Differential risk factor patterns for a positive treadmill test among subjects with and without ultrasound-based fatty liver

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Abstract

Introduction: It is not clear whether the risk factors for CVD in subjects with NAFLD are the same for subjects without NAFLD. We analyze the risk factor patterns for a positive treadmill test in asymptomatic subjects with and without ultrasound-based fatty liver.

Material and methods: This was a cross-sectional study in voluntary subjects from January 2005 to January 2007. Adult subjects with alcohol consumption < 20 g per day and without liver diseases were included. Anthropometric, biochemical, ultrasound imaging, and exercise treadmill testing data were collected. Use of univariate and multivariate analyses identified the variables that predicted a positive exercise treadmill test.

Results: One thousand four hundred twenty one subjects were included. The prevalence of metabolic syndrome and NAFLD was 37.3 and 30.2%, respectively. No differences were observed in the positive treadmill test (1.3% in non-NAFLD group vs. 2.3% in NAFLD group, $p = 0.176$). In subjects with NAFLD, systolic blood pressure ≥ 130 mm Hg was associated with a positive treadmill test (OR = 4.705, 95% CI 1.285-17.231). In subjects without NAFLD, waist circumference (OR = 8.750, 95% CI 1.830-41.843) and metabolic syndrome (OR = 3.802, 95% CI 1.121-12.987) were factors for a positive treadmill test.

Conclusions: Although some evidence demonstrates that subjects with NAFLD had increased risk for CVD, these risk factors are different from those observed in the general population.

Key words: cardiovascular disease, metabolic syndrome, liver steatosis, blood pressure.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic consequence of metabolic syndrome (MS) [1]. Secondary to the high prevalence of obesity and MS, NAFLD is today one of the most common causes of gastroenterology consultations in the clinical setting [2]. In this context, gastroenterologists are exposed to large numbers of subjects with increased risk factors for the development of cardiovascular disease (CVD).

Cardiovascular disease is the most common cause of death and will continue to be so for at least the next 30 years [3]. Because MS is an important risk factor for CVD, it is logical to expect an increased risk of CVD among subjects with NAFLD. Several lines of evidence indicate that subjects with NAFLD have increased values for (a) indirect markers of CVD, such as mean intima-media thickness, even without abnormal liver function tests [4] and ultra-sensitive C-reactive protein (US-CRP) [5]; and (b) direct markers of CVD (coronary angiography studies demonstrating that NAFLD is independently associated with CVD) [6].

Recently, the Firenze Bagno a Ripoli study showed that γ-glutamyl transpeptidase or aspartate aminotransferase (AST) is an independent predictor of CVD [7], and this finding was confirmed in other European [8] and American populations [9].

However, it is not clear whether the risk factors for CVD in subjects with NAFLD are the same for subjects without NAFLD. The aim of this study was to analyze the risk factor patterns for a positive treadmill test in asymptomatic subjects with and without ultrasound-based fatty liver.

Material and methods

This was a cross-sectional study performed in ambulatory voluntary subjects from January 2005 to January 2007. Adult asymptomatic subjects with alcohol consumption below 20 g per day were included. Patients with liver disease from any other cause were excluded. Anthropometric, biochemical, ultrasound imaging, and exercise treadmill testing data were collected for all subjects. The study was approved by the Human Subjects Committee as conforming to the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consent was obtained from all participants before entry.

Physical examination

Body weight was measured in light clothing and without shoes, to the nearest 0.10 kg. Height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. "Overweight" was defined as a BMI of 25-29.9 kg/m^2 and "obesity" as a BMI of ≥ 30 kg/m^2. Three blood pressure readings were taken at 1 min intervals, and the average of the first and third readings was used in the analysis.

Analytical procedures

Blood samples were collected from all patients after a fast of 8 h, for the determination of serum concentrations of glucose, total cholesterol, cholesterol associated with high-density lipoprotein (HDL cholesterol), cholesterol associated with low-density lipoprotein (LDL cholesterol), triglycerides, AST, alanine aminotransferase (ALT), albumin, and total bilirubin. Plasma glucose was measured in duplicate in the fasting state using an automated analyzer. The coefficient of variation for a single determination was 1.5%. Cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic colorimetric methods, using CHOL, HDL–C plus (second generation), and triglyceride assays, respectively (Roche Diagnostics Co., Indianapolis, IN, USA). LDL cholesterol concentrations were calculated using the Friedewald formula [11] or measured by an enzymatic colorimetric method when triglyceride levels were higher than 150 mg/dl.

