CHD is Associated With Higher Grades of NAFLD Predicted by Liver Stiffness

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Background and Aim: Accumulating clinical and epidemiologic evidence indicates that nonalcoholic fatty liver disease (NAFLD) is not only associated with liver-related morbidity and mortality, but also with a greater risk of coronary heart disease (CHD). However, there is currently no diagnostic parameter for NAFLD that has been determined to reliably indicate the presence of CHD as a co-morbidity. We evaluated the liver stiffness and visceral fat thickness of NAFLD patients ultrasonographically to explore the relationship between liver stiffness, visceral fat thickness, and CHD, aiming to find explore the relationship between the liver stiffness and CHD.

Methods: We enrolled 120 consecutive patients who had been initially diagnosed with CHD on the basis of their symptoms. All patients underwent coronary angiography or computed tomography angiography, and were classified into a CHD group and a non-CHD group on the basis of the results. All patients underwent liver ultrasonography, shear-wave elastography, and visceral fat thickness measurement.

Results: NAFLD and visceral fat thickness were significantly positively correlated with CHD and Gensini score (P<0.001). Multivariate regression showed that age, male, cholesterol, liver stiffness, and visceral fat thickness were determinants of CHD. Age, cholesterol, liver stiffness, and visceral fat thickness cut-off points for the prediction of CHD were above 50 years old [area under the curve (AUC): 0.678; sensitivity, 68.4%; specificity, 64.8%], >6.1 kPa (AUC: 0.798; sensitivity, 50%; specificity, 92.6%), and >7.41 cm (AUC: 0.694; sensitivity, 52.6%; specificity, 87%), respectively. Compared with the use of age, gender, and cholesterol (model 1), the addition of the liver stiffness cut-off to model 1 resulted in a stronger predictive value (P=0.005).

Conclusions: High-grade NAFLD is more present in symptomatic CHD. The higher degree of liver stiffness in patients with NAFLD, the higher risk of CHD in these NAFLD patients.

Key Words: nonalcoholic fatty liver disease, coronary heart disease, liver stiffness, visceral fat thickness

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases,1 and its prevalence is rising because of the increasing prevalence of obesity and type 2 diabetes,2,3 such that it has become a public health problem of epidemic proportions worldwide. Accumulating clinical and epidemiologic evidence indicates that NAFLD is not only associated with liver-related morbidity and mortality, but also with a greater risk of coronary heart disease (CHD).4-8 However, there is currently no diagnostic parameter for NAFLD that has been determined to reliably indicate the presence of CHD as a co-morbidity.

A proportion of patients with NAFLD demonstrate progressive liver fibrosis (LF).2 Liver biopsy, the gold standard for the assessment of LF, is a costly procedure that is associated with a risk of severe complications. Recently, elastography, an imaging method, has been shown to be a reliable method of assessing LF.9-11 and studies have shown that shear-wave elastography (SWE) and magnetic resonance elastography (MRE) are the most accurate methods for staging fibrosis in NAFLD patients.12,13 Such ultrasonographic methods provide an ideal noninvasive assessment of diffuse liver disease, because they are inexpensive and widely available. Therefore, we prefer to use ultrasonography (US) for the assessment of liver elasticity.

In this study, we evaluated liver stiffness and visceral fat thickness in patients with and without symptomatic CHD aiming to explore the different grade of NAFLD in these study groups.

METHODS

Patients

We enrolled 120 consecutive patients in our hospital who had been admitted to the Cardiology Department (age range, 25 to 76 y; 76 men and 44 women). Patients who were initially diagnosed with CHD on the basis of their symptoms were included. The CHD definition and diagnostic criteria are included in the previous guidelines.14 The exclusion criteria were heart failure with cardiac function grades III or IV, presence of acute or previous myocardial infarction, acute or chronic renal failure, acute or chronic liver failure, chronic systemic inflammatory disease, stroke, and known hypersensitivity to iodine-based contrast agents.

