Prostaglandins & other Lipid Mediators 124 (2016) 27–33

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

# Systemic saturated lysophosphatidylcholine is associated with hepatic function in patients with liver cirrhosis

Sabrina Krautbauer[a,c], Kristina Eisinger[a], Reiner Wiest[b], Gerhard Liebisch[c], Christa Buechler[a,*]

[a] Department of Internal Medicine I, Regensburg University Hospital, D-93042 Regensburg, Germany
[b] Department of Visceral Surgery and Medicine, University Inselspital, Bern, Switzerland
[c] Institute for Clinical Chemistry and Laboratory Medicine, Regensburg University Hospital, Regensburg, Germany

ARTICLE INFO

*Article history:*
Received 2 February 2016
Received in revised form 1 June 2016
Accepted 1 June 2016
Available online 2 June 2016

*Keywords:*
Phosphatidylcholine
Ascites
CHILD-PUGH score
Galectin-3

ABSTRACT

Serum lysophosphatidylcholine (LPC) is described to decline in patients with chronic liver diseases. Here it was evaluated which of the LPC species are associated with liver function. LPC species were quantified by direct flow-injection electrospray ionization tandem mass spectrometry in serum of 45 patients with mainly alcoholic liver cirrhosis. Saturated LPC is 52.1 (31.7–110.0) μmol/l in serum of patients with CHILD-PUGH score C (decompensated liver cirrhosis) and significantly lower compared to patients with well-compensated disease (CHILD-PUGH score A) with 114.1 (12.3–401.4) μmol/l. Mono- and polyunsaturated LPC are not changed in these groups. Saturated LPC is negatively correlated with the model for end-stage liver disease score, bilirubin and galectin-3 and positively with Quick prothrombin time. Ascites and varices are complications of liver cirrhosis. Saturated LPC does, however, not correlate with hepatic venous pressure gradient, ascites volume and variceal size. Unexpectedly, saturated LPC measured in serum of 42 patients declines from 88.4 (27.8–177.5) μmol/l to 72.4 (27.6–141.8) μmol/l shortly after transjugular intrahepatic portosystemic shunt implantation. Hepatic vein saturated LPC (82.3 (12.4–161.7) μmol/l) is higher than portal vein levels (78.8 (10.1–161.0) μmol/l) suggesting hepatic release of this lipid species. Current data demonstrate that systemic saturated LPC species are reduced in patients with decompensated liver cirrhosis and associated with mortality risk.

© 2016 Elsevier Inc. All rights reserved.

## 1. Introduction

Liver cirrhosis is the end stage of different forms of liver injury independent of disease etiology [1]. Chronic hepatitis B and C virus infections, alcohol abuse and non-alcoholic steatohepatitis (NASH) are the major causes of liver fibrosis [1–3].

Liver cirrhosis is associated with disturbed lipid metabolism and reduced serum lipoproteins [4]. Albumin which is produced by the liver is also diminished [5]. Lysophosphatidylcholine (LPC) in serum binds to albumin and is further a component of very low density lipoprotein, low density lipoprotein and high density lipoprotein [6]. This suggests that impaired hepatic lipid metabolism contributes to reduced serum LPC.

LPC species decrease in serum of hepatitis virus B infected patients with chronic liver disease when compared to healthy controls. Interestingly, only minor changes are identified in those infected with hepatitis virus C [7]. Several LPC species are further diminished in hepatitis B virus infection caused cirrhotic patients [7]. In patients suffering from hepatitis B related hepatocellular carcinoma several hepatic LPC species are even induced compared to the adjacent and normal tissues [8]. Serum LPC has, however, not been measured in this study [8].

Decrease of distinct LPC species in serum has also been reported in mice with liver steatosis and non-alcoholic steatohepatitis (NASH) [9,10]. In the steatotic and NASH liver several LPC species are elevated [11,12]. This suggests that impaired hepatic release of LPC may at least in part contribute to lower serum levels in rodents and eventually patients with metabolic liver diseases.

LPC exerts inflammatory activities and induces the expression of adhesion molecules, growth factors and scavenger receptors in immune cells [13]. Injection of LPC in rodents increases aminotransferases in serum and promotes hepatitis and hepatocyte death [12]. LPC nevertheless activates type II natural killer T-cells and subsequent anergy induction of type I natural killer T-cells protects from concanavalin A-induced chronic liver injury in mice [14]. Preventive treatment with LPC in murine peritoneal sepsis

* Corresponding author.
*E-mail address:* christa.buechler@klinik.uni-regensburg.de (C. Buechler).

http://dx.doi.org/10.1016/j.prostaglandins.2016.06.001
1098-8823/© 2016 Elsevier Inc. All rights reserved.

enhances bacterial clearance and animal survival [15]. These contrasting effects of LPC may be related to the use of differenct LPC species [13].

Pro- and anti-atherogenic effects of LPC have been described and differential effects are explained by chain length and the degree of saturation of the fatty acyl moiety [16]. Further studies are needed to evaluate signaling of single LPC species in more depth to resolve this issue.

Phospholipase A2 and lecithin-cholesterol acyltransferase (LCAT) activity as well as hepatic release contribute to plasma LPC levels [17–19]. Liver function and subsequently release of hepatic metabolites is impaired in patients with liver cirrhosis [4,20] suggesting that reduction of at least some serum LPC species may be related to the degree of hepatic injury. This has been analyzed in the current study.

