Serum fetuin-A and vitamin D in children with mild-to-severe chronic kidney disease: a cross-sectional study

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Abstract

Background. Fetuin-A and vitamin D are significant correlates of cardiovascular morbidity in paediatric chronic kidney disease (CKD) patients. It is thus far unknown, whether or not serum fetuin-A is affected by the vitamin D status or treatment with vitamin D preparations in these patients.

Methods. In a cross-sectional study, serum concentrations of fetuin-A, 25-hydroxyvitamin D₃ (25OHD) and 1,25-dihydroxyvitamin D₃ (calcitriol) levels were determined in 112 paediatric patients with mild-to-severe CKD (Stages 1–5) and after renal transplantation. A25OHD supplementation and/or calcitriol treatment were given in 64% of the patients.

Results. Fetuin-A levels were clearly reduced in dialysis patients but were comparable to healthy controls in those with moderate CKD and after transplantation. Although 64 and 46% of all patients received 25OHD and/or calcitriol treatment, 48 and 20% of patients were 25OHD and/or calcitriol deficient, respectively. Within the whole patient cohort, fetuin-A correlated with serum calcium and yearly weight-related 25OHD dosage (each P < 0.01) but not with the vitamin D status per se. Multiple regression analysis revealed the need for dialysis treatment and cumulative 25OHD dosage as independent predictors of fetuin-A concentrations (model $r^2 = 0.17$). In dialysis patients, fetuin-A was inversely correlated with serum C-reactive protein but positively correlated with cumulative calcitriol dosage and serum parathormone (each $P < 0.01$).

Conclusions. Fetuin-A levels are clearly reduced in children on dialysis but not in those with moderate CKD and after transplantation. Besides the degree of microinflammation, the cumulative intake of 25OHD and calcitriol are significantly correlated to fetuin-A in these patients. The impact of vitamin D treatment appears to be at least partly mediated by serum calcium.

Keywords: children; chronic kidney disease; fetuin-A; treatment; vitamin D

Introduction

Fetuin-A is constitutively produced in the liver and for some time has been known as a negative acute-phase protein [1]. Beyond this, the glycoprotein fetuin-A serves a multitude of biological functions as diverse as antagonizing growth factor-mediated signalling, ensuring skeletal matrix mineralization and inhibiting ectopic calcification [2–4]. As a consequence of multifunctionality, elevated and reduced serum concentrations of fetuin-A are increasingly recognized as a risk marker of cardiovascular and metabolic diseases in the general population and in chronic kidney disease (CKD). In the general population, elevated serum concentrations of fetuin-A were identified as a risk marker for diabetes, metabolic syndrome, myocardial infarction and stroke [5–7]. In contrast, advanced vascular calcification in adults suffering from end-stage renal disease has been associated with diminished fetuin-A serum concentrations which in turn were identified as an inflammation-related predictor of cardiovascular and all-cause mortality in dialysis patients [8, 9]. It has been suggested that both the disturbed mineral metabolism and chronic uraemia contribute to fetuin-A depletion and concomitant progression of ectopic calcification [10–12].

In paediatric CKD patients, conflicting results were reported, i.e. in children on dialysis treatment fetuin-A serum concentrations were found to be either similar to healthy controls or reduced [13, 14]. Another study investigating both the serum fetuin-A concentrations and the cardiac calcification score in paediatric dialysis patients revealed overall increased fetuin-A levels and a negative relationship between fetuin-A levels and the degree of cardiac calcification [15].

However, calcification in CKD patients reflects more complex aberrations of mineral metabolism than solely a disturbed fetuin-A homeostasis and vitamin D as an established key regulator for mineral uptake has to be considered as well. In fact, it has been demonstrated recently that both sub- and supraphysiological 1,25-dihydroxyvitamin D₃ (calcitriol) levels are associated with cardiovascular complications, e.g. ectopic calcification, in children with end-stage
renal disease [16]. Furthermore, few studies in adult CKD patients point to an association between fetuin-A and vitamin D: (i) 1,25-dihydroxyvitamin D₃ (calcitriol) and fetuin-A serum levels correlated significantly in adults with diabetic nephropathy (CKD 4) and radiographically confirmed coro-
nary artery calcification [17] and (ii) administration of cal-
citriol for treatment of secondary hyperparathyroidism was accompanied by a significant increase in serum fetuin-A in adult dialysis patients [18].

