Differential effects of growth hormone therapy in malnourished hemodialysis patients

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Background. Malnutrition is common in chronic hemodialysis patients and is associated with increased morbidity and mortality. Several factors such as metabolic acidosis, hyperparathyroidism, and insulin as well as growth hormone (GH) resistance may lead to enhanced protein catabolism. Recombinant human growth hormone (rhGH) has been proposed as treatment for malnourished hemodialysis patients. Differential and anthropometric parameters, on bone turnover, and in lumbar spine increased significantly after three months of therapy with rhGH, whereas other parameters of PMNL function were not affected by GH. QoL was slightly improved in the GH-treated group, but decreased markedly in the placebo group.

Conclusions. Three months of treatment with rhGH in malnourished patients on chronic hemodialysis causes a significant increase in IGF-I levels without significant changes in nutritional and anthropometric parameters. In contrast, bone turnover was enhanced with an initial decrease in BMD at the lumbar spine, and phagocytic activity of PMNLs was increased.

Up to 70% of patients with chronic renal failure (CRF) on hemodialysis suffer from malnutrition, one of the main causes for their increased morbidity and mortality [1–6]. Protein requirements often are increased in these patients, but protein intake as well as protein synthesis are usually reduced. Besides uremic toxicity, infections, psychosocial factors, and amino acid abnormalities, metabolic acidosis and endocrine abnormalities such as insulin resistance, hyperparathyroidism, and growth hormone insensitivity enhance protein catabolism [7]. Increasing the dialysis dose is one way to counteract these effects [8, 9]. In addition, the administration of erythropoietin and the correction of metabolic acidosis as well as intradialytic parenteral nutrition (IPDN) have been shown to affect nutritional and anthropometric parameters favorably [10–13].

Patients with CRF on hemodialysis are resistant to the actions of growth hormone (GH), insulin, and insulin-like growth factor I (IGF-I). Chronic metabolic acidosis, inflammation, high concentrations of IGF-binding proteins (IGFBPs), and therefore decreased bioavailability of IGF-I as well as reduced nutrient intake are the main factors that might induce resistance to GH and IGF-I [14–19]. Whereas rhGH substitution therapy in patients with growth hormone deficiency (GHD) has shown favorable effects on body composition, lipid profile and bone

Key words: chronic renal failure, protein catabolism, bone turnover, erythropoietin, metabolic acidosis, nutrition and dialysis.

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mineral density [20–22], only supraphysiological doses of GH and IGF-I induced a net decrease in total urea nitrogen appearance in CRF patients [23–25]. Also, two recently published studies demonstrated improvements in anthropometric measurements, a decrease in predialytic BUN levels, and an increase in serum albumin concentrations [26, 27].

The aim of the present study was to extend the hitherto described observations of the effects of supraphysiological rhGH doses in malnourished patients on chronic hemodialysis with low IGF-I concentrations. These low IGF-I levels may indicate profound GH resistance as well as reduced nutrient intakes. In addition to nutritional and anthropometric parameters, parameters of bone metabolism and bone mineral density (BMD), function of polymorphonuclear leukocytes, and quality of life (QoL) were determined in a double blind, placebo-controlled, three-month trial.

METHODS

Patients

Nineteen malnourished patients (10 females and 9 males) with a mean age of 59.3 ± 13.4 years on chronic hemodialysis entered this study after informed consent was given. Patients had to be on chronic hemodialysis for at least six months. Patients fulfilling at least three out of the four following criteria were included into the study: serum cholesterol and transferrin levels <200 mg/dL, serum albumin concentrations <41 g/L, and a body weight of <80% of the optimal body weight. The protocol was approved by the Human Ethics Committee of the University of Vienna. Eighteen patients finished the three-month study. One patient (receiving placebo) died because of cardiovascular failure after one month. Chronic hemodialysis was performed three times weekly in all patients using bicarbonate and biocompatible high (N = 10) or low-flux dialyzers (N = 9), the duration was four hours in most patients and was not changed during the observation period.

