Association between nonalcoholic fatty liver disease and the incidence of cardiovascular and renal events

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Background: **Recent data suggest that the presence of non-alcoholic fatty liver disease (NAFLD) may be linked to increased cardiovascular and chronic kidney diseases. Here we assess whether NAFLD, as diagnosed by ultrasound, predicts the risk of incident cardiovascular and renal impairment events.**

Methods: **A total of 1150 patients with normal or near normal liver and kidney functions, and without protienuria or histories of cardiovascular accident were included in this multicenter prospective observational cohort study. All patients were subjected to full clinical evaluation, laboratory investigation including estimation of the GFR and immunonephelometric evaluation for protienuria, and abdominal ultrasonography for diagnosis of NAFLD. The metabolic syndrome was defined according to the modified National Cholesterol Education Program (NCEP)–ATP criteria. All patients followed up periodically over three years for the incidence of cardiovascular (including coronary heart disease, ischemic stroke and cerebral hemorrhage) and renal impairment events.**

Results: **Only 747 (62.25%) patients completed the follow-up examination and were included in the final analysis. 35.8% of them fulfilled the sonographic criteria of NAFLD. The frequency of cardiovascular accident and renal impairment was significantly higher in them: 136 patients (50.7%) vs. 110 (23%); $P < 0.001$ for cardiovascular events, 88 (32.8%) vs. 88 (18.4%), $P < 0.001$ for microalbuminuria; and 24 (8.9%) vs. 14 (2.9%), $P < 0.001$ for macroalbuminuria. Also, mean estimated glomerular filtration rate (eGFR) was significantly lower in patients with NAFLD (96 ± 23.28 vs. 111 ± 28.37; $P < 0.001$). Logistic regression analysis revealed that NAFLD was the best predictor for cardiovascular and renal impairment.**

Conclusion: **NAFLD is a good predictor of cardiovascular and renal diseases.**

Keywords: NAFLD, Cardiovascular diseases, Chronic renal impairment, Ultrasonography

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical condition characterized by histological features resembling that of alcohol-induced liver injury, but occurs in patients who do not abuse alcohol. NAFLD encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis [1].

It frequently occurs with features of the metabolic syndrome (MetS) [2]. The MetS is known to be a strong predictor of NAFLD and is a well-known precursor of cardiovascular disease (CVD), but the potential cardiovascular risk of NAFLD itself has not been well investigated [3].

Recent cross-sectional studies have documented that patients with NAFLD have a markedly greater carotid artery wall thickness than those without NAFLD [4,5]. However, carotid artery wall thickness is only a marker of early generalized atherosclerosis [6], so it is currently uncertain whether NAFLD is significantly associated with increased risk of future cerebrovascular events.

Growing evidence suggests that NAFLD may be linked to an increased risk for chronic kidney disease (CKD) especially in a population with type-2 diabetes [7]. The treatment of earlier stages of nephropathy, especially in diabetes, is effective in slowing progression toward end stage renal disease [8,9]. Thus, the early detection of precursors and risk factors for CKD is very important.

Objectives: To identify the prevalence of NAFLD and to assess whether NAFLD is associated with an increased incidence of CKD and CVD, including coronary heart disease (CHD), ischemic stroke and cerebral hemorrhage.

Abbreviations and Acronyms

NAFLD	= non-alcoholic fatty liver disease
NCEP	= national cholesterol education program
eGFR	= estimated glomerular filtration rate
CKD	= chronic kidney disease
CVD	= cardiovascular disease
BMI	= body mass index
ALT	= alanine aminotransferase
AST	= aspartate aminotransferase
T.	= cholesterol, total cholesterol
LDL-C	= low density lipoprotein cholesterol
HDL-C	= high density lipoprotein cholesterol
UA	= unstable angina
MI	= myocardial infarction
CHD	= coronary heart disease
DDM	= duration of diabetes mellitus
N	= number
SD	= standard variation
BMI	= body mass index
WC	= waist circumference
FBS	= fasting blood sugar
SBP	= systolic blood pressure
DBP	= diastolic blood pressure
DM	= diabetes mellitus
HbA1c	= glycosylated hemoglobin
MetS	= metabolic syndrome
GGT	= gamma glutamyl transaminase

Patients and methods

Ethics

The study protocol was approved by the local ethical committee. No interference with normal routine patient management or invasive medical procedures was required by the protocol. Investigators decided on the treatment that was in the best interest of their patients.

