

Subclinical abnormal glucose tolerance is a predictor of death in liver cirrhosis

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Abstract

AIM: To determine if subclinical abnormal glucose tolerance (SAGT) has influence on survival of non-diabetic patients with liver cirrhosis.

METHODS: In total, 100 patients with compensated

liver cirrhosis and normal fasting plasma glucose were included. Fasting plasma insulin (FPI) levels were measured, and oral glucose tolerance test (OGTT) was performed. According to OGTT results two groups of patients were formed: those with normal glucose tolerance (NGT) and those with SAGT. Patients were followed every three months. The mean follow-up was 932 d (range of 180-1925). Survival was analyzed by the Kaplan-Meier method, and predictive factors of death were analyzed using the Cox proportional hazard regression model.

RESULTS: Of the included patients, 30 showed NGT and 70 SAGT. Groups were significantly different only in age, INR, FPI and HOMA2-IR. Patients with SAGT showed lower 5-year cumulated survival than NGT patients (31.7% vs 71.6%, $P = 0.02$). Differences in survival were significant only after 3 years of follow-up. SAGT, Child-Pugh B, and high Child-Pugh and Model for End-Stage Liver Disease (MELD) scores were independent predictors of death. The causes of death in 90.3% of cases were due to complications related to liver disease.

CONCLUSION: SAGT was associated with lower survival. SAGT, Child-Pugh B, and high Child-Pugh and MELD scores were independent negative predictors of survival.

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Key words: Diabetes mellitus; Liver cirrhosis; Oral glucose tolerance test; Survival; Glucose metabolism disorders

Core tip: In this controlled prospective long term study we demonstrated that subclinical forms of abnormal glucose tolerance (IGT) or diabetes mellitus (DM) may influence survival of non-diabetic cirrhotic patients. Previously it had been demonstrated that clinically overt

DM is associated with low survival of cirrhotic patients. This issue is important since a high proportion of cirrhotic patients (about 70%) without history of DM and with normal fasting plasma glucose have subclinical abnormal glucose tolerance. The use of oral glucose tolerance test for early recognition and treatment of DM may improve prognosis of these patients.

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INTRODUCTION

Overt diabetes mellitus (DM) has been reported in 21%-30% of patients with liver cirrhosis (LC)^[1]. DM may arise from a progressive disorder of insulin secretion in the presence of liver and muscle resistance to insulin^[2,3].

DM is related to LC in two ways: (1) type 2 DM (T2DM) (often associated with metabolic syndrome) causes nonalcoholic fatty liver disease (steatosis, steatohepatitis, LC, and hepatocellular carcinoma)^[4-7]; and (2) DM may develop as a complication of LC, which is known as "hepatogenous diabetes" (HD)^[8,9]. As liver disease advances, DM becomes clinically evident^[10,11]. T2DM and HD are associated with an increased risk of complications of chronic liver diseases and mortality^[7,9,12-17].

On the other hand, subclinical abnormal glucose tolerance (SAGT) disorders, such as impaired glucose tolerance or DM (called subclinical since they are detected only by means of an oral glucose tolerance test), may be observed in 45% and 22%, respectively, of patients with LC and no history of DM^[18,19]. Therefore, the prevalence of DM and impaired glucose tolerance (IGT) may be underestimated when only fasting plasma glucose (FPG) levels are taken into account. Our group has recently published a study determining the prevalence of T2DM, DH and IGT in patients with LC who underwent oral glucose tolerance test (OGTT). In total, 86% of the cases had either overt or subclinical IGT and DM, with or without insulin resistance (IR)^[18].

The negative influence of SAGT on the survival of cirrhotic patients was demonstrated in one study carried out in Japan, which found that patients with IGT or DM diagnosed by OGTT had a significantly lower 5-year survival rate^[20]. However, similar findings have not been reported by others elsewhere.

The aims of this study were: (1) to evaluate if SAGT has any influence on survival of patients with compensated LC and normal FPG levels; and (2) to identify mortality predictors.

