JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Fatty liver with metabolic disorder, such as metabolic dysfunction-associated fatty liver disease, indicates high risk for developing diabetes mellitus

Teruki Miyake[1]*, Bunzo Matsuura[2], Shinya Furukawa[3], Toru Ishihara[4], Osamu Yoshida[1], Masumi Miyazaki[1], Kyoko Watanebe[1], Akihito Shiomi[1], Hironobu Nakaguchi[2], Yasunori Yamamoto[1], Yohei Koizumi[1], Yoshio Tokumoto[1], Masashi Hirooka[1], Eiji Takeshita[1], Teru Kumagi[5], Masanori Abe[1], Yoshio Ikeda[1], Takeru Iwata[4], Yoichi Hiasa[1]

[1]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Toon, Japan, [2]Department of Lifestyle-Related Medicine and Endocrinology, Ehime University Graduate School of Medicine, Toon, Japan, [3]Health Services Center, Ehime University, Matsuyama, Japan, [4]Ehime General Health Care Association, Matsuyama, Japan, and [5]Postgraduate Medical Education Center, Ehime University Graduate School of Medicine, Toon, Japan

Keywords
Diabetes mellitus, Fatty liver, Metabolic disease

***Correspondence**
Teruki Miyake
Tel.: +81 89 960 5308
Fax: +81 89 960 5310
E-mail address:
miyake.teruki.mg@ehime-u.ac.jp

J Diabetes Investig 2022; 13: 1245–1252

doi: 10.1111/jdi.13772

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is diagnosed after excluding other liver diseases. The pathogenesis of NAFLD when complicated by other liver diseases has not been established completely. Metabolic dysfunction-associated fatty liver disease (MAFLD) involves more metabolic factors than NAFLD, regardless of complications with other diseases. This study aimed to clarify the effects of fatty liver occurring with metabolic disorders, such as MAFLD without diabetes mellitus (DM), on the development of DM.

Materials and Methods: We retrospectively assessed 9,459 participants who underwent two or more annual health check-ups. The participants were divided into the MAFLD group (fatty liver disease with overweight/obesity or non-overweight/obesity complicated by metabolic disorders), simple fatty liver group (fatty liver disease other than MAFLD group), metabolic disorder group (metabolic disorder without fatty liver disease), and normal group (all other participants).

Results: The DM onset rates in the normal, simple fatty liver, metabolic disorder, and MAFLD groups were 0.51, 1.85, 2.52, and 7.36%, respectively. In the multivariate analysis, the MAFLD group showed a significantly higher risk of DM onset compared with other three groups ($P < 0.01$). Additionally, the risk of DM onset was significantly increased in fatty liver disease with overweight/obesity or pre-diabetes ($P < 0.01$).

Conclusions: Fatty liver with metabolic disorders, such as MAFLD, can be used to identify patients with fatty liver disease who are at high risk of developing DM. Additionally, patients with fatty liver disease complicated with overweight/obesity or prediabetes are at an increased risk of DM onset and should receive more attention.

INTRODUCTION

Certain changes to a person's lifestyle, including increased dietary and fat intake and decreased physical activity, can induce various metabolic diseases. Among them, diabetes mellitus (DM) increases the incidence of cardiovascular disease and cancer[1–4]; furthermore, it is considered to have a significant effect on healthy life expectancy[5]. Therefore, there is a need to identify high-risk populations for DM and to provide lifestyle interventions.

Received 30 November 2021; revised 27 January 2022; accepted 13 February 2022

Nonalcoholic fatty liver disease (NAFLD) affects the development of DM[6–10]. However, since NAFLD is diagnosed after excluding other liver diseases, the pathogenesis of NAFLD when complicated by other liver diseases has not been established completely. Furthermore, since there are numerous patients with fatty liver disease, providing interventions for all of them is difficult; moreover, there is a need to stratify their risk of the development of DM.

Metabolic dysfunction-associated fatty liver disease (MAFLD), which is defined as fatty liver disease combined with obesity, diabetes, and metabolic diseases, regardless of the presence of other liver diseases, was proposed by the American Gastroenterological Association and the European Association for the Study of the Liver in 2020[11,12]. MAFLD is considered a fatty liver disease containing more metabolic factors than NAFLD; however, the impacts of MAFLD on the development of various metabolic disorders remain unclear. Therefore, we aimed to clarify the effects of fatty liver with some metabolic diseases, including MAFLD, on the development of DM.

MATERIALS AND METHODS

This community-based longitudinal cohort study examined the medical records of 9,817 Japanese participants (4,793 men and 5,024 women). The participants were aged 21–78 years and underwent two or more annual health examinations at the Ehime General Health Care Association from April 2003 to March 2017. Annual health examinations were conducted to record the medical history and prescribed medications, perform body measurements, and assess routine biochemical variables.

