

Clinical Manifestations and Treatment Options in Patients with Cirrhosis and Diabetes Mellitus

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Key Words

Diabetes mellitus · Glycemic control · Hepatogenous diabetes · Impaired glucose tolerance · Cirrhosis

Abstract

Background: Diabetes is frequently diagnosed in patients with cirrhosis and represents an important risk factor for morbidity and mortality. Pharmacological therapy is limited due to hepatotoxicity and the risk of hypoglycemia. Investigations on medical practice in this patient population, frequency of diabetes-associated complications and the impact of quality of metabolic control are rare. **Aims and Methods:** A retrospective analysis was performed to compare the effects of hypoglycemic treatment, the achieved glycemic control under therapy, the prevalence of typical cirrhosis-related or microangiopathic complications, and cardiovascular comorbidities between a group of diabetic patients with cirrhosis (n = 87) and a nondiabetic cirrhotic population (n = 198). **Results:** The prevalence of diabetes in our cohort was 30.5%. Of all diabetic patients, 39.1% received therapy which might potentially result in serious side effects in patients

with end-stage liver disease. The rate of ongoing alcohol abuse (28.7%) and noncompliance under medication (41.4%) was high. Only 28.7% of all diabetic subjects showed satisfactory (as defined by $HbA_{1c} \leq 6.5\%$) glycemic control under therapy. Patients achieving satisfactory control experienced a lower rate of certain cirrhosis-related complications such as hepatic encephalopathy (HE) and hepatocellular carcinoma (HCC), arterial hypertension, and hypercholesterolemia. HE was significantly more frequent in diabetic than nondiabetic cirrhotic patients [HE 36.6% (diabetics) vs. 20.7% (nondiabetics), $p = 0.001$; $OR_{adj} = 3.21$ (CI: 1.63, 6.28)], whereas no significant difference in the frequency of HCC [18.4% (diabetics) vs. 14.1% (nondiabetics), $p = 0.606$] was observed. In the majority of our diabetic population (59.7%), no microvascular damage was diagnosed. However, diabetic patients had a borderline significant high prevalence of arterial hypertension [48.3% (diabetics) vs. 26.8% (nondiabetics), $p = 0.078$; $OR_{adj} = 1.68$ (CI: 0.944, 2.978)] and high cholesterol levels [17.2% (diabetics) vs. 8.6% (nondiabetics), $p = 0.120$, $OR_{adj} = 1.93$ (CI: 0.842, 4.410)]. **Conclusion:** Antidiabetic therapy in cirrhotic diabetic patients often seems to be inappropriate in everyday medicine, while glycemic control is fre-

quently not satisfactory, possibly due to incompliance or insufficient metabolic control. HE occurs more often in cirrhotic patients with diabetes than in nondiabetic patients with cirrhosis. The rate of macro- and microangiopathic complications even in the diabetic cohort is low.

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Introduction

Both impaired glucose tolerance and overt diabetes mellitus have a high prevalence in cirrhosis. In most cases, the manifestation of the diabetic condition seems to follow the presence of cirrhosis and is therefore called hepatogenous diabetes (HD). [1]. Interestingly, a normalization of the diabetic state was observed after orthotopic liver transplantation [2, 3].

It is not possible to distinguish between HD and ordinary type 2 diabetes by assessing biochemical or genetic parameters. However, HD is considered as a different diabetic entity as it is characterized by certain features such as lack of family diabetes history and a low rate of macro- and microangiopathic complications [4]. According to the literature, more than 20% and up to 60% of all cirrhotic patients are affected by diabetes, while the prevalence of glucose intolerance and insulin resistance occur in up to 100% [5–9]. The occurrence of a disturbed glucose metabolism seems to be aggravated by the severity of liver disease [10].

However, HD represents an important risk factor for overall mortality [11]. Interestingly, death mainly occurs due to hepatocellular failure and not because of diabetic microvascular complications, as is often the case in type 2 diabetes [5, 11]. Diabetic cirrhotic patients are prone to develop more typical complications of cirrhosis including an increased rate of gastrointestinal bleeding, recurring episodes of hepatic encephalopathy (HE), more bacterial infections, hepatocellular carcinoma (HCC) and diuretic-resistant refractory ascites [12–18].

Although control of the diabetic condition is of particular importance in cirrhotic patients to reduce the onset of typical complications of cirrhosis, there is insufficient clarity about the practicability of antidiabetic therapy and the most efficacious therapy. Furthermore, the prognostic impact of satisfactory glycemic control under hypoglycemic therapy in patients with diabetes and cirrhosis has not been assessed sufficiently thus far. Since glycemic control is fundamental in diabetes to reduce microvascular complications and because investigations on current practices of treatment in diabetic and cirrhotic

patients are extremely sparse, a retrospective analysis of a series of patients with cirrhosis and diabetes in a tertiary referral center was performed. Outcomes of interest included the medication used and frequency of cirrhosis-related and diabetes-induced complications in comparison with cirrhotic subjects without diabetes.

