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ORIGINAL ARTICLE

Prospective Study

Fatty liver disease: Disparate predictive ability for cardiometabolic risk and all-cause mortality

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Abstract

AIM: To assess the association of a surrogate of fatty liver disease (FLD) with incident type-2 diabetes, coronary heart disease, and all-cause mortality.

METHODS: In a prospective population-based study on 1822 middle-aged adults, stratified to gender, we used an algorithm of fatty liver index (FLI) to identify associations with outcomes. An index $\geqslant$ 60 indicated the presence of FLD. In Cox regression models, adjusted for age, smoking status, high-density lipoprotein cholesterol, and systolic blood pressure, we assessed the predictive value of FLI for incident

diabetes, coronary heart disease (CHD), and all-cause mortality.

RESULTS: At a mean 8 year follow-up, 218 and 285 incident cases of diabetes and CHD, respectively, and 193 deaths were recorded. FLD was significantly associated in each gender with blood pressure, total cholesterol, apolipoprotein B, uric acid, and C-reactive protein; weakly with fasting glucose; and inversely with high-density lipoprotein-cholesterol and sex hormone-binding globulin. In adjusted Cox models, FLD was (with a 5-fold HR) the major determinant of diabetes development. Analyses further disclosed significant independent prediction of CHD by FLD in combined gender [hazard ratio (HR) = 1.72, 95% confidence interval (CI): 1.17-2.53] and men (HR = 2.35, 95%CI: 1.25-4.43). Similarly-adjusted models for all-cause mortality proved, however, not to confer risk, except for a tendency in prediabetics and diabetic women.

CONCLUSION: A surrogate of FLD conferred significant high risk of diabetes and coronary heart disease, independent of some metabolic syndrome traits. All-cause mortality was not associated with FLD, except likely in the prediabetic state. Such a FLI may reliably be used in epidemiologic studies.

Key words: All-cause death; Coronary heart disease; Hepatic steatosis; Metabolic syndrome; Turkish adult risk factor study

Core tip: We prospectively assessed in 1822 adults the association between a validated surrogate of fatty liver disease (FLD) and the incidence of type-2 diabetes, coronary heart disease (CHD), and all-cause mortality by stratifying to gender and using adjusted Cox regression models. At a mean 8 year follow-up, FLD was the major determinant of developing diabetes and was a significant predictor of CHD. Similarly-adjusted models for all-cause mortality did not confer risk, except for slightly in prediabetics and diabetic women. Involvement of circulating lipoprotein(a) in autoimmune activation may be an underlying mechanism. Such a FLD surrogate may be used in epidemiologic studies.

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INTRODUCTION

Steatohepatitis designates fatty infiltration and inflammation of the liver and has features closely associated with the metabolic syndrome (MetS)[1]. Liver biopsy, ultrasonography, serum liver enzymes and, more recently, an algorithm-based surrogate have been commonly used in identifying the presence of non-alcoholic fatty liver disease (NAFLD) and its relationship to adverse outcomes. As a growing public health issue, NAFLD has been demonstrated in the past decade to be associated with MetS[2], type-2 diabetes[3-5], cardiovascular events[6-9], and chronic kidney disease[10-12]. A complex bidirectional relationship between the development of diabetes and progression to non-alcoholic steatohepatitis promoting hepatic fibrogenesis and insulin resistance has been identified[1]. Risk of all-cause death is also predicted by NAFLD[13-15], but conflicting results have been reported[9,16] regarding overall and cause-specific mortality. Despite an increased association with independent cardiovascular disease (CVD) prevalence and NAFLD in United States adults (The National Health and Nutrition Examination Survey (NHANES)-Ⅲ), NAFLD did not predict mortality over a 14 year period[16].

The complex inter-relationships between NAFLD, visceral obesity, and insulin resistance[17] require further elucidation. Since most of the prospective studies on NAFLD have been performed in population samples of Western Europe, United States, and East Asia; investigation of different ethnicities is necessary to clarify better variation in the relationship. The controversial relationship between NAFLD and risk of overall mortality, as compared to that of diabetes and CVD, may be highly relevant for the pathophysiology of the associations and possibly related to ethnic differences.

Turkish adults are prone to MetS[18], diabetes mellitus[19], and chronic hepatitis. Cardiovascular risk profiles are characterized by a high prevalence of abdominal obesity in males, overall obesity in females, low high-density lipoprotein (HDL)-cholesterol, high triglyceride, and intermediate total cholesterol levels. Current smoking protects against abdominal obesity[18]. One-fifth of non-diabetic Turks exhibit impaired fasting glucose[20]. On one hand, evidence is growing that microbiota contribute to the pathogenesis of insulin resistance, abdominal obesity, and progression of NAFLD[1,21]. On the other hand, autoimmune activation based on enhanced proinflammatory state may be a common mechanism underlying these diseases in middle-aged and elderly Turkish adults[22]. Prospective evaluation of the same sample regarding the relationships among fatty liver disease (FLD), cardiometabolic disease risk, and all-cause death might reveal novel information.

Clinical and epidemiological studies using an algorithm-based surrogate of FLD to investigate related outcomes have been published[13,23]. We, therefore, aimed in this study to assess prospectively and simultaneously the impact of an algorithm-derived surrogate of FLD on diabetes, CHD, and overall

mortality in a population-based sample representative of middle-aged Turkish adults at a lengthy follow-up period.

MATERIALS AND METHODS

Population sample

The Turkish Adult Risk Factor Study is a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey that has been carried out periodically, almost biennially, since 1990 in 59 communities scattered throughout all geographical regions of the country[24]. It comprises a representative sample of the Turkish adult population. Serum γ-glutamyltransferase (GGT) determinations were made in the 2003/04 survey, during which GGT was measured in all 1822 participants who attended the survey (examination in 60%) out of an eligible 3037 participants. Follow-up extended to the 2012/13 survey.

