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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

   WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJH* as 0.52. The *WJH*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Hepatology is 42/70.

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ORIGINAL ARTICLE

Observational Study

Prevalence of nonalcoholic fatty liver disease and its association with age in patients with type 2 diabetes mellitus

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Abstract

BACKGROUND
Type 2 diabetes mellitus (T2DM) is a risk factor for nonalcoholic fatty liver disease (NAFLD).

AIM
To determine the prevalence and clinical correlates of NAFLD in a large cohort of patients with T2DM.

METHODS
Four hundred thirty-seven participants with T2DM who consulted at Meijo Hospital from April 2019 to September 2020 and underwent computed tomography (CT) were assessed. The mean age was 74 ± 13 years, and 269 were men. Hepatic attenuation minus splenic attenuation (CT_{L-S}) less than 1 Hounsfield unit was considered fatty liver. NAFLD was defined as fatty liver in the absence of significant alcohol consumption and hepatitis virus infection. A multiple logistic regression was used to assess the independent factors associated with NAFLD.

RESULTS
NAFLD was identified in 25.2% of the participants. Young age (odds ratio [OR] = −0.945; 95% confidence interval [CI]: 0.922–0.969), higher hemoglobin levels (OR = 1.501, 95%CI: 1.278–1.764), lower high-density lipoprotein (HDL) cholesterol

levels (OR = 0.971, 95%CI: 0.953–0.989), and the absence of dialysis (OR = 0.109, 95%CI: 0.014–0.856) were independent predictors of NAFLