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ORIGINAL ARTICLE

Circulating fibroblast growth factor 21 in patients with liver cirrhosis

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Abstract Fibroblast growth factor 21 (FGF21) is an adipokine and hepatokine, and its hepatic expression is induced in the injured liver. Adiponectin, whose systemic levels are positively correlated with measures of hepatic injury in patients with liver cirrhosis, is a downstream effector of FGF21. The aim of the present study was to identify possible associations of serum FGF21 with measures of liver function in patients with liver cirrhosis. FGF21 was determined by ELISA in serum of 42 patients. FGF21 was not linked to disease severity assessed by the Child–Pugh and MELD score. Levels were not changed in those patients with varices and/or ascites. Systemic FGF21 did not correlate with markers of liver and kidney function, inflammatory proteins or adipokines like adiponectin. Levels in hepatic and portal vein of 37 patients were also measured, but there was no transhepatic FGF21 gradient. Three months after insertion of a transjugular intrahepatic shunt hepatic venous pressure gradient was markedly improved, while FGF21 in serum of these 13 patients was not changed. The present study shows that hepatic release and systemic FGF21 are not linked to measures of liver function in patients with liver cirrhosis.

Keywords Adiponectin · Ascites · Portal vein · Child–Pugh

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Introduction

Liver cirrhosis is a serious disease with high mortality in patients with decompensation and secondary complications which are mostly esophageal varices, ascites and hepatic encephalopathy. Furthermore, patients with liver cirrhosis often develop insulin resistance [1–4]. Insulin resistance in cirrhotic patients is associated with the progression of fibrosis and portal hypertension [5, 6].

The adipokine adiponectin exerts pleiotropic protective effects in metabolism and protects from insulin resistance and liver injury. In obesity, circulating adiponectin is reduced and lower levels contribute to metabolic diseases and disturbed glucose homeostasis. Adiponectin ameliorates hepatic steatosis, inflammation and fibrosis and further protects hepatocytes from cell death [7, 8].

Unexpectedly, adiponectin serum levels are increased in patients with liver cirrhosis. In these cohorts, positive correlations of systemic adiponectin with Child–Pugh and MELD scores have been described [9–13].

Systemic levels of adiponectin are regulated by its production in adipose tissues suggesting that synthesis is induced in cirrhotic patients [14]. The liver is the main organ for adiponectin excretion, and impaired liver function in patients with liver cirrhosis may further contribute to raised adiponectin serum levels [14]. Comparable adiponectin concentrations in systemic, hepatic vein and portal vein blood argue against an impaired hepatic elimination of adiponectin in these patients [12, 15]. Nevertheless, one study describes a lower hepatic clearance rate in patients with decompensated liver cirrhosis, indicating that impaired excretion may contribute to increased systemic adiponectin at least in patients with advanced disease [16].

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Transjugular intrahepatic portosystemic shunts (TIPS) lower portal pressure. This intervention is further associated with gain of body cell and muscle mass [17, 18]. Of note, 6 months after TIPS, serum adiponectin is induced by about 60% [19]. Higher adiponectin may reflect an improved function of adipose tissues and/or altered hepatic elimination.

Fibroblast growth factor 21 (FGF21) is abundantly expressed in the liver and is also released from adipose tissues, skeletal muscle and other organs [20, 21]. Injection of FGF21 improves insulin response, liver steatosis and lowers systemic glucose in diet-induced obese mice [22]. In white fat tissues, FGF21 stimulates browning and thereby enhances energy expenditure [23]. FGF21 further induces white adipose tissue and circulating adiponectin, and the metabolic effects of FGF21 are mediated by adiponectin [24].

In murine liver, FGF21 is induced in response to the hepatotoxic chemicals diethylnitrosamine and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [25, 26]. Strong hepatic upregulation of FGF21 has been reported in mice fed a methionine choline-deficient diet to induce non-alcoholic steatohepatitis (NASH) and mice deficient in genes like p53 prone to hepatocarcinogenesis [26, 27]. In patients with fatty degeneration, hepatitis, liver cirrhosis and liver cancer, hepatocyte FGF21 is increased compared to cells residing in the healthy liver [26]. Serum FGF21 in mice positively correlates with its hepatic expression [26]. Systemic FGF21 may, therefore, become a useful biomarker for noninvasive diagnosis of liver injury.

The aim of the present study was to evaluate whether serum FGF21 is associated with stages of liver disease and its complications in patients with liver cirrhosis. FGF21 was also measured in systemic, hepatic and portal vein blood to identify possible variations in these different compartments.

Materials and methods

Transjugular intrahepatic portosystemic shunt (TIPS)

Forty-two patients with liver cirrhosis were enrolled in the study. Etiology of liver disease was alcoholic in 37 patients, hepatitis C infection in two patients and of other reasons in three patients. Patients were electively treated by TIPS implantation. Complications of liver cirrhosis were variceal bleeding (14 patients), hepatorenal syndrome (1 patient), refractory ascites (26 patients) and other reasons (1 patient). TIPS (Viatorr-Stent, Putzbrunn, Germany) was inserted as described [28]. During stent implantation, samples of one of the hepatic veins (HVS) which was not drained by the TIPS stent, of the portal vein (PVS) and of a peripheral vein (SVS) were obtained. Patient samples analyzed herein have been completely/partly used in previous studies [15, 29–33].

Routine laboratory parameters such as alanine aminotransferase and aspartate aminotransferase were measured by the local Institute for Clinical Chemistry and Laboratory Medicine. The study complies with the Declaration of Helsinki. All patients gave written informed consent, and the study was approved by the Ethical Committee of the University Hospital of Regensburg.

ELISA

FGF21 ELISA was from R&D Systems (Wiesbaden, Nordenstadt, Germany). Serum was diluted 20-fold for FGF21 analysis.

Statistics

Data are shown as median and range of the values (IBM SPSS Statistics 21.0). Statistical differences were analyzed by two-tailed Mann–Whitney *U* test (IBM SPSS Statistics 19.0). Paired data were analyzed by *t* test (MS Excel). Spearman's correlation was calculated using the IBM SPSS Statistics 21.0 software. A p value of <0.05 was regarded as significant. Data are displayed as box plots (median, lower and upper quartiles and range of the values are illustrated).

Results

Association of FGF21 with gender, age, blood pressure and type 2 diabetes

In the 33 male and 9 female patients, serum FGF21 levels were similar ($p = 0.143$) (Fig. 1a). Levels did not correlate with the age of the patients ($p = 0.622$). While twelve patients were diagnosed type 2 diabetic, their systemic FGF21 levels were comparable to those of non-diabetic cirrhotic patients ($p = 0.301$, Fig. 1b). Glucose intolerance is common in patients with liver cirrhosis [34, 35], but fasting insulin levels have not been documented to calculate homeostatic model assessment insulin resistance (HOMA-IR) for the patients enrolled. To partly address this issue, FGF21 levels were compared in patients with fasting normo- and hyperglycemia (glucose $>$ 126 mg/dl [36]) which was known for 20 patients, and patients with normal and increased (>5.7% [36]) HbA1c (documented for 25 patients). However, FGF21 was similar in the nine patients with hyperglycemia and the five patients with raised HbA1c when compared to the respective controls (Fig. 1c, d).

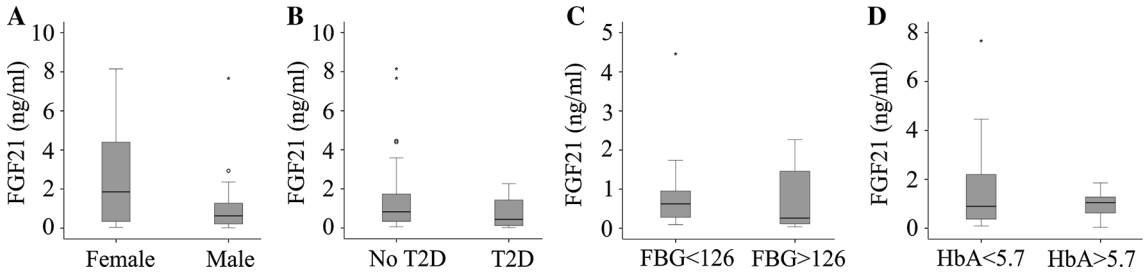

Fig. 1 FGF21 levels stratified for gender, type 2 diabetes, fasting blood glucose and HbA1c. **a** FGF21 in serum of female and male liver cirrhosis patients. **b** FGF21 in serum of non-diabetic and type 2 diabetic (T2D) liver cirrhosis patients. **c** FGF21 in serum of patients with normal and raised fasting blood glucose (FBG > 126 mg/dl). Data for only 20 patients were documented. **d** FGF21 in serum of patients with normal and high HbA1c (HbA > 5.7%). Data for only 25 patients were documented

Blood pressure had been documented in 38 patients, but neither systolic ($p = 0.623$) nor diastolic ($p = 0.550$) blood pressure was correlated with systemic FGF21 (data not shown).

Association with hepatic function

Serum levels of FGF21 did not correlate with MELD score ($p = 0.224$, Fig. 2a) or Child–Pugh score ($p = 0.156$) and were similar in serum of patients with score A (11 patients), B (14 patients) or C (17 patients) (Fig. 2b). No correlations were found with bilirubin ($p = 0.271$), albumin ($p = 0.659$), Quick prothrombin time ($p = 0.109$), aspartate aminotransferase ($p = 0.542$) and alanine aminotransferase ($p = 0.813$). Alkaline phosphatase was documented for 37 patients and showed a trend to be positively correlated with FGF21 ($r = 0.293$, $p = 0.078$).

Association with kidney function

FGF21 did not correlate with serum creatinine ($p = 0.669$) or creatinine clearance ($p = 0.507$) and tended to be negatively associated with serum urea ($r = -0.324$, $p = 0.050$) which was known from 37 patients. Accordingly, levels were similar in patients with a creatinine clearance of <70 ml/min (lowest normal value is 70 ml/min, 25 patients) when compared to those with normal clearance rate (17 patients) (Fig. 2c).

Association with ascites and varices

Serum FGF21 tended to be negatively correlated with hepatic venous pressure gradient (HVPG) documented for 40 patients ($r = -0.290$, $p = 0.070$, Fig. 3a). Levels were nevertheless comparable in those with no (6 patients), little (10 patients), modest (4 patients) and massive (22 patients) ascites (Fig. 3b). Patients without (9 patients), with small (7 patients) and large (26 patients) varices had similar FGF21 serum levels (Fig. 3c).

Association with systemic adipokines and inflammatory markers

Interestingly, serum FGF21 did not correlate with any of the adipokines measured previously in subgroups of these patients. Adiponectin [15] (40 patients, $p = 0.807$, Fig. 4a), chemerin [31] (42 patients, $p = 0.251$) and leptin [15] (37 patients, $p = 0.678$) were not associated with FGF21. Galectin-3 which is released by immune cells and associated with liver fibrosis had been determined in 37 patients and did not correlate with FGF21 ($p = 0.206$) [32, 37]. Resistin is mainly produced by macrophages and was not associated with FGF21 levels ($p = 0.545$, 37 patients) [15, 38]. Visfatin did not correlate with FGF21 ($p = 0.689$, 37 patients). Omentin in serum is not correlated with severity of liver cirrhosis defined by Child–Pugh or MELD score [30] and does also not correlate with

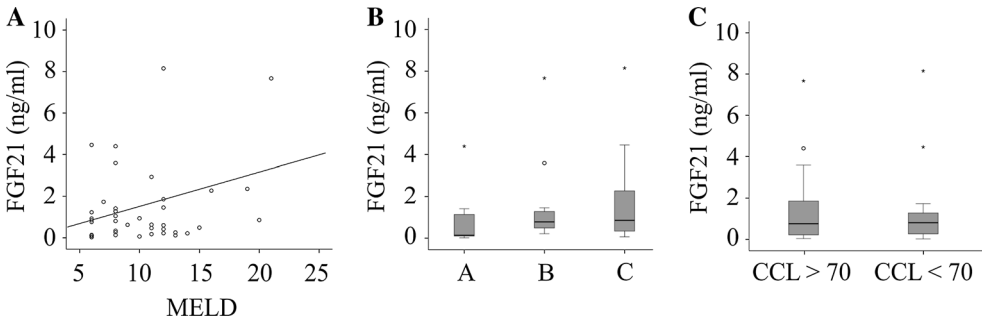

Fig. 2 FGF21 levels, liver and kidney function. **a** Correlation of FGF21 in serum with MELD score. **b** FGF21 in serum of liver cirrhosis patients stratified for Child–Pugh score. **c** FGF21 serum levels in patients with normal (CCL > 70 ml/min) and impaired creatinine clearance (CCL < 70 ml/min)

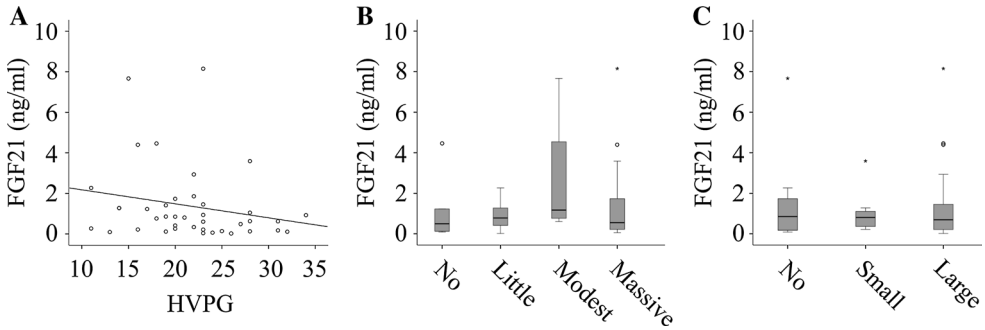

Fig. 3 FGF21 levels and secondary complications of liver cirrhosis. **a** Correlation of FGF21 in serum and hepatic venous pressure gradient (HVPG). **b** FGF21 in serum of liver cirrhosis patients stratified for extent of ascites. **c** FGF21 in serum of liver cirrhosis patients stratified for variceal size

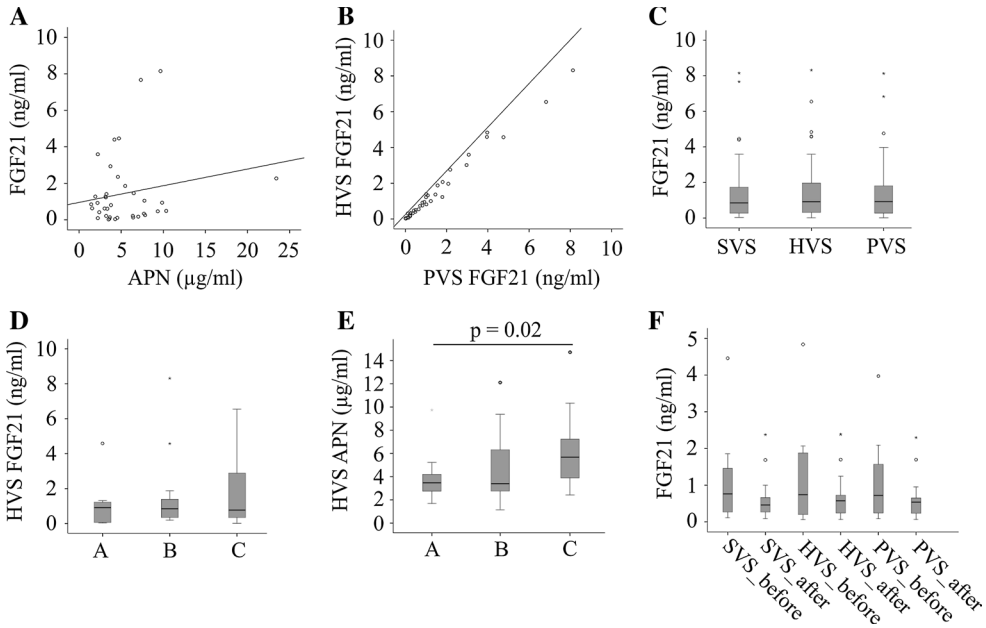

Fig. 4 FGF21 correlation with adiponectin and levels in different blood compartments before and after TIPS. **a** Correlation of serum FGF21 with adiponectin (APN). **b** Correlation of FGF21 in hepatic venous (HVS) and portal venous (PVS) blood. **c** FGF21 in systemic venous blood (SVS), HVS and PVS of 37 patients. **d** HVS FGF21 stratified for Child–Pugh score. **e** HVS adiponectin stratified for Child–Pugh score. **f** FGF21 in SVS, HVS and PVS shortly before and 3 months after TIPS of 13 patients

