PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• BRIEF REPORTS •

Clinical significance of serum IGF-I, IGF-II and IGFBP-3 in liver cirrhosis

Yun-Lin Wu, Jing Ye, Shu Zhang, Jie Zhong, Rong-Ping Xi

Yun-Lin Wu, Jing Ye, Shu Zhang, Jie Zhong, Rong-Ping Xi, Department of Gastroenterology, Ruijin Hospital, Shanghai Second Medical University, Shanghai 200025, China
Supported by the Medical Development Project of Asahi Fund of Japan
Correspondence to: Dr. Yun-Lin Wu, Department of Gastroenterology, Ruijin Hospital, Shanghai Second Medical University, Shanghai 200025, China. carlionje8@hotmail.com
Telephone: +86-21-64370045 Ext. 665246
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Abstract

AIM: To investigate the relationship between insulin-like growth factor-I, -II (IGF-I and IGF-II), IGF-binding protein 3 (IGFBP-3) and Child-Pugh score in patients with liver cirrhosis, and to search for potential clinical markers of liver function.

METHODS: Forty-four patients with advanced liver cirrhosis of viral origin were divided into 3 groups according to severity of cirrhosis (Child-Pugh score) and 38 healthy subjects served as controls. Serum levels of IGF-I, IGF-II and IGFBP-3 were measured by immunoradiometric assay.

RESULTS: Serum IGF-I, IGF-II and IGFBP-3 levels were significantly lower in patients with cirrhosis than in controls, and serum concentrations of IGF-I, IGF-II and IGFBP-3 were associated with the severity of liver dysfunction, and dropped sharply during the progression of liver failure. Among these 3 parameters, serum IGF-II was the most sensitive and effective indicator for liver dysfunction. Concentrations of IGF-I <30 ng/mL, IGF-II <200 ng/mL and IGFBP-3 <6 ng/mL implied a negative prognosis for patients with liver cirrhosis.

CONCLUSION: Serum IGF-I, IGF-II and IGFBP-3 may provide a new dimension in the assessment of liver dysfunction. Combined detection of serum IGF-I, IGF-II and IGFBP-3 with Child-Pugh score is more effective in predicting prognosis than Child-Pugh score alone.

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INTRODUCTION

Insulin-like growth factor-I and II (IGF-I, IGF-II), two major forms of insulin-like growth factors (IGFs) family, are single-chain molecules with three intrachain disulfide bridges consisting of 70 (M_r 7 646) and 67 (M_r 7 471) amino acid residues respectively[1,2]. Both of them may be considered as important anabolic hormones which are active throughout one's life, inducing anabolic metabolism and stimulating DNA synthesis, cell proliferation and meiotic division[3,4]. Compared with IGF-I, IGF-II is more well-known as a tumor genesis marker[5]. As serum IGF-II may be produced and secreted by hepatoma cells, the hormone could accelerate or magnify its function of continuously stimulating cell growth by directly or indirectly combining with its receptor in neighboring cells or hepatoma cells themselves to form intracellular shortcuts[6,7].

Insulin-like growth factor binding protein-3 (IGFBP-3) consisting of 264 amino acid residues binds nearly 95% circulating IGFs in the human body, forming a stable ternary complex (M_r 150 000) with the acid-labile subunit (ALS). The complex is believed to serve as a reservoir in circulation to prolong half-lives of both IGF-I and IGF-II[8,9]. Since most circulating IGF-I, IGF-II and IGFBP-3 are synthesized by hepatocytes, lower levels of the above three parameters should be found in patients with liver diseases[10]. This study was designed to clarify the influences of associated liver cirrhosis as assessed by Child-Pugh score (CP score) on these parameters, to determine whether measurement of these three parameters could reflect the severities of cirrhosis and liver dysfunction, to reveal whether the combination of these three parameters with CP score could be a more reasonable clinical option for evaluating liver function.