The body mass index (BMI; kg/m^2) was calculated using body weight and height, measured wearing only a light gown. Blood pressure was assessed with an automatic sphygmomanometer in a seated position. Blood samples were collected after fasting for >10 h. The risk of diabetes was determined based on the levels of fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c). Liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were analyzed. Lipid profiles were determined by assessing triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels. Furthermore, creatinine (Cre), hepatitis B surface antigen (HBs-Ag), and hepatitis C antibody (anti-HCV) levels were measured. Before the physical examination, health workers asked the participants to complete a questionnaire assessing their medical history; prescribed medications; family history of DM to the second degree; health-related behaviors, including exercise (no habit or awareness of exercise vs periodic exercise) and snacking habits (no snacking vs snacking ≥1 time/day); alcohol consumption (men: ≥210 g/week, women: ≥140 g/week), and smoking status[13]. An experienced technician diagnosed fatty liver disease by abdominal ultrasonography without considering the participants' data. Of the four fatty liver disease diagnostic criteria (hepatorenal echocardiographic contrast, liver brightness, deep attenuation, and vascular blurring), fatty liver disease was diagnosed based on hepatorenal contrast and liver brightness[14,15].

Definitions

The MAFLD group comprised participants with fatty liver disease who were overweight/obese (BMI ≥23 kg/m^2) or non-overweight/obese with a metabolic disorder. The criteria for metabolic disorders were defined, based in part, on the criteria for MAFLD[11], and the diagnosis was based on the presence of two or more of the following metabolic risks: hypertension: blood pressure ≥130/85 mmHg or anti-hypertension drug treatment; high TG levels (TG ≥1.70 mM or lipid-lowering drug treatment; low HDL-C levels (HDL-C <1.04 mM for men and <1.30 mM for women); pre-diabetes: impaired fasting glucose (fasting glucose levels 5.55–6.94 mM) or HbA1c between 5.7% and 6.4% without anti-diabetes treatment. The simple fatty liver group comprised participants with fatty liver disease other than the MAFLD group, while the metabolic disorder group comprised participants with metabolic disorders without fatty liver disease. The remaining participants were included in the normal group.

Diabetes mellitus onset was identified when the blood test examination and questionnaire at the health check-up visit revealed fasting glucose levels ≥6.99 mM, HbA1c ≥6.5%, or initiation of anti-diabetes drug treatment.

After examination of the medical records, 359 patients with diabetes were excluded using the following exclusion criteria: currently receiving antidiabetic medications (n = 120), fasting glucose levels ≥6.99 mM (n = 267), or HbA1c ≥6.5% (n = 310) (Figure 1). The final analysis comprised 9,459 participants (4,509 men and 4,950 women) of Ehime University Hospital (Figure 1). The observed mean duration was 5.53 ± 3.53 years (men: 5.32 ± 3.53 years, women: 5.73 ± 3.51 years). This study was approved by the Research Ethics Committee of Ehime University Hospital following the tenets of the Declaration of Helsinki and its later amendments (approval number: 1709007; University Hospital Medical Information Network ID: UMIN000011953), and was conducted in compliance with the Guidelines for Good Clinical Practice and local

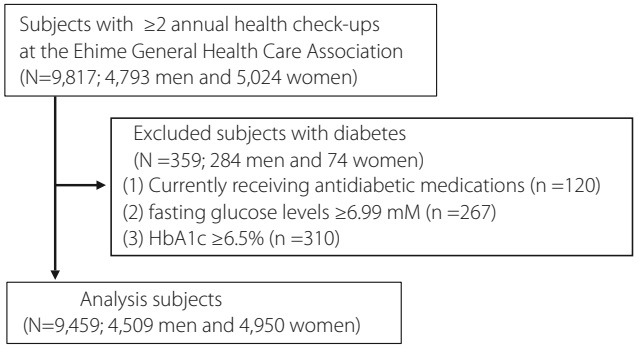

Figure 1 | Study flowchart.

ethical and legal requirements. All participants were allocated a numerical code to ensure their anonymity. Additionally, all data were preserved in a secure database.

