A cohort study of insulin-like growth factor 1 and mortality in haemodialysis patients

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Abstract

Background: Protein-energy wasting (PEW) is highly prevalent in haemodialysis (HD) patients and associated with increased mortality and cardiovascular disease (CVD). Insulin-like growth factor 1 (IGF-1) correlates to markers of PEW and CVD. Disturbances in the growth hormone axis in end-stage renal disease (ESRD) could have an impact on survival through increased PEW and CVD.

Methods: A cohort of 265 incident HD patients (median age 68 years, 59% males) was followed for 3 years. Subjects were categorized according to IGF-1 levels at dialysis initiation. Outcome and comorbidity data were retrieved from national registers. The Kaplan–Meier diagram and Cox proportional hazards model were used for the analysis of survival.

Results: Patients with IGF-1 levels in the lowest tertile were characterized by female sex, low creatinine, hypoalbuminemia and high C-reactive protein (CRP) levels. IGF-1 levels within the lowest tertile were associated with increased mortality [hazard ratio (HR) 2.4, 95% confidence interval (CI) 1.7–3.4]. This association persisted when corrected for demographic factors (age, sex) and comorbidities (diabetes mellitus, CVD, heart failure) in multivariable analysis. Including high-sensitivity C-reactive protein (hs-CRP) and serum creatinine in the model had a small effect on the magnitude of the hazard. When serum albumin was added to the model, the HR declined from 2.2 to 1.6, but remained significant (P = 0.02).

Conclusion: Low IGF-1 levels associate with increased mortality in HD, independent of biomarkers of inflammation (hs-CRP) and PEW (creatinine, albumin). Serum albumin modulates the relationship between IGF-1 levels and mortality, indicating shared pathophysiological pathways with IGF-1.

Key words: albumin, end-stage renal disease, inflammation, insulin-like growth factor 1, survival analysis

Introduction

Protein-energy wasting (PEW) is highly prevalent in end-stage renal disease (ESRD) patients undergoing haemodialysis (HD) [1]. Several surrogate markers of PEW are associated with increased mortality and cardiovascular disease (CVD), especially when inflammation is present. Hypoalbuminemia has been viewed as a marker of PEW, but is confounded by inflammation and urinary losses [2–4]. Insulin-like growth factor 1 (IGF-1)
correlates more strongly than albumin with anthropometric and biochemical markers of PEW and malnutrition [5]. IGF-1 mediates the effects of growth hormone (GH) on lipid, glucose and protein metabolism and cardiovascular function [6]. Reduced levels of IGF-1 have been associated with CVD and all-cause mortality in the general population [7]. Inefficiency of the GH/IGF-1 axis may contribute to PEW in ESRD, where IGF-1 activity is reduced due to increased levels of IGF-1 binding proteins (IGFBPs) and altered receptor and post-receptor signalling. Although circulating levels of GH are increased in CKD [8], its effects are blunted due to reduced receptor numbers and alterations in post-receptor intracellular signalling pathways [6]. GH and IGF-1 activity is also reduced in inflammatory states [9]. Disturbances in the GH/IGF-1 axis could have an impact on survival in ESRD through increased PEW and CVD. We therefore investigated IGF-1 as a predictor of mortality and its relation to inflammation and albumin in a cohort of 265 incident HD patients.

Methods

Study design

This study represents a retrospective analysis of a cohort of incident HD patients recruited from a single HD centre at Örebro University Hospital, Sweden. Subjects were recruited during 1991–2009 and followed for up to 3 years. The study was approved by the regional ethics committee at Uppsala University Hospital, Sweden.