Chronic renal failure was due to various etiologies including polycystic kidney disease (N = 1), chronic glomerulonephritis (N = 10), chronic pyelonephritis (N = 4), diabetic and/or hypertensive nephropathy and nephroangiosclerosis (N = 4). Two of the patients were type I diabetics requiring insulin. One patient was a type II diabetic. No patient had a history of a malignoma. Ten patients had a history of cardiovascular disease.

Study design and treatment schedule

The hypothesis to be tested by this study was to examine whether rhGH therapy in pharmacological doses improves nutritional and anthropometric parameters or has some impact on bone metabolism or granulocyte function in hemodialysis patients.

The study was prospective, randomized, double blind, and placebo controlled (GH/placebo). The patients received either recombinant GH (Genotropin R by Pharmacia, Stockholm, Sweden) or placebo, which was supplied in identical cartridges for reconstitution with 1 mL of water for injection with 3 mg of m-cresol. The rhGH dose was 0.125 IU/kg (40.5 µg/kg) three times a week during the first four weeks and 0.25 IU/kg (81 µg/kg) thereafter three times a week after each dialysis session. In five of these patients, the dose had to be reduced temporarily (1 week) by 50% because of adverse events.

Adverse events. Five patients developed a shunt thrombosis (3 patients receiving GH and 2 placebo). Six patients (5 patients receiving GH, 1 placebo) suffered from arthralgias, and one patient receiving GH suffered from newly developed headache. One patient who received placebo died because of cardiovascular failure after one month.

Biochemical, immunological, and anthropometric measurements were performed in all subjects after the long dialysis-free period. Blood was drawn before and after the first dialysis of the week and again before the next dialysis for urea determinations used to calculate urea kinetics (URR, PCR, Kt/V). Blood hemoglobin, blood glucose, and serum biochemistries were analyzed by routine methods. Serum C reactive protein (CRP) was measured by using an immunonephelometric method (Tina-quant; Böhringer Mannheim, Mannheim, Germany). Albumin, prealbumin, cholesterol, cholinesterase, protein, and transferrin were determined by nephelometry (Nephelometer BNA II; Behring Diagnostics, Marburg, Germany).

Insulin-like growth factor I (IGF-I) was quantified by a radioimmunoassay (RIA). Serum samples were extracted by acid-ethanol method and diluted 1:20 prior to determination. IGF-I rabbit antisem was provided by the Hormone Distribution Program of NIDDK (Bethesda, MD, USA) and was used at a final dilution of 1:5000. The international reference preparation rhIGF-I 87/518 was from NIBSC (UK) and was used as standard. The tracer, prepared by iodination of recombinant IGF-I and purified by HPLC, was from Amersham (Little Chalfont, Buckinghamshire, UK). The detection limit of the assay was 0.1 ng/tube. The intraassay coefficient of variation was 11.8% at 153 ng/mL, and the interassay coefficient of variation at 182 ng/mL was 9.4%. The RIA for IGFBP-3 (Miadiagnostik, Germany) utilized a specific high polyclonal rabbit antibody. The tracer was prepared by direct radiodiopination of pure IGFBP-3 and standards refer to a stable derivate of IGFBP-3 with a molecular weight of 30.5 kD. Serum was considerably diluted before analysis, but no extraction step was required. The sensitivity of the assay was 0.006 ng/mL.

Serum levels of intact parathyroid hormone (PTH) (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) and serum osteocalcin (OC; CIS International,
Gif sur Yvette, France) were measured by commercially available RIAs. The intra-assay and interassay coefficients of variance (CV) were 7.5 and 6.8%, respectively, for intact PTH, and 3.8% and 5.2%, respectively, for serum osteocalcin. Serum concentrations of carboxyterminal propeptide of type I procollagen (PICP), n-terminal propeptide of type III procollagen (PIIINP) as well as the telopeptide ICTP, were measured by commercially available RIA (Orion Diagnostica, Espoo, Finland). The intra-assay CVs for PICP, PIIINP, and ICTP were 2.7, 2.5, and 2.8%, respectively. The interassay CVs were 6.6, 3.2, and 4.1%, respectively. An ELISA (Osteometer, BioTech, Herlev, Denmark) was performed to determine the serum Crosslapse™.

