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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

# Multivariate analysis of risk factors for the development of type 2 diabetes in nonalcoholic fatty liver disease

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**Abstract**
*Purpose* Diabetes is present in patients with nonalcoholic fatty liver disease (NAFLD). The aim of this retrospective cohort study was to assess the cumulative development of type 2 diabetes and predictive factors for its development in Japanese patients with NAFLD.
*Methods* A total of 6003 NAFLD patients diagnosed by ultrasonography were enrolled. The mean follow-up period was 4.9 years. An overnight (12 h) fasting blood sample or a casual blood sample was taken for routine analyses during follow up. The primary outcome was the development of type 2 diabetes. Evaluation was performed by using the Kaplan–Meier method and Cox proportional hazards analysis.
*Results* Of the 6003 NAFLD patients, 411 patients developed type 2 diabetes. The cumulative development rate of type 2 diabetes was 6.8% at the 5th year and 17.7% at the 10th year. Multivariate Cox proportional hazards analysis showed that type 2 diabetes development in patients with NAFLD occurred when patients had prediabetes status (hazard ratio 6.39; 95% confidence interval 5.00–8.18; $P < 0.001$), mean serum gamma-glutamyltransferase (GGT) level of more than 109 IU/l (hazard ratio 1.60; 95% confidence interval 1.22–2. 02; $P < 0.001$), mean serum triglyceride (TG) level of more than 150 mg/l (hazard ratio 1.28; 95% confidence interval 1.05–1.55; $P = 0.020$), and physical activity of less than 60 min per week (hazard ratio 1.60; 95% confidence interval 1.25–2.00; $P < 0.001$).
*Conclusions* The improvement of prediabetes status and physical activity, and the normalization of mean GGT and TG levels during follow up are important to prevent the development of T2DM in patients with NAFLD.

**Keywords** Nonalcoholic fatty liver disease · Type 2 diabetes mellitus · Cohort study

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the more common causes of chronic liver disease in the western world [1–4]. Recently, it has developed rapidly in many Asian nations [5, 6]. NAFLD is considered to be the liver component of metabolic syndrome. It is associated with obesity, dyslipidemia, pituitary dysfunction, hypertension, sleep apnea, and type 2 diabetes mellitus (T2DM) [4, 7–12] NAFLD often causes cardiovascular disease and stroke. Thus, NAFLD is emerging as a new significant health problem in many countries.

Although there is growing evidence to support the concept that NAFLD is a risk factor for developing T2DM, there have been few interventional studies to confirm this issue [13]. This issue needs to be confirmed with long-term follow up of patients with a high risk of developing diabetes. Thus, prospective studies including metabolic evaluations are clearly needed to clarify these issues.

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With this background in mind, a cohort study was initiated to investigate the cumulative incidence of and risk factors for T2DM after prolonged follow up in patients with NAFLD. The strengths of the current study lie in the large number of patients included and the long-term follow up of the patients.

## Methods

### Patients

The number of patients who were diagnosed with fatty liver by ultrasonography (US) [14] between January 1997 and December 2007 at the Department of Hepatology, Toranomon Hospital, Tokyo, Japan was 10210. Of these, 6403 Japanese patients satisfied the following enrollment criteria; (1) no evidence of diabetes mellitus determined by plasma glucose and hemoglobin A1c (HbA1c), i.e., plasma glucose concentration of less than 126 mg per dl (6.9 mmol per l) in the fasting state, or less than 200 mg per dl (11.0 mmol per l) in the casual state and/or 2 h after a 75-g oral glucose load; HbA1c less than 5.8%; (2) current and past daily alcohol intake of less than 40 g/week; (3) negativity for hepatitis B surface antigen, hepatitis C virus (HCV) antibodies, antinuclear antibodies, and antimitochondrial antibodies in serum, as determined by radioimmunoassay, enzyme-linked immunosorbent assay, or spot hybridization; (4) no underlying systemic disease, such as systemic lupus erythmatosus or rheumatoid arthritis; (5) no evidence of hepatocellular carcinoma nodules as shown by US and/or computed tomography (CT). Patients with any of the following criteria were excluded from the study: (1) those who were taking medicines known to alter glucose tolerance, (2) those who had illnesses that could seriously reduce their life expectancy or their ability to participate in the trial, and (3) those who had findings suggestive of other chronic liver disease. Patients were classified as having normal glucose (normal glucose group) or prediabetes (prediabetes group) based on their fasting plasma glucose (FPG), casual plasma glucose, or 2-h plasma glucose, as follows. The normal glucose group had an FPG of less than 100 mg/dl, casual plasma glucose of less than 140 mg/dl, and/or 2-h plasma glucose of less than 140 mg/dl and the prediabetes group had an FPG of 100–125 mg/dl, casual plasma glucose of 140–200 mg/dl, and/or 2-h plasma glucose of 140–200 mg/dl [15].