Hypertension was defined by systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or the current use of anti-hypertensive medication. Diabetes was defined by glycated hemoglobin concentration ≥6.5%, fasting plasma glucose >7 mmol/L, or the current use of anti-diabetic medication. Patients were also classified as smokers (current smoker or a history of smoking) and nonsmokers (never smoked).

According to the results of coronary computed tomography angiography or CAG, the participants were divided into a CHD group and a non-CHD group. All patients provided written informed consent after they received advice regarding the potential risks of radiation exposure, the administration of...
Anthropometric Measurements

Body mass index was calculated as body mass (kg) divided by the square of height (m) of the participants. Waist circumference was measured at the anatomic waistline, which is at the natural indentation between the iliac crest and the 10th rib. Hip circumference was measured at the peak of the curve of the buttocks.

NAFLD

We used a Doppler ultrasound system (Aixplorer; SuperSonic Imagine, Aix-en-Provence, France) and an SC6-1 probe to obtain a sagittal view of the right lobe of the liver and right kidney, a transverse view of the left lateral segment of the liver and spleen, and a transverse view of the liver and pancreas, and to examine any focal areas of altered echogenicity. The degree of echogenicity was graded as follows: grade (G) 0, normal echogenicity; G1, slight, diffuse increase in fine echoes in liver parenchyma, with normal visualization of the diaphragm and intrahepatic vessel margins; G2, moderate, diffuse increase in fine echoes, with slightly impaired visualization of intrahepatic vessels and the diaphragm; G3, marked increase in fine echoes, with poor or nonvisualization of the intrahepatic vessel margins, diaphragm, and posterior right lobe of the liver.15

Ultrasoundographic evaluation was performed by 2 physicians with > 5 years’ experience each, both of whom were unaware of the aims of the study.

SWE Imaging

All patients underwent SWE using a curvilinear transducer (bandwidth, 6 to 1 MHz) (Aixplorer; SuperSonic Imagine, Aix-en-Provence, France). Patients were instructed to relax and hold their breath during their natural breathing cycle while measurements were made, and breathing pattern rehearsals were permitted before the actual scanning to avoid variation. All the patients were studied in the right decubitus position with their right arm extended above their head. SWE was performed on segment VIII of the liver over 3 consecutive intercostal spaces in dual mode (elastograms displayed alongside gray-scale sonograms in real time). The operator chose the best static SWE display images, onto which rectangular and circular regions of interest were positioned, 1 to 3 cm from the capsular surface of the liver, for subsequent analysis. Once the optimal sizes of the regions of interest were chosen, they were fixed for the subsequent measurements made in each subject. During this process, special attention was paid to the avoidance of focal lesions, vessels, biliary structures, or artifacts resulting from nearby lung gas or cardiac movement. From the circular region of interest, the mean, SD, and minimum and maximum stiffness values (in kilopascals) were recorded. The mean values obtained from 3 measurements per organ were used for subsequent statistical analysis.16

All SWE examinations were performed by a single sonographer with 5 years’ experience of elastographic techniques, who was unfamiliar with the patients. To evaluate the reproducibility of the SWE technique, the first 30 patients enrolled in the study underwent an additional liver elastographic examination performed by a second operator (with 4 years’ experience of elastographic techniques), and the mean liver stiffness values were compared. There was no significant difference between the 2 sets of measurements ($P = 0.853$).

Measurement of Visceral Fat Thickness

We used the same Doppler ultrasound system and SC6-1 probe to measure the thickness of each participant’s visceral fat depot.17 After overnight fasting, subjects underwent ultrasonographic fat measurements in the morning. The probe was placed at the midpoint between the xiphoid process and the umbilicus to obtain cross-sectional measurements. The distance from the trailing edge of the linea alba to the anterior wall of the abdominal aorta was designated V1 and the distance from the posterior edge of the external oblique muscle to the right edge of the spinal column was designated V2. Ultrasonographic measurements were performed by 2 physicians with > 5 years’ experience each, both of whom were unaware of the aims of the study.