MATERIALS AND METHODS

Patients

Patients with LC, who were seen in our hospital from August 2007 to August 2012, were prospectively evaluated. Only those with normal FPG (< 100 mg/dL), no history of overt DM, with clinical or histological diagnosis of LC, aged over 18 years old and without clinically evident complications of liver disease (*e.g.*, esophageal or gastric variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, infection, spontaneous bacterial peritonitis, and moderate to severe ascites), were selected for the study (patients with complications were excluded in order to avoid the effect of medications used for treating them, on glucose metabolism of patients). Clinical diagnosis of LC was made by using a combination of clinical symptoms, laboratory tests and imaging studies (abdominal ultrasonography or CT scan)^[21,22]. The etiology of cirrhosis was determined as follows: Alcohol-related cirrhosis was determined when daily alcohol consumption was > 80 g in men and > 40 g in women for at least 10 years with negative viral, metabolic and autoimmune markers. Diagnosis of hepatitis C virus and B virus related cirrhosis was determined with specific viral markers (HBsAg or anti-HCV). Autoimmune liver disease was diagnosed with specific autoimmune markers (anti-nuclear antibodies, anti-smooth muscle antibodies or liver-kidney antimicrosomal antibodies). Meanwhile, cryptogenic cirrhosis was established in the absence of any of the causes above described^[23].

Informed consent was obtained from each patient. The protocol was approved by The Research and Ethics Committee of the Faculty of Medicine of the Autonomous University of Nuevo Leon in Monterrey.

Fasting plasma insulin and OGTT

Fasting plasma insulin (FPI) levels were measured and OGTT was performed according to the World Health Organization criteria^[24]. Patients were fasted for at least 12 h, and baseline plasma glucose was measured; then, they were given an oral glucose load (75 g). Additionally, plasma glucose (PG) levels were measured every 30 min for 2 h. The results were interpreted as follows: a) normal glucose tolerance (NGT) if 2-h PG was < 140 mg/dL; IGT if 2-h PG between 140 mg/dL and 200 mg/dL; and DM if 2-h PG > 200 mg/dL. Plasma HbA1c was not used for diagnosing DM due to its low sensitivity reported in cirrhotic patients^[19].

FPI was measured using the electrochemiluminescence method (normal values: 5-20 μ U/mL). HOMA2-IR index (Homeostasis Model Assessment 2-Insulin Resistance Index) was calculated using the following online software (<http://www.dtu.ox.ac.uk/homacalculator/index.php>).

Assessments

The following data were recorded in a database specially

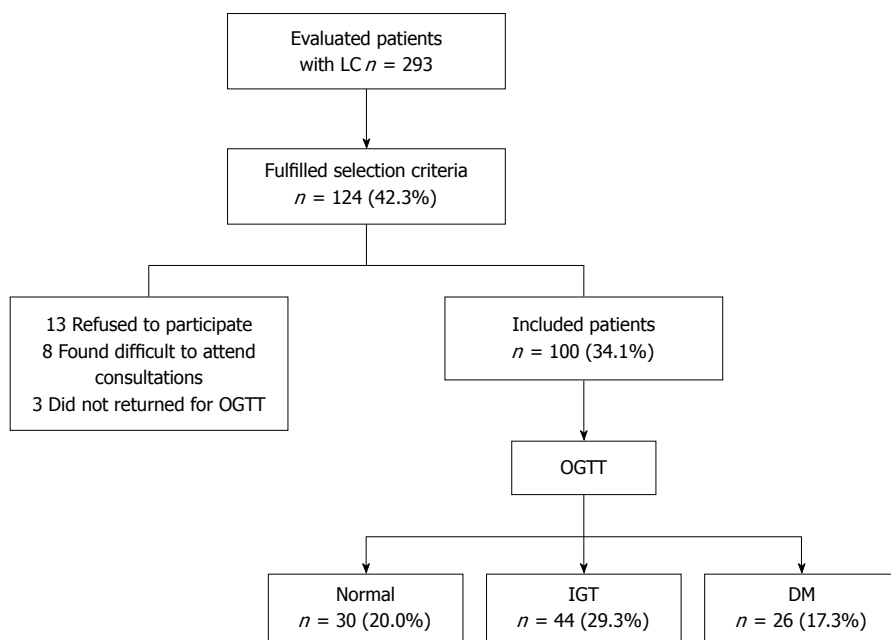


Figure 1 Flowchart describing how selection of patients for the study was done. LC: Liver cirrhosis; OGTT: Oral glucose tolerance test; IGT: Impaired glucose tolerance; DM: Diabetes mellitus.

