IGF-1 and Survival in ESRD

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Summary
Background and objectives IGF-1 deficiency links to malnutrition in CKD patients; however, it is not clear to what extent it associates with survival among these patients.

Design, setting, participants, & measurements Serum IGF-1 and other biochemical, clinical (subjective global assessment), and densitometric (dual energy x-ray absorptiometry) markers of nutritional status and mineral and bone metabolism were measured in a cohort of 365 Swedish clinically stable CKD stage 5 patients (median age of 53 years) initiating dialysis between 1994 and 2009; in 207 patients, measurements were also taken after 1 year of dialysis. Deaths were registered during a median follow-up of 5 years. Associations of mortality with baseline IGF-1 and changes of IGF-1 after 1 year of dialysis were evaluated by Cox models.

Results At baseline, IGF-1 concentrations associated negatively with age, diabetes mellitus, cardiovascular disease, poor nutritional status, IL-6, and osteoprotegerin and positively with body fat mass, bone mineral density, serum phosphate, calcium, and fibroblast growth factor-23. At 1 year, IGF-1 had increased by 33%. In multivariate regression, low age, diabetes mellitus, and high serum phosphate and calcium associated with IGF-1 at baseline, and in a mixed model, these factors, together with high fat body mass, associated with changes of IGF-1 during the first 1 year of dialysis. Adjusting for calendar year of inclusion, age, sex, diabetes mellitus, cardiovascular disease, IL-6, and poor nutritional status, a 1 SD higher level of IGF-1 at baseline associated with lower mortality risk (hazard ratio, 0.57; 95% confidence interval, 0.32 to 0.98). Persistently low or decreasing IGF-1 levels during the first 1 year on dialysis predicted worse survival (adjusted hazard ratio, 2.19; 95% confidence interval, 1.06 to 4.50).

Conclusion In incident dialysis patients, low serum IGF-1 associates with body composition and markers of mineral and bone metabolism, and it predicts increased mortality risk.

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Introduction
The growth hormone (GH) and IGF system plays an important role for anabolism, body growth, and body composition (1), because it regulates metabolic processes, which are needed for the growth of cells and tissues, including bone growth and density (2). Patients with CKD display a variety of metabolic and nutritional abnormalities, including resistance to the action of GH and IGF-1 (3). Many CKD patients show signs of protein-energy wasting (PEW) reflected by sarcopenia and dynapenia (4), which in part, could be caused by abnormalities in the GH/IGF-1 axis.

There are scarce and inconsistent data regarding the relation between IGF-1 and mortality. In the general population, low IGF-1 levels associate with increased risk of congestive heart failure (5) and ischemic heart disease (6), and a high IGF-1 is linked to cancer growth (7) and higher mortality among cancer patients (8,9). Low IGF-1 levels did not relate to all-cause mortality among elderly Finish men (10), whereas low levels of IGF-1 were independently associated with increased risk of ischemic heart disease mortality in elderly subjects (11).

There are few studies in adult CKD stage 5 patients addressing the mortality risk associated with a low IGF-1. Two studies showed that prevalent hemodialysis (HD) patients who died had lower IGF-1 levels than survivors (12,13), but it is not known whether IGF-1 in incident dialysis patients predicts mortality. Considering that a low IGF-1 level in CKD patients is related to body composition, particularly muscle wasting (14,15) and lower bone mineral density (BMD) (16), both of which predict mortality, we hypothesized that a low IGF-1 concentration may be linked to increased mortality in patients starting on dialysis.

We analyzed the baseline serum IGF-1 concentration and the longitudinal change of IGF-1 over 1 year in CKD stage 5 patients starting on dialysis in relation to BMD, nutritional status, metabolic parameters, and mortality. To the best of our knowledge, this study is the first study analyzing the mortality predictive role of IGF-1 in nondialyzed CKD stage 5 patients and the mortality risk associated with IGF-1 change after initiation of dialysis treatment in these patients.
Materials and Methods

In this post hoc analysis of cross-sectional and longitudinal follow-up data from a cohort study of incident dialysis patients (17), IGF-1 was measured in frozen samples obtained at baseline and in a subgroup of patients, 1 year after the initiation of dialysis. Exclusion criteria included age <18 or >75 years, signs of overt infection, and unwillingness to participate. We enrolled 365 CKD stage 5 patients (61% men; median age of 55 years) who were investigated at the initiation of renal replacement therapy at the Karolinska University Hospital in Huddinge, Sweden, between 1994 and 2009. Patient characteristics are shown in Table 1.