| TABLE 1. Subject Characteristics Versus CHD Status |
|----------------------------------------|-------------------|-----------------|-----------|
| Parameters                             | Non-CHD (n = 60)  | CHD (n = 60)    | P         |
| Age (y)                                | 52.71 ± 12.11     | 60.03 ± 10.78  | 0.001     |
| Male gender (yes%)                     | 30 (50)           | 46 (76)        | 0.004     |
| Comorbidities                          |                   |                 |           |
| T2DM (yes%)                            | 4 (6)             | 15 (25)        | 0.011     |
| Hypertension (yes%)                    | 27 (45)           | 39 (65)        | 0.043     |
| History of smoking (yes%)              | 14 (23)           | 27 (45)        | 0.020     |
| Blood lipid                            |                   |                 |           |
| Cholesterol (mmol/L)                   | 3.52 ± 0.89       | 4.09 ± 0.84    | 0.001     |
| HDL-C (mmol/L)                         | 1.02 ± 0.36       | 0.87 ± 0.18    | 0.000     |
| LDL-C (mmol/L)                         | 2.04 ± 0.78       | 2.43 ± 0.67    | 0.003     |
| Glycated hemoglobin                    | 5.59 ± 1.01       | 6.32 ± 1.41    | 0.001     |
| Myocardial enzyme                      |                   |                 |           |
| Creatine kinase (U/L)                  | 83.54 ± 37.93     | 101.15 ± 98.26 | 0.829     |
| Creatine kinase isoenzyme (U/L)        | 10.63 ± 5.76      | 14.07 ± 9.10   | 0.022     |
| Hydroxybutyrate dehydrogenase (U/L)    | 153.65 ± 27.14    | 148.21 ± 43.11 | 0.286     |
| Lactate dehydrogenase (U/L)            | 201.77 ± 33.26    | 229.43 ± 211.13| 0.939     |
| Anthropometry                          |                   |                 |           |
| BMI (kg/m²)                            | 26.79 ± 2.16      | 27.02 ± 2.89   | 0.904     |
| WC (cm)                                | 96.51 ± 6.93      | 97.37 ± 7.8    | 0.725     |
| HC (cm)                                | 97.02 ± 7.27      | 98.06 ± 6.74   | 0.629     |
| Fat thickness measures                 |                   |                 |           |
| V1 (cm)                                | 6.58 ± 0.73       | 7.67 ± 1.58    | 0.000     |
| V2 (cm)                                | 6.47 ± 0.69       | 7.53 ± 1.58    | 0.000     |
| NAFLD and liver function               |                   |                 | < 0.001   |
| G0 (%)                                 | 20 (33)           | 3 (5)          |           |
| G1 (%)                                 | 31 (52)           | 33 (55)        |           |
| G2 (%)                                 | 9 (15)            | 9 (15)         |           |
| G3 (%)                                 | 0                 | 15 (25)        |           |
| SWE (kPa)                              | 4.82 ± 0.92       | 6.37 ± 1.39    | < 0.001   |
| Anamine aminotransferase (U/L)         | 26.17 ± 16.33     | 34.93 ± 20.65  | 0.009     |
| Aspartate aminotransferase (U/L)       | 20.48 ± 7.39      | 23.78 ± 9.34   | 0.043     |

Data are given as mean ± SD or n (%).

CHD indicates coronary heart disease; HC, hip circumference; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.

