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Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: Results of a pilot randomized controlled clinical trial☆

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***Background/Aims*: Insulin-like growth factor I (IGF-I) is an anabolic hormone synthesized in the liver whose levels decrease sharply in liver cirrhosis.**

***Methods*: We conducted a randomized double-blind placebo-controlled clinical trial to evaluate the effect of subcutaneous administration of IGF-I (20 μg/kg/day with dose escalation to 50–100 μg/kg/day) for 4 months in patients with alcoholic or primary biliary cirrhosis (PBC) and subnormal IGF-I levels. Eight alcoholics and one PBC entered the placebo group and seven alcoholics and two PBC the treatment group. Biochemistry, body composition, muscle mass and strength, and resting energy expenditure (REE) were evaluated.**

***Results*: Total serum IGF-I and IGF-I/IGFBP-3 ratio (a surrogate marker of IGF-I biovailability) increased in the treatment group but IGF-I values still remained below normal limits in the treated patients. No differences were observed in body composition, muscle strength or muscle mass between groups. However, IGF-I therapy increased significantly serum albumin ($P=0.038$) and this improvement correlated positively with variation of IGF-I/IGFBP-3 ratio. IGF-I treatment also tended to increase REE ($P=0.085$); this difference was significant ($P=0.049$) in the subgroup of alcoholic patients.**

***Conclusions*: A short course of IGF-I increased albumin levels and tended to improve energy metabolism in liver cirrhosis. These findings warrant larger clinical trials to assess the clinical benefit of IGF-I in cirrhotic patients.**

***Keywords*: Liver cirrhosis; Liver function; Nutrition; Body composition; Resting energy expenditure; IGF-I; IGFBP3; Child–Pugh score**

1. Introduction

Hepatocytes are the main source of circulating insulin-like growth factor-I (IGF-I), a potent anabolic hormone whose secretion is stimulated by growth hormone (GH) [1,2]. IGF-I circulates bound to 6 different IGF binding proteins (IGFBP-1 to −6), interacts with specific receptors on target tissues (bone, intestine, testis, muscle, etc) and also acts on hypothalamus to suppress GH

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secretion [3–5]. The liver is also the major producer of IGFBPs, mainly IGFBP-1 and IGFBP-3. IGFBP-3 sequesters IGF-I in the vascular system, increasing its half-life and providing an IGF-I reservoir. The ratio of total IGF-I/IGFBP-3 is considered as a surrogate index of IGF-I bioavailability [5].

In subjects with liver cirrhosis plasma levels of total IGF-I, free IGF-I and IGFBP-3 are decreased while GH is increased, indicating resistance to GH and reduced hepatic functional reserve [6–8]. Liver cirrhosis is, therefore, an IGF-I deficiency state, the severity of which correlates with the progression of the liver disease [6–10]. Indeed, many of the clinical features of advanced cirrhosis such as malnutrition, muscle wasting, loss of bone mass, and hypogonadism could be ascribed to deficient IGF-I anabolic activity. The possible therapeutic use of IGF-I in liver cirrhosis is supported by studies in cirrhotic rats demonstrating that IGF-I replacement therapy (20 μg/kg): (a) increases food intake, nitrogen balance and food efficiency [11]; (b) enhances intestinal absorption of glucose and aminoacids [12]; (c) increases bone density [13]; (d) corrects hypogonadism [14]; (e) diminishes oxidative liver damage [15]; (f) improves liver function [15] and (g) decreases liver fibrogenesis [15].

Based on these premises we decided to perform a small controlled clinical trial to evaluate the effects of IGF-I replacement therapy in patients with liver cirrhosis of non-viral origin. Because of the reported growth-promoting and antiapoptotic properties of IGF-I, in this pilot study we excluded cirrhotic patients with higher risk of cancer development such as those with haemochromatosis or chronic hepatitis B or C virus infection.

