A Comparison of Circulating and Regional Growth Hormone-Binding Protein in Cirrhosis

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The growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis is disturbed in cirrhosis, with elevated basal GH and low IGF-I levels relating to liver function and prognosis. In plasma, GH is bound to a high-affinity GH-binding protein (GHBP), which has been found to be slightly reduced in cirrhosis, but with huge variations. GHBP is identical to the extracellular part of the hepatic GH receptor, but other tissues may contribute to the circulating GHBP levels. The aim was therefore to measure circulating and regional concentrations of GHBP in relationship to hepatic function and body composition in patients with cirrhosis (n = 38) and controls with normal liver function (n = 29). Blood samples from the hepatic, renal, and femoral veins and the femoral artery were collected simultaneously during a hemodynamic investigation. Plasma GHBP was directly measured by a specific and sensitive fluoroimmunoassay. Circulating GHBP levels were identical in the patients and controls (mean ± SD) 1.03 ± 0.56 nmol/L and 1.02 ± 0.55 nmol/L, respectively (not significant). We found no significant hepatic, renal, or peripheral arteriovenous extractions or generations of GHBP, and it did not significantly correlate to liver function. In the controls, GHBP correlated significantly with body mass index (BMI) ($r = .60$, $P < .005$), whereas this relationship was not found in the patients with cirrhosis. In conclusion, high-affinity GHBP appears to be normal in patients with cirrhosis, with no significant hepatic generation or renal extraction and no association with the severity of the liver disease. Thus, our study supports the hypothesis that tissues other than the liver, despite its abundant GH receptors, may contribute to the circulating GHBP.

PATIENTS WITH CIRRHOSIS exhibit characteristic alterations in the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis.[1-3] These changes include elevated circulating concentrations of basal and pharmacologically-stimulated GH and suppressed serum IGF-I.[4-8] The principal IGF-I binding protein, IGF-binding protein-3 (IGFBP-3), and the acid-labile subunit of the IGF-IGFBP-3-complex (ALS) are comparably reduced with significant relationships to hepatic function and prognosis.[6,7,9-11] GH acts on GH receptors in the liver and other tissues and induces important anabolic actions.[12,13] In the circulation, GH is partially bound to growth hormone-binding protein (GHBP), which, in amino acid sequence, is identical to the external part of the GH receptor.[14] Previous studies of GHBP in patients with cirrhosis have shown a slightly reduced relative binding capacity compared with that in controls, but with large variations in the cirrhotic patients.[15-18] But, in most studies, GHBP has been indirectly determined as the GH-binding capacity. In some studies, significant associations have been reported with hepatic function.[16,19,20] The aims of the present study were to directly measure GHBP levels in different vascular beds, hepatic production, and renal extraction in patients with cirrhosis and in controls in relationship to liver function and body composition using an assay specific for the high-affinity GHBP.

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MATERIALS AND METHODS

Study Population

The study population consisted of 38 patients (30 men, 8 women) with histologically verified cirrhosis. Twenty-eight patients had a history of alcohol abuse, ie, a consumption exceeding 50 g/d for more than 5 years. All had abstained from alcohol for at least 1 week before the study, and none had withdrawal symptoms. Ten patients had nonalcoholic cirrhosis classified as either posthepatitic or cryptogenic. According to the modified Child-Turcotte classification,[21] 11 patients belonged to class A, 14 to class B, and 13 to class C. Sixteen of the patients with ascites were treated with diuretics and were put on a sodium-restricted diet of 40 mmol/d. Ultrasonography or paracentesis confirmed the presence of mild or moderate ascites. None of the patients had hepatic encephalopathy above grade I or had experienced recent gastrointestinal bleeding. All patients and control subjects underwent a hemodynamic investigation to assess the degree of portal hypertension. The clinical and biochemical characteristics of the patients are summarized in Table 1.

The control group consisted of 29 patients with normal liver function. They underwent a hemodynamic investigation to exclude renovascular hypertension or intestinal ischemia. None of these diagnoses were confirmed in any of the controls entered in the study. Patients and controls participated after giving their informed consent according to the Helsinki II Declaration, and the study was approved by the Ethics Committee for Medical Research in Copenhagen (V.100.2086/99). No complications or side effects were encountered during the study.