## 2. Materials and methods

### 2.1. Transjugular intrahepatic portosystemic shunt (TIPS)

Forty five patients with liver cirrhosis were included in the study and patient demographics and laboratory parameters have already been described [21]. The patients were 54 (26–81) years old, nine were females and 12 had type 2 diabetes. Median MELD score was 9 (6–21). Twelve patients had CHILD-PUGH score A –, 16 B – and 17 C liver cirrhosis. There were 6 patients without, 13 with little, 4 with modest and 22 with massive ascites. Nine of the patients had no varices, seven small and 29 large varices. Etiology of liver disease was alcoholic in 38 of the patients, hepatitis C infection in 3 and of other reason in 4 patients. Patients were electively treated by transjugular intrahepatic portosystemic shunt (TIPS) implantation due to complications of liver cirrhosis such as variceal bleeding (15 patients), hepatorenal syndrome (1 patient), refractory ascites (27 patients) or other reasons (2 patients). The procedure of TIPS implantation has been described and TIPS (Viatorr-Stent, Putzbrunn, Germany) was inserted in the fasted state according to Rössle and Gerbes [22]. During TIPS implantation, samples of one of the hepatic veins (HVS) not being drained by the TIPS-stent, of the portal vein (PVS) and of one peripheral vein such as the superior caval vein (SVS) were obtained simultaneously. Patients samples analyzed herein have been used in previous studies [21,23–25].

Blood was also collected directly after TIPS implantation and dilation to its final lumen (before ending the procedure and dismissing the patient to the ward). Three months after placement of the stent (to investigate patency of the shunt) blood was drawn again from the superior caval vein, portal vein and from another hepatic vein to prevent sampling from the extended portal venous tract [26].

All blood samples were collected in tubes with ethylenediaminetetraacetic acid (EDTA) as anticoagulant and serum was obtained by centrifuging for 10 min at 2500*g*.

Standard laboratory parameters such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured routinely by the Institute for Clinical Chemistry and Laboratory Medicine at the University Hospital of Regensburg. 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.

### 2.2. Quantification of lipids

Lipid species in serum were quantified by direct flow injection electrospray ionization tandem mass spectrometry (ESI-MS/MS) in positive ion mode using the analytical setup and strategy described previously [9,27]. EDTA plasma samples were used for quantitative analysis. Prior to lipid extraction, non-naturally occurring species were added as internal standards to compensate for variations in sample preparation and in the ionization efficiency. For calibrating samples, defined quantities of the lipid species were added and vacuum-dried. Twenty microliters of EDTA plasma was extracted according to the procedure described by Bligh and Dyer [28]. The separated chloroform phase was dried and dissolved in 10 mmol/l ammonium acetate in methanol-chloroform (3:1 by volume). Twenty microliters of this solution was injected and data were acquired.

Quantification was achieved by a precursor ion scan of *m*/*z* 184 specific for phosphocholine-containing lipids [29]. Free cholesterol (FC) and cholesteryl ester (CE) were quantified using a fragment ion of *m*/*z* 369 after selective derivatization of FC [30]. Self-programmed Excel macros sorted the results, calculated the ratios to the internal standards, generated calibration curves, and calculated quantitative values [31].

### 2.3. Statistics

Data are shown as box blots (IBM SPSS Statistics 21.0). Statistical differences were analyzed by two-tailed Mann-Whitney U Test (IBM SPSS Statistics 21.0). ANOVA with post hoc Bonferroni correction was applied for multiple comparisons. Spearman correlation was calculated using the IBM SPSS Statistics 21.0 software and was corrected for multiple comparisons (p-values calculated were multiplied by the number of different correlations analyzed). Paired data were analyzed by *t*-test (Microsoft Excel).

## 3. Results

### 3.1. Association with gender, diabetes and blood pressure

Forty five patients suffering from clinically diagnosed liver cirrhosis were included in the study. Saturated, monounsaturated (MUFA) and polyunsaturated (PUFA) LPC species were measured in serum. In this cohort PUFA LPC was higher in females (13.9 (7.9–23.0) μmol/l versus 9.2 (2.1–23.0) μmol/l in serum of males) while saturated LPC and MUFA LPC were similar in both genders (Fig. 1A and data not shown). Saturated, MUFA and PUFA LPC did not correlate with the age of the patients (data not shown).

Saturated, MUFA and PUFA LPC did not correlate with diastolic and systolic blood pressure which had been documented for 40 patients (data not shown). Twelve of the patients had type 2 diabetes but saturated, MUFA and PUFA LPC were not changed in this subgroup (Fig. 1B and data not shown).

### 3.2. LPC in serum of patients with liver cirrhosis

LPC is well described to be reduced in serum of patients with liver cirrhosis [7]. In patients with CHILD-PUGH score C (decompensated liver cirrhosis) compared to patients with CHILD-PUGH score A (well-compensated liver cirrhosis) total LPC was nearly 2-fold reduced (Fig. 1C and Table 1). Here, it was analyzed which of the systemic LPC species are associated with hepatic injury.

### 3.3. Association of saturated LPC with liver function

Reduced serum LPC in patients with decompensated liver cirrhosis compared to patients with well-compensated disease was due to lower levels of saturated LPC while MUFA LPC and PUFA LPC were not changed (Fig. 1D and Table 1). Of the saturated LPC species measured the highly abundant LPC species 16:0 and 18:0 were reduced while the low abundant form LPC 15:0 was not diminished (Fig. 1E, F and Table 1). There were no differences in the saturated LPC species LPC 16:0 and 18:0 in patients with CHILD-PUGH score

Download English Version:

https://daneshyari.com/en/article/2019434

Download Persian Version:

https://daneshyari.com/article/2019434

Daneshyari.com