

# Diagnosis and Clinical Implications of Diabetes in Liver Cirrhosis: A Focus on the Oral Glucose Tolerance Test

Tsutomu Nishida

*Department of Gastroenterology, Toyonaka Municipal Hospital, Toyonaka, Osaka 560-8565 Japan*

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The liver and skeletal muscles are responsible for maintaining glucose metabolism. As chronic liver disease progresses to cirrhosis, the loss of liver function is exacerbated and leads to the deterioration of skeletal muscle. Consequently, impaired glucose tolerance (IGT) and insulin resistance are often observed in patients with liver cirrhosis. Early stage cirrhosis with hepatogenous diabetes is characterized by marked postprandial hyperglycemia and hyperinsulinemia. Generally, it is possible to underestimate IGT when using either the conventional fasting plasma glucose (FPG) criterion or hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels despite their status as the gold standard for diagnosing diabetes. The number of cirrhotic patients with diabetes tends to be underestimated because many of these patients show lower FPG levels or HbA<sub>1c</sub>, which masks their IGT. In such cases, the oral glucose tolerance test is recommended to evaluate patients with suspected postprandial hyperglycemia who present with a normal FPG. Moreover, in addition to the Child–Pugh score, the early detection of diabetes may be a useful prognostic marker for patients with liver cirrhosis.

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**Freeform/Key Words:** liver cirrhosis, diabetes, glucose intolerance, oral glucose tolerance test, prognosis

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It has been well established since the late 1960s that impaired glucose tolerance (IGT) and insulin resistance often occur in patients with chronic liver disease [1]. Specifically, overt diabetes with fasting hyperglycemia and frank glycosuria has been reported in 15% to 30% of patients with liver cirrhosis [1–5]. There are two types of diabetes concomitant with chronic liver diseases: conventional type 2 diabetes mellitus (DM), which either develops in advance of or simply coincides with chronic liver disease, and hepatogenous diabetes, in which chronic liver disease causes diabetes. Recently, DM itself has been implicated in the pathogenesis of cirrhosis caused by nonalcoholic steatohepatitis [6]. Moreover, the therapeutic administration of corticosteroids, interferons, and other drugs to treat chronic hepatitis may also result in hyperglycemia [7–9]. IGT and chronic liver disease are thought to interact with each other and gradually accelerate the other's progression. Therefore, the precise mechanism of IGT in patients with chronic liver disease appears complex, and it can be difficult to differentiate the causes.

We previously reported that aside from albumin levels, early detection of IGT via an oral glucose tolerance test (OGTT) was the most useful prognostic marker for patients with liver cirrhosis [10]. It is important to detect IGT early in cirrhotic patients, but this can be challenging because in patients with compensated liver cirrhosis, IGT may be misdiagnosed as normal glucose tolerance (NGT), and physicians forgo any specific examinations designed to more accurately estimate glucose metabolism [11].

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Abbreviations: 2h-PG, 2-hour plasma glucose; ADA, American Diabetes Association; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

In this review, we discuss the prevalence of IGT, especially hepatogenous diabetes in liver cirrhosis, and examine its prognostic impact based on the OGTT, which is the most reliable diagnostic criterion for determining IGT in cirrhotic patients.

## 1. Mechanism of Impaired Glucose Homeostasis in Liver Cirrhosis

The liver is primarily responsible for maintaining glucose metabolism by storing glucose and producing endogenous glucose from glycogen stores in the liver; these activities contribute to preserving normal blood glucose levels [12]. In addition, skeletal muscle is also fundamentally important in maintaining glucose homeostasis [13]. Generally, decreased glucose deposition in skeletal muscle and increased endogenous glucose production contribute to the development of postprandial hyperglycemia in patients with type 2 DM [14]. Liver cirrhosis is indicated by decreases in both hepatocyte mass and skeletal muscle during disease progression, and liver cirrhosis with early stage hepatogenous diabetes is characterized by marked postprandial hyperglycemia and increased insulin resistance [15]. Several studies have suggested that the inhibition of hepatic glucose production via elevated insulin activity is normal [16, 17] but that insulin-stimulated glucose uptake into the skeletal muscle is impaired in patients with liver cirrhosis [18, 19]. Moreover, either a diminished hepatocyte mass [20] or portosystemic shunt [21] in cirrhotic patients can cause hyperinsulinemia and progression toward insulin resistance via downregulation of the insulin receptor [22]. This insulin resistance increases the demand for pancreatic insulin secretion and finally leads to overt DM [1, 4]. The precise molecular mechanism of impaired insulin activity in the skeletal muscles of cirrhotic patients is still unclear; however, it may depend on the patients' liver function and skeletal muscle mass.