Catheterization

The patients and controls underwent the procedure in the morning after an overnight fast and at least 1 hour resting in the supine position. Catheterization of hepatic and renal veins and femoral artery was performed as described elsewhere.[22] Under local anaesthesia, a Cournand or Swan-Ganz catheter, size 7-F, was guided to the localizations via the femoral route under fluoroscopic control. Pressures were measured directly by a capacitance transducer (Simonsen & Weel, Copenhagen, Denmark). Hepatic blood flow (HBF) was determined by the indocyanine green (ICG) constant infusion technique. ICG clearance was measured as the infusion rate divided by the arterial plasma concentration of ICG. The galactose elimination capacity (GEC), an

estimate of the functional hepatocyte mass, was determined after infusion of 0.5 g of galactose per kilogram body weight.

Body Composition

The percentages of lean body mass and fat body mass were measured by dual-energy x-ray absorptiometry (DXA) in 11 fasting patients in the supine position. A Norland XR 36 (Nordland Medical Systems, Fort Atkinson, WI) whole-body x-ray densitometer was used. The instrument uses a rectilinear scanner, which runs at medium speed to detect the density differences in the subject lying on the scan table. Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$.

Blood Sampling

Serum concentrations of albumin, bilirubin, aspartate aminotransferase, alkaline phosphatases, coagulation factors II, VII, and X, creatinine, sodium, and potassium were determined by routine methods in an autoanalyzer (SMAC, Technicon Instruments, Tarrytown, NY). Blood samples (10 mL) were collected simultaneously from the hepatic vein/femoral artery and renal vein/femoral artery discharging blood from the catheter dead space. The samples were centrifuged immediately at 4°C, and the plasma was stored at -25°C until assayed for GHBP.

The extraction ratios of GHBP from the liver, kidney, and femoral bed were calculated as (arterial concentration-venous concentration)/arterial concentration.

Assays

GHBP was determined by an in-house time-resolved fluroroimmunoassay (GHBP TR-FIA). Plates from a commercially available immunoassay for GH, (Wallac Oy, Turku, Finland)[23] were used. In brief, GH was added in an amount large enough to saturate GHBP thus, making it possible to catch the complex with the immobilized monoclonal antibody against GH on the precoated plates. Europium-labeled antibody against GHBP (Mab 263, Amgen, Brisbane, Australia) was then added. The calibration curve was prepared by dilution of recombinant fully glycosylated GHBP dissolved in fetal calf serum. The intra-assay coefficient of variation was 3.44% (n = 42). The interassay coefficients of variation were 6.3% and 12%, at 1.4 nmol/L and 0.56 nmol/L, respectively. The detection limit of the assay was 0.04 nmol/L. The detection limit of arteriovenous concentration difference was: at a plasma level of 1.00 nmol/L, SD of GHBP in artery (C_a) and vein (C_v) was 0.0344 nmol/L. Hence, SD of (C_a-C_v) is $\ddot{O}(0.0344^2 + 0.0344^2) = 0.0486$ nmol/L and $t_{n-1,P<.05} \cdot SEM = (SD\sqrt{n}) \cdot t_{n-1,P<.05} = 0.033$, 0.019, and 0.018 nmol/L for n = 11, 27, and 29, respectively. Thus, the detection limit of mean arteriovenous extraction, based on analytical error of GHBP is 1.8% to 3.3%. Validation of the TR-FIA assay with a previously developed immunofunctional assay for direct determination of GHBP has shown a direct and significant correlation ($r = .89$, $P = .001$) throughout the normal range of GHBP.[23]

Plasma GH concentrations were determined by an immonoflourometric assay (TR-IFMA, Delfia, Wallac, Finland). At GH concentrations of 0.23 ng/mL and 2.98 ng/mL, the intra-assay coefficients of variation were 3.0% and 2.3% and the interassay coefficients of variation 2.4% and 1.3%, respectively. The detection limit was 0.01 ng/mL.

IGF-related parameters were determined at the Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, and values of the control group have recently been reported.[24] The normal range of IGF-I and IGFBP-3 for healthy adults has also been reported.[25]

Statistics

The results are given as mean and standard deviations. The Mann-Whitney test was used to compare differences between patients and controls. The Wilcoxon test for paired data was used to analyze differences in the concentrations of different vascular beds. Correlations were performed with the Spearman rank correlation test. The 2-tailed significance level of the type I error was fixed at 5%.

