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Impact of overt and subclinical hepatogenous diabetes and metformin treatment on circulatory function, renal function and hemodynamics, inflammatory activity, and prognosis in patients with cirrhosis and ascites

Ilias Tsiakas[a], Maria Kosmidou[b], Grigorios Despotis[a], Dimitrios Biros[a], Spiridon Tsiouris[c], Xanthi Xourgia[c], Lampros Lakkas[d], Georgios S. Markopoulos[e], Eleni Bairaktari[f], Georgios Kolios[f], Haralampos Milionis[a], Georgios Kalambokis[a]

University Hospital of Ioannina; Papageorgiou Hospital, Thessaloniki, Greece

Abstract

Background Hepatogenous diabetes (HD) is common in advanced cirrhosis. The oral glucose tolerant test (OGTT) is frequently diagnostic, as fasting blood glucose (FBG) may be normal. We investigated the impact of FBG- and OGTT-diagnosed HD, and metformin treatment, on circulatory function, renal function and perfusion, and inflammatory activity in patients with cirrhosis and ascites. Also, long-term prognosis of HD under metformin/metformin-based treatment was assessed.

Methods Mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR) as MAP/CO ratio, plasma renin activity (PRA), plasma aldosterone, glomerular filtration rate (GFR), renal blood flow (RBF), and plasma levels of lipopolysaccharide-binding protein (LBP), tumor-necrosis factor-α (TNF-α) and interleukin-6 were evaluated at baseline in patients with and without HD, and after 6 months of metformin treatment for newly diagnosed HD.

Results Compared to OGTT-HD (n=34) and no-HD (n=37), FBG-HD patients (n=35; newly-diagnosed, n=13) had significantly lower SVR (P=0.02/P=0.01), GFR (P=0.01/P=0.008) and RBF (P=0.02/P=0.01), and significantly higher CO (P=0.04/P=0.03), PRA (P=0.009/P=0.006), and levels of LBP (P=0.01/P=0.008) and TNF-α (P=0.03/P=0.02). Initiation of metformin in OGTT-HD and FBG-HD patients induced significant increases in SVR (P=0.02/P=0.04), GFR (P=0.02/P=0.04) and RBF (P=0.04/P=0.05), and significant decreases in PRA (P=0.02/P=0.03) and LBP (P=0.02/P=0.04). Three-year survival in OGTT-HD was significantly higher than in FBG-HD (75.3% vs. 55.3%; P=0.03) and similar to no-HD (81.7%).

Conclusions Circulatory function and renal function and perfusion are aggravated by FBG-HD compared to OGTT-HD or no-HD, possibly because of greater inflammatory activity, while they improve significantly after metformin treatment. Early treatment of HD with metformin may improve prognosis.

Keywords Hepatogenous diabetes, oral glucose tolerant test, metformin, systemic inflammation, circulatory function

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Conflict of Interest: None

Correspondence to: Georgios Kalambokis, MD, PhD, First Division of Internal Medicine Department, Medical School, University of Ioannina, Ioannina 45500, Greece, e-mail: gkalambo@uoi.gr

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Introduction

Cirrhosis is characterized by intestinal bacterial overgrowth and dysbiosis leading to increased passage of bacteria and their products into the portal and systemic circulation, mainly due to the increased portal hypertension-related permeability of the intestinal barrier [1]. Translocated gut-derived molecules such as lipopolysaccharide (LPS), also referred to as endotoxin, trigger a systemic inflammatory response with release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6. Subsequently, these inflammatory mediators stimulate the production of potent

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vasodilators, mainly nitric oxide (NO), causing splanchnic arterial vasodilation and a reduction in effective arterial blood volume [2,3]. As liver disease progresses to the decompensated phase, the circulatory dysfunction becomes more intense, activating potent sodium retaining and vasoconstricting mechanisms, such as the renin–angiotensin–aldosterone system, which contribute to the development of ascites and renal function impairment [4].

Glucose metabolism disorders are highly prevalent in patients with cirrhosis. Most of the patients with cirrhosis present impaired glucose tolerance (IGT) and up to 35-70% suffer from diabetes mellitus (DM) [5]. HD refers to DM that occurs after the onset of cirrhosis as a result of the chronic liver disease. HD may be observed in more than one fifth of patients with cirrhosis, and the highest prevalence has been reported among those with more advanced liver disease [6,7].

The pathogenesis of HD is not fully understood. It primarily involves a reduction in the liver's capacity to inactivate insulin, and the presence of portosystemic shunts that cause hyperinsulinemia and downregulation of insulin receptors, leading to insulin-resistance (IR), while a link between HD and systemic inflammation has also been assumed [6-8]. Fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) levels may be inappropriately normal in the majority of patients with cirrhosis, because of hepatic dysfunction and the reduced erythrocyte lifespan associated with hypersplenism. Hence, an oral glucose tolerance test (OGTT) is commonly required to set the diagnosis of HD [5,6].

