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Insulin-Like Growth Factor Binding Protein-3 in Patients with Liver Cirrhosis

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Summary

Aim of the study was to evaluate serum levels of insulin-like growth factor binding protein-3 in patients with liver cirrhosis and to compare serum IGFBP-3 levels with other liver function tests. Fifty-one patients with liver cirrhosis were selected for our study. We measured IGFBP-3 (1.67±1.06 mg/l, mean ± SD), albumin (32±8 g/l), prealbumin (0.22±0.14 g/l), AST (2.29±2.38 μkat/l), ALT (2.11±4.83 μkat/l) and cholinesterase (mean 78.6±45.2 μkat/l) in the serum. There was a significant positive correlation of serum IGFBP-3 with serum albumin and serum cholinesterase. The correlation coefficient was much lower between serum IGFBP-3 and serum prealbumin. There was no significant correlation between serum AST, ALT and IGFBP-3. Serum IGFBP-3 proves to be a better marker for the hepatic synthetic capacity than serum albumin or cholinesterase.

Key words
Liver cirrhosis • GFBP-3 • Liver tests

Introduction

The insulin-like growth factor (IGF)-binding proteins (IGFBPs) carry IGFs in the serum and regulate their activity and bioavailability. The main IGFBP in the serum is IGFBP-3, which binds most circulating IGFs and is known to form a 150 kDa ternary complex with IGFs and the acid-labile subunit (Collett-Solberg *et al.* 1998). Six IGFBPs have been isolated and chemically characterized. IGFBP-3 has the highest serum concentration among all IGFBPs. IGF-I and its BPs are produced in several tissues, the liver being of primary importance (Tavill 1972, Zapf *et al.* 1990, Donaghy *et al.* 1995).

In patients with hepatic cirrhosis, a reduction of serum albumin and other plasma proteins is a common finding and endocrine functions are often also disturbed in patients with chronic hepatic disease (Sherlock 1993).

Chronic liver disease is associated with marked changes in body composition. These changes are accompanied with impaired generation of IGF-I and altered production of IGFBP-3. Several studies reported that serum IGFBP-3 levels were abnormally low in patients with liver cirrhosis and correlated with the severity and that the levels were significantly lower than normal mean values in the healthy population. The close correlation of IGFBP-3 levels with hepatic functions indicates a dominant regulatory role of hepatocytes (Donaghy *et al.* 1995).

The observed decreases in IGF-I, IGF-II and IGFBP-3 in patients with hepatic failure and their subsequent restoration after liver transplantation probably

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result primarily from the reduced number of functional hepatocytes in end-stage liver disease and their subsequent replacement by healthy hepatic tissue. These changes may also result from hormonal alterations and nutritional deficiencies known to exist in patients with severe liver dysfunction (Schalch *et al* 1998).

It has been shown that serum IGFBP-3 is also a useful parameter in diagnosing growth hormone (GH) deficiency. Besides various other factors that modulate serum levels of IGF-I and IGFBP-3, e.g. age, sexual development, nutrition, thyroid hormones, hepatic or renal function, GH is certainly a major regulator of both peptides. The importance of GH is suggested by low IGF-I and IGFBP-3 levels in GH-deficient children which increase during GH treatment and by high levels in acromegaly which decrease after successful therapy (Blum *et al.* 1993).

IGFBP-1 and -2 levels reflect changes related to nutrition, insulin secretion, fetal development and malignancy (Ranke *et al.* 1997).

The insulin-like growth factors have diverse anabolic cellular functions and structure similar to those of proinsulin. The distribution of IGFs and their receptors in a wide variety of organs and tissues enables the IGFs to exert endocrine, paracrine and autocrine effects on cell proliferation and differentiation, caloric storage and skeletal elongation. IFG-I exhibits particular metabolic responsiveness and circulating IGF-I originates predominantly in the liver (Philips *et al.* 1998).

Over 50 % of children with established cirrhosis have evidence of growth failure and malnutrition and this is associated with and may be caused by an impaired generation of IGF-I and altered production of IGFBPs. Orthotopic liver transplantation is a successful treatment for many children and leads to improved growth and nutrition (Holt *et al.* 1998).

Methods

Fifty-one patients (28 males, aged 52.3±13.5 years; 23 females, aged 45.4±22.8 years) with liver cirrhosis were selected for our study. All patients had histologically proven cirrhosis and all patients were biochemical euthyroid and without cardiac, respiratory or renal dysfunction.

For control group we selected 40 healthy volunteers (26 males and 14 females, mean age 46.1 years). In this group we measured serum IGFBP-3.

In the group with liver cirrhosis, we measured serum IGFBP-3, albumin, prealbumin, transaminases and cholinesterase. Immediately after venepuncture sera were separated by centrifugation and stored at –20 °C until further analysis.