Methods

Study Population

Retrospectively, the data from hospitalized cirrhotic patients with and without diabetes during a 4-year period (January 2005 to May 2008) from the database of the departments of gastroenterology and endocrinology of Bogenhausen Hospital were evaluated. A total of 285 patients with cirrhosis were admitted during this period; of these patients, 87 also suffered from diabetes. Patient records were evaluated with special focus on family history of diabetes, laboratory parameters (including HbA_{1c}, preprandial plasma glucose and postprandial plasma glucose), typical diabetes complications (such as chronic diabetic nephropathy, neuropathy and retinopathy), comorbidities eventually contributing to higher morbidity and mortality (such as coronary heart disease, stroke, hypertension and dyslipidemia), antidiabetic medication, information about compliance (based on doctors', patients' and relatives' reports), and alcohol consumption. Cirrhosis was established by either histology or by clinical, laboratory, and radiographic findings. The entire etiologic spectrum of cirrhosis was included. A Child-Pugh (CP) classification score was calculated for each patient (CP A, up to 7 points; CP B, 8–10 points; CP C, >11 points). Detailed clinical characteristics were extracted from the data base as detailed as possible, e.g. history of ascites or HCC (diagnosed by abdominal ultrasound) and portal hypertension (PH; diagnosed by endoscopy). The diagnosis of HE was based on the patient's clinical presentation, usually supported by blood ammonia level and/or pathological results of neuropsychometric testing. Patients with multiple hospitalizations were counted only once, and their earliest hospitalization data was chosen as the index hospitalization. None of the diabetic cirrhotic patients had a family history of first-degree relatives with diabetes, making the diagnosis of HD highly probable. Glycemic control was diagnosed by evaluation of glycosylated hemoglobin level (HbA_{1c}), fasting plasma glucose or peak postprandial plasma glucose.

Recent recommendations for adults with diabetes under therapy recommend a HbA_{1c} to be as close to normal (6.5%), representing normal fasting and postprandial glucose concentrations without significant hypoglycemia and a fasting plasma glucose <130 mg/dl (<7.2 mmol/l) or a peak postprandial plasma glucose <180 mg/dl (10.0 mmol/l), respectively [19]. Glycemic control is fundamental to reduce microvascular complications. Therefore, we compared diabetic patients with satisfactory glycemic control (as described before) with those showing insufficient glycemic control [HbA_{1c} >6.5%; fasting plasma glucose >130 mg/dl (>7.2 mmol/l); peak postprandial plasma glucose >180 mg/dl (10.0 mmol/l)] concerning the frequency of typical cirrhosis-related complications (ascites, PH, HCC and HE) and microvascular complications. The nondiabetic population of cirrhotic patients served as the control group.

Typical diabetes-related complications (e.g. chronic nephropathy, neuropathy and retinopathy) were diagnosed by standard diagnostic procedures (screening for microalbuminuria; pinprick sensation, temperature and vibration perception; and eye examination by an ophthalmologist).

Since cirrhotic patients with diabetes are prone to develop episodes of hypoglycemia, especially when receiving insulin therapy, we also assessed the occurrence of decreased plasma glucose levels [<70 mg/dl (<3.9 mmol/l)] or documented hypoglycemia.

Statistical Analyses

Statistical analysis was performed using PASW Statistics 17.0 (SPSS Inc., Chicago, Ill., USA). Qualitative data are presented as absolute and relative frequencies, and quantitative data are presented as the median and range (minimum, maximum). For comparison of cirrhotic patients with and without diabetes regarding complications, logistic regression models were fitted to adjust for age, gender and CP status since both groups differed in these variables. Bar plots show the relevant frequencies of complications and differences between the groups. Adjusted ORs with 95% CI are presented as measures of association. For comparison of binary variables between subgroups (e.g. diabetics with sufficient vs. insufficient glycemic control, different antidiabetic treatments), χ^2 tests including Fisher's exact test were conducted. All tests were performed on a two-sided level of significance of $\alpha = 0.05$. Since all tests were performed in an explorative manner, no adjustment for multiple comparisons was conducted.

Results

Clinical Characteristics of Study Population

The clinical characteristics of all cirrhotic patients [$n = 285$ (179 men, 106 women); diabetic group: $n = 87$ (64 men, 23 women)] with and without diabetes are presented in table 1.

The median age was 63.4 years [nondiabetic group: 61 years (range: 23–93); diabetic group: 69 years (range: 43–93)]. The etiology of cirrhosis was alcohol abuse in 173 patients [60.7% (nondiabetic group: 64.6%; diabetic group: 51.7%)], cryptogenic in 40 [14% (nondiabetic group: 7.1%; diabetic group: 29.9%)], hepatitis B in 7 [2.5% (nondiabetic group: 1.5%; diabetic group: 4.6%)], hepatitis C in 27 [9.5% (nondiabetic group: 10.1%; diabetic group: 8%)], other specific causes (including primary biliary cirrhosis, hemochromatosis and autoimmune hepatitis) in 21 [7.4% (nondiabetic group: 9.1%; diabetic group: 3.4%) and combined causes in 17 [6% (nondiabetic group: 7.6%; diabetic group: 2.3%)]. On the basis of CP classification, 113 patients [39.6% (nondiabetic group: 38.8%; diabetic group: 46%)] belonged to stage A cirrhosis, 100 [35.1% (nondiabetic group: 33%; diabetic group: 43.7%)] were in stage B and 62 [21.8% (nondiabetic group: 28.2%; diabetic group: 10.3%)] in stage C. Based on the hospital

records, 147 patients [51.6% (nondiabetic group: 61.6%; diabetic group: 28.7%)] reported ongoing alcohol abuse, while 112 [39.3% (nondiabetic group: 38.4%; diabetic group: 41.4%)] were described as noncompliant, e.g. concerning regular intake of medication and following the doctor's advice. The rate of noncompliance was significantly higher in diabetic subjects ($p = 0.0001$; CI: 0.076, 0.428)], especially in patients demonstrating insufficient glycemic control (45 vs. 32% in diabetics with sufficient glycemic control). Since our study was performed retrospectively, we could not determine whether a cirrhotic patient fulfilled the criteria of compliance in 93 cases (32.6%).

Alcohol abuse was significantly higher in nondiabetic cirrhotic patients ($p = 0.0001$; CI: 0.147, 0.498) and in increased age ($p = 0.007$; CI: 0.949, 0.992) and severity of cirrhosis ($p = 0.009$; CI: 1.281, 4.213). Thus, the influence of the nondiabetic condition might be biased by a higher fraction of alcohol-induced cirrhosis compared to our diabetic group (64.6 vs. 51.7%).