JMP version 14.2.0 software (SAS Institute Japan, Tokyo, Japan) was used for statistical analyses. Assumptions of normal distribution were assessed using the Kolmogorov-Smirnov-Lilliefors test. Since the continuous variables proved to be non-normally distributed, they were analyzed using the Steel-Dwass test. Categorical variables were analyzed using the χ^2 test. The Wilcoxon signed-rank test was used to compare continuous variables representing baseline and endpoint characteristics. We performed univariate and multivariate Cox proportional hazards regression analyses to assess hazard ratios (HRs) and 95% confidence intervals (CIs) for DM development. Multivariate analyses were adjusted for the following variables: age; sex; Cre levels; exercise, snacking, drinking, and smoking habits; and family history of diabetes. The combined risk of fatty liver disease for DM was assessed using univariate and multivariate Cox proportional hazards regression analyses that were adjusted for sex; age; Cre; exercise, snacking, drinking, and smoking habits; family history of diabetes; and metabolic disorders, including overweight/obesity, hypertension, high TG levels, low HDL-c levels, or pre-diabetes. All data are expressed as the median (interquartile range) or number (percentage). Statistical significance was determined with P values <0.05.

RESULTS

Characteristics of the participants

Table 1 shows the baseline characteristics of each group. The onset rates of diabetes mellitus in the normal, simple fatty liver, metabolic disorder, and MAFLD groups were 0.51, 1.85, 2.52, and 7.36%, respectively (Table 1). Compared with the normal group, the other groups had a significantly higher proportion of males; were older; and had higher BMIs; increased BP and FPG, HbA1c, AST, ALT, Cre levels, and TG; lower HDL-C levels; a lower proportion of snacking habits; and a higher proportion of current smokers (Table 1). The metabolic disorder group had a higher proportion of participants who performed periodic exercise and were drinkers than the other groups (Table 1). There were 128 patients with HBs-Ag, 91 patients with anti-HCV, and 752 drinkers (Table 1).

The endpoint characteristics were similar to the baseline characteristics (Table 2). Compared with the normal group, the other groups had higher BMIs; increased BP and FPG, HbA1c, AST, ALT, Cre, and TG levels; lower HDL-C levels; a lower proportion of individuals with snacking habits; and higher proportion of current smokers (Table 2). The metabolic disorder group had a higher proportion of participants who performed periodic exercise and were drinkers than the other groups (Table 2).

Table 1 | Baseline characteristics

	Normal (n = 4,930)	Simple fatty liver (n = 271)	Metabolic disorder (n = 2,377)	MAFLD (n = 1,881)	P
Sex (male), %	1,482 (30.1)	151 (55.7)	1,450 (61.0)	1,426 (75.8)	<0.01
Age, years	40 (34–47)	42 (36–49)*	45 (37.5–52)†,§	44 (38–51)‡,‖,¶	<0.05
BMI, kg/m^2	20.4 (19–21.5)	21.8 (20.7–22.3)*	24.1 (23.2–25.5)†,§	26 (24.3–28.1)‡,‖,¶	<0.01
SBP, mmHg	105 (97–114)	110 (101–119)*	118 (108–132)†,§	123 (112–135)‡,‖,¶	<0.01
DBP, mmHg	65 (59–72)	67 (63–75)*	74 (66–84)†,§	77 (69.5–87)‡,‖,¶	<0.01
FPG, mM	4.94 (4.66–5.16)	5.11 (4.89–5.38)*	5.22 (4.94–5.55)†,§	5.38 (5.11–5.72)‡,‖,¶	<0.01
HbA_{1c}, %	5.4 (5.1–5.6)	5.5 (5.2–5.7)*	5.5 (5.2–5.7)†	5.6 (5.4–5.8)‡,‖,¶	<0.01
AST, IU/L	19 (16–22)	20 (17–24)*	20 (17–24)†	24 (20–30)‡,‖,¶	<0.01
ALT, IU/L	14 (12–19)	21 (14–30)*	19 (14–26)†	30 (21–45)‡,‖,¶	<0.01
Cre, μM	61.9 (53.0–70.7)	61.9 (53.0–77.8)*	70.7 (61.9–79.6)†,§	70.7 (61.9–79.6)‡,‖,¶	<0.01
TG, mM	0.73 (0.57–0.99)	1.07 (0.73–1.45)*	1.12 (0.80–1.61)†	1.62 (1.12–2.31)‡,‖,¶	<0.01
HDL-c, mM	1.86 (1.61–2.15)	1.58 (1.35–1.92)*	1.58 (1.32–1.86)†	1.35 (1.17–1.61)‡,‖,¶	<0.01
Periodic exercise[a], n	1487 (30.2%)	78 (28.9%)	818 (34.4%)	515 (27.4%)	<0.01
Snacking habits[b], n	3507 (71.1%)	168 (62.0%)	1454 (61.2%)	1091 (58.0%)	<0.01
Drinker[c], n	317 (6.4%)	22 (8.1%)	238 (10.0%)	175 (9.3%)	<0.01
Current smoker, n	767 (15.6%)	57 (21.0%)	645 (27.1%)	570 (30.3%)	<0.01
Family history of diabetes, n	964 (19.6%)	56 (20.7%)	439 (18.5%)	391 (20.8%)	0.28
Onset of diabetes mellitus[d], n	25 (0.51%)	5 (1.85%)	60 (2.52%)	139 (7.36%)	<0.01

