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Original Article

Study on Insulin Like Growth Factor-1 As a Marker of Severity of Liver Dysfunction in Patients with Liver Cirrhosis

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Abstract

Background: *Insulin Like Growth Factor-1 (IGF-1) is a polypeptide hormone predominantly synthesized in liver. It has been reported that serum IGF-1 concentrations low in hypopitutuitarism, malnutrition and various diseases particularly in patients with chronic liver disease. The aim of the study was to see the level of IGF-1 in patients with cirrhosis and its relation with severity of liver dysfunction.*

Materials and Methods : *This study was carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. 40 persons (30 patients of cirrhosis of liver and 10 healthy individuals) were selected and grouped as Group-1 : 10 Child grade A patient, Group - 2 : 10 Child grade B patient, Group - 3 : 10 Child grade C cirrhotic patients and Group - 4 : 10 healthy subjects. Patients with recent antiviral therapy, acute illness, hepatocellular carcinoma and spontaneous bacterial peritonitis were excluded from the study. IGF-1 was measured using IMMULITE, DPC, USA which employs automated chemiluminescent immunoassays.*

Results : *Among 30 cirrhotic patients 26 were male and 4 were female. Mean age was 38.83 ± 14.08 years. Etiology of cirrhosis was hepatitis B virus in 23 patient, hepatitis C virus in 1 patient, Cryptogenic in 6 patients. Healthy subjects were hepatitis B and C virus negative with normal liver function test and mean age was 36.40 ± 7.76 years, Mean serum IGF-1 was 82 ± 10.85 ng/ml in Child grade A, 50.77 ± 7.47 ng/ml in Child grade B, 29.69 ± 3.17 ng/ml in Child grade C patients and 130.96 ± 2.43 ng/ml in healthy individuals.*

Conclusion : *Serum level of IGF -1 is low in patients with cirrhosis of liver than healthy individuals and reflects the severity of liver dysfunction in different clinical stage.*

Key words : Insulin like growth factor- 1; Growth hormone; Cirrhosis of liver.

INTRODUCTION

Insulin Like Growth Factor-1 (IGF-1) is a basic single chain, polypeptide hormone of 70 amino acid which have structural and biochemical similarities to human proinsulin[1]. IGF-1 is an anabolic hormone produced in different tissues, although liver account for 90% of the circulating hormone[2]. Synthesis of IGF-1 is regulated by Growth Hormone (GH) Insulin, Thyroxine and nutrition In fact growth hormone is the strongest secretagogue of IGF 1 and it promotes IGF-1 gene transcription in the liver after binding to growth hormone receptor[3].

IGF-1 which mediates the effects of GH and whose production by the liver is stimulated by GH, is reduced in the serum of cirrhotics[3]. The serum level of the major binding proteins are also altered, which may affect the bioavailability of IGF-1[2]. Administration of recombinant growth hormone to patients with cirrhosis results in a rise in IGF-1. Experimentally, IGF-1 prevents testicular changes associated with cirrhosis[1].

Serum IGF-1 levels were found to be very significantly lower in patients with cirrhosis in comparison with healthy individuals[4]. In another study it is found that serum IGF-1 level is decreased in patients with liver cirrhosis. In this study found that serum free IGF-1 level lower than 0.2 ng/L in five patients who died during follow up. Four patients whose serum free IGF-1 above 0.3 ng/L survived. Serum free IGF-1 was significantly reduced in patients with albumin lower than 30 gm/L. So it can predict the prognosis of patients with severe liver disease[5].

Lower levels of IGF-1 were found in patients of Child stage B and C in comparison with Child stage A. The decreased level of IGF-1 is proportional to the deterioration of clinical conditions. The etiology of cirrhosis seems not to influence significantly the levels, at least for the same clinical stage[4].

As the liver is the main site of IGF-1 synthesis the decreased level of the IGF-1 in patients with cirrhosis is belived to be the result of decreased production in the liver. The increased biological degration due to lower binding to its main binding protein, the IGFBP-3 (Also found significantly lower in patients with cirrhosis) is belived to be another important cause[6]. On the other hand, as liver cirrhosis may be characterized as a GH resistant state, the low IGF-1 level could also reflect this resistance[7,8]. IGF-1 level was significantly lower in CLD patients than in age and sex matched healthy controls. IGF-1 significantly decreased with every stage of cirrhosis according to Child's stage criteria and was independent of the aetiology of liver cirrhosis[9].