2. Materials and methods

We designed a randomized, double-blind, placebo controlled pilot study to investigate whether IGF-I replacement therapy could benefit cirrhotic patients. The study was performed in two centers: Clinica Universitaria of Navarra (Spain) and University Hospital Groningen (The Netherlands).

2.1. Patient selection and eligibility

Patients were males or females aged 18–70 years with alcoholic cirrhosis (with at least 3 months of abstinence as assessed by patient's interview) or primary biliary cirrhosis, plasma IGF-I levels below the lower age-adjusted 5th percentile (two standard deviations below the age-adjusted normal level) and willing and able to give written informed consent to participate in the study.

The exclusion criteria were: etiologies other than alcohol or primary biliary cirrhosis, tense ascites requiring repeated paracenteses, severe peripheral edema, hospitalization for gastrointestinal bleeding, spontaneous bacterial peritonitis or other life-threatening complications within 3 months of entering the study, encephalopathy requiring protein restriction or precluding collaboration, drug abuse, hematocrit $\leq 28\%$, creatinine $>$ 2 mg/dl, serum sodium ≤ 125 mmol/l, bilirubin ≥ 10 mg/dl, prothrombin time ≥ 10 s prolonged, PSA ≥ 4 μg/l, α-fetoprotein ≥ 10 μg/l or mass lesion on abdominal ultrasound within 3 months before entering the study, clinical conditions that would compromise exercise testing, past or present history of malignancy within the last 10 years with the exception of curatively treated basal cell carcinoma, anti-diabetic therapy, proliferative retinopathy and coexistence of any other diseases or medication which might interfere with the assessment of nutritional status. Usual therapy of the complications of cirrhosis such as neomycin, lactulose, lactitiol, diuretics and propanolol were allowed.

3. Study design

The patients were randomized to receive human recombinant IGF-I (Chiron Corp., Emeryville, CA, USA) or placebo for 120 days. We used a 1:1 randomization with a block size of 2. The randomization was stratified by investigative site and etiology. The starting dose of IGF-I was 20 μg/kg administered as a single subcutaneous injection within 60 min after breakfast. The dose was selected based on preclinical data showing beneficial effects and absence of hypoglycemia with this dose in cirrhotic rats [11–15]. Study subjects remained in the hospital the first day for observation and instruction on self-injection and monitoring the blood glucose every 4 h. The dose was adjusted according to plasma levels of total IGF-I measured in the out-patient clinic at 09.00 h (prior to that day's IGF-I dose) weekly during the first month. A normal IGF-I level was defined as a concentration within 1 SD of the normal level adjusted for age. If total IGF-I level was low, the dose was increased at increments of 5–10 μg/kg/day up to a maximal dose of 50 μg/kg/day (Pamplona cohort) or 100 μg/kg/day (Groningen cohort). Patients in the placebo group received subcutaneous vehicle (sodium succinate, pH 6). The dose of placebo was adjusted in the same way as that of IGF-I. IGF-I values were made available to only one investigator in each center who was responsible for adjusting the dose of IGF-I and who did not participate in patient's evaluation. All other investigators involved were blinded.

The following parameters were analyzed at baseline and at the end of the study period: levels of total and free IGF-I, IGFBP-3, liver biochemistry, muscle mass (quadriceps on dominant side of the body by CT scan), muscle strength (isokinetic exercise of quadriceps on dominant side), body composition by dual-energy-X-ray-absorptiometry (DEXA), respiratory quotient and resting energy expenditure (indirect calorimetry) and assessment of the quality of life (SF-36 questionnaire). Quadriceps muscle mass and strength as well as lean body mass were selected as the primary efficacy measures. Fat mass, bone mineral density, liver function tests, Child–Pugh score, respiratory quotient, resting energy expenditure and quality of life were secondary end points.

4. Determinations

Serum concentration of total and free IGF-I and IGFBP-3 were determined as previously reported [16]. Muscle mass was measured using CT-scan (SOMATON PLUS 4. Siemens, Forcheim, Germany) [17]. CT of the dominant