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THE FRAMINGHAM RISK SCORE AND HEART DISEASE IN NONALCOHOLIC FATTY LIVER DISEASE

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Abstract

BACKGROUND—The accuracy of the Framingham risk score (FRS) in identifying patients with nonalcoholic fatty liver disease (NAFLD) at higher 10-year coronary heart disease (CHD) risk remains unknown.

AIM—We aimed at evaluating both the baseline probability of CHD as predicted by the FRS and the actual long-term occurrence of CHD in NAFLD patients.

METHODS—This was a longitudinal study of a community-based cohort. A total of 309 NAFLD patients were followed-up for 11.5±4.1 years (total 3554 person-years).

RESULTS—The overall calculated 10-year CHD risk was significantly higher in the NAFLD cohort than the absolute CHD risk predicted by the FRS for persons of the same age and sex (10.9±9.3% vs. 9.9±5.9%, respectively, $P<0.0001$), and higher in men than women (12.6±10.3% vs. 9.6±8.1%, respectively, $P=0.006$). New onset CHD occurred in 34 patients (11% vs. 10.9% predicted at baseline, $P=NS$) whereas 279 (89%) patients did not developed CHD. By multivariable analysis, the FRS was the only variable significantly associated with new onset CHD (OR=1.13, 95% CI 1.05-1.21; $P=0.001$). A FRS cut-point of 11 in women, and 6 in men had a sensitivity of 80% and 74%, respectively, and a negative predictive value of 97% and 93%, respectively.

CONCLUSIONS—NAFLD patients have a higher 10-year CHD risk than the general population of the same age and sex. The FRS accurately predicts the higher 10-year CHD risk in NAFLD patients, and helps identify those patients expected to derive the most benefit from early intervention to prevent CHD events.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in Western countries. An increasing prevalence of NAFLD is associated with the increasing prevalence of obesity and diabetes [1]. Obesity and diabetes are significantly

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associated with increasing cardiovascular events and mortality. The mortality rate of NAFLD patients has been found to be higher than that in the general United States population [2], and, cardiovascular events was the first or second most common cause of death in four large series of patients with NAFLD confirmed by liver biopsy or imaging [2-5]. Thus, current evidence indicates that NAFLD, obesity and the metabolic syndrome have a strong association [6-8], and that one of the most common causes of death among NAFLD patients is cardiovascular disease [2-5]. However, the absolute proportion of patients with NAFLD dying from cardiovascular events is relatively small, and increases from 3.8% within 8 years of NAFLD diagnosis [2] to about 12% within 20 years of NAFLD diagnosis [5]. In addition, some recent studies that have used elevated alanine aminotransferase (ALT) as a surrogate for NAFLD diagnosis have failed to show a significant association between ALT levels and cardiovascular mortality [9-11]. Furthermore, ALT seems to exhibit a U-shaped association with total mortality [12], and the association of ALT with cardiovascular events may be similarly shaped with increased risk also apparent at low ALT concentrations [9].

Two recent reviews of the literature had reached conflicting conclusions [13,14]. Ghouri et al. concluded that the association between NAFLD and cardiovascular risk is inconsistent and that a diagnosis of NAFLD is insufficient to consider NAFLD patients as being at high risk for cardiovascular disease [13]. Targher et al. however recommended monitoring and evaluation of the risk of cardiovascular disease all patients with NAFLD [14]. Thus, although cardiovascular events are a common cause of death in NAFLD, there is conflicting evidence to recommend routine counseling and cardiovascular risk screening in all patients with NAFLD [13,14]. Based on all this, it seems more important to identify the subgroup of NAFLD patients at higher risk for cardiovascular disease who are expected to derive the most benefit from early intervention to prevent cardiovascular outcomes.

