Estimated Prevalence of Advanced Hepatic Fibrosis by Elastography in Patients with Type 2 Diabetes

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. The grade of hepatic fibrosis is known to be closely associated with over-all or liver-related mortality in NAFLD. In order to detect early stage of hepatocellular carcinoma (HCC), it is essential to identify advanced hepatic fibrosis in NAFLD. To avoid invasive liver biopsies, several modalities have developed for evaluating hepatic fibrosis, including elastography (FibroScan and magnetic resonance elastography) and noninvasive tests (NITs) such as fibrosis-4 index and NAFLD fibrosis score. Patients with type 2 diabetes is twice at higher risk for incident HCC compared to the non-diabetic population. Although type 2 diabetes is also associated with fibrosis progression of NAFLD, the precise prevalence of advanced hepatic fibrosis in type 2 diabetes remains unknown. To detect or prevent the development of HCC in type 2 diabetes, mining patients with advanced fibrosis (stage 3/4) is important. It is estimated that approximately 17% of patients with type 2 diabetes receiving liver biopsies had advanced fibrosis. Population-based data are essential because of excluding selection bias. In this review, we review estimated prevalence of advanced hepatic fibrosis in patients with type 2 diabetes by using non-invasive elastography.

Keywords: Diabetes, Hepatic fibrosis, Elastography, Fibroscan, Magnetic resonance elastography

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death worldwide. The main etiology of HCC has been hepatitis virus infection for several decades. The development of anti-hepatitis viral agents, including direct acting antivirals for hepatitis C virus (HCV) or nucleoside analogues for hepatitis B virus
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(HBV), can lead to decrease in incidence of HCC worldwide [1]. In Japan, the prevalence of so-called “non-HBV, non-HCV HCC (NBNC-HCC)” has been increasing (32.5% of HCC in 2015) [2]. An estimated 400 million individuals have diabetes worldwide, among whom 85-95% have type 2 diabetes (T2D). There is emerging evidence of a link between T2D and an increased risk of developing cancer and death from cancer. In a meta-analysis of 13 case-control and 13 cohort studies, diabetes was associated with increased HCC risk (odds ratio [OR]: 2.5 and hazard ratio [HR]: 2.5) [3]. A more recent meta-analysis of 23 cohort studies reported a pooled relative risk (RR) of 2.0 [4]. In recent two large cohorts of U.S. men and women, with over 26 year of follow-up, T2D is significantly associated with incident HCC. This risk was enhanced in patients with a prolonged duration of T2D, and in those with an increasing number of comorbid metabolic conditions (dyslipidemia, obesity, and hypertension) [5]. T2D was associated with a 26% increased risk of death from any cancer also in Asians. The HR of HCC is 2.05 [6]. In Japan, Nakamura and colleagues demonstrated that HCC was the fifth leading causes of mortality (6.0%) in 45,708 Japanese diabetic patients at 241 hospitals during 2001-2010 [7]. Since the tenth cause is liver cirrhosis (3.3%), 9.3% of diabetic patients totally died from liver related diseases in Japan. It is important to identify those patients with T2D who have a high risk of developing HCC. Risk factors for incident HCC in T2D patients have not been established. Three parameters which are associated with HCC incidence are old age (>65yr), low triglyceride level (<150mg/dl) and high gamma-glutamyl transferase (GGT) level (>40IU/L) [8]. A multicenter study from Japan by Korenaga and colleagues demonstrated that the SNPs of PNPLA3 and juxtaposed with another zinc finger protein 1 (JAZF1) were associated with development of HCC in T2DM patients without hepatitis virus infection [9]. That study included 389 T2D patients, including 59 patients with HCC (T2D-HCC) and 330 patients without HCC (T2D-non-HCC). Compared to T2D-non-HCC patients, T2D-HCC patients had the significantly higher frequency of the PNPLA3 G allele (OR=2.53, P=1.05×10^-5). Moreover, among the 115 T2D patients with PNPLA3 genotype GG, HCC patients had the significantly higher frequency of the JAZF1 rs864745 G allele (OR=3.44, P=0.0002). We conclude that SNPs of PNPLA3 and JAZF1 may be associated with an increased risk of developing HCC among T2D patients without viral hepatitis.