Design

This multicenter prospective observational cohort study enrolled 1150 patients between January 2009 and February 2010 with normal or near normal liver and kidney functions, and without overt protienuria or history of cardiovascular events.

Exclusion criteria

Patients with (a) previous history of CVD, including unstable angina (UA), myocardial infarction (MI), coronary revascularization, ischemic stroke, cerebral hemorrhage; (b) previous history of overt protienuria, or eGFR < 60 ml/min/1.73 m^2, or were receiving medical treatment for current kidney disease at the time of their initial examinations; (c) with known history of liver disease including viral, genetic, autoimmune, and drug-induced liver disease or those with positive test for hepatitis B antigen or hepatitis C antibody; and (d) with a history of alcohol intake or cancer.

Prior to starting the study, the objectives and methods were explained to all patients.

Evaluation of patients

All patients were subjected to:

(1) *Full clinical evaluation:* Special emphasis on history of smoking and alcohol consumption, assessment of vital signs (including BP; measured in the supine position after 15 min of bed rest), and symptoms of renal impairment (e.g. vomiting, blurred vision and/or change

urine output) were also taken in consideration. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the participant's height in meters. Waist circumference (WC) was measured in a standing position at the level of the umbilicus.

(2) *Laboratory investigations*

- Routine labs, including liver function test: alanine aminotransferase (ALT) and aspartate aminotransferase (AST); hepatitis B antigen and hepatitis C antibody; kidney function tests: creatinine and urea; FBS; HbA1c; urine analysis; lipid profile (Total cholesterol, LDL-C, HDL-C and serum triglyceride using 12–14 h fasting blood sample).
- Lab specific for the study:
  (i) eGFR:- according to the Modification of Diet in Renal Disease (MDRD) equation: [10]

$$\text{eGFR}(\text{ml/min}/1.73\ \text{m}^2) = 186 \times (\text{Creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if black})$$

(i) Urinary albumin excretion rate was measured from an early morning urine sample as albumin-to-creatinine ratio by an immunonephelometric method; microalbuminuria and macroalbuminuria (overt proteinuria) were present when urinary albumin excretion was 30–299 μg/mg creatinine and ⩾300 μg/mg creatinine, respectively [8]. Renal impairment was defined as eGFR ⩽ 60 ml/min/1.73 m^2 and/or overt protienuria.

(3) Electrocardiography.

(4) Radiological examination including abdominal ultrasound to exclude chronic liver disease and to diagnose fatty liver. This was carried out by a trained operator blinded to participants' clinical and laboratory characteristics. Four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) are required to diagnose NAFLD [11].

(5) MetS components were determined according to NCEP-ATP-III criteria [12], using the following values: (i) WC ⩾ 102 cm for males and ⩾88 cm for females; (ii) Triglycerides ⩾150 mg/dL; (iii) HDL-C < 40 mg/dL for males and <50 mg/dL for females; (iv) BP ⩾ 130/85 mmHg; and (v) FBS level ⩾ 100 mg/dL. Patients using antihypertensive drugs or hypoglycemic drugs are accepted as having a positive MetS criterion. MetS is confirmed when three of five components are present.

Follow-up

The patients were followed up periodically every 6–12 months for a period of three years, for the incidence of cardiovascular and kidney events. Cardiovascular events include CHD, ischemic stroke and cerebral hemorrhage. CHD includes UA, acute MI, silent MI and coronary revascularization. CVD was confirmed by reviewing medical records of the hospital and electrocardiogram changes. Non-fatal cerebrovascular accident, confirmed by medical records, showed new-onset neurological symptoms lasting >24 h with diagnostic imaging tests (computed tomography or nuclear magnetic resonance). Kidney events were assessed if eGFR progressed to <60 ml/min/1.73 m^2 and/or protienuria.