Antidiabetic Treatment in Patients with Diabetes and Cirrhosis

The antidiabetic treatment in diabetic patients with cirrhosis ($n = 87$) was as follows (fig. 1): (1) insulin therapy alone in 49 patients (56.3%; conventional therapy in 28, intensive therapy in 21), (2) insulin (conventional therapy) in combination with oral hypoglycemic agents in 8 [9.2%; metformin in 5, sulfonylurea derivatives (SU; glimepiride) in 1], (3) exclusively oral hypoglycemic agents in 20 (23%) and (4) dietary treatment (e.g. carbohydrates with a low glycemic index) in 10 (11.5%).

Diabetic subjects receiving oral antidiabetic therapy were treated with SU (glimepiride, glibenclamide, glipizide) in 19 cases [21.8%; in 15 cases as monotherapy, 1 in combination with α -glucosidase inhibitors (acarbose) and 3 in combination with insulin], metformin in 8 patients [9.2%; 5 cases in combination with insulin, 2 in combination with other oral antidiabetic agents (repaglinide and pioglitazone, thiazolidinedione) and in 1 case as monotherapy], meglitinide (repaglinide) in 1 patient as monotherapy and 1 subject in combination with metformin.

Remarkably, 34 patients (39.1%) received antidiabetic medication which should be generally avoided in cirrhosis because of the danger of lactate acidosis and an increased risk to develop iatrogenic hypoglycemia (metformin in 8, SU in 19, long-acting insulin analogue in 6, thiazolidinedione in 1). Hypoglycemia was reported in 11 patients (12.6%), especially when receiving long-acting

Table 1. Clinical characteristics of all patients with cirrhosis (without and with diabetes mellitus)

	All patients (n = 285)	Nondiabetic subjects (n = 198)	Diabetic subjects (n = 87)	Sufficient glycemic control (n = 25)	Insufficient glycemic control (n = 62)
Sex	285 (100)	198 (100)	87 (100)	25 (28.7)	62 (71.3)
Male	179 (62.8)	115 (58.1)	64 (73.6)	21 (84)	43 (69)
Female	106 (37.2)	83 (41.9)	23 (26.4)	4 (16)	19 (30.6)
Mean age, years (range)	63.4 (23–93)	61 (23–93)	69 (43–93)	69 (47–93)	69 (43–87)
<i>Etiology</i>					
Alcohol abuse	173 (60.7)	128 (64.6)	45 (51.7)	16 (64)	29 (46.8)
Cryptogenic	40 (14)	14 (7.1)	26 (29.9)	7 (28)	19 (30.6)
Hepatitis B	7 (2.5)	3 (1.5)	4 (4.6)	1 (4)	3 (4.8)
Hepatitis C	27 (9.5)	20 (10.1)	7 (8)	0 (0)	7 (11.3)
Other specific causes ¹	21 (7.4)	18 (9.1)	3 (3.4)	1 (4)	2 (3.2)
Combined causes	17 (6)	15 (7.6)	2 (2.3)	0 (0)	2 (3.2)
CP A	113 (39.6)	73 (38.8)	40 (46)	9 (36)	31 (50)
CP B	100 (35.1)	62 (33)	38 (43.7)	13 (52)	25 (40.3)
CP C	62 (21.8)	53 (28.2)	9 (10.3)	3 (12)	6 (9.7)
Unknown	10 (3.5)	10 (5.1)	0 (0)	0 (0)	0 (0)
Persistent alcohol abuse	147 (51.6)	122 (61.6)	25 (28.7)	8 (32)	17 (27.4)
Noncompliance	112 (39.3)	76 (38.4)	36 (41.4)	8 (32)	28 (45.2)
Compliance	80 (28.1)	47 (23.7)	33 (37.9)	9 (36)	24 (38.7)
Unknown	93 (32.6)	75 (37.9)	18 (20.7)	8 (32)	10 (16.1)
Ascites	164 (57.5)	122 (61.6)	42 (48.3)	13 (52)	29 (46.8)
Portal hypertension	181 (63.5)	129 (65.2)	52 (59.8)	15 (60)	37 (59.7)
Hepatic encephalopathy	73 (25.6)	41 (20.7)	32 (36.8)	7 (28)	25 (40.3)
Hepatocellular carcinoma	44 (15.4)	28 (14.1)	16 (18.4)	4 (16)	12 (19.4)
Coronary heart disease/stroke	52 (18.2)	21 (10.6)	31 (35.6)	9 (36)	22 (35.5)
Arterial hypertension	95 (33.3)	53 (26.8)	42 (48.3)	8 (32)	34 (54.8)
Hypercholesterolemia	32 (11.2)	17 (8.6)	15 (17.2)	1 (4)	14 (22.6)

Values are given as n (%) unless otherwise indicated.

¹ 21/285 (primary biliary cirrhosis 10; hemochromatosis 2; autoimmune hepatitis 7; low cardiac output 3).

insulin analogue therapy alone or in combination with SU (in 6 subjects) and in more advanced (> stage A) cirrhosis (in 11 subjects).

Glycemic Control in Patients with Diabetes and Cirrhosis under Antidiabetic Therapy

The basic data of all diabetic patients concerning glycemic control, hypoglycemia rate and microvascular complications are shown in table 2. Glycemic control was sufficient [as defined by fasting plasma glucose <130 mg/dl (>7.2 mmol/l); peak postprandial plasma glucose <180 mg/dl (10.0 mmol/l)] in only 25 patients (28.7%). HbA_{1c} values were only moderately increased in most cases (mean HbA_{1c} value: 7.1%, range: 4.5–12.7%). Diabetics

with acute gastrointestinal bleeding (n = 25) had slightly higher mean HbA_{1c} values than those without bleeding (n = 62; 7.4 vs. 7.1%, respectively), while mean HbA_{1c} values were almost equal in patients with (n = 52) or without (n = 35) PH (7.1 vs. 7.2%, respectively).