Data are presented as median (interquartile range) or number (percentage). The Steel-Dwass test and χ^2 test were used to analyze continuous and categorical variables, respectively. Differences were considered significant at $P < 0.05$ (*normal vs simple fatty liver, †normal vs metabolic disorder, ‡normal vs MAFLD, §simple fatty liver vs metabolic disorder, ‖simple fatty liver vs MAFLD, ¶metabolic disorder vs MAFLD). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides. [a]Exercise habit: no habit or awareness of exercise vs periodic exercise. [b]Snacking habit: no snacking vs snacking ≥1 time/day. [c]Drinker: men: ≥210 g/week, women: ≥140 g/week) [d]DM onset was defined as fasting glucose levels ≥6.99 mM, HbA1c ≥6.5%, or initiation of anti-diabetes treatment.

Table 2 | Endpoint characteristics

Group	Normal (*n* = 4,930)	Simple fatty liver (*n* = 271)	Metabolic disorder (*n* = 2,377)	MAFLD (*n* = 1,881)	*P*
BMI, kg/m^2	20.6 (19.3–22)	21.9 (20.7–22.8)*	24.2 (22.8–26)†,§	25.9 (24–28.2)$^{\ddagger,\|,\P}$	<0.01
SBP, mmHg	105 (96–115)	111 (101–119)*	118 (107–131)†,§	122 (111–134)$^{\ddagger,\|,\P}$	<0.01
DBP, mmHg	66 (59–73)	70 (64–76)*	75 (67–84)†,§	78 (70–87)$^{\ddagger,\|,\P}$	<0.01
FPG, mM	4.94 (4.72–5.22)	5.16 (4.88–5.44)*	5.22 (4.94–5.61)†,§	5.44 (5.11–5.91)$^{\ddagger,\|,\P}$	<0.01
HbA_{1c}, %	5.4 (5.2–5.5)	5.5 (5.2–5.6)*	5.5 (5.2–5.7)†	5.6 (5.4–5.8)$^{\ddagger,\|,\P}$	<0.01
AST, IU/L	19 (17–23)	22 (18–26)*	21 (18–25)†	23 (19–30)$^{\ddagger,\|,\P}$	<0.01
ALT, IU/L	15 (12–19)	21 (14–33)*	19 (15–26)†	27 (19–42)$^{\ddagger,\|,\P}$	<0.05
Cre, μM	61.9 (53.0–70.7)	67.2 (54.8–77.8)*	70.7 (61.0–80.4)†,§	73.4 (62.8–82.2)$^{\ddagger,\|,\P}$	<0.01
TG, mM	0.76 (0.58–1.03)	1.02 (0.73–1.48)*	1.07 (0.77–1.60)†	1.42 (0.99–2.06)$^{\ddagger,\|,\P}$	<0.01
HDL-c, mM	1.74 (1.50–2.02)	1.48 (1.27–1.76)*	1.48 (1.27–1.76)†	1.30 (1.14–1.55)$^{\ddagger,\|,\P}$	<0.01
Periodic exercise[a], *n*	1823 (37.0%)	101 (37.3%)	1017 (42.8%)	710 (37.8%)‡	<0.01
Snacking habits[b], *n*	3539 (71.8%)	175 (64.6%)	1449 (61.0%)	1090 (58.0%)	<0.01
Drinker[c], *n*	365 (7.4%)	24 (8.9%)	235 (9.9%)	176 (9.4%)	<0.01
Current smoker, *n*	645 (13.1%)	48 (17.7%)	544 (22.9%)	496 (26.4%)	<0.01

Data are presented as median (interquartile range) or number (percentage). The Steel-Dwass test and χ^2 test were used to analyze continuous and categorical variables, respectively. Differences were considered significant at $P < 0.05$ (*normal vs simple fatty liver, †normal vs metabolic disorder, ‡normal vs MAFLD, §simple fatty liver vs metabolic disorder, $^{\|}$simple fatty liver vs MAFLD, ¶metabolic disorder vs MAFLD). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides. [a]Exercise habit: no habit or awareness of exercise vs periodic exercise. [b]Snacking habit: no snacking vs snacking ≥1 time/day. [c]Drinker: men: ≥210 g/week, women: ≥140 g/week).

The comparisons of characteristics between baseline and endpoint revealed that BMI, DBP, and AST levels at endpoint were higher than at baseline among the normal, simple fatty liver, and metabolic disorder groups (Table 3). The FPG levels at endpoint were higher than at baseline among normal, metabolic disorder, and MAFLD groups (Table 3). In all groups, Cre levels at endpoint were higher than at baseline, and HDL-c levels at endpoint were lower than at baseline (Table 3). The proportion of individuals with periodic exercise habits was higher at endpoint than at baseline among all groups and the proportion of current smokers was lower at endpoint than at baseline among normal, metabolic disorder, and MAFLD groups (Table 3).