The Framingham risk score (FRS) provides an estimate for the coronary heart disease (CHD) risk of the general United States population [15,16]. Small cross-sectional studies have reported a predicted higher 10-year CHD risk as determined by the FRS in patients with NAFLD [17,18]. However, as patients included in those studies [17,18] were evaluated at a single point in time and they had no long-term follow-up, it remains unclear whether the proportion of NAFLD patients predicted with a high risk for CHD in fact was the same proportion of patients who developed CHD over time. Thus, we aimed at evaluating both the baseline probability of CHD using the FRS, and the long-term occurrence of CHD in NAFLD patients who underwent long-term follow-up. We also assessed the sensitivity, specificity, positive and negative predictive values of the FRS in predicting CHD in NAFLD patients.

MATERIALS AND METHODS

Study Population: baseline demographic data

This was a longitudinal, long-term follow-up study of a community-based cohort of patients with well-characterized NAFLD as previously described [2]. Patients residing in Olmsted County, Minnesota who had been diagnosed with NAFLD, fatty liver, hepatic steatosis, steatohepatitis, or cryptogenic cirrhosis over a 20-year period between January 1, 1980, and January 1, 2000, were identified using the resources of the Rochester Epidemiology Project. The Rochester Epidemiology Project is a unique infrastructure that links and indexes the medical records of the population living in Olmsted County, Minnesota [19]. According to census data, the total population in Olmsted County in the year 2000 was 124,000 people. The proportion of whites in the population was 90.3% compared with the general US population of 75.1%. The proportion of people with high school graduate or higher education, and with Bachelor's degree or higher was 91.1% and 34.7%, respectively as

compared to 80.4% and 24.4% respectively in the general US population. Although fatty liver was recognized prior to 1980, this liver condition was better characterized in 1980 [20], therefore, we chose to identify patients after this date. The diagnosis of NAFLD was based on the following criteria: 1) imaging studies (i.e., ultrasonography, CT scan, or MRI) confirming the presence of fat infiltration of the liver, and/or a liver biopsy showing steatosis in at least 5% of hepatocytes; and 2) exclusion of liver diseases of other etiology including alcohol-induced or drug-induced liver disease, autoimmune or viral hepatitis, and cholestatic or metabolic/genetic liver disease. These other liver diseases were excluded using standard clinical, laboratory, imaging, and liver biopsy data. Patients with an average daily alcohol consumption of at least 20g in women, or 30g in men were excluded.

All clinical data of the patient population (Table 1) were collected within seven days of the time of NAFLD diagnosis. The definition of metabolic syndrome was based on the 2001 National Cholesterol Education Program Adult Treatment Panel III criteria recently modified by the American heart Association and the National Heart, Lung and Blood Institute [21]. The diagnosis of metabolic syndrome requires presence of at least three of the following five features; central obesity (based on waist circumference), increased glucose levels -fasting glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes, fasting hypertriglyceridemia (fasting triglyceride ≥ 150 mg/dL), fasting low HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women) or hypertension (BP $\geq 130/85$ mmHg or receiving treatment). BMI was calculated as weight divided by height squared (kg/m^2). As the majority of patients did not have waist circumference measurements, we defined obesity using BMI ≥ 30 kg/m^2 in accordance with the World Health Organization definition of the insulin resistance syndrome [22]. The age range of 30-74 years was chosen to be consistent with the age range used in the original FRS calculation [16].

A total of 484 patients were diagnosed with NAFLD during the study period. A detailed history and physical examination was recorded by a health care provider using standardized protocols. One hundred and seventy five patients were excluded due to missing data needed for FRS calculation (N=107), patients' age out of range of 30-74 years (N=53) and patients with overt CHD confirmed at baseline (N=15). Hence, a total of 309 patients with NAFLD were included in this study. Overt CHD was defined by clinical criteria and/or coronary angiographic criteria. All participants were followed through a detailed review of their medical records until May 31, 2008. The study was approved by the Institutional Review Board of the Mayo Clinic and all participants provided permission for their medical information to be used for research.