There is growing evidence that patients with cirrhosis and diabetes carry a greater risk of developing ascites [9-11] and renal dysfunction [9-13]. Although the mechanisms involved remain elusive, it can be suggested that the development of HD in the course of decompensated cirrhosis (DC) could cause further deterioration of circulatory function. At present, management guidelines for HD—and in particular OGTT-diagnosed HD—are lacking. Long-term use of metformin in patients with diabetes and cirrhosis is considered safe [6,14] and has been associated with reduced decompensation rates [15] and survival benefit [15-17], even in patients with advanced cirrhosis [17].

The primary aim of the present study was to investigate the impact of FBG- and OGTT-diagnosed HD, as well as the impact of treating newly-diagnosed HD with metformin, on circulatory function, renal function and hemodynamics, and systemic inflammatory activity in patients with cirrhosis and ascites. The long-term prognosis of FBG- and OGTT-diagnosed HD treated with metformin-based regimens was also evaluated.

[a]First Division of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece (Ilias Tsiakas, Grigorios Despotis, Dimitrios Biros, Haralampos Milionis, Georgios Kalambokis); [b]Third Department of Internal Medicine, Papageorgiou Hospital, Thessaloniki, Greece (Maria Kosmidou); [c]Laboratory of Nuclear Medicine, University Hospital of Ioannina, Ioannina, Greece (Spiridon Tsiouris, Xanthi Xourgia); [d]Second Department of Cardiology, University Hospital of Ioannina, Ioannina, Greece (Lampros Lakkas); [e]Hematology Laboratory, Unit of Molecular Biology and Translational Flow Cytometry, University Hospital of Ioannina, Ioannina, Greece (Georgios S. Markopoulos); [f]Biochemistry Laboratory, University Hospital of Ioannina, Ioannina, Greece (Eleni Bairaktari, Georgios Kolios)

Patients and methods

Patients

Patients with liver cirrhosis and ascites consecutively seen at the outpatient hepatology clinics of the University Hospital of Ioannina, Greece, from January 2017 to January 2022 were prospectively evaluated. Written informed consent was obtained from every participant. The study conformed to the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. The diagnosis of cirrhosis was based on clinical and laboratory findings, endoscopy, imaging studies, or on liver biopsy. HD was defined as FBG≥126 mg/dL or a 2-h BG level ≥200 mg/dL during OGTT [18]. The OGTT was performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. A 2-h BG level of 140-199 mg/dL was diagnosed as IGT. IR was calculated using the homeostatic model assessment-insulin resistance (HOMA-IR) formula: FBG (mg/dL) × fasting insulin (mU/mL)/405, with a cutoff of >2.

Patients were included if they had: a) diuretic-responsive ascites; b) age between 18 and 75 years; and c) stable serum creatinine <1.5 mg/dL, with an estimated glomerular filtration rate (GFR) >50 mL/min using the Cockcroft-Gault equation, and absence of renal impairment on urinalysis and ultrasound. Exclusion criteria were: a) diabetes diagnosed prior to the diagnosis of cirrhosis; b) risk factors for diabetes, including body mass index >27 kg/m^2, hyperlipidemia, positive family history of diabetes [5,6], and history of non-alcoholic fatty liver disease; c) insulin-treated diabetes; d) uncontrolled diabetes, defined as fasting FBG>130 mg/dL or HbA1c>7% under treatment [19]; e) hepatic encephalopathy not controlled by treatment; f) history of variceal bleeding or bacterial infection at least 3 months prior to inclusion; g) portal vein thrombosis by Doppler ultrasonography; h) hepatocellular carcinoma or other malignancy; i) recent (within 6 months) or active ethanol use; k) Child-Pugh score>12 points; l) transjugular intrahepatic portosystemic shunt (TIPS) insertion; m) ongoing steroid therapy; and n) history of chronic pancreatic, cardiovascular or pulmonary disease. Liver disease severity was assessed by Child-Pugh score/class and model for end-stage liver disease (MELD). Beta-blockers and diuretics were not withheld during the investigations. Antidiabetic treatment in patients with known HD was discontinued on the day of OGTT. All patients were on a sodium-restricted diet. Moderate caloric restriction and exercise were recommended in patients with HD when feasible [6].