Statistical analysis

Data of each patient was collected in a special file, coded and fed to the computer on a statistical package using SPSS software for windows, version 18 for (SPSS Inc., Chicago IL, USA). Descriptive statistics were done including mean, standard of deviation for the non-categorical variables and prevalence for categorical variables. Continuous variables were evaluated using *t*-test and categorical variables using Chi square. Logistic regression was used to analyze correlation between the incidence of cardiovascular and renal impairment events and NAFLD. $P < 0.05$ will be considered statistically significant.

Results

Demographic data

All 1150 patients in this study had normal and near normal kidney function and no overt protienuria or history of cardiovascular accident at baseline. However, only 747 (64.95%) of these patients attended and completed the follow-up examination, and were included in the final analysis. In terms of demographic variables, eGFR, and NAFLD status, the patients who completed the follow-up examination were essentially similar to the 403 (35.05%) patients who did not attend the follow-up examinations. (Table 1).

The 268 (35.8%) patients who fulfilled the sonographic criteria of NAFLD were predominantly smokers and had significantly higher BMI. This group also had higher systolic and diastolic BP. Patients on antihypertensive drugs were significantly higher (Table 2).

Diabetes mellitus (DM) was not significantly higher in NAFLD patients with higher HbA_{1c} but

Table 1. Baseline clinical profile of all included participants.

Variables		Participants who completed the follow-up period	Participants who did not complete follow-up period	*P* value
		N = 747 (64.95%)	*N* = 403 (35.05%)	
Age (years)	Mean ± SD	51.44 ± 11.32	50.84 ± 10.46	0.201
Sex (male)	*N*(%)	266(48.9%)	202(50.1%)	0.845
BMI (kg/m^2)	Mean ± SD	34 ± 4.34	34.35 ± 3.82	0.178
WC (cm)	Mean ± SD	105.22 ± 8.5	105.18 ± 8.02	0.464
Smokers	*N*(%)	166(22.48%)	86(21.3%)	0.643
SBP (mmHg)	Mean ± SD	134.82 ± 14.80	136.55 ± 14.33	0.055
DBP (mmHg)	Mean ± SD	83.86 ± 8.30	84.48 ± 8.20	0.231
Antihypertensive	*N*(%)	242(32.4%)	139(34.5%)	0.605
DM	*N*(%)	431(57.7%)	252(62.5%)	0.345
FBS (mg/dL)	Mean ± SD	108.10 ± 16.82	107.90 ± 15.90	0.840
HbA_{1c} (%)	Mean ± SD	3.57 ± 3.16	3.26 ± 3.13	0.125
DDM (years)	Mean ± SD	31.84 ± 29.60	31.16 ± 28.37	0.741
Oral hypoglycemia	*N*(%)	384(51.4%)	216(53.6%)	0.675
Insulin therapy	*N*(%)	65(8.7%)	38(9.4%)	0.706
T. cholesterol (mg/dL)	Mean ± SD	214.45 ± 45.85	210.48 ± 40.88	0.145
HDL-C (mg/dL)	Mean ± SD	46.19 ± 7.09	46.91 ± 7.98	0.111
LDL-C (mg/dL)	Mean ± SD	133.21 ± 30.84	130.45 ± 27.68	0.133
Triglyceride (mg/dL)	Mean ± SD	160.17 ± 48.35	158.73 ± 44.29	0.620
ALT (U/L)	Mean ± SD	57.20 ± 27.96	57.67 ± 29.0	0.790
AST (U/L)	Mean ± SD	44.34 ± 19.06	43.86 ± 20.84	0.704
MetS	Mean ± SD	2.97 ± 1.05	2.89 ± 1.07	0.216
MetS	*N*(%)	506(67.7%)	287(71.2%)	0.559
eGFR (ml/min/1.73 m^2)	Mean ± SD	107 ± 26.56	107 ± 24.84	0.825
NAFLD	*N*(%)	268(35.8%)	149(36.9%)	0.762

Table 2. Clinical profile of the patients included in the final analysis in relation to NAFLD.