Hepatitis viral infection is one of the main causes of liver disease. Interestingly, some studies have shown that patients with hepatitis C virus (HCV) infection have a higher prevalence of diabetes than patients with hepatitis B virus (HBV) [23, 24]. A recent meta-analysis comparing HCV- and HBV-infected patients also supports the association between HCV infection and type 2 DM [25, 26]. As a mechanism of a higher prevalence of DM among patients with HCV infection, HCV itself is thought to introduce insulin resistance. Various experimental models have suggested that a direct effect of HCV infection in the liver, namely HCV proteins' promotion of the degradation of insulin receptor substrate 1, leads to insulin resistance [27, 28]. Moreover, Paziienza *et al.* reported that different genotypes of HCV determined differences in the degree of insulin resistance [29]. Therefore, the severity of glucose homeostasis impairment appears to depend on various factors but primarily on the severity of chronic liver disease, skeletal muscle volume, and the presence of a portosystemic shunt. Deterioration of liver function and loss of skeletal muscle are common pathological conditions of liver cirrhosis. Skeletal muscle loss adversely affects the clinical outcomes of patients with chronic liver disease, primarily due to malnutrition [30], but its precise mechanism of action is still unknown [31]. Impaired glucose homeostasis in patients with liver cirrhosis is caused by a defect in glucose uptake into both hepatic tissue and skeletal muscle [15]. Moreover, type 2 DM itself is known to be a risk factor for chronic liver disease [32, 33] because it results in defects in skeletal muscle glucose metabolism [34–36]. Both cirrhosis and diabetes are asymptomatic during the early stages of disease in some situations; consequently, they may feed back onto each other in a vicious cycle that disrupts glucose metabolism and liver function during the natural course of liver cirrhosis. Finally, in cirrhotic patients with overt DM, it is difficult to distinguish between conventional and hepatogenous diabetes.

## 2. Diagnosis of IGT in Liver Cirrhosis

The prevalence of IGT in cirrhotic patients is highly variable because of the differences in the stages and etiology of liver disease and the diagnostic methods used [37]. A diagnosis of diabetes is based on either hemoglobin A1C (HbA<sub>1c</sub>) or plasma glucose criteria, the latter of which are indicated by either the fasting plasma glucose (FPG) levels or the 2-hour plasma

glucose (2h-PG) value after the administration of 75 g of oral glucose (*i.e.*, the OGTT) [38]. In 1979, the National Diabetes Data Group in the United States [39] and, subsequently, the World Health Organization Expert Committee on Diabetes Mellitus [40] published recommendations for the diagnosis of diabetes as either glucose levels  $\geq 140$  mg/dL in the fasting state or  $\geq 200$  mg/dL as measured with the OGTT. In 1997, the American Diabetes Association (ADA) revised the diagnostic criteria for FPG and reduced the cutoff value from 140 mg/dL to 126 mg/dL because the original value corresponded to a much higher value than the 2h-PG cutoff of 200 mg/dL [41]; thus, the FPG (126 mg/dL) and the 2h-PG cutoff values were appropriately aligned to allow a more accurate diagnosis of diabetes. However, the concordance between the FPG and the 2h-PG level and between the HbA<sub>1c</sub> criteria and either glucose-based test is imperfect. The HbA<sub>1c</sub> cutoff for a diagnosis of diabetes is  $>6.5\%$ , which corresponds to an increased prevalence of any retinopathy (a known complication of diabetes) [42]. Interestingly, the FPG and 2h-PG values were at least as predictive as the HbA<sub>1c</sub> levels [42]. Data from the National Health and Nutrition Examination Survey indicated that an HbA<sub>1c</sub> cutoff  $\geq 6.5\%$  identified one-third more cases of undiagnosed diabetes than an FPG cutoff of  $\geq 126$  mg/dL [43]. Therefore, the HbA<sub>1c</sub> test has several advantages over the FPG and OGTT, including greater convenience (*e.g.*, no fasting requirement) [38].