Study design

All patients were screened within the predefined study period for the presence of HD and enrolled into one of the

following study groups, until each group consisted of at least 30 patients: a) the first group included patients with HD diagnosed by FBG levels (FBG-HD or overt HD) prior to or at inclusion in the study; b) the second group included patients with HD diagnosed by OGTT (OGTT-HD or subclinical HD) at entry; and c) the third group included patients without HD. The investigations were performed within 3 consecutive days, at 8.00 am, after an overnight fast. On the first day, plasma and serum samples were obtained in the supine position for measurement of vasoactive factors (plasma renin activity [PRA], and plasma levels of aldosterone) and inflammatory markers (serum lipopolysaccharide-binding protein [LBP], TNF-α, and IL-6) and were stored at -80°C until analysis. Blood samples for the measurement of FBG, HbA1c, serum insulin levels, complete blood count, liver and renal biochemistry, and coagulation profiles, and urine samples for evaluation of microalbuminuria, were also obtained. Subsequently, OGTT was performed in patients without known HD. Transthoracic echocardiography and evaluation of systemic hemodynamics and effective renal plasma flow (ERPF) were performed on the second day. GFR was measured radioisotopically on the third day, and subsequently all patients with newly diagnosed OGTT-HD and FBG-HD received metformin treatment at a dose of 850 mg once daily, which was increased to twice daily (1700 mg) after 1 week if well tolerated, and the studies were repeated after 6 months. During the follow up, metformin was temporarily discontinued in the acute phase of variceal bleeding and bacterial infection, and when the calculated GFR fell below 50 mL/min, and permanently in patients with persistently reduced GFR or liver failure. Patients were followed until permanent discontinuation of metformin (patients with HD), death, liver transplantation, TIPS insertion, or January 2025. All patients with normal FBG repeated OGTT yearly and received metformin if HD was diagnosed. All patients with FBG-HD were initially treated with metformin; if needed, a dipeptidyl peptidase 4 inhibitor (DDP4i) and/or a sodium–glucose co-transporter-2 inhibitor (SGLT2i) was subsequently added [6]. Liver-related deaths were recorded during an observation period of 3 years, and were defined as due to variceal bleeding, hepatorenal syndrome, bacterial infections, hepatocellular carcinoma or liver failure, as previously reported [20].

Evaluation of systemic hemodynamics

Two-dimensional echocardiography (Philips EPIQ 7C, Philips Healthcare, Andover, MA, USA) was used to assess cardiac output (CO). Mean arterial pressure (MAP) and heart rate were measured by an automated oscillometric device. The ratio MAP to CO was used as an index of systemic vascular resistance (SVR).

Evaluation of renal function and hemodynamics

ERPF and GFR were evaluated as previously reported [20]. In brief, an activity of approximately 111 MBq (3 mCi) of 99^{m}Technetium-mercapto-acetyl-triglycine (99^{m}Tc-MAG3; NephroMAG 0,2 mg, ROTOP Pharmaka GmbH, Dresden, Germany), or 148 MBq (5 mCi) of 99^{m}Tc-diethylene-triamine-pentaacetic acid (99^{m}Tc-DTPA; PENTACIS, CIS bio international, Saclay, France), were injected as a bolus intravenously for the calculation of ERPF and GFR, respectively. At least a 24-h interval was left between the 2 tracer studies to avoid interference between them. The ERPF and GFR were measured by calculating the plasma disappearance rate for each radiopharmaceutical, through antecubital blood sampling at 10 and 95 min post-injection for 99^{m}Technetium-mercapto-acetyl-triglycine, and at 120 and 240 min for 99^{m}Tc-diethylene-triamine-pentaacetic acid. The radioactivity within each blood sample was measured in a well-type gamma counter (Atomlab 950 Medical Spectrometer, Biodex Medical Systems, USA). The ERPF was corrected for the 99^{m}Technetium-mercapto-acetyl-triglycine extraction ratio to yield the renal plasma flow using the standard formula. Renal blood flow (RBF) was calculated as renal plasma flow/1-hematocrit.

Assays

Blood glucose, serum insulin, HbA1c, and urine albumin

Serum glucose levels were measured by the hexokinase method. Serum insulin was determined by the Beckman Coulter Unicell DXI 800 immunoassay analyzer. HbA1c was measured by an ion exchange HPLC system (Variant II, Bio-Rad Laboratories, Hercules, CA, USA) and urine albumin by the bromocresol green method on an AU5800 Clinical Chemistry analyzer (Beckman Coulter, Hamburg, Germany). We defined microalbuminuria as a urine albumin/creatinine ratio >30 μg/mg.