Variables		NAFLD		*P* value
		No: *N* = 479 (66.2%)	Yes: *N* = 268 (35.8%)	
Age (years)	Mean ± SD(range)	51.11 ± 10.65(29–78)	52.10 ± 12.46(30–78)	0.078
Sex (male)	*N*(%)	233(48.6%)	133(49.6%)	0.245
BMI (kg/m^2)	Mean ± SD(range)	34.35 ± 3.8(26–45)	33.37 ± 5.11(26–45)	0.013
WC (cm)	Mean ± SD(range)	105.12 ± 7.97(89–129)	105.40 ± 9.38(89–128)	0.853
Smokers	*N*(%)	106(22.1%)	62(23.1%)	<0.001
SBP (mmHg)	Mean ± SD(range)	136.61 ± 14.62(110–175)	131.61 ± 14.83(110–169)	<0.001
DBP (mmHg)	Mean ± SD(range)	84.50 ± 8.35(70–110)	82.74 ± 8.11(70–100)	0.017
Antihypertensive	*N*(%)	159(33.2%)	83(30.9%)	<0.001
DM	*N*(%)	218(45.5%)	213(79.4%)	0.055
FBS (mg/dL)	Mean ± SD(range)	108 ± 16.16(78–158)	108.27 ± 17.98(79–146)	0.969
HbA_{1c} (%)	Mean ± SD(range)	2.78 ± 3.14(0–9)	4.96 ± 2.68(0–11.6)	<0.001
DDM (years)	Mean ± SD(range)	23.55 ± 29.44(0–120)	46.65 ± 30.06(0–132)	<0.001
Oral hypoglycemia	*N*(%)	204(42.5%)	180(67.2%)	0.001
Insulin therapy	*N*(%)	24(5%)	41(15.3%)	<0.001
T. cholesterol (mg/dL)	Mean ± SD(range)	198.06 ± 35.65(131–294)	243.75 ± 47.48(139–345)	<0.001
HDL-C (mg/dL)	Mean ± SD(range)	48.02 ± 6.96(32–66)	42.94 ± 6.09(33–58)	<0.001
LDL-C (mg/dL)	Mean ± SD(range)	121.04 ± 23.67(80–181)	154.96 ± 30.25(80–212)	<0.001
Triglyceride (mg/dL)	Mean ± SD(range)	151.49 ± 44.24(69–243)	175.68 ± 51.48(78–278)	<0.001
ALT (U/L)	Mean ± SD(range)	49.82 ± 24.06(18–134)	70.40 ± 29.6(21–134)	<0.001
AST (U/L)	Mean ± SD(range)	39.66 ± 17.37(18–94)	52.68 ± 19.14(20–102)	<0.001
MetS	Mean ± SD(range)	2.86 ± 1.07(0–5)	3.16 ± 0.98(1–5)	0.01
MetS	*N*(%)	294(61.4%)	212(79.1%)	<0.001

duration of diabetes mellitus (DDM) was longer. Patients using oral hypoglycemic drugs and insulin therapy were also significantly higher in the NAFLD group (Table 2).

NAFLD patients also had significantly higher levels of cholesterol, LDL-C, triglyceride and liver enzymes and lower levels of HDL-C (Table 2).

Table 3. The frequency of cardiovascular incident and renal impairment in relation to NAFLD.

Variables		NAFLD		*P* value
		No: *N* = 479 (66.2%)	Yes: *N* = 268 (35.8%)	
Cardiovascular accident	*N*(%)	110(23%)	136(50.7%)	<0.001
CHD				
UA	*N*(%)	16(3.3%)	39(14.6%)	<0.001
MI	*N*(%)	21(4.4%)	16(6%)	<0.001
Silent MI	*N*(%)	21(4.4%)	25(9.3%)	<0.001
Revascularization	*N*(%)	40(8.3%)	51(19%)	<0.001
Cerebrovascular				
Ischemic stroke	*N*(%)	38(7.9%)	44(16.4%)	<0.001
Cerebral hemorrhage	*N*(%)	25(5.2%)	24(9%)	<0.001
Protienuria				
Microalbuminuria	*N*(%)	88(18.4%)	88(32.8%)	<0.001
Macroalbuminuria	*N*(%)	14(2.9%)	24(8.9%)	<0.001
eGFR	Mean ± SD(range)	111 ± 28.37(81–154)	96 ± 23.28(64–148)	<0.001

The frequency of MetS and the mean number of MetS risk factors were significantly higher in those with NAFLD (Table 2).