The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. All individuals gave written consent to participation. Data were obtained by history questionnaire, physical examination of the cardiovascular system, sampling of blood, and recording of a resting electrocardiogram.

Measurements of risk variables

Blood pressure (BP) was measured in the sitting position on the right arm, and the mean of two recordings at least 5 min apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00, Basel, Switzerland) with the subject standing and wearing only underwear at the level midway between the lower rib margin and the iliac crest. Self-reported cigarette smoking was categorized into never smokers, former smokers (discontinuance for 3 mo or longer), and current smokers (regularly 1 or more cigarettes daily). Anyone who consumed alcohol at least once a week was considered a user of alcoholic drinks.

Biochemical parameters were assayed in a central laboratory. Blood samples were shipped to Istanbul and stored in deep-freeze at -75 ℃ until analyzed. Serum concentrations of total and HDL-cholesterol (directly without precipitation) and triglycerides were determined using enzymatic kits from Roche Diagnostics with a Hitachi 902 analyzer (Tokyo, Japan). Concentrations of sex hormone-binding globulin (SHBG) and total testosterone were determined by the electrochemiluminescence immunoassay ECLIA on Roche Elecsys 2010 (Roche Diagnostics). Serum concentrations of apolipoprotein (apo) A-I, apo B, lipoprotein (Lp)(a) and high-sensitivity C-reactive protein (CRP) was measured with nephelometry by BN ProSpec analyzer (Siemens Healthcare Diagnostics, Munich, Germany). Serum GGT activity was assayed by Cobas c 501 analyzer (Roche Diagnostics GmbH). Plasma fibrinogen was assayed by the modified Clauss method using Fibrintimer Ⅱ coagulometer and Multifibren U kit (Siemens Healthcare Diagnostics).

Definitions

Individuals with diabetes were diagnosed with criteria of the American Diabetes Association[25], namely plasma fasting glucose ≥ 126 mg/dL (or 2 h postprandial glucose > 200 mg/dL) and/or the current use of diabetes medication. Prediabetes was identified by fasting glucose of 100-125 mg/dL. Individuals with MetS were identified when three out of the five criteria of the National Cholesterol Education Program (ATP Ⅲ) were met, modified for prediabetes and for abdominal obesity using ≥ 95 cm as cutoff point in men, as assessed in the Turkish Adult Risk Factor study[18]. For women, the cutoff point ≥ 88 cm was retained based on our own prospective analyses. Homeostatic model assessment (HOMA) was estimated by the standard equation using fasting glucose and insulin levels.

Identification of CHD was based on the presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardiogram (ECG)[26], or a history of myocardial revascularization. Typical angina and, in women, age > 45 years were prerequisite for a diagnosis when angina was isolated. ECG changes of "ischemic type" greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively. Death was identified *via* the information from first-degree relatives, records of local health personnel, and/or the nation-wide Identity Participation System.

Estimation of hepatic steatosis by an algorithm

We used a previously reported algorithm to detect fatty liver based on body mass index (BMI), waist circumference, triglycerides, and GGT[27] using the following equation.

$$= (e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745})/(1 + e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745}) \times 100$$

In agreement with the authors, we used an index < 30 to indicate absence of FLD, ≥ 60 for presence of FLD, and 30-59 for probable presence of FLD.

Data analysis

Descriptive parameters are shown as mean ± standard deviation or in percentages. Two-sided *t*-tests and Pearson's χ^2 tests were used to analyze the differences in means and proportions between groups. Due to the skewed distribution, log-transformed values were used for triglycerides, CRP, GGT, and Lp(a) for analyses. Analysis of variance (ANOVA) was used to detect difference across multiple groups, whereby a difference between two groups was determined using Bonferroni corrections. Estimates [and 95% confidence

Table 1 Baseline characteristics of the study sample, by gender and fatty liver disease categories (n = 1822)