**Figure 1:** A few patients among 100 NAFLD will develop HCC (25% rule) [10-14].

Nonalcoholic fatty liver disease (NAFLD) is becoming a major cause of HCC, with a steadily rising trend compared to virus-induced chronic hepatitis. NAFLD is closely associated with T2D. One fourth of the adult population (25%) is globally suffering from NAFLD [10]. In U.S., across the 6-year period (2004 to 2009), the number of NAFLD-HCC showed a 9% annual increase. However, the leading cause of NAFLD is cardiovascular disease (42%) followed by extrapancreatic cancer (20%), and liver-related mortality (9%) [11]. We believe that a few patients among 100 NAFLD patients will develop HCC [12]; 25% (6.7-29%) of NAFLD can progress to NASH [13], 25% (6.7-29%) of NASH can lead to cirrhosis, and 25% of NASH-cirrhosis develop HCC for about 10 years [14] (We name “25% rule”) (Figure 1). Sirtuin-1 (SIRT1) is vital for the physiological function of healthy tissues. SIRT1 deletion in mice hepatocytes results in hepatic steatosis or hepatitis. SIRT1 overexpression reduced the release of pro-inflammatory cytokines and increased cell viability. Previous studies have reported that hepatic SIRT1 plays a major role in ameliorating steatosis and inhibiting inflammation in NAFLD by modifying the acetylation status of the different target molecules. SIRT1 can ameliorate liver fibrosis by blocking hepatic stellate cell activation in mice. Impact of expression of SIRT1 on hepatocarcinogenesis of NAFLD is conflicting. In the future, it should be clarified whether plasma SIRT1 levels or histological SIRT1 expression may be relevant to NAFLD, advanced hepatic fibrosis, and HCC [15-19]. The several risk factors for incident HCC in ultrasonography (US) diagnosed NAFLD from a Japanese cohort are identified, including serum AST level ≥40 IU/L (HR: 8.20; 95% CI: 2.56-26.26; P<0.001), platelet count <150 × 10^3/μl (HR: 7.19; 95% CI:
Table 1: Evaluation Method of Hepatic Fibrosis using Elastography

Vibration-controlled transient elastography (VCTE)

To assess liver fibrosis, several noninvasive US-based elastography techniques have been developed. These methods include VCTE (FibroScan; Echosens, Paris, France), acoustic radiation force impulse imaging and shear wave elastography. US-based VCTE performed with the FibroScan (Echosens) is the most thoroughly validated and commonly used elastography method worldwide [24-33]. VCTE is equipped with a one-dimensional probe and an ultrasonic transducer mounted on the axis of a vibrator. A vibration of mild amplitude and low frequency is transmitted from the vibrator onto the tissue by the transducer itself, which induces propagation of an elastic shear wave through the tissue. The propagation velocity is directly related to the stiffness of the medium, defined by the Young modulus expressed in kilopascals (E ≒ 3000). VCTE was developed approximately 10 years ago as the first US-based elastography method. It has since been validated for liver fibrosis assessment and was recently included in the European Association for the Study of the Liver Guidelines for fibrosis assessment in patients with chronic B and C hepatitis infection. Furthermore, VCTE received approval from the United States Food and Drug Administration on 5 April 2013, and it is expected that its use will subsequently increase not only in Europe but also the United States. A systematic review and meta-analysis of VCTE in patients with NAFLD by Kwok et al. indicated that VCTE is good for the diagnosis of stage 3 fibrosis (85% sensitivity and 82% specificity) and excellent for stage 4 (92% sensitivity and 92% specificity). However, it has a slightly lower accuracy for diagnosing stage 2 fibrosis (79% sensitivity and 75% specificity) [34]. The benefits of VCTE include its rapidity and painlessness, quick availability of the result, high intra- and inter-operator reproducibility (intra-class correlation coefficient [ICC] of 0.98) [35], and good diagnostic accuracy that has been validated in many studies. Clinical use of VCTE has generally been limited because of its high failure rate or unreliable results. These limitations are commonly a result of obesity, operator inexperience, narrow intercostal spaces, a thick chest wall, and ascites [36,37]. In a previously published study, the rate of failed and unreliable measurements by VCTE using the standard M probe was 5.8% to 29.2% [37,38]. To improve this problem, the VCTE device has three different probes for measurement in various circumstances: The S probe (5.0MHz) for children, the M probe (3.5MHz) for adults, and the XL probe (2.5MHz) for overweight patients.