Kanda *et al.* [44] reported that the HbA<sub>1c</sub> levels in patients with comorbid cirrhosis and diabetes were lower than those in patients with type 2 diabetes because of increased red blood cell turnover due to hypersplenism. Therefore, HbA<sub>1c</sub> is not good marker for the diagnosis of diabetes in cirrhotic patients, and the ADA recommends that only blood glucose criteria should be used to diagnose diabetes in patients with conditions associated with increased red cell turnover. In fact, we previously reported that the mean HbA<sub>1c</sub> level in cirrhotic patients with diabetes was 5.7%, which falls within the normal range and emphasizes the tendency of HbA<sub>1c</sub> to be lower in cirrhotic patients with DM [45].

However, we are skeptical of using the FPG cutoff of 126 mg/dL as the standard for diagnosing diabetes in patients with cirrhosis. In 1999, we reported that the FPG level is insufficient for diagnosing diabetes in cirrhotic patients [11]. As described earlier, patients with cirrhosis have been shown to develop insulin resistance in both the liver and the skeletal muscles [15], which may cause a more marked elevation in postprandial glucose levels. Hyperglycemia due to liver cirrhosis was included in the classification and diagnosis of diabetes based on the same FPG cutoff value, unlike the diagnostic criteria for gestational DM. To clarify the appropriate plasma glucose cutoff levels for accurately diagnosing diabetes in cirrhotic patients, we previously analyzed the FPG and 2h-PG during the OGTT in 60 patients ( $67 \pm 8$  years, body mass index  $22.5 \pm 3.1$  kg/m<sup>2</sup>) with compensated liver cirrhosis due to HCV. Based on the OGTTs, the scatterplots of the FPG and 2h-PG values and the linear regression analysis revealed that an FPG of 107 mg/dL [95% confidence interval (CI), 71 to 143 mg/dL] corresponded to a 2h-PG value of 200 mg/dL. Moreover, 9 out of 42 patients (21%) who presented with a normal FPG ( $<110$  mg/dL) were classified as diabetic. We believe that the conventional FPG criteria are too high and are not applicable for evaluating glucose tolerance in cirrhotic patients. We propose a reduction of the FPG criterion for diagnosing diabetes in cirrhotic patients.

Koga *et al.* [46] proposed a novel parameter called chronic liver disease HbA<sub>1c</sub> that combined the average of the measured HbA<sub>1c</sub> and glycated albumin/3. Recently, Matsumoto *et al.* [47] reported that hypoalbuminemia and an elevated ICGR-15 were independent risk factors for DM in cirrhotic patients who had FPG levels  $<126$  mg/dL.

This evidence indicates that it is possible to underestimate the glucose tolerance of cirrhotic patients by using conventional FPG criterion or HbA<sub>1c</sub>, which are gold standards for diagnosing diabetes. We emphasize that patients with compensated liver cirrhosis are usually asymptomatic and are regarded as normal individuals absent a detailed blood test and special examinations. Therefore, an OGTT is recommended for screening cirrhotic patients with lower FPG levels ( $<110$  mg/dL) for diabetes if they are suspected to have either postprandial hyperglycemia or hypoalbuminemia.

