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Cardiovascular Disease in Cirrhosis

A Point-Prevalence Study in Relation to Glucose Tolerance

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OBJECTIVE: Impaired glucose tolerance or diabetes are frequently observed in cirrhosis. Overt diabetes was reported to affect long term survival of cirrhotic patients by increasing the risk of hepatocellular failure, without increasing the risk of diabetes-associated cardiovascular events.

METHODS: We evaluated the prevalence of cardiovascular disease in 122 patients with cirrhosis, subdivided according to their glucose tolerance. The following parameters were considered: arterial pressure, peripheral vascular disease (ankle to brachial pressure ratio), ischemic heart disease, microalbuminuria, retinopathy. The prevalence of abnormal findings was compared with that observed in 60 randomly selected patients with non–insulin-dependent diabetes and in 40 controls.

RESULTS: Noninsulin-dependent diabetic patients and patients with cirrhosis and diabetes were comparable for age, metabolic control, and smoking habits; the duration of diabetes was 5 yr longer for noninsulin-dependent diabetes. In cirrhosis, the prevalence of micro- and peripheral macroangiopathy, as well as coronary heart disease, was not different in relation to glucose tolerance, it was comparable to that of controls, and significantly lower than that observed in noninsulin-dependent diabetes.

CONCLUSIONS: Cirrhotic patients, even in the presence of overt diabetes, are at low risk of cardiovascular disease. The low prevalence may be related to shorter duration of diabetic disease, also in relation to reduced life expectancy, as well as to liver disease-induced abnormalities protecting the cardiovascular system from atherosclerosis. (Am J Gastroenterol 1999;94:655–662. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

Carbohydrate metabolism, both in the fasting postabsorptive state and in response to oral glucose or meals, is grossly abnormal in most patients with liver cirrhosis. In a few patients overt diabetes may be present, usually associated with hyperinsulinemia, and similar to type II (noninsulin-dependent) diabetes mellitus.

The exact prevalence of diabetes and glucose intolerance in cirrhosis is variable, in relation to severity of disease and criteria of glucose intolerance (1–3). According to criteria of National Diabetes Data Group (4), the prevalence of diabetes (19%) and glucose intolerance (17%) is higher in cirrhosis than in chronic hepatitis (16% and 13%, respectively) (3), suggesting a role of decreased liver function and/or portal systemic shunting. This study included only cirrhotic patients with normal body weight and without ascites; it is conceivable that, in patients with more advanced disease, the prevalence may be still higher.

In most cases diabetes seems to follow cirrhosis, being associated with advanced disease, but in a few cases diabetes seems to precede cirrhosis or the symptoms of both diseases are simultaneously found. In an old study on 504 patients, cirrhosis came first in 45% of cases, diabetes was first in 40%, and in 15% the two diseases were simultaneously found (5). In a more recent series including 106 patients with cirrhosis and clinically detectable diabetes, cirrhosis was first in only 25% of cases and diabetes was first in 44%, leaving a 31% of simultaneous association (6).

Such a large prevalence of diabetes would be expected to produce a significant morbidity and mortality in cirrhosis because of diabetes-associated complications. Diabetes *per se* is a risk factor of paramount importance for cardiovascular disease (7), leading to an increased prevalence of coronary heart disease, macrovascular disease, stroke, and cardiac failure (8). Part of the risk may be mediated by increased blood pressure (9) or microalbuminuria (10). In particular, a raised urinary albumin excretion rate is a likely expression of diffuse vascular damage (11), and is associated with cardiovascular disease also in nondiabetic patients (12, 13).

Only a few data have been reported on the prognostic significance of diabetes in cirrhosis. In a large series of patients with cirrhosis, the presence of diabetes was not a significant risk factor for mortality in a Cox regression model (14), but subjects were in fairly good conditions, and diabetes was relatively rare. Also in familial hemochromatosis, where diabetes is a nearly constant finding, diabetes was no longer associated with increased mortality after adjustment for cirrhosis (15). Only recently a retrospective/prospective study showed that patients with cirrhosis and clinically detectable diabetes are at increased risk for mor-

tality (6), but unexpectedly the causes of death were mainly related to liver failure and not to diabetes-associated cardiovascular complications.