Serum IGFBP-3 was determined by a two-site immunoradiometric assay (IRMA) using DSL-6600 IGFBP-3 coated-tube IRMA kit (Diagnostic System Laboratories, Webster, TX). The minimal detection limit of the assay was 0.0005 mg/l. The IGFBP-3 inter- and intraassay CV were less than 6 %.

Conventional liver biochemical tests (aspartate aminotransferase – AST, alanine aminotransferase – ALT, cholinesterase, albumin, prealbumin) were performed using a clinical chemistry automatic analyzer ADVIA 1650 (Bayer Diagnostics, Tarrytown, New York, USA). AST, ALT and albumin were measured by commercial AST kit, ALT kit and albumin kit (Bayer Diagnostics, Tarrytown, New York, USA), cholinesterase by commercial CHE kit (ROCHE, Mannheim, Germany) and prealbumin by commercial Prealbumin Rabbit Anti-Human kit (DAKO).

ANOVA correlation analysis was used for statistical analysis. Significance level was assigned at value $P<0.0001$.

Results

Mean levels of the liver biochemical tests measured in our 51 patients with liver cirrhosis are given in Table 1. We measured the aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT ratio) in all patients (mean 1.86±1.43). Thirty-eight patients from our 51 patients had a value for AST/ALT ratio ≥1.

Table 1. Values of the liver biochemical tests in 51 patients with liver cirrhosis

IGFBP-3	mg/l	1.67 ± 1.06
Albumin	g/l	32 ± 8
Prealbumin	g/l	0.22 ± 0.14
Cholinesterase	μkat/l	78.6 ± 45.2
AST	μkat/l	0.29 ± 2.38
ALT	μkat/l	2.11 ± 4.83

Data are Means ±SD

We found a significant positive correlation between serum IGFBP-3 and serum albumin ($r=0.72$, $P<0.0001$) (Fig. 1) and cholinesterase ($r=0.67$, $P<0.0001$) (Fig. 2). The correlation coefficient was much lower between serum IGFBP-3 and serum prealbumin ($r=0.44$,

P<0.001) (Fig. 3). Between IGFBP-3 and the AST/ALT ratio a negative correlation was found (r=0.62, P<0.005). There was no significant correlation between serum transaminases and IGFBP-3. In our group of patients with liver cirrhosis, serum IGFBP-3 levels were significantly lower (1.67±1.06 mg/l, absolute range was 0.22-4.71 mg/l) than in healthy controls (3.27±1.11 mg/l, absolute range was 2.08-6.53 mg/l.

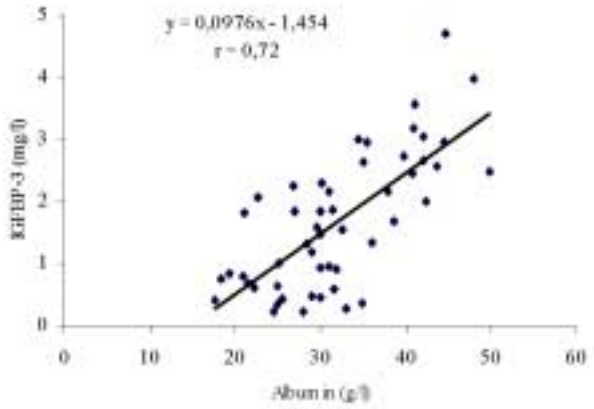

Fig. 1. *Correlation between IGFBP-3 and albumin in 51 patients with liver cirrhosis (P<0.0001).*

Discussion

The determination of serum IGFBP-3 level is a clinically useful marker for the assessment of the synthetic capacity of hepatocytes in cirrhotic patients and an early predictor of hepatic dysfunction. IGFBP-3 may provide important additional information on metabolic status in patients with liver disease. Serum IGFBP-3 seems to be a more sensitive marker than serum albumin for the assessment of the synthetic capacity of hepatocytes in liver cirrhosis (Shaarawy *et al.* 1998). 50 % reduction in serum IGFBP-3 levels is in agreement with no reduction in serum albumin levels in early liver cirrhosis (Shaarawy *et al.* 1998). The sensitivity and specificity of the serum IGFBP-3 test in cases of liver cirrhosis was found to be 76 % and 100 %, respectively. The predictive value for a positive IGFBP-3 test was 100 % whereas it was 55 % for a negative test (Shaarawy *et al.* 1998). Together with IGFBP-3 the AST/ALT ratio can be a good marker for hepatic dysfunction. The AST/ALT ratio ≥1 has been shown to have a positive predictive value for the diagnosis of cirrhosis in patients. We found in our study a negative correlation between IGFBP-3 and the AST/ALT ratio.