FGF21 ($p = 0.591$, 37 patients). CRP is an established marker of inflammation [39], and no association with serum FGF21 could be seen ($p = 0.704$, 40 patients).

Systemic, hepatic vein and portal vein FGF21

FGF21 is highly expressed in the liver. To assess whether levels in the hepatic vein are increased, FGF21 was measured in systemic (SVS), hepatic vein (HVS) and portal vein blood (PVS) of 37 patients. SVS FGF21 positively correlated with PVS ($r = 0.972$, $p < 0.001$) and HVS ($r = 0.984$, $p < 0.001$) levels. Significant positive correlations were also identified for PVS and HVS FGF21 ($r = 0.983$, $p < 0.001$, Fig. 4b). Concentrations of FGF21 did not differ in the three compartments (Fig. 4c). Importantly, FGF21 in the hepatic vein was similar in patients with compensated and decompensated liver cirrhosis as determined by Child–Pugh score (Fig. 4d). In the latter group, adiponectin in the hepatic vein was significantly higher (Fig. 4e). Concordantly, HVS adiponectin but not HVS FGF21 correlated with MELD score ($r = 0.476$, $p = 0.002$).

FGF21 three months after TIPS

FGF21 was measured in SVS, HVS and PVS of 13 patients 3 months after TIPS. While HVPG was significantly reduced ($p < 0.001$) and ascites extend tended to be lower ($p = 0.053$), FGF21 levels were not changed in these compartments (Fig. 4f).

Discussion

In patients with liver cirrhosis, systemic FGF21 is not associated with Child–Pugh or MELD score, kidney dysfunction, ascites and variceal size. Hepatic vein FGF21 is

similar in patients with well-compensated and decompensated liver cirrhosis, arguing against a strong hepatic upregulation of FGF21 in those patients with worse liver function.

FGF21 is abundantly expressed in the liver and is induced in stressed murine liver [25, 26] with mice showing a strong correlation of hepatic and serum FGF21 levels [26]. Hepatic FGF21 is further increased in the injured human liver, and higher amounts of FGF21 protein have been detected by immunohistochemistry in hepatocytes in chronic hepatitis and cirrhosis [26]. Serum FGF21 is, however, not associated with the degree of liver dysfunction, and levels do not correlate with Child–Pugh and MELD score in patients with liver cirrhosis. This observation is principally in agreement with the study from Ucar et al., demonstrating that systemic FGF21 is not associated with fibrosis scores in patients with hepatitis B infection [40]. In chronic hepatitis C-infected patients, serum FGF21 is strongly induced in those with liver steatosis but is not raised with increasing fibrosis stage [41]. The cohort of this current study enrolled patients with mainly alcoholic liver cirrhosis. Therefore, lack of serum FGF21 elevation in patients with worse liver function seems to be a feature of hepatitis B and C cirrhosis and alcoholic liver cirrhosis.

In patients with non-alcoholic fatty liver disease (NAFLD), hepatic FGF21 mRNA levels and serum FGF21 are increased. There is a strong, positive correlation of hepatic expression and circulating FGF21, indicating that the liver-produced protein markedly determines systemic levels. However, patients with cirrhosis were not enrolled in this study. Though hepatic and serum FGF21 have been associated with degree of liver steatosis, its association with fibrosis has not been defined in this investigation [42]. Future studies have to evaluate whether hepatic FGF21 protein is differentially expressed in patients with well-compensated and decompensated liver cirrhosis.