No cross-sectional study on the prevalence of cardiovascular disease has ever been reported in cirrhosis. In this prospective study we enrolled a large series of patients with cirrhosis, stratified according to their degree of impaired glucose metabolism, to determine the prevalence of micro and macrovascular disease. Results were compared with those obtained in a consecutive series of outpatients with noninsulin-dependent diabetes mellitus and in an age-matched control population.

MATERIALS AND METHODS

Patients

The study was carried out in our Department of Internal Medicine, including a Liver Disease Section and a Diabetes Clinic. In the period between January 1992 and December 1993, 97 new patients with cirrhosis were observed and enrolled in the study. During 1994–1995, 25 more patients with cirrhosis and diabetes were studied, with the final number of patients with cirrhosis totaling 122. This was done to obtain a larger series of patients with cirrhosis and diabetes comparable to noninsulin-dependent diabetic subjects. Clinical data, pertinent liver function tests, and indices of glucose metabolism are given in Table 1. The cirrhosis was of viral origin in 66% of cases (HBV, 15 cases; HCV, 66 cases) and of alcoholic origin in 32 cases. The remaining nine patients had primary biliary cirrhosis (six patients), α_1-antitrypsin deficiency (one case), Wilson's disease (one case), and familial hemochromatosis (one case). Approximately 30% of them had been admitted for diagnostic purposes, 50% for cirrhosis-associated complications (ascites, gastrointestinal hemorrhage). Twenty-five patients had been admitted because of ultrasound evidence of focal liver lesion, and were studied before any specific treatment (ethanol injection, transcatheter arterial chemoembolization). Esophageal varices were present in 83 patients.

Patients were divided in three groups, according to their fasting and/or 2-hr blood glucose in response to an oral glucose tolerance test (OGTT) (4). A first group (47 patients) had normal glucose tolerance; a second group (27 patients) had impaired glucose tolerance; the third group (48 patients) had diabetes mellitus, diagnosed on the basis of fasting hyperglycemia and/or treatment with insulin or oral hypoglycemic agents (36 cases), or solely on the basis of the 2-hr blood glucose during OGTT above 11 mmol/L (11 cases). Diabetes was untreated, or was treated by simple dietary advice in 32 cases, by oral hypoglycemic agents in 10 cases, and by long acting insulin in six cases.

Sixty outpatients with noninsulin-dependent diabetes mellitus (NIDDM) were also studied as controls. They were selected in random order among NIDDM patients attending the Diabetes Clinic (two patients/day), and were thoroughly investigated using the same protocol used for cirrhotic pa-

Table 1. Pertinent Clinical and Laboratory Data in the Various Groups of Subjects Under Study (Mean [SD])

	Sex (M/F)	Age (yr)	BMI* (kg/m^2)	Glucose (mmol/L)	HbA_{1c} (%)	Insulin (pmol/L)	Albumin (g/L)	Bilirubin (mg/dl)	Proth Ac* (%)	Platelets (10^3/mmc)	Triglycerides (mg/dl)	Cholesterol (mg/dl)
Cirrhosis												
All cases (122)	81/41	18–81	25.2 [3.6]	6.9 [3.7]†	7.4 [2.3]†	97 [29]†	31.0 [4.6]	2.3 [3.0]	60 [15]	91 [46]†	94 [32]†	138 [46]†
Normal glucose tolerance (47)	32/15	18–74	25.2 [3.1]	4.8 [0.6]	4.1 [0.3]	107 [23]†	32.0 [3.7]	1.6 [1.2]	60 [13]	84 [28]†	89 [31]†	137 [40]†
Impaired glucose tolerance (27)	19/8	40–71	24.5 [3.3]	4.8 [0.6]	4.8 [0.8]	120 [29]†	29.6 [4.2]	1.9 [0.9]	62 [15]	103 [67]†	93 [26]†	149 [63]†
Diabetes (48)	30/18	38–81	25.6 [4.2]	10.2 [4.1]†	8.2 [1.9]†	74 [16]	30.9 [5.4]	3.3 [4.5]	61 [17]	92 [47]†	100 [40]†	133 [38]†
NIDDM (60)	40/20	35–74	27.5 [4.4]	9.6 [3.2]†	7.9 [1.7]†	68 [17]	37.1 [4.5]	0.8 [0.4]	92 [9]	253 [83]	163 [50]‡	219 [41]‡
Controls (40)	30/10	38–76	23.4 [3.7]	4.9 [0.6]	4.1 [0.5]	53 [17]	37.9 [3.6]	0.9 [0.5]	92 [7]	230 [65]	135 [52]	192 [26]