		Men (n = 877)				Women (n = 945)			
	n	No NAFLD mean ± SD n = 198	Probable NAFLD mean ± SD n = 263	NAFLD mean ± SD n = 416	ANOVA P value	No NAFLD mean ± SD n = 252	Probable NAFLD mean ± SD n = 241	NAFLD mean ± SD n = 452	ANOVA P value
Age, yr	1822	52.8 ± 12.7	53.4 ± 12	51.7 ± 9.3	0.16	47.5 ± 10.3	51.9[2] ± 10.5	54.8 ± 9.9	< 0.001
Waist circumference, cm	1811	83.3 ± 8.1	92.4[2] ± 7.4	100.6 ± 9	< 0.001	79 ± 9	89[2] ± 7.5	99.4 ± 9.7	< 0.001
Body mass index, kg/m^2	1808	24.1 ± 3.3	27.2[2] ± 2.7	30.9 ± 4	< 0.001	26.2 ± 4.4	30.2[2] ± 3.8	34.5 ± 5.5	< 0.001
Systolic BP, mmHg	1822	120 ± 18	126[2] ± 21	132.5 ± 23	< 0.001	121 ± 19	132[2] ± 24	142 ± 27	< 0.001
Diastolic BP, mmHg	1822	75 ± 11	80[2] ± 11	85.6 ± 13.5	< 0.001	77 ± 12	83[2] ± 13	88 ± 14	< 0.001
Total cholesterd, mg/dL	1822	168 ± 34	178[2] ± 34	192 ± 39	< 0.001	174 ± 34	190[2] ± 37	201 ± 41	< 0.001
LDL cholesterd, mg/dL	1424	108 ± 32	112 ± 29	116[2] ± 33	0.037	105[2] ± 28	120 ± 33	126 ± 36	< 0.001
HDL cholesterd mg/dL	1820	42[2] ± 12	37 ± 11	35.3 ± 11	< 0.001	47.7 ± 13	46 ± 13	43[2] ± 12	< 0.001
Lipoprotein(a)[1], mg/dL	1186	8.3 × 2.74	7.76 × 2.77	9.12 × 3.14	0.34	11.8 × 2.76	12.7 × 3.13	10.47 × 2.9	0.11
Fasted glucose, mg/dL	1822	99 ± 27	100 ± 30	104 ± 37	0.099	97 ± 19	100 ± 31	105[2] ± 35	0.001
F. triglyceride[1], mg/dL	1413	95 × 1.48	126[2] × 1.55	174 × 1.72	< 0.001	87 × 1.47	110[2] × 1.53	148 × 1.69	< 0.001
γ-glutamyl transferase[1], U/L	1822	17 × 1.48	21.9[2] × 1.59	37.2 × 1.87	< 0.001	12.9 × 1.62	15.8[2] × 1.65	24.5 × 1.87	< 0.001
Fasted insulin, mIU/L	1636	6.94 × 2.36	8.00 × 2.00	11.0[2] × 2.02	< 0.001	6.98 × 1.87	8.75[2] × 1.97	11.0 × 1.87	< 0.001
Apolipoprotein A-I, g/L	1740	1.40 ± 0.24	1.35 ± 0.24	1.346[2] ± 0.24	0.042	1.55 ± 0.30	1.51 ± 0.26	1.50 ± 0.28	0.082
Apolipoprotein B, g/L	1759	0.94[2] ± 0.26	1.05 ± 0.19	1.09 ± 0.29	< 0.001	1.03 ± 0.27	1.04 ± 0.28	1.13[2] ± 0.31	< 0.001
Creatinine, mg/dL	1504	0.937± 0.17	0.976 ± 0.26	1.01 ± 0.37	0.023	0.80 ± 0.42	0.80 ± 0.44	0.805 ± 0.20	0.98
SHBG[1], nmol/L	1304	43.8 × 1.7	39 × 1.6	33.4[2] × 1.63	< 0.001	55.4 × 1.7	46.2[2] × 1.7	48.2 × 1.73	< 0.001
Testosterone[1], nmol/L	1412	19.2 × 4.2	15.8 × 3.3	15.1 × 3.3	0.16	0.79 × 3.66	0.70 × 3.1	0.79 × 3.8	0.50
Uric acid, mg/dL	1821	5.51 ± 1.3	5.82 ± 1.3	6.36[2] ± 1.6	< 0.001	4.23 ± 1.2	4.6[2] ± 1.1	5.15 ± 1.4	< 0.001
C-reactive protein[1], mg/L	1788	1.64[2] × 3.13	1.93 × 3.0	2.39 × 2.75	< 0.001	1.41 × 3.15	2.53[2] × 2.8	3.75 × 2.65	< 0.001
Current; past smokers, %	1817	59.4[2]; 18.8	47.5; 23.4	46.1; 25.4	0.037	27.4[2] ; 3.2	14.1; 3.3	10.2; 4.4	< 0.001
CHD prevalence, n (%)	1820	5 (2.5)	11 (4.2)	31 (7.5[2])	0.02	6 (2.4)	11 (4.6)	29 (6.4)	0.056

[1]Log-transformed values, SD range is obtained by dividing or multiplying with the given SD; [2]Denote significant difference, from the remaining two groups, those in italics borderline significant difference. NAFLD: Non-alcoholic fatty liver disease; CHD: Coronary heart disease; LDL: Low density lipoprotein; BP: Blood pressure; HDL: High-density lipoprotein; SHBG: Sex hormone-binding globulin.

intervals (CI)] for relative risk (RR) of the dependent variable were obtained by use of Cox proportional hazard regression analyses in models that controlled for potential confounders, including cardiovascular risk factors and HOMA. A value of $P < 0.05$ on the two-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, IL, United States).

RESULTS

The study sample consisted of 1822 middle-aged adults (877 men and 945 women). CHD in 93 and diabetes in 103 subjects were identified at baseline. FLD was detected in 48% and there was no FLD in one-quarter of the sample at baseline. Follow-up averaged 8.0 ± 2.7 and 7.8 ± 2.8 years for mortality and incident CHD, respectively, with similar gender distribution (P = 0.52), yielding 14540 person-years for mortality. Fourteen percent of men and 1% of women were categorized as alcohol users. Six percent of males used alcohol at a daily mean equivalent to 19 mL ethanol and the remainder much less. Liver diseases of specific causes were not reported.

Table 1 shows the characteristics of the study sample at baseline, stratified to gender and FLD status. Significant differences in values across the sex-specific categories are noted in virtually all variables, except creatinine and testosterone, as well as age, fasting glucose, and Lp(a) in men. Notably, MetS traits were increased in subjects with FLD (blood pressure, HDL-cholesterol and glucose [borderline in males]), and insulin, apoB, SHBG, uric acid, and CRP levels were elevated as well. A significantly higher proportion of participants with no FLD were current smokers.

Pearson correlations of the fatty liver index (FLI) with relevant variables in males and females are provided in Table 2. BP, fasting insulin, total cholesterol, apoB, uric acid, and CRP were positively correlated, and SHBG and HDL-cholesterol were inversely correlated, in each gender. Age and fasting glucose were positive correlates in women alone, and alcohol usage was a positive correlate in men, while apoA-I, Lp(a), creatinine, and testosterone were not correlated with the FLI.

Kaplan-Meier plots were constructed for survival and survival free of diabetes/CHD, as seen in Figure 1. These demonstrated significantly lower survival free of diabetes and of incident CHD for participants with FLD at baseline. Subjects categorized as probable FLD also separated from those with no FLD in regard to CHD. However, overall survival curves were similar in the three groups.