Baseline Framingham Risk Scores calculation

The FRS is calculated using a standard score sheet that is gender specific, and includes the following variables: age, blood pressure, total cholesterol, HDL-cholesterol, smoking history, and history of diabetes [16]. The FRS sheets were used for estimating the 10-year probability of developing CHD in our patients with NAFLD. The FRS sheets also provide the comparative average 10-year CHD risk of the Framingham subjects of same age and gender as the NAFLD patients [16]. Thus, this comparative average 10-year CHD risk refers to the risk estimate derived from the experience of the Framingham Heart Study population [16].

Current smoking status was defined as any self-reported smoking. Hypertension was defined as mean resting blood pressure $\geq 130/85$ mmHg, over 2 measurements or use of antihypertensive medications at the onset of NAFLD diagnosis. Fasting blood levels of glucose, triglycerides, total cholesterol, and HDL cholesterol were measured in a standardized laboratory.

Follow-up data

Cardiac events were recorded during the follow-up period. Since the FRS predicts events for a period of 10 years, only those events occurring within 10 years of NAFLD diagnosis were considered in the analysis for those patients who had more than 10 years of follow-up. The definition of a CHD event was based on an extensive review of the medical records with designation as validated congestive heart failure, unstable angina or myocardial infarction, and/or a documented flow-limiting stenosis from angiography or angina requiring revascularization during follow-up [16]. Primary outcomes of this study were deaths from any cause or CHD events. Information about the causes of death and non-fatal CHD events was obtained. Follow-up time was calculated from the time between the dates of NAFLD diagnosis (i.e., baseline) to the date of event of CHD or death whichever occurred first. Data on all medications taken during follow-up were gathered from a detailed review of medical and pharmacy records of each patient.

Statistical Analyses

Statistical analyses were performed with SPSS version 15.0 software. Subjects were categorized by gender and the presence of new CHD events. Continuous variables were presented as mean $\pm$ standard deviation (SD) and categorical data were presented as numbers (percentage). Independent t tests were used for comparison of continuous variables whereas Chi-square test was used for comparison of numbers (proportions). Two-sided p values < 0.05 were considered to indicate statistical significance. Logistic regression analysis was used to identify the factors significantly associated with new CHD events in NAFLD patients. Only those variables with a p value < 0.1 by univariate analysis were included in multivariate analysis. In order to avoid overestimation of the model, we excluded from the multivariate analysis those individual variables used to calculate the Framingham Risk Score. We used the ROC curve analysis to identify the cut-off value of the FRS with the highest sensitivity and specificity to distinguish between patients who developed new onset of CHD and those who did not.

RESULTS

Clinical Features at Presentation

The 309 NAFLD patients were predominantly middle-aged (49.1 ± 11.1 ; range 30-74 years). Most patients were Caucasian (95.8%) with an equal gender distribution. The main demographic, clinical features and laboratory tests are summarized in Table 1. The metabolic syndrome was found in two-thirds. In particular, obesity was present in 73.8% of the population. The average values of ALT and AST levels were one and a half to two times higher than normal range while mean values of glucose, cholesterol and triglyceride were higher than the upper limit of normal.

The calculated 10-year CHD risk in patients with NAFLD was $10.9 \pm 9.3\%$ and significantly higher in men than women ($12.6 \pm 10.3\%$ vs. $9.6 \pm 8.1\%$, respectively, $P = 0.006$). The average 10-year CHD risk was $9.9 \pm 5.9\%$. The calculated 10-year CHD risk in the NAFLD cohort was significantly higher than the average 10-year CHD risk ($10.9 \pm 9.3\%$ vs. $9.9 \pm 5.9\%$, respectively; $P < 0.0001$).

Long-Term Follow-Up

The 309 NAFLD patients were followed-up for a mean of 11.5 ± 4.1 years for a total of 3554 person-years of follow-up. The follow-up was almost identical in men and women ($p = 0.9$). Forty one patients (13.3%) died during follow-up (Table 2). The leading causes of death were non-liver cancer ($n=17/41$; 42%). Ten patients ($n=10/41$; 24%) died from CHD

which was the second leading cause of death. Four patients (n=4/41; 10%) died from stroke and complications, and 2 (n=2/41; 5%) patients died from liver-related complications.