Next, we assessed predictive factors for T2DM in patients with NAFLD. All of the studies were performed retrospectively by collecting and analyzing data from the patient records. This study was approved by the Institutional Review Board of our hospital.

### Medical evaluation

Diagnosis of fatty liver was based on the presence of an ultrasonographic pattern consistent with bright liver (brightness and posterior attenuation) with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. US was performed with a high-resolution, real-time scanner (model SSD-2000; Aloka, Tokyo, Japan; Mode Logic-700 MR; GE-Yokokawa Medical Systems, Tokyo, Japan). Body weight was measured with the patient in light clothing and without shoes, to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm. Height and weight were recorded at baseline, and the body mass index (BMI) was calculated as weight (in kg)/height (in $m^2$).

All the patients were interviewed at the Toranomon Hospital using a questionnaire that gathered information on demographic characteristics, medical history, and health-related habits, including questions on alcohol intake and physical activity per week.

### Follow up

The initiation of follow up was the day of the first diagnosis of NAFLD, determined by using abdominal US. After that, patients were followed up monthly to 6-monthly at the Toranomon hospital. Physical examination and biochemical tests were conducted at each examination, together with regular checkups, using abdominal CT or US imaging in each patient. An overnight (12 h) fasting blood sample or a casual blood sample was taken for routine analyses. These analyses included transaminase activity, gamma-glutamyltransferase (GGT), total cholesterol, and triglyceride (TG).

The primary outcome was T2DM, diagnosed by the use of the 2003 criteria of the American Diabetes Association [15]. That is, the criteria for the diagnosis of diabetes mellitus included: (a) casual plasma glucose 200 mg/dl or more; (b) FPG 126 mg/dl or more; (c) 2-h post-glucose (oral glucose tolerance test) 200 mg/dl or more. Five hundred and two patients were lost to follow up. Because the appearance of T2DM was not identified in these 502 patients, they were considered as censored data in the statistical analysis [16]. Patients treated with anti-insulin resistance agents were regarded as withdrawals at the time of starting the anti-insulin resistance treatment.

### Statistical analysis

The cumulative incidence rate of T2DM was calculated from the first time NAFLD was confirmed by US to the appearance of T2DM, using the Kaplan–Meier method.

**Table 1** Characteristics of subjects enrolled

| Characteristic | |
|---|---|
| *N* | 6003 |
| Sex (male/female) | 5298/705 |
| Age (years) | 48.8 ± 8.6 |
| Height (cm) | 167.8 ± 7.3 |
| Body weight (kg) | 70.6 ± 9.7 |
| BMI | 25.1 ± 2.6 |
| Albumin (g/dl) | 4.2 ± 0.2 |
| Blood glucose level (normal/prediabetes) | 3517/2486 |
| FPG (mg/dl) | 98.9 ± 9.3 |
| Triglyceride (mg/dl) | 160.8 ± 105.4 |
| Total cholesterol (mg/dl) | 210.3 ± 32.2 |
| HDL cholesterol (mg/dl) | 47.7 ± 11.9 |
| AST (IU/L) | 28.7 ± 14.5 |
| ALT (IU/L) | 36.4 ± 25.1 |
| GGT (IU/L) | 73.5 ± 79.7 |
| Hemoglobin (g/dl) | 15.0 ± 1.1 |
| Platelet count ($\times 10^4$/mm$^3$) | 23.0 ± 4.8 |
| Follow-up period (years) | 4.9 ± 3.0 |

Data are numbers of patients or mean ± SD

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *FPG* fasting plasma glucose, *GGT* gamma-glutamyltransferase

Differences in the development of T2DM were tested using the log-rank test. Independent factors associated with the incidence rate of T2DM were analyzed by the Cox proportional hazard model. The following 11 variables were analyzed as potential covariates for the incidence of T2DM: age, sex, glucose level (normal or prediabetes), BMI, albumin level, alanine aminotransferase (ALT) level, GGT level, TG level, and total cholesterol level at the initiation of follow up at our hospital; and physical activity and mean serum levels of ALT, GGT, and TG during follow up. A $P$ value of less than 0.05 was considered significant. Data analysis was performed using the computer program SPSS package (SPSS 11.5 for Windows, SPSS, Chicago, IL, USA).