Glycemic control was insufficient in 36 (73%) of the patients receiving insulin therapy (fig. 2) and in 7 subjects (88%) when combined with oral antidiabetic drugs. In the subgroup which received exclusively dietary regimes and physical exercise, 50% showed sufficient glycemic control.

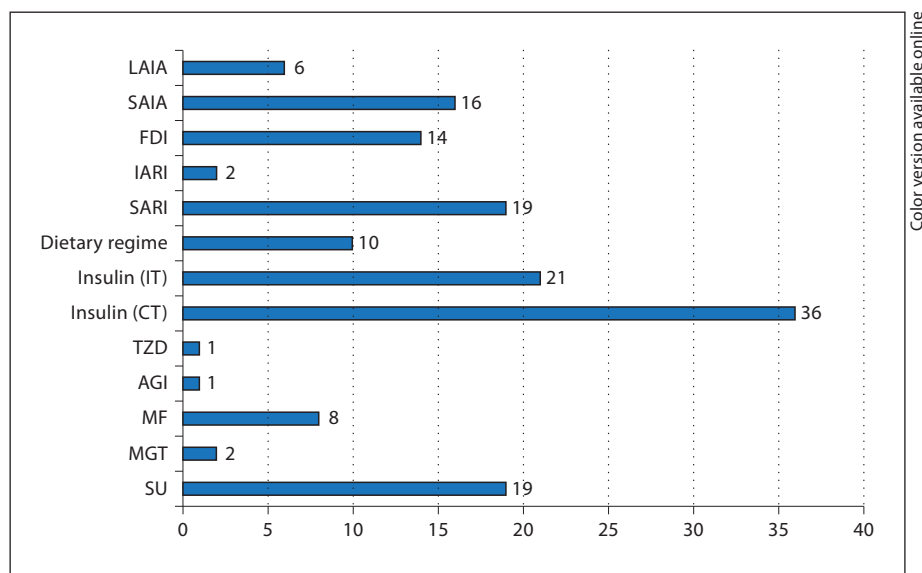
Patients with stage A cirrhosis revealed higher mean HbA_{1c} values and higher fasting plasma glucose compared with stage B cirrhotic patients (7.2%/158 mg/dl vs.

Table 2. Clinical characteristics of glycemic control, hypoglycemia rate, and microvascular and neuropathic diabetes complications in all patients with cirrhosis and diabetes (n = 87)

	All (n = 87)	CP A (n = 40)	CP B (n = 38)	CP C (n = 9)	Sufficient glycemic control (n = 25)	Insufficient glycemic control (n = 62)	Insulin (n = 49)	Insulin + OAD (n = 8)	OAD (n = 20)	Diet (n = 10)
HbA _{1c}	7.1	7.2	6.3	8.4	5.7	7.6	7.1	8.4	7.1	6.5
Preprandial capillary glucose, mg/dl	145	158	146	175	131	160	144	168	149	135
Postprandial capillary glucose, mg/dl	210	250	195	380	180	300	210	280	205	185
Hypoglycemia, n (%)	11 (12.7)	2 (5) ¹	9 (23.7) ¹	0 (0) ¹	8 (32) ¹	4 (6.5) ¹	6 (12.2) ¹	3 (33.3) ¹	3 (12.5) ¹	0 (0) ¹
Diabetic nephropathy, n (%)	23 (27)	3 (7.5) ¹	13 (34.2) ¹	6 (66.7) ¹	4 (16) ¹	19 (31) ¹	16 (32.7) ¹	0 (0) ¹	4 (16.7) ¹	3 (37.5) ¹
Diabetic polyneuropathy, n (%)	5 (5.7)	2 (5) ¹	3 (7.9) ¹	0 (0) ¹	2 (8) ¹	4 (6.5) ¹	5 (10) ¹	0 (0) ¹	0 (0) ¹	0 (0) ¹
Diabetic retinopathy, n (%)	6 (7.3)	5 (12.5) ¹	1 (2.6) ¹	2 (22.2) ¹	0 (0) ¹	6 (9.7) ¹	6 (12.2) ¹	0 (0) ¹	0 (0) ¹	0 (0) ¹

¹ Percentage for each individual proportion (n) of interest.

Fig. 1. Antidiabetic treatment in 87 patients with cirrhosis and diabetes. MGT = Meglitinide; MF = metformin; RPG = repaglinide; OAD = oral anti-diabetic drugs; TZD = thiazolidinedione; AGI = α -glucosidase inhibitors; SARI = short-acting regular insulin; IARI = intermediate-acting regular insulin; FDI = fixed-dose pre-mixed insulin; SAIA = short-acting insulin analogue (glulisine, aspartate); LAIA = long-acting insulin analogue (glargine); IT = intensive therapy; CT = conventional therapy.



6.8%/146 mg/dl, respectively). Glycemic control was insufficient in 31 (78%) of the patients with stage A cirrhosis, in 25 (66%) with stage B cirrhosis and in 6 (67%) with stage C cirrhosis (mean HbA_{1c} value: 8.4%; fasting plasma glucose: 175 mg/dl; p = 0.463; fig. 3).