Table 3 displays findings of Cox regression analyses for the prediction by FLD of diabetes mellitus and CHD, adjusted for five other conventional cardiovascular risk factors and stratified to gender. It is evident that FLD was (with a 5-fold relative risk) the major determinant of the development of diabetes, besides (inversely) serum uric acid. In regard to incident CHD, FLD proved

Table 2 Pearson correlations of fatty liver index (n = 1822) with relevant variables

	Men		Women	
	n	*r*	*n*	*r*
Age	877	-0.04	945	0.28
Body mass index	869	0.71	939	0.68
Systolic BP	877	0.27	945	0.38
Diastolic BP	877	0.34	945	0.36
Total cholesterol	877	0.27	945	0.28
HDL cholesterol	877	-0.22	945	-0.19
C-reactive protein[1]	864	0.16	924	0.41
Apo A-I	841	-0.08	899	-0.07
Apo B	844	0.18	915	0.19
Lipoprotein(a)[1]	549	0.02	637	-0.05
Fasting glucose	877	0.09	945	0.12
Sex h-b globulin[1]	623	-0.23	681	-0.26
Testosterone[1]	642	-0.08	708	0.01
Uric acid	869	0.23	938	0.20
Creatinine	735	0.04	785	0.00
Fasting insulin	775	0.33	861	0.33
Alcohol usage	873	0.11	941	-0.06

[1]Coefficients in bold denote $P \leq 0.002$, in italics $P < 0.05$. BP: Blood pressure; HDL: High-density lipoprotein.

to be a significant predictor [hazard ratio (HR) = 1.72, 95%CI: 1.17-2.53] independent of age, presence of diabetes, systolic BP, and current smoking.

With respect to overall mortality, however, age, diabetes, and -in non-diabetic men- current smoking were determinants, whereas FLD and HOMA index did not emerge as independent predictors (Table 4). We further analyzed similar regression models for mortality stratifying to glucose categories (normoglycemia, impaired fasting glucose and diabetes). Tendency to excess independent mortality risk for FLD (HR = 2.69, 95%CI: 0.42-17) and HOMA index was restricted to prediabetic men in whom age had an exceptionally high HR. In women - albeit non-significant - increasing HRs were noted for both FLD and HOMA index from normoglycemia to diabetes categories.

In order to assess whether some of the components of the FLI, rather than the overall algorithm, were determinants of outcomes, we analyzed the Cox models separately with the four components (Table 5). These demonstrated a greater impact of triglycerides and GGT levels and - to some extent - of abdominal obesity but not of overall obesity, which interestingly and significantly protected against risk of death.

Risk of death related to the three glucose categories is schematized in Figure 2.

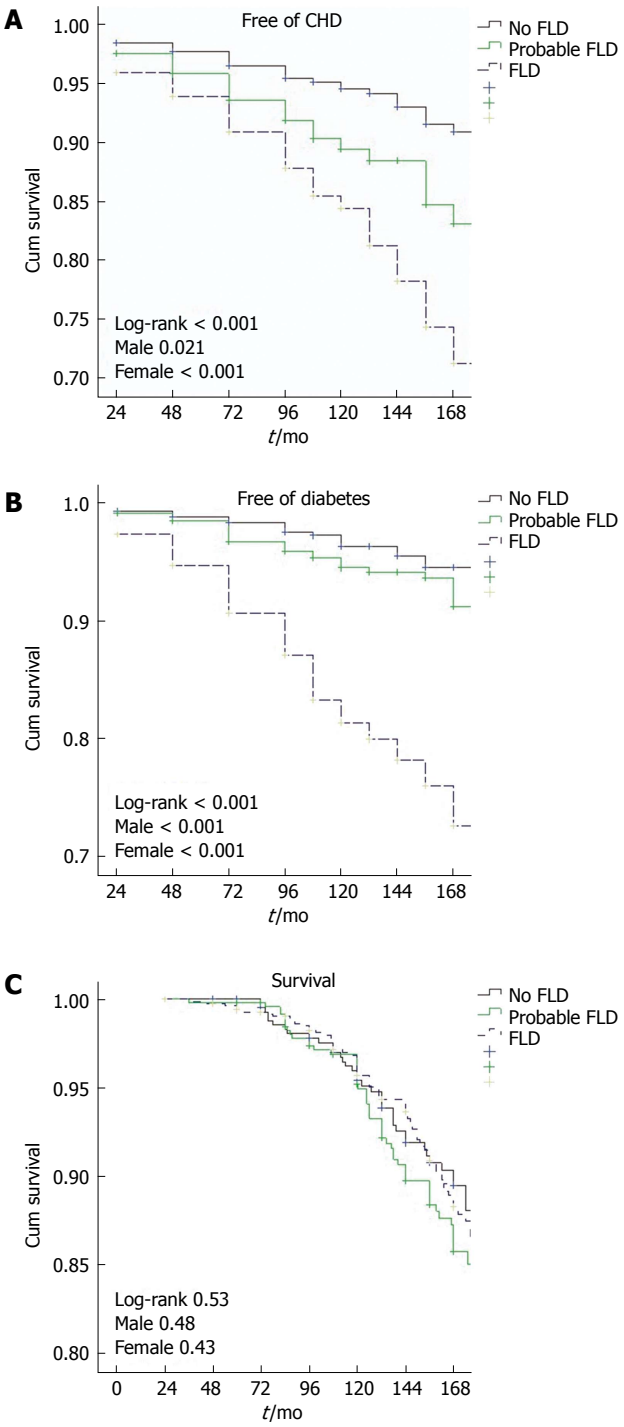

Figure 1 Diagram depicts Kaplan-Meier plots in the whole sample for survival and (exclusive of those with diabetes/coronary heart disease) survival free of diabetes/coronary heart disease. Significantly (Log-rank < 0.001) lower survival free of diabetes and of incident CHD are noted for participants with FLD at baseline. Subjects categorized as probable FLD separated from those with no FLD in regard to CHD. However, no significant difference was elicited (Log-rank 0.53) with respect to mortality. Log-rank values were similar in the sexes. BP: Blood pressure; CHD: Coronary heart disease; FLD: Fatty liver disease.