Recent advances in the treatment of cirrhosis and its complications have remarkably improved the prognosis of patients with cirrhosis. At this point, the diabetic vascular complications caused by the development of chronic postprandial hyperglycemia in patients with cirrhosis cannot be overlooked. It is unclear whether diabetic vascular complications such as cardiovascular disease or chronic kidney disease affect the prognosis of these patients. The current criteria for diagnosing diabetes are based on HbA<sub>1c</sub>, FPG, and 2h-PG, with values over the respective cutoff points corresponding to a higher prevalence of retinopathy. Therefore, it is undetermined whether an early diagnosis of hepatogenous diabetes improves the patient's prognosis or prevents diabetic vascular complications. Indeed, Holstein *et al.* [48] reported no cardiovascular deaths; however, during an average 5-year follow-up, 52% of cirrhotic patients died of complications of cirrhosis. Therefore, the validity of these criteria for correctly diagnosing diabetes in cirrhotic patients remains unclear. Other criteria might be considered for diagnosing diabetes in cirrhotic patients based on their prognosis or diabetic complications.

### 3. Prevalence of IGT in Liver Cirrhosis Based on OGTT

Unfortunately, there are no specific criteria for diagnosing IGT in cirrhotic patients; therefore, we must apply the same criteria for hepatically healthy patients and cirrhotic patients. Using those criteria, we consider that the 2h-PG determined by the OGTT is the most reliable diagnostic criterion for identifying IGT in cirrhotic patients. The prevalence of diabetes in cirrhotic patients is highly variable, primarily because of the differences in applied diagnostic methods. To more precisely evaluate the prevalence of IGT, we studied articles published since 1997 that used the OGTT. These articles were identified via a Medline search of the revised ADA criteria using the following terms: (diabetes[ALL] OR glucose intolerance [ALL]) AND oral glucose tolerance test[ALL] AND liver cirrhosis[ALL]. Additional studies were located through manual searches of references. We excluded non-English publications and publications focusing on cystic fibrosis, nonalcoholic steatohepatitis, HIV-positive patients, or patients who underwent liver transplantation. Table 1 shows the prevalence of IGT based on the OGTT among the included studies. Of a total of 1747 cirrhotic patients in 12 studies, 580 had diabetes (mean prevalence 35.1%, 95% CI, 22.8% to 47.4%), 399 had IGT (27.8%; 95% CI, 21.2% to 34.4%), and 664 had NGT (37.6%; 95% CI, 25.5% to 49.7%) diagnosed with an OGTT (the latter two values exclude a total of 87 patients because the details of patients with non-DM glucose tolerance impairments were not described) [49].

### 4. Prognosis of Cirrhotic Patients With Diabetes

Liver cirrhosis itself is not a single-organ disorder because it is accompanied by various complications, such as varices, hepatorenal syndrome, hepatic encephalopathy, infection, and diabetes. These factors strongly affect patient prognosis, as does the natural course of exacerbated liver dysfunction. The recent advent of liver transplantation has not only significantly improved the survival of patients with decompensated cirrhosis [50] but has also normalized their glucose tolerance and insulin sensitivity [51]. Unfortunately, most cirrhotic patients, particularly decompensated cirrhotic patients, still have a poor prognosis because liver transplantation is not a standard treatment of cirrhotic patients worldwide. Generally, the prognosis of patients with cirrhosis is variable because of factors such as etiology, severity, the presence of complications, and comorbid conditions. When a patient with chronic liver status develops decompensated cirrhosis, his or her mortality rate is generally high. In a review of 118 studies, D'Amico *et al.* [52] reported that the Child–Pugh score was the best predictor of mortality in patients with cirrhosis; however, it is difficult to predict the prognosis of patients with compensated cirrhosis.

The Child–Pugh score was originally developed to predict the risk of operative mortality in cirrhotic patients with bleeding esophageal varices [53] and has been widely used to assess