However, in paediatric CKD patients, the association between serum fetuin-A and vitamin D status and treatment with either 25-hydroxyvitamin D₃ or active vitamin D (calcitriol) has thus far not been elucidated. We therefore investigated these parameters in a large cross-sectional study with paediatric CKD patients on conservative (CKD 1–4) and renal replacement therapy (dialysis and renal transplantation (RTx)).

Patients and methods

Patients

The study received appropriate ethics committee approval from the institu-
tional review board in accordance with the Declaration of Helsinki. Sub-
jects and/or their parents gave assent and written informed consent to participate in the study. All children aged 0–18 years suffering from CKD Stages 1–5 on conservative treatment, dialysis or after RTx treated at our institution were eligible for this study. Children with acute infections as well as those with metabolic disorders, chronic inflammatory or hepatic disease were excluded. A total of 112 patients (65 boys/47 girls) agreed to participate and were enrolled between August 2006 and December 2010. Patient characteristics including biochemical data, underlying renal diseases and relevant medication are given in Tables 1 and 2. The mean time spent on dialysis was 1.2 years (range 0.25–16.5 years) and mean Kt/Vurea in patients on haemodialysis (HD) and peritoneal dialysis (PD) was 1.68 (1.4–2.5) and 1.85 (1.7–2.6), respectively. The calcium concentration in the routinely used dialysates (HD and PD) was 1.25 mmol/L. The mean time since RTx was 5.6 years (range 0–15.6 years) and it was the first transplantation for all of our patients. Seven and 12 patients had received a graft from a deceased and a living-related donor, respectively. Treatment of CKD-mineral and bone disease was in adherence to the KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease [19]. In particular, patients received 25-
hydroxyvitamin D₃ (2000 IU/day) when 25OHD levels were <75 nmol/ L (vitamin D insufficiency). Calcitriol was started when parathormone (PTH) levels were above the stage-specific range. In our cohort, 72 of 112 (64%) patients received 25-hydroxyvitamin D and 52 (46%) patients were treated with calcitriol (mean dosage, 8.3 ng/kg/day and range 1–70 ng/kg/day). Phosphate binders were used in 43 (38%) patients (Table 1). None of our patients underwent parathyroidectomy. Anti-hypertensive drugs consisting of one or more therapeutics were given in 101 (90%) patients (angiotensin-converting enzyme inhibitors, n = 72; angiotensin receptor type 1 inhibitors, n = 29; beta-blocker, n = 63; calcium channel blocker, n = 42; furosemide, n = 82, vasodilator, n = 18). Immunosup-
pression in RTx patients consisted of cyclosporine A (n = 15), tacrolimus (n = 4), mycophenolate mofetil (n = 19) and prednisolone (n = 9).

Controls

The control group consisted of 246 healthy children without relevant cardio-
vascular risk factors [20]. These children presented at the same insti-
tution for diagnostic workup either before minor surgery or secondary to non-inflammatory diseases like epilepsy, idiopathic short stature and orthostatic complaints.

Methods

Height and weight were assessed in all subjects and the LMS method was used to calculate individual standard deviation (SD) scores of the body mass index (BMI-SDS) [21]. For calculation of age- and gender-related SD scores for height, the first Zurich longitudinal study was used as a reference [22]. The Schwartz formula was employed to estimate individual glomerular filtration rates (eGFR) [23] and patients were classified into CKD Stages 1–5 according to the guidelines of the National Kidney Foundation Kidney Disease Outcome Quality Initiative [24]. In dialysis patients, eGFR was arbitrarily set to 5 mL/min/1.73m². Blood samples were obtained in the morning in the fasting state, and serum samples were stored at −80°C until quantitative determination of fetuin-A, 1,25-dihydroxyvitamin D₃, and 25-hydroxyvitamin D₃. Clinical data and results from routine labor-
atory analysis were gathered by interview and chart review. In a paedi-
atri study population, a broad distribution of body weight and size is present per se. In addition, calcitriol treatment in pediatric CKD patients is usually adapted to body weight [19]. Therefore, weight-averaged yearly vitamin D intake was calculated and used rather than absolute dosages to elucidate treatment-related effects on fetuin-A in children.