DISCUSSION

In this follow-up analysis of a cohort representative of middle-aged and elderly Turkish adults, we examined the independent predictive value of FLD, derived from a FLI, for the risks of type-2 diabetes, CHD, and overall mortality. The FLI was correlated with MetS traits as well as with markers of enhanced low-grade systemic inflammation (total cholesterol, apoB, uric acid, CRP, and SHBG levels). FLD was a powerful predictor of incident diabetes and disclosed a nearly 2-fold relative risk for CHD compared to participants without FLD.

Table 3 Adjusted Cox regression analyses of fatty liver disease for prediction of type-2 diabetes and incident coronary heart disease, by gender (and diabetic status)

	Total		Men		Women	
	HR	95%CI	HR	95%CI	HR	95%CI
Diabetes *n* =	203/1490[1]		110/707[1]		93/783[1]	
Gender, female	0.82	0.56; 1.20				
Age, 11 yr[2]	1.14	0.97; 1.34	1.13	0.90; 1.41	1.14	0.90; 1.46
Current smoking, *n* = 480	1.38	0.94; 2.00	1.35	0.84; 2.16	1.39	0.74; 2.69
Former smoking, *n* = 183	1.32	0.83; 2.08	1.22	0.72; 2.06	1.98	0.72; 5.48
HDL-cholesterol, 12 mg/dL	0.91	0.78; 1.06	0.96	0.77; 1.21	0.89	0.71; 1.10
Systolic BP, 25 mmHg	1.16	1.00; 1.38	1.28	1.03; 1.60	1.08	0.88; 1.35
Uric acid, 1.3 mg/dL	0.87	0.76; 0.996	0.81	0.67; 0.97	0.94	0.76; 1.15
Probable FLD, *n* = 423	1.44	0.80; 2.57	1.57	0.72; 3.43	1.28	0.52; 3.12
FLD, *n* = 673	4.93	2.98; 8.14	4.80	2.40; 9.59	5.33	2.53; 11.2
DM incid. per 1000 person-yr	16.6		18.8		14.5	
CHD: Diabetic sample *n* =	88/409[1]		45/192[1]		43/217[1]	
Gender, female	0.95	0.55; 1.63				
Age, 11 years	1.18	0.94; 1.49	1.27	0.90; 1.80	1.10	0.79; 1.56
Current smoking	1.12	0.64; 1.95	1.46	0.68; 3.15	0.66	0.25; 1.75
Former smoking	1.13	0.56; 2.31	1.36	0.59; 3.13	1.12	0.15; 8.52
Alcohol usage, yes/no	0.50	0.12; 2.10	0.58	0.14; 2.45		No user
HDL-cholesterol, 12 mg/dL	0.78	0.61; 1.00	0.90	0.62; 1.28	0.69	0.48; 0.99
Systolic BP, 25 mmHg	0.95	0.72; 1.28	0.98	0.60; 1.60	0.93	0.65; 1.31
Uric acid, 1.3 mg/dL	0.98	0.79: 1.23	0.73	0.54: 0.999	1.35	0.99: 1.84
Probable FLD	1.45	0.66; 3.18	1.68	0.56; 5.05	1.32	0.42; 4.11
FLD	3.59	1.78; 7.23	4.61	1.72; 12.4	3.12	1.17; 8.35
CHD inciden. per 1000 person-yr	25.3		27.4		23.4	
CHD: Whole sample *n* =	237/1505[1]		104/716		133/789[1]	
Gender, female	1.34	0.96; 1.86				
Age, 11 yr	1.48	1.27; 1.71	1.54	1.26; 2.00	1.43	1.17; 1.73
Current smoking	1.50	1.06; 2.13	1.80	1.12; 2.90	1.13	0.64; 1.98
Former smoking	1.02	0.64; 1.63	0.92	0.51; 1.64	1.82	0.79; 4.17
Alcohol usage, yes/no	0.80	0.37; 1.74	0.79	0.36; 1.75		Too few
HDL-cholesterol, 12 mg/dL	0.90	0.78; 1.02	1.04	0.84; 1.28	0.81	0.69; 0.98
Systolic BP, 25 mmHg	1.25	1.08; 1.42	1.31	1.12; 1.27	1.25	1.05; 1.45
Presence of diabetes	1.44	0.98; 2.13	1.81	1.04; 3.17	1.13	0.65; 1.95
Probable FLD	1.26	0.83; 1.92	1.79	0.92; 3.47	0.99	0.57; 1.73
FLD	1.72	1.17; 2.53	2.35	1.25; 4.43	1.42	0.86; 2.35
CHD incid. per 1000 person-yr	18.9		17.5		19.7	

[1]Number of cases/number at risk; [2]Referent was no FLD (*n* = 393 in the model for CHD). Mean age at baseline was 52.1 yr. Prevalent diabetes/coronary diseases were excluded. HDL: High-density lipoprotein; FLD: Fatty liver disease; CHD: Coronary heart disease; BP: Blood pressure.

All-cause mortality, however, was not independently related to baseline FLD, or to HOMA index, except for disclosing a tendency in prediabetic men and a tendency in women increasing in categories from normoglycemia to diabetes. These findings are in agreement with most previous reports and -regarding mortality- with studies on general population samples. We suspect the discrepancy between the relationship to outcomes (mortality *vs* cardiometabolic risk) in subjects with FLD is a consequence of (gender-modulated) circulating Lp(a) levels.

Correlation of FLI with MetS traits and low-grade inflammation markers

The close association between impaired glucose regulation and lipid metabolism with NAFLD is widely recognized[28]. It has been proposed that fatty liver represents a (novel) component of the MetS[2]. Correlation of the FLI with MetS traits in the present study is in line with this and other reports. The index was also significantly correlated with serum apoB, uric acid, and CRP and inversely correlated with circulating SHBG-all markers of proinflammatory state in our experience. Hence, male and female participants identified with FLD harbored both MetS components and markers of enhanced subclinical inflammation.