**Table 1. Prevalence of IGT in Liver Cirrhosis Patients, as Diagnosed Using the OGTT**

Ref	Year	Etiology	No. of Patients With Liver Cirrhosis	Mean Age, y (Range)	Prevalence of IGT
Holstein <i>et al.</i> [48]	2002	Various Alcohol: 60% Hep C: 19%	52 [35] <sup>a</sup> Child A:B:C = 23:19:10	DM: 59.6 ± 10.7 (38–75), IGT: 54.2 ± 11.0 (36–75), NGT: 60.5 (59–62)	DM: n = 37 (71%) (n = 20, 57%) <sup>a</sup> IGT: n = 13 (25%) (n = 13, 37%) <sup>a</sup> NGT: n = 2 (3.8%) (n = 2, 6%) <sup>a</sup>
Tietge <i>et al.</i> [72]	2004	Not described	100 Child classification not described	44 ± 2	DM: n = 35 (35%) IGT: n = 38 (38%) NGT: n = 27 (37%)
Nishida <i>et al.</i> [10]	2006	Various Hep C: 67.9%	56 Child A:B:C = 34:15:7	62 ± 9	DM: n = 21 (38%) IGT: n = 13 (23%) NGT: n = 22 (39%)
García-Compeán <i>et al.</i> [73]	2012	Various Alcohol: 50.8%	130 Child A:B:C = 66:53:11	55.6 ± 11.4	DM: n = 25 (19.2%) IGT: n = 27 (20.8%) NGT: n = 50 (38.5%)
Matsumoto <i>et al.</i> [47]	2012	Hep B: 36.5% Hep C: 63.5%	263 Child classification not described	51.6 ± 11.2	DM: n = 44 (16.7%) IGT: n = 73 (27.8%) NGT: n = 146 (55.5%)
Jeon <i>et al.</i> [49]	2013	Various Alcohol: 69.6% Hep B: 17.0%	195 Child A:B:C = 80:93:22	53.0 ± 10.2	DM: n = 108 (55.4%) Non-DM: n = 87 (44.6%)
García-Compeán <i>et al.</i> [60]	2014	Various Cryptogenic: 26%	100 Child A:B:C = 47:53:0	53.19 ± 11.8	DM: n = 26 (17.3%), IGT: n = 44 (29.3%) NGT: n = 30 (20%)
Taguchi <i>et al.</i> [74]	2014	Various Hep C: 57.4%	61 Child A:B:C = 48:13:0	64.4 ± 1.3	DM: n = 28 (45.9%), IGT: n = 12 (19.7%) NGT: n = 21 (34.4%),
Kaur <i>et al.</i> [75]	2015	Hep C	80 Child A:B:C = 22:38:40	55.89 ± 11.22	DM: n = 0 (0%), IGT: n = 29 (36.3%) NGT: n = 51 (63.8%)
Grancini <i>et al.</i> [76]	2015	Various Hep C: 41.8%	160 Child A:B:C = 39:82:49	54.5 ± 8.7	DM: n = 84 (48.6%), IGT: n = 60 (35.8%) NGT: n = 26 (15.6%)
Calzadilla-Bertot <i>et al.</i> [77]	2016	Hep C	250 Child A:B:C = 208:42:0	Median 60 (IQR, 50–63)	DM: n = 67 (26.8%), IGT: n = 53 (21.2%), NGT: n = 130 (52.0%)
Marselli <i>et al.</i> [78]	2016	Various Hep C: 49% Hep B: 18% Dysmetabolic cirrhosis: 22% Other: 11%	300 Child A:B:C = 208:42:0	56 ± 9	DM: n = 105 (35%), Prediabetes, including impaired fasting glycemia and IGT): n = 36 (12%) NGT: n = 159 (53%)

Abbreviations: Hep, hepatitis; IQR, interquartile range.

<sup>a</sup>Three-hour OGTT with 100 g glucose was performed in 35 patients with no previous known IGT. DM was diagnosed in 57% (20/35) of the patients; IGT was diagnosed in 37% (13/35) of the patients; only 2 patients with Child A cirrhosis (6%) had NGT.

the severity of liver dysfunction. The initial version of the Child–Pugh score included ascites, hepatic encephalopathy, nutritional status, total bilirubin, and albumin. Pugh *et al.* [54] modified the Child–Pugh classification by adding prothrombin time and removing nutritional status. Recently, the number of patients who died of variceal bleeding has decreased because of improved endoscopic treatments [55]. Specifically, recent Japanese guidelines proposed the combination of endoscopic treatment and  $\beta$ -blockers for the secondary prophylaxis of