*BMI = body mass index (Weight/Height^2); Proth Ac = prothrombin activity.
† Significantly different from controls.
‡ Significantly different from the corresponding value of patients with cirrhosis and diabetes.
Liver function tests (albumin, bilirubin, prothrombin activity) were altered in all groups of patients with cirrhosis, but not in patients with NIDDM.

tients. Because these patients are routinely submitted to most of the investigations of the present study every 6–12 months, all tests performed in the last 2 months were not repeated. NIDDM had been diagnosed by 10.1 (SD 6.8) yr, and was treated by diet, oral hypoglycemic agents, and in only six cases by insulin because of secondary failure.

Forty subjects without any clinical evidence or previous history of cardiovascular or hepatic disease were also studied as controls. They were randomly selected among patients admitted to the department because of diseases involving the gastrointestinal tract (peptic disease, biliary stones, irritable bowel syndrome, or inflammatory bowel disease) or urinary tract (kidney stones). In all cases fasting blood glucose was $<$6.5 mmol/L.

All subjects had normal renal function (plasma creatinine $<$1.2 mg/dl). In each subject present and past smoking habits were recorded. Smokers were defined as persons smoking more than one cigarette per day or known to have smoked within three yr before the study.

All subjects gave their consent to take part in the study, which included only noninvasive measurements and was approved by the Senior Staff Committee of the Department.

Methods

The study of the cardiovascular system was performed in the morning, and included the following evaluations: ECG recording, arterial pressure, ankle-to-brachial systolic blood pressure, hypertensive or diabetic retinal disease, and microalbuminuria.

A 12-lead ECG recording was coded by a trained observer using the Minnesota code (16). Coronary heart disease was defined as the presence of either major or minor changes of the following Minnesota code items (Q/QS waves, 1:1-3; S-T depression, 4:1-4, T-wave inversion or flattening, 5:1-3, and left-bundle-branch block, 7.1).

Arterial blood pressure was measured twice in the right arm after at least 10 min rest in the supine position by a standard mercury sphygmomanometer (cuff size 12.5 $\times$ 40 cm). Diastolic blood pressure was recorded at the disappearance of the Korotkoff sound (phase V). Arterial hypertension was diagnosed according to World Health Organization (WHO) criteria (17) (systolic pressure $\geq$160 mm Hg, and/or diastolic pressure $\geq$95 mm Hg, or if any antihypertensive treatment was being prescribed). The blood pressure value used in the analysis is the average of the two measurements read at the nearest 5 mm Hg. In patients with cirrhosis the use of diuretics was not considered a marker of hypertension, provided that patients were not diagnosed as hypertensive before the beginning of diuretic therapy.

Ankle systolic pressure was measured with the participant in a supine position at both right and left posterior tibial arteries using a Doppler ultrasound probe. Peripheral vascular disease was defined as an ankle-to-brachial systolic blood pressure $<$0.90 in either leg.

Fundus oculi was examined by a trained ophthalmologist and each subject was classified in one of four categories: no retinopathy, or background, proliferative, or hypertensive retinopathy.

Microalbuminuria was measured on overnight urine samples by an immunonefelometric assay (Istituto Behring S.p.A., Scoppito, L'Aquila, Italy). The lower limit of detection was 0.8 μg/ml. Inter- and intra-assay coefficients of variation were 4.5% and 7%, respectively. Microalbuminuria and macroalbuminuria were defined as an albumin excretion rate in the range between 20 and 200 μg/min and $>$200 μg/min, respectively, in the absence of urinary tract infections. In the presence of urinary tract infection, the test was repeated within a few days, after specific antibiotic treatment.

OGTT was performed using the standard 75-g load in 200 ml of water. Plasma glucose was measured in the fasting state and 30, 60, 90, and 120 min after the load. Glucose was determined in duplicate by the glucose oxidase technique on an automated analyzer. The coefficient of variation of any determination was $\pm$1.5%. Fasting insulin concentrations were measured in noninsulin-treated subjects by an immunoenzymometric assay (AIA-PACK IRI, AIA-1200 system, Tosoh, Tokyo, Japan) with intra- and inter-assay coefficients of variation for the quality control $\leq$7%.