Risk of DM onset with simple fatty liver, metabolic disorder, and MAFLD

Univariate analysis revealed that simple fatty liver, metabolic disorder, and MAFLD were significant risk factors for DM compared with the normal group. Further, MAFLD had a higher risk of DM onset than simple fatty liver and metabolic disorder (simple fatty liver, HR: 3.61, 95% CI: 1.38–9.43; metabolic disorder, HR: 5.41, 95% CI: 3.39–8.62; MAFLD, HR: 18.46, 95% CI: 12.06–28.27) (*P*-trend <0.01; Table 4). In addition, multivariate analysis adjusted for sex, age, BMI, Cre, exercise habit, snacking habit, drinking habit, smoking habit, and family history of diabetes showed a significantly increased risk of DM onset in the other three groups compared with the normal group (simple fatty liver, aHR: 2.76, 95% CI: 1.05–7.23; metabolic disorder, aHR: 3.62, 95% CI: 2.24–5.85; MAFLD, aHR: 11.03, 95% CI: 7.03–17.28) (*P*-trend <0.01; Table 4).

In the normal, simple fatty liver, metabolic disorder, and MAFLD groups, the 1-year DM onset rates were 0.04%, 0%, 0.03%, and 0.5%, respectively; the 3-year DM onset rates were 0.11%, 0.43%, 1.06%, and 3.15%, respectively; the 5-year DM onset rates were 0.44%, 1.64%, 2.07%, and 5.37%, respectively; and the 10-year DM onset rates were 0.69%, 3.72%, 5.25%, and 16.68%, respectively.

Risk of fatty liver disease combined with other factors

Next, we examined the factors that exacerbated the risk of fatty liver disease in DM. Fatty liver disease with overweight/obesity or pre-diabetes significantly increased the risk of DM onset compared with fatty liver disease with other metabolic diseases (overweight/obesity, HR: 3.21, 95% CI: 1.75–5.94; pre-diabetes, HR: 8.54, 95% CI: 4.92–14.82, respectively; Table 5). Additionally, multivariate analysis adjusted for sex; age; BMI; Cre levels; exercise habit; snacking habit; drinking habit; smoking habit; family history of diabetes; and metabolic disorders, including overweight/obesity, hypertension, high TG levels, low HDL-c levels, or pre-diabetes, showed a significantly increased risk of DM onset in fatty liver disease with overweight/obesity and pre-diabetes (overweight/obesity, HR: 2.18, 95% CI: 1.15–4.13; pre-diabetes, HR: 7.82, 95% CI: 4.37–13.99, respectively; Table 5). In the fatty liver with overweight/obesity and pre-diabetes groups, the 1-year DM onset rates were 0.54 and 0.07%, respectively; the 3-year DM onset rates were 3.28 and 4.65%, respectively; the 5-year DM onset rates were 5.53 and 7.89%, respectively; and the 10-year DM onset rates were 16.99 and 24.1%, respectively.