**Bone densitometry**

X-ray films of the lumbar and thoracic spine and the hip were obtained to exclude the possibility of spine fractures or severe osteoarthritis. BMD was measured using dual-energy x-ray absorptiometry (DEXA) on a QDR 2000 TM device (Hologic R, Waltham, MA, USA). Sites of measurements were the lumbar spine (L1 to L4) and the left femoral neck. The in vivo precision of DEXA was 0.71% for the lumbar spine and 1.0% for the femoral neck.

**Preparation of PMNLs**

Polymorphonuclear leukocytes (PMNLs) were prepared from 10 mL heparinized (10 U/mL Liquemin; Roche, Basle, Switzerland) whole blood as described by Harbeck et al [28]. Leukocyte-rich plasma was obtained using a 25 unidimensional items measuring the quality of life in adults with GHD. This questionnaire consists of aspects that are affected by GHD [38, 39]. Responses gradient. This was centrifuged at 500 g for 25 minutes are of the yes/no type. High scores reflect a bad QoL.

**Statistical methods**

The statistical analysis was performed using SAS software (version 6.09E). We employed the GLM procedure (to take into account the possible unbalanced data) for detecting deviations in the course of time using the number of the patient and the time as class variables, but specifying the number of the patient as a random effect (that is, considering joint observations). We used Tukey's studentized range test (HSD) on the means of the main effects (that is, time) to locate the points in time where significant deviations occur. Variables of interest were described by their means and standard deviations (SD) and differences were considered significant with $P < 0.05$.

**RESULTS**

Patient characteristics are shown in Table 1. Baseline nutritional and anthropometric parameters as well as chest, thoracic-midaxillary, suprailiacal, paraumbilical, subscapular, triceps, front thigh (suprapatellar), biceps and popliteal [34]. Skinfolds were measured to the nearest 0.2 mm, as the mean of three readings by the same investigator to eliminate the intertester variability. Measurements were performed after hemodialysis. Total body fat (TBF) was calculated from the formula of Allen et al [35]. The lean body mass (LBM) was derived by subtracting TBF from body mass.

**Quality of life**

Health-related quality of life (QoL) was measured using the self-rating questionnaire the Nottingham Health Profile (NHP I), where patients had to answer 38 questions concerning problems with emotional reaction, sleep, energy, pain, physical mobility, and social life, [36, 37], and the AGHDA, which is a self-administered questionnaire designed specially to evaluate quality of life in adults with GHD. This questionnaire consists of 25 unidimensional items measuring the quality of life aspects that are affected by GHD [38, 39]. Responses are of the yes/no type. High scores reflect a bad QoL in both questionnaires and improvements in QoL are reflected by a decrease in the scores.

### Table 1. Baseline characteristics of 19 patients on chronic hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>GH group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male/female</td>
<td>3/6</td>
<td>6/4</td>
<td>&lt;0.36</td>
</tr>
<tr>
<td>Age years</td>
<td>54.2 ± 14.3</td>
<td>65.1 ± 11.4</td>
<td>&lt;0.27</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>8.7 ± 2.0</td>
<td>9.7 ± 2.1</td>
<td>&lt;0.19</td>
</tr>
<tr>
<td>PCR</td>
<td>0.82 ± 0.14</td>
<td>0.75 ± 0.11</td>
<td>&lt;0.17</td>
</tr>
<tr>
<td>URR</td>
<td>0.71 ± 0.08</td>
<td>0.66 ± 0.04</td>
<td>&lt;0.50</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.4 ± 0.31</td>
<td>1.24 ± 0.30</td>
<td>&lt;0.50</td>
</tr>
</tbody>
</table>

Abbreviations are: GH, growth hormone; PCR, protein catabolic rate; URR, urea reduction ratio; Kt/V, dialysis dose.
parameters of bone metabolism and PMNL function were comparable in both groups (Tables 2 and 3).

