World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i24.7427

World J Gastroenterol 2015 June 28; 21(24): 7427-7435
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Liver fibrosis markers of nonalcoholic steatohepatitis

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Author contributions: Enomoto H and Koga M wrote and edited the manuscript; all authors participated in the studies and were involved in the manuscript revision and approved the final version of the manuscript.

Conflict-of-interest: The authors declare no conflicts of interest.

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Received: February 20, 2015
Peer-review started: February 22, 2015
First decision: April 13, 2015
Revised: April 27, 2015
Accepted: May 7, 2015
Article in press: May 7, 2015
Published online: June 28, 2015

Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the major causes of chronic liver injury. NAFLD includes a wide range of clinical conditions from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and liver cirrhosis. The histological findings of NASH indicate hepatic steatosis and inflammation with characteristic hepatocyte injury (*e.g.*, ballooning degeneration), as is observed in the patients with alcoholic liver disease. NASH is considered to be a potentially health-threatening disease that can progress to cirrhosis. A liver biopsy remains the most reliable diagnostic method to appropriately diagnose NASH, evaluate the severity of liver fibrosis, and determine the prognosis and optimal treatment. However, this invasive technique is associated with several limitations in routine use, and a number of biomarkers have been developed in order to predict the degree of liver fibrosis. In the present article, we review the current status of noninvasive biomarkers available to estimate liver fibrosis in the patients with NASH. We also discuss our recent findings on the use of the glycated albumin-to-glycated hemoglobin ratio, which is a new index that correlates to various chronic liver diseases, including NASH.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Liver fibrosis; Glycated albumin; Glycated hemoglobin

Core tip: Due to the increasing prevalence of obesity and diabetes, nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. In particular, nonalcoholic steatohepatitis (NASH), a subgroup of NAFLD, has become a major health concern. A liver biopsy remains the gold standard method for the accurate diagnosis of NASH and the evaluation of the degree of liver fibrosis. However, due to the limitations associated with the performance of liver biopsies, noninvasive biomarkers have been proposed to estimate the degree of liver fibrosis.

Recently, new approaches based on glycated proteins have been developed, and these methods may help to improve the management of NAFLD/NASH.

Enomoto H, Bando Y, Nakamura H, Nishiguchi S, Koga M. Liver fibrosis markers of nonalcoholic steatohepatitis. *World J Gastroenterol* 2015; 21(24): 7427-7435 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i24/7427.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i24.7427

INTRODUCTION

Hepatic steatosis indicates the accumulation of fat in excess of 5%-10% of the total liver weight[1]. Alcoholic consumption is one of the main causes of liver damage, and the presence of steatosis in alcoholic liver disease is related to the progression of liver fibrosis and cirrhosis[2,3]. Although hepatic steatosis due to nonalcoholic factors was regarded as a non-progressive benign disease, it has been noted that obese patients and those with diabetes mellitus may develop steatohepatitis that pathologically mimics alcoholic liver injury[1,4].

In 1980, Ludwig *et al*[5] reported 20 cases of nonalcoholic steatohepatitis in which the histological findings were nearly identical to alcoholic liver damage and which could progress to cirrhosis. In 1986, Schaffner *et al*[6] proposed the idea of "nonalcoholic fatty liver disease (NAFLD)" which was clinically similar to alcoholic liver disease, irrespective of the absence of an excessive alcohol intake. The definition of NAFLD requires the evidence of hepatic steatosis, either by imaging or by histology, in the absence of the typical causes for secondary hepatic fat accumulation, such as significant alcohol consumption, the use of steatogenic medication or hereditary disorders[7].

NAFLD is histologically classified into either non-alcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). The histological findings of NAFL demonstrate hepatic steatosis without the evidence of hepatocellular injury (*e.g.*, ballooning of the hepatocytes), and NAFL usually follows a benign clinical course. Conversely, the histological findings of NASH are barely distinguishable from those of alcoholic liver disease, which are characterized by the presence of hepatic steatosis and inflammation with a distinctive hepatocyte injury (*e.g.*, ballooning degeneration), and NASH is considered to be a potentially health-threatening disease that may progress to cirrhosis in 10%-15% of patients[8]. NAFLD typically develops based on various metabolic disorders such as obesity, diabetes mellitus, and dyslipidemia; however, the prognosis and outcome of the patients with advanced liver fibrosis are predominantly determined by the liver disease-related clinical events, including hepatic failure and hepatocellular carcinoma[9,10]. Therefore, physicians are required to accurately differentiate NASH from NAFL and evaluate the severity of liver fibrosis in order to determine the prognosis and optimal treatment[7].