The patients were invited to perform a second assessment after ~1 year of dialysis therapy. Reasons for not attending the second assessment included death (n=24), kidney transplantation (n=40), and unwillingness or inability to participate (n=57). From the remaining 244 patients, we excluded 10 patients with dialysis duration (vintage) <3 months and 27 additional patients without sufficient serum for analysis of IGF-1 at baseline, 12 months, or both. In the remaining subgroup of 207 patients (62% men; median age of 55 years), a follow-up investigation was performed. No differences were observed in general clinical and demographic characteristics between the included 207 patients and non-included patients (data not shown). Most patients took antihypertensive medications (98%), phosphate binders (81%), and diuretics (82%), and vitamins B, C, and D (73% of patients received oral vitamin D analogs) were supplemented in accordance with clinical practice.

At baseline and after 1 year, the patients underwent dual energy x-ray absorptiometry on a DPX-L device (Lunar Corp., Madison, WI) to measure total body BMD, total fat mass, and total lean body mass. PEW was assessed by subjective global assessment (SGA). GFR was calculated as the mean of creatinine and urea clearances from 24-hour urine collections. The ethics committee of Karolinska Institutet approved the study protocol, and informed consent was obtained from each individual.

Biochemical Methods

At baseline and after 1 year, venous blood samples were drawn after an overnight fast and stored at −70°C pending biochemical analyses. Serum IGF-1, IGF-1 binding protein-3 (IGFBP-3), and plasma IL-6 were measured on an Immulite Automatic Analyzer (DPC Corp., Los Angeles, CA). The intra-assay coefficient of variation for IGF-1 was 4.3%, and the interassay coefficient of variation was 6.9%. IGFBP-1 was analyzed by ELISA (IEMA Test; Medix Biochemica, Kauniainen, Finland). Intact fibroblast growth factor-23 (FGF-23) was measured with ELISA (Kainos Laboratories International, Tokyo, Japan). Serum osteoprotegerin (OPG) was analyzed by ELISA (R&D Systems Inc., Minneapolis, MN). The remaining biochemical analyses (including parathyroid hormone [PTH], phosphate, and calcium) were performed using routine methods at the Department of Clinical Chemistry at Karolinska University Hospital, Huddinge, Sweden.