During the follow-up period, 246 (35.8%) patients developed cardiovascular events; 131 (53.2%) patients developed cerebrovascular events; 82 (62.6%) developed ischemic stroke; 49 (37.4%) developed cerebral hemorrhage; 138 (56.1%) developed cardiovascular events; 55 (39.9%) developed UA; 37 (26.8%) developed MI; and 46 (33.3%) developed silent MI. Ninety one (37%) patients underwent revascularization (60 patients for percutaneous revascularization and 31 patients for surgical revascularization).

Cardiovascular events were significantly higher in those with sonographic findings of NAFLD (50.7% vs. 23%, $P < 0.001$) (Table 3).

The baseline characteristics of patients who developed cardiovascular events during the follow-up period were: older age (59.97 ± 10.92 vs. 47.25 ± 8.92 years. $P < 0.001$), more likely to be male (59.3% vs. 43.9%, $P = 0.006$) and more likely to be smokers (24.7% vs. 17.9%, $P = 0.03$). The incidence of DM was significantly higher in those who developed cerebrovascular events during the follow-up period (71.1% vs. 51.1%, $P < 0.001$) with significantly higher HbA_{1c} (4.44 ± 2.98 vs. 3.14 ± 3.16%, $P < 0.001$) and with considerably longer DDM (40.53 ± 31.91 vs. 27.56 ± 30.66 years, $P < 0.001$). Also, the use of oral hypoglycemic drugs was notably higher in these patients (63.4% vs. 45.5%, $P < 0.001$). However, the level of FBS and the number of patients using insulin therapy did not significantly differ between the two groups (108.48 ± 16.70 vs. 107.32 ± 17.08 mg/dl, $P = 0.91$ and 7.4% vs. 11.4%, $P = 0.061$, respectively).

They also had a significantly higher level of cholesterol, LDL-C, triglyceride and liver enzymes ($P < 0.001$ for all), but the level of HDL-C did not significantly differ between the two groups ($P = 0.059$).

The frequency of NAFLD was considerably greater in those who developed cardiovascular events during follow-up (55.3% vs. 26.3%, $P < 0.001$). The frequency and the mean number of MetS risk factors did not significantly differ between the two groups (68.7% vs. 65.9%, $P = 0.44$ and 3 ± 1.08 vs. 2.91 ± 0.98, $P = 0.88$, respectively).

During the follow-up period, 214 (28.6%) patients developed renal impairment, 176 (82.6%) developed microalbuminuria, and 37 (17.4%) developed macroalbuminuria. The mean eGFR was significantly lower in those who developed renal impairment (i.e. protienuria) during the follow-up period.

The frequency of renal impairment was higher in those with sonographic findings of NAFLD. Also, mean eGFR was significantly lower in NAFLD group (96 ± 23.28 vs. 111 ± 28.37, $P < 0.001$) (Table 3).

The baseline characteristics of patients who developed renal impairment during the follow-up period were: older age (52.95 ± 11.97 vs. 50.82 ± 11.04 years. $P = 0.01$), more likely to be smokers (28.5% vs. 20%, $P < 0.001$) and had considerably increased WC (106.78 ± 10.08 vs. 104.60 ± 7.7 cm, $P = 0.022$). The frequency of DM was much higher in those who developed renal impairment during follow-up (98.1% vs. 41.7%, $P < 0.001$) with significantly higher fasting blood sugar (110.77 ± 18.25 vs. 107.02 ± 16.11 mg/dl, $P = 0.035$) and HbA_{1c} (6.29 ± 1.14 vs. 2.47 ± 3.05%, $P < 0.001$) and much longer DDM (67.12 ± 21.26 vs. 17.67 ± 22.84 yrs, $P < 0.001$). The use of oral hypo-

Table 4. Logistic regression in relation to cardiovascular and renal impairment events.