In NIDDM patients and in cirrhotic patients, glycosylated hemoglobin (hemoglobin A_{1C}) was determined by an automated HPLC method (HA 8110, Menarini Divisione Diagnostici, Firenze, Italy).

Liver function tests were determined by routine laboratory methods.

Statistical Analysis

All statistical analyses were carried out on a personal computer by means of StatView II program (Abacus Concepts, Berkeley, CA). Differences in parametric tests among groups were analyzed for significance using the unpaired *t* test and analysis of variance (ANOVA). For each test the number of abnormal results was recorded for each patient group, and the prevalence between groups was tested for significance using R $\times$ C contingency tables.

As several comparisons were simultaneously performed among five groups of subjects, there is a considerable risk of mass significance. Therefore the significance limit was reduced, according to Duncan's multiple range (18), to $p' = 1 - \sqrt[(n-1)]{(1-p)}$, where $p = 0.05$ and $n = 5$. The final critical value of significance was therefore 0.012.

RESULTS

The various groups were well matched for age, sex, and body mass index, which ranged from severe malnutrition (16.3 kg/m^2) to frank obesity (36.1) (Table 1). In patients with cirrhosis there were no remarkable differences in liver function tests in relation to glucose tolerance (Table 1). Only bilirubin was higher in patients with cirrhosis and diabetes, given the presence of four cases of primary biliary cirrhosis in this subgroup. Also the prevalence of esopha-

Table 2. Prevalence of Pathological Results Indicative of Cardiovascular Disease in the Various Groups of Subjects Under Study (% [95% Confidence Interval])

	Arterial Hypertension	Ankle-to-Brachial Blood Pressure Ratio	Ischemic ECG Findings	Microalbuminuria	Retinopathy
Cirrhosis					
All cases (122)	5.7 [2.5–12.5]	6.6 [2.8–12.5]	9.0 [4.5–15.4]	10.7 [5.7–17.3]	12.3 [7.7–20.8]
Normal glucose tolerance (47)	4.3 [0.5–14.5]	2.1 [0.0–11.3]	8.5 [2.4–20.4]	12.8 [4.8–25.7]	6.4 [1.3–17.5]
Impaired glucose tolerance (27)	3.7 [0.1–19.0]	0.0 [0.0–12.8]	7.4 [0.9–24.3]	3.7 [0.1–19.0]	7.4 [0.9–24.3]
Diabetes (48)	8.3 [2.3–20.0]*	14.6 [6.1–27.8]*†	10.4 [3.5–22.7]*	12.5 [4.7–25.2]*	25.0 [13.6–39.6]*†
Type 2 diabetes mellitus (60)	31.7 [20.3–145.0]‡	36.7 [24.6–50.1]‡	31.7 [20.3–45.0]‡	31.7 [20.3–45.0]‡	60.0 [46.5–72.4]‡
Controls (40)	5.0 [0.6–16.9]	15.0 [5.7–29.8]	15.0 [5.71–29.8]	2.5 [0.1–13.1]	10.0 [2.8–23.7]

*Significantly different from NIDDM.
† Significantly different from the other groups of cirrhotic patients.
‡ Significantly different from controls.

geal varices was comparable (normal glucose tolerance, 64%; impaired glucose tolerance, 69%; diabetes, 74%).

Cirrhotic patients had a very low prevalence of signs of cardiovascular disease, being comprised between 2.6% (arterial hypertension) and 13.9% (retinopathy) (Table 2). In addition, whenever pathological results were recorded, they were borderline abnormal. Blood pressure did never exceed 170 mm Hg (systolic) and 110 (diastolic); the lower limit of ankle-to-brachial blood pressure ratio was 0.5, and only one patient was frankly macroalbuminuric. There was a trend toward a larger prevalence of abnormal results in cirrhotic patients with diabetes, which was statistically significant only for peripheral vascular disease and retinopathy.