RESULTS

The characteristics of the patients with cirrhosis are shown in Table 1. The circulating concentrations of GHBP in 38 patients with cirrhosis were 1.03 ± 0.56 nmol/L versus 1.02 ± 0.55 nmol/L in the controls (not significant [NS]), see Fig 1.

The hepatic venous and arterial concentrations and extractions of GHBP and GH are shown in Table 2. There was no significant hepatic, renal, or peripheral femoral extraction or generation of GHBP in the patients with cirrhosis (Tables 2 and 3, $P = .1$). Circulating and hepatic venous single sample concentrations of GH were significantly higher in the cirrhotic patients than in the controls (Tables 1 and 2, $P < .005$), and the hepatic extraction of GH was significantly lower in the cirrhotic patients than in the controls (Table 2, $P < .005$). The hepatic extraction of GH correlated negatively with the Child-Turcotte score and serum aspartate aminotransferase ($r = -.40$ and $r = -.44$, respectively, $P < .05$). There was a slight renal extraction of GH (Table 3, $P < .01$), but no significant extraction in the femoral bed in the cirrhotic patients.

We found no significant correlations of circulating GHBP on the one hand and indicators of hepatic dysfunction on the other, including Child-Turcotte score ($r = .16$, NS), GEC ($r = -.43$, $P = .08$), or ICG clearance ($r = -.15$, NS). GHBP did not correlate with GH-dependent parameters, such as IGF-I ($r = -.20$, NS), IGFBP-3 ($r = .03$, NS), ALS ($r = -.06$, NS), and GH ($r = -.05$, NS). Neither did we find any significant difference in hepatic or circulating GHBP with respect to etiology of the liver disease.

In the patients with cirrhosis, we found no significant differences with respect to BMI between Child classes A, B, and C. There were no significant relationships between GHBP and BMI within each Child class or in the total patient population ($r = .22$, NS). Nor were we able to detect a significant relationship between GHBP and lean body mass and fat body mass in the cirrhotic patients, whereas there was a significant correlation between BMI and GHBP in the controls ($r = .60$, $P < .005$, Fig 2).

DISCUSSION

The main finding of the present study is that levels of circulating GHBP in patients with cirrhosis are not significantly altered from normal levels. Furthermore, GHBP levels did not predict the degree of liver dysfunction or body composition in cirrhotic patients. Finally, we were not able to demonstrate any significant hepatic, renal, or peripheral arterial-venous gradients of GHBP.

GH is secreted by the anterior pituitary gland in a pulsatile fashion regulated by GH-releasing hormone and somatostatin.[26] Circulating GH stimulates GH-sensitive tissues to produce IGF-I by the activation of the GH receptor.[12,13] In plasma, GH is bound partially to the high-affinity GHBP, which has been shown to correspond to the extracellular part of the hepatic GH receptor.[13,27,28] It is believed that plasma GHBP is produced by proteolytic cleavage of the extracellular domain of

Table 1. Clinical and Biochemical Characteristics of 38 Patients With Cirrhosis and 29 Controls