Study population

We included patients starting HD without a previous history of dialysis treatment or renal transplantation. Of 461 persons starting HD at our centre during 1991–2009 without prior renal replacement therapy, 268 were asked to participate in the study cohort. The only exclusion criterion was unwillingness to participate (n = 3). The long period of inclusion was mandated by the slow recruitment rate due to this being a single-centre study and that all available patients were not assessed for eligibility. The median age was 68 years (interquartile range 58–76 years) and 59% were male. Causes of renal failure included diabetic nephropathy (n = 59), nephroclerosis (n = 48), glomerulonephritis (n = 37), pyelonephritis (n = 14), polycystic kidney disease (n = 12), others (n = 73) and unknown (n = 22). One hundred five (40%) individuals had a history of cerebrovascular, peripheral vascular or coronary heart disease (grouped as CVD); 74 (28%) had heart failure (HF) and 96 (36%) had diabetes mellitus. Selected characteristics of the study population are presented in Table 1. Although detailed data on ethnicity were not available, the majority of HD patients in Sweden are Caucasian.

Procedures and variables

Serum samples were obtained at the start of the first dialysis session or up to 11 days before and stored at −20°C. Clinical biochemical parameters (creatinine, albumin, haemoglobin) were measured using routine methods at Örebro University Hospital. After the end of follow-up, serum samples were analyzed for IGF-1, IGF-1 binding protein-3 (IGFBP-3) and high-sensitivity C-reactive protein (hs-CRP) by immunometric assays on an Immunlite 1000 Analyzer (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) and according to the instructions of the manufacturer.

All participants in the study were registered in the Swedish Renal Registry, maintained by the Swedish Society of Nephrology (http://www.medscinet.net/smrr/). Demographic data, cause of renal failure, time to renal transplantation and cases of regained renal function were retrieved from this register. Comorbidity data were obtained from inpatient diagnoses in the Swedish National Patient Register (http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish/). This register, launched in 1964, has complete coverage of inpatient care since 1982 and has been validated for a number of diagnoses [10]. Survival time and cause of death were obtained from the Swedish Cause of Death Register. The latter two registers are administered by the Swedish National Board of Health and Welfare. Registry data of comorbidities, cause of renal failure and cause of death are based on the clinical diagnosis by the reporting physician.

Table 1. Demographic, clinical and laboratory characteristics of 265 incident dialysis patients by IGF categories (lower tertile versus the rest)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 265)</th>
<th>Non-low IGF-1 (n = 177)</th>
<th>Low IGF-1 (n = 88)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low IGF-1, %</td>
<td>33</td>
<td>0</td>
<td>100</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex, female, %</td>
<td>41</td>
<td>32</td>
<td>58</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36</td>
<td>33</td>
<td>43</td>
<td>0.13*</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>40</td>
<td>37</td>
<td>45</td>
<td>0.22*</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>28</td>
<td>25</td>
<td>33</td>
<td>0.25*</td>
</tr>
<tr>
<td>AV-fistula, %</td>
<td>25</td>
<td>28</td>
<td>19</td>
<td>0.15*</td>
</tr>
<tr>
<td>Collagen vascular disease, %</td>
<td>14</td>
<td>10</td>
<td>20</td>
<td>0.03*</td>
</tr>
<tr>
<td>Malignancy, %</td>
<td>17</td>
<td>15</td>
<td>20</td>
<td>0.31*</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>65.8 (13.4)</td>
<td>64.9 (14)</td>
<td>67.6 (11.9)</td>
<td>0.11b</td>
</tr>
<tr>
<td>IGF-1, ng/mL, mean (SD)</td>
<td>127 (78.5)</td>
<td>166 (67.6)</td>
<td>49.4 (17.3)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>IGFBP-3, μg/mL, median (IQR)</td>
<td>3.71 (1.6)</td>
<td>4.26 (1.49)</td>
<td>2.62 (1.23)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>hs-CRP, mg/L, mean (SD)</td>
<td>23 (8.02–64.5)</td>
<td>18.1 (7.45–56)</td>
<td>34.8 (11.3–83.9)</td>
<td>0.04c</td>
</tr>
<tr>
<td>Creatinine, μmol/L, mean (SD)</td>
<td>738 (311)</td>
<td>767 (291)</td>
<td>680 (342)</td>
<td>0.04c</td>
</tr>
<tr>
<td>Albumin, g/L, mean (SD)</td>
<td>33.6 (5.9)</td>
<td>35.3 (5.08)</td>
<td>30.2 (6.02)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Haemoglobin, g/L, mean (SD)</td>
<td>100 (15.1)</td>
<td>101 (14.6)</td>
<td>98.4 (16)</td>
<td>0.16c</td>
</tr>
</tbody>
</table>

Low IGF-1 category represents the lower tertile of IGF-1 distribution. IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; IQR, interquartile range; hs-CRP, high-sensitive C-reactive protein.