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Blood Parameter Measurements

Venous blood was collected from all subjects on the morning after fasting for 8 hours. The blood parameters measured included serum total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), myocardial enzyme activities, and liver enzyme activities.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). All descriptive data were expressed as the mean ± SD, median and interquartile range (25th and 75th percentiles), or percentage. The 2 groups were compared with respect to each parameter using Student unpaired t test, the Mann-Whitney U test, or the χ² test, as appropriate. The relationships between 2 continuous variables were evaluated using linear regression analysis, while the relationships between 2 categorical variables and non-normally distributed data were evaluated using Spearman regression analysis. Binary regression analysis was used to determine the predictors of CHD, adjusting for clinical risk factors (including age, male sex, diabetes mellitus, hypertension, smoking habit, serum cholesterol, fat thickness, and fatty liver). We chose the variables that are recognized risk factors for CHD in the literature into the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off points for fatty liver to predict significant CHD, and to assess whether the assessment of fatty liver provided additional predictive value for the presence of significant CHD to that of traditional risk factors. A P-value of <0.05 was considered to represent statistical significance.

RESULTS

General Characteristics

The general characteristics are listed according to CHD status in Table 1. In the CHD group, mean age, serum total cholesterol, LDL-C, and glycated hemoglobin were higher than in the non-CHD group. The values for the male patients in the CHD group were also higher than those for men in the non-CHD group. The numbers of patients with type 2 diabetes mellitus, hypertension, and a history of smoking in the CHD group were higher than those in the non-CHD group. The 2 groups had similar mean body mass index, waist circumference, hip circumference, and serum myocardial enzyme activities. Visceral fat thickness (V1 and V2) in the CHD group was higher than in the non-CHD group. The number of patients

FIGURE 1. The NAFLD according to CHD status. The liver stiffness measurement, V1 and V2 according to NAFLD status. There was a significant difference of NAFLD between the 2 groups (P < 0.001) (A). When the patients were further divided into subgroups according to their NAFLD grade, there was a correlation between liver stiffness and NAFLD grade (P < 0.001, B). V1 and V2 also differed across the 4 groups (P < 0.001 and 0.010, respectively; C, D). ANOVA indicates analysis of variance; CHD, coronary heart disease; NAFLD, nonalcoholic fatty liver disease.
with NAFLD of G3 in the CHD group was higher than in the non-CHD group, and the number of patients with NAFLD of G0 in the CHD group was less than in the non-CHD group. Liver stiffness, and serum alanine aminotransferase activities, in the CHD group were much higher than in the non-CHD group.

Liver Stiffness, V1, and V2
The percentages of participants with NAFLD of each grade in the CHD group were G0: 5%, G1: 55%, G2: 15%, and G3: 25%; and the percentages in the non-CHD group were G0: 33%; G1: 52%; G2: 15%; and G3: 0%. There was a significant difference in this distribution between the 2 groups (P < 0.001) (Fig. 1A). When the patients were further divided into subgroups according to their NAFLD grade, there was a correlation between liver stiffness and NAFLD grade (P < 0.001, Fig. 1B). V1 and V2 also differed across the 4 groups (P < 0.001 and 0.010, respectively; Figs. 1C, D).

Correlation Analysis of the Relationship Between CHD and Gensini Score
The correlation analysis showed that CHD was significantly correlated with age, gender, the presence of type 2 diabetes, hypertension, cholesterol, HDL-C, LDL-C, V1, V2, the presence of NAFLD, and liver stiffness. For patients with CHD, the Gensini score correlated with the presence of hypertension, V1, V2, the presence of NAFLD, and liver stiffness (Table 2 and Figs. 2A–C).

Multivariate Indicators of CHD
For multivariate regression analysis, the differences between non-CHD and CHD groups included age, male, T2DM, hypertension, history of smoking, cholesterol, HDL-C, LDL-C, glycated hemoglobin, fat thickness measures (V1 and V2), NAFLD, and SWE are all included in the multivariable analysis queue. And the result showed that age, gender, cholesterol, liver stiffness, and V2 were predictive of the presence of CHD in our study (Table 3).