Malnutrition is frequent in patient with cirrhosis (A severe catabolic illness) and influence significantly the survival. IGF-1 has direct anabolic effect in metabolism of proteins and carbohydrates and it increases the utilization of glucose. Besides IGF-1 and GH have immunoregulatory effect by enhancing TNF-α production by monocytes and macrophages and by modulating natural killer cell actions. It has also been found that IGF-1 may be an important trophic factor for the central nervous system and that it may have strong implication in the restoration of osteopenia and hypogonadism in cirrhosis[4].

IGF-1 level is altered with a direct reaction to the clinical condition and possibly independently from the cause of live cirrhosis. Moreover it seems that IGF-1 could be used as an efficient marker of the functional capacity of the cirrhosis liver.

MATERIALS AND METHODS

This is a prospective comparative study on the level of serum IGF-1 in cirrhosis patients and healthy subjects. This study was done in the Department of Hepatology, Bangbandhu Sheikh Mujib Medical University (BSMMU). For this purpose 40 subjects were selected and grouped as follows:

Group-I: Consisted of 10 Child grade A cirrhosis patients

Group-II: Consisted of 10 Child grade B cirrhosis patients

Group-III: Consisted of 10 Child grade C cirrhosis patients

Group-IV: Control consisted of 10 healthy subjects having HBsAg negativity, anti HCV negativity and normal ALT levels. Each subject was explained clearly about the nature and purpose of this study and informed consent was obtained from all the cases.

Exclusion criteria

i) Recent antiviral therapy (Within 6 months)
ii) Acute viral hepatitis
iii) Drug induced hepatitis
iv) Patients suffering from other illness like TB, HCC, SBP
v) Refusal to follow the study protocol
vi) Any acute illness.

Prior to commencement of this study, protocol was approved by the protocol review committee of the Department of Hepatology and clearance was taken from the ethical committee of BSMMU. The aims and objects of the study along with its procedure, risk and benefits of this study were explained to the patients in easily understandable local language and then informed written consent was taken from each patient. It was assured that all information and records would be kept confidential.

Thirty patients of Cirrhosis (Child A=10, Child B=10, Child C=10) were provisionally selected for the study from the outpatient Department of Hepatology, BSMMU. They were admitted in the hospital. Detailed history of each patient was taken, clinical examination and laboratory investigations were done and records. A present data form was filled for every patients.

Ten healthy subjects were selected for the study from the outpatient Department of Hepatology and voluntary blood donor from the Department of Transfusion Medicine, BSMMU. Detailed history, clinical examination and laboratory investigations were done and recorded. A present data form was also filled for every subjects.

Cirrhosis was diagnosed histopathologically for Child grade A patients. In Child grade B and C patients was diagnosed with endoscopically proven oesophageal varices and ultrasonographic evidence of coarse liver and ascites.

A written consent was taken from the patient before liver biopsy. None of the patients developed any complication following liver biopsy.

With all aseptic precautions 5ml of venous blood was collected from antecubital vein by a disposable plastic syringe, After removal of the needle from the syringe, blood sample were collected in a dry clean glass test tube. It is left for 30 minutes for complete clot formation. After 30 minutes blood was centrifuged and serum was separated and stored in -70^0c in the Department of virology, BSMMU, till the procedure was carried out.

IGF-1 was measured using IMMULITE, DPC, USA, which employs automated chemiluminescent immune assays. Measurement of IGF-1 was done in Immunology Department BSMMU.

Base line investigation including Hb%, ESR, Total count of WBC (TC) Differential count of WBC (DC) Urine R/M/E, Blood sugar, Serum bilirubin, serum albumin, ALT, alkaline phosphatase, prothrombin time, ultrasonography of hepatobiliary system, Chest X-ray P/A view and Endoscopy of the upper GIT was done in all subjects.

Serological markers for hepatotropic virus including HBsAg and anti HCV were done in all subjects.

RESULTS

This prospective case control study was done to evaluate serum IGF-1 level in cirrhotic patients in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka. The study population was divided into four separate group of equal number of patients and controls.

Serum IGF-1 level were determined in all patients and healthy controls by chemiluminescent immune assay using kit (Diagnostic product corporation, Immulite IGF-1, USA). It has an analytical sensitivity of 20 ng/ml.