## Results

### Patients' characteristics

Table 1 shows the characteristics of the 6003 patients diagnosed with NAFLD in the present study. The mean age was 48.8 years, and most patients were male (88.3%). The prediabetes rate at the starting time of follow up was 41.4% (2486/6003). The rates of elevated mean GGT and TG during follow up were 17.4% (1046/6003) and 42.7% (2564/6003), respectively. The mean follow-up period was 4.9 years.

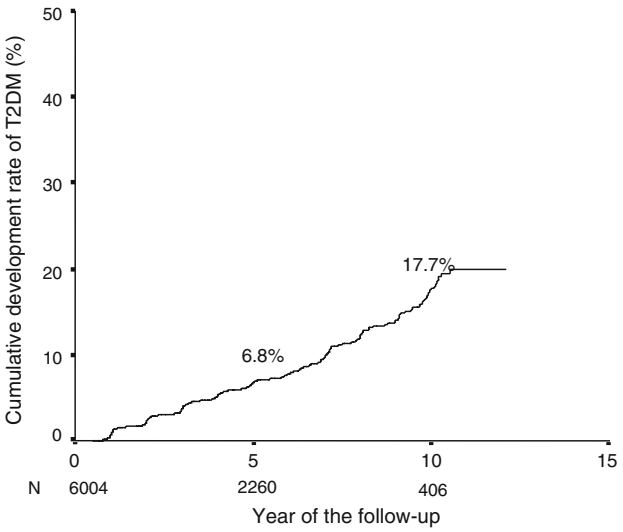


**Fig. 1** Cumulative development rate of type 2 diabetes mellitus (*T2DM*) in 6003 patients with nonalcoholic fatty liver disease (NAFLD)

### Incidence of T2DM in patients with NAFLD

Of the 6003 NAFLD patients, 411 patients developed T2DM. The cumulative development rates of T2DM in the 6003 patients with NAFLD were 6.8% at the 5th year and 17.7% at the 10th year, determined by the Kaplan–Meier method (Fig. 1). The factors associated with the incidence of T2DM are shown in Table 2. Multivariate Cox proportional hazards analysis showed that the development of T2DM in patients with NAFLD occurred when the patient had prediabetes (hazard ratio 6.39; 95% confidence interval 5.00–8.18; $P < 0.001$), mean serum GGT level of more than 109 IU/l (hazard ratio 1.60; 95% confidence interval 1.22–2. 02; $P < 0.001$), mean serum TG level of more than 150 mg/l (hazard ratio 1.28; 95% confidence interval 1.05–1.55; $P = 0.020$), and physical activity of less than 60 min per week (hazard ratio 1.60; 95% confidence interval 1.25–2.00; $P < 0.001$).

Prediabetes enhanced the development of T2DM by about nine point five times compared to the normal glucose level. In addition to prediabetes, the three factors of physical activity of less than 60 min per week, and elevated mean GGT and/or TG levels during follow up were high risk factors for developing diabetes. The cumulative development rates of T2DM based on differences of glucose levels at the initiation of follow up and differences in mean GGT and mean TG between levels during follow up, as well as such differences of physical activity, are shown in Fig. 2. Prediabetes was the strongest predictor compared to physical activity, mean GGT, and mean TG.

**Table 2** Predictive factors for T2DM development

| Variables | Univariate analysis | | Cox regression | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age[a] (years, ≥50/<50) | 1.21 (0.99–1.48) | 0.063 | | |
| Gender[a] (F/M) | 0.77 (0.54–1.09) | 0.144 | | |
| BMI[a] (≥25/<25) | 1.24 (1.02–1.50) | 0.030 | | |
| ALT[a] (IU/L, ≥36/<36) | 1.22 (1.00–1.49) | 0.048 | | |
| GGT[a] (IU/L, ≥109/<109) | 1.42 (1.13–1.80) | 0.003 | | |
| Glucose level[a] (prediabetes/normal) | 9.97 (7.55–13.17) | <0.001 | 6.39 (5.00–8.18) | <0.001 |
| Triglyceride[a] (mg/dl, ≥150/<150) | 1.19 (0.97–1.47) | 0.095 | | |
| Total cholesterol[a] (mg/dl, ≥220/<220) | 0.99 (0.81–1.21) | 0.890 | | |
| Albumin[a] (g/dl, <3.9/≥3.9) | 1.12 (0.85–1.46) | 0.428 | | |
| Mean ALT[b] (IU/L, ≥36/<36) | 1.62 (1.30–2.02) | <0.001 | | |
| Mean GGT[b] (IU/L, ≥109/<109) | 2.05 (1.65–2.52) | <0.001 | 1.60 (1.22–2.02) | <0.001 |
| Mean triglyceride[b] (mg/dl, ≥150/<150) | 1.52 (1.25–1.84) | <0.001 | 1.28 (1.05–1.55) | 0.020 |
| Physical activity[c] (±) | 1.95 (1.53–2.48) | <0.001 | 1.60 (1.25–2.00) | <0.001 |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *HR* hazard ratio, *GGT* gamma-glutamyltransferase

[a] Data at the initiation of follow-up

[b] Data during follow up

[c] −, Physical activity of less than 60 min per week during follow up; +, physical activity of 60 min or more per week during follow up

### Incidence of T2DM in NAFLD patients with and without prediabetes

As noted above, prediabetes was an important factor in enhancing the development of T2DM. Next, we assessed whether the three factors of physical activity, mean GGT, and mean TG during follow up were important in reducing the development of T2DM in NAFLD patients with prediabetes. We classified all the patients into three risk groups based on the combination of the three factors of physical activity, mean GGT, and mean TG during follow up. The low-risk group was defined as patients with physical activity of 60 min or more per week; normal mean GGT, at 109 IU/l or less; and normal mean TG, at less than 150 mg/dl during follow up. The high-risk group was defined as patients with physical activity of less than 60 min per week; abnormal mean GGT, at more than 109 IU/l; and abnormal mean TG, at 150 mg/dl or more during follow up. The intermediate-risk group was defined as patients excluded from the low- and high-risk groups. In the patients with prediabetes, the low-risk group showed a significant reduction in the development of T2DM compared with the high-risk and intermediate-risk group (Fig. 3a). In the patients with normal glucose levels, the development rate of T2DM was significantly different among the three groups (Fig. 3b).

## Discussion

We have described the incidence of the development of diabetes in NAFLD patients in the present study. Our present study indicated that the annual incidence of T2DM during prolonged follow up in NAFLD patients was about 1.7%. The present study was limited by being a retrospective cohort trial. Another limitation of the study was that patients were treated with different types of exercise and diet. Moreover, although NAFLD can be categorized into simple steatosis and steatohepatitis, in the present study the condition was evaluated without histological differentiation between simple steatosis and steatohepatitis. This heterogeneity makes it slightly difficult to interpret the results of the study. On the other hand, the strengths of the present study are that it was a long-term follow up with large numbers of patients included.

The present study showed several findings with regard to the development of T2DM in NAFLD patients. First, patients with NAFLD were at high risk of developing of T2DM compared with the risk in patients with HCV infection. Our previous study showed that the annual incidence of T2DM among patients with HCV was 0.8–1.0% [17]. On the other hand, the annual incidence of T2DM among patients with NAFLD was about 1.7% in the present study. Several reports have shown that nonalcoholic steatohepatitis (NASH) exerts more severe insulin resistance, which closely correlates with T2DM, than simple steatosis [18–22]. In the present study, NAFLD patients were evaluated without discriminating between NASH and simple steatosis by histological examination. However, if the disease in NAFLD patients could be discriminated by histological examination, we predict that patients with NASH would have a high annual incidence compared to those with simple steatosis.

Second, prediabetes was the most important factor that enhanced the development of T2DM in patients with NAFLD. Prediabetes enhanced the development of T2DM by about 6.4 times compared to that in patients with a normal glucose level. This result shows that NAFLD