MATERIALS AND METHODS

Patients

From February to September 2001, 44 patients with hepatitis B-induced liver cirrhosis (30 males and 14 females with a mean age of 57.41 years, ranging from 38 to 83) were studied. Patients with liver cirrhosis were diagnosed by liver biopsy and/or by computerized tomography, ultrasonography and clinical biochemical examinations, according to Chinese diagnostic criteria of liver cirrhosis set up in 1995. Patients were divided into 3 groups by CP score: Fifteen people in the group of CP A (scored 5-6), 19 in the group of CP B (scored 7-10) and 10 in the group of CP C (scored 11-15). A total of 38 healthy subjects were served as controls (23 males and 15 females, mean age of 49.97 years, ranging from 35 to 82). After detection of serum IGF-I, IGF-II and IGFBP-3 levels, patients were followed-up in the liver clinic for a period of 6 mo.

Study protocols

Serum IGF-I was quantified by immunoradiometric assay kit (Immunotech A BECKMAN Company). Serum levels of IGF-II and IGFBP-3 were detected by DSL-2 600 ACTIVETM immunoradiometric assay kits (Diagnostic System Laboratories Inc, USA).

Sample collection, procession and storage were referred to the following: A 6 mL venipuncture blood was collected into a dry, heparinized tube in the morning from every subject. Then serum or plasma was separated from cells by centrifugation. Samples should be kept at below -30 °C after aliquoting so as to avoid repeated freezing and thawing.

Assay procedures were firmly accorded to instructions of the kits. Briefly, taking protocol of IGF-II for example, first, 100 μL of the reconstituted standards, controls and pretreated samples were added to appropriate tubes. Then all the tubes were mixed and incubated at room temperature for 3 h, centrifuged at 180 r/m, and decanted except for total count tubes by simultaneous inversion. The tubes were shaken violently to facilitate complete drainage and allowed to drain on absorbent for 1-2 min. Two

milliliters of deionized water was added to all tubes, except total count tubes, and the tubes were decanted. After 100 μL of anti-IGF-II [^{125}I] reagents was added, all tubes were mixed by shaking and were incubated at room temperature for 1 h on a shaker at 180 r/min, then were decanted except for total count tubes by simultaneous inversion. The tubes were struck sharply on absorbent material for 1-2 min and analyzed, after 2 mL of wash solution being added to each tube except for total count tubes. All tubes were counted in a gamma counter for 1 min after decantation.

Statistical analysis

Data were listed as mean±SD. Comparison between means was tested by Student's *t* test, Friedman's ANOVA and Duncan test in SAS. *P* value less than 0.05 was considered significant.

RESULTS

Serum IGF-I, IGF-II and IGFBP-3 in cirrhotic liver tissues and matched controls

The mean values for IGF-I, IGF-II and IGFBP-3 in 44 cirrhotic patients (66±58, 367±193 and 12.0±7.6 ng/mL, respectively) were significantly lower than those in 38 healthy subjects (260±74, 1 094±119 and 39±7 ng/mL, respectively, $P<0.001$, Table 1). Since mean values of the three parameters were negatively correlated to age according to our statistical show (r = -0.646, -0.612, -0.609), data were revised with covariance analysis to obviate age-related effect on three parameters, and similar result was obtained ($P<0.001$).

Serum IGF-I, IGF-II and IGFBP-3 levels in patients with different CP scores

The mean values for IGF-I, IGF-II and IGFBP-3 were 119±67, 507±185 and 19±8 ng/mL, respectively, in CP A; 45±29, 343±154 and 10±5 ng/mL, respectively, in CP B. The mean values for IGF-I, IGF-II and IGFBP-3 in patients classed as Child-Pugh C stage, the worst stage of liver dysfunction with incurable ascites and elongation of APTT (activated partial thromboplastin time), were 27±11, 201±115 and 6±3 ng/mL, respectively. Significant difference of the three parameters was found between control group and any stage of cirrhosis ($P<0.001$). These three parameters gradually diminished, along with disease progression. Statistic analysis also showed that the mean levels for IGF-I and IGFBP-3 in CP A were significantly higher than those in CP B/C ($P<0.001$), and these values were a little higher in CP B than in CP C, however no significant difference of the two parameters was observed between these 2 categories ($P>0.05$). Only mean levels of IGF-II showed clear statistical difference in patients between CP B and CP C ($P<0.05$), suggesting that IGF-II reduced significantly due to the severity of liver dysfunction (Table 2, Figure 1). Thus serum IGF-II was a more sensitive and effective indicator than IGF-I and IGFBP-3. Furthermore, the depressed IGF-II level was significantly correlated with the IGF-I variation, as well as with CP score ($P<0.001$).