	Cirrhotic Patients (n = 38)	Controls (n = 29)
Patient characteristics		
Height (cm)	171 ± 7	169 ± 9
Weight (kg)	71.4 ± 16.2	68.5 ± 19.1
BMI (kg/m^2)	24.1 ± 4.5	23.6 ± 5.7
Age (yr)	53.9 ± 9.7	65.5 ± 11.9
Child class (A/B/C)	11/14/13	—
Ascites (yes/no)	16/22	0/29
Hepatic venous pressure gradient (mm Hg <5)*	15.3 ± 5.4†	2.4 ± 0.9
Hepatic blood flow (L/min; 0.5-2.3)	1.13 ± 0.49	1.01 ± 0.29
Hepatic plasma flow (L/min; 0.3-1.4)	0.78 ± 0.34	0.58 ± 0.12
ICG clearance (L/min; 0.30-0.70)	0.30 ± 0.13†	0.42 ± 0.10
Total lean mass (kg)	47.76 ± 6.94	—
Total fat mass (kg)	21.15 ± 9.45	—
Blood biochemistry		
Serum aspartate aminotransferase (U/L; 10-40)	54 ± 28‡	24 ± 12
Serum bilirubin (μmol/L; 2-17)	36 ± 35‡	7 ± 2
Serum alkaline phosphatases (U/L; 50-275)	352 ± 220‡	194 ± 54
Plasma coagulation factors II, VII, and X (U; 0.70-1.30)	0.58 ± 0.22‡	1.13 ± 0.16
Serum albumin (μmol/L; 540-800)	472 ± 80†	617 ± 68
Serum creatinine (μmol/L; 49-121)	82 ± 38	101 ± 37
Serum sodium (mmol/L; 136-146)	136 ± 4	140 ± 3
Plasma IGF-I (μg/L)	63.6 ± 39.3†	129 ± 56
Plasma ALS (μg/mL)	4.88 ± 3.0†	15.4 ± 5.5
Plasma IGFBP-3 (μg/L)	1177 ± 688†	2422 ± 790
Plasma GH (ng/mL)	1.49 ± 1.91†	0.91 ± 1.74

NOTE. Mean ± SD.
*Reference intervals in parentheses.
†$P < .005$.
‡$P < .05$.

the GH receptor.[13] Animal studies have shown that serum concentrations of GHBP are positively correlated with the number of hepatic GH receptors,[29] and that increasing concentrations of GHBP may modulate the binding of GH to its receptor and thus exert a negative effect on receptor recycling and synthesis.[30] The average concentration of GHBP in human serum is about 1 nmol/L, but with wide variations according to, for instance, metabolic states and variations in GH concentrations.[15,28]

Circulating GHBP in cirrhosis has been investigated in earlier studies. Most of the published studies favor slightly reduced GHBP levels in patients with cirrhosis as compared with controls.[16,17,19,20] Thus, in the study of Baruch et al,[16] circulating GHBP was reduced by 14% to 36% in cirrhotic patients.

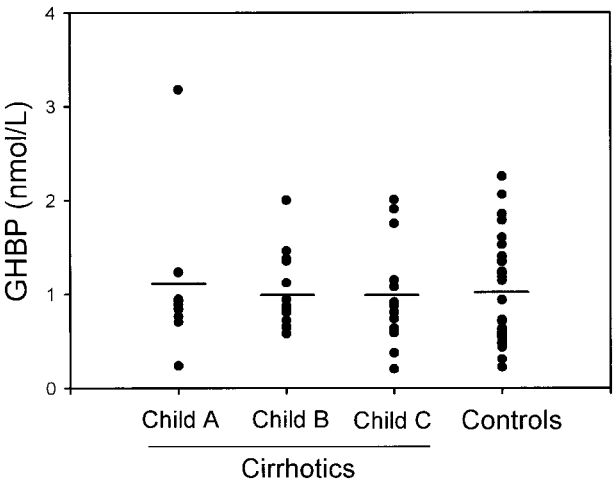

Fig 1. Circulating (arterial) concentrations of GHBP in patients with cirrhosis (n = 38) divided according to the modified Child-Turcotte classification (Child class A (n = 11); Child class B (n = 14); Child class C (n = 13)) and in controls with normal liver function (n = 29). GHBP in patients with cirrhosis was 1.03 ± 0.56 nmol/L (mean ± SD) *v* 1.02 ± 0.55 nmol/L in the controls (NS). There was no significant difference in GHBP between Child classes A, B, and C.

Table 2. Hepatic and Femoral Arterial GHBP and GH Plasma Concentrations and Extractions in Patients With Cirrhosis and Controls

	Cirrhotic Patients (n = 27)	Controls (n = 29)
GHBP		
Hepatic vein (nmol/L)	0.94 ± 0.49	1.03 ± 0.55
Femoral artery (nmol/L)	0.98 ± 0.47	1.02 ± 0.55
Hepatic extraction ratio (%)	4.3 ± 19.4	−1.4 ± 7.4
GH		
Hepatic vein (ng/mL)	1.31 ± 1.27*	0.71 ± 1.63
Femoral artery (ng/mL)	1.40 ± 1.27*†	0.91 ± 1.74†
Hepatic extraction ratio (%)	9.4 ± 12.8†‡	30.3 ± 21.1‡

NOTE. Mean ± SD.
*Significantly different from controls, $P < .005$.
†Significantly different from venous values, $P < .005$.
‡Significantly different from 0, $P < .005$.