Established laboratory procedures for biochemical serum analysis, e.g. determination of phosphate, calcium and creatinine, were used and performed at the Department of Clinical Chemistry, University Medical Hospital, Rostock. In the same laboratory, concentrations of iPTH (biointact PTH; aa 1–84), 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ were determined. Whereas an automated chemiluminescence immunoas-
say system (Elecsys; Roche, Basel, Switzerland) was used for the deter-
nation of iPTH and 25-hydroxyvitamin D₃, serum concentrations of 1,25-dihydroxyvitamin D₃ were measured with a solid-phase immunoas-
say (Immuno-diagnostik, Bensheim, Germany). Serum concentrations of 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ were classified

Table 1. Baseline demographic and clinical characteristics of the patient cohort

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
</tr>
<tr>
<td>Underlying renal disease</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies of kidney and urinary tract</td>
<td>47</td>
</tr>
<tr>
<td>Congenital nephropathies</td>
<td>26</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>19</td>
</tr>
<tr>
<td>Others</td>
<td>20</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensive drugs</td>
<td>101</td>
</tr>
<tr>
<td>Ca-containing phosphate binder</td>
<td>26</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>17</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>72</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>52</td>
</tr>
<tr>
<td>Erythropoietine</td>
<td>38</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>44</td>
</tr>
</tbody>
</table>

*only given in patients with CKD stage 5.
### Results

Overall, fetuin-A serum concentrations were reduced in CKD patients compared to healthy children. Subgroup analysis revealed significantly diminished levels of fetuin-A in dialysis patients and in those with CKD Stage 2, whereas rather similar concentrations in patients with CKD Stages 1, 3, 4 and after RTx were noted (Figure 1, Table 2). Fetuin-A was lower in HD patients compared to PD patients (0.33 ± 0.08 g/L versus 0.44 ± 0.15 g/L, P < 0.01, Table 3). Data on the serum concentration of 25-hydroxyvitamin D$_3$ and/or 1,25-dihydroxyvitamin D$_3$ were available for 101 and 97 patients, respectively. In particular, 53 of 101 patients (52%) presented with normal

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#### Table 2. Clinical characteristics and biochemical data according to renal function

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR (mL/min/1.73m$^2$)</th>
<th>Age (years)</th>
<th>Height-SDS</th>
<th>BMI-SDS</th>
<th>Albumin (g/L)</th>
<th>CRP (mg/L)</th>
<th>Calcium (mmol/L)</th>
<th>Phosphate (mmol/L)</th>
<th>PTH (ng/L)</th>
<th>25(OH)D$_3$ (nmol/L)</th>
<th>1,25(OH)$_2$D$_3$ (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (10)</td>
<td>96.0 (92–125)</td>
<td>8.0 a,b</td>
<td>3.00–0.85</td>
<td>0.49 a,b</td>
<td>7.2 b (0.29–5.74)</td>
<td>1.00 a,b</td>
<td>2.43 (1.87–2.70)</td>
<td>1.48 (0.94–1.97)</td>
<td>13.6 (8.35–21.0)</td>
<td>77.8 (10.40–17.20)</td>
<td>1.25 (0.15–0.63)</td>
</tr>
<tr>
<td>2 (10)</td>
<td>32.0 (20–46.9)</td>
<td>14.8 a,b</td>
<td>4.4 to 1.27</td>
<td>0.25 a,b</td>
<td>11.9 (6.9–20.7)</td>
<td>1.48 a,b</td>
<td>2.41 (1.87–2.70)</td>
<td>1.53 (0.94–1.97)</td>
<td>13.6 (8.35–21.0)</td>
<td>77.8 (10.40–17.20)</td>
<td>1.25 (0.15–0.63)</td>
</tr>
<tr>
<td>3 (10)</td>
<td>16.0 (10–25.3)</td>
<td>14.8 a,b</td>
<td>3.69 to 1.59</td>
<td>0.33 a,b</td>
<td>11.9 (6.9–20.7)</td>
<td>1.48 a,b</td>
<td>2.41 (1.87–2.70)</td>
<td>1.53 (0.94–1.97)</td>
<td>13.6 (8.35–21.0)</td>
<td>77.8 (10.40–17.20)</td>
<td>1.25 (0.15–0.63)</td>
</tr>
<tr>
<td>4 (10)</td>
<td>15.6 (10–25.3)</td>
<td>14.8 a,b</td>
<td>3.69 to 1.59</td>
<td>0.33 a,b</td>
<td>11.9 (6.9–20.7)</td>
<td>1.48 a,b</td>
<td>2.41 (1.87–2.70)</td>
<td>1.53 (0.94–1.97)</td>
<td>13.6 (8.35–21.0)</td>
<td>77.8 (10.40–17.20)</td>
<td>1.25 (0.15–0.63)</td>
</tr>
<tr>
<td>5 (10)</td>
<td>16.0 (10–25.3)</td>
<td>14.8 a,b</td>
<td>3.69 to 1.59</td>
<td>0.33 a,b</td>
<td>11.9 (6.9–20.7)</td>
<td>1.48 a,b</td>
<td>2.41 (1.87–2.70)</td>
<td>1.53 (0.94–1.97)</td>
<td>13.6 (8.35–21.0)</td>
<td>77.8 (10.40–17.20)</td>
<td>1.25 (0.15–0.63)</td>
</tr>
</tbody>
</table>