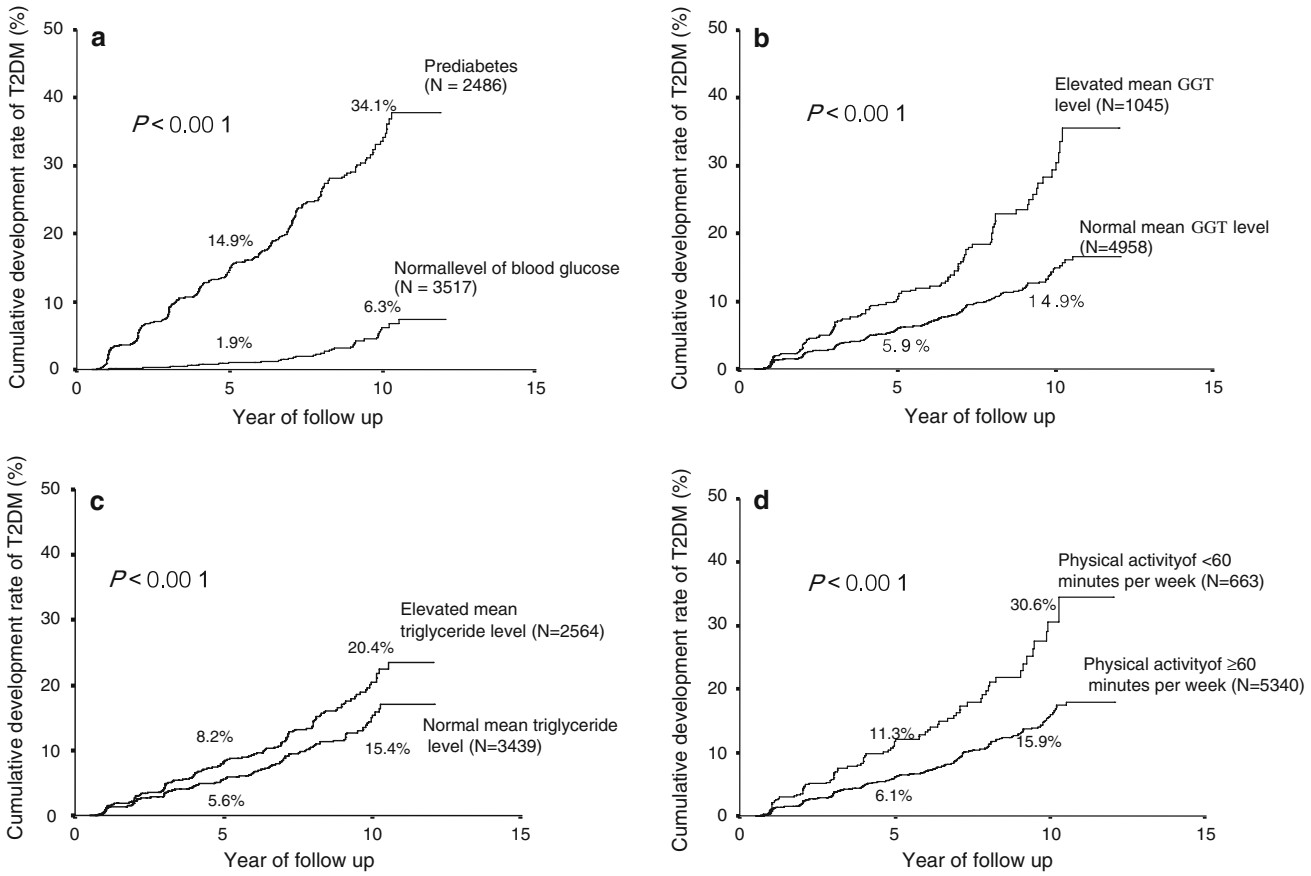


**Fig. 2** Cumulative development rate of T2DM in NAFLD patients. **a** Cumulative development rate of T2DM based on differences between glucose levels at the initiation of follow up and during follow up. **b** Cumulative development rate of T2DM based on the differences between mean gamma-glutamyltransferase (*GGT*) levels at the initiation of follow up and during follow up. **c** Cumulative development rate of T2DM based on the differences between mean triglyceride levels at the initiation of follow up and during follow up. **d** Cumulative development rate of T2DM based on the differences between physical activity at the initiation of follow up and during follow up