Furthermore, we performed an analysis using Fisher's exact test to evaluate the influence of antidiabetic therapy and patient compliance upon the frequency of typical cirrhosis-related as well as cardiovascular comorbidities. To analyze the influence of antidiabetic treatment, all diabetic patients were divided into 4 different groups: (1) subjects receiving oral antidiabetic therapy (n = 20), (2) patients receiving insulin (n = 49), (3) patients receiving insulin plus oral antidiabetic drugs (n = 8) and (4) pa-

tients receiving only dietary treatment (n = 10). Fisher's exact test revealed no significant statistical differences between the different groups regarding the occurrence of HE (p = 0.896), ascites (p = 0.376), PH (p = 0.820), HCC (p = 0.941), coronary heart disease/stroke (p = 0.572), arterial hypertension (p = 0.170) and hypercholesterolemia (p = 0.380). Compliance was significantly correlated with a lower rate of HE (p = 0.028), but demonstrated no significant influence upon the occurrence of ascites (p = 1), PH (p = 0.631), HCC (p = 0.384), coronary heart disease/stroke (p = 0.224), arterial hypertension (p = 0.232) and hypercholesterolemia (p = 0.360).

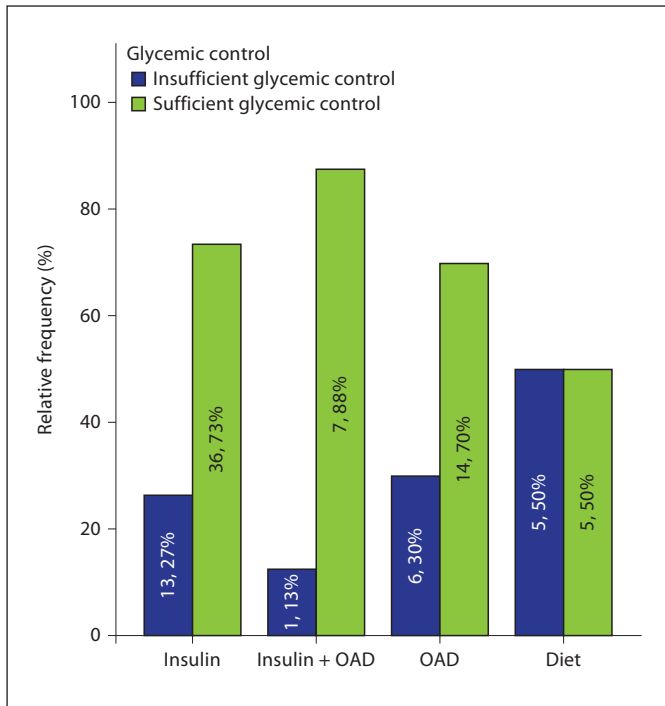


Fig. 2. Glycemic control under different antidiabetic regimens. $p = 0.376$.

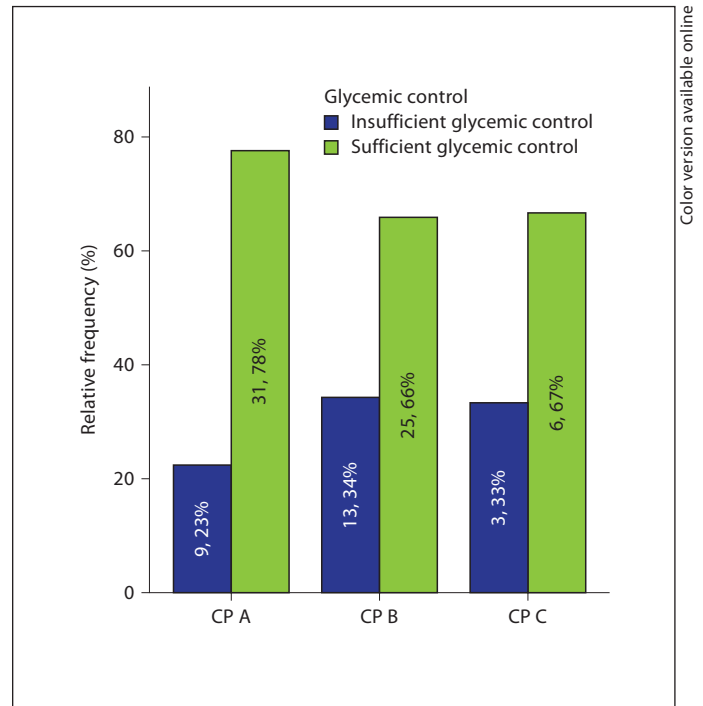


Fig. 3. Glycemic control of all cirrhotic subjects with HD according to CP classification A-C. $p = 0.463$.

Specific Complications of Diabetes and Cardiovascular Comorbidities in Cirrhotic Patients with and without Diabetes

The rate of specific complications of diabetes in our diabetic cirrhotic patients was low. Diabetic nephropathy could be diagnosed in only 23 patients (26%), diabetic polyneuropathy in 5 (5.7%) and diabetic retinopathy in 6 (6.9%) according to the diagnostic criteria mentioned above (table 2). The incidence of these specific complications of diabetes was increased according to severity of cirrhosis according to CP classification [stage A: 10/40 subjects (26.1%) vs. stage B: 17/38 subjects (46.2%) vs. stage C: 8/9 subjects (88.3%)] and occurred mainly in patients showing insufficient glycemic control (29/34). Fifty-three (59.7%) of the subjects in the diabetic subgroup revealed no signs of microvascular damage. The prevalence of cardiovascular complications associated with diabetes, compared with the nondiabetic subgroup, was as follows (table 1; fig. 1): coronary heart disease/stroke in 52 [18.2% (nondiabetic group: 10.6%; diabetic group: 35.6%)], arterial hypertension in 95 [33.3% (nondiabetic group: 26.8%; diabetic group: 48.3%)] and hypercholesterolemia in 32 [11.2% (nondiabetic group: 8.6%; diabetic group: 17.2%)].