Non-alcoholic fatty liver disease definition

The diagnosis of NAFLD was based on ultrasonographic findings compatible with hepatic steatosis. Real-time ultrasonographic studies were performed while the subjects were fasting. A 3.5 MHz transducer (Elegra, Siemens Medical Systems, Mountain Grove, CA, USA) was used to obtain the following images: sagittal view of the right lobe of the liver and right kidney; transverse view of the left lateral segment of the liver and spleen; transverse view of the liver and pancreas, and any focal areas of altered echotexture. A bright liver echo pattern that signified a discrepancy higher than expected in the echo amplitude between the liver and kidney parenchyma was considered to indicate steatosis. In the second evaluation, all studies for each subject were viewed side-by-side in a masked fashion ($\kappa = 0.92$).

Metabolic syndrome

Metabolic syndrome was defined according to the criteria of the Executive Summary of the Third Report of the National Cholesterol Education Program as the presence of three or more of the following criteria [12].

Abdominal obesity: waist circumference ≥ 102 cm in men and > 88 cm in women, but because the waist circumference measure was not available for all patients, we used a validated ideal BMI (> 22 kg/m^2 in men and > 23 kg/m^2 in women),

which detects diabetes mellitus and high blood pressure with similar efficacy to waist circumference [13]. Hypertriglyceridaemia: triglycerides ≥ 150 mg/dl. HDL cholesterol: HDL < 40 mg/dl in men and < 50 mg/dl in women. High blood pressure: ≥ 130/85 mm Hg. High fasting glucose: ≥ 100 mg/dl.

Ultra-sensitive C-reactive protein

Ultra-sensitive C-reactive protein was measured in 1 ml of blood following an overnight fast. The serum was frozen at –73°C and processed within 30 days using a chemiluminescent immunoassay system (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA) with a dynamic range of 0.02-250 mg/l and a coefficient of variation of less than 15% [14].

Cardiovascular disease

For the purpose of this paper, CVD was investigated in all subjects by exercise treadmill testing, using the Q-Stress system (Quinton Instrumentation Technologies, Mexico, Mexico), following the Bruce protocol [15]. We recorded: blood pressure and heart rate at each exercise stage and at peak exercise, time to onset of angina, and 1 mm ST-segment depression, ST-segment depression at peak exercise, maximal ST-segment depression, presence of cardiac arrhythmias; metabolic equivalents and double product (heart rate in bpm × systolic blood pressure in mm Hg), and total exercise duration. Myocardial ischaemia was defined as the presence of 0.1 mV horizontal or downsloping ST-segment depression 80 ms after the J-point during exercise or recovery. Cardiac arrhythmias were defined as ventricular premature beats of Lown grade II or higher. All studies were performed and interpreted by the same cardiologist on two separate occasions. We decided to use the exercise treadmill test as a marker of CVD because it is a non-invasive test with good performance in assessing coronary pathology [16].

Statistical analysis

Continuous variables are presented as means ± standard deviations (SD). Quantitative data were analyzed using Student's *t* test and one-way analysis of variance (ANOVA) for two or more independent groups, respectively. Differences in the proportions of categorical data were found with Fisher's exact test when the number of patients was ≤ 5, and with the χ^2 test for 2 × 2 tables when the number of subjects in each cell was > 5. Univariate analyses identified the clinical and biochemical variables that predicted a positive exercise treadmill test. All variables with a p value < 0.2 in univariate analyses were included in a multivariate backward stepwise logistic regression analysis. A p value of 0.05 or less was considered significant. All data were analyzed using SPSS, PC version 12.0 (Chicago, IL, USA).

