Colestimide co-administered with atorvastatin attenuates the progression of vascular calcification in haemodialysis patients

Vascular calcification is believed to have a crucial role in the excess cardiovascular mortality and morbidity in patients with end-stage renal disease (ESRD). Recent evidence suggests that uraemic vascular calcification is an active cell-mediated process [1]. An epidemiological study observed an association between lipid-lowering therapy and vascular calcification [2]. However, no prospective investigation has been published to prove an effect of lipid-lowering therapy on the progression of vascular calcification in patients with ESRD.

We therefore conducted the present study that prospectively compared the rate of change in the amount of vascular calcification before and during lipid-lowering therapy in haemodialysis patients. The aortic calcification index (ACI) was estimated by computed tomography (CT) as described previously [3]. At the time of the first CT, fasting lipid levels as well as serum levels of calcium (Ca) and phosphorus levels were measured and lipid-lowering therapy with colestimide (1.5 g/day) and atorvastatin (10 mg/day) was initiated. Patients were instructed to keep any other medical therapy unchanged.

A total of 29 patients completed the protocol and could be evaluated. Progression of aortic calcification was significantly less pronounced during treatment with colestimide and atorvastatin compared with the period before treatment was initiated. The mean ACI in the first CT was 35.6 ± 20.2%. The median ACI in the second CT, after an average interval of 22.9 ± 3.2 months on treatment, was 29.0 ± 16.2% (P < 0.05). Average total cholesterol and LDL cholesterol levels in the untreated period were 246 ± 38 and 156 ± 41 mg/dl, respectively. A mean reduction of 21% (total cholesterol) and 44% (LDL cholesterol) was achieved. Patients were instructed to keep any other medical therapy unchanged.

Our preliminary, uncontrolled investigation is the first report that prospectively examines the influence of both colestimide and atorvastatin on the progression of vascular calcification in haemodialysis patients. It is unclear how changes in aortic calcification were achieved by lipid-lowering therapy. One possible explanation is that colestimide acts as a bile acid sequestrant and is therefore capable of reducing serum phosphorus levels as described previously [4], and that atorvastatin and colestimide significantly reduced LDL cholesterol levels. A randomized, placebo-controlled study is required to determine whether colestimide and atorvastatin inhibit vascular calcification in patients with ESRD.

Conflict of interest statement. None declared.

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Effect of renal failure and dialysis on circulating ghrelin concentration in children

Sir,

Ghrelin promotes the release of growth hormone, elevates food intake and induces obesity [1]. In healthy children, ghrelin concentrations are inversely correlated with body mass index and age [2]. Circulating ghrelin levels of humans do not show gender-related differences [3]. In adult patients with end-stage renal disease (ESRD), a three-fold rise in plasma ghrelin levels has been reported. Bilateral nephrectomy in mice causes a marked increase of plasma ghrelin levels. Ghrelin concentrations decline significantly during haemodialysis (HD) [4]. It was the objective of the present study to investigate whether ghrelin is elevated in serum of paediatric patients with renal failure and whether it is eliminated by HD, because there have been no data in children so far.

Subjects and methods. Ghrelin concentrations were measured in serum of eight chronic HD patients, six automated peritoneal dialysis (APD) patients and 14 patients with chronic renal failure (CRF) not yet on dialysis. Each patient group was compared with a control group of healthy children matched according to BMI and age. Patient data are shown in Table 1. Serum ghrelin before and after HD was compared. Furthermore, ghrelin concentrations in dialysate samples collected 5 min after the beginning and after 1, 2, 3 and 3.5–4.5 h of dialysis were evaluated. Immunoreactive ghrelin concentrations were measured using a commercial radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA) [5]. Mann–Whitney test was performed to compare patient groups with control groups. Paired values were compared using Wilcoxon matched pairs test. A P value of < 0.05 was considered significant.

Results. Ghrelin was detected in all dialysate samples. Its dialysate concentration remained stable during the HD session (data not shown). The amount of cleared plasma ranged from 2.46 to 2.931/h. Ghrelin in serum declined significantly (P < 0.03) during HD. It was significantly elevated in HD patients before HD compared with healthy subjects (P < 0.05). No significant difference to healthy children was observed after HD. In APD patients (P < 0.001) and CRF patients (P < 0.03), we observed a significant elevation as well, compared with healthy controls. For results see Table 1.

Discussion. Our results show that ghrelin is significantly elevated in serum of children with CRF or ESRD treated by HD or APD. Ghrelin is cleared by HD. This is consistent with data in adults [4]. The high clearance of ghrelin either suggests a powerful counter-regulation of serum ghrelin by


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increased secretion or high tissue concentrations. In case of a long-lasting normalization, ghrelin may provide an additional mechanism negatively influencing energy intake and growth hormone secretion in HD patients.

Conflict of interest statement. None declared.