In multivariate analysis, we found a significant effect of the diabetic condition on the occurrence of coronary heart disease/stroke [$p = 0.0001$; $OR_{adj} = 3.40$ (CI: 1.71, 6.74)], arterial hypertension [$p = 0.078$; $OR_{adj} = 1.68$ (CI: 0.944, 2.9789)] and hypercholesterolemia [$p = 0.120$; $OR_{adj} = 1.93$ (CI: 0.842, 4.410)].

When analyzing only the diabetic population concerning the impact of glycemic control under antidiabetic medication, no apparent differences between the two subgroups (sufficient and insufficient glycemic control) could be found regarding the incidence of cardiovascular comorbidities (sufficient glycemic control: 36% vs. insufficient glycemic control: 35.5%; $p = 1.000$), but concerning arterial hypertension (sufficient glycemic control: 32% vs. insufficient glycemic control: 54.8%; $p = 0.062$) and hypercholesterolemia (sufficient glycemic control: 4% vs. insufficient glycemic control: 22.2%; $p = 0.057$).

Prevalence of Typical Cirrhosis-Related Complications in the Study Population

The prevalence of typical complications associated with cirrhosis was as follows (table 1; fig. 4): ascites in 164 patients [57.5% (nondiabetic group: 61.6%; diabetic group:

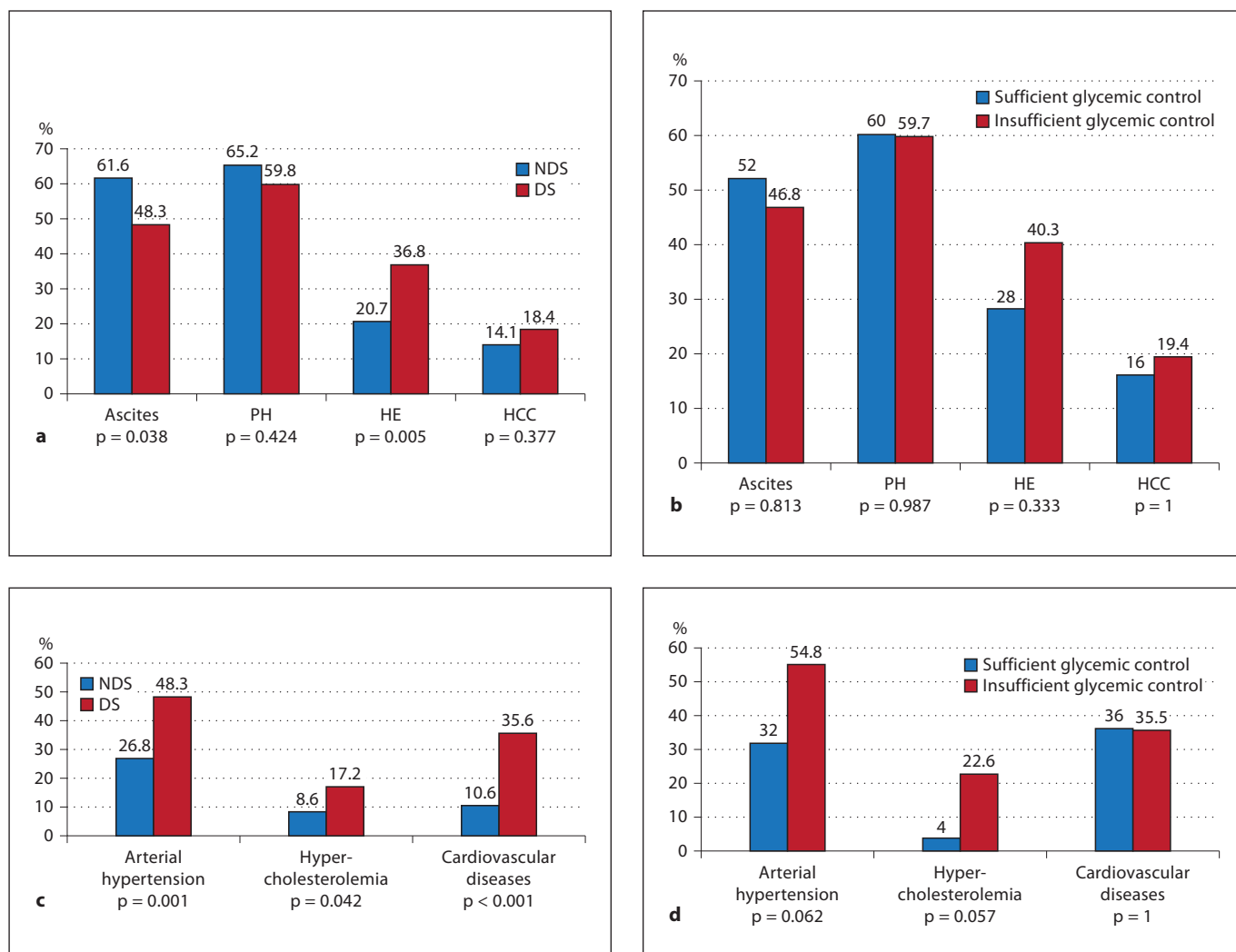


Fig. 4. Rate of cirrhosis-related-complications (ascites, PH, HE, HCC) and of cardiovascular-related complications in cirrhotic patients with (diabetic subjects, DS) and without (nondiabetic subjects, NDS) diabetes mellitus (a, b) and in diabetic subjects demonstrating sufficient and insufficient glycemic control (c, d).

48.3%), PH in 181 [63.5% (nondiabetic group: 65.2%; diabetic group: 59.8%)], HE in 73 [25.6% (nondiabetic group: 20.7%; diabetic group: 36.8%)] and HCC in 44 [15.4% (nondiabetic group: 14.1%; diabetic group: 18.4%)].