The IGF-I concentration increased significantly from 169.2 ± 95.6 to 262.9 ± 144.4 ng/mL ($P < 0.01$) after three months in the group receiving rhGH, whereas IGF-I levels showed no significant changes in the placebo group. IGF-BP3 levels increased only slightly after three months in the therapy group ($P = NS$; Fig. 1).

Serum albumin, prealbumin, transferrin, cholesterol, HDL cholesterol, cholinesterase, as well as predialytic creatinine and blood urea nitrogen (BUN) showed no significant changes during the three months course in the placebo group as well as in the therapy group (Table 2). Percent total body fat ($\%$TBF) was slightly, but not significantly, reduced in the GH-treated patients, whereas lean body mass (LBM) remained stable in both groups. CRP levels were slightly elevated in both groups (GH-treated group: $0.7 ± 0.3$ vs. $0.9 ± 0.4$ mg/dL, placebo group: $2.2 ± 0.9$ vs. $2.6 ± 1.2$ mg/dL after 3 months) without correlation to the nutritional and anthropometric parameters. Blood glucose levels rose in two patients (receiving rhGH) with pre-existing diabetes requiring an increase in the insulin dose of one patient with diabetes mellitus type I, all other patients showed no changes in their fasting glucose or HbA1c levels.

Serum markers of bone formation (PICP, OC, AP) as well as markers of bone resorption (ICTP, serum Crosslaps™) and parathyroid hormone (PTH) were evaluated during these three months. A significant increase in PICP from 250.1 ± 112.6 to 478.5 ± 235.2 μg/L ($P < 0.01$) was observed, the increase in OC after 3 months was statistically not significant (Fig. 2). PIINP, a non-bone specific marker of collagen production, rose significantly during the three months of rhGH therapy (9.9 ± 4.9 to 14 ± 6.5 μg/L, $P < 0.01$). In parallel with the markers of bone formation ICTP as a marker of bone resorption showed a slight, but not significant increase after three months of therapy (50.3 ± 18.5 vs. 70.0 ± 39.5 μg/L, $P = NS$; Fig. 2), whereas serum Crosslaps™ remained stable during the whole period. Since most of the patients in this study suffered from a secondary hyperparathyroidism, intact PTH was already elevated at baseline and rose from 198.0 ± 139.2 to 293.4 ± 144.8 ng/mL ($P = NS$) in the treatment group; serum calcium concentrations were comparable at baseline and after three months in both groups. BMD of the lumbar spine showed a significant decrease after three months in the treatment group (0.8 ± 0.17 vs. 0.77 ± 0.16 g/cm², $P < 0.01$), whereas it remained stable in the femoral neck during the whole period (Fig. 3).

At baseline phagocytic activity was lower in the group

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### Table 2. Nutritional parameters in 19 patients on chronic hemodialysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0 months</th>
<th>$P$ value</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin g/L</td>
<td>GH</td>
<td>38.5 ± 4.2</td>
<td>$&lt;0.44$</td>
<td>39.2 ± 6.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>39.9 ± 3.7</td>
<td></td>
<td>42.3 ± 5.7</td>
</tr>
<tr>
<td>Prealbumin mg/dL</td>
<td>GH</td>
<td>26.5 ± 7.6</td>
<td>$&lt;0.74$</td>
<td>26.7 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>27.7 ± 8.0</td>
<td></td>
<td>32.0 ± 5.7</td>
</tr>
<tr>
<td>Transferrin mg/dL</td>
<td>GH</td>
<td>172.9 ± 38.6</td>
<td>$&lt;0.97$</td>
<td>190 ± 57.8</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>173.4 ± 30</td>
<td></td>
<td>174 ± 37.8</td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td>GH</td>
<td>165.3 ± 32</td>
<td>$&lt;0.23$</td>
<td>158.6 ± 33.9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>188.2 ± 39.4</td>
<td></td>
<td>180.2 ± 22</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>GH</td>
<td>46.4 ± 11.7</td>
<td>$&lt;0.58$</td>
<td>43 ± 13.1</td>
</tr>
<tr>
<td>mg/dL</td>
<td>Placebo</td>
<td>51 ± 18.6</td>
<td></td>
<td>49.1 ± 17.6</td>
</tr>
<tr>
<td>Choline sterase</td>
<td>GH</td>
<td>3.6 ± 1.1</td>
<td>$&lt;0.18$</td>
<td>3.7 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3.8 ± 1.2</td>
<td></td>
<td>3.9 ± 0.9</td>
</tr>
<tr>
<td>Predialytic U/L</td>
<td>GH</td>
<td>8.8 ± 2.0</td>
<td>$&lt;0.36$</td>
<td>8.9 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>9.7 ± 2.1</td>
<td></td>
<td>9 ± 2.0</td>
</tr>
<tr>
<td>Predialytic BUN</td>
<td>GH</td>
<td>58.6 ± 19</td>
<td>$&lt;0.37$</td>
<td>64.5 ± 14</td>
</tr>
<tr>
<td>mg/dL</td>
<td>Placebo</td>
<td>67 ± 17.5</td>
<td></td>
<td>74 ± 20</td>
</tr>
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</table>