ESTIMATION OF THE DEGREE OF LIVER FIBROSIS WITH NONINVASIVE BIOMARKERS

In patients with chronic liver diseases (CLDs), continuous inflammation and tissue injury cause fibrotic changes in the liver. Liver fibrosis leads to several serious problems, including disturbed metabolic functions, an increased risk of cancer development, and portal hypertension-associated symptoms such as ascites and gastroesophageal varices.

Although imaging modalities are capable of detecting the presence of hepatic steatosis, it is not easy to diagnose NASH without a histological assessment. A liver biopsy therefore remains not only the most reliable diagnostic tool for confirming NASH, but also the most promising means of identifying many of the important clinical features of the patient, including the severity of hepatic inflammation and fibrosis[7]. Although a liver biopsy can histologically determine the degree of liver fibrosis, the procedure is a costly and uncomfortable technique, which is associated with a small risk of complications[11-13]. In addition, there is the potential for a sampling error, because only 1/50000 of the organ is available for the histological assessment[12]. Furthermore, inter- and intra-investigator variances are present in up to 20% of the clinical samples[13]. Recently, several imaging tools have been developed to estimate liver fibrosis, and the clinical utility of these new modalities has been reported[1,9,14-17]. Unlike liver biopsy, these modalities can be repeatedly performed over a period of time with minimal invasion. However, these excellent but expensive items are not readily available in all institutions, while noninvasive biomarkers of fibrosis can be easily measured in a large number of patients. Therefore, there is a need for serum markers which can be routinely assessed *via* laboratory tests. To date, many noninvasive markers have been proposed to evaluate the degree of liver fibrosis[18-20].

During the turnover of fibrosis in the liver, the components of the extracellular matrix (ECM) are considered to be released into circulation, and some ECM-associated molecules, such as hyaluronic acid and type Ⅳ collagen, have been used as biomarkers to estimate the degree of liver fibrosis[21,22]. Additionally, a decreased platelet count was reported to correlate with the progression of liver fibrosis and therefore be a marker of the severity of liver fibrosis[23,24]. In addition to these markers, the AST-to-ALT ratio (AAR) is regarded as a well-known classical biomarker which

increases with the advancement of liver fibrosis[24,25].

In 2001, Imbert-Bismut *et al*[26] investigated hepatitis C virus (HCV)-positive patients and proposed a novel index, the "FibroTest score," which is computed based on the patient's age, gender and levels of serum haptoglobin, α2-macroglobulin, apolipoprotein A1, γ-glutamyl transpeptidase (GGT) and bilirubin. In 2002, Forns *et al*[27] developed another scoring system, the "Forns score," which involves an algorithm that includes the platelet count, the GGT, the patient' s age and cholesterol level. These scores are novel and important in that they allow for the degree of liver fibrosis to be assessed using only blood tests. However, the FibroTest score is a combination of six parameters, and the Forns score is calculated using a complicated formula. Therefore, neither of these markers is easy to apply in daily practice. In 2003, Wai *et al*[28] investigated several combinations of clinical variables which are commonly used in daily practice, and proposed the AST-to-platelet ratio index (APRI). This index allows for the estimation of liver fibrosis using a simple formula that is calculated using only two daily clinical variables. Subsequently, the FIB-4 index, which is determined by the age, AST, ALT, and platelet count, was proposed. In addition, many other biomarkers, such as the Fibrosis Probability Index[29,30], FibroMeter[31], Lok index[32], FibroIndex[33], Original European Liver Fibrosis (OELF) test[34] and FIBROSpect[35], were reported with regard to their clinical utility in the assessment of the degree of liver fibrosis.

LIVER FIBROSIS MARKERS IN NAFLD/NASH

Despite the fact that liver biopsy is the most reliable method to diagnose and evaluate the progression of NAFLD/NASH, NAFLD affects 10% to 24% of the general population in various countries[36], and it is unrealistic to perform liver biopsies in all NAFLD patients. Therefore, many biomarkers of liver fibrosis have been applied as liver fibrosis markers for NAFLD/NASH patients.