esophageal variceal bleeding because it decreases rebleeding events and mortality (evidence level A, strength 2) [50]. In addition to the Child–Pugh score, diabetes can predict the mortality of patients with cirrhosis and can determine their prognosis [10, 56, 57]. However, few studies have assessed the prognostic value of varying degrees of IGT (including diabetes) in patients with liver cirrhosis. In a retrospective study, Bianchi *et al.* [58] first reported that diabetes was partially correlated with a long-term poor prognosis for cirrhotic subjects. Complications of diabetes are generally not directly responsible for the death of cirrhotic patients, although such complications may contribute to the increased risk of hepatocellular failure, and diabetes was no longer a risk factor when varices were added as a factor. In 2004, Moreau *et al.* [59] reported in a multivariate Cox model that an older age, hepatocellular carcinoma (HCC), diabetes, and the etiology of the cirrhosis were independent factors in the death of cirrhotic patients with refractory ascites. The survival rates of cirrhotic patients with and without diabetes were 18% and 58%, respectively. Moreau *et al.* concluded that cirrhotic patients with diabetes had an extremely poor prognosis but that the Child–Pugh score was not a sufficient predictor of this prognosis.

In 2006, we prospectively evaluated and reported the prognosis of patients with IGT as determined by the 75-g OGTT based on previous reports describing diabetes as a prognostic indicator. Our investigation showed that the 5-year survival rate of cirrhotic patients with NGT was 94.7%, that of patients with IGT was 68.8%, and that of patients with DM was 56.6%. These data revealed that the survival rate of cirrhotic patients with DM significantly differed from the survival rate of patients with NGT based on an OGTT. Based on multiple regression analysis, this study showed that DM could be a second powerful independent negative predictor of survival in addition to albumin [10]. Similarly, García-Compeán *et al.* [60] also reported that cirrhotic patients with subclinical IGT based on OGTT results had a significantly worse prognosis than cirrhotic patients with NGT (5-year cumulative survival 31.7% vs 71.6%, respectively;  $P = 0.02$ ; Table 2).

With the advancement of treatment of varices, antiviral therapy against HBV or HCV, HCC treatments, and nutrition support, the prognosis of patients with cirrhosis has improved remarkably, especially for patients with decompensated cirrhosis [50]. Therefore, an early diagnosis of IGT and subsequent interventions may further improve the prognosis of patients with cirrhosis.

However, Sangiovanni *et al.* [61] performed a 17-year cohort study of 214 patients and reported that diabetes had no impact on the survival of patients with HCV-induced cirrhosis. Therefore, there may be not enough evidence to support the assertion that diabetes is a negative prognostic factor in cirrhotic patients.

Early intervention for IGT may have a favorable impact on cirrhotic patients. However, oral hypoglycemic agents and insulin may sometimes lead to hypoglycemia and lactic acidosis because of impaired liver metabolism resulting from liver dysfunction. Therefore, there is inadequate evidence to support a recommendation for the management of diabetes in patients with cirrhosis, particularly in the early stage. Recently, many antidiabetes agents have been developed and made available for cirrhotic patients. Some reviews have introduced the treatment of DM in patients with chronic liver disease [62, 63]. In the future, we should examine the effect of interventions to combat IGT and the restoration of normal glucose levels on the prognosis of patients with cirrhosis.

## 5. Cirrhotic Patients With Diabetes and HCC

HCC is a primary tumor of the liver that can manifest in patients with chronic liver disease. It occurs in 70%–90% of all patients, particularly those with chronic hepatitis B or C, and is the sixth most prevalent cancer and the third leading cause of cancer-related death [64]. In particular, patients with cirrhosis have a much higher risk of developing HCC, which is one of the major causes of death in patients with liver cirrhosis. Recently, a meta-analysis by Yang *et al.* [65] suggested that patients with DM may have an elevated risk of developing HCC; those who do present with HCC also have a worse prognosis than nondiabetic patients with