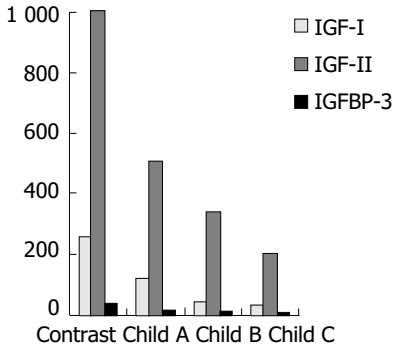

Figure 1 Serum IGF-I, IGF-II and IGFBP-3 levels in patients with different Child-Pugh scores.

DISCUSSION

Low levels of circulating IGF-I in cirrhosis have been described[11]. In recent studies, Assy *et al*[12]. confirmed that basal IGF-I and IGFBP-3 levels were significantly lower in patients with liver cirrhosis in their pilot study of IGF-I generation test, in which the two parameters were observed before and after stimulation with recombinant human growth hormone (rhGH). It was also approved by Donaghy *et al*[13]. that basal IGF-I and IGFBP-3 levels dropped markedly in cirrhosis due to severe GH resistance in these patients, caused by the feedback maladjustment of GH-IGF-I-IGFBP-3 axis. He considered that the fact of impaired IGF-I and IGFBP-3 production and the severity of GH resistance seen in cirrhosis likely reflected the effect of injury to the liver, the central organ of the endocrine GH-IGF-IGFBP-3 axis. GH resistance, an increasingly recognized feature related to the reduction of IGF-I, IGF-II and IGFBP-3 in liver dysfunction, may have been further pathogenically effected by the severity of liver dysfunction, disorder of portosystemic shunting and malnutrition of hepatic storage. In addition, the production/secretion of GH receptor was also markedly reduced due to severely damaged hepatocytes, thus leading to the disturbance of feedback maladjustment and GH resistance[14,15].

Table 1 Serum concentrations of IGF-I, IGF-II and IGFBP-3 in patients with liver cirrhosis and healthy subjects

Category	*n*	IGF-I (ng/mL)	IGF-II (ng/mL)	IGFBP-3 (ng/mL)
Cirrhosis	44	66±58[b]	367±193[b]	12±8[b]
Control	38	260±74	1 094±119	39±7

[b]$P<0.001$ *vs* control.

Table 2 Serum concentrations of IGF-I, IGF-II and IGFBP-3 in healthy subjects and patients with different CP scores

Category	*n*	IGF-I (ng/mL)	P^1	IGF-II (ng/mL)	P^1	IGFBP-3(ng/mL)	P^1
Control	38	260±75	0.001	109±119	0.001	39±7	0.001
CP A	15	119±67	0.001	507±185	0.001	19±8	0.001
CP B	19	45±29	0.001	343±154	0.001	10±5	0.001
CP C	10	27±11	0.001	201±115	0.001	6±3	0.001

P^1 represents the statistical comparison in columns between healthy subjects and patients with different Child Pugh scores (A: scored 5-6; B: scored 7-10; C: scored 11-15). $P<0.001$ *vs* between different groups of the same parameter.

Our data confirmed that serum IGF-I, IGF-II and IGFBP-3 levels were significantly lower in patients with liver cirrhosis than those in control group. Circulating concentrations of IGF-I, IGF-II and IGFBP-3 were decreased in patients with liver cirrhosis and apparently correlated with the degree of liver dysfunction. These lines of evidence indicate that impaired hepatic IGF-I, IGF-II and IGFBP-3 levels may be the real potential indicators for evaluation of liver dysfunction and clinical outcome.