In patients with cirrhosis and diabetes, cardiovascular involvement was remarkably lower than that observed in NIDDM, where 32–60% of subjects had evidence of vascular disease, depending on the test considered. The two groups (cirrhosis + diabetes and NIDDM) were not different in relation to short- and long-term metabolic control (fasting hyperglycemia and glycosylated hemoglobin; Table 1). However, the duration of diabetes was longer in NIDDM than in patients with cirrhosis and diabetes (10.1 [6.8] yr *vs* 5.9 [4.4]; $p < 0.01$), and the age of first evidence of diabetes was younger in NIDDM (50.1 [9.5] *vs* 54.8 [9.6]; $p < 0.01$]).

Smoking was an additional risk factor in 35% of control subjects, in 29% of patients with cirrhosis, and in 23% of NIDDM subjects (not different between groups, Fig. 1). In cirrhosis, it was not different in relation to glucose tolerance. In the whole population, the prevalence of abnormal results was generally higher in smokers as compared with nonsmokers (11–24% *vs* 14–29%), but the differences were not statistically significant.

A family history of diabetes (first degree relative) was present in 20% of controls, 24% of patients with cirrhosis, and 53% of NIDDM patients (Fig. 1). In patients with cirrhosis and diabetes it was not different from NIDDM.

Cholesterol levels were, on average, lower than normal in cirrhosis and higher than normal in NIDDM patients. In 13 of 40 control subjects (32%) these levels exceeded the recommended upper limit of 200 mg/dl. This was also the case in nine of 122 patients with cirrhosis (7%), including the six patients with primary biliary cirrhosis, and in 42 of 60 NIDDM patients (60%). Similarly, triglyceride levels were low in cirrhosis, without differences in relation to glucose tolerance, and significantly increased in NIDDM patients (p *vs* controls and *vs* cirrhosis, <0.01).

Insulin levels were on average increased in cirrhosis, mainly in patients with normal or impaired glucose tolerance. In patients with cirrhosis and diabetes they were in the normal range, as were in patients with NIDDM.

In most subjects abnormal results were associated. Of 40 controls, 14 had one or more abnormal results (35%). The prevalence was slightly lower in all cases with cirrhosis (39 of 122 = 32%). It was very low in subjects with normal

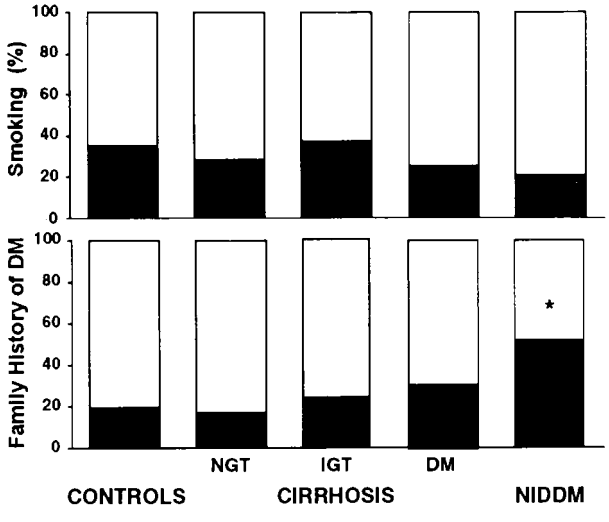

Figure 1. Prevalence of smoking habits and family history of diabetes mellitus in control subjects, in patients with cirrhosis divided according to glucose tolerance (NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = overt diabetes) and in patients with noninsulin-dependent diabetes mellitus (NIDDM). **p versus* controls: 0.002; *p versus* DM 0.035.

Table 3. Effects of Cigarette Smoking on the Prevalence of Cardiovascular Disease in Patients Admitted to Study

	Cigarette Smoking	
	Positive	Negative*
Cirrhosis		
All cases (122)	16/37 = 43% [27–61]	23/85 = 27% [18–38]
Normal glucose tolerance (47)	5/15 = 33% [12–62]	6/32 = 19% [7–36]
Impaired glucose tolerance (27)	3/10 = 30% [7–65]	2/17 = 12% [1–36]
Diabetes (48)	8/12 = 67% [35–90]	15/36 = 42% [26–59]
Type 2 diabetes mellitus (60)	14/14 = 100% [77–100]	35/46 = 76% [62–87]
Controls (40)	7/14 = 50% [23–77]	7/26 = 27% [12–48]

Patients with pathologic findings in one or more of the 5 tests (blood pressure, ankle-to-brachial pressure ratio, ECG, microalbuminuria, retinopathy) were considered positive for cardiovascular disease (% [95% confidence interval]).