Prediction of diabetes and CHD by FLD

In these middle-aged and elderly adults, FLD prevailed in 48%, a substantially higher prevalence than in other population samples. In a slightly younger adult sample from the United States, ultrasonography-defined NAFLD prevalence was reported as 19.5%[16]. Current participants with FLD likely represent, moreover, a higher degree of fat accumulation and inflammation in the liver, as may be assessed from stronger HRs associated with incident cardiometabolic risk. NAFLD prevailed at a lower rate in other reports[4,5] as well.

We confirmed results of previous prospective studies documenting significant prediction of type-2

Table 4 Adjusted Cox regression analyses of fatty liver disease for prediction of overall mortality, by gender and diabetic status

	Total		Men		Women	
	HR	95%CI	HR	95%CI	HR	95%CI
Diabetic sample *n* =	30/118[1]		20/59[1]		10/59[1]	
Gender, female	0.71	0.25; 2.00				
Age, 11 yr	2.74	1.43; 5.22	2.61	1.19; 5.73	3.48	1.02; 12.0
Current *vs* non-smoker	0.94	0.30; 3.02	1.38	0.37; 5.18	*n* = 2	protecting
Former smoking, *n* = 170	1.17	0.40; 3.40	2.20	0.61; 7.85	*n* = 2	Too few
HDL-cholesterol, 12 mg/dL	0.81	0.55; 1.20	0.72	0.41; 1.24	0.77	0.43; 1.36
Systolic BP, 25 mmHg	1.16	0.74; 1.81	0.82	0.40; 1.72	1.25	0.62; 2.60
HOMA index, 2-fold	1.15	0.89; 1.49	1.03	0.75; 1.41	1.47	0.95; 2.27
Probable FLD, *n* = 25	0.48	0.15; 1.55	0.35	0.09; 1.34	*n* = 12	risk-
FLD, *n* = 66	0.74	0.24; 2.24	0.72	0.20; 2.57	*n* = 36	conferring
Death rate per 1000 person-yr	30.2		38.2		22.4	
Prediabetic sample[2] *n* =	32/268[1]		17/119[1]		15/149[1]	
HOMA index, 2-fold	1.25	0.93; 1.68	1.33	0.80; 2.23	1.32	0.87; 2.00
Probable FLD *n* = 57	1.05	0.25; 4.40	0.70	0.10; 4.77	1.19	0.10; 14.5
FLD *n* = 116	2.07	0.52; 8.19	2.69	0.42; 17.0	1.30	0.12; 14.7
Death rate per 1000 person-yr	14.0		17.2		11.8	
Normoglycemic sample *n* =	89/1268[1]		54/610[1]		35/658[1]	
Gender, female	0.77	0.42; 1.40				
Age, 11 yr	3.76	2.85; 4.97	3.91	2.69; 5.68	3.41	2.24; 5.17
Current *vs* never smoking	2.39	1.27; 4.51	2.99	1.36; 6.56	0.98	0.22; 4.38
Former smoking, *n* = 170	1.04	0.46; 2.34	1.16	0.47; 2.87	*n* = 15	Too few
HDL-cholesterol, 12 mg/dL	1.05	0.84; 1.31	1.07	0.78; 1.46	1.07	0.78; 1.51
Systolic BP, 25 mmHg	1.03	0.80; 1.31	1.13	0.80; 1.64	0.98	0.67; 1.38
HOMA index, 2-fold	1.02	0.88; 1.17	1.10	0.94; 1.29	0.79	0.62; 1.007
Probable FLD *n* = 312	0.89	0.47; 1.68	0.55	0.24; 1.31	2.02	0.75; 5.39
FLD *n* = 500	0.68	0.34; 1.36	0.58	0.24; 1.40	0.96	0.32; 2.88
Death rate per 1000 person-yr	8.1		10.0		6.3	
Whole sample *n* =	151/1654[1]		91/788[1]		60/866[1]	
Gender, female	0.73	0.46; 1.17				
Age, 11 yr[3]	3.38	2.69; 4.19	3.48	2.60; 4.65	3.34	2.36; 4.74
Current *vs* never smoking, *n* = 414	1.67	1.03; 2.70	2.01	1.13; 3.57	0.96	0.29; 3.17
Former smoking, *n* = 170	0.92	0.52; 1.64	0.99	0.52; 1.88	*n* = 22	Too few
Alcohol usage, yes/no, *n* = 116	0.84	0.37; 1.90	0.73	0.32; 1.67	*n* = 2	Too few
HDL-cholesterol, 12 mg/dL	1.02	0.87; 1.11	1.09	0.85; 1.38	0.94	0.73; 1.22
Systolic BP, 25 mmHg	1.03	0.86; 1.25	1.00	0.78; 1.31	1.08	0.84; 1.42
Prediabetes, *n* = 220	1.30	0.82; 2.07	1.08	0.56; 2.09	1.73	0.89; 3.35
Presence of diabetes, *n* = 104	2.70	1.73; 4.22	2.22	1.52; 4.86	2.76	1.32; 5.76
HOMA index, 2-fold	1.08	0.97; 1.21	1.12	0.99; 1.27	0.98	0.80; 1.20
Probable FLD, *n* = 394	0.79	0.48; 1.31	*0.58*	0.31; 1.11	1.42	0.57; 3.50
FLD *n* = 681	0.84	0.50; 1.39	0.83	0.44; 1.56	1.03	0.41; 2.59
Death rate per 1000 person-yr	10.8		13.3		7.9	

[1]Number of deaths/number at risk; [2]Adjusted also for sex, age, current smoking, systolic BP, HDL-cholesterol; [3]Referent was no FLD (*n* = 412). Mean age at baseline was 52.1 years. Missing HOMA index values limited by 15% the sample and deaths. HDL: High-density lipoprotein; FLD: Fatty liver disease; HOMA: Homeostatic assessment; BP: Blood pressure.

diabetes by NAFLD diagnosed by ultrasonography. In study samples exceeding 12000 subjects, Yamada *et al*[4] in Japanese and Sung *et al*[5] in South Korean people found over 5-year follow-ups that NAFLD independently predicted diabetes risk at about 2- to 2.5-fold HRs, respectively. In prior prospective studies on Japanese people with smaller sample sizes[29,30], the related HRs ranged between a non-significant value and 4.6. In this study, the predictive value of FLD for this association was over 5-fold that of individuals without FLD, independent of sex, age, smoking status, systolic blood pressure, serum HDL-cholesterol level, and uric acid level. This HR was similar to that found in French men but lower than that in women in the highest versus the lowest quartile of FLI[31].