Though no significant difference of serum IGF-I and IGFBP-3 was observed between CP B and CP C in our study, serum IGF-II responded comparably lower in patients with CP C than with CP B, confirming that fluctuation of serum IGF-II level remained statistically significant even in patients with severe liver dysfunction assessed by CP score, and the range of serum IGF-II concentrations was much more clearly delineated from normal to excessively low in patients with severe dysfunction than the case for serum IGF-I and IGFBP-3. With regards to the facts above, serum IGF-II concentration could be an important indicator for hepatic dysfunction and clinical prognosis, and was more sensitive and effective than serum IGF-I and IGFBP-3. The assumption was also supported by Nicolic[16], who recently reported that serum IGF-II was lower in patients of cirrhosis than in healthy subjects, and that serum IGF-II was markedly lower in patients with Child-Pugh B/C score (P<0.05). Moreover, he found that serum IGF-II was significantly correlated with IGF-I and CP score (P = 0.007). So Nicolic suggested that single IGF-II determination, a safe, reliable and convenient measurement, may be applicable for the assessment of patients with liver cirrhosis instead of GH stimulated IGF-I generation test and combined measurement of serum IGF-I, IGF-II and IGFBP-3. Other studies showed that both IGF-II and IGF-I were synthesized by hepatocytes, however, specific IGF-II mRNA has been found in hepatocytes, which indicated the impaired serum IGF-II production was the direct effect of decreased liver function, while baseline IGF-I and IGFBP-3 levels were decreased under other circumstances, besides liver dysfunction, such as low serum albumin, malnutrition and glucose metabolic abnormality, most of which are the complications of cirrhosis[17-19].

Our research confirmed that serum concentrations of IGF-I, IGF-II and IGFBP-3 were correlated with CP scores (P<0.001), which is consistent with previous studies[20,21]. Thus, we investigated serum levels of IGF-I, IGF-II and IGFBP-3 that had similar effects on evaluation of hepatic dysfunction and proposed that the combined detection of serum IGF-I, IGF-II and IGFBP-3 effectively predicted functional liver reserve, prognostic and clinical states of the patients. More relation has been found between IGF-I and the degree of portal hypertension and portosystemic shunting compared with the degree of liver function impairment[22,23]. In agreement with our results, IGFBP-3 has been reported suitable to predict liver synthetic capacity, because IGFBP-3 uniquely reflects GH activity, so it is down-regulated during depletion of either GH or its receptor, and diminished even in the presence of rebounded GH concentration[24,25]. Biological functions of IGF-I and IGF-II are modulated by specific high-affinity IGFBP-3. IGFBP-3 level might be less age-dependent than IGF-I level[26-28]. The significance of IGF-II detection has been described above.

Assy *et al*[29]. measured serum levels of IGF-I and IGFBP-3 before and 24 h after a single subcutaneous injection of rhGH (0.14 U/kg bw). IGF-I level below 10 nmol/L was considered indicative of a poor prognosis with 15% survival at one year, whereas above 10 nmol/L indicated a 100% survival rate in 1-2 years. He then concluded that stimulated IGF-I of less than 10 nmol/L might be a true predictor of a negative prognosis in patients with liver cirrhosis. Castilla-Cortazar *et al*[30-32]. obtained similar results in their study.

In our research, all patients were followed up in the liver clinic for a period of 6 months after the measurement, among which 6 patients' levels were below the specific levels (IGF-I <30 ng/mL, IGF-II <200 ng/mL and IGFBP-3 <6 ng/mL), and 5 (83%, 4 in CP C, 1 in CP B) of them died of liver failure or bleeding in less than half a year. It is suggested that hepatic cirrhosis patients with low baseline IGF-I, IGF-II and IGFBP-3 levels have a lower survival rate than those with high levels. In agreement with our result, Assy[12] also speculated that CP score alone could not be regarded as an ideal predictive method for patients with liver cirrhosis.

So, combined evaluation of baseline IGF-I, IGF-II and IGFBP-3 with CP score gives better prediction than CP score alone of patients' liver function. It appears to be a good predictor of survival and an early indicator of liver dysfunction. However, long-term follow-up with multi-center and large sampled studies are expected.

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