New onset CHD occurred in 34 (11%) of the NAFLD patients including 19/144 (13.2%) men and 15/165 (9.1%) women. This 11% actual occurrence of new onset CHD was not significantly different from the FRS estimated 10-year CHD risk of $10.9 \pm 9.3\%$ ($p = \text{NS}$) in the NAFLD cohort. Ten of these 34 patients (5 men, 5 women) died from CHD. Table 3 summarizes the results of the univariate analysis of those variables with a P value < 0.1 comparing patients with and without new onset CHD: as shown, patients with new onset CHD were older, and were more likely to have metabolic syndrome, a lower diastolic blood pressure, higher serum glucose levels, lower HDL levels and higher FRS score than NAFLD patients without new CHD events (Table 3). By multivariate analysis, however, only the FRS remained statistically significant (odd ratio, 1.24; 95% CI, 1.05, 1.21; $P = 0.001$). The proportion of patients taking medications for the treatment of diabetes, hypertension or dyslipidemia was not significantly different between patients with and without new CHD events. Based on ROC curves analysis, a FRS score ≥ 11 in women (or a calculated 10-year CHD risk $\geq 11\%$) had a sensitivity of 80%, specificity of 68%, PPV of 20%, and NPV of 97%. A FRS score ≥ 6 in men (or the calculated 10-year CHD risk $\geq 10\%$) had a sensitivity of 74%, specificity of 54%, PPV of 19.4%, and NPV of 93%. Figure 1 shows the time to event of new onset CHD in FRS ≥ 11 in women plus ≥ 6 in men vs. FRS < 11 in women plus FRS < 6 in men.

DISCUSSION

Our study describes both predicted and actual development of new CHD events (34/309, 11%) and CHD-related mortality (10/309, 3.2%) in NAFLD patients during long-term follow-up. Specifically, we found that the proportion of new onset of CHD was almost identical to that predicted at baseline by the FRS. As the FRS is easily calculated in the office setting, routine calculation of the FRS in NAFLD patients may be beneficial in identifying those NAFLD patients at highest risk of CHD outcomes. Our data suggest that a cut-point of 11 for women and 6 for men is the most sensitive cut-point for predicting CHD events, and patients with scores in or above these values may necessitate a more aggressive cardiac follow-up. Our data demonstrate that within 10 years of NAFLD diagnosis, the vast majority (89%) of patients will not develop CHD, and that they can accurately be identified by calculating their FRS; the NPV (i.e., appropriate identification of patients without developing CHD) of a FRS less than 11 in women and less than 6 in men was 97% and 93% respectively. Thus, by calculating the FRS we can confidently predict the risk of developing CHD in the vast majority of NAFLD patients at the time of diagnosis of the liver disease.

The all-cause mortality, CHD-related deaths, and CHD-new events rate in our study (13.3%, 3.2%, and 11%, respectively) were fairly similar to the figures (12%, 1.1%, and 8.9%, respectively) reported by Schindhelm et al. [23] in a population-based study from the Netherlands. However, the rate of CHD-related mortality in our study was lower than that reported by Eksteadt et al. [3] from Sweden (3.2% vs. 8.5%). Differences in study patient populations may explain this difference; for instance the prevalence of diabetes or impaired glucose tolerance, a well-known risk factor for increased CHD-mortality was almost four times higher in the Swedish study than in our study; in addition, Swedish patients with a history of CHD at baseline were not excluded.