designed for the study: gender, age, and family history of DM as well as laboratory blood test results (serum hemoglobin, leukocytes, platelets, BUN, creatinine, albumin, bilirubin, aspartate aminotransferase, γ -glutamyltranspeptidase, alkaline phosphatase, cholesterol, triglycerides, and INR). The body mass index (BMI) was calculated and construed as follows: normal if < 24.9 , overweight if between 25 and 29.9, and obesity if > 30 ^[25]. Liver function was estimated using Child-Pugh and Model for End-Stage Liver Disease (MELD) classifications^[26,27].

Follow-up

All patients were followed every 3 mo in the outpatient department. A full clinical examination was made in each interview. Laboratory blood testing (serum hemoglobin, hematocrit, blood cell count, glucose, creatinine, BUN, liver function tests and coagulation tests) was also performed. Moreover, plasma alpha-fetoprotein and liver ultrasonography were performed every 6 mo. Additionally, hospital admissions were recorded during which clinical course of the patient was determined. Patients or their relatives were contacted by telephone when he or she did not attend to appointments. Callings were done in order to determine the clinical status of the patient, or to inquire whether their death occurred.

During follow-up patients were treated with life style and diet modifications, and in particular cases with oral hypoglycemic agents or insulin administration. No anti-diabetic medication was given to those with impaired glucose tolerance.

Statistical analysis

Continuous variables are expressed as means and standard deviations, while non-continuous variables as me-

dians and ranges. Categorical variables are expressed as relative proportions. Intergroup comparisons were made by Student's t , χ^2 and Mann-Whitney tests. Variables were analyzed using the Cox proportional hazard regression model in order to determine independent predictive factors of mortality^[28]. Only the variables that were statistically significant in univariate analysis were analyzed in multivariate analysis. The results were expressed as HR with 95%CI, and the P value was calculated.

The cumulative survival was analyzed using the Kaplan-Meier method, and the curves were compared using log-rank test. A P value less than 0.05 was considered statistically significant. All statistical analyses were done using the statistical package SPSS v17.0 (Chicago, Illinois, United States).

RESULTS

Patient population

Of 293 cirrhotic patients evaluated, 124 (42.3%) met the inclusion criteria. However, 24 (8.1%) of them were not finally included due to the following reasons: 13 refused to participate in the study, 8 found difficult to attend consultation because they lived in another state, and 3 did not attend their appointments for performing OGTT (Figure 1).

Finally, 100 (34.1%) patients were included in the study. Their clinical and biochemical characteristics are shown in Table 1. Although BMI is not the best parameter for assessing nutritional status in cirrhotic patients (particularly in those with ascites), this method showed that most of them (69%) were overweight or obese. The etiology of cirrhosis was predominantly alcoholic and cryptogenic (47% and 26%, respectively). The diagnosis

Table 1 Clinical and biochemical characteristics of cirrhotic patients

Variable	Total (n = 100)	NGT (n = 30)	SAGT (n = 70)
Age, yr	53.9 ± 11.8	49.0 ± 12.0	56.0 ± 11.1 ¹
BMI, kg/m ²	26.9 ± 4.2	26.4 ± 4.40	27.21 ± 4.15
Males	60 (60)	18 (60)	42 (60)
Etiology: Alcohol	47 (47)	14 (46.6)	33 (47.1)
HBV	4 (4)	1 (3.3)	3 (4.2)
HCV	13 (13)	2 (6.6)	11 (15.7)
Autoimmunity	10 (10)	3 (10)	7 (10)
Cryptogenic	26 (26)	10 (33.3)	16 (22.8)
Liver biopsy	44 (44)	13 (43.3)	31 (44.2)
Length of LC, mo	21.6 ± 27.6	21.4 ± 30.6	21.7 ± 33.2
Hemoglobin, g/dL	11.8 ± 2.3	11.6 ± 2.1	11.9 ± 2.3
Platelets, × mm ³	128140 ± 89501	159186 ± 112108	114834 ± 73269
INR	1.3 ± 0.3	1.2 ± 0.3	1.36 ± 0.3 ²
Creatinine, mg/dL	0.8 ± 0.2	0.90 ± 0.33	0.83 ± 0.2
Albumin, g/dL	3.2 ± 0.73	3.33 ± 0.71	3.21 ± 0.74
ALT, UI/L	46.5 ± 40.8	48.9 ± 53.9	45.4 ± 34.0
Total bilirubin, mg/dL	1.71 ± 0.90	1.55 ± 0.88	1.78 ± 0.91
Fasting plasma insulin, μU/mL	15.9 ± 10.2	11.9 ± 7.6	18.2 ± 11 ³
HOMA2 score	2.67 ± 1.6	2.36 ± 1.46	4.6 ± 3.3 ⁴
Child-Pugh A	47 (47)	15 (50)	32 (45.7)
B	53 (53)	15 (50)	38 (54.2)
Child Pugh score	6.8 ± 1.8	6.5 ± 1.61	6.82 ± 1.67
MELD score	8.94 ± 4.8	8.3 ± 5.2	9.21 ± 4.63
Survival, d	1237 (990-1925)	1448 (1256-1925)	1116 (990-1790) ⁵

Data are expressed as absolute numbers (percentage) or mean ± SD. ¹P = 0.003; ²P = 0.025; ³P = 0.03; ⁴P = 0.009; ⁵P = 0.045. NGT: Normal glucose tolerance; SAGT: Subclinical abnormal glucose tolerance; HOMA: Homeostatic model assessment; LC: Liver cirrhosis. BMI: Body mass index; MELD: Model for End-Stage Liver Disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; ALT: Alanine transaminase.

of LC was confirmed by liver biopsy in 44% of cases. In total, 47% and 53% of patients were assigned into the groups A and B of the Child-Pugh classification, respectively. The mean Child-Pugh score was 6.9 ± 1.8 points and the mean MELD score was 8.9 ± 4.8. The mean values of FPI levels and HOMA2-IR index were 15.9 ± 10.2 μU/mL and 2.67 ± 1.6, respectively.

Clinical characteristics and survival rate of patients

Two groups were formed according to the results of OGTT: those with NGT (30 patients) and those with SAGT (70 patients, 44 with IGT and 26 with DM). Clinical and biochemical characteristics are shown in Table 1. SAGT patients were significantly older and had higher values of INR, FPI and HOMA2-IR. Although Child-Pugh and MELD scores were mildly higher in patients with SAGT, these differences were not statistically significant.

Follow-up

The mean follow-up was 932 d (range 180-1925). At the end of follow-up, 19 (19%) patients (5 NGT patients and 14 SAGT patients) developed overt IGT (7 cases) or overt DM (12 cases). All patients with SAGT were prescribed dietary and life style modifications. At different

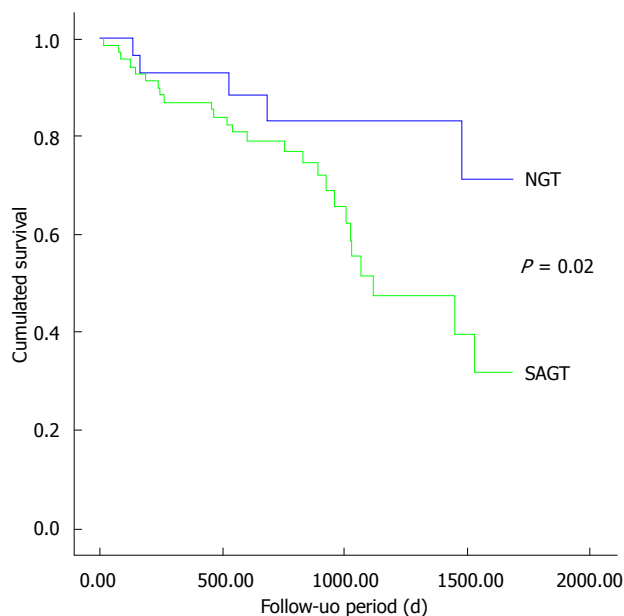


Figure 2 Cumulated survival of cirrhotic patients with normal glucose tolerance or subclinical abnormal glucose tolerance. Note that significant differences between both groups are evident after 3 years of follow-up. NGT: Normal glucose tolerance; SAGT: Subclinical abnormal glucose tolerance.

