Influence of peritoneal loss of GHBP, IGF-I and IGFBP-3 on serum levels in children with ESRD

Sir,

Growth retardation is an important consequence of end stage renal disease (ESRD) in childhood. There have been several reports on the role of growth hormone (GH) and GH-related growth factors such as insulin-like growth factor (IGF-I) in ESRD. GH binds to the GH binding protein (GHBP), a 60 kDa protein, and forms a 85 kDa complex in serum. About 50% of the GH in serum is present in this form. The 60 kDa GHBP is identical to the extracellular domain of the GH receptor that mediates normal GH action. IGF-I is bound to specific binding proteins in the circulation. In human serum, IGFBP-3, a 150 kDa glycoprotein complex, was found to be the predominant protein, binding >95% of IGF-I. In uremia, there is an excess of IGFBP-3, with molecular fragments of 12–150 kDa, caused by reduced renal clearance. IGFBP-3 has been shown to strongly inhibit IGF-I action. In peritoneal dialysis (PD), substantial amounts of proteins like albumin, immunoglobulins and complement factors are lost with the dialysate. We investigated the loss of GHBP, IGF-I and IGFBP-3 in order to assess whether these losses contribute to the growth retardation in children on peritoneal dialysis.

Serum and peritoneal fluid concentrations of GHBP. IGF-I and IGFBP-3 were studied in eight children on PD. The mean age was 10.9 ± 3.5 (SD) years. Puberty was defined as a testicular volume of >4 ml in boys and in girls breast development more than stage 2 according to Tanner. The creatinine clearance was less than 5 ml/min/1.73 m². Mean duration of dialysis was 21 months. Four patients were treated with GH (3 IU/m²/day) for at least 6 months.

Samples from 24-h dialysate collection were analysed for GHBP, IGF-I and IGFBP-3. Dialysate losses of IGF-I and IGFBP-3 per day were calculated using the concentration of protein present in the dialysate (concentration × volume/day).

GHBP levels were measured by separation of the GHBP-bound and free fraction using fast protein liquid chromatography. Levels of GHBP below 10 pmol/l were not detectable. IGF-I was determined by radioimmunoassay after acidification and C18 extraction of plasma or dialysate samples. The concentrations of IGFBP-3 in plasma and dialysate were determined by a commercial direct radioimmunoassay (Nichols Institute, The Netherlands). Methods of determination were the same in dialysate and serum.

Data are expressed as mean ± SD, but when the data were not normally distributed, median values are given. Differences between groups were analysed using the Mann-Whitney U test. A P value <0.05 was taken to indicate statistical significance.

Mean serum GHBP was low (271 ± 131.5 pmol/l). GHBP was not detectable in peritoneal fluid. Mean serum levels of IGF-I were normal to elevated (38.9 ± 24.6 nmol/l). Mean serum levels of IGFBP-3 were also elevated (6.1 ± 1.34 µg/ml). Serum GHBP, IGF-I and IGFBP-3 were significantly higher in the two pubertal children as normal ranges are age- and sex-dependent. The median daily peri-

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3. Erdem I, Sayiner AA, Ozacar T, Bilgic A. Transmission risk of hepatitis C and D virus in screened blood units. 11th World Congress of Anaesthetologists, Sydney, Australia, 14–20 April, 1996. Abstract

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Table 1. Serum and dialysate IGF-I, IGFBP-3 and GHBP concentrations. GHBP was not detectable in peritoneal fluid

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of Patients</th>
<th>Median</th>
<th>Mean</th>
<th>SD</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Gender (M/F)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td></td>
<td>11.5</td>
<td>10.9</td>
<td>3.5</td>
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<tr>
<td>HSDS</td>
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<td>−1.37</td>
<td>−2.3</td>
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<td>GH treatment</td>
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<td></td>
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<tr>
<td>Serum IGF-I (nmol/l) (n=8)</td>
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<td>26.6</td>
<td>38.9</td>
<td>24.6</td>
<td>31.3–86.9</td>
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<tr>
<td>Pubertal (n=2)</td>
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<td>24.5</td>
<td>26.7</td>
<td>8.9</td>
<td>9.7–45.1</td>
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<tr>
<td>Prepubertal (n=6)</td>
<td></td>
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<tr>
<td>Serum IGFBP-3 (µg/ml) (n=8)</td>
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<td>6.4</td>
<td>6.1</td>
<td>1.34</td>
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<td>6.8</td>
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<td>0.57</td>
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<td>5.75</td>
<td>5.9</td>
<td>1.49</td>
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<td>271</td>
<td>131.5</td>
<td>431–1892</td>
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<td>234.0</td>
<td>218</td>
<td>116.9</td>
<td>267–1638</td>
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<tr>
<td>Dial IGF-I (nmol/l)</td>
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<td>0.88</td>
<td>1.0</td>
<td>0.80</td>
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<td>Dial IGFBP-3 (µg/ml)</td>
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<td>0.11</td>
<td>0.11</td>
<td>0.01</td>
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<td>24-h IGF-I dialysate loss as % of</td>
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<td>9.7</td>
<td>10.9</td>
<td>6.7</td>
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<td>calculated total serum IGF-I</td>
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<tr>
<td>24-h IGFBP-3 dialysate loss as %</td>
<td></td>
<td>5.5</td>
<td>6.2</td>
<td>1.97</td>
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<td>of calculated total serum IGFBP-3</td>
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</table>

hsds, height standard deviation score; GH, growth hormone treatment; F, female; M, male; Normal range: ±2 SD.

tonel loss of IGF-I and IGFBP-3 was 9.7% and 5.5% of the total amount present in serum, respectively. Treatment with GH, only had influence on dialysate levels of IGF-I and IGFBP-3 (P<0.02 and P<0.04) in comparison to the children without GH-treatment.

Kagan et al. detected GHBP activity in peritoneal effluent in adults [7]. They reported that GHBP activity in peritoneal fluid was only 1.4% of that in serum. In our patients the concentration in dialysate was less than 4% of the serum concentration. The protein loss in peritoneal fluid is dependent on the molecular mass and the serum concentration. The relation between dialysate/serum (d/s) ratio of proteins and molecular weight was found to be linear, when plotted on a double logarithmic scale [8]. The d/s ratio of IGF-I (9.7%) with a molecular weight of 7.5 kDa is in the same range as loss of PTH, a protein with a molecular weight of 7–9 kDa. Kale et al. also found that the IGF-I concentration in peritoneal fluid was 10% of the serum concentration [9]. The d/s ratio of IGFBP-3 was 5.5%. This percentage is in accordance with the loss of albumin (5.4%) with a molecular weight of 65–69 kDa. Kale et al. also demonstrated that peritoneal fluid had more low molecular (35 kDa) than high molecular (150 kDa) forms of IGFBP-3.

In this study in children with ESRD, the losses of GHBP, IGF-I and IGFBP-3 in peritoneal fluid were limited. These losses play no major role in poor growth in children on PD.

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Neurotoxicity due to imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis

Sir,

Recently in this journal Dr Campise [1] described a patient treated with continuous ambulatory peritoneal dialysis (CAPD) who presented neurotoxicity after treatment with imipenem/cilastatin (1/C). We would like to report our experience with two patients undergoing CAPD who were treated with that antibiotic because of peritonitis.