The estimated 10-year CHD risk derived from the FRS in our patients with NAFLD (12.6% in men and 9.6% in women) is similar to the figures of 13.6% and 12.1% in men and women, respectively reported by Ioannou et al. [17]. Using data from the NHANES III, Ford et al. demonstrated that the proportion of people in the general US population with a higher

10-year risk for CHD significantly increased with advancing age and it was higher in men than in women [24]. In our study, we found a similar significant correlation with older age, and although not statistically significant, there were proportionally more events among men than among women.

The main strengths of our study are the inclusion of NAFLD patients from the community along with the long-term follow-up. All patients had nearly complete data for 10-year CHD risk calculation and were followed up for new CHD events. However, a limitation of our study is the lack of a matched non-NAFLD control population. As mentioned before, the FRS standard sheets were created using data from a well characterized population from Framingham, MA [16]. Thus, by using the FRS standard sheets, the 10-year CHD risk of our NAFLD patients was indeed compared to the average 10-year CHD risk of the original population enrolled in the Framingham Heart Study [16]. Although the FRS sheets allow matching by age and gender, and both the Framingham and Olmsted county populations are predominantly composed on Caucasians, further studies including a well characterized non-NAFLD control population are necessary. In addition, since data for this study were gathered by review of medical records, our study may have some of the bias inherent to historical cohorts.

In conclusion, our study confirms prior observations from small cross-sectional studies that patients with NAFLD have a higher 10-year CHD risk than predicted in the general population of same age and gender. Additionally, our study demonstrates that the FRS accurately predicts the actual 10-year CHD risk in patients with NAFLD. A FRS of 11 in women and 6 in men allows the identification of NAFLD patients that may benefit the most from intensive medical therapy to prevent development of CHD.

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Abbreviations

NAFLD	nonalcoholic fatty liver disease
ALT	alanine aminotransferase
FRS	Framingham risk score
CHD	coronary heart disease
CT	computed tomography
MRI	magnetic resonance imaging
HDL	high-density lipoprotein
BP	blood pressure
BMI	body mass index
SD	standard deviation
ROC	receiver operating characteristic
AST	aspartate aminotransferase

PPV	positive predictive value
NPV	negative predictive value
NHANES	National Health and Nutrition Examination Survey

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Figure 1. Showed time to events of CHD or death of patients with high CHD risk vs. patients with low CHD risk at baseline (Log-rank test statistics = 22.78, $P < 0.0001$).