Magnetic resonance elastography (MRE)

Magnetic resonance elastography (MRE) is a noninvasive magnetic resonance imaging (MRI)-based method measuring liver stiffness by using a modified phase-contrast method. MRE can assess the entire liver with a high success rate. MRE is not operator dependent or affected by obesity or ascites and is currently the most accurate imaging tool for the detection of liver fibrosis, more effective than TE alone or TE with serum biomarkers combined [39-45]. Two imaging modalities were compared in Table 1.

| Table 1: Elastography (MR elastography vs. VCTE) |
| Modality | MR elastography | VCTE |
|---|---|---|
| Strength | · Accuracy for identify hepatic fibrosis  
· Not affected by obesity or ascites  
· Can also evaluate steatosis (using PDFF), inflammation (using multiparametric MRI), iron deposit, and the existence of HCC  
· Good reproducibility  
· Relatively high cost | · Convenience  
· Short processing time  
· Portability  
· Relatively low cost  
· Can also evaluate steatosis (using CAP)  
· Covered by health insurance (in Japan) |
The Relationship between Hepatic Fibrosis and Type 2 Diabetes

Cross sectional studies

Angulo and colleagues from U.S. showed that T2D was independently associated with severe fibrosis in NAFLD [46]. According to a large cohort (n=1,365) from a multi-center study by Japan Study Group of NAFLD (JSG-NAFLD), the existence of T2D was closely associated with liver fibrosis severity in Japanese patients with NASH [47]. On the basis of a cohort with biopsy-proven NAFLD from JSG-NAFLD (n=361), HOMA-IR (>2.90) were found to be independent predictors of advanced fibrosis in the estimation and validation group [48]. According to data from 262 German patients with non-cirrhotic NAFLD on liver biopsy, multivariate logistic regression demonstrated that diabetes (odds ratio [OR]=4.68, 95% confidence interval [CI] 2.17-10.10) and hypertension (OR=2.91, 95% CI 1.12-7.18) were independently associated with advanced hepatic fibrosis [49]. In this way T2D or insulin resistance must be associated with advanced hepatic fibrosis in NAFLD.

Longitudinal studies

Adams et al. reported that T2D and low initial fibrosis stage are associated with a higher rate of fibrosis progression in 103 NAFLD patients who underwent serial liver biopsies with a mean interval of 3.2±3.0 years between biopsies [50]. In Japanese NAFLD cohort, the presence of T2D was an independent risk factor for progression to advanced liver fibrosis (HR, 1.879) evaluated by fibrosis-4 (FIB-4) index in addition to advanced age and low albumin concentration [51]. Furthermore, longer duration of T2DM has also been reported to be an independent risk factor for progressive fibrosis in patients with NAFLD [52]. Hamaguchi and colleagues showed that the change in glycated hemoglobin (ΔHbA1c) was strongly associated with serial change of hepatic fibrosis based on data of NAFLD patients with T2D receiving repeat liver biopsies [53]. They recommend that strict diabetic control is required for inhibiting fibrosis progression in NAFLD patients with T2D. In a prospective cohort study of 40,700 adults with NAFLD, obesity and weight gain are independently associated with increased risk of fibrosis progression, based on APRI [54]. In 80 NASH patients who had undergone serial liver biopsies in this retrospective cohort study, poor response of alanine aminotransferase (ALT) levels, increase in HbA1c levels, and presence of the tumor necrosis factor risk allele in the rs1799964 SNP were identified as independent risk factors contributing to histological progression in NASH patients [55]. MRE can also reflect hepatic fibrosis after pharmacotherapies.

Estimated Prevalence of Advanced Hepatic Fibrosis by Elastography in Patients with Type 2 Diabetes

Table 2: Estimated prevalence of significant/advanced hepatic fibrosis by elastography in patients with type 2 diabetes.