Results

A total of 1421 subjects were included during the study period, with mean age 46 ±11 years and a predominance of men (n = 920, 64.7%). The mean BMI was 26.7 ±4.1 kg/m^2, and 259 subjects (18.2%) were obese (BMI ≥ 30 kg/m^2). The prevalence of MS was 37.3%; that of NAFLD was 30.2%. Patients with NAFLD had a higher prevalence of obesity (37.4 vs. 9.8% for patients without NAFLD, p < 0.001) and MS (61.4 vs. 26.8%, p < 0.001) and higher values for US-CRP (49 vs. 28%, p < 0.001). Interestingly, in the total sample, no statistical differences were observed between these two groups in the treadmill test results (1.3% for the non-NAFLD group vs. 2.3% for the NAFLD group, p = 0.176) (Table I).

The subjects were classified according to treadmill test result and NAFLD status. In patients with a positive treadmill test, differences were observed in weight (p = 0.002), BMI (p = 0.008), and the prevalence of obesity (p = 0.019) (Table II). In subjects with a negative treadmill test, similar differences were observed as in Table I.

In subjects with NAFLD, univariate analysis was used to identify those patients with a high risk of CVD. The differences between patients with negative and positive treadmill test were systolic blood pressure ≥ 130 mm Hg (p = 0.029), diastolic blood pressure ≥ 85 mm Hg (p = 0.092), combination of both (p = 0.036), and obesity (p = 0.183) (Table III). On multivariate analysis, only systolic blood pressure ≥ 130 mm Hg remained a significant factor (OR = 4.705, 95% CI 1.285-17.231, p = 0.019) even with the inclusion of smoking status in the model (OR = 3.859, 95% CI 1.070-13.922, p = 0.039) (Table IV).

Using these findings to identify patients with NAFLD and a high risk of CVD, we observed that a high systolic blood pressure value was associated with a higher prevalence of positive treadmill tests (7.1%, p = 0.011).

To corroborate the differential risk patterns for CVD among subjects with and without NAFLD, we performed univariate and multivariate analyses to detect the risk factors for CVD among subjects without NAFLD and with normal levels on liver function tests (Table V). In this subgroup, waist circumference (OR = 8.750, 95% CI 1.830-41.843, p = 0.007) and MS (OR = 3.802, 95% CI 1.121-12.987, p = 0.032) were independently associated with a positive treadmill test (Table IV).

Discussion

In this study we analyzed a sample of asymptomatic subjects using non-invasive tools, and

Table I. Analysis of demographic, clinical, biochemical and treadmill test data according to NAFLD status

Variable	NAFLD (–) (n = 988)	NAFLD (+) (n = 433)	P-value
Age [years]	45.29 ±11.82	47.51 ±10.19	< 0.001
Gender (male)	578 (58.5%)	343 (79.2%)	< 0.001
Weight [kg]	71.67 ±13.16	84.33 ±15.30	< 0.001
Height [m]	1.67 ±0.09	1.69 ±0.09	< 0.001
Body mass index [kg/m^2]	25.55 ±3.48	29.39 ±4.36	< 0.001
Obesity (body mass index ≥ 30 [kg/m^2]	97 (9.8%)	162 (37.4%)	< 0.001
Abdominal circumference [cm]	88.45 ±11.22	99.43 ±12.90	< 0.001
Systolic blood pressure [mm Hg]	113.26 ±14.49	120.48 ±13.66	< 0.001
Diastolic blood pressure [mm Hg]	75.34 ±8.83	80.53 ±8.86	< 0.001
Haemoglobin [g/dl]	15.38 ±1.35	16.02 ±1.25	< 0.001
Leucocytes [10^3/ml]	6.16 ±1.66	6.61 ±1.78	< 0.001
Platelets [10^3/ml]	244.91 ±58.52	236 ±51.34	0.008
Glucose [mg/dl]	93.00 ±20.74	106.40 ±37.67	< 0.001
Uric acid [mg/dl]	5.81 ±3.39	6.56 ±1.28	0.005
Creatinine [mg/dl]	0.91 ±0.36	0.95 ±0.18	0.149
Total cholesterol [mg/dl]	205.25 ±39.29	212.29 ±40.85	0.002
LDL cholesterol [mg/dl]	132.99 ±33.13	133.69 ±37.08	0.736
HDL cholesterol [mg/dl]	43.10 ±14.34	37.75 ±10.28	< 0.001
Triglycerides [mg/dl]	154.08 ±92.28	220.14 ±129.43	< 0.001
US-CRP [mg/l]	2.92 ±4.96	4.14 ±4.70	< 0.001
US-CRP > 3 mg/l	276 (28%)	215 (49%)	< 0.001
Current smoking	394 (39.9%)	170 (39.2%)	0.860
Albumin [g/dl]	4.06 ±0.28	4.08 ±0.27	0.178
Total bilirubin [mg/dl]	0.92 ±0.43	0.96 ±0.38	0.168
Alanine amino-transferase [UI/l]	27.03 ±15.24	46.08 ±31.53	< 0.001
Aspartate amino-transferase [UI/l]	25.74 ±10.25	33.51 ±17.43	< 0.001
Alkaline phosphatase [UI/l]	66.82 ±22.27	72.48 ±21.33	< 0.001
Metabolic syndrome (3 criteria)	265 (26.8%)	266 (61.4%)	< 0.001
Treadmill test (positive)	13 (1.3%)	10 (2.3%)	0.176