Table 3. Renal, Femoral Venous, and Femoral Arterial Plasma GHBP Concentrations and Extractions in Eleven Patients With Cirrhosis

	GHBP (nmol/L)	GH (ng/mL)
Renal vein	0.92 ± 0.51	1.44 ± 1.03
Femoral artery	0.96 ± 0.52	1.49 ± 0.99
Renal extraction ratio (%)	6.8 ± 13.2	8.4 ± 14.7*
Femoral vein	1.20 ± 0.71	1.70 ± 2.96
Femoral artery	1.16 ± 0.76	1.71 ± 3.04
Femoral extraction ratio (%)	−8.1 ± 20.3	−6.6 ± 29.7

NOTE. Mean ± SD.
*Significantly different from 0, $P < .05$.

Moreover, significant correlations of GHBP have been found in relationship to the Pugh score, serum bilirubin, and serum albumin. Comparable results have been reported by Hattori et al.[19] In their study, GHBP was reduced by 28% in patients with cirrhosis as compared with controls. In that study, the investigators demonstrated a direct correlation between GHBP on the one hand and IGF-I and coagulation factors on the other. In a recent study by Assy et al,[18] a similar association between GHBP and IGF-I and IGFBP-3 has been reported. In our study, we were unable to detect any significant differences in the circulating level of GHBP of patients with cirrhosis and controls. We believe some of these differences could be ascribed to the use of different assays. GHBP levels were estimated as GH binding activities in most of the previously published studies.[19,20,31,32] Several of these assays are sensitive to endogenous GH, so mathematical corrections must be made after assaying procedures to abolish the influence of endogenous GH. As basal GH levels are increased in cirrhosis, it cannot be ruled out that artificially low levels of GHBP have been estimated using binding assays, despite mathematical correction. In addition, most assays used to determine GH binding activities, to some degree, also detect the low-affinity GH binding protein, which is not related to the GH-receptor. It has been suggested that the low-affinity GH binding protein is a truncated alpha-2-macroglobulin.[33] Therefore, variations in GH-binding activities may reflect variations in the low-affinity GH-binding protein as well. It is important to specify what is measured by the current assay. In some conditions, the choice between a direct and an indirect assay is less critical. In cirrhotic patients, specific determination of the high-affinity GH-receptor–related GHBP should be preferred beyond the binding activity assays because of the possible influence of low-affinity binding proteins and because of the risk of influence of GH, the levels of which may be elevated in cirrhotic patients. Another reason for the discrepant results could be explained by the heterogeneity of the study populations with respect to severity and etiology of the liver disease. However, in our study, 13 of the cirrhotic patients belonged to the Child-Turcotte class C group, and their GHBP values were not significantly lower than those of patients with less advanced disease. Unlike some studies, we were not able to confirm a significant relationship between GHBP and either of the reported indicators of liver function, IGF-I, or IGFBP-3. However, we confirmed a direct, significant correlation between GHBP and BMI in the controls, a relationship that is well-known,[23,34] but this relationship was not found in the cirrhotic patients. Typically, BMI correlates to fat mass, but in our cirrhotic patients, the presence of fluid retention may weaken this relationship[35] and explain why we did not find any relationship between BMI and levels of GHBP.

GH receptors are present in a variety of cells, including hepatocytes.[12,30,36] The liver is thought to be the most abundant source of circulating GHBP, and animal studies have suggested that serum GHBP levels are positively correlated with the number of hepatic GH receptors.[30,37,38] In a recent experimental study, partial hepatectomy of adult rats decreased the GHBP levels, which subsequently returned to baseline level along with the regeneration of the liver.[29] The results of that study indicate that the liver, at least in rats, plays an important role in the determination of the serum GHBP levels. In our study, however, we found no significant differences between hepatic venous GHBP and the systemic level when measured simultaneously in the femoral artery, and hence no evidence of hepatic overflow of GHBP. Likewise, we found a trend towards a small