**Table 2. Prognosis of Cirrhotic Patients With and Without Diabetes**

Ref	Year	n	Etiology	Prognosis
Bianchi <i>et al.</i> [58]	1994	382	Various Alcohol: 27.7%	5-y survival DM: ~41% <sup>a</sup> Non-DM: ~56% <sup>a</sup> ( $P = 0.005$ )
Holstein <i>et al.</i> [48]	2002	52	Various Alcohol: 60% Hep C: 19%	31% (19/37) of patients with hepatogenous diabetes died within $5.6 \pm 4.5$ (0–18.4) y after the histological diagnosis of liver cirrhosis and within $5.7 \pm 4.7$ (0–24.3) y after the diagnosis of diabetes. There was no statistical significance between the survival rates of patients with diabetes and those of patients with IGT.
Moreau <i>et al.</i> [59]	2004	100	Various Alcohol: 81%	2-y survival DM: 18% Non-DM 58% ( $P = 0.0004$ )
Nishida <i>et al.</i> [10]	2006	56	Various Hep C: 67.9%	5-y survival DM: 56.6% (compared with NGT, $P = 0.0086$ ) IGT: 68.8% NGT: 94.7%
Quintana <i>et al.</i> [79]	2011	110	Various Alcohol: 40.9%	Cumulative survival was 69% in patients without DM and 48% in patients with DM ( $P < 0.05$ ) after 900-d follow-up
García-Compeán <i>et al.</i> [60]	2014	100	Various Cryptogenic: 26%	5-y survival SAGT <sup>b</sup> : 31.7% NGT: 71.6% ( $P = 0.02$ )

Abbreviations: Hep, hepatitis; SAGT, subclinical abnormal glucose tolerance.

<sup>a</sup>Three-hour OGTT with 100 g glucose was performed in 35 patients with no previous known IGT. DM was diagnosed in 57% (20/35) of the patients; IGT was diagnosed in 37% (13/35) of the patients; only 2 patients with Child A cirrhosis (6%) had NGT.

<sup>b</sup>Not described but estimated from the available Kaplan–Meier curve.

HCC. One of the mechanisms speculated to be related to the development of hyperinsulinemia in cirrhotic patients is a well-known carcinogenic process in several organs [66]. Epidemiological studies have shown that DM is a risk factor for HCC in patients with chronic hepatitis C [67, 68], but other studies have shown no association between DM and HCC [69, 70]. Our previous study did not reveal an increased risk of developing HCC after a diagnosis of IGT based on an OGTT [10]. Therefore, it is unclear whether DM is an important risk factor for HCC. The major source of the controversy regarding the association of DM with HCC is the inconsistent criteria for diagnosing DM. Recently, Takahashi *et al.* [71] reported HCC occurrence rates of 3.3 and 4.3% at 3 and 5 years, respectively, in HCV-RNA–positive patients with either NGT or IGT who completed interferon therapy; however, in patients who were diagnosed with DM on the 75-g OGTT, those rates were 15.0 and 28.1%, respectively. The OGTT may also be an important and reliable diagnostic method for detecting IGT in cirrhotic patients, with the goal of predicting the development of HCC in patients with cirrhosis.

## 6. Conclusion

DM is associated with a higher rate of comorbidities and poor prognosis in patients with cirrhosis, but diagnosing diabetes in patients with early stage cirrhosis is difficult because these patients can present false negative fasting glucose or HbA<sub>1c</sub> results, thus mimicking NGT. Therefore, the OGTT is recommended for diagnosing the early stages of diabetes in cirrhotic patients. Unfortunately, there is not enough of an evidence base to make recommendations for management, including medication use, in the early stages of diabetes in cirrhotic patients. However, it seems reasonable to recommend an OGTT to identify

hepatogenous diabetes in patients with liver disease with impaired fasting glucose (100 to 125 mg/dL) or an impaired HbA<sub>1c</sub> (5.7% to 6.4%). Consequently, subclinical IGT, as estimated by the OGTT, may be a useful prognostic factor.

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Address all correspondence to: Tsutomu Nishida, MD, Department of Gastroenterology, Toyonaka Municipal Hospital, 4-14-1 Shibahara, Toyonaka, Osaka 560-8565 Japan. E-mail: [tnishida@gh.med.osaka-u.ac.jp](mailto:tnishida@gh.med.osaka-u.ac.jp).

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