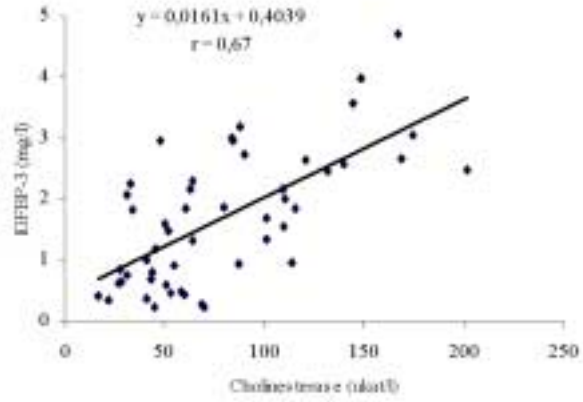

Fig. 2. *Correlation between IGFBP-3 and cholinesterase in 51 patients with liver cirrhosis (P<0.0001).*

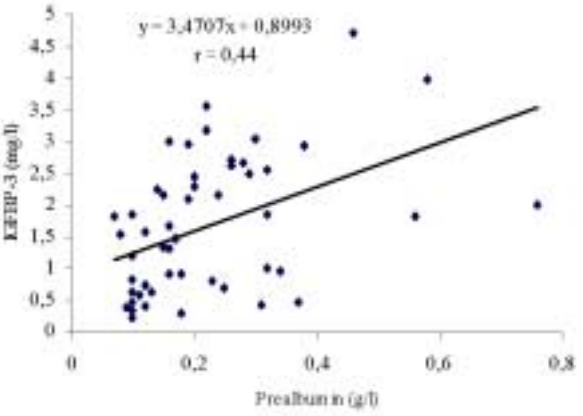

Fig. 3. *Correlation between IGFBP-3 and prealbumin in 51 patients with liver cirrhosis (P<0.001).*

Donaghy *et al.* (1995) reported that serum IGFBP-3 levels were abnormally low in patients with cirrhosis. The high GH and low IGF-1 levels, associated with an inverse relationship between high IGFBP-1 and low IGFBP-3 levels observed in their study were similar to those observed in nutritionally deprived patients with anorexia nervosa. Malnutrition may therefore be the common causative factor in chronic liver disease, modulating production of IGFBPs and the GH-resistant state (Donaghy *et al.* 1995). Our study has also revealed a significant decrease of serum IGFBP-3 levels in patients with liver cirrhosis. *In vitro* studies have demonstrated IGFBP-3 production from human fetal liver explants but not from isolated hepatocytes in a primary culture, suggesting production from nonparenchymal cells. Nevertheless, findings of very low IGFBP-3 levels in liver disease suggest a dominant role of the hepatocytes in IGFBP-3 production, possibly through a paracrine

effect on a nonparenchymal cell or alternatively through production of the acid labile subunit, which is necessary for the formation of a stable ternary complex (Donaghy *et al.* 1995).

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References

BLUM WF, ALBERTON-WIKLAND K, ROSBERG S, RANKE MB: Serum levels of insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 reflect spontaneous growth hormone secretion. *J Clin Endocrinol Metab* **76**: 1610-1616, 1993.

COLLETT-SOLBERG PF, NUNN SE, GIBSON TB, COHEN P: Identification of novel high molecular weight insulin-like growth factor-binding protein-3 association proteins in human serum. *J Clin Endocrinol Metab* **83**: 2843-2848, 1998.

DONAGHY A, ROSS R, GIMSON A, HUGHES SC, HOLLY J, WILLIAMS R: GH, IGF-1 and IGFBP-3 in chronic liver disease. *Hepatology* **21**: 680-688, 1995.

HOLT RI, BAKER AJ, JONES JS, MIELL JP: The insulin/like growth factor and binding protein axis in children with end-stage liver disease before and after orthotopic liver transplantation. *Pediatr Transplant* **2**: 76-84, 1998.

PHILIPS LS, PAO CI, VILLAFUERTE BC: Molecular regulation of insulin-like growth factor-I and its principal binding protein, IGFBP-3. *Prog Nucleic Acid Res Mol Biol* **60**: 195-265, 1998.

RANKE MB, ELMLINGER M: Functional role of insulin-like factor binding proteins. *Horm Res* **48**: 9-15, 1997.

SCHALCH S, KALAYOGLU M, PIRSCH JD, YANG H, RASLICH M, RAJPAL S: Serum insulin-like growth factors and their binding proteins in patients with hepatic failure and after liver transplantation. *Metabolism* **47**: 200-206, 1998.

SHAARAWY M, FIKRY MA, MASSOD BA, LOTFY S: Insulin-like growth factor binding protein-3: a novel biomarker for the assessment of the synthetic capacity of hepatocytes in liver cirrhosis. *J Clin Endocrinol Metab* **83**: 3316-3319, 1998.

SHERLOCK S: Assessment of liver function. In: *Diseases of the Liver and Biliary System*. SHERLOCK S, DOOLEY J (eds), London: Blackwell Scientific, 1993, p.17.

TAVILL AS: The synthesis and degradation of liver produced proteins. *Gut* **13**: 225-235, 1972.

ZAPF J, KIEFER M, MERRYWEATHER JU: Isolation from adult human serum of four IGFBPs and molecular cloning of one of them. *J Biol Chem* **265**: 14892-14898, 1990.

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