacidol dosage (1αD3).

*P < 0.05, **P < 0.01 vs sevelamer group.

P < 0.05, ^P < 0.01 vs lanthanum group.
Correlation analysis was performed to determine whether there were any factors associated with trace element deficiency (Table 3). CRP was transformed to log CRP for analysis, due to non-uniform distribution of raw data. Serum zinc was positively associated with serum albumin and dialysis vintage, whereas copper was associated with CRP, and negatively with daily urine output and serum bicarbonate. Selenium levels were associated with serum albumin (F 20.36, β 0.174, confidence limits (CL) 0.086–0.265, P < 0.001; and dialysis vintage—F 8.1, β 0.008, CL 0.002–0.013, P = 0.005). Whereas log CRP (F 31.4, β 0.34, CL 0–1.97, P < 0.001) and urine volume (F 5.1, β 0.01, CL −0.002–0, P = 0.024) remained significant for copper, the associations with selenium reduced to serum albumin (F 23.2, β 0.016, CL 0.02–0.1, P < 0.001) and race (F 31.4, β 0.36, P = 0.032), with selenium levels being greater in non-Caucasoids (0.9 ± 0.02 vs 0.76 ± 0.02 μmol/L, P < 0.01) (Table 4).

### Discussion

In our cohort of chronic stable outpatients attending for high-flux dialysis, 12.9% of patients were prescribed oral or intravenous trace element supplementation. Of the remainder, 5.5% of patients had low plasma copper values, 37.4% low zinc and 45.6% low selenium. Previous studies and a meta-analysis have reported that dialysis patients are likely to have similar copper values to healthy controls, but several studies have reported low zinc levels [3]. Several other metals, such as aluminium [12], and other elements, including silica [13], are known to accumulate in dialysis patients with loss of residual renal function. Residual urine output had a simple inverse correlation with copper, which was maintained on logistic regression, but not selenium, despite selenium being excreted in the urine, whereas both copper and zinc are predominantly excreted in the faeces.

Previous reports have suggested that ion exchange resins can bind trace elements [8]. Sevelamer, an ion exchange resin used as a phosphate binder in clinical practice, binds both copper and zinc, particularly at acid levels being greater in non-Caucasoids (0.9 ± 0.02 vs 0.76 ± 0.02 μmol/L, P < 0.01) (Table 4).
The effect of phosphate binders on trace element concentrations in haemodialysis patients

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μ remained significant as independent variables, with an

gistic regression analysis, only CRP and urine output re-

with daily urine output and serum bicarbonate, but on lo-

Copper was initially associated with CRP, and negatively

was associated with albumin but had no relationship with

low ferritin and low zinc levels [21]. In our cohort, zinc

tins [20]. In addition, malnourished patients may have both

had low ferritin and low zinc levels [21]. In our cohort, zinc

d with serum albumin and dialysis vintage, with an increase in zinc levels of

were lower in the sevelamer group, compared with those prescribed calcium-

or lanthanum-based phosphate binders, it is most

likely that the sevelamer group were compliant with their

The lanthanum group had higher phosphate le-

vels, although this could be due to increased non-compliance;

a recent Pan Thames audit showed that other factors such as
dialysis modality [15] and ethnicity also affect phosphate

Thus, the higher phosphate levels in the lanthanum
group could be due to the increased number of Caucasoids.

In addition, as lanthanum carbonate has only relatively

been introduced into the UK, it may have been preferentially prescribed to patients with poor phosphate

control.

Previous studies have reported lower lipid profiles in

haemodialysis patients treated with sevelamer [17], but

also lower pre-dialysis bicarbonate in those prescribed se-

velamer hydrochloride compared with sevelamer bicarbon-

ate [18]. However, we were unable to demonstrate any
difference in midweek pre-dialysis serum bicarbonate

and chloride concentrations between the groups.

Although our initial supposition was that trace elements

may be lower in patients prescribed sevelamer compared

with those prescribed calcium- or lanthanum-based phosphate binders, we went on to analyse other factors affecting

trace element levels. Zinc was associated with serum albumin

and dialysis vintage, with an increase in zinc levels of

0.17 μmol/L for each 1-g/L increase in serum albumin and

0.096 μmol/L for each year of dialysis. Several other me-
tals, including lead, are known to accumulate with dialysis vintage, typically due to reduced renal clearance and con-
tamination of dialysate water [19]. Zinc is a divalent metal ion, which can bind ferritin, and has been reported to have greater binding in haemodialysis patients with high ferri-
tins [20]. In addition, malnourished patients may have both low ferritin and low zinc levels [21]. In our cohort, zinc

was associated with albumin but had no relationship with

CRP, suggesting that zinc levels reflect nutritional status.

Copper was initially associated with CRP, and negatively

with daily urine output and serum bicarbonate, but on lo-
gistic regression analysis, only CRP and urine output re-
mained significant as independent variables, with an increase in serum copper of 3 μmol/L for every 10-fold in-
crease in CRP and 1 μmol/L for every 100-mL increase in

urine output. Copper is secreted into the bile and may be-
come elevated in patients with diseases affecting biliary

drainage. Of patients, 5.5% were found to have an elevated
copper, and further investigation of this group revealed a

number of patients with underlying pancreatic, biliary or
hepatic disease, as analysis of dialysate water samples did

not show any copper excess [22]. The association between

CRP and copper is interesting, as previous reports observed an increased release of aluminium with inflammation [23].

This could be due to release of copper-containing proteins such as caeuroplasm, which is an acute phase protein.

Selenium appeared initially to be related to a wide range of

variables, but on further examination, only albumin and racial origin remained significant, with an increase of

0.016 μmol/L for every 1-g/L albumin increase, and in-
creased in patients from the ethnic minorities. Selenium

is involved with antioxidant systems, and this would be

in keeping with the simple negative correlation found with CRP. However, the strongest association was with albumin,
suggesting a nutritional link. In the general US population,

associations between selenium and both total cholesterol

and LDL-cholesterol have been reported, and also with HDL-cholesterol, but only at low selenium levels [24].

Similar findings have been reported in the UK population,

which has lower selenium levels than the USA, for choles-
terol and LDL-cholesterol [25]. The difference in selenium

between US and UK populations suggests that selenium le-

vels are dietary dependent. Our cohort came from an inner
city catchment area, and selenium levels were higher in the

non-Caucasoids: Oriental Asian, South Asian subcontinent

and African–Afro-Caribbean minority. These UK minori-
ties are more likely to be vegetarian than the Caucasian

UK population.

Despite widespread dietary sources of zinc and copper, some 12.9% of our dialysis cohort had been prescribed trace element supplementation, and of the others, 37.4% had low zinc values, 5.5% low copper and 45.6% low selenium. Although in vitro studies have suggested that ion exchange resins including sevelamer hydrochloride could bind trace elements and micronutrients, we found no difference in copper or zinc levels, compared with those prescribed calcium- or lanthanum-based phosphate binders, and indeed, selenium was greater in the sevelamer group. Although our results could be potentially affected by patient compliance with medications, it is reassuring that cholesterol levels were lower in the sevelamer group, suggesting significant patient compliance. Trace element concentrations were more linked to serum albumin, a marker of general nutritional status, although there were some differences between ethnic groups, suggesting that dietary intake also affects trace element concentrations.

Conflict of interest statement. None declared.

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The link between bone and coronary calcifications in CKD-5 patients on haemodialysis

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Abstract
Background. Vascular calcifications are frequent in Stage 5 chronic kidney disease (CKD-5) patients receiving haemodialysis. The current study was designed to evaluate the associations between bone turnover/volume and coronary artery calcifications (CAC).

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