US-CRP – ultrasensitive-C reactive protein

identified a high-risk group for CVD within the group of patients with NAFLD. According to our results, subjects with NAFLD and high systolic blood pressure have an increased risk of CVD.

Although there was no significant difference (only a trend) in the prevalence of positive treadmill tests among subjects with and without NAFLD, we identified different risk factors for CVD in the two groups. The risk factors for patients without NAFLD were the same as those for the general population [18, 19], which emphasizes the differences in risk patterns according NAFLD status. This distinction could be useful in the clinical setting to identify high-risk subjects.

According to our results, high blood pressure emerges as a new discriminatory factor among subjects with NAFLD with which to identify those patients at risk of CVD. To the best of our knowledge, this is the first study to demonstrate that blood pressure levels are associated with CVD in NAFLD patients. This finding is in agreement with previous results showing that high blood pressure has an effect on peripheral vascular structural and functional parameters, independently of MS [20], and that the utility of MS in predicting death from CVD is limited [21], contrary to the high utility of blood glucose or blood pressure [22]. In fact, in patients with diet-controlled type 2 diabetes mellitus, NAFLD increases the risk of CVD (assessed by carotid artery intima-media thickness), which is mainly attributed to elevated blood pressure [23].

This cross-sectional study has the intrinsic limitations of this kind of study, and only epidemiological associations could be derived from this design. Prospective studies must be performed to confirm these initial findings. Additionally, the low number of events could limit the power of the statistical analysis.

In this work, we found different risk factor patterns for CVD considering the NAFLD status. This is particularly important considering that, at this time, there are no other recommendations for preventative measures or diagnostic approaches to CVD in subjects with NAFLD, apart from those described for MS [28-30]. Consequently, identifying groups at high risk of CVD could have important implications, and a more aggressive approach may be required.

In conclusion, although some evidence demonstrates that subjects with NAFLD had increased risk for CVD, these risk factors are different from those observed in the general population. Future prospective studies are necessary to confirm this initial epidemiological evidence.