Variables	Cardiovascular events			Renal impairment events		
	Exp (beta)	95%CI	*P* value	Exp (beta)	95%CI	*P* value
Age (years)	1.027	0.65–1.61	0.907	1.006	0.97–1.03	0.670
Gender	1.159	1.13–1.18	0.005	1.147	0.63–1.85	0.646
Weight (kg)	0.983	0.94–1.02	0.377	1.015	0.97–1.05	0.451
BMI (kg/m^2)	0.958	0.85–1.07	0.446	0.972	0.86–1.09	0.633
WC (cm)	1.031	0.99–1.07	0.119	1.009	0.96–1.05	0.707
Smoker (yes vs. no)	0.707	0.37–1.33	0.283	1.319	0.57–3.04	0.112
SBP (mmHg)	1016	0.98–1.04	0.293	1.033	0.99–1.07	0.071
DBP (mmHg)	0.981	0.92–1.03	0.514	0.941	0.87–1.01	0.122
Antihypertensive (yes vs. no)	1.283	0.63–2.61	0.492	1.067	0.41–2.76	0.894
FBS (mg/dL)	0.995	0.98–1.01	0.551	1.013	0.99–1.03	0.163
HbA_{1c} (%)	1.033	0.99–1.07	0.071	0.954	0.74–1.27	0.013
DDM (years)	0.995	0.97–1.01	0.110	1.094	1.07–1.11	0.009
Oral hypoglycemia (yes vs. no)	2.709	0.65–3.27	0.171	0.305	0.04–2.09	0.228
Insulin therapy (yes vs. no)	1.984	0.50–3.82	0.327	0.321	0.05–1.96	0.219
T. cholesterol (mg/dL)	1.014	0.99–1.03	0.061	1.015	1.00–1.02	0.011
HDL-C (mg/dL)	0.982	0.95–1.01	0.237	0.970	0.92–1.02	0.250
LDL-C (mg/dL)	1.003	0.99–1.01	0.024	0.998	0.98–1.01	0.756
Triglyceride (mg/dL)	1.001	0.99–1.01	0.075	0.994	0.98–1.01	0.129
ALT (U/L)	0.999	0.99–1.01	0.806	1.010	0.98–1.03	0.429
AST (U/L)	1.003	0.96–1.04	0.867	0.992	0.96–1.02	0.651
MetS (yes vs. no)	0.800	0.36–1.77	0.127	1.070	0.39–2.93	0.085
MetS (mean)	0.864	0.57–1.30	0.108	0.638	0.39–1.02	0.078
NAFLD (yes vs. no)	5.210	1.93–4.25	<0.001	1.015	1.70–4.02	0.005

glycemic drugs and insulin therapy was higher in those who developed renal impairment during the follow-up period (80.8% vs. 39.6%, $P < 0.001$ and 25.23% vs. 2%, $P < 0.001$, respectively). These patients also had a significantly higher level of cholesterol, LDL-C, triglyceride and liver enzymes ($P < 0.001$). However, the level of HDL-C was much lower in those who developed renal impairment during follow-up ($P < 0.001$).

The incidence of NAFLD was notably higher in patients with renal impairment during follow-up than those without (51.9% vs. 29.3%, $P < 0.001$). The mean number of MetS risk factors was 3.20 ± 0.96 in patients with renal impairment, which is higher than those who did not develop renal impairment during the follow-up period (2.87 ± 1.07, $P = 0.003$).

Correlative analysis

Correlations of cardiovascular and renal impairment events with NAFLD in addition to other risk factors were analyzed by forward logistic regression analysis. NAFLD was the best predictor for cardiovascular and renal impairment as indicated by the highest Exp to odds ratio in both (Table 4).