times of follow-up, oral antidiabetic medications were prescribed in 6, and subcutaneous insulin was prescribed in 2 out of 12 patients with overt DM.

In total, 49% of alcoholic patients consistently stopped alcohol consumption, 47% of patients with hepatitis C virus infection were treated with antiviral therapy, 50% and 90% of patients with hepatitis B virus infection or autoimmune liver disease were treated. There were no dropouts.

Cumulative survival

The mean survival time was 1448 d (range: 1256-1925) in the patients with NGT, while it was 1116 d (range 990-1790) in the patients with SAGT (P = 0.045). Cumulative survival curve of patients with NGT and SAGT is shown in Figure 2. SAGT patients had significantly lower survival (P = 0.02).

One to 5-year survival rates are shown in Table 2. Statistically significant differences were observed only after three years of follow-up. Increasing differences were observed over time until the end of follow-up.

Causes of death

In total 31 patients died (5 from the NGT group and 26 from the SAGT group). The causes of death are shown in Table 3. Twenty eight (90.3%) patients died due to the following complications related to liver disease: 8 due to esophageal variceal bleeding (25.8%), 6 due to chronic liver failure (19.3%), 5 due to spontaneous bacterial peritonitis and other infections (16.2%), 5 due to hepatorenal syndrome (16.2%) and 4 due to hepatocellular carcinoma (12.9%). Additionally, 2 of the remaining patients died due to renal impairment (6.4%), and 1 due to cardiovas-

Table 2 Annual cumulated survival of cirrhotic patients *n* (%)

Year(s)	NGT (<i>n</i> = 30)	SAGT (<i>n</i> = 70)	<i>P</i> value (χ^2 test)
1	2 (93)	9 (87)	0.36
2	4 (83.2)	14 (79)	0.34
3	4 (83.2)	23 (51.4)	0.04
4	4 (83.2)	24 (47.5)	0.03
5	5 (71.6)	26 (31.7)	0.02

NGT: Normal glucose tolerance; SAGT: Subclinical abnormal glucose tolerance.

cular disease (3.2%). There were no significant differences in the causes of death among patients with NGT *vs* those with SAGT.

Predictors of death

Serum creatinine, albumin, INR, Child-Pugh B, Child-Pugh and MELD scores, SAGT as well as FPI were statistically significant according to univariate analysis. However, only Child-Pugh B (HR = 8.2, 95%CI: 2.0-28.5, *P* = 0.02), Child-Pugh score (HR = 10.2, 95%CI: 2.4-21.9, *P* = 0.008), MELD score (HR = 12.3, 95%CI: 6.4-33.6, *P* = 0.001) and SAGT (HR = 3.2, 95%CI: 2.8-54.2, *P* = 0.01) were independent predictors of survival according to multivariate analysis (Table 4).

DISCUSSION

Our study suggests that SAGT may have negative impact on the survival of patients with LC, as those who showed this abnormality had lower 5-year survival than those who had NGT. Significant differences in survival were observed after 3 years of follow-up (Table 2). These results are consistent with another study carried out in Japan, with 58 cirrhotic patients without overt DM who underwent OGTT^[20]. In that study, 5-year survival rate was lower in patients with IGT and DM compared to those with NGT. Albumin and abnormal OGTT were independent negative predictors of survival^[20]. Despite the similarities in results of both studies, ours differs in the following points: (1) 74% of our patients had alcoholic and cryptogenic cirrhosis, while 78.5% of patients in the Japanese study had viral etiology (HBV and HCV). The causes of chronic liver disease in our patients were identical to those observed in most Western countries, where alcohol and metabolic syndrome are the predominant causes (especially nowadays, the frequency of obesity and nonalcoholic fatty liver disease have dramatically increased), while viral etiology is predominantly observed in Asian countries^[29-31]; (2) At time of inclusion, our patients did not have liver-related complications, whereas in the Japanese study, up to 30% had ascites and hepatic encephalopathy; and (3) The number of patients in our study was almost twice.