Table 3 | The differences in characteristics between baseline and endpoint

Group	Normal (n = 4,930)			Simple fatty liver (n = 271)			Metabolic disorder (n = 2,377)			MAFLD (n = 1,881)		
BMI, kg/m^2	20.4 (19–21.5)	20.6 (19.3–22)	<0.01	21.8 (20.7–22.3)	21.9 (20.7–22.8)	<0.01	24.1 (23.2–25.5)	24.2 (22.8–26)	<0.01	26 (24.3–28.1)	25.9 (24–28.2)	0.11
SBP, mmHg	105 (97–114)	105 (96–115)	0.94	110 (101–119)	111 (101–119)	0.09	118 (108–132)	118 (107–131)	<0.01	123 (112–135)	122 (111–134)	<0.01
DBP, mmHg	65 (59–72)	66 (59–73)	<0.01	67 (63–75)	70 (64–76)	<0.01	74 (66–84)	75 (67–84)	<0.01	77 (69.5–87)	78 (70–87)	0.18
FPG, mM	4.94 (4.66–5.16)	4.94 (4.72–5.22)	<0.01	5.11 (4.89–5.38)	5.16 (4.88–5.44)	0.08	5.22 (4.94–5.55)	5.22 (4.94–5.61)	<0.01	5.38 (5.11–5.72)	5.44 (5.11–5.91)	<0.01
HbA_{1c}, %	5.4 (5.1–5.6)	5.4 (5.2–5.5)	<0.01	5.5 (5.2–5.7)	5.5 (5.2–5.6)	0.33	5.5 (5.2–5.7)	5.5 (5.2–5.7)	<0.01	5.6 (5.4–5.8)	5.6 (5.4–5.8)	0.05
AST, IU/L	19 (16–22)	19 (17–23)	<0.01	20 (17–24)	22 (18–26)	<0.01	20 (17–24)	21 (18–25)	<0.01	24 (20–30)	23 (19–30)	0.21
ALT, IU/L	14 (12–19)	15 (12–19)	<0.01	21 (14–30)	21 (14–33)	0.04	19 (14–26)	19 (15–26)	0.70	30 (21–45)	27 (19–42)	<0.01
Cre, μM	61.9 (53.0–70.7)	61.9 (53.0–70.7)	<0.01	61.9 (53.0–77.8)	67.2 (54.8–77.8)	<0.01	70.7 (61.9–79.6)	70.7 (61.0–80.4)	<0.01	70.7 (61.9–79.6)	73.4 (62.8–82.2)	<0.01
TG, mM	0.73 (0.57–0.99)	0.76 (0.58–1.03)	<0.01	1.07 (0.73–1.45)	1.02 (0.73–1.48)	0.47	1.12 (0.80–1.61)	1.07 (0.77–1.60)	0.53	1.62 (1.12–2.31)	1.42 (0.99–2.06)	<0.01
HDL-c, mM	1.86 (1.61–2.15)	1.74 (1.50–2.02)	<0.01	1.58 (1.35–1.92)	1.48 (1.27–1.76)	<0.01	1.58 (1.32–1.86)	1.48 (1.27–1.76)	<0.01	1.35 (1.17–1.61)	1.30 (1.14–1.55)	<0.01
Periodic exercise[a], n	1487 (30.2%)	1823 (37.0%)	<0.01	78 (28.9%)	101 (37.3%)	0.04	818 (34.4%)	1017 (42.8%)	<0.01	515 (27.4%)	710 (37.8%)	<0.01
Snacking habits[b], n	3507 (71.1%)	3539 (71.8%)	0.48	168 (62.0%)	175 (64.6%)	0.53	1453 (61.2%)	1449 (61.0%)	0.88	1091 (58.0%)	1090 (58.0%)	0.96
Drinker[c], n	317 (6.4%)	365 (7.4%)	0.06	22 (8.1%)	24 (8.9%)	0.76	238 (10.0%)	235 (9.9%)	0.88	175 (9.3%)	176 (9.4%)	0.96
Current smoker, n	767 (15.6%)	645 (13.1%)	<0.01	57 (21.0%)	48 (17.7%)	0.33	645 (27.1%)	544 (22.9%)	<0.01	570 (30.3%)	496 (26.4%)	<0.01

The Wilcoxon signed rank test and χ^2 test were used to analyze continuous and categorical variables, respectively. Differences were considered significant at $P < 0.05$. Data are presented as median (interquartile range) or number (percentage). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides. [a]Exercise habit: no habit or awareness of exercise vs periodic exercise. [b]Snacking habit: no snacking vs snacking ≥1 time/day. [c]Drinker: men: ≥210 g/week, women: ≥140 g/week)

Table 4 | The risk for the onset of diabetes mellitus

	Normal	Simple fatty liver	Metabolic disorder	MAFLD	*P* for trend
Crude HR (95% CI)	1.00	3.61 (1.38–9.43)	5.41 (3.39–8.62)	18.46 (12.06–28.27)	<0.01
Adjusted HR† (95% CI)	1.00	2.76 (1.05–7.23)	3.62 (2.24–5.85)	11.03 (7.03–17.28)	<0.01

Differences were considered statistically significant for $P < 0.05$. BMI, body mass index; CI, confidence interval; Cre, creatinine; HR, hazard ratio; SBP, systolic blood pressure. †Multivariate Cox proportional hazards regression analysis was adjusted for sex, age (years), BMI (kg/m^2), SBP (mmHg), Cre (μM), exercise habits, snacking habits, drinking habits, smoking status, and family history of diabetes.