*Statistical significance was tested with χ² test.

Statistical significance was tested with Student’s t-test.

*Statistical significance was tested with Wilcoxon-Mann-Whitney test.
Comorbidities were defined from International Classification of Diseases, Ninth Revision (ICD-9) codes or corresponding codes in ICD-8 or ICD-10 as follows (ICD-9 codes in parentheses): CVD includes ischaemic heart disease (410–414 and surgery codes for coronary artery bypass graft and percutaneous coronary intervention), peripheral vascular disease (440, 250G) and cerebrovascular disease (430–38). Collagen vascular disease includes psoriasis and similar disorders, polycythaemia nodosa and allied conditions, diffuse diseases of connective tissue, rheumatoid arthritis and other inflammatory polyarthropathies (696, 446, 710, 714). Malignancy includes all malignant tumours except skin cancer, tumours of unknown nature and cancer in situ (140–171 and 174–209). Other comorbidities were diabetes mellitus (250) and HF (428). Comorbidity was noted if diagnosis was present at any time before initiation of dialysis.

Data on vascular access at the initiation of dialysis was retrieved from medical records and classified as arteriovenous fistula (AVF) or non-AVF. A variable for the period of inclusion was calculated (years 1991–95, 1996–2000, 2001–5 and 2006–9).

### Statistical analysis

Descriptive data are presented in Table 1 as mean (SD) if continuous and percentage if categorical. The significance level was set at P < 0.05. For comparisons between groups, χ² test was applied for categorical variables and Student’s t-test for continuous variables. Normal distribution of data was assessed by visual inspection of density and Q–Q plots. CRP appeared non-normally distributed and Wilcoxon–Mann–Whitney test was employed in its analysis.

A Cox proportional hazards model was used for univariable and multivariable analysis of survival. Cases were censored at renal transplantation (n = 49) or regained renal function (n = 7) and follow-up was 3 years from inclusion (n = 265). In multivariable analysis, we included established cardiovascular risk factors (age, sex, diabetes mellitus, HF and history of CVD) and selected biochemical markers. Kaplan–Meier analysis was used to obtain a survival diagram, with log-rank test for difference between groups. Numbers were rounded at two significant digits for ratios and three for descriptive data, trailing zeroes omitted.

### Results

#### IGF-1

The median IGF-1 of the study population (118 ng/mL) was within the normal (95%) range according to the manufacturer of the enzyme–linked immunosorbent assay kit (69–200 ng/mL for age range 66–70 years).

Characteristics according to IGF-1 levels are presented in Table 1. Low IGF-1 was defined as levels below the 33rd percentile (lowest tertile) of the study population, which corresponded to 75 ng/mL. Patients in the low IGF-1 group were more often female, had a history of collagen vascular disease, higher hs-CRP and lower serum creatinine, serum albumin and IGFBP-3. There were no significant differences in age, haemoglobin levels or prevalence of diabetes mellitus, HF, malignancy or CVD.

The association of IGF-1 with collagen vascular disease was not statistically significant when investigated via a multivariable linear regression model including sex (P = 0.17).

#### Analysis of survival

During a follow-up of up to 36 months, 134 (51%) persons died, 49 (18%) were transplanted and 7 (3%) regained renal function.