The mechanism by which SAGT may be involved in the occurrence of death of cirrhotic patients is difficult to explain. DM may induce progression of liver fibrosis, inflammation and liver failure, or may increase cardiovas-

Table 3 Causes of death *n* (%)

Cause	Total (<i>n</i> = 31)
Variceal bleeding	8 (25.8)
Liver failure	6 (19.3)
SBP e infection	5 (16.2)
Hepatorenal syndrome	5 (16.2)
HCC	4 (12.9)
Renal impairment	2 (6.4)
Cardiovascular	1 (3.2)

SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma.

cular complications and atherosclerosis. In a study with virus C-infected patients, IR and DM were significantly associated with liver fibrosis^[32]. Furthermore, in other reports, it has been suggested that DM can increase fibrosis, incidence of hepatocellular carcinoma, and resistance to antiviral therapy in patients with hepatitis C^[33]. DM may be involved in the progression of liver fibrosis and inflammation through diverse mechanisms: it is likely that adipokine production (such as leptin and Tumor necrosis factor- α , which activate inflammatory pathways exacerbating liver injury) is increased by insulin resistance^[34-36]. Leptin and oxidative stress associated with liver inflammation may activate transforming growth factor beta 1 (TGF- β 1), which is one of the most potent profibrogenic cytokines produced in the liver. TGF- β 1 activates hepatic stellate cells which are the major source of collagen I and III and extracellular matrix proteins^[37-39]. In our study, SAGT as well as high Child-Pugh and MELD scores were independent predictors of death. This suggests that SAGT combined with other etiologic agents of liver cirrhosis might have induced liver failure and death.

On the other hand, as it has been pointed out in other publications, most of our patients with SAGT died from liver disease related complications^[9,20,40] (Table 3). DM increases the incidence of severe infections by inducing immunosuppression. Cirrhotic patients with DM have a higher prevalence of infections compared to non-diabetic ones. In a recent study, spontaneous bacterial peritonitis was more frequent in patients with cryptogenic cirrhosis (which is associated with DM) compared to those with cirrhosis of other causes^[41]. These infected patients had higher in-hospital mortality due to sepsis, liver failure, and hepatorenal syndrome^[42]. In addition, DM may increase the risk of variceal bleeding, as postprandial hyperglycemia that occurs in diabetic patients produces splanchnic vasodilatation and increases the flow and pressure of the porto systemic venous system^[43]. Also, esophageal variceal bleeding increases the risk of infection and death by inducing bacterial intestinal translocation^[44]. DM has been also associated with an increased risk of hepatic encephalopathy (HE). A significant association between malnutrition and diabetes with HE was observed in a study with cirrhotic patients^[45]. In multivariate analysis, Child-Pugh classification, malnutrition and DM showed independent correlations with HE. Plasma ammonium ion levels were related to insulin resistance and muscle mass. Authors

Table 4 Univariate and multivariate analyses: Independent predictors of death

Variable	HR	95%CI	P value	HR	95%CI	P value
Creatinine	1.6	1.2-40.2	0.030	2.62	0.5-3.46	0.650
Albumin	3.4	1.8-22.3	0.015	6.3	0.4-32.1	0.180
INR	2.2	1.6-32.4	0.050	3.5	0.3-23.6	0.230
Child-Pugh B	7.2	3.4-33.0	0.0003	8.2	2.0-28.5	0.020
Child Pugh score	5.2	2.9-25.8	0.008	10.2	2.4-21.9	0.008
MELD score	8.1	4.2-18.7	0.001	12.3	6.4-33.6	0.001
SAGT	4.5	2.0-15.2	0.042	3.2	2.8-54.2	0.010
Fasting serum insulin	1.2	1.0-33.5	0.040	3.2	0.1-27.3	0.320

MELD: Model for end stage liver disease; INR: International normalized ratio; SAGT: Subclinical abnormal glucose tolerance.

concluded that nutritional status and insulin resistance might be implicated in the pathogenesis of HE^[45].