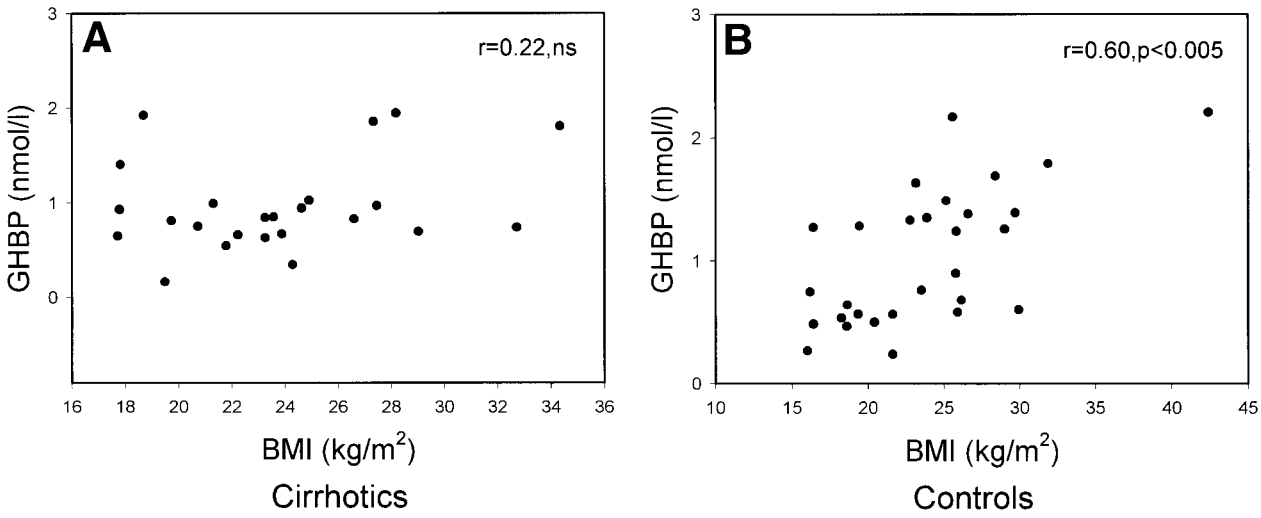

Fig 2. (A) Relationship between GHBP and BMI in patients with cirrhosis ($r = .22$, NS) and (B) controls ($r = .60$, $P < .005$).

renal extraction, which also did not reach significance. The absence of any detectable hepatic generation of GHBP could be due to (1) simultaneous release and degradation in the liver, (2) low local clearance of GHBP ($t_{½}$ of GHBP approximately 1 hour), and (3) immunoreactivity to degradation products.[39] Owing to statistical variation, a small hepatic release (up to 3.3%) cannot be excluded. With the hepatic plasma flow of 0.78 L/min, this corresponds to 0.98 nmol/L · 0.78 L/min · 0.033 = 0.025 nmol/min. $T_{½}$ of GHBP is approximately 60 minutes, and if it is assumed that V_D equals 6 L, the overall plasma clearance estimate of GHBP is $(D_D/t_{½}) \cdot \ln 2 = 70$ mL/min. Hepatic production corresponds in the present study (steady state) to up to (0.025 nmol/min)/0.98 nmol/L = 26 mL/min, which means that the majority of circulating GHBP is likely to have a nonhepatic origin. There are so far no in vivo studies to suggest that the liver is the only source of GHBP. In contrast, there are in vitro studies that demonstrate that several tissues contribute to the soluble GHBP.[40] Our data add to the hypothesis that peripheral tissues also play a role for the circulating GHBP.[35] A trend towards peripheral contribution to the circulating GHBP was suggested by a borderline significant generation of GHBP of 8% from the femoral venous area in these patients. Future studies should include measurement of GH receptors in peripheral tissues to examine the relationship between circulating GHBP and receptor density in these tissues.

In conclusion, we did not find GH receptor-derived circulating GHBP reduced or related to liver function in patients with cirrhosis. The results support the hypothesis that extrahepatic tissues may contribute to the generation of circulating high-affinity GHBP. Because our findings are in contrast to previous reports, further investigation should clarify the tissue origin of circulating GHBP.

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