Table 1. Data of patient groups and control groups matched according to BMI and age

<table>
<thead>
<tr>
<th>Number of patients (n)</th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>10</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [male (m)/female (f)]]</td>
<td>1 m/7 f</td>
<td>6 m/1 f</td>
<td>5 m/1 f</td>
<td>8 m/2 f</td>
<td>6 m/8 f</td>
<td>7 m/8 f</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.7 ± 0.6</td>
<td>15.2 ± 0.5</td>
<td>13.3 ± 1.8</td>
<td>13.2 ± 1.2</td>
<td>11.4 ± 1.3</td>
<td>11.3 ± 1.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.9 ± 1.3</td>
<td>18.9 ± 0.7</td>
<td>17.9 ± 1.0</td>
<td>17.8 ± 0.8</td>
<td>17.9 ± 0.9</td>
<td>17.5 ± 0.6</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>&lt;10</td>
<td>176.3 ± 7.6</td>
<td>&lt;10</td>
<td>179.6 ± 8.7</td>
<td>34.6 ± 6.0</td>
<td>172.5 ± 5.9</td>
</tr>
<tr>
<td>Creatinine i.s. (mg/dl) (before HD)</td>
<td>681.2 ± 119</td>
<td>60.1 ± 1.8</td>
<td>461 ± 74.3</td>
<td>52.1 ± 4.4</td>
<td>261 ± 36.2</td>
<td>47.7 ± 3.5</td>
</tr>
<tr>
<td>Urea i.s. (mg/dl) (before HD)</td>
<td>17.3 ± 1.8</td>
<td>4.3 ± 0.3</td>
<td>19.2 ± 1.9</td>
<td>4.4 ± 0.2</td>
<td>14.4 ± 1.5</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Ghrelin i.s. (pg/ml) (after HD)</td>
<td>1285 ± 308*</td>
<td>542 ± 140</td>
<td>2076 ± 226***</td>
<td>603 ± 113</td>
<td>1740 ± 152*</td>
<td>1181 ± 203</td>
</tr>
</tbody>
</table>
| GFR, glomerular filtration rate; i.s., in serum; (NS), not significant; *P<0.05; ***P<0.001. Values are expressed as the mean±standard error of the mean (SEM).

Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis

Sir,

Metformin has been used for many decades as an effective glucose-lowering medication in the treatment of type 2 diabetes mellitus. Recent studies clearly demonstrated that metformin reduced secondary complications of diabetes mellitus type 2 without promoting weight gain, which is in contrast to treatment with insulin and/or sulphonylurea [1]. Lactic acidosis is a serious side effect observed with metformin treatment and an incidence rate of 9 lactic acidoses per 100 000 person-years of metformin treatment, as has been calculated [2]. This side effect is usually found in patients receiving metformin despite major contraindications, such as renal insufficiency and/or cardiopulmonary instability. The mortality in metformin-induced lactic acidosis is very high and has been estimated to be >50% [3]. Only a small number of cases of metformin overdoses with lactic acidosis have been described in the literature [4].

We report the case of a patient with severe lactic acidosis and cardiocirculatory arrest caused by metformin intoxication. Despite a plasma metformin concentration of 191 mg/l (to our knowledge the highest reported value in the literature), the patient recovered totally after treatment with a combination of intermittent haemodialysis and high-volume continuous haemofiltration.

A 42-year-old man was admitted with nausea and vomiting. The patient declared that he wanted to kill himself, but denied that he had taken any medications or drugs. His past medical history included type 2 diabetes that was treated with initial unknown types of oral hypoglycaemics. On admission, the patient was in a stable condition and initial routine laboratory workup was normal.

Four hours later, the patient complained of severe dyspnoea. Laboratory studies revealed a metabolic acidosis (pH 7.20, pCO₂ 37 mmHg, bicarbonate 15.8 mmol/l, anion gap 18) and a lactate concentration of 8.9 mmol/l. The patient was transferred to the intensive care unit (ICU), where he developed respiratory insufficiency and severe hypotension, resulting in intubation, mechanical ventilation and administration of dopamine and noradrenaline infusion. Laboratory workup showed further progression of the lactic acidosis (pH 6.89, pCO₂ 30 mmHg, bicarbonate 6.7 mmol/l, lactate 21.6 mmol/l) and a serum creatinine of 1.8 mg/dl. Urine analysis was negative for ketones.

In the meantime, a relative reported that metformin is part of the patient’s medication. This information in combination with the patient’s initial declaration of intending to harm himself led to the assumption of a metformin-induced lactic acidosis.

We started intermittent haemodialysis for 11 h (with 1 h interruption) in order to remove metformin and lactate as fast as possible and to correct acidosis. However, blood lactate levels remained very high and progressive haemodynamic instability occurred. Haemodialysis treatment was stopped and continuous veno-venous haemofiltration (CVVH) with bicarbonate substitute was started. Because of a further rise in the lactate level (25.8 mmol/l) and the poor clinical course of the patient, we intensified the extracorporeal elimination treatment using a second CVVH machine with a femoral catheter access. Under this...