Use of a Combination of Fatty Liver, Age, and Serum Cholesterol for the Prediction of CHD
The optimal cut-off points for the prediction of CHD, obtained using ROC curve analysis, are shown in Figure 3. The cut-offs for age, cholesterol, liver stiffness, and V2 for the prediction of CHD were above 50 years old [area under the curve (AUC) 0.678; sensitivity 87%; specificity 42.6%]; > 3.76 mmol/L (AUC 0.687; sensitivity 68.4%; specificity 64.8%); > 6.1 kPa (AUC 0.798; sensitivity 50%; specificity 92.6%); and > 7.41 cm (AUC 0.694; sensitivity 52.6%; specificity 87%), respectively. Compared with the use of age, gender, and cholesterol alone (model 1), the addition of a cut-off for liver stiffness to model 1 resulted in a stronger predictive value (model 1 vs. model 2: P = 0.005). However, compared with the inclusion of age, gender, cholesterol, and liver stiffness (model 2), the addition of the V2 cut-off value did not yield a stronger predictive value (model 2 vs. model 3: P = 0.114).

**DISCUSSION**
In this study, we found that the proportion of patients with NAFLD, especially those with G3, was significantly higher in the CHD group than in the non-CHD group, and that NAFLD grade was significantly positively correlated with both CHD and the Gensini score. In addition, we found that visceral fat thickness was significantly higher in the CHD group than in the non-CHD group, and this was also significantly positively correlated with CHD and the Gensini score.

The negative impact of NAFLD on the risk of CHD has been the subject of intense scientific interest over the last decade. This association is worthy of attention because it has important implications for the screening and surveillance strategies that should be used for the growing number of patients with NAFLD. Studies conducted in Italy have shown that the prevalence of CHD in patients with diabetes (type 1 or type 2) and NAFLD is significantly higher than in patients without NAFLD, and that NAFLD is a risk factor for CHD, independent of traditional risk factors. Furthermore, Mirbagheri and colleagues have shown that NAFLD is the strongest predictor of CHD, more so than both age and diabetes. Indeed, after correction for traditional risk factors, there is still a strong relationship between NAFLD and CHD. Our results are consistent with those of previous studies. Although the pathophysiological mechanisms linking NAFLD with CHD are not completely understood, NAFLD is associated with the metabolic syndrome, which comprises abdominal obesity, ectopic fat accumulation, hyperglycemia, insulin resistance, atherogenic dyslipidemia, and hypertension, all of which predispose toward inflammation and atherosclerosis. CHD ultimately develops as the result of a series of pathologic processes. Numerous studies have shown that NAFLD is an independent predictor of CHD. However, to our knowledge, no quantitative index related to NAFLD has been identified that

| Table 2. Univariate Indicators of CHD and Gensini Score |
|-----------------|-----------------|-----------------|
| **Parameters**  | **CHD**         | **Gensini Score** |
| Age (y)         | 0.310           | 0.001           |
| Male gender (yes or no) | -0.277         | 0.002           |
| BMI (kg/m²)     | -0.011          | 0.905           |
| WC (cm)         | 0.033           | 0.726           |
| HC (cm)         | 0.045           | 0.631           |
| Comorbidities   |                |                 |
| T2DM (yes or no) | 0.251           | 0.006           |
| Hypertension (yes or no) | 0.201       | 0.028           |
| History of smoking (yes or no) | 0.228 | 0.012           |
| Blood lipid     |                |                 |
| Cholesterol (mmol/L) | 0.316         | 0.001           |
| HDL-C (mmol/L)  | -0.338          | < 0.001         |
| LDL-C (mmol/L)  | 0.277           | 0.003           |
| Fat thickness measures |            |                 |
| V1 (cm)         | 0.364           | < 0.001         |
| V2 (cm)         | 0.355           | < 0.001         |
| NAFLD and liver function |       |                 |
| NAFLD           | 0.422           | < 0.001         |
| SWE (kPa)       | 0.519           | < 0.001         |
| Aniline aminotransferase (U/L) | 0.249       | 0.008           |
| Aspartate aminotransferase (U/L) | 0.193 | 0.042           |