Discussion

That NAFLD is significantly associated with an increased risk of future cardiovascular and renal impairment events may help to explain underlying mechanisms and may be of clinical importance for undertaking preventive and therapeutic strategies. We have prospectively assessed the prevalence of NAFLD and its association with the increased incidence of CKD and CVD.

We report that 35.8% of the patients who completed the follow-up period had sonographic criteria of NAFLD. Of these, 79.4% had type-2 DM, which supports the results of studies showing NAFLD prevalence in the 15–30% range in the general population, its almost certain increase [13,14], and the higher risk of patients with type-2 diabetes for developing NAFLD as well as fibrosis and cirrhosis. Other studies estimate that approximately 70–75% of patients with type-2 diabetes have NAFLD [11,14].

Our major findings were that NAFLD is associated with and is the best predictor of increased risk for cardiovascular and renal impairment events. These findings are corroborated by a recent study of 10,337 healthy Korean men followed for approximately 3.5 years, showing that mildly elevated serum Gamma glutamyl transaminase (GGT) concentrations, as surrogate markers of NAFLD [14], are associated with an increased risk for CKD [15].

Several cross-sectional studies have demonstrated an association between NAFLD and intima-media thickness and/or plaques of carotid artery that were used as measures of early athero-

sclerosis [5,16]. In a prospective case-control study, Targher et al report that NAFLD is a strong predictor for future cardiovascular events among type-2 diabetic patients [17]. As type-2 diabetes constitutes a very high-risk population for CVD, it was uncertain whether the study could be extrapolated to the general population. In a study of 14,874 middle-aged Finnish patients, mildly elevated GGT levels were independently associated with an increased risk of ischemic stroke in both sexes [18]. Among 7,613 middle-aged British men followed for 11.5 years, elevated GGT levels were independently associated with a significant increase in mortality from all causes and from CHD [19].

Studies conducted by Masahide et al. [20] and Targher et al. [12] reported that both NAFLD and the MetS were predictors of cardiovascular events. Since there is a close association between the MetS – which is a well-known atherogenic condition – and NAFLD, then the mechanisms linking NAFLD with cardiovascular events are at least partly mediated by the atherogenic abnormalities of the MetS. In fact, a correlation between the severity of liver histology of NAFLD and early carotid atherosclerosis has been reported [16], while the association between liver histology and severity of the MetS has been noted as well [21]. In a multivariate analysis based on the model that included NAFLD and the MetS simultaneously as covariates, both Targher et al. [12] and Masahide et al. [20] found that NAFLD but not the MetS retained an independent correlation with cardiovascular events. This suggests that NAFLD is not only a marker of cardiovascular and renal impairment events but may also be involved in their pathogenesis.

The possible mechanisms may include increased oxidative stress, subclinical inflammation, lipid abnormalities, endothelial dysfunction and an abnormal adipocytokine profile [22].

Current understanding of the pathogenesis of NAFLD implies that lipids accumulate in hepatocytes, mainly in the form of triacylglycerol, in the presence of insulin resistance. The biological mechanisms potentially responsible for accelerated atherogenesis in NAFLD may either have origins in the visceral adipose tissue, in the liver, or in the liver as the target of systemic abnormalities [23].

A leading role in the development of insulin resistance, inflammation and NAFLD is likely to be played by excess adiposity, including ectopic fat deposition. This ectopic fat is a source of multiple factors involved in atherogenesis, such as NEFA, hormones, pro-inflammatory cytokines and adipocytokines [24].

Moreover, ectopic fat deposition in visceral adipose depots and heart increases the expression of several pro-inflammatory mediators leading to local macrophage infiltration and associated systemic chronic inflammation [24,25].

The potential implications of our findings for patient care are that the detection of NAFLD during ultrasound examination especially in people with type-2 diabetes should alert clinicians to the coexistence or future development of other complications (including renal impairment and CVD). Thus, identifying people with NAFLD would highlight a subgroup of individuals who have type-2 diabetes and who should be targeted with intensive therapy to decrease the risk for developing CRD and CVD events.