General fibrosis markers in NAFLD/NASH

Many biomarkers for liver fibrosis, which had been previously evaluated for the patients with viral hepatitis (particularly HCV-infected patients), have also been validated in patients with NAFLD/NASH. In addition to the patients with viral hepatitis, the serum levels of hyaluronic acid and type Ⅳ collagen were reported to increase in association with the progression of liver fibrosis in NAFLD[37,38]. Sakugawa *et al*[38] investigated a total of 112 NAFLD patients and demonstrated these ECM-related markers to be valuable markers of liver fibrosis. Regarding the presence of fibrosis at any stage (Stage 1-4), hyaluronic acid and type Ⅳ collagen 7S were reported to have AUROCs of 0.80 and 0.83, respectively. The values of hyaluronic acid and type Ⅳ collagen 7S also had AUROCs of 0.80 and 0.82, respectively, for the prediction of advanced fibrosis (Stage 3-4). Yoneda *et al*[39] investigated a total of 1,048 patients with NAFLD and reported a significant association between the decreased platelet count and the severity of liver fibrosis. Although a platelet count was reported to show an excellent AUROC of 0.92 for the prediction of cirrhosis (Stage 4), it showed only a moderate AUROC of 0.77 for the prediction of advanced fibrosis (Stage 3-4). Irrespective of the clinical relevance of these markers, it is difficult to evaluate the degree of liver fibrosis adequately according to these variables alone.

Several liver fibrosis markers, which have been validated with multiple-variable algorithms, such as the APRI[28], FIB-4[29], FibroTest[26], and the Enhanced Liver Fibrosis (ELF) test[40], have also been validated in the NAFLD population, where they may identify patients with liver fibrosis. These indices have been reported to demonstrate AUROCs between 0.67-0.90 for the differentiation of the severity of fibrosis[41-45].

The APRI, which is a simple marker calculated by two variables (AST and platelet count), was reported to have an AUROC of 0.85 for advanced fibrosis (Stage 3-4) in 111 NAFLD patients[41]. Since the APRI is easily measurable without any special equipment, its diagnostic performance was evaluated and compared with that of the other fibrosis markers. The AUROCs of APRI for the prediction of advanced/severe fibrosis (Stage 3-4) were reported to range from 0.67 to 0.87[42]. The FIB-4 index calculated with four variables (age, AST, ALT, and platelet count) was reported to have an AUROC of 0.80 for advanced fibrosis (Stage 3-4) in 541 NAFLD patients, although the score was difficult to use for the diagnosis of NASH[43]. The FibroTest is an algorithm derived from a regression analysis of haptoglobin, α2-macroglobulin, apolipoprotein A1, bilirubin, GGT, age and gender. Its predictive values have been reported to have an AUROC of 0.81 for advanced fibrosis (Stage 3-4) and an AUROC of 0.88 for cirrhosis (Stage 4) in NAFLD[44]. The ELF test[40] has been proposed to be a modified panel of the OELF test[34]. The OELF test includes four variables [age, HA, N-terminal peptide of pro-collagen Ⅲ (P3NP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP 1)], whereas the ELF test is calculated by the three variables (excluding age). When the ELF was validated for NAFLD[40], its predictive values were determined as an AUROC of 0.82 for moderate fibrosis (Stage 2-4) and an AUROC of 0.90 for advanced fibrosis (Stage 3-4). Additionally, the ELF test has been suggested to be associated with the clinical outcome[45]. However, most of these markers (other than the ELF panel) were primarily validated for the patients with HCV-related CLD, and their diagnostic performances were not adequate when these markers

Table 1 General liver fibrosis markers for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

Biomarkers	Items	Cohort	AUROC for diagnosis	Ref.
General markers for liver fibrosis (solo makers)				
Hyaluronic acid		112	Stage 1-4: 0.80, Stage3-4: 0.80	Sakugawa *et al*[38], 2005
Type Ⅳ collagen 7S		112	Stage 1-4: 0.83, Stage3-4: 0.82	Sakugawa *et al*[38], 2005
Platelet count		1048	Stage 3-4: 0.77, Stage4: 0.92	Yoneda *et al*[39], 2011
General markers for liver fibrosis (algorithm based makers)				
FibroTest	α2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin	267	Stage 2-4: 0.81, Stage 4: 0.88	Ratziu *et al*[44], 2006
APRI	AST, platelet count	111	Stage 3-4: 0.85	Kruger *et al*[41], 2011
FIB4 index	Age, AST, ALT, platelet count	541	Stage 3-4: 0.802	Shah *et al*[43], 2009
ELF (enhanced liver fibrosis panel)	HA, TIMP1, P3NP	192	Stage 2-4: 0.82, Stage 3-4: 0.9	Guha *et al*[40], 2008

APRI: AST-to-platelet ratio index.

were applied to the patients with NAFLD/NASH. Table 1 shows the validations of general biomarkers for the histological degree of fibrosis in NAFLD/NASH patients.