The correlation analysis showed that CHD was significantly correlated with age, gender, the presence of type 2 diabetes, hypertension, cholesterol, HDL-C, LDL-C, V1, V2, the presence of NAFLD, and liver stiffness; BMI indicates body mass index; CHD, coronary heart disease; HC, hip circumference; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NAFLD, Nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.
could be used to predict the development of CHD in patients with this disease. A proportion of patients with NAFLD demonstrate progressive LF, the severity of which can be quantified noninvasively in a number of ways. In this study, we used SWE, because MRE and SWE have been shown to have the highest diagnostic accuracy for the staging of fibrosis in NAFLD patients and MRE is the more expensive technique. In our study, the SWE values for patients in the CHD group were significantly higher than those for patients in the non-CHD group, and we also found that the degree of liver stiffness significantly correlates with CHD and Gensini score. This indicates that liver stiffness is associated with the development of CHD.

After adjustment for common risk factors, such as the presence of hypertension or diabetes, we found that age, gender, cholesterol, liver stiffness, and V2 are predictors of CHD. The accuracy of SWE values for the diagnosis of CHD is demonstrated by an AUC of 0.798 using a cut-off value of 6.1 kPa, while the AUC for V2 was 0.694 using a cut-off value of 7.41 cm. Compared with the use of age, sex, and cholesterol (model 1), the addition of liver stiffness and V2 (model 2 and model 3) was more predictive of CHD (model 1 vs. model 2, \( P = 0.005 \); model 1 vs. model 3, \( P = 0.001 \)). However, compared

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**TABLE 3. Multivariate Indicators of Coronary Heart Disease**

| Parameters | \( B \) | \( P \) | Upper Limit | Lower Limit |
|------------|---------|--------|-------------|-------------|
| Age (y)    | 0.129   | <0.001 | 1.060       | 1.222       |
| Sex        | -2.525  | <0.001 | 0.017       | 0.367       |
| Cholesterol| 1.704   | <0.001 | 2.145       | 14.079      |
| SWE        | 1.404   | <0.001 | 1.880       | 8.820       |
| V2         | 0.922   | 0.008  | 1.270       | 4.974       |

The multivariate regression showed that age, gender, cholesterol, liver stiffness, and V2 were predictive of the presence of coronary heart disease in our study.

CI indicates confidence interval; SWE, shear-wave elastography.

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**FIGURE 2.** Correlation with Gensini Score. For patients with coronary heart disease, the Gensini score correlated with the presence of hypertension, V1, V2, the presence of nonalcoholic fatty liver disease, and liver stiffness (A–C). SWE indicates shear-wave elastography.

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with the inclusion of liver stiffness, the inclusion of V2 does not add additional diagnostic value (model 2 vs. model 3, \( P = 0.114 \)).

High-grade NAFLD is more present in symptomatic CHD. The higher degree of liver stiffness in patients with NAFLD, the higher risk of CHD in these NAFLD patients. This is the first study to show that the higher degree of liver stiffness in patients with NAFLD, the higher risk of CHD.

This study has several potential limitations. First, the design of this clinical study was cross-sectional and was conducted at a single center in a relatively small number of subjects. Second, the ROC results cannot be applied more broadly to patients with suspected CHD. Third, the sensitivity and specificity of liver stiffness and V2 for the diagnosis of CHD should be assessed in a future, larger study. Fourth, we did not consider the impact of medication on these parameters. Fifth, we did not explore the relationship between the performance of aspartate aminotransferase to platelets ratio index (APRI), fibrosis-4 index (FIB-4), BARD score, NAFLD fibrosis score (NFS), FibroScan, MRE and CHD, and we did not know which indicator was better for predicting the CHD compared with SWE. In the next study, we may compare the above indicators of liver fiber with SWE.

In conclusion, high-grade NAFLD is more present in symptomatic CHD. The higher degree of liver stiffness in patients with NAFLD, the higher risk of CHD in these NAFLD patients. Further investigation, involving a large-scale prospective study, is warranted to determine the accuracy and the clinical efficacy of the measurement of liver stiffness in patients with NAFLD for the diagnosis of CHD.

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