### Table 3. Anthropometric parameters in 19 patients on chronic hemodialysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0 months</th>
<th>$P$ value</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight kg</td>
<td>GH</td>
<td>60.5 ± 12</td>
<td>$&lt;0.25$</td>
<td>59.9 ± 13</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>59.8 ± 11</td>
<td></td>
<td>60 ± 10</td>
</tr>
<tr>
<td>LBM kg</td>
<td>GH</td>
<td>44.5 ± 8.3</td>
<td>$&lt;0.10$</td>
<td>44.3 ± 8.5</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>44.8 ± 7.2</td>
<td></td>
<td>44.5 ± 8</td>
</tr>
<tr>
<td>TBF %</td>
<td>GH</td>
<td>17.5 ± 10</td>
<td>$&lt;0.54$</td>
<td>16.7 ± 10</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>17.1 ± 9</td>
<td></td>
<td>16.9 ± 8</td>
</tr>
<tr>
<td>Skinfold thickness mm</td>
<td>GH</td>
<td>84.7 ± 46</td>
<td>$&lt;0.95$</td>
<td>81 ± 44</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>82.6 ± 38</td>
<td></td>
<td>83.7 ± 39</td>
</tr>
</tbody>
</table>

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Fig. 1. Mean insulin-like growth factor-I and (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels during three months treatment with growth hormone (GH; □) or placebo (□) in 19 malnourished hemodialysis patients. Values are expressed as mean ± SD and differences (baseline vs. 3 months) were considered significant with $P < 0.05$. 

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Fig. 2. Markers of bone formation (PICP and OC; A, B) and markers of bone resorption (ICTP and Crosslaps; C, D) during three months treatment with rhGH (solid line) or placebo (dashed line) in 19 malnourished hemodialysis patients. Values are expressed as mean ± SD and differences (baseline vs. 3 months) were considered significant *P < 0.05.

Fig. 3. Bone mineral density (BMD) of the lumbar spine (A) and the femoral neck (B) during three months treatment with GH (solid line) or placebo (dashed line) in 19 malnourished hemodialysis patients. Values are expressed as mean ± SD and differences (baseline vs. 3 months) were considered significant with P < 0.05.

receiving rhGH, but increased significantly after three months (Fig. 4). In contrast, no changes were observed in the placebo-treated patients. None of the other tests of PMNL function (metabolic burst, intracellular killing, glucose uptake, intracellular calcium concentration) was affected by GH (data not shown).

The QoL of these patients improved after three months of rhGH therapy as evidenced by a decrease in mean QoL AGHDA (Quality of Life Assessment of Growth Hormone Deficiency in Adults) score of 1.4 points, whereas the AGHDA score increased by 2.4 points in the placebo group. NHP I showed no changes in either group during the three months (Fig. 5).