Table II. Differences among NAFLD status, according to result of treadmill test

Variable	Treadmill test (–)		*P*-value	Treadmill test (+)		*P*-value
	NAFLD (–) (n = 975)	NAFLD (+) (n = 423)		NAFLD (–) (n = 13)	NAFLD (+) (n = 10)	
Age [years]	45.23 ±11.82	47.49 ±10.15	< 0.001	49.92 ±10.92	48.10 ±12.53	0.713
Gender (male)	569 (58.3%)	334 (78.9%)	< 0.001	9 (69.2%)	8 (80%)	0.660
Weight [kg]	71.66 ±13.20	84.21 ±15.35	< 0.001	72.41 ±10.41	89.52 ±12.40	0.002
Height [m]	1.67 ±0.09	1.69 ±0.09	< 0.001	1.68 ±0.09	1.73 ±0.10	0.313
Body mass index [kg/m^2]	25.55 ±3.48	29.38 ±4.3	< 0.001	25.38 ±3.30	29.91 ±4.11	0.008
Obesity (body mass index ≥ 30 kg/m^2)	96 (9.8%)	156 (36.8%)	< 0.001	1 (7.7%)	6 (60%)	0.019
Abdominal circumference [cm]	88.35 ±11.27	99.43 ±13.17	< 0.001	91.11 ±9.7	99.33 ±6.65	0.051
Systolic blood pressure [mm Hg]	113.22 ±14.38	120.15 ±13.64	< 0.001	114.23 ±17.77	126.00 ±13.49	0.077
Diastolic blood pressure [mm Hg]	75.32 ±8.7	80.32 ±8.80	< 0.001	75.85 ±10.54	84.00 ±9.66	0.088
Haemoglobin [g/dl]	15.38 ±1.34	16.01 ±1.25	< 0.001	15.33 ±2.30	16.25 ±1.17	0.535
Leucocytes [10^3/ml]	6.16 ±1.67	6.6 ±1.79	< 0.001	6.16 ±1.21	6.68 ±1.66	0.336
Platelets [10^3/ml]	244.58 ±57.70	236.41 ±51.35	0.019	269.85 ±103.317	246.60 ±52.47	1.000
Glucose [mg/dl]	92.75 ±19.42	106.42 ±37.84	< 0.001	111.38 ±66.41	105.30 ±31.25	0.804
Uric acid [mg/dl]	5.82 ±3.44	6.60 ±1.27	< 0.001	5.51 ±1.39	5.81 ±1.38	0.494
Creatinine [mg/dl]	0.91 ±0.36	0.95 ±0.18	0.183	0.85 ±0.14	0.94 ±0.13	0.106
Total cholesterol [mg/dl]	205.06 ±39.42	212.44 ±40.87	< 0.001	219.53 ±24.40	206.10 ±41.49	0.402
LDL cholesterol [mg/dl]	132.88 ±33.24	133.98 ±37.21	0.355	141.38 ±22.27	121.50 ±30.34	0.137
HDL cholesterol [mg/dl]	43.11 ±14.41	37.67 ±10.28	< 0.001	42.30 ±7.00	41.08 ±10.16	0.535
Triglycerides [mg/dl]	153.56 ±91.91	220.00 ±128.42	< 0.001	193.15 ±114.66	226.30 ±175.70	0.756
US-CRP [mg/l]	2.92 ±4.99	4.18 ±4.74	< 0.001	2.46 ±2.09	2.42 ±2.05	0.926
US-CRP > 3 mg/l	273 (28%)	212 (50.1%)	< 0.001	3 (23.1%)	3 (30%)	1.000
Metabolic syndrome (3 criteria)	262 (26.8%)	261 (61.7%)	< 0.001	3 (23.1%)	5 (50%)	0.221
Current smoking	386 (39.6%)	164 (38.7%)	0.812	8 (61.5%)	6 (60%)	1.000
Albumin [g/dl]	4.06 ±0.28	4.09 ±0.26	0.097	4.07 ±0.25	3.87 ±0.46	0.351
Total bilirubin [mg/dl]	0.92 ±0.43	0.96 ±0.39	0.006	0.99 ±0.40	0.89 ±0.24	0.672
Alanine aminotransferase [UI/l]	26.89 ±15.20	46.26 ±31.81	< 0.001	38.23 ±30.44	38.50 ±14.23	0.321
Aspartate aminotransferase [UI/l]	25.66 ±10.13	33.57 ±17.59	< 0.001	31.85 ±16.86	30.90 ±7.89	0.335
Alkaline phosphatase [UI/l]	66.42 ±20.20	72.46 ±21.29	< 0.001	97.31 ±81.66	73.40 ±23.85	0.710

US-CRP – ultrasensitive-C reactive protein

Table III. Risk factors associated with a positive treadmill test in subjects with NAFLD (univariate analysis)