In NAFLD patients, serum FGF21 is not correlated with fasting plasma glucose [42]. Associations of systemic FGF21 with HOMA-IR and impaired fasting glucose have not been identified in hepatitis C-infected patients [41]. In the cohort studied herein, FGF21 is not raised in type 2 diabetic patients, those patients with impaired fasting glucose or abnormal HbA1c. Separate studies describe positive associations of FGF21 and measures of impaired glucose homeostasis [43, 44]. This finding is principally similar to adiponectin which is reduced in insulin-resistant patients [7]. In liver cirrhosis patients which are mostly insulin resistant, adiponectin is even markedly increased and is not associated with HOMA-IR [9, 45].

FGF21 is not altered in liver cirrhosis patients with impaired creatinine clearance. In patients with chronic and acute renal dysfunction, FGF21 is induced in serum [46, 47]. Changes of FGF21 are positively related to changes in creatinine and negatively to creatinine clearance and estimated glomerular filtration rate [46, 47]. Negative associations of serum FGF21 and estimated glomerular filtration rate have been further identified in type 2 diabetes patients [48]. Though these observations suggest that the renal excretion is the main route for FGF21 elimination [46], this assumption is not supported by the present findings.

Serum CRP is an established inflammatory marker, and positive associations of CRP and FGF21 have been described in type 2 diabetes patients [49]. CRP does, however, not correlate with FGF21 in patients with liver cirrhosis.

FGF21 is also secreted by adipose tissues, and biological effects of this protein are partly mediated by adiponectin [23, 24]. Serum adiponectin is increased in liver cirrhosis patients and is positively associated with disease severity [9, 12]. Positive associations with MELD score and increased adiponectin in serum of patients with decompensated liver cirrhosis have been confirmed in the patients enrolled in the present study. Higher adiponectin levels are not accompanied by changes in FGF21 in patients with liver cirrhosis. Further, no associations with additional adipokines could be identified.

Chemerin induces FGF21 in primary human hepatocytes, and serum levels of both proteins are positively correlated in NAFLD patients [50]. FGF21 in turn lowers chemerin in the supernatants of adipocytes [51]. In liver cirrhosis patients, serum chemerin declines with worse hepatic function [31, 52]. Mutual effects on the release of these proteins do not translate into correlations of the respective serum levels in the patients with liver cirrhosis.

In rodents fed a high-fat diet, an upregulation of FGF21 protein and downregulation of visfatin protein in the liver, adipose tissue and plasma have been described [53]. Visfatin is positively linked to Child–Pugh score in patients with liver cirrhosis [11, 15]. In the present cohort, serum levels of visfatin and FGF21 were not correlated.

Omentin is modestly induced by FGF21 in preadipocytes [51], and we are unaware of further studies reporting on an association of these two proteins. Omentin is, like FGF21, not associated with Child–Pugh or MELD score [30] and does not correlate with FGF21. Galectin-3 is an established profibrotic protein in murine and human liver fibrosis, and its serum levels are positively associated with Child–Pugh score in patients with liver cirrhosis [32, 54]. Resistin is also higher in patients with decompensated disease [10, 55]. To our knowledge, however, no studies analyzing relationships of galectin-3 or resistin with FGF21 exist. In patients with liver cirrhosis, serum levels of these proteins are not associated with FGF21.

To sum up, several adipokines are differentially associated with disease severity in liver cirrhosis, while FGF21 is not changed and does not correlate with these proteins.

FGF21 tends to be negatively correlated with hepatic venous pressure gradient. Although this gradient is reduced after TIPS as expected [18], FGF21 is not changed. This excludes that hepatic venous pressure gradient directly affects FGF21 levels. TIPS lowers the hepatic capacity to clear endogenous proteins or gut-derived products [18, 56], but FGF21 is not induced after this intervention. Therefore, FGF21 does not seem to be largely excreted by the liver.

One major limitation of this study is that liver tissues of the patients were not available and hepatic FGF21 has not been analyzed. Further research is needed to address this issue. Patients enrolled mostly suffered from alcoholic liver cirrhosis, and findings cannot be extrapolated to other disease etiologies.

In conclusion, present study shows that FGF21 in serum is not a marker of hepatic and renal dysfunction in patients with mainly alcoholic liver cirrhosis.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study complies with the Declaration of Helsinki. All patients gave written informed consent, and the study was approved by the Ethical Committee of the University Hospital of Regensburg.

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