*In the whole group of 222 subjects, cigarette smoking increased the risk of cardiovascular disease from 65/157 = 41% (nonsmokers) to 37/65 = 57% (smokers), $p = 0.049$. No statistically significant differences were found in the various subgroups.

glucose tolerance (11 of 47 = 23%) and not significantly increased in patients with associated diabetes (23 of 48 = 48%). In NIDDM it was very high (49 of 60 = 82%), and significantly increased in comparison to both controls and patients with cirrhosis and diabetes. When only subjects with a family history of diabetes were selected, NIDDM patients had a higher prevalence of cardiovascular disease (26 of 32 = 81%) compared with patients with cirrhosis and diabetes (five of 15 = 33%; $p = 0.0037$).

In the whole series, smoking increased the risk of overall cardiovascular disease by nearly 50% (from 41% to 57%; $p = 0.049$). This was also true in the various groups, but the difference was not statistically significant because of the low number of patients and events (Table 3).

Heavy alcohol consumption in cirrhosis did not change the risk of cardiovascular disease significantly. One or more tests were altered in 12 of 32 cases of alcoholic cirrhosis (37%) and in 27 of 90 cases in cirrhosis of different etiology (30%). However, cigarette smoking was more common in alcoholic *versus* nonalcoholic cirrhosis (41% *vs* 27%).

DISCUSSION

It is currently believed that cardiovascular disease is rare in cirrhosis, but epidemiological data are limited (19, 20). The present study confirms that cirrhotic patients, even in the presence of overt diabetes, have a low prevalence of cardiovascular disease. This may be related to a shorter duration of diabetes, also in relation to reduced life expectancy, as well as to protective factors (namely reduced blood pressure and low cholesterol levels).

The association between cirrhosis and diabetes has long been reported (21). At least three mechanisms may be involved: a) a fortuitous association of two relatively common diseases; b) the effects of common pathogenic factors (alcohol, iron overload); and c) a specific defect of carbohydrate metabolism due to failure of the central organ of glucose homeostasis. The first mechanism may be operative in patients with type 1 diabetes, in whom diabetes comes first by several years, but cannot be ruled out when diabetes develops in mature patients with cirrhosis. A positive family history of diabetes may be a marker of a fortuitous association. The second mechanism cannot easily be ruled out in a few patients, but in the majority of patients with viral-induced liver disease is not operative. The third mechanism raised a lot of interest, because of its physiopathologic implications. Several recent review articles have specifically addressed this point (22, 23), which is beyond the scope of our study. Once patients with type 1 diabetes have been excluded, as in the present study, any attempt to characterize patients with cirrhosis and diabetes in relation to the first pathogenic mechanism becomes largely arbitrary. Also the temporal relationship between the two diseases is misleading, because of time lag between the beginning of disease and clinical symptoms in both NIDDM and cirrhosis. Patients with NIDDM may present cardiovascular involvement at the time of diagnosis (24), because of a long lasting preclinical stages. Similarly, in a remarkable proportion of cirrhotic patients, diagnosis is made in the presence of advanced disease with ascites and/or gastrointestinal bleeding (25); and in nearly half of patients with compensated disease, this advanced stage is reached after 10 yr or more (26). For this reason no attempt was made to differentiate patients with cirrhosis and diabetes on the basis of which disease came first.

The study included several investigations to detect localized and/or diffuse micro- and macrovascular involvement. ECG was coded according to the Minnesota code, and only items indicative of definite coronary artery disease were included. Very few epidemiological studies are available on the prevalence of coronary heart disease in cirrhosis. Excluding subjects with alcohol-related disease and patients with primary biliary cirrhosis and elevated cholesterol levels, the prevalence of myocardial infarction is lower than expected in cirrhosis (19, 20), but no data have ever been reported in relation to glucose metabolism. The present study confirms that cirrhosis is rarely associated with coronary heart disease, and diabetes adding to cirrhosis does not consistently increase the risk.

This consideration is also valid for peripheral vascular disease. Ankle to brachial blood pressure ratio reflects the presence of atherosclerotic abnormalities of leg arteries, and

is a good indicator of generalized atherosclerosis (27, 28). Peripheral vascular disease is supposed to be rare in cirrhosis (29). Our data strongly support this current opinion also in cirrhosis-associated diabetes when compared with NIDDM, in which the low prevalence of hypertension, a primary risk factor for atherosclerosis, is likely to reduce the risk of macrovascular disease.