Metabolism-based fibrosis markers developed for NAFLD/NASH

Most of the patients with NASH have several metabolic dysfunctions, including obesity, diabetes mellitus, and dyslipidemia, and their clinical features may differ from other chronic liver diseases, such as hepatitis virus-associated CLDs[7]. Therefore, simple markers derived from a logistic regression analysis of large cohorts with NAFLD/NASH have also been developed and validated. In 1999, Angulo *et al*[46] reported three factors (older age, obesity, and the presence of diabetes mellitus) to be independent predictors of severe hepatic fibrosis in the patients with NASH. In 2001, the HAIR scoring system, which was generated based on three clinical items (the presence of systemic Hypertension, elevated ALT and Insulin Resistance) was reported to have a sensitivity of 80% and specificity of 89% for NASH in the patients undergoing bariatric surgery[47]. Ratziu *et al*[48] reported the BAAT score (consisting of the BMI, ALT, Age and Triglyceride levels) had an AUROC of 0.84 for the prediction of septal liver fibrosis (Stage 2-4). In 2007, Angulo *et al*[49] proposed the NAFLD fibrosis score (determined by the presence of diabetes, AST, ALT, the BMI, platelet count and albumin) and reported it to be a specific marker for NAFLD with an AUROC of 0.84 for advanced fibrosis (Stage 3-4). In a recent meta-analysis of 13 studies consisting of 3064 patients, the AUROC for the NAFLD fibrosis score was found to be 0.85 for the prediction of advanced fibrosis[50]. The BARD score, which was determined by three items (BMI > 28 kg/m^2, AST/ALT Ratio > 0.8, and Diabetes), was evaluated in a cohort of 827 NAFLD patients and showed an AUROC of 0.81 for predicting advanced liver fibrosis (Stage 3-4). Notably, the BARD score was reported to be valuable for excluding the patients without advanced fibrosis due to its high negative predictive value (⩾ 95%)[51].

In addition to the aforementioned biomarkers, several diagnostic markers have also been proposed for the assessment of liver fibrosis in NAFLD/NASH. The FibroMeter is an index which is determined by the age, weight, fasting glucose, AST, ALT, ferritin and platelet count, and has also been validated in a NAFLD population[52]. This marker was reported to have a high diagnostic performance with an AUROC of 0.94 for significant fibrosis (Stage 2-4), 0.94 for severe fibrosis (Stage 3-4) and 0.90 for cirrhosis (Stage 4). The NAFIC score is a simple scoring system determined by three variables, including the serum ferritin level [⩾ 200 ng/mL (female) or ⩾ 300 ng/mL (male)], fasting insulin (⩾ 10 μU/mL), and type Ⅳ collagen 7S (⩾ 5.0 ng/mL). The index was reported to show an AUROC of 0.834 for significant fibrosis and 0.869 for severe fibrosis (Stage 3-4) in Japanese patients[53]. The NAFLD Diagnostic Panel is an index, which is obtained by the following items: DM, gender, BMI, triglycerides, and CK18 fragments (M30: apoptosis, M65-M30: necrosis). The panel was reported to have an AUROC of 0.80 for predicting any degree of fibrosis (Stage 1-4) and an AUROC of 0.81 for predicting advanced fibrosis (Stage 3-4)[54]. Irrespective of the excellent diagnostic performance of the methods shown in the above-described studies, the patients were heterogeneous in characteristics and were sometimes highly selected; the clinical significance of the markers should therefore be confirmed and validated in different cohorts. The biomarkers developed for NAFLD/NASH for predicting the degree of fibrosis are shown in Table 2.