### Table 1. Baseline characteristics for all patients (n=365) and patients who remained on treatment with peritoneal dialysis (n=92) and hemodialysis (n=115) at 1 year (and who were then reinvestigated after 1 year on dialysis)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All Patients (n=365)</th>
<th>PD (n=92)</th>
<th>HD (n=115)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>53.0 (12.6)</td>
<td>52.4 (12.1)</td>
<td>53.5 (12.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Men, %</td>
<td>61</td>
<td>65</td>
<td>58</td>
<td>0.32</td>
</tr>
<tr>
<td>DM (present), %</td>
<td>31</td>
<td>26</td>
<td>26</td>
<td>0.99</td>
</tr>
<tr>
<td>CVD (present), %</td>
<td>35</td>
<td>25</td>
<td>28</td>
<td>0.58</td>
</tr>
<tr>
<td>GFR, ml/min per 1.73 m²</td>
<td>6.5 (2.3)</td>
<td>NA</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>Dialysis time, mo</td>
<td>—</td>
<td>12 (1)</td>
<td>12 (1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>—</td>
<td>18</td>
<td>12</td>
<td>0.24</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>3.3 (0.6)</td>
<td>3.3 (0.6)</td>
<td>3.4 (0.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>SGA&gt;1, %</td>
<td>31</td>
<td>29</td>
<td>28</td>
<td>0.81</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>6.4 (3.3–10)</td>
<td>6.2 (3.8–10.8)</td>
<td>5.9 (3.1–9.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
<td>6.04 (1.73)</td>
<td>6.00 (1.86)</td>
<td>6.38 (1.80)</td>
<td>0.19</td>
</tr>
<tr>
<td>Calcium, mg/dl</td>
<td>9.88 (1.04)</td>
<td>9.92 (1.12)</td>
<td>9.88 (1.20)</td>
<td>0.81</td>
</tr>
<tr>
<td>PTH, ng/L</td>
<td>225 (108–371)</td>
<td>209 (102–332)</td>
<td>257 (120–404)</td>
<td>0.31</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>21.6 (10.1)</td>
<td>21.0 (10.7)</td>
<td>23.8 (11)</td>
<td>0.11</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>49.4 (11.5)</td>
<td>47.5 (11.3)</td>
<td>51.8 (11.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total BMD, g/cm²</td>
<td>1.14 (0.12)</td>
<td>1.13 (0.10)</td>
<td>1.17 (0.12)</td>
<td>0.03</td>
</tr>
<tr>
<td>FGF-23, pg/ml</td>
<td>3268 (719–8417)</td>
<td>2327 (678–6667)</td>
<td>4822 (1459–11285)</td>
<td>0.03</td>
</tr>
<tr>
<td>OPG, μg/ml</td>
<td>2061 (1473–2910)</td>
<td>1813 (1298–2628)</td>
<td>1787 (1279–2624)</td>
<td>0.91</td>
</tr>
<tr>
<td>IGFBP-1, μg/L</td>
<td>13.9 (6.8–23.6)</td>
<td>13.6 (6.9–23.6)</td>
<td>12.7 (6.8–22.9)</td>
<td>0.25</td>
</tr>
<tr>
<td>IGFBP-3, mg/L</td>
<td>5.1 (4.0–6.1)</td>
<td>5.0 (4.2–6.1)</td>
<td>5.3 (4.4–6.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>IGF-1, μg/L</td>
<td>191.9 (90.5)</td>
<td>187.2 (75.3)</td>
<td>191.3 (93.9)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), percentage, or median (interquartile range). PD, peritoneal dialysis; HD, hemodialysis; DM, diabetes mellitus; CVD, cardiovascular disease; NA, not applicable; SGA, subjective global assessment; PTH, parathyroid hormone; BMD, bone mineral density; FGF-23, fibroblast growth factor-23; OPG, osteoprotegerin; IGFBP-1, IGF binding protein-1; IGFBP-3, IGF binding protein-3.
Statistical Analyses
Comparisons of variables between two groups were performed using nonparametric Wilcoxon or \( \chi^2 \) test. For the analysis of correlates of IGF-1 variation, we compared (1) patients with high IGF-1 at both baseline and 1 year or who shifted from low to high IGF-1 (persistently high/increasing group) with (2) patients with low IGF-1 at both baseline and 1 year or who declined from high to low IGF-1 (persistently low/decreasing group). Low IGF-1 was defined as IGF-1 less than median level, and high IGF-1 was defined as more than or equal to median (181 ng/ml at baseline and 240 ng/ml after 1 year on dialysis). Correlations were estimated by standardized \((\beta)\) regression coefficients. Correlates of IGF-1 were analyzed by multivariate regression models with parameters showing significant associations. Correlates of IGF-1 change over 1 year of dialysis were tested by mixed models including both fixed effects and random effects to account for the change of IGF-1 caused by repeat observations of the same patient. The fixed effects in the model included baseline values of age, sex, diabetes mellitus (DM), and history of cardiovascular disease (CVD).

Survival during follow-up was analyzed by a log-rank test and represented as a Kaplan–Meier curve. Hazard ratios (HRs) for 1 SD higher level of IGF-1 were calculated with Cox proportional hazard models and competing risk models with transplantation as a competing risk. Calendar year of inclusion, age, sex, DM, history of CVD, dialysis modality, IL-6, and PEW were considered as possible confounding factors; age and IL-6 were analyzed as continuous variables in the Cox models.

Data are presented as mean (SD) or median (interquartile range), depending on their distribution. Statistical significance was set at \( P<0.05 \). All statistical tests were performed using SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, NC).

Results
Clinical Characteristics and Correlations
IGF-1 levels were assessed at baseline in all 365 patients, and 207 of 365 patients also had IGF-1 levels assessed after 1 year on dialysis. The median concentration of IGF-1 in the latter group of 207 patients increased (by +33%) from 181 (87–320) to 240 ng/ml (114–413; \( P<0.001 \)) after 1 year on dialysis. IGF-1 increased after initiation of dialysis in both patients starting on peritoneal dialysis (PD) and patients starting on HD, with no statistically significant difference between the two dialysis modalities (Figure 1). Baseline values for all patients and PD and HD patients who were reinvestigated after 1 year on dialysis are shown in Table 1.

Univariate associations between IGF-1 and other variables at the initiation of dialysis in all 365 CKD stage 5 patients initiating dialysis are shown in Table 2. IGF-1 levels were negatively related to age, DM, CVD history, PEW, IL-6, and OPG and positively related to serum phosphate and calcium, body fat mass, BMD, and FGF-23.

Correlates of Baseline IGF-1 and IGF-1 Changes
Using multivariate regression models, age (\( \beta=-0.17, P=0.02 \)), serum phosphate (\( \beta=0.15, P=0.02 \)), and serum calcium (\( \beta=0.17, P=0.01 \)) were identified as correlates of IGF-1 among 365 patients initiating dialysis.