### Table 2. Univariable HRs (and 95% CIs) of selected covariates and the risk of all-cause mortality (N = 265)

| Variable         | HR (95% CI) | P-value
|------------------|-------------|----------
| Low IGF-1        | 2.4 (1.7–3.4) | <0.001   
| Sex, female      | 1.3 (0.92–1.8) | 0.14     
| Diabetes mellitus| 1.2 (0.84–1.7) | 0.35     
| Cardiovascular disease | 1.6 (1.1–2.3) | 0.006    
| Heart failure    | 1.8 (1.3–2.6) | 0.001    
| AV fistula       | 0.59 (0.38–0.91) | 0.02     
| Collagen vascular disease | 1.5 (0.97–2.4) | 0.07     
| Malignancy       | 1.7 (1.1–2.5) | 0.01     
| Age, years       | 1.3 (1–1.6) | 0.02     
| IGF-1, ng/mL     | 0.66 (0.53–0.81) | <0.001   
| IGFBP-3, μg/mL   | 0.65 (0.53–0.8)  | <0.001   
| hs-CRP, mg/L     | 1.3 (1.1–1.4) | 0.001    
| Creatinine, µmol/L | 0.65 (0.52–0.82) | <0.001   
| Albumin, g/L     | 0.64 (0.54–0.75) | <0.001   
| Haemoglobin, g/L | 0.9 (0.75–1.1) | 0.23     

HRs for continuous variables are per standard deviation increment. Low IGF-1 category represents the lower tertile of IGF-1 distribution against the other two tertiles combined. HR, hazard ratio; CI, confidence interval; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; hs-CRP, high-sensitive C-reactive protein.

Causes of death included cardiovascular causes (n = 67, 50%), withdrawal of dialysis (n = 23, 17%), infection (n = 16, 12%), malignancy (n = 9, 7%), others (n = 15, 11%) and unknown (n = 4, 3%).

Univariable correlations to survival are presented in Table 2, with hazard ratios (HRs) for continuous variables describing standard deviation increments. Age, history of HF, malignancy or CVD and the absence of an AVF at dialysis initiation were associated with increased mortality risk. On the other hand, diabetes, collagen vascular disease and female sex were not associated with mortality. Among laboratory variables, serum albumin, creatinine, IGF-1, IGFBP-3 and hs-CRP correlated to outcome.

Kaplan–Meier analysis (Figure 1) showed that IGF-1 tertiles were associated with patient survival (log-rank P < 0.001). The association of low IGF-1 with survival was further examined using the Cox proportional hazards model (Table 3). IGF-1 levels with the lowest tertile distribution were strongly associated with increased risk of death [HR 2.4 (95% CI 1.7–3.4)] as compared with the middle and highest tertiles. This association persisted when corrected for demographic factors (age, sex) and comorbidities (diabetes mellitus, CVD, HF) in multivariable analysis (Table 3). Including hs-CRP and creatinine in the model had a small effect on the magnitude of the hazard. When serum albumin was added to the model, the HR declined from 2.2 to 1.6 but remained significant (P = 0.02).

Causes of ESRD and their association with IGF-1 categories and survival are presented in the supplementary material (Supplementary data, Tables S3 and S4).

### Discussion

We report that patients with a low level of IGF-1 at the start of HD have an increased 3-year mortality rate. This confirms the results from previous cohort studies of both prevalent [11–13] and incident [14] dialysis patients. Others have not found significant associations between IGF-1 levels and survival [15, 16]. Beberashvili et al. [17] found that low levels of IGF-1 were associated with increased mortality in HD, but only in combination with high levels of IL-6. Importantly, in the present study, low IGF-1 associated with survival independent of hs-CRP, creatinine and serum albumin.
Insulin-like growth factor 1 and mortality

IGF-1 is thought to be a marker of PEW and malnutrition [5]. It has also been suggested that low IGF-1 could be a causative factor for PEW and CVD [7]. In the present study, IGF-1 correlated both to serum creatinine, which in dialysis patients is a crude marker of lean body mass [18], and to hs-CRP. When adjusting for these markers, IGF-1 remained independently associated with survival. Albumin levels were lower among those with low IGF-1 and had a clear effect on the relationship between IGF-1 and survival, independent of hs-CRP and creatinine. This may indicate that serum albumin and IGF-1 reflect common pathophysiological pathways other than PEW and inflammation [19].