NAFLD has been shown to predict incident CVD[6-9]. The prospective analysis over a 14-year follow-up in approximately 11600 participants of NHANES-Ⅲ demonstrated an independent association between NAFLD by ultrasonography and cardiovascular disease[9], similar to our current findings. However, the strong predictive ability of FLD for CHD among our diabetic subjects was substantially attenuated in the whole male sample when diabetes was included in the adjustments and was reduced to a non-significant level in female participants. It appears that in Turkish women who are prone to autoimmune activation NAFLD and diabetes, each conferring CHD risk, emerging bidirectional changes[1] mediate each other and attenuate this risk. Thus, both the substrate (prevalent CHD or diabetes) and gender modulate this risk. In fact, in Chinese patients with suspected CHD (*n*

Table 5 Adjusted Cox regression analyses of components of fatty liver index for prediction of type-2 diabetes, incident coronary heart disease and mortality, by gender

	Total		Men		Women	
	HR	95%CI	HR	95%CI	HR	95%CI
Diabetes						
Waist circumference, 12 cm	1.70	1.33; 2.15	1.64	1.13; 2.38	1.78	1.27; 2.46
Body mass index, 5 kg/m^2	1.10	0.91; 1.33	1.06	0.80; 1.40	1.11	0.86; 1.44
Triglycerides, 90 mg/dL	1.22	1.06; 1.40	1.09	0.91; 1.31	1.43	1.20; 1.71
γ-glutamyltransferase, 1.7-fold	2.19	1.61; 2.99	2.44	1.52; 3.92	2.22	1.44; 3.43
CHD						
Waist circumference, 12 cm	1.21	0.80; 1.82	1.21	0.20; 1.82	1.02	0.78; 1.33
Body mass index, 5 kg/m^2	1.01	0.84; 1.20	0.77	0.52; 1.14	0.98	0.80; 1.20
Triglycerides, 90 mg/dL	1.19	1.03; 1.35	1.20	1.01; 1.43	1.12	0.84; 1.31
γ-glutamyltransferase, 1.7-fold	1.52	0.94; 2.44	1.52	0.94; 2.44	1.64	1.16; 2.31
Mortality						
Waist circumference, 12 cm	1.31	1.00; 1.74	1.21	0.81; 1.80	1.38	0.90; 2.11
Body mass index, 5 kg/m^2	0.73	0.56; 0.96	0.68	0.45; 1.03	0.82	0.56; 1.20
Triglycerides, 90 mg/dL	1.12	0.96; 1.31	1.28	1.01; 1.57	0.91	0.70; 1.20
γ-glutamyltransferase, 1.7-fold	1.37	0.97; 1.93	1.28	0.79; 2.06	1.62	0.95; 2.77

Models were adjusted also to sex, age, smoking status, systolic BP, HDL-cholesterol. Further, uric acid protected men against diabetes and weakly tended to protect women against CHD.

= 713), significant association between FLI and CHD was not detected[32].

Lack of prediction of mortality risk by NAFLD

Reasons for the paradoxical lack of NAFLD on mortality risk remain unclear. Using the NHANES-Ⅲ survey data, all-cause mortality for alanine transferase-defined NAFLD over a mean 8.7 year follow-up was marginally increased (HR = 1.37)[13], a risk confined to the age group 45-54. Women, Mexican Americans, non-smokers, and those with MetS or diabetes were more likely to have NAFLD. A more recent analysis of NHANES-Ⅲ survey data confirmed that ultrasonography-defined NAFLD did not increase the risk of mortality[33]. However, NAFLD with evidence of advanced fibrosis (only one out of 30 NAFLD cases) using non-invasive marker panels was associated with increased mortality, mainly attributable to cardiovascular causes. NAFLD fibrosis score was based on an algorithm using additional data on impaired fasting glucose/diabetes, as well as inflammation-related parameters such as aspartate aminotransferase/alanine aminotransferase ratio, platelet count, and serum albumin level.

GGT, a participant in the degradation of the antioxidant glutathione and, hence, capable of inducing pro-oxidant effect, is a major component of the FLI. GGT was shown to be independently and inversely associated with the mean low density lipoprotein (LDL) particle size in asymptomatic elderly subjects with dyslipidemia[34]. Though the FLI was found to predict all-cause mortality in the Cremona study, characterized by a cohort having a high prevalence of MetS and insulin resistance, it was the significant association of the HOMA index with the FLI that emerged as a mediator of mortality risk[15]. Lp(a) constitutes a typical example of small dense LDL and was documented elsewhere[35] and in the TARF study[36] to be inversely associated with HOMA index.

Our multivariable analysis with the four components of the FLI explains in part the lack of association with risk of death, insofar as BMI emerged (especially in men) as protective against mortality risk. Moreover, on our previous findings[37] showed that a disparate independent association existed among sexes between serum GGT and Lp(a) levels, with high Lp(a) levels in men and low levels in women (reflecting autoimmune activation), and this may have been pivotal for the associations of FLI with the risks of death and, in women, with incident CHD. Diabetic status, a major confounder of and interactor with an underlying autoimmune activation, may have, therefore, largely mediated FLD [and low Lp(a) concentrations] and attenuated the outcome of mortality.