Table 5 | Risk of fatty liver in combination with other factors

	Crude HR (95% CI)	*P*-value	Adjusted HR† (95% CI)	*P*-value
Overweight/obese	3.21 (1.73–5.94)	<0.01	2.18 (1.15–4.13)	0.02[a]
Hypertension	1.77 (1.28–2.46)	<0.01	1.18 (0.83–1.69)	0.35[b]
High TG level	1.85 (1.33–2.58)	<0.01	1.25 (0.86–1.81)	0.24[c]
Low HDL-C level	1.41 (0.91–2.20)	0.13		
Pre-diabetes	8.54 (4.92–14.82)	<0.01	7.82 (4.37–13.99)	<0.01[d]

Differences were considered statistically significant for $P < 0.05$. BMI, body mass index; CI, confidence interval; Cre, creatinine; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SBP, systolic blood pressure; TG, triglycerides. †Multivariate Cox proportional hazards regression analysis was adjusted for sex, age (years), BMI (kg/m^2), SBP (mmHg), Cre (μM), exercise habits, snacking habits, drinking habits, smoking status, and family history of diabetes, along with metabolic disorders as follows: [a]hypertension, high TG levels, low HDL-C levels, and pre-diabetes; [b]overweight/obese, high TG levels, low HDL-C levels, and pre-diabetes; [c]overweight/obese, hypertension, low HDL-C levels, and pre-diabetes; [d]overweight/obese, hypertension, high TG levels, and low HDL-C levels.

DISCUSSION

We observed that fatty liver with metabolic disorders, such as MAFLD, indicated an increased risk of DM onset compared with simple fatty liver and metabolic disorders. Additionally, fatty liver disease in the presence of overweight/obesity or pre-diabetes showed a higher risk of DM onset compared with fatty liver disease with other metabolic disorders. Therefore, MAFLD, especially fatty liver disease with overweight/obesity or pre-diabetes, is an appropriate disease concept for the risk of DM development.

Nonalcoholic fatty liver disease is a significant risk factor for DM; moreover, NAFLD is strongly associated with DM[6–10]. Additionally, a previous examination of the relationship between the changes in fatty liver status over time and the risk of DM onset indicated that, although improvement of fatty liver did not reduce the risk of developing DM as low as that in non-fatty liver patients, exacerbation of the severity of fatty liver disease notably increased the risk of DM onset[16]. Therefore, it is important to intervene in cases of fatty liver disease to reduce the risk of DM onset. However, since NAFLD is diagnosed after excluding other liver diseases, it is difficult to properly evaluate various diseases that could complicate NAFLD pathogenesis, including viral hepatitis, alcoholic liver disease, and autoimmune liver diseases. In 2020, the concept of MAFLD was proposed, which facilitated the pathogenesis of fatty liver disease[11,12]. Although we included 128 patients with HBs-Ag, 91 patients with anti-HCV, and 752 drinkers, the relationship between fatty liver disease and diabetes could be accurately represented. Additionally, MAFLD is a good predictive factor of hepatic fibrosis[17] and mortality[18,19]. There is a need for future studies on MAFLD to confirm whether MAFLD is carries increased risk factors for other diseases[20].

Our findings confirmed that fatty liver disease was classified according to the risk of DM. Liang *et al.*[21] reported that compared with participants without fatty liver disease, patients with MAFLD and NAFLD had an increased risk of DM onset (estimated risk ratio [RR] 2.08, 95% CI 1.72–2.52; RR 2.01, 95% CI 1.65–2.46, respectively) after adjustment for age, sex, educational background, smoking status, and leisure-time exercise. Moreover, the change from NAFLD to MAFLD had no effect on the relationship with diabetes. However, since this previous study compared disease concepts, there was an overlap in the target participants with NAFLD and MAFLD. Therefore, our findings are important since we stratified participants based on their risk of DM development, and they demonstrated that a diagnosis of MAFLD can be used to identify patients at a higher risk of developing DM. Additionally, we analyzed the factors that specifically increased the risk of fatty liver disease.

Our study strengths are that only five data points were missing from the entire cohort of patients and visits (one BMI measurement, and two points each for exercise and snacking habits). However, this study has several limitations. First, because we did not collect data pertaining to waist circumference, insulin levels, or high-sensitivity C-reactive protein levels, we could not assess all the MAFLD components. Therefore, it is possible that the number of patients with MAFLD was

underestimated. Second, although abdominal ultrasonography is a reliable diagnostic method with high sensitivity and specificity for fatty liver disease[22,23], we could not assess the effects of the severity of fatty liver disease on DM development since we could not determine the extent of fatty liver disease and fibrosis. Third, self-reported data were used for some of the factors surveyed, which may compromise the accuracy of the survey results. Fourth, the data are not truly continuous because they were collected only once a year at annual health check-ups. Fifth, it is possible that some of the participants who developed DM after the health check-up missed the next health check-up. Therefore, the number of patients who developed diabetes may have been underestimated. Finally, since we only studied the Japanese population, studies with other populations are needed to confirm the generality of our results.

In conclusion, our findings demonstrated that a diagnosis of MAFLD can be used to classify a high risk of DM onset among patients with fatty liver disease. Additionally, among patients with fatty liver disease, those with fatty liver who are also overweight/obese or have pre-diabetes are at a higher risk of developing DM. Therefore, clinicians should be particularly vigilant when treating patients with fatty liver complicated by metabolic disorders, such as MAFLD, to prevent the development of DM. Stratifying the risk of fatty liver can allow the identification of, and interventions for, patients at a high risk of diabetes development.