In multivariate analysis, we found a significant effect of diabetic condition [$p = 0.001$; $OR_{adj} = 3.21$ (CI: 1.63, 6.28)] and severity of cirrhosis ($p = 0.001$; CI: 1.005, 4.125) on the occurrence of HE, but none for age ($p = 0.43$) and gender ($p = 0.517$). We found a significant influence of the severity of cirrhosis (as assessed by CP score) on the occurrence of ascites ($p = 0.001$; CI: 3.798, 12.966), but none for age ($p = 0.82$), gender ($p = 0.781$) and diabetic condition ($p = 0.6$). Regarding PH, multivariate analysis showed

a significant influence of the severity of cirrhosis ($p = 0.001$; CI: 1.469, 4.591), but none for age ($p = 0.398$), gender ($p = 0.988$) and diabetes ($p = 0.832$; $OR = 0.939$). Regarding HCC, we found a significant influence of age ($p = 0.002$; CI: 1.018, 1.084; chances per year are increased by the factor $OR_{adj} = 1.05$) and a gender effect for men ($p = 0.035$), but none for diabetic condition ($p = 0.606$) and severity of cirrhosis ($p = 0.71$).

When analyzing only patients with cirrhosis and diabetes (by performing χ^2 tests including Fisher's exact test), the rate of HE in patients with insufficient glycemic control was higher compared to those with sufficient glycemic control (insufficient glycemic control: 40.3% vs.

sufficient glycemic control: 28%; $p = 0.333$). No differences between the two subgroups regarding glycemic control (sufficient and insufficient) could be found regarding occurrence of ascites (sufficient glycemic control: 52.2% vs. insufficient glycemic control: 46.8%; $p = 0.813$), PH (sufficient glycemic control: 60.2% vs. insufficient glycemic control: 59.7%; $p = 1.000$) and HCC (sufficient glycemic control: 16.1% vs. insufficient glycemic control: 19.4%; $p = 1.000$).

Discussion

Impaired glucose tolerance and diabetes occur frequently in patients with cirrhosis [11, 20, 21]. A diabetic condition following cirrhosis is named HD. Suspected causes include obesity, chronic HCV infection, iron overload, alcohol abuse and insulin resistance of the peripheral tissues due to hyperinsulinemia which is caused by a reduced insulin extraction rate in the liver, portosystemic shunts and raised levels of contra-insulinary hormones including glucagon, insulin-like growth factor and growth hormone [11, 20–24].

Diabetes therapy in patients with liver cirrhosis is complex in daily routine due to liver damage which may reduce metabolism and thereby elimination of certain drugs or a potential hepatotoxicity of some oral antidiabetic drugs [11, 25]. In contrast to the situation in type 2 diabetes mellitus, there are no recommendations or guidelines for adequate treatment of HD. Furthermore, lower hepatic insulin extraction, reduced hepatic glycogen stores and impaired glucagon catabolism increase the risk of hypoglycemia under antidiabetic therapy [11]. Interestingly, some new studies have demonstrated that the choice of antidiabetic medication may represent possible measures of cancer prevention since treatment with metformin may reduce significantly the risk of HCC [26, 27].

Surprisingly, the effect of HD on the clinical outcome of cirrhosis has been evaluated in only few studies. Holstein et al. [4] analyzed the outcome of diabetes in a cirrhotic cohort and found a low rate of cardiovascular diseases and retinopathic complications. Kim and Choi [28] performed a study to assess differences between HD and type 2 diabetes, and found significantly higher ratios of postprandial plasma glucose/fasting plasma glucose and fasting plasma insulin in HD compared to type 2 diabetes. A general problem of most of the published studies which investigated the frequency of cirrhosis-related complications in diabetic cirrhotic patients such as HE or

HCC is that they only included relatively small population sizes [12, 13, 16].

To the best of our knowledge, no study has assessed the prognostic impact of satisfactory glycemic control under hypoglycemic therapy in patients with diabetes and cirrhosis thus far.

To compare the effects of hypoglycemic treatment, the achieved glycemic control under therapy, the prevalence of typical cirrhosis-related or microangiopathic complications, and cardiovascular comorbidities between a group of cirrhotic patients with and without diabetes, we performed a retrospective analysis in a tertiary referral center.

Although the majority of our diabetic population (56%) suffered from advanced cirrhosis (> stage A), which represents a situation of particular caution concerning the choice of medication due to increased hepatotoxicity, a high proportion of the diabetic patients (39.1%) received antidiabetic medication which might result in serious side effects, especially in patients with end-stage liver disease. These include metformin, SU with a long elimination half-life and insulin therapy (containing fixed-dose and long-acting insulin regimes), causing possibly lactic acidosis and severe iatrogenic hypoglycemia. Additionally, 28.7% of all diabetic patients reported ongoing alcohol abuse while 41.4% were described as noncompliant concerning intake of medication, which may represent counterindications for pharmacological antidiabetic therapy. Interestingly, most of the diabetic patients in the present study (71.3%) showed no sufficient glycemic control, independent of the antidiabetic regime used (fig. 4). In our study, hypoglycemia was reported in 12.6% of the patients and occurred especially with insulin therapy and in more advanced (>stage A) cirrhosis.

While good glycemic control is considered crucial in type 2 diabetes in order to delay or reduce long-term microvascular complications, this problem has not been thoroughly assessed in cirrhotic patients with diabetes thus far. In the present study, the majority of patients with cirrhosis fulfilled the criteria of insufficient glycemic control (fig. 3). Diabetic patients with insufficient glycemic control had a higher rate of HE [40.3% compared to 28% (when glycemic control was sufficient), $p = 0.333$]. However, this association was not statistically significant. Compliance was significantly correlated with a lower rate of HE ($p = 0.028$). In addition, no obvious differences could be found between the subgroups with sufficient and insufficient antidiabetic therapy regarding the occurrence of ascites (52 vs. 46.8%, $p = 0.813$), PH (60 vs. 59.7%, $p = 1.000$) and HCC (16 vs. 19.4%, $p = 1.000$) or the

occurrence of cardiovascular comorbidities (36 vs. 35.5%, $p = 1.000$). However, arterial hypertension and hypercholesterolemia were more frequent in diabetic patients with insufficient glycemic control (32 vs. 54.8%, $p = 0.062$; and 4% vs. 22.2%, $p = 0.057$, respectively).