Microvascular disease was assessed on the basis of retinal disease, and signs of both diabetic and hypertensive involvement were considered. This probably accounts for the larger than expected prevalence of retinal involvement found in our patients, as well as in controls in relation to several previous reports (30–32). In addition, patients were generally older than those reported in most studies, and the prevalence of background retinopathy is increased as the patients become older and in relation to disease duration (33). However, considering only diabetic retinopathy (background or proliferative), it was present in two of 27 patients with cirrhosis and IGT, in eight of 48 patients with cirrhosis and diabetes, and in nearly 50% of NIDDM patients (29 of 60). It was absent in controls and in cirrhosis with normal glucose metabolism.

Finally, urinary albumin excretion was measured as a sign of widespread vascular damage (11). A lot of data are available on the predictive value of microalbuminuria on mortality in patients with NIDDM (10, 34, 35) and its close association with coronary heart disease, heart failure, and peripheral vascular disease (36–38). Similar data have also been obtained in nondiabetic subjects (12, 13), suggesting that an increased urinary albumin excretion rate may be the effect of a generalized dysfunction of vascular endothelium (39). This hypothesis explains the association observed in NIDDM (30) between microalbuminuria and elevated systolic blood pressure, marker of a reduced vascular compliance reflecting widespread vascular damage. In cirrhosis, lower than normal blood pressure levels and systemic vasodilation (40) possibly prevent kidney damage and microalbuminuria also in the presence of overt diabetes.

The risk of cardiovascular disease was not biased in cirrhosis by confounding factors such as smoking habits and family history of diabetes. Smoking was rather common, but not different among the various groups. It definitely increased the risk of cardiovascular disease in the whole population, in agreement with large epidemiological studies (41) as well as in the various groups of patients. A family history of diabetes was more common in NIDDM when compared with subjects with cirrhosis and diabetes, as already observed by Vidal *et al*. (42). These two groups of patients have different metabolic abnormalities (42), possible expression of different pathogenic factors. When the analysis was limited to patients with positive family history, possible marker of genetic predisposition to diabetes, differences were still present between patients with cirrhosis and diabetes compared with NIDDM, confirming the protective role of liver disease in diabetes-associated complications.

Also, alcohol intake *per se* has recently been associated with a reduced risk of cardiovascular disease (41). Our study was not specifically designed to test this hypothesis, and alcohol intake was not recorded in nonalcoholic patients. In general, the study does not support a protective role of alcohol, inasmuch as the cardiovascular involvement in patients with alcoholic cirrhosis was as rare as in nonalcoholic patients. However, heavy alcohol intake in cirrhosis was more frequently associated with smoking, possibly masking the effects of alcohol.

The decisive factors not shared by cirrhosis-associated diabetes and NIDDM seem to be clinical and metabolic. Duration of diabetes was nearly doubled in NIDDM, and age at first evidence of diabetes was 5 yr younger in NIDDM. Accordingly, a considerable proportion of patients with cirrhosis and diabetes are expected never to develop diabetic complications, because of a reduced, cirrhosis-related life expectancy. In addition, cirrhotic patients have several laboratory and metabolic abnormalities potentially reducing cardiovascular risk (low platelet count, lipid concentrations, and coagulation factors), not present in NIDDM.

A special problem concerns insulin levels in cirrhosis, which are elevated both in the fasting state and throughout the day (43). The role of hyperinsulinemia in cardiovascular disease has hotly been debated on the basis of association of hyperinsulinemia and atherosclerosis (44), mainly in nondiabetic populations (45), as well as of the potential effects of insulin resistance in abolishing the effects of hyperinsulinemia (46). In our population plasma insulin levels were not a marker of vascular disease, but more specific studies are needed.

All these factors possibly contribute to the unexpected finding of a prognostic significance of diabetes for long term survival of cirrhosis not related to diabetes-associated events (6), and have clinical implications. Provided that diabetes does not contribute to malnutrition in cirrhosis, limiting energy supply or wasting energy and proteins in urine because of massive glycosuria, the treatment of the diabetic disease associated with cirrhosis may be far less aggressive than that used in NIDDM.

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