| Imaging Modalities | Author                  | Paper          | N    | COI      | Prevalence | Risk factors                                                                 |
|--------------------|-------------------------|----------------|------|---------|------------|-------------------------------------------------------------------------------|
| VCTE               | de Ledinghen [58] (France) | Dig Liver Dis 2012 | 277  | ≥8.7kpa | 15.5%      | ≥50yr, T2DM, retinopathy (-), No history of leg ulcer history of leg ulcer |
|                    | Casey [59] (Australia)  | Scand J Gastroenterol 2012 | 74   | ≥7.6kpa | 35%        | High body weight (high BMZ), WC, BP, TG, FPG, HbA1c, ALT, Urinary Albu/Cr ratio |
|                    | Sobbonslidsuk [60] (Thailand) | Asian Pac J Cancer Prev. 2015 | 141  | ≥7.0kpa | 16.1%      | Age, overweight, CTP elevation                                                |
|                    | Kwok [61] (Hong Kong)   | Gut 2016       | 1770 | ≥9.6kpa | 17.1%      | High body weight (high BMZ), WC, BP, TG, FPG, HbA1c, ALT, Urinary Albu/Cr ratio |
|                    | Roulot [62] (France)    | Liver Int 2017 | 669  | ≥8.0kpa | 12.7%      | Age, overweight, CTP elevation                                                |
|                    | Lai [63] (Malaysia)     | J Gastroenterol Hepatol 2019 | 557  | ≥9.6kpa (M.Probe) | 21.0%      | HDL-C, ALT, GTP, PLT                                                        |
|                    | Demir [64] (Turkey)     | Turk J Gastroenterol 2019 | 124  | ≥9.6kpa (M.Probe) | 25%        |                                                                               |
|                    | Mantovani [65] (Italy)  | Diabetes Metab. 2019 | 137  | ≥7.0kpa | 17.5%      | AST, WC, C, peptide                                                        |
|                    | Mansour [66] (Iran)     | Acta Diabetol 2019 | 108  | ≥8.0kpa | 24.1%      |                                                                               |
|                    | Lee HW [67] (Hong Kong) | Hepatology 2020 | 611  | >10.0kpa | 20.3%      |                                                                               |
Of the patients with NAFLD and T2D who undergo liver biopsies based on data of seven studies, 17% (95% CI 7.2-34.8) have advanced fibrosis [56]. Another study showed that the percentages of advanced fibrosis in biopsy proven NAFLD patients with T2DM were 56.5% [57]. However, selection bias must exist in these studies using histological diagnosis, because liver biopsy is invasive, expensive procedure, and difficult to be consented by patients. Several studies tried to estimate the true prevalence of advanced hepatic fibrosis by non-invasive elastography in patients with T2D. Most of these studies used VCTE except two studies from US and South Korea (Table 2).

VCTE [58-67]

Significant hepatic fibrosis (liver stiffness measurement [LSM]>7.0kPa) was more common in diabetic patients (16.1 or 17.5%) [60]. The prevalence of severe hepatic fibrosis (LSM≥9.6-10.0kPa) is estimated to be 7.3-24.9%. Asian populations tend to have higher prevalence of advanced fibrosis compared to the West, although cutoff value of VCTE for detecting advanced fibrosis is variable. Prevalence of advanced fibrosis may be influenced by the distribution of age, sex, body mass index (BMI), diabetic control status, and anti-diabetic medications. In a recent study from Hong-Kong, 20.3% with T2DM showed LSM>10.0kPa. Among 487 patients with baseline LSM<10kPa, 21 (4.3%) had follow-up LSM>10kPa in 3 years. Baseline BMI, ALT and ∆ALT were independent factors associated with LSM increase [67]. Body weight and serum ALT should be strictly controlled in NAFLD with T2D.

MR elastography [68,69]

The prevalence of advanced fibrosis seems to be lower by evaluated using MR elastography compared to VCTE. Optimal cutoff values should be settled using these two modalities in an international multi-center study [68]. The prevalence of F2 (≥3.0kPa) and F3 (≥3.6kPa) in the overall cohort (n=2,170) receiving health check-up was 5.1% and 1.3% respectively. In patients with diabetes, 12.5% had≥F2 and 4.3% ≥F3 [69]. The reason why the prevalence of advanced fibrosis seems to be lower in MRE than VCTE remains to be resolved. The plausible examination is that LSM by VCTE might be influenced by a variety of factors such as congestion, steatosis, inflammation, and bile cholestasis. False positive rate is higher in VCTE than MRE. Strengths and weakness of each imaging modality were compared between MRE and VCTE (Table 1). Accuracy and reproducibility are superior in MRE to in VCTE. Moreover, multiparametric MRI can estimate hepatocyte ballooning and inflammation. In contrast, VCTE has several advantages such as portability, short processing time, and relatively low cost. MRE cannot be applied to individuals with hepatic iron overload due to the interfering signal intensity. Moreover, the cost of MRE and its dependence on MRI facilities limit its wide application. Among two imaging modalities, VCTE will be positioned as the 1st triaging tool for excluding no/ mild fibrosis, and MRE is used as confirmed diagnosis by hepatology specialists.

Conclusion

A significant proportion of patients with T2D is estimated to have underlying advanced fibrosis which was evaluated by elastography (Fibroscan and MR elastography). In order to detect early HCC or prevent incident HCC, patients with T2D should be screened for identifying advanced hepatic fibrosis. Accumulating evidence suggest that ALT, body weight, HbA1c levels (ABC) should be controlled to prevent progression of hepatic fibrosis in T2D [70].

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