Diabetic microvascular complications seem to occur less frequently in cirrhotic diabetics than in patients with ordinary type 2 diabetes without simultaneous cirrhosis [5, 11]. In accordance with the published medical literature, the rate of diabetes-related sequelae in the present study was low and occurred mainly in patients with advanced cirrhosis (> stage A according to CP classification) and in patients showing insufficient glycemic control (table 2). In the majority of our diabetic population (59.7%), no microvascular damage could be diagnosed. However, cardiovascular complications such as coronary heart disease or stroke occurred more often in the diabetic population than in the nondiabetic patients [35.6 vs. 10.6%; multivariate analysis $p = 0.0001$; $OR_{adj} = 3.40$ (CI: 1.71, 6.74)]. Arterial hypertension and hypercholesterolemia were more frequent in diabetic cirrhotic patients (48.3 and 17.2%, respectively) compared to nondiabetic patients (26.8 and 8.6%, respectively). The high proportion of cardiovascular diseases and arterial hypertension in the diabetic cohort might also be related to the relatively higher average age of 69 years in this group.

Independent from glycemic control, previous studies demonstrated that HD represents an important risk factor for total mortality since diabetic patients with simultaneous cirrhosis are prone to develop certain common complications such as ascites and HE more frequently compared to nondiabetic cirrhotic patients [11, 12–18, 22]. In the present study, HE and HCC could be diagnosed more frequently in diabetic patients (36.8 and 18.4%, respectively) compared to the nondiabetic subgroup (20.7 and 14.1%, respectively). However, ascites and PH occurred more frequently in nondiabetic cirrhotic patients (61.6 and 65.2%, respectively) than in the diabetic subgroup (48.3 and 59.8%, respectively). Since multivariate analysis demonstrated a significant effect of the severity of cirrhosis (as assessed by CP score) on the occurrence of ascites ($p = 0.001$; CI: 3.798, 12.966) and PH ($p = 0.001$; CI: 1.469, 4.591), the higher frequency of these two complications seems to be due to the higher proportion of advanced cirrhosis in the nondiabetic population (rate of stage C cirrhosis in nondiabetics 28.2 vs. 10.3% in diabetics). Another explanation might be the significantly higher frequency of alcohol abuse in nondiabetic (61.6%) than in diabetic cirrhotic patients (28.7%) in the present study.

Taking the results together, one can say that antidiabetic therapy in cirrhotic diabetic patients often seems to be inappropriate in everyday medicine while glycemic control is frequently not satisfactory, possibly due to alcohol abuse, in compliance and insufficient metabolic control. HE occurs more often in cirrhotic patients with diabetes than in nondiabetic patients with cirrhosis. The rate of macro- and microangiopathic complications in diabetic subjects seems to be much lower than one can expect in patients with type 2 diabetes. Therefore, an antidiabetic treatment should be started mainly to avoid certain typical cirrhosis-related complications such as HE and HCC.

Nevertheless, HD which develops as a complication of cirrhosis is not recognized by the American Diabetes Association and the World Health Organization as a specific independent entity [11, 19]. Yet, all of the oral antidiabetic drugs may cause potential hepatotoxic effects and hypoglycemia, especially in advanced cirrhosis, and should therefore be used with caution. As a result, the safest and most efficacious therapy for diabetic condition in cirrhosis is still unclear. Furthermore, the prognostic benefit of a strict glycemic control under therapy on the clinical course of liver disease has not been established.

Some limitations of this study should be considered. First, the present study was performed retrospectively and included a relatively low number of patients with different causes of cirrhosis, e.g. alcohol abuse and chronic viral hepatitis, who received satisfactory antidiabetic treatment. Secondly, as discussed above, there is no specific biochemical or molecular marker to distinguish between HD and type 2 diabetes mellitus. However, the diagnosis of HD is arbitrarily defined by the onset of the diabetic condition after a diagnosis of cirrhosis was made, by lack of family history of diabetes and very rare microangiopathic complications. According to these criteria, the present study population consisted of subjects suffering from HD and not type 2 diabetes. Thirdly, the conventional diagnostic hallmarks of diabetes mellitus including glycosylated hemoglobin level (HbA_{1c}), which represents a doubtful parameter of long-term glycemic control in cirrhotic patients, do not seem to be perfect markers in HD. Nevertheless, the diagnosis of diabetes was performed according to recent recommendations for adults with diabetes [HbA_{1c} as close to normal (6.5%) representing normal fasting and postprandial glucose concentrations without significant hypoglycemia and a fasting plasma glucose <130 mg/dl (<7.2 mmol/l) or a peak postprandial plasma glucose <180 mg/dl (10.0 mmol/l), respectively] [19].

To conclude, disturbances of glucose metabolism in patients with cirrhosis affect prognosis and the complication and mortality rates. Therefore, guidelines or guideline-like recommendations are necessary for general practitioners, as well as gastroenterologists and hepatologists treating patients with chronic liver diseases. Furthermore, the impact of satisfactory glycemic diabetes therapy in cirrhotic patients should be confirmed by pro-

spective intervention studies analyzing additionally the safety profile of antidiabetic medication in chronic liver disease.

Disclosure Statement

None.

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