Identical superscripts denote significant differences (P < 0.05) between groups sharing the same superscript.

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![Fig. 1](image.png)

**Fig. 1.** Fetuin-A serum concentrations according to different stages of CKD before and after RTx compared to healthy children (Co). *P < 0.01 versus controls. Fetuin-A serum concentration in healthy children (n = 246) was determined recently [20].
25-hydroxyvitamin D levels (cholecalcidiol > 75 nmol/L), whereas insufficiency (50–75 nmol/L), mild deficiency (25–50 nmol/L) and severe deficiency (<25 nmol/L) had to be considered in 27 (27%), 18 (18%) and 3 (3%) patients, respectively. Mean calcitriol levels were 97.7 ± 64.4 pmol/L, and calcitriol levels were within the normal range (43–149 pmol/L) in 60 patients (62%; 90.5 ± 27.3 pmol/L) and above or below the normal range in 18 (19%) and 19 (19%) patients, respectively. No signs of vitamin D toxicity were observed in those patients, with serum calcitriol/25OHD levels above the upper normal limit. Serum calcitriol levels were positively correlated with eGFR, whereas no such relationship was observed for cholecalciferol (Figure 2A and B). Moreover, a significant association between 25OHD levels and serum calcium was present (Figure 2C).

Fetuin-A was positively correlated with serum calcium ($r = 0.296$, $P < 0.01$) and albumin ($r = 0.303$, $P < 0.01$) in the CKD patients but not in the controls. However, neither albumin-corrected calcium nor serum phosphate levels were related to fetuin-A (Figure 3 and data not shown). Irrespective of the CKD stage, the yearly weight-related cholecalciferol dosage, but not the vitamin D status (25OHD and calcitriol) per se, correlated with fetuin-A (Figure 4A). Likewise, a similar relationship between calcitriol dosage and fetuin-A was observed in dialysis patients (Figure 4B). Furthermore, in these patients, fetuin-A showed a negative and positive correlation with CRP and PTH, respectively (Figure 5).

On multiple linear regression analysis, CKD Stage 5 and 25OHD dosage independently predicted serum fetuin-A concentrations (cumulative $r^2 = 0.17$; $P < 0.01$), whereas all other factors including serum calcium were excluded from the final model (Table 4). Underlying renal disease, duration of CKD, nutritional state (height,-weight- and BMI-SD scores, serum albumin) and immunosuppressive/anti-hypertensive therapy were not significantly correlated with serum fetuin-A.

**Discussion**

This study provides evidence that compared to healthy children, serum fetuin-A is reduced in children on dialysis but not in transplanted children and in those with moderate CKD. Within our study population, fetuin-A was

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**Table 3. Clinical characteristics and biochemical data in dialysis patients**