Variable	OR (95% CI)	*P*-value
Age >45 years	0.713 (0.203-2.498)	0.748
Gender	1.042 (0.217-4.995)	1.000
Obesity (body mass index ≥ 30 kg/m^2)	2.567 (0.713-9.238)	0.186
Alanine aminotransferase upper normal limit	0.738 (0.154-3.531)	1.000
Aspartate aminotransferase upper normal limit	0.939 (0.196-4.496)	1.000
Both aminotransferase upper normal limits	0.631 (0.132-3.016)	0.732
Impaired fasting glucose or diabetes mellitus	0.925 (0.193-4.432)	1.000
Triglycerides ≥ 150 mg/dl	0.651 (0.181-2.346)	0.501
HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women	0.708 (0.180-2.790)	0.705
Systolic blood pressure ≥ 130 mm Hg	4.756 (1.299-17.418)	0.029
Diastolic blood pressure ≥ 85 mm Hg	3.512 (0.878-14.056)	0.092
Blood pressure: ≥ 130/85 mm Hg	3.897 (1.080-14.060)	0.036
High fasting glucose: ≥ 100 mg/dl	0.952 (0.199-4.562)	1.000
Waist circumference > 102 cm in men and > 88 cm in women**	NC*	NC
Metabolic syndrome (3 criteria)	0.605 (0.173-2.124)	0.515
US-CRP > 3 mg/l	0.427 (0.109-1.672)	0.338
Current smoking	2.360 (0.656-8.489)	0.201
Alanine aminotransferase/aspartate aminotransferase > 1	1.056 (0.220-5.065)	1.000

**Not calculated due to no event being observed in one side of the variable*

***Because the waist circumference measure was not available in all patients we used a validated ideal BMI (> 22 kg/m^2 in men and > 23 kg/m^2 in women) that detects diabetes mellitus and high blood pressure with similar efficacy as waist circumference* [13]

Table IV. Independent risk factors associated with a positive treadmill test in subjects without NAFLD and normal liver function tests, and NAFLD (multivariate analysis)

Patients	β coefficient	Standard error	Wald X^2	OR (95% CI)	*p* value
with NAFLD					
Constant	4.114	0.412	99.897		
Systolic blood pressure ≥ 130 mm Hg	1.549	0.662	5.468	4.705 (1.285-17.231)	0.019
without NAFLD					
Constant	4.170	0.459	82.460		
Waist circumference > 102 cm in men and > 88 cm in women**	2.169	0.798	7.380	8.750 (1.830-41.843)	0.007
Metabolic syndrome	1.337	0.624	4.596	3.802 (1.121-12.987)	0.032

***Because the waist circumference measure was not available for all patients, we used a validated ideal BMI (> 22 kg/m^2 in men and > 23 kg/m^2 in women), which detects diabetes mellitus and high blood pressure with similar efficacy to waist circumference* [13]

Table V. Risk factors associated with a positive treadmill test in subjects without NAFLD and normal liver function tests (univariate analysis)

Variable	OR (95% CI)	*P*-value
Age > 45 years	1.858 (0.540-6.390)	0.374
Gender (male)	1.319 (0.384-4.538)	0.766
Obesity (body mass index ≥ 30 kg/m^2)	1.004 (0.127-7.939)	1.000
Impaired fasting glucose or diabetes mellitus	4.794 (1.003-22.922)	0.030
Triglycerides ≥ 150 mg/dl	1.273 (0.386-4.203)	0.761
HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women	1.213 (0.352-4.172)	1.000
Systolic blood pressure ≥ 130 mm Hg	2.107 (0.263-16.857)	0.405
Diastolic blood pressure ≥ 85 mm Hg	4.683 (0.980-22.372)	0.090
Blood pressure ≥ 130/85 mm Hg	1.678 (0.358-7.873)	0.378
High fasting glucose ≥ 100 mg/dl	5.213 (1.088-24.986)	0.021
Waist circumference > 102 cm in men and > 88 cm in women**	6.493 (1.390-30.303)	0.010
Metabolic syndrome (3 criteria)	2.461 (0.745-8.131)	0.193
US-CRP > 3 mg/l	0.583 (0.125-2716)	0.736
Current smoking	1.792 (0.543-5.915)	0.365
Alanine aminotransferase/aspartate aminotransferase > 1	0.771 (0.234-2.545)	0.766

***Because the waist circumference measure was not available for all patients, we used a validated ideal BMI (> 22 kg/m^2 in men and > 23 kg/m^2 in women), which detects diabetes mellitus and high blood pressure with similar efficacy to waist circumference* [13]

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