Table 1

Characteristic data of NAFLD patients

Variables Mean $\pm$ SD or Number (%)	Total (N= 309)	Men (N= 144)	Women (N= 165)
A. Demographic data			
Age (years)	49.1 $\pm$ 11.1	47.1 $\pm$ 10.6	50.8 $\pm$ 11.3 *
Race, number (%)			
- White	296 (95.8%)	138 (95.8%)	158 (95.8%)
- American Indian	7 (2.3%)	1 (0.7%)	6 (3.6%)
- Asian	2 (0.6%)	1 (0.7%)	1 (0.6%)
- African American	1 (0.3%)	1 (0.7%)	0 (0%)
- Others	3 (1.0%)	3 (2.1%)	0 (0%)
B. CHD risk factors			
Systolic BP (mmHg)	136.0 $\pm$ 17.0	133.8 $\pm$ 16.4	137.8 $\pm$ 17.8 *
Cholesterol (mg/dL)	217.9 $\pm$ 43.4	212.2 $\pm$ 39.4	222.9 $\pm$ 46.1 *
HDL-cholesterol (mg/dL)	42.3 $\pm$ 13.0	38.0 $\pm$ 9.5	46.1 $\pm$ 14.5 *
History of smoking	40 (12.9%)	21 (14.6%)	19 (11.5%)
History of diabetes	63 (20.4%)	22 (15.3%)	41 (24.8%)
Diastolic BP (mmHg)	82.4 $\pm$ 8.9	82.7 $\pm$ 8.8	82.1 $\pm$ 9.1
Obesity (BMI $\geq$ 30 kg/m ²)	228 (73.8%)	107 (74.3%)	121 (73.3%)
BMI ($\geq$ 30 kg/m ²)	33.6 $\pm$ 5.9	32.9 $\pm$ 4.9	34.2 $\pm$ 6.7 *
Triglyceride (mg/dL)	228.8 $\pm$ 147.3	226.6 $\pm$ 135.8	230.8 $\pm$ 157.5
Presence of Metabolic Syndrome (3 criteria)	203 (65.7%)	93 (64.6%)	110 (66.7%)
Framingham risk score (FRS)	6.6 $\pm$ 5.6	5.7 $\pm$ 3.3	7.4 $\pm$ 6.9
Calculated 10-year CHD risk (%)	10.9 $\pm$ 9.3%	12.6 $\pm$ 10.3%	9.6 $\pm$ 8.1% *
C. Laboratory tests			
AST (8-48 U/L)	51.6 $\pm$ 56.3	48.1 $\pm$ 55.3	54.7 $\pm$ 57.1
ALT (7-55 U/L)	76.9 $\pm$ 48.5	80.7 $\pm$ 45.8	73.1 $\pm$ 50.9
Total bilirubin (0.1-1.0 mg/dL)	0.7 $\pm$ 0.5	0.8 $\pm$ 0.5	0.6 $\pm$ 0.5 *
Alkaline phosphatase (45-115 U/L)	195.9 $\pm$ 80.7	185.7 $\pm$ 84.6	204.9 $\pm$ 76.2 *
Albumin (3.5-5.0 g/dL)	4.3 $\pm$ 0.4	4.3 $\pm$ 0.5	4.2 $\pm$ 0.4
Glucose (70-100 mg/dL)	119.1 $\pm$ 46.9	113.2 $\pm$ 39.3	124.1 $\pm$ 52.3 *

Note.

* *P*value < 0.05 for men vs. women

Table 2

Causes of death (n = 309)

Cause of death	Number (%)
All-cause of death	41/309 (13.3%)
Non-liver cancer	17/41 (42%)
Breast cancer	4/41 (10%)
Colon cancer	3/41 (7%)
Gastric cancer	2/41 (5%)
Pancreatic cancer	1/41 (2%)
Leiomyosarcoma	1/41 (2%)
Lymphoma	1/41 (2%)
Lung cancer	1/41 (2%)
Thyroid cancer	1/41 (2%)
Endometrial cancer	1/41 (2%)
CHD	10/41 (24%)
Stroke	4/41 (10%)
Liver-related complications	2/41 (5%)
Chronic obstructive pulmonary disease	2/41 (5%)
Pulmonary embolism	1/41 (2%)
Others	5/41 (12%)

Table 3

Comparison of NAFLD patients with and without new CHD

Variables Mean $\pm$ SD, Number (%)	NAFLD patients without new CHD (N=275)	NAFLD patients with new CHD (N=34)	P value
Age (years)	48.3 $\pm$ 10.7	55.7 $\pm$ 11.8	<0.0001
History of diabetes	18.9%	32.3%	0.07
Presence of Metabolic syndrome (3 criteria)	63.6%	82.4%	0.03
Diastolic BP (mm Hg)	82.9 $\pm$ 8.4	78.4 $\pm$ 11.8	0.04
Glucose (mg/dL)	117.2 $\pm$ 45.2	134.4 $\pm$ 57.9	0.047
HDL-cholesterol (mg/dL)	42.9 $\pm$ 13.3	38.0 $\pm$ 9.7	0.04
Total cholesterol (mg/dL)	216.4 $\pm$ 43.4	230.2 $\pm$ 41.8	0.08
Triglyceride (mg/dL)	223.1 $\pm$ 140.2	273.5 $\pm$ 190.5	0.064
Framingham risk score (FRS)	6.2 $\pm$ 5.6	9.8 $\pm$ 4.5	<0.0001
CHD risk at 10 years (based on baseline FRS)	10.3 $\pm$ 8.8%	16.9 $\pm$ 10.9%	<0.0001