A mixed model including fixed factors and random factors measured before and after 1 year showed that higher serum phosphate, calcium, and body fat mass values and the fixed factors low age and no diabetes predicted higher variability of IGF-1 levels over time (data not shown).

Association between the IGF-1 Concentration and Mortality
During a median follow-up of 5 years, the overall mortality rate (28% among all 365 patients) was higher (36%) among patients with IGF-1 less than median than...
patients with IGF-1 greater than or equal to median (17%) at baseline. A crude Cox model showed that a 1 SD higher level of IGF-1 at baseline associated with less all-cause mortality, with a crude HR of 0.42 (95% confidence interval [95% CI], 0.31 to 0.57) in the whole group of 365 CKD stage 5 patients starting on dialysis. After adjusting for calendar year of inclusion, age, sex, DM, CVD, IL-6, and poor nutritional status (SGA>1), the survival benefit remained significant (HR, 0.57; 95% CI, 0.32 to 0.98). A spline curve showed that there was a gradual decrease of HR for all-cause mortality during a median follow-up of 5 years, with a higher IGF-1 level in the group of all 365 patients (Figure 2A). In addition, Figure 2B shows that 102 patients with a higher IGF-1 level in the group of all 365 patients cause mortality during a median follow-up of 5 years, whereas the association between IGF-1 levels and mortality was only significant among those patients who were treated by HD at 1 year, whereas the association between IGF-1 levels and mortality was not significant among PD patients; the reason for this discrepancy is not clear. To the best of our knowledge, no previous studies addressed the mortality risk associated with the change of IGF-1 levels in ESRD patients (and no study analyzed the possible impact of different dialysis treatments). Just a few previous studies studied the effect of IGF-1 on mortality in renal disease patients. Thus, serum IGF-1 was found to predict mortality in a cohort of intensive care unit patients with AKI (18). Consistent with the current study, another cross-sectional study, including 127 prevalent HD patients with up to 36 months follow-up, reported an inverse association between IGF-1 levels and all-cause mortality (12). Another study showed that low IGF-1 was associated with midterm mortality in 64 HD patients (13).

There are many possible, biologically plausible, positive reasons that could explain the apparent positive association between IGF-1 and survival as observed in the current study. Thus, IGF-1 can decrease serum glucose, promote the intracellular transport of glucose, suppress the lipolysis, enhance protein synthesis, and improve nitrogen balance and bone growth (19,20). Thus, although the exact mechanisms by which IGF-1 could promote survival in ESRD patients are not clear, one study showed that short-term administration of recombinant human IGF-1 (Rh-IGF-1) can improve GFR and promote anabolic response in PD patients with poor nutritional status (21). In acute uremic rats, Rh-IGF-1 was shown to accelerate recovery and reduce catabolism (22). However, the efficacy and long-term clinical usefulness of GH or Rh-IGF-1 therapy in CKD patients remain unclear.

Another main finding in the current study is that IGF-1 displayed strong links with mineral and bone metabolism parameters, including a positive relationship between IGF-1 and BMD (Table 2). Circulating IGF-1 plays a key role as regulator of bone growth and BMD, which has been shown in animal studies (2,23). Deficiencies in IGF-1 and alterations of its binding proteins IGFBP-1, -3, and -4 are thought to be major causes of the decrease in BMD that occurs with ageing (2,24). Cross-sectional studies in the general population on the link between serum IGF-1 and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>β-Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>−0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>0.03</td>
<td>0.68</td>
</tr>
<tr>
<td>DM (present)</td>
<td>−0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD (present)</td>
<td>−0.23</td>
<td>0.001</td>
</tr>
<tr>
<td>SGA&gt;1, %</td>
<td>−0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>−0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
<td>0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>Calcium, mg/dl</td>
<td>0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>PTH, ng/L</td>
<td>−0.09</td>
<td>0.18</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>−0.06</td>
<td>0.40</td>
</tr>
<tr>
<td>Total BMD, g/cm²</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>FGF-23, pg/ml</td>
<td>0.27</td>
<td>0.002</td>
</tr>
<tr>
<td>OPG, pg/ml</td>
<td>−0.18</td>
<td>0.03</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; CVD, cardiovascular disease; SGA, subjective global assessment; PTH, parathyroid hormone; BMD, body bone mineral density; FGF-23, fibroblast growth factor-23; OPG, osteoprotegerin.
BMD showed conflicting results. Low serum IGF-1 associated with lower BMD and increased risk of osteoporotic fractures independently of BMD in postmenopausal women (25). However, other studies found no association between IGF-1 and BMD (26) or osteoporosis (27). Although few studies explored the role of IGF-1 for BMD in ESRD patients, one study including 32 renal transplantation patients found no significant association between IGF-1 and BMD (28). In our study, there was a significant increase of IGF-1 concentration after initiation of renal replacement therapy.