<table>
<thead>
<tr>
<th></th>
<th>CKD 5 ($n = 26$)</th>
<th>HD ($n = 16$)</th>
<th>PD ($n = 10$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.3 ± 6.5</td>
<td>16.9 ± 2.2</td>
<td>10.5 ± 7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height-SD score</td>
<td>−1.13 ± 1.40</td>
<td>−1.5 ± 1.55</td>
<td>−0.51 ± 0.88</td>
<td>0.077</td>
</tr>
<tr>
<td>BMI-SD score</td>
<td>−0.02 ± 1.48</td>
<td>0.07 ± 1.37</td>
<td>−0.16 ± 1.69</td>
<td>0.697</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>781 ± 231</td>
<td>786 ± 212</td>
<td>775 ± 269</td>
<td>0.912</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>41 ± 58</td>
<td>52 ± 71</td>
<td>24 ± 20</td>
<td>0.252</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>32.8 ± 6.4</td>
<td>33.4 ± 7.2</td>
<td>31.9 ± 5.3</td>
<td>0.600</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>9.6 ± 22.9</td>
<td>14.43 ± 28.4</td>
<td>1.96 ± 1.57</td>
<td>0.484</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.33 ± 0.20</td>
<td>2.35 ± 0.22</td>
<td>2.29 ± 0.16</td>
<td>0.542</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.76 ± 0.45</td>
<td>1.78 ± 0.42</td>
<td>1.84 ± 0.52</td>
<td>0.759</td>
</tr>
<tr>
<td>PTH (ng/L)</td>
<td>303 ± 175</td>
<td>243 ± 106</td>
<td>395 ± 226</td>
<td>0.066</td>
</tr>
<tr>
<td>25(OH)D (nmol/L)</td>
<td>74.1 ± 29.6</td>
<td>77.4 ± 34.0</td>
<td>69.6 ± 23.6</td>
<td>0.587</td>
</tr>
<tr>
<td>1.25(OH)2D3 (pmol/L)</td>
<td>48 ± 60</td>
<td>51.6 ± 70.3</td>
<td>42.9 ± 41.5</td>
<td>0.773</td>
</tr>
<tr>
<td>Fetuin-A (g/L)</td>
<td>0.37 ± 0.12</td>
<td>0.33 ± 0.08</td>
<td>0.44 ± 0.15</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Fig. 2. Correlation between calcitriol (A) and 25OHD (B) levels with eGFR and between calcium and 25OHD serum concentration (C) in the whole patient cohort. A, $r = 0.60$; $P < 0.001$; C, $r = 0.44$, $P < 0.0001$. 
significantly associated with serum calcium, yearly weight-related 25OHD dosage and the requirement for dialysis treatment. However, serum calcium appeared to impact on fetuin-A only indirect, presumably via 25OHD, as calcium was not included in the final model of the multiple regression analysis.

While the association between fetuin-A and renal function is not entirely new, the interdependency between fetuin-A and 25OHD/calcitriol is striking. Clearly, our study is neither suited to discriminate effect and cause with respect to these variables nor to elucidate how 25OHD and/or calcitriol impact on hepatic fetuin-A synthesis and secretion. However, our data strongly indicate that such a mechanism is likely to exist. While the main function of 25OHD probably is being a circulating precursor of calcitriol, the latter is a pleiotropic hormone acting through the vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily (for reference see [26, 27] and references cited therein). Ligand-bound VDR required dimerization with the retinoid-X receptor (RXR) for binding to vitamin D-responsive elements. These are found predominantly, although not exclusively, in the promoter region of target genes and binding of the VDR-RXR heterodimer to these sites induces or represses gene expression via recruitment of co-regulators. Both, the VDR and 1-α-hydroxylase (CYP27B1) are present not only in the kidney but also in a wide variety of organs including skin, prostate, breast, placenta, intestinal cells, immune cells and osteoblasts (for review see [26–28] and references cited therein). Thus, calcitriol together with its cognate receptor is a ‘broad spectrum hormone’ presumably regulating 3% of the human genome [29] and it might well be that fetuin-A is also under control of calcitriol. Although to the best of our knowledge within the fetuin-A promoter, no vitamin D-responsive element has been identified, the findings within this and other studies support this notion. Indeed, in non-dialysed adults with diabetic nephropathy and coronary

Fig. 3. Fetuin-A serum concentrations as a function of serum calcium (A and C) and phosphate (B and D) in the whole patient cohort (A and B) and healthy controls (C and D). (A, $r = 0.30, P < 0.01$).

Fig. 4. Fetuin-A serum concentrations as a function of yearly weight-related 25OHD dosage in the whole patient cohort (A) and association between serum fetuin-A levels and yearly weight-related calcitriol dosage in 26 dialysis patients (B). Open symbols denote patients on PD and closed symbols denote patient on HD. (A, $r = 0.263, P < 0.01$; B, $r = 0.388, P < 0.05$).
artery calcification, calcitriol levels were shown to be significantly correlated with serum fetuin-A [17]. Moreover, in adult dialysis patients suffering from secondary hyperparathyroidism, calcitriol was shown not only to suppress PTH but apparently to stimulate serum fetuin-A levels [18]. Whether or not this is a direct calcitriol–VDR-mediated effect or indirectly related to the calcaemic effects remains to be elucidated. In fact, fetuin-A is an important molecular cargo ensuring transport of calcium and phosphate to the sites of mineralization while at the same time acting as a circulating calcification inhibitor [3].