Fig. 4. Phagocytic activity of polymorphonuclear leukocytes (PMNL) during 3 months of treatment with GH (solid line) or placebo (dashed line) in 19 malnourished hemodialysis patients. Values are expressed as mean ± SD and differences (baseline vs. 3 months) were considered significant with P < 0.05.

DISCUSSION

In the past ten years, several studies have shown significant effects of rhGH substitution therapy on body composition (LBM, %TBF) [20–22], bone mineral density (BMD) [40, 41] and quality of life in adult patients with growth hormone deficiency (GHD). Immunological parameters such as natural killer-cell activity and phagocytosis also have been improved by GH administration in hypophysectomized rats [42]. In accordance with these results in GHD patients, short- and long-term studies with rhGH in uremic patients on chronic hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) have recently reported an increase in serum albumin concentrations and favorable effects on several anthropometric parameters and handgrip strength [23–27]. In our placebo-controlled, double-blind study, over a period of three months no changes in nutritional and anthropometric parameters were observed despite a significant increase in IGF-I levels. However, rhGH therapy induced an increase in bone turnover combined with a decrease in BMD at the lumbar spine, an increase in phagocytic activity as well as a slight improvement in quality of life.
Patients with CRF have a high incidence of protein-caloric malnutrition, and malnutrition is a strong predictor of morbidity and mortality in these individuals [5]. Most research on anabolic hormones in catabolic conditions has recently been performed with rhGH. While CRF patients have normal or even slightly elevated GH levels and sometimes also normal IGF-I levels, resistance to the anabolic actions of IGF-I in the skeletal muscle has been described [14, 17]. Beside metabolic acidosis [18], inflammation, and reduced nutrient intakes [19], this resistance in the skeletal muscle has been attributed to defects in cellular signaling with a defect in tyrosine kinase activity of the IGF-I receptor and to the presence of circulatory inhibitors such as elevated IGFBPs. In chronic renal failure, IGFBP-3 is usually elevated resulting in reduced IGF-I bioavailability [43, 44]. Therefore, the rationale for treating CRF patients on hemodialysis with rhGH was the use of pharmacological GH doses in an attempt to overcome GH resistance and to promote protein anabolism. Higher doses and/or higher frequency of GH applications might have led to higher IGF-I concentrations, but more likely to an increase in side effects.

The nutritional status of our patients was assessed using several parameters including serum albumin, pre-albumin, cholesterol, HDL cholesterol, cholinesterase, IGF-I, transferrin, predialytic creatinine, and BUN, as well as anthropometric parameters (LBM, %TBF, and skinfold thickness) [45–48]. Among those, serum albumin levels correlated best with morbidity and mortality, with concentrations below 35 g/L associated with a two-fold risk in mortality [5]. During the three months of GH therapy no significant changes in the nutritional or the anthropometric parameters were observed. In contrast to previously published studies in patients on chronic hemodialysis, where an increase in serum albumin concentrations and improvement in anthropometric parameters has been described [26, 27], our patients had markedly lower IGF-I levels before and during therapy to rhGH. This might explain the discrepant findings to some extent, since our patients might have exhibited a more severe form of malnutrition and catabolism resulting in more pronounced GH-resistance. This would be in line with preliminary data showing that malnourished patients who were severely ill and eating poorly during GH therapy demonstrated almost no improvement in nitrogen balance and albumin concentrations, despite positive effects on bone turnover [49].