NEW APPROACHES TO LIVER FIBROSIS BY FOCUSING ON GLYCOBIOLOGY

Liver fibrosis markers based on glycosylated proteins

Glycosylation is one of major posttranslational enzymatic modifications of the proteins. Because many glycosylated proteins in the serum are generated in

Table 2 Liver fibrosis markers developed for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

Liver fibrosis markers for NAFLD	Items	Cohort	AUROC for diagnosis	Ref.
HAIR	Hypertension, ALT, insulin resistance	105	Stage 3-4: 0.90	Dixon *et al*[47], 2001
BAAT score	BMI, Age, ALT, Triglycerides	93	Stage 2-4: 0.84	Ratziu *et al*[48], 2000
NAFLD Fibrosis score	Age, BMI, Hyperglycemia, Platelet count, Albumin, AST/ALT ratio	733	Stage 3-4: 0.84	Angulo *et al*[49], 2007
BAAD score	BMI, AST/ALT ratio, DM	827	Stage 3-4: 0.81	Harrison *et al*[51], 2008
FibroMeter NAFLD	Glucose, AST, Platelet count, ALT, Ferritin, Body Weight, Age	235	Stage 2-4: 0.943	Calès *et al*[52], 2009
NAFLD Diagnostic Panel	DM, Gender, BMI, Triglycerides, CK18 fragments (apoptotic and necrotic)	79	[1]Stage 1-4: 0.81,[2]Stage 2-4: 0.80	Younossi *et al*[54], 2011
NAFIC score	Ferritin, IRI, type Ⅳ collagen 7S	619	Stage 2-4: 0.834, Stage 3-4: 0.869	Sumida *et al*[53], 2011

[1]Presence of any degree of fibrosis; [2]Presence of advanced fibrosis (at least moderate portal or pericellular fibrosis, bridging fibrosis, or cirrhosis). NAFLD: Nonalcoholic fatty liver disease.

the liver, a decreased liver function is expected to relate to the changes in protein glycosylation and recent studies suggest that serum N-glycome may be a valuable biomarker of CLDs[55-58]. According to the differences in the N-glycome patterns, two biomarkers, the GlycoCirrhoTest[55] and the GlycoFibroTest[56], have been reported to predict the presence of cirrhosis and fibrosis, respectively. In addition, new glycomics-based approaches were reported to succeed in the noninvasive evaluation of liver fibrosis[57-60], and a recently established glycosylated protein-associated maker, M2BP (Wisteria floribunda agglutinin-positive Mac-2 binding protein), was reported to be a useful marker of liver fibrosis in various CLDs, including NASH[60].

Liver fibrosis markers based on glycated proteins: The glycated albumin-to-glycated hemoglobin ratio as a biomarker of liver fibrosis

Although the qualitative changes of glycosylated proteins are excellent tools for estimating the degree of liver fibrosis, the methods are not readily applied to daily practice. The term "glycation" is now generally used as a non-enzymatic spontaneous modification of proteins by saccharides[61,62], and glycated proteins, particularly glycated hemoglobin (HbA1c) and glycated albumin (GA), are widely used as indices of the glycemic control in the patients with diabetes mellitus[63,64]. We herein focused on the quantitative changes of these commonly measured glycated proteins during the progression of liver fibrosis.

The lifespan of erythrocytes is approximately 120 d, and the HbA1c level typically reflects the degree of glycemia for the previous months[65]. The GA level correlates with the plasma glucose level over the previous few weeks, because the turnover of albumin is approximately three weeks[66,67]. Although the normal GA to HbA1c ratio (GA/HbA1c ratio) is approximately 3, the value changes based on the patient's condition[68]. Because of hypersplenism, the lifespan of erythrocytes in the CLD patients is shorter than that noted in healthy individuals; thus, the HbA1c levels are lower in the patients with CLD relative to the plasma glucose level. In contrast, the turnover period of serum albumin in the CLD patients is longer than that observed in healthy persons in order to compensate for the decreased production of albumin in the liver. Therefore, the GA levels in the CLD patients are higher, relative to the degree of glycemia[68,69]. Since the HbA1c levels are lower and the GA levels are higher in the CLD patients, the GA/HbA1c ratio is considered to be higher in the patients with CLD in comparison to healthy subjects.

We previously investigated the GA/HbA1c ratio in CLD patients and reported that the GA/HbA1c ratio indicated an inverse correlation with the indicators of the hepatic function (*e.g.*, the hepaplastin test, cholinesterase and abumin levels), regardless of the mean plasma glucose level, thus suggesting that the GA/HbA1c ratio increases as the liver fibrosis progresses[70]. However, this report did not discuss the association of the GA/HbA1c ratio with the histological stage of fibrosis in the CLD patients. We further investigated the relationships between the GA/HbA1c ratio and the histological findings in various types of CLD, including HCV-related CLD, hepatitis B virus (HBV)-related CLD and NASH[71-73].