Limitations

(1) We used an eGFR instead of a directly measured GFR to define renal impairment. A recent review reported that current GFR estimates had greater inaccuracy in populations without known chronic renal impairment than in those with the disease. However, current GFR estimates facilitate the detection, evaluation, and management of CRD, and many organizations recommend the use of equations with eGFR for the evaluation of renal function [8].

(2) NAFLD diagnosis was based on ultrasound imaging and exclusion of other secondary causes of chronic liver disease but was not confirmed by liver biopsy. It is known that none of the radiologic features can distinguish between non-alcoholic steatohepatitis and other forms of NAFLD and that only liver biopsy can assess the severity of damage and the prognosis. However, liver biopsy would be impossible to perform routinely, and liver ultrasonography is by far the most common way of diagnosing NAFLD in clinical practice. It has a sensitivity of 89% and a specificity of 95% in detecting moderate and severe steatosis, but this sensitivity is reduced when hepatic fat infiltration upon liver biopsy is <33%. Thus, some of those classified as having no NAFLD in this study could have underlying NAFLD, despite normal serum liver enzymes and a negative ultrasonography [13,14].

Conclusion

NAFLD is a strong predictor of CVD and renal impairment. Clinical implications conclude that ultrasonography of the liver, as a non-invasive and easily applicable test, may be a useful tool for risk evaluation of cardiovascular and renal impairment events. In addition to lifestyle modifications to reduce fat deposition, patients with NAFLD may need further exploration for risk factors of cardiovascular and renal diseases.

References

[1] Targher G, Marra F, Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? Diabetologia 2008;51(11):1947–53.
[2] Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol 2004;19(8):854–8.
[3] Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med 2005;143(10):722–8.
[4] Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men: role of visceral fat accumulation. Diab Care 2004;27(10):2498–500.
[5] Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. Arterioscler Thromb Vasc Biol 2005;25(5):1045–50.
[6] O'Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. Am J Cardiol 2002;90(10C):18L–21L.
[7] Targher G, Chonchol M, Bertolini L, Rodella S, Zenari L, Lippi G, et al. Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease. J Am Soc Nephrol 2008;19(8):1564–70.
[8] Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. N Engl J Med 2006;354(23):2473–83.
[9] Fioretto P, Bruseghin M, Berto I, Gallina P, Manzato E, Mussap M. Renal protection in diabetes: role of glycemic control. J Am Soc Nephrol 2006;17(4 Suppl 2):S86–9.
[10] Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139(2):137–47.
[11] Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diab Care 2007;30(5):1212–8.
[12] Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med 2007;24(1):1–6.
[13] Day CP. Non-alcoholic fatty liver disease: current concepts and management strategies. Clin Med 2006;6(1):19–25.
[14] Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diab Care 2007;30(3):734–43.
[15] Ryu S, Chang Y, Kim DI, Kim WS, Suh BS. Gamma-glutamyltransferase as a predictor of chronic kidney disease in non-hypertensive and non-diabetic Korean men. Clin Chem 2007;53(1):71–7.
[16] Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, et al. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diab Care 2006;29(6):1325–30.
[17] Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005;54(12):3541–6.
[18] Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31(8):1851–5.
[19] Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischaemic heart disease and all causes. Am J Epidemiol 1995;142(7):699–708.
[20] Masahide H, Takao K, Noriyuli T, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. Gastroenterology 2007;13(10):1579–84.
[21] Ryan MC, Wilson AM, Slavin J, Best JD, Jenkins AJ, Desmond PV. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. Diab Care 2005;28(5):1222–4.
[22] Santoliquido A, Di Campli C, Miele L, Gabrieli ML, Forgione A, Zocco MA, et al. Hepatic steatosis and vascular disease. Eur Rev Med Pharmacol Sci 2005;9(5):269–71.
[23] Targher G, Bertolini L, Rodella S, Lippi G, Franchini M, Zoppini G, et al. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring) 2008;16(6):1394–9.
[24] Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006;444(7121):875–80.
[25] Adiels M, Taskinen MR, Borén J. Fatty liver, insulin resistance, and dyslipidemia. Curr Diab Rep 2008;8(1):60–4.