In the current study, IGF-1 concentration after initiation of renal replacement therapy and changes of calcium and phosphate were associated with IGF-1 change over 1 year of dialysis, whereas we could not document any link between IGF-1 and PTH. Because calcium and phosphate are key regulators of PTH, it is likely that calcium and phosphate may influence the IGF-1 system directly or indirectly through the PTH pathway. Thus, phosphate and calcium modulate the osteoblastic proliferation through IGF-1 in \textit{in vivo} studies (29–31). The bone-forming effects of PTH require involvement of IGF-1, suggesting that IGF-1 plays a role as a potential mediator of the anabolic action of PTH (32). \textit{Vice versa}, earlier studies revealed that PTH stimulates IGF-1 production in osteoblasts (33). Studies of relationships between FGF-23 and BMD showed conflicting results. One study in CKD stages 2–5 patients found no association between FGF-23 and BMD (34), and another study in HD patients found no association as well (35). In the current study, FGF-23 positively related to IGF-1 at baseline; this finding is accordance with other studies, which showed inverse relationships between BMD and FGF-23 in ESRD and CKD patients (36–39). These studies stated that IGF-1 is involved in the NF-κB ligand and FGF-23/Klotho pathways (40). It may seem contradictory that IGF-1 was positively related to the two potential mortality
risk markers (phosphate and FGF-23) but inversely related to DM and CVD. However, the positive links between the anabolic hormone IGF-1, the growth factor FGF-23, and phosphate may reflect their links to bone health, whereas IGF-1 (as a nutritional marker) is lower in conditions linked to PEW, such as DM and CVD.

Finally, serum IGF-1 is a marker of nutritional status in ESRD patients (41,42), and in the current study, there was an inverse association between IGF-1 and nutritional status assessed by SGA. Chronic metabolic acidosis is known to reduce GH release from the pituitary, leading to lower levels of IGF-1 production (43). In the current study, acidosis was presumably better controlled after the initiation of dialysis, and this result could have contributed to increased GH and IGF-1 concentrations. Among postmenopausal women, the serum IGF-1 concentration correlated with lean body mass but not fat body mass (25), whereas in another study, IGF-1 levels were found to be significantly higher among obese than nonobese subjects (44). Furthermore, in the HERITAGE family study (HEalth, RIsk factors, exercise Training And GEnetics), an IGF-1 gene polymorphism associated with body fat mass and fat free mass (45). In the current study, we found that body fat mass associated with IGF-1 variation during 1 year of dialysis, whereas IGF-1 did not associate with lean body mass. Nevertheless, IGF-I is found to be a marker of undernutrition in prevalent HD patients (41).

There are some limitations and strengths that should be noted. First, this study is an observational study, which does not allow conclusions in regards to causality. Second, only those patients who survived and were willing to participate in the follow-up investigation at 1 year are included in the longitudinal part of the study, which may lead to biased conclusions regarding links between IGF-1 changes and survival. Third, a restricted amount of variables was analyzed; inclusion of unmeasured potential confounders, such as GH, IGFBP-1, -3 (other than at baseline), and -4, and indices of glucose metabolism and
genetic factors, could have changed the conclusions. However, this study is the first study to explore, in some detail, the role of IGF-1 concentrations at different time points and the changes during 1 year of dialysis on mortality in incident dialysis patients.

In summary, in CKD stage 5 patients initiating dialysis, the serum IGF-1 concentration increased after 1 year of dialysis. The IGF-1 concentrations at baseline as well as changes in IGF-1 over 1 year were independent predictors of 5-year mortality. The IGF-1 concentration associated with BMD and at baseline, other mineral and bone metabolism parameters, such as phosphate, calcium, FGF-23, and OPG. Also, in addition to age and diabetic status, phosphate, calcium, and body fat mass correlated with IGF-1 variation during 1 year of dialysis treatment. These results indicate that IGF-1 status in ESRD patients associates with body composition and markers of mineral and bone metabolism and that IGF-1 is a strong independent predictor of mortality risk in CKD stage 5 patients.

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Disclosures

B.L. is employed by Baxter Healthcare Corporation. P.S. serves on the Advisory Board of Gambro Inc. None of the other authors declare any conflict of interest.

References


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