Both high and low IGF-1 levels have been associated with CVD in the general population. High levels also predict the presence of CKD [20]. In ESRD, a univariable association of IGF-1 with cardiovascular disease (CVD) was not significant in the low and non-low IGF-1 groups and the association of IGF-1 with mortality was independent of CVD. This may indicate that the association of IGF-1 and CVD found in the general population is not as prominent in ESRD. It should be emphasized that patients with CKD who progress to ESRD represent a select group, having both progressed in their renal failure and survived years of a pro-atherogenic and toxic uraemic milieu. Therefore, serum IGF-1 in ESRD may reflect other pathological conditions than it does in earlier stages of CKD and in the general population.

In renal failure, IGF-1 activity is reduced due to the accumulation of IGF-1 binding proteins, which lowers the free bioactive fraction of IGF-1 [21]. This should lead to a compensatory increase of total IGF-1 through decreased feedback inhibition of GH release from the pituitary gland, leading to an increase in GH levels [8, 22]. In renal failure, concomitant resistance to GH may blunt this compensatory response. Our results suggest that the levels of total IGF-1 per se predict worse outcomes, perhaps because lower levels reflect a state of more profound GH resistance where decreased IGF-1 activity is aggravated by a relative IGF-1 deficiency.

Several important limitations of the study should be acknowledged. Although the intention was to include all incident HD patients at Orebro University Hospital from 1991 to 2009, a large proportion of the total population of incident dialysis patients could not be included due to exclusion criteria or because it was not possible to obtain blood samples due to logistic reasons. This may affect the external validity of our results. Also, retrieval of data on possible confounders such as concomitant medication, height and smoking status was not possible. Furthermore, it should be noted that hs-CRP levels were very high in all groups. This reflects the broad selection criteria for this study, where patients with acute infections and acute inflammatory conditions may be more prevalent than in studies of stable HD patients. The long inclusion period may lead to selection bias due to changes over time in demographics, criteria for starting renal replacement therapy and comorbidity in the dialysis population, as well as analytical interference due to degradation of the analyzed markers in stored serum. For clinical laboratory variables, changes in calibration and methods may interfere. To assess the influence of these factors, the period of inclusion was used as a variable in the statistical analysis and variations in baseline laboratory variables over time were investigated. We found no association between the period of inclusion and outcome or IGF-1 (data not shown). Using t-test, IGFBP-3 was significantly lower for those included in 2001–9 and creatinine lower in 1996–2005 compared with other periods of inclusion. For IGF-1, hs-CRP, haemoglobin and albumin, no significant differences were seen. Results including IGFBP-3 or serum creatinine should therefore be interpreted with caution. However, long storage time did not seem to affect levels of IGF-1 [23].

Information on comorbidities was retrieved from national registries, utilizing ICD coding. Changes in reporting or coding over time may therefore have influenced the degree to which different conditions were captured. Although the frequency of some comorbidities varied over time (Supplementary data, Table S2), there was no association between the period of inclusion and outcome or IGF-1 levels (data not shown).

Limitations inherent in observational cohort studies include the lack of a control group and the potential of unidentified confounding variables. The retrospective analysis opens up the possibility that data on comorbidities and causes of ESRD may not have been rigorously collected.

In summary, HD patients with IGF-1 in the lowest tertile have increased mortality. This group is further characterized by hypoalbuminemia and high CRP levels. Although this reflects the presence of PEW and inflammation, these factors may not fully explain the association of IGF-1 and mortality.
Supplementary data
Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement
O.H. has received lecturing fees from Baxter, Fresenius, Bayer and the Swedish Society of Internal Medicine as well as travel funding from Sandoz. B.L. is employed by and has received grants, lecturing fees, consultancy fees and travel funding from Baxter Healthcare. P.S. has received grants from Bayer, lecturing fees from AbbVie, Shire, Bayer, Pfizer and Asahi and has been a member of scientific advisory boards of ARO group (Amen), Vifor, Keryx and Astellas. None of the other authors declare any conflict of interest.

References