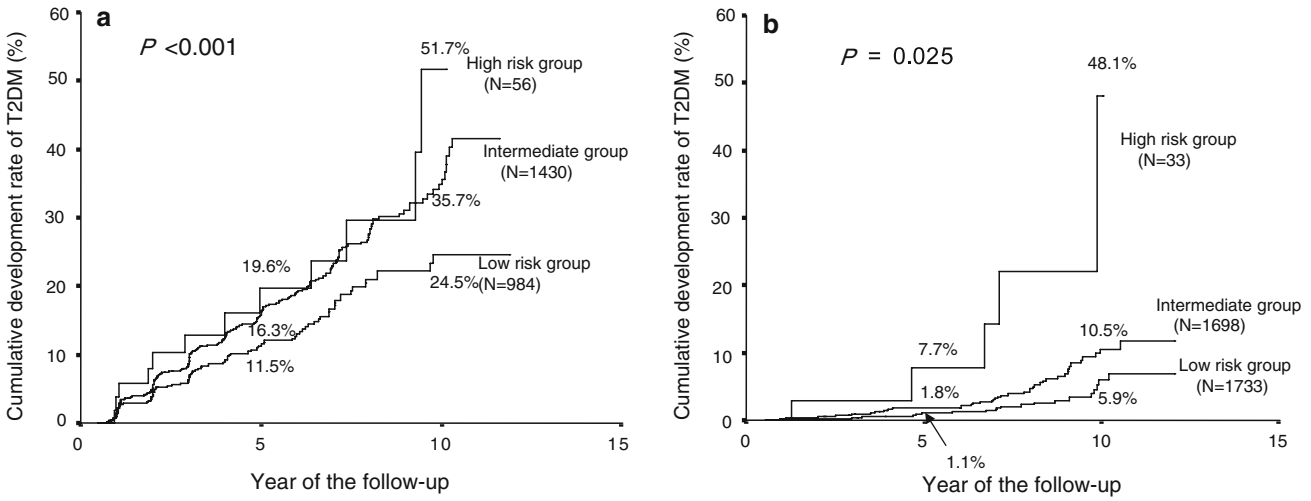


**Fig. 3** **a** Cumulative development rate of T2DM in NAFLD patients with prediabetes based on risk stratification according to differences in physical activity, mean levels of GGT, and mean levels of triglyceride during follow up. **b** Cumulative development rate of T2DM in NAFLD patients with normal glucose level based on risk stratification according to differences in physical activity, mean levels of GGT, and mean levels of triglyceride during follow up

patients with prediabetes should be carefully followed to reduce the development of T2DM. The next problem is that the prediabetes rate in patients with NAFLD was high. The present study showed that the prediabetes rate in NAFLD patients without T2DM was about 40% at the time of the initiation of follow up.

Third, in addition to prediabetes, physical activity of less than 60 min per week, and elevation of mean GGT and TG during follow up enhanced the development of T2DM in patients with NAFLD. The hazard ratio for these factors was weaker than that for prediabetes status. However, physical activity of 60 min or more per week, and normalization of mean GGT and TG during follow up reduced the development of T2DM even in NAFLD patients with prediabetes. The finding that physical activity reduced the development of T2DM is in accordance with the data reported by the Diabetes Prevention Program Research Group [22]. About the GGT level, Fraser et al. [23] have shown that GGT is associated with T2DM and/or insulin resistance by a metaanalysis. Normalization of mean GGT and TG during follow up is speculated to relieve the degree of steatosis. Thus, regarding the daily management of patients with NAFLD, physicians should pay attention to the onset and early diagnosis of T2DM. When NAFLD occurs, improvement of prediabetes status and physical activity, and normalization of mean GGT and TG during follow up is important to prevent the onset of T2DM.

There was not a significant difference between male and female patients in the development of T2DM in the present study. Serum ALT and GGT levels are usually higher in males than in females. In the present study, the serum ALT at the initiation of follow up was 37.6 ± 25.1 IU/l in males and 27.3 ± 33.7 IU/l in females. The serum GGT at the initiation of follow up was 78.4 ± 82.8 IU/l in males and 36.2 ± 30 IU/l in females. However, age at the initiation of follow up was 48.3 ± 8.4 years in males and 53.1 ± 8.7 years in females. The results show that the development of T2DM in males was the same as that in females due to their young age, in spite of the elevation of serum ALT and GGT.

The prevalence of T2DM is increasing dramatically in the United States, and increases in many newly developed and developing countries in Asia, including Japan, have been ever greater over the past decades [24]. Now, approximately 8–10% of adults in Japan have T2DM. T2DM is a serious, costly disease. Treatment of T2DM may prevent some of its devastating complications, but does not usually restore normoglycemia or eliminate all the adverse consequences [25]. In general, T2DM is associated with a genetic predisposition, but it is also strongly influenced by lifestyle-related factors, such as eating habits and/or physical activity [22, 24, 25]. The risk factors associated with T2DM include family history, age, gender, obesity, smoking, HCV infection, visceral fat, and physical activity. The present study shows that the four factors of glucose level, physical activity, mean GGT, and mean TG are associated with the development of T2DM in patients with NAFLD.

In conclusion, our retrospective study suggests that the annual incidence of T2DM among patients with NAFLD was about 1.7%. The improvement of prediabetes status and physical activity, and the normalization of mean GGT and TG during follow up are important to prevent the development of T2DM in patients with NAFLD.

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**Conflict of interest statement** The authors declare that there is no conflict of interest associated with this study.

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