Table I : Base line clinical data of cirrhotic patients at enrollment in the study (n=30)

Variables	Results
Age (Yrs) Mean ± SD	38.83 ± 14.08
Sex	
Male	26
Female	4
Etiology of cirrhosis	
Hepatitis B	23
Hepatitis C	1
Cryptogentic	6
Alcoholism	0
Healthy subjects (Group-IV). n=10	
Age (Yrs) Mean ± SD	36.40 ± 7.76
Hepatitis B	0
Hepatitis C	0
Alcoholism	0

Table II : Biochemical profile of cirrhotic patients enrolled in the study (n=30)

Variables	Results
Albumin (gm/l)	31.94 ± 9.28
ALT (u/l)	54.83 ± 34.87
PT (secs)	18.20 ± 5.26
Bilirubin (µmol/l)	31.67 ± 26.25
Alkaline phosphatase	142.10 ± 95.19
Random Blood Sugar (mmol/l)	5.70 ± 1.44

Table III : Biochemical profile of Child grade A patients (Group-I), n=10

Variables	Results
Albumin (gm/l)	41 ± 6.12
ALT (u/l)	54.03 ± 21.09
PT (secs)	14.58 ± 1.38
Bilirubin (µmol/l)	27.79 ± 34.47
Alkaline phosphatase	103.80 ± 72.69
Random Blood Sugar (mmol/l)	5.22 ± 1.21

Table IV : Biochemical profile of Child grade B patients (Group-II) n=10

Variables	Results
Albumin (gm/l)	31 ± 6.32
ALT (u/l)	86.60 ± 39.14
PT (secs)	17.13 ± 1.95
Bilirubin (µmol/l)	28.88 ± 16.77
Alkaline phosphatase	162.90 ± 115.09
Random Blood Sugar (mmol/l)	5.51 ± 1.41

Table V : Biochemical profile of Child grade C patients (Group-III) n=10

Variables	Results
Albumin (gm/l)	23.82 ± 5.89
ALT (u/l)	50.92 ± 35.73
PT (secs)	22.90 ± 6.56
Bilirubin (µmol/l)	38.36 ± 25.98
Alkaline phosphatase	159.60 ± 90.64
Random Blood Sugar (mmol/l)	6.44 ± 1.56

Table VI : Average age, sex, and result of IGF-1 in cirrhotic patients and control group (n=40)

Variables	Cirrhotics	Control
Respondents	30	10
Sex		
Male	26	10
Female	4	0
Age (Yrs) (M ± SEM)	38.83 ± 2.57	36.40 ± 7.76 (p = 0.608)
IGF-1 (ng/ml)		
(M ± SEM)	49.42 ± 5.23	103.96 ± 19.93 (p = 0.001)

Table VII : Characteristics and result of IGF-1 in Cirrhotic patients classified as Child A, B and C (n=30)

Variables	Grade A	Grade B	Grade C
Respondents	10	10	10
Age (yrs)			
(M ± SEM)	35.40 ± 4.19	39.30 ± 4.62	41.80 ± 4.75 (p=0.608)
IGF-1 (ng/ml)			
(M ± SEM)	67.82 ± 10.85	50.77 ± 7.47	29.69 ± 3.17 (p=0.01)

Table VIII : Characteristics and results of IGF-1 level in cirrhotic patients classified as Child A depending on the cause of cirrhosis

Variables	Hepatitis B	Cryptogenic
Respondents	6	4
Sex		
Male	5	2
Female	1	2
Age (Yrs)		
(M ± SEM)	34.66 ± 5.25	36.50 ± 7.88 (p=0.804)
IGF-1 (ng/ml)		
(M ± SEM)	82.23 ± 13.77	46.20 ± 12.25 (p=0.106)

Table IX : Correlation of IGF-1 with albumin & prothombin time in Child grade A, B and C patients

	Parameter	Child A Mean ± SD	Child B Mean ± SD	Child C Mean ± SD
IGF-1 vs Albumin	IGF-1 (ng/ml	67.82 ± 34.33	50.77 ± 23.62	29.69 ± 10.05
	Albumin (gm/l)	41.00 ± 6.1	31.00 ± 6.32	23.82 ± 5.89
IGF-1 vs PT	IGF-1 (ng/ml)	67.82 ± 34.33	50.77 ± 23.62	29.69 ± 10.05
	PT (secs)	14.58 ± 1.38	17.13 ± 1.95	22.90 ± 6.56
		r value 0.377* & -0.004*	r value -0.333* & 0.150*	r value -0.276* & -0.019*
		p value 0.282 & 0.992	p value 0.347 & 0.678	p value 0.439 & 0.958

DISCUSSION

The IGF-1 is a single chain peptide with structure similar to proinsulin[1]. IGF-1 level rises after birth, probably as a result of increased GH secretin. IGF-1 is produced in a variety of organs and tissues, but the liver is the major source of circulating IGF-1[10, 11]. Several studies showed that partial hepatectomy or liver disease results in low circulating IGF-1 activity[12,13].