On the other hand, some authors reported low frequency of diabetic complications in cirrhotic patients^[46]. However, these observations have been recently challenged: in two published studies, patients with chronic hepatitis C compared to controls, showed significant higher carotid intima media thickness, greater number of carotid plaques and carotid atherosclerosis affection^[47,48]. In one of these studies^[47], older age and severe hepatic fibrosis were independently associated with early carotid atherosclerosis. In the other one^[48], diabetes and metabolic syndrome were associated with carotid plaques. The precise prevalence of cardiovascular disease or atherosclerosis and their role in the induction of death in cirrhotic patients with DM need to be defined in future well conducted studies.

In our study, we did not observe significant differences in the causes of death among patients with NGT compared to those with SAGT (Table 3). This may be due to the small number of individuals in each group. Some differences might be clearly evident using a larger sample of patients.

Although the negative impact of DM on survival of cirrhotic patients is well known a long time ago, the beneficial effects of early detection and treatment of DM and IGT for reducing complications and mortality rates have not been clearly determined. In our study, analysis of this issue was not performed due to the low number of patients. This important point has to be determined in future studies.

In conclusion, SAGT disorders were associated with reduced long term survival in patients with compensated LC and normal FPG. Additionally, SAGT, Child-Pugh B, and high Child-Pugh and MELD scores were independent negative predictors of survival. These findings suggest that SAGT may give rise to morbid conditions that increase mortality of patients. According to this, OGTT is useful for accurate assessment of mortality in non-diabetic cirrhotic patients.

COMMENTS

Background

Overt diabetes mellitus (DM) may be found in 30% of patients with liver cir-

rhosis of diverse etiology. Since a long time ago, it has been known that overt DM is linked to a reduction of survival of patients with liver cirrhosis. Causes of death of these patients are mostly due to liver disease complications. Nonetheless, 60% of non-diabetic patients with liver cirrhosis may have abnormal glucose tolerance disorders, either impaired glucose tolerance (IGT) or DM, after an oral glucose tolerance test.

Research frontiers

The impact of subclinical forms of IGT and DM on survival of cirrhotic patients has not been extensively described. In this paper, the authors demonstrate that patients with these forms of abnormal glucose tolerance have reduced long term survival than those with normal glucose tolerance. Nevertheless, this study does not allow demonstrating the mechanisms by which abnormal glucose tolerance may reduce survival of patients

Related publications

The impact of subclinical forms of abnormal glucose tolerance on survival of cirrhotic patients has been described in only one study performed in Japan. In this study, patients with IGT and DM detected by oral glucose tolerance test (OGTT) had reduced 5-year survival than those with normal glucose tolerance.

Innovations and breakthroughs

Most of the patients in the previously published study had cirrhosis of viral etiology and 30% had liver complications, while in this study, patients were clinically compensated and most of them had alcoholic and cryptogenic etiology. In addition the sample size of this study was double.

Applications

The practical applications of the findings of this study are clear: early detection of abnormal glucose tolerance conditions through OGTT allows early treatment of DM and consequently a reduction of complications and mortality of patients. The use of OGTT is suggested in all patients with liver cirrhosis without previous DM, in order to assess prognosis of survival. Those with DM may be included in a close monitoring and an early treatment program. Future studies concerning the mechanisms by which DM induces death of cirrhotic patients may allow focusing prevention and therapeutic measures.

Terminology

Subclinical abnormal glucose tolerance refers to impaired glucose tolerance and diabetes mellitus detected by an oral glucose tolerance test.

Peer review

The investigators correlated the subclinical abnormal glucose tolerance and reduced survival in cirrhosis patients, and found that the subclinical abnormal glucose tolerance was associated with lower survival.

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