Since FLD, HOMA index, and age in current prediabetic men had higher HRs and higher Lp(a) concentrations than in the remaining two categories, serum Lp(a) may not be involved in the autoimmune complex underlying its relation to FLD and HOMA index, which is in contrast to the relatively elevated HRs for mortality. The independent contribution to the risk of death, likely *via* cardiorenal disease, may well be reflected in the high HR of age. In women, the persistent increase in HRs of FLD and HOMA index may be a consequence of the increasing involvement of circulating Lp(a) in autoimmune activation from normoglycemia onwards.

Our observations in men support the view that the development of diabetes from prediabetes attenuates the independent risk of death for FLD[38,39]. Age-adjusted mortality in patients with NAFLD was, indeed, reported to be associated with IFG[40].

A critical role of serum GGT in the pathogenesis of IFG was suggested in a large Korean population-based

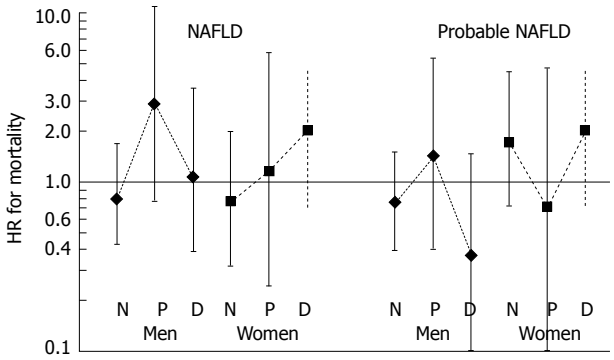

Figure 2 Diagram of multivariable adjusted hazard ratios are depicted for death of fatty liver disease in the 3 glucose categories. Though significant findings were not obtained, the risk of overall mortality among normoglycemic (N) individuals with fatty liver disease was lower than in subjects with no fatty liver disease. Risk increased in prediabetes (P) and tended so in diabetic (D) women, while declining in men with diabetes. NAFLD: Non-alcoholic fatty liver disease.

study that assessed the varying association of the enzyme level with BMI[41]. In our evaluation of subjects with IFG, we observed a parallel trend between serum Lp(a) and GGT in women regardless of the presence of MetS but in men in the absence of MetS alone[20].

Limitations and strengths

FLD was defined herein not by imaging methods or histology but by an algorithm based on obesity markers, fasting triglyceride, and GGT levels. This method has been validated in several epidemiologic studies[15,23], and other methods are costly and impractical to identify FLD in large epidemiologic studies. Collinearity between FLI and metabolic factors such as Lp(a) levels or obesity cannot be ruled out. The study sample size, long follow-up, and analysis stratified to gender are strengths of the study. Concomitant investigation of diabetes, CHD, and overall mortality in the same study sample is a major strength that allowed for the detection of emerging differences in the underlying pathogenesis.

FLD, defined by a FLI, was detected in one-half of a population-based cohort. FLD was a powerful predictor of incident diabetes and disclosed a nearly 2-fold HR for the risk of CHD, compared to participants without FLD. In essential agreement with most previous reports on general population samples, all-cause mortality, however, was not independently related to baseline FLD, or to HOMA index, except for a tendency in prediabetic men as well as prediabetic and diabetic women. Associations between BMI, GGT, and Lp(a) concentrations may herein be pivotal. Further research seeking the association between FLD and mortality risk should address the impact of circulating Lp(a) in the separate glycemic states in larger population samples.

COMMENTS

Background

Liver biopsy, ultrasonography, serum liver enzymes, and, more recently, an algorithm-based surrogate of fatty liver disease (FLD) have been commonly used in identifying the presence of non-alcoholic fatty liver disease (NAFLD), closely associated with features of the metabolic syndrome (MetS), and its relationship to adverse outcomes. NAFLD, a growing public health issue, has been demonstrated to be associated with MetS, type-2 diabetes cardiovascular events, and chronic kidney disease, but controversy exists on its predictive ability for overall mortality.

Research frontiers

Diabetic status, a recognized major confounder in the bidirectional relationship between FLD and cardiovascular morbidity and mortality, appears to be a major area requiring future research. Another hotspot that further research should be engaged, especially in population subgroups prone to metabolic syndrome, is the potential disparate independent association potentially existing among sexes between serum γ-glutamyltransferase (GGT) (a component of the FLI) and lipoprotein (Lp)(a) levels and their influence on outcome.

Innovations and breakthroughs

The lack of a relationship between NAFLD and risk of overall mortality as compared to its independent prediction of diabetes and cardiovascular disease has been intriguing. An algorithm consisting of body mass index, waist circumference, triglycerides, and GGT has been used elsewhere and herein to detect fatty liver. Confirmation in the present study that risk of death was essentially not predicted by FLI may be due to underlying involvement of circulating Lp(a) in autoimmune activation and the generally confounding role of diabetes, which may have largely mediated FLD and attenuated the outcome of mortality.

Applications

The previously proposed FLD index may reliably be utilized as a surrogate in population screening for the detection of fatty liver.

Terminology

Steatohepatitis designates fatty infiltration and inflammation of the liver.

Peer-review

The authors examined prospectively in over 1800 middle-aged Turkish adults the association of a surrogate of FLD, consisting of adiposity measures, triglyceride, and GGT levels, with type-2 diabetes, coronary heart disease (CHD), and all-cause mortality. Multivariably adjusted Cox regression analyses were used. Over an average 8-year follow-up, FLD was found as the major determinant of incident diabetes at a high relative risk. CHD was significantly and independently predicted by FLD in men alone and in the whole study sample. Despite these, and in line with several previous reports on the controversial topic, the authors detected no significant excess risk of death, though a tendency to increased risk was observed in the prediabetic state. Authors attributed the lack of prediction by FLI possibly to serum Lp(a) being involved in autoimmune activation and to a confounding role of the diabetic status mediating FLD.

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