We studied the GA/HbA1c ratios in a total of 142 patients with HCV infection and discovered that the ratio increased with the progression of the liver fibrotic stage[71]. The GA/HbA1c ratio was additionally found to be associated with the histological severity of liver fibrosis in the patients with HBV infection and to be positively related to two well-established markers of liver fibrosis, the FIB-4 and APRI indices[72]. We further investigated the NASH patients and found that the GA/HbA1c ratio increased with an increase in the histological severity of liver fibrosis[73]. These findings suggest that the GA/HbA1c ratio is a novel biomarker of liver fibrosis in the patients with NASH as well as those infected with hepatitis viruses. The results of the GA/HbA1c ratios in the patients with various CLDs are summarized in Table 3. Although the AUROCs were not determined in these studies, comparisons

Table 3 Glycated albumin-to-glycated hemoglobin ratio (GA/HbA1c ratio) and liver fibrosis

Patients	Cohort	Main results	Ref.
Various CLDs	82	The GA/HbA1c ratio was associated with hepatic functions (decreasing hepaplastin test and cholinesterase levels) independent of the mean plasma glucose levels	Bando *et al*[70], 2009
HCV-positive CLD	142	The GA/HbA1c ratio increased in association with the histological severity of liver fibrosis. The diagnostic performance of APRI improved when combined with the GA/HbA1c ratio	Aizawa *et al*[72], 2012
HBV-positive CLD	176	The GA/HbA1c ratio increased in line with the severity of fibrosis. The GA/HbA1c ratios were inversely correlated with four variables of liver function (the prothrombin time percentage, platelet count, albumin value and cholinesterase value)	Enomoto *et al*[73], 2014
NASH	36	The GA/HbA1c ratio was negatively correlated with ALT and platelet count. The GA/HbA1c ratio was positively correlated with the degree of liver fibrosis	Bando *et al*[74], 2012

CLDs: Chronic liver diseases; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Nonalcoholic steatohepatitis.

of the diagnostic performance of the GA/HbA1c ratio and other biomarkers would provide important and interesting information.

Although a number of biomarkers have been developed, none of them are ideal (*i.e.*, a simple, inexpensive, reproducible, easily measurable test without any special equipment and capable of high diagnostic performance)[74]. It is notable that the rate of change of the GA/HbA1c ratio among the fibrosis stages is relatively small, and this ratio alone cannot be a decisive biomarker for the evaluation of liver fibrosis (similar to the other currently available biomarkers). In addition, some diseases and conditions are associated with high or low GA/HbA1c ratios[68]. For instance, because the GA/HbA1c ratio is affected by changes in glycemic control, it cannot to be used in patients with unstable glycemic control. The ratio may also be inaccurate as a sole liver fibrosis marker in patients with conditions that affect the level of HbA1c, such as anemia caused by non-hepatic diseases and variant hemoglobin. The ratio also differs in patients with abnormal albumin metabolism, such as nephrotic syndrome, thyroid disease and in patients who undergoing glucocorticoid therapy. Therefore, the GA/HbA1c ratio may not sufficiently reflect the degree of liver fibrosis in CLD patients with certain clinical conditions.

However, the GA/HbA1c ratio is unique and interesting in that the value can be calculated with only the levels of two common glycated proteins and correlates to the degree of liver fibrosis in various CLDs. A new biomarker based on a combination of factors, including the GA/HbA1c ratio, would provide a better noninvasive assessment of liver fibrosis. The current findings should therefore shed some new light on the evaluation of liver fibrosis.

CONCLUSION

NASH is one of major causes of chronic liver injury and non-viral cirrhosis. Although a liver biopsy remains the gold standard for the diagnosis of NASH and the evaluation of the severity of liver fibrosis, this technique has several disadvantages in relation to its routine and repeated use. Many serum biomarkers have been proposed in order to estimate the degree of liver fibrosis in NASH patients noninvasively. In addition, new methods based on glycated proteins have been recently developed. These new approaches may provide better insight into the clinical management of NAFLD/NASH.

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P- Reviewer: Carulli L, Daltro C, de Oliveira CPMS, Federico A, Gong ZJ, Kayadibi H, Sato K **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Zhang DN

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ISSN 1007-9327