ACKNOWLEDGMENTS

This study was supported by a research grant from JSPS KAKENHI (JP19K11743). We are grateful to Editage (www.editage.com) for providing English language editing.

DISCLOSURE

The authors declare that they have no conflicts of interest.

Approval of the research protocol: This study was approved by the Research Ethics Committee of Ehime University Hospital (approval number: 1709007).

Informed consent: N/A. Since this study protocol was retrospective in manner and all the participants' data were de-identified, it was not necessary to obtain informed consent from participants in this study.

Registry and the registration no. of the study/trial: October 3, 2013 University Hospital Medical Information Network ID: UMIN000011953.

Animal studies: N/A.

REFERENCES

1. Leon BM, Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; 6: 1246–1258.
2. Noto H, Tsujimoto T, Sasazuki T, *et al*. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Endocr Pract* 2011; 17: 616–628.
3. Sasazuki S, Charvat H, Hara A, *et al*. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. *Cancer Sci* 2013; 104: 1499–1507.
4. Shima T, Uto H, Ueki K, *et al*. Hepatocellular carcinoma as a leading cause of cancer-related deaths in Japanese type 2 diabetes mellitus patients. *J Gastroenterol* 2019; 54: 64–77.
5. Kyu HH, Abate D, Abate KH, *et al*. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1859–1922.
6. Miyake T, Hirooka M, Yoshida O, *et al*. Differences in the risk of fatty liver for onset of impaired fasting glucose according to baseline plasma glucose levels. *J Gastroenterol* 2017; 52: 237–244.
7. Shibata M, Kihara Y, Taguchi M, *et al*. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; 30: 2940–2944.
8. Li CH, Chou YT, Shen WC, *et al*. Increased risks of different grades of non-alcoholic fatty liver disease in prediabetic participants with impaired fasting glucose and glucose tolerance, including the isolated glycosylated hemoglobin levels of 5.7–6.4% in a Chinese population. *J Diabetes Investig* 2020; 11: 1336–1343.
9. Mantovani A, Byrne CD, Bonora E, *et al*. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. *Diabetes Care* 2018; 41: 372–382.
10. Miyake T, Matsuura B, Furukawa S, *et al*. Nonalcoholic fatty liver disease is a risk factor for glucose intolerance onset in men regardless of alanine aminotransferase status. *J Diabetes Investig* 2021; 12: 1890–1898.
11. Eslam M, Newsome PN, Sarin SK, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020; 73: 202–209.
12. Eslam M, Sanyal AJ, George J, *et al*. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020; 158: 1999–2014.
13. Okamoto M, Miyake T, Kitai K, *et al*. Cigarette smoking is a risk factor for the onset of fatty liver disease in nondrinkers: a longitudinal cohort study. *PLoS One* 2018; 13: e0195147.
14. Kojima S-I, Watanabe N, Numata M, *et al*. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. *J Gastroenterol* 2003; 38: 954–961.
15. Wai JW, Fu C, Wong VW. Confounding factors of non-invasive tests for nonalcoholic fatty liver disease. *J Gastroenterol* 2020; 55: 731–741.
16. Sung KC, Wild SH, Byrne CD. Resolution of fatty liver and risk of incident diabetes. *J Clin Endocrinol Metab* 2013; 98: 3637–3643.

17. Yamamura S, Eslam M, Kawaguchi T, *et al*. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. *Liver Int* 2020; 40: 3018–3030.
18. Wang X, Wu S, Yuan X, *et al*. Metabolic dysfunction-associated fatty liver disease and mortality among Chinese adults: a prospective cohort study. *J Clin Endocrinol Metab* 2022; 107: e745–e755.
19. Huang QI, Zou X, Wen X, *et al*. NAFLD or MAFLD: which has closer association with all-cause and cause-specific mortality? Results from NHANES III. *Front Med* 2021; 8: 693507.
20. Younossi ZM, Rinella ME, Sanyal AJ, *et al*. From NAFLD to MAFLD: implications of a premature change in terminology. *Hepatology* 2021; 73: 1194–1198.
21. Liang Y, Chen H, Liu Y, *et al*. Association of MAFLD with diabetes, chronic kidney disease, and cardiovascular disease: a 4.6-year cohort study in China. *J Clin Endocrinol Metab* 2022; 107: 88–97.
22. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? *Eur J Gastroenterol Hepatol* 2003; 15: 539–543.
23. Wieckowska A, McCullough AJ, Feldstein AE. Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. *Hepatology* 2007; 46: 582–589.