On the one hand, 25OHD via formation of calcitriol stimulates gastrointestinal calcium uptake and on the other hand suppress PTH-mediated calcium release from the skeleton. Irrespective of the triggering event, either mediator impact on the calcium homeostasis and as such requires fetuin-A as an important inhibitor of calcification. In this scenario, calcium would be the responsible trigger for fetuin-A synthesis. Indeed, serum concentrations of calcium and fetuin-A were significantly correlated in our study population. However, serum calcium was excluded as an independent predictor of serum fetuin-A in the final regression model. This strongly suggests that 25OHD dosage as a stimulator of intestinal calcium uptake rather than serum calcium itself was the triggering event.

Within the dialysis population, cumulative calcitriol intake, serum PTH and CRP correlated with fetuin-A. Both calcitriol and PTH enhance serum calcium via stimulation of either gastrointestinal uptake or skeletal release. Thus, in either situation, fetuin-A is required to chelate calcium and to prevent formation of insoluble calcium phosphates.

Treating adult or paediatric CKD patients with high dosages of calcitriol bears the risk of chronic toxicity, especially in those on dialysis treatment with parallel administration of calcium-containing phosphate binders [30–32]. Thus, the positive correlation between cumulative calcitriol intake and serum fetuin-A in dialysis patients must be taken cautiously, although our calcitriol dosages were rather low (mean dosage, 8.3 ng/kg/day) and no signs of vitamin D toxicity were present.

Fetuin-A appeared to be higher in children on PD compared to those on HD. Recently, it has been shown that in adult patients on PD, fetuin-A levels are lowest in those with concomitant malnutrition, inflammation and overt vascular calcification [12]. By and large our patients were not malnourished, and elevated CRP levels were observed in patients on HD only. This might at least partly explain the rather normal fetuin-A levels in PD patients.

Interestingly, serum fetuin-A levels were significantly reduced not only in patients on dialysis but also in those with CKD Stage 2 while those with moderate CKD (Stages 3 and 4) presented with apparently normal fetuin-A concentrations. A putative bias due to differences in age or gender is rather unlikely since we and others could clearly demonstrate that fetuin-A levels are independent of age and gender after the neonatal period [20, 33]. Instead, this might reflect adaptation to (mild) uraemia and the concomitant distinct effects on mineral metabolism. This point of view is supported by the fact that fetuin-A deficiency appears to be transient in relation to progression of CKD.

In adult patients with mild-to-moderate CKD, normal or reduced fetuin-A levels were reported [34, 35]. This discrepancy might be, at least partly, due to methodological problems, e.g. specificity and sensitivity of the antibodies and post-translational modifications of fetuin-A [36]. Moreover, the proportion of mineral-loaded fetuin-A rather than total serum fetuin-A has been suggested as a surrogate marker of calcification stress [37].

The present study has several limitations. First, due to the cross-sectional study design, it was not possible to investigate direct longitudinal effects of vitamin D supplementation/treatment on serum fetuin-A levels. Secondly, we did not address the functional consequences of the vitamin D status/treatment and fetuin-A deficiency in our CKD population.

In conclusion, fetuin-A levels are clearly reduced in children on dialysis treatment but not in those with moderate CKD and after RTx. Besides the degree of microinflammation, the cumulative intake of 25OHD and calcitriol are significant correlates of serum fetuin-A in these patients.

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Table 4. Multiple linear regression analysis of independent predictors of fetuin-A serum levels in the entire study population.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Standardized β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 5</td>
<td>−0.203</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>25OHD dosage</td>
<td>0.243</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Model $R^2 = 0.17$, $P < 0.01$. 

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Fig. 5. Fetuin-A serum concentrations as a function of CRP (A) and PTH (B) levels in dialysis patients. A, $r = −0.442, P < 0.05$; B, $r = 0.734, P < 0.001$. Open symbols denote patients on PD and closed symbols denote patients on HD.
The impact of vitamin D treatment on fetuin-A appears to be at least partly mediated by serum calcium.

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Conflict of interest statement. Our work is original and was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The results presented in this paper have not been published previously in whole or part, except in abstract form. Each author has participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript and approved the final version of the manuscript.

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