Inflammatory markers

The LEGENDplex™ Human TNF-α Capture Bead B3, 13X (Cat. No. 740053, Biolegend, USA) and the LEGENDplex™ Human IL-6 Capture Bead A7, 13X (Cat. No. 740044, Biolegend, USA) were used for the measurement of TNF-α and IL-6 serum levels, respectively, according to the manufacturer's instructions. The samples were analyzed in duplicate by Cytometric Bead Array flow cytometry in a BD FACSCalibur Flow Cytometer using CellQuest V3 Software (BD Biosciences, San Jose, CA, USA), and the data were analyzed using LEGENDplex™ Data Analysis Software V8.0 (BioLegend, USA). The assay sensitivities were 1.97 pg/mL for TNF-α and 2.01 pg/mL for IL-6. A commercially available enzyme-linked immunosorbent assay kit (ALX-850-304-KI01, Enzo Life sciences, Farmingdale, NY, USA) was used to measure serum LBP concentrations in accordance with the manufacturer's instructions. The assay sensitivity was 5ng/mL. Values of TNF-α, IL-6 and LBP below the detection limit level of the assay's sensitivity were assigned a value of 1.97 pg/mL, 2.01 pg/mL, and 5 ng/mL, respectively.

Vasoactive factors

PRA and plasma concentrations of aldosterone were measured by specific radioimmunoassays (RIAZEN Renin plasma activity, ZenTech, Belgium; RIA Aldosterone, IMMUNOTECH, Czech Republic, respectively). The radioactivity from the radioimmunoassay samples was counted in a gamma scintillation counter (Wizard 2, Perkin Elmer, USA).

Statistical analysis

The baseline characteristics were expressed as absolute and relative frequencies for categorical variables and as mean ± standard error for continuous variables. Pearson's chi-square test and Student's unpaired *t*-test were used to compare categorical and continuous variables, respectively. The cumulative probability of survival in the 3 patient-groups was estimated using Kaplan-Meier analysis and differences were compared using the log-rank test. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 26.0 statistical package (IBM Corp., Armonk, N.Y., USA).

Results

Finally, 116 eligible patients were enrolled: 35 with FBG-HD (known, n=22 [diagnosed prior to decompensation, n=2]; diagnosed at inclusion, n=13), 34 with OGTT-HD, and 37 without HD. Among patients with known FBG-HD, metformin (1700 mg, n=21; 850 mg, n=4) was combined with other antidiabetics in 9 (36%) patients (DDP4i, n=6; SGLT2i, n=2; DDP4i and SGLT2i, n=1). IGT was demonstrated in 24 (64.8%) patients without HD. As shown in Table 1, the clinical characteristics, including liver-disease severity, did not differ among patient groups. MELD score and Child-Pugh class were also similar between patients with known and newly-diagnosed FBG-HD (13.6±1.9 vs. 13.2±2.2 and A/B/C: 6/13/3 vs. 3/8/2, respectively). All patients with chronic hepatitis B (n=14) had undetectable HBV-DNA under treatment with antiviral agents and all patients with chronic hepatitis C (n=8) had received curative treatment with direct-acting antivirals prior to entry in the study. FBG, serum insulin levels and HOMA-IR index were significantly higher in patients with FBG-HD compared to those with OGTT-HD and patients without HD. Patients with OGTT-HD had higher serum insulin levels and HOMA-IR index than patients without HD, although the difference did not attain statistical significance (P=0.07 and P=0.06, respectively). HbA1c values did not differ between study groups. Metformin was permanently discontinued in 4 patients (FBG-HD, n=2; OGTT-HD, n=2) during follow up, because of sustained reductions in GFR.

Baseline systemic hemodynamics, neurohumoral factors, and renal function and hemodynamics

Patients with FBG-HD had significantly lower SVR (P=0.02), and significantly higher CO (P=0.04) and PRA (P=0.009), compared to patients with OGTT-HD. GFR and RBF were significantly lower in patients diagnosed with FBG-HD than in those with OGTT-HD (P=0.01 and P=0.02, respectively) (Table 2). Significantly lower SVR (P=0.01), along with significantly higher CO (P=0.03) and PRA (P=0.006), and significantly lower GFR (P=0.008) and RBF (P=0.01), were also noted in patients with FBG-HD compared to those without HD. Patients with OGTT-HD had lower PRA, with the difference reaching close to statistical significance (P=0.06), and significantly lower GFR (P=0.04) than patients without HD.

Baseline inflammatory markers

LBP and TNF-α levels were significantly higher in patients with FBG-HD compared to those with OGTT-HD (P=0.01 and P=0.03, respectively) and patients without HD (P=0.008 and P=0.02, respectively) (Table 2). LBP levels were higher in patients with OGTT-HD compared to those without HD, although the difference did not reach statistical significance (P=0.08).

Impact of metformin treatment in patients with HD diagnosed at inclusion

All patients who received metformin were alive at 6 months. Four patients with OGTT-HD (11.7%) and 2 (20%) with newly-diagnosed FBG-HD did not tolerate the dose of 1700 mg and continued with 850 mg. Linagliptin was added to metformin in 2 patients with FBG-HD.

Glycemic parameters

FBG, serum insulin levels and HOMA-IR index were not changed by metformin treatment in patients with OGTT-HD (Table 3), whereas they decreased significantly in those with FBG-HD (Table 4).

Systemic hemodynamics, neurohumoral factors, renal function and hemodynamics, and inflammatory markers

A significant increase in SVR (P=0.02) and a decrease in CO (P=0.04) along with a significant reduction in PRA (P=0.02) and significant increases in GFR (P=0.02) and RBF (P=0.03) were noted after metformin treatment in patients with OGTT-HD (Table 3). These changes were associated with

Table 1 Clinical and laboratory data of patients with FBG- and OGTT-diagnosed HD, and patients without HD at the time of inclusion

Data	FBG-HD (n=35)	OGTT-HD (n=34)	No-HD (n=37)	P-value*	P-value**	P-value***
Clinical characteristics						
Age (years)	54.7±2.3	55.6±2.4	54.2±1.9	0.7	0.6	0.8
Gender (male)	25 (71.4%)	26 (76.4%)	26 (70.2%)	0.6	0.5	0.6
Etiology of cirrhosis (alcohol/viral/other****)	22/8/5	22/6/6	26/8/3	0.8	0.6	0.4
History of variceal bleeding (n, %)	5 (14.2%)	3 (8.8%)	3 (8.1%)	0.4	0.4	0.9
History/presence of hepatic encephalopathy (n, %)	3 (8.5%)	2 (5.8%)	2 (5.4%)	0.6	0.5	0.9
Child-Pugh A/B/C	9/21/5	8/22/4	10/23/4	0.9	0.9	0.9
MELD score	13.4±2.1	13.3±1.9	13.1±2	0.6	0.8	0.7
Beta-blockers (n, %)	22 (62.8%)	20 (58.8%)	22 (59.4%)	0.7	0.7	0.9
Laboratory characteristics						
FBG (mg/dL)	123.2±3.3	97.3±2.8	89.5±2.9	<0.001	<0.001	0.1
HbA1c (%)	5.4±0.7	5±0.5	4.9±0.6	0.2	0.2	0.4
Serum insulin (μU/mL)	21.9±1.8	14.1±1.5	10.2±1.7	0.001	<0.001	0.07
HOMA-IR	6.7±0.9	3.4±0.6	2.2±0.7	<0.001	<0.001	0.06
Urine albumin/creatinine ratio (μg/mg)	23.2±2.1	20.7±1.8	20.1±1.6	0.4	0.4	0.6

Data are reported as mean ± standard error or absolute (percentage)
*FBG-HD vs. OGTT-HD; **FBG-HD vs. no HD; ***OGTT-HD vs. no HD; ****no patient was taking steroids for autoimmune liver disease at inclusion and during follow up
FBG, fasting blood glucose; HD, hepatogenous diabetes; OGTT, oral glucose tolerance test; MELD, model for end-stage liver disease; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance

Table 2 Systemic hemodynamics, neurohumoral factors, renal function and hemodynamics, and inflammatory activity markers in patients with FBG- and OGTT-diagnosed HD, and patients without HD at the time of inclusion

Factors	FBG-HD (n=35)	OGTT-HD (n=34)	No-HD (n=37)	P-value*	P-value**	P-value***
Systemic hemodynamics						
Mean arterial pressure (mmHg)	80.7±1.1	81.3±1.3	81.5±1.4	0.2	0.2	0.4
Cardiac output (L/min)	6.64±0.25	6.32±0.26	6.21±0.25	0.04	0.03	0.1
Systemic vascular resistance (dyn/s/cm^{-5})	1215±48	1285±56	1312±62	0.02	0.01	0.2
Neurohumoral factors						
Plasma renin activity (ng/mL/h)	9.3±0.52	5.24±0.55	4.01±0.46	0.009	0.006	0.06
Aldosterone (ng/mL)	324±42	295±53	289±48	0.2	0.1	0.4
Renal function and hemodynamics						
Glomerular filtration rate (mL/min)	70.4±1.5	77.3±1.6	83.1±1.7	0.01	0.008	0.04
Renal blood flow (mL/min)	570±30	614±36	634±41	0.02	0.01	0.1
Inflammatory factors						
Lipopolysaccharide-binding protein (ng/mL)	12.2±1.8	7.5±1.4	6.5±1.9	0.01	0.008	0.08
Tumor necrosis factor-α (pg/mL)	14.7±1.9	8.6±2.1	7.2±2.6	0.02	0.03	0.2
Interleukin-6 (pg/mL)	12.8±2.5	12±3.8	9.4±3.2	0.5	0.2	0.2

Data are reported as mean ± standard error
*FBG-HD vs. OGTT-HD; **FBG-HD vs. no HD; ***OGTT-HD vs. no HD
FBG, fasting blood glucose; HD, hepatogenous diabetes; OGTT, oral glucose tolerance test

significant decreases in LBP (P=0.02) and TNF-α levels (P=0.05). Similar significant changes of SVR (P=0.04), PRA (P=0.03), GFR (P=0.04), RBF (P=0.05) and LBP (P=0.04) were noted in patients with newly-diagnosed FBG-HD (Table 4).

Evolution of glycemic disorders during follow up

During a 3-year observation period, none of the metformin-treated patients with OGTT-HD developed FBG-HD. Among patients without HD, 12 (32.4%) were diagnosed with HD by OGGT, but none developed FBG-HD under metformin treatment. Four of 13 (30.7%) patients without baseline glycemic disorder developed IGT during follow up.

Survival

At 3-year follow up, 32 of 106 (30.1%) patients had died: 4 from non-liver related causes (malignancy in 2 [1 patient with FBG-HD and 1 without HD], and cardiovascular disease in 2 [all with FBG-HD]); and 28 (26.4%) from liver-related

Table 3 Impact of metformin treatment for 6 months in patients with OGTT-diagnosed HD (n=34)

Parameters	Baseline	6 months	P-value
Glycemic characteristics			
FBG (mg/dL)	98.3±2.8	97.2±3.2	0.5
HbA1c (%)	5±0.5	4.9±0.6	0.4
Serum insulin (μU/mL)	14.1±1.5	12.9±1.7	0.3
HOMA-IR	3.4±0.6	3.1±0.8	0.3
Systemic hemodynamics			
Mean arterial pressure (mmHg)	81.3±1.3	81.3±1.2	0.5
Cardiac output (L/min)	6.32±0.26	6.1±0.3	0.04
Systemic vascular resistance (dyn/s/cm^{-5})	1285±56	1337±41	0.02
Neurohumoral factors			
Plasma renin activity (ng/mL/h)	5.24±0.55	3.86±0.33	0.02
Aldosterone (ng/mL)	295±53	276±47	0.2
Renal function and hemodynamics			
Glomerular filtration rate (mL/min)	77.3±1.6	82.9±6	0.02
Renal blood flow (mL/min)	614±38	632±29	0.03
Inflammatory factors			
Lipopolysaccharide-binding protein (ng/mL)	7.5±1.4	6.1±1.3	0.02
Tumor necrosis factor-α (pg/mL)	8.6±2.1	6.6±2.3	0.05
Interleukin-6 (pg/mL)	12±3.8	10±4.2	0.3

Data are reported as mean±standard error

OGTT, oral glucose tolerance test; HD, hepatogenous diabetes; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance

Table 4 Impact of metformin treatment for 6 months in patients with FBG-HD diagnosed at inclusion (n=13)

Parameters	Baseline	6 months	P-value
Glycemic characteristics			
FBG (mg/dL)	136.8±3.6	102±4.2	0.009
HbA1c (%)	5.4±0.7	5.4±0.8	0.7
Serum insulin (μU/mL)	25.2±1.9	19.2±1.7	0.01
HOMA-IR	8.5±1.6	4.9±1.7	0.003
Systemic hemodynamics			
Mean arterial pressure (mmHg)	80.1±1.3	80.8±1.5	0.6
Cardiac output (L/min)	6.58±0.26	6.31±0.29	0.06
Systemic vascular resistance (dyn/s/cm^{-5})	1225±61	1282±68	0.04
Neurohumoral factors			
Plasma renin activity (ng/mL/h)	8.78±0.4	6.36±0.59	0.03
Aldosterone (ng/mL)	303±37	316±54	0.3
Renal function and hemodynamics			
Glomerular filtration rate (mL/min)	70.3±1.6	76.4±1.8	0.04
Renal blood flow (mL/min)	559±50	598±44	0.05
Inflammatory factors			
Lipopolysaccharide-binding protein (ng/mL)	11.9±2.1	7.8±2.2	0.04
Tumor necrosis factor-α (pg/mL)	13.7±2.9	8.1±3.3	0.07
Interleukin-6 (pg/mL)	12.1±3.5	11.4±3.7	0.4

Data are reported as mean ± standard error

FBG, fasting blood glucose; HD, hepatogenous diabetes; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance

causes (variceal bleeding [n=6], hepatorenal syndrome [n=4], bacterial infections [n=10], hepatocellular carcinoma [n=5], and liver failure [n=3]). Liver-related deaths were significantly more frequent in patients with FBG-HD (n=17/35, 48.5%) compared to those with OGTT-HD (n=9/34, 26.4%; P=0.04) and patients without HD (n=8/37, 18.9%; P=0.01), whereas no differences were noted between patients with OGTT-HD and those without HD. Overall, patients with FBG-HD had significantly worse 3-year survival than those with OGTT-HD (55.3% vs. 73.3%, P=0.03) and patients without HD (55.3% vs. 81.7%, P=0.01) (Fig. 1). Survival rates were similar between patients with OGTT-HD and without HD.

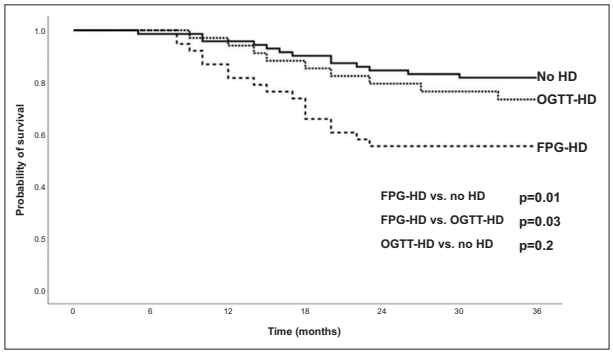

Figure 1 Three-year survival in patients with overt and subclinical hepatogenous diabetes, and patients without hepatogenous diabetes. All patients with hepatogenous diabetes received metformin or metformin/based treatment during follow up

HD, hepatogenous diabetes; FBG, fasting blood glucose; OGTT, oral glucose tolerance test

Discussion

The diabetogenic potential of liver cirrhosis has long been recognized and increases in parallel with the severity of liver disease [6,7]. Recent studies demonstrated a prevalence of HD ranging from 28.9% to 50% in cohorts of patients with predominantly decompensated cirrhosis, the diagnosis of HD being based on OGGT in more than 60% of patients. On the other hand, IGT has been noted in up to half and IR in nearly three-quarters of patients with advanced cirrhosis [12,21,22]. Diabetes in patients with cirrhosis has been reported to increase the risk of developing ascites [9-12], including refractory ascites [23], and renal dysfunction [9-13], which may occur independently of liver disease severity [9]. These observations

raise the question whether the occurrence of HD in patients with DC due to ascites could aggravate existing circulatory disorders.

Indeed, overt HD in our study was associated with worse systemic hemodynamics compared to patients with subclinical HD and those without HD, as indicated by the significant changes in SVR and CO, which were accompanied by marked homeostatic stimulation of renin synthesis. The markedly higher serum insulin levels could contribute to greater circulatory derangement in patients with overt HD, as insulin-induced arterial vasodilation—likely mediated by increased NO synthesis [24]—has been reported in patients with [25] and without cirrhosis [26]. On the other hand, high values of IR, as observed in patients with overt HD, have been associated with more accentuated hyperdynamic syndrome in patients with cirrhosis [27]. However, the most interesting finding of our study was the link between overt HD and more pronounced systemic inflammatory activity, as shown by the significantly higher levels of inflammatory mediators in the FBG-HD group compared to the OGTT-HD and no-HD groups. Accordingly, it is reasonable to suggest that the magnitude of the inflammatory burden could account for the different impact of overt and subclinical HD on circulatory function [3,28]. In the present study, LBP was utilized as a surrogate marker of LPS, the major molecular component of the outer membrane of gram-negative bacteria, since the latter has a half-life of only 2-4 min as compared to 12-24 h for LBP [29].

Systemic inflammation—including LPS-dependent production of proinflammatory cytokines such as TNF-α and IL-6—has been implicated in the development of type 2 DM [30,31]. In this respect, it is tempting to hypothesize that a more intense inflammatory potential in a number of patients with cirrhosis may predispose to the onset of overt HD. Several lines of evidence, however, indicate that there may also be a reverse link between diabetes and inflammation, in that overt diabetes may contribute to continued inflammatory activity [32,33]. Indeed, overt HD could indirectly cause endotoxemia and increased cytokine levels by increasing the prevalence of intestinal bacterial overgrowth and gut permeability [34]. In addition, prolonged hyperglycemia is known to mediate the formation of advanced glycosylation end-products, which stimulate the secretion of cytokines [35]. Finally, the marked increase in serum insulin levels might also promote inflammatory activity in patients with FBG-HD [36].

Our results further demonstrated a negative impact of overt HD on renal function and perfusion in nonazotemic patients with cirrhosis and ascites, which could possibly be attributed to worse systemic hemodynamics and greater activation of vasoactive mediators in this patient group. In this regard, Spadaro *et al* showed that overt diabetes in patients with cirrhosis may enhance renal vasoconstriction, causing renal hypoperfusion [37]. A relationship between high IR and the severity of portal hypertension has also been reported [27], which could increase renovascular resistance [38]. Finally, experimental evidence has shown that LPS may directly impair renal function in cirrhosis, via distortion of glomerular integrity and renal vasoconstriction, independently of changes in systemic hemodynamics [39]. In our study, a trend toward higher serum insulin levels, IR, PRA, and LBP was noted in patients with OGTT-HD compared to patients without HD. Though these changes did not reach statistical significance, cumulatively they may account for the worse renal function observed in patients with OGTT-HD compared to those without HD.

The long-term administration of metformin enhanced systemic hemodynamics, as well as renal function and perfusion, in patients with subclinical and overt HD, along with amelioration of inflammatory activity. In this respect, metformin has been shown to improve both gut dysbiosis and intestinal barrier integrity, thus protecting against LPS entry into the circulation [40,41]. Moreover, experimental data have indicated that metformin may reduce LPS-stimulated production of NO [42] and proinflammatory cytokines, including TNF-α [40,43,44]. Considering that none of the patients with subclinical HD treated with metformin developed overt HD, it is plausible that the anti-inflammatory effects of metformin may impede the evolution of subclinical HD to overt diabetes. It should also be noted that the use of metformin in our study had an impact on insulin levels and IR only in patients with overt HD, and not at the subclinical stage.

Survival of patients with cirrhosis, ascites, and subclinical HD treated with metformin was similar to those without HD. By contrast, in the study by Kang *et al* [12], patients with DC and untreated subclinical HD had significantly lower survival than those without HD. On the other hand, the patients with overt HD in our study had the worst prognosis, despite metformin-based treatment. Our findings suggest that the early detection of HD at its subclinical stage, which is characterized by less intense circulatory and renal impairment and inflammatory activity, could be a major determinant of prognosis.

The main strength of the present study is that it is the first to assess the circulatory, renal, and inflammatory-modulating effects of overt and subclinical HD and metformin, as well as the prognostic impact of long-term metformin treatment in patients with DC and HD. However, our study also had some limitations. First, the number of patients included was relatively small, although clear differences were found between the study groups. Second, there have been no further studies in patients with subclinical HD not taking metformin or in patients without HD, which could further illustrate the effects of metformin use. Third, it is uncertain whether our results apply to all patients with advanced cirrhosis, because we arbitrarily excluded patients with a Child-Pugh score >12 and/or refractory ascites, on the basis that these patients usually have marked circulatory dysfunction and a poor short-term prognosis. Finally, the FBG-HD group consisted of patients with newly diagnosed as well as known HD. This heterogeneity may have influenced the results, because patients with newly diagnosed FBG-HD may have a different risk profile compared to those with long-standing diabetes. Nevertheless, the severity of cirrhosis at baseline was similar in both groups.

In conclusion, overt HD in patients with cirrhosis and ascites is associated with greater impairment of circulatory function, and renal function and perfusion, than subclinical

HD or the absence of HD, possibly because of greater systemic inflammatory activity. Treatment of subclinical and overt HD with metformin in these patients exerts beneficial circulatory, renal and anti-inflammatory effects. Early detection of HD at subclinical stages by OGTT and initiation of metformin may improve the clinical outcome, whereas the prognosis is worse when treatment starts at the stage of overt HD. Further well-designed large-scale studies are needed to confirm the observed benefits of metformin in patients with DC and HD, and to understand the mechanisms involved.

Summary Box

What is already known:

- Hepatogenous diabetes (HD) occurs commonly in advanced cirrhosis
- Hyperinsulinemia is implicated in the pathogenesis of HD, via a reduced liver capacity to inactivate insulin and portosystemic shunting
- HD has been associated with an increased risk of developing complications related to circulatory disorders, such as ascites and renal dysfunction

What the new findings are:

- Overt HD in patients with cirrhosis and ascites predisposes to worse circulatory function, and renal function and perfusion, linked to greater systemic inflammation
- The long-term use of metformin in patients with subclinical and overt HD exerts beneficial circulatory and renal effects, along with a reduction in inflammatory activity
- Early initiation of metformin in patients with HD diagnosed by an oral glucose tolerant test improves their prognosis, whereas the clinical outcome is worse when treatment starts at the stage of overt HD

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