Nutritional and metabolic factors affect the immune system of uremic patients and malnutrition is known to impair the function of PMNL and cellular host defense [50, 51], resulting in an increased incidence of infections. Infections are the most common cause for hospitalization and the second leading cause of death in this population [5, 52]. Increased resting levels of intracellular calcium, mainly due to elevated parathyroid levels, iron overload, zinc deficiency, malnutrition and circulating plasma inhibitors appear to be responsible for the impaired cellular host defense with impaired PMNL function, impaired phagocytosis, and decreased glucose uptake [50, 51]. There is also clinical evidence for profound defects in the specific immune defense in uremia, such as high suscepti-
bility to viral infections, a deficient response of T-lymphocytes and significantly depressed specific antibody responses. GH was able to increase the activity of cytotoxic T-lymphocytes in vitro and of natural killer cell activity in vivo, to prime macrophages for superoxide anion release and augment respiratory burst in neutrophils [42]. In GH-deficient patients the diminished natural killer-cell activity could be partially restored by GH. In the present study, GH stimulated phagocytic activity of PMNLs significantly after three months of therapy, which could be of clinical relevance in patients with chronic renal failure requiring renal replacement therapy. However, other parameters of granulocyte function (intracellular killing, glucose uptake, metabolic burst, and intracellular calcium concentrations) were not affected by GH. Furthermore, no significant changes in CRP serum concentrations or the incidence of infections in both groups were observed, but clearly the number of subjects was too small and the observation period too short to expect the latter.

Bone metabolism is affected in patients on chronic hemodialysis and leads to skeletal abnormalities known as renal osteodystrophy. These changes can occur early in the course of renal failure and are caused by several pathologic mechanisms, such as phosphate retention and decreased 1,25-dihydroxyvitamin D synthesis, resulting in PTH hypersecretion and high turnover osteopathy. However, low turnover osteopathy, including adynamic bone disease [53, 54], also results in low BMD. Both GH and IGF-I have marked effects on bone metabolism and bone mineral density. GH can stimulate chondrocyte growth and function and can directly or indirectly increase bone turnover by stimulating osteoblasts and osteoclasts and inducing collagen synthesis [55]. In growth hormone-deficient (GHD) patients, GH substitution therapy has been shown to enhance bone turnover with a decrease in BMD after six months of therapy followed by an increase after 18 months [33]. One study by Gram et al, where rhGH was administered over a period of six months in chronic dialysis patients, showed an increase in procollagen I carboxyterminal peptide (PICP), a marker of bone formation as well as in the n-terminal propeptide of type III procollagen (PIIINP), a non–bone-specific marker of collagen synthesis, but bone mineral density decreased significantly [56]. In accordance with these data, a significant increase in bone turnover with an increase in PICP and PIIINP and minor changes in ICTP and OC was observed in the present study. As iPTH increased slightly in both groups during the three-month period, iPTH does not seem to be responsible for the observed effects on bone turnover. Furthermore, BMD was unaffected in the femoral neck, but was significantly decreased in the lumbar spine after three months of therapy with rhGH. In analogy to the findings in patients with GHD, we speculate that prolonged GH therapy leads to an increase in BMD.

In conclusion, we have shown that pharmacological doses of rhGH increase IGF-I concentrations and induce an increase in bone turnover with a decrease in BMD of the lumbar spine. In addition in our malnourished hemodialysis patients there was an enhanced phagocytic activity of PMNLs and a slight improvement in QoL. However, no changes in nutritional and anthropometric parameters could be detected. Thus, in our severely malnourished patients, even supraphysiological doses of GH were only partially able to overcome GH resistance.

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APPENDIX

Abbreviations used in this article are: BMD, bone marrow density; BUN, blood urea nitrogen; CRF, chronic renal failure; CRP, C reactive protein; DEXA, dual energy X-ray absorptiometry; GH, growth hormone; HDL, high density lipoprotein; HPLC, high-pressure liquid chromatography; ICTP, telopeptide; IGFBP, insulin-like growth factor binding protein; IGF-I, insulin-like growth factor-I; IPDN, intradialytic parenteral nutrition; KT/V, dialysis dose; LBM, lean body mass; NHP I, Nottingham Health Profile instrument; OC, osteocalcin; PCR, protein catabolism rate; PICP, procollagen I carboxyterminal peptide; PIIINP, n-terminal propeptide of type III procollagen; PMNL, polymorphonuclear leukocyte; PTH, parathyroid hormone; QoL, quality of life; QoL-bone mineral density. GH can stimulate chondrocyte AGHDA, Quality of Life Assessment of Growth Hormone Deficiency in Adults; rhGH, recombinant human growth hormone; RIA, radioimmunoassay; TBF, total body fat; URR, urea reduction ratio.

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