The pathophysiology of metabolic complications of cirrhosis (i.e insulin resistance, wasting of skeletal muscle, osteodystrophy) is poorly understood. The lack of unknown factor "Liver factor" that acts on peripheral tissues has been hypothesized[14]. Nimer et al showed that baseline IGF-1 levels were significantly lower in patients with cirrhosis than in controls, but no differences in patients groups. This study also showed that, IGF-1 generation after rnGH administration, significantly increased in healthy controls, while no change occurred in cirrhosis patients. As a result, they established IGF-1 as a possible marker for liver functional reserve in patients with liver cirrhosis[15].

Study conducted by Taeke F et al measured the serum IGF-1 level in 05 subjects. In which normal subjects (n=12) mean IGF-1 level was 132 ng/ml. in child A cirrhosis IGF-1 level was 82 ng/ml, Child B cirrhosis IGF-1 level was 58 ng/ml, Child C cirrhosis IGF-1 level was 29 ng/ml. So the study suggest that IGH-1 level is correlated with liver function in accordance with their clinical stage[9].

Study conducted by Moller S et al measured ALS, IGF-1, IGFBP-3 in 25 patients with cirrhosis and in 30 healthy controls. In which mean IGF-1 concentration was 66.8 ng/ml in cirrhotic patients and 128.2 ng/ml in healthy controls. As we know in circulation IGF-1 is bound to IGFBP-3 and ALS. In which IGFBP-3 and ALS were significantly reduced in cirrhotic patients in comparison to healthy controls[1].

Another study conducted by Vyzantiadis T et al estimated IGF-1 level in 40 cirrhotic (Child A=26, Child B and C = 14) patients whose level was 57.4 ± 7.0 ng/ml and in 20 healthy controls whose level was 198.8 ± 16.3 ng/ml. but in Child grade A the IGF-1 level was 72.8 ± 9.3 ng/ml and in Child grade B and C was 28.9 ± 3.0 ng/ml[4].

In our study, serum IGF-1 level were found to be very significantly lower in patients with cirrhosis in comparison with the group of healthy individuals p = 0.001 (Table VI). Also, significantly lower levels were found in patients of Child grade B and C in comparison with Child grade A p = 0.01 (Table VII). The above findings show that the decrease of IGF-1 level is proportional to degree of deterioration of clinical condition. The aetiology of cirrhosis seems not to influence significantly the levels, at least for the same clinical stage p=0.106 (Table VIII).

Present study also shows that, in Child grade A patients, the mean albunin level was 41 ng/ml which was within normal limit but the IGF-1 level was 67.82 ng/ml which was much lower than the normal level (Table IX). So it may be predicted that IGF-1 is more sensitive marker than serum albumin level. Moreover IGF-1 level did not correlate with albumin level r=0.377. IGF-1 level also did not correlate with prothrombin time. r = -0.004 (Table IX). Similar observation was also seen in Child B & Child C patients (Table IX).

So the results of this study are comparable with other studies done earlier. Results of all studies are almost similar.

As the liver is the main site of IGF-1 synthesis, the decreased levels of the IGF-1 in patients with cirrhosis is believed to be result of decreased hepatic production. This study shows that IGF-1 levels are altered with a direct relationship to the clinical condition and possibly independently from the cause of liver cirrhosis. Moreover, it seems that IGF-1 could be used as an efficient marker of the functional capacity of the cirrhotic liver.

CONCLUSIONS

Cirrhosis is a common medical problem in our country. It is one of the leading cause of death in Bangladesh. Sequele of cirrhosis progress to hepatic failure and hepatocelular carcinoma leading to death. Serum IGF-1 level can be used as a good marker for cirrhotic patients. This study was designed to estimate the IGF-1 level in cirrhotic patients and healthy controls and its correlation with Child Pugh class, marker of hepatic function and serum level in cirrhotic patients according to the Child classification.

So from the findings of this study it can be concluded that, IGF-1 synthesis is decreased in liver cirrhosis and reflects the severity of the clinical stage. It represents a good marker of hepatic function. The etiology of cirrhosis does not seem to influence its level.

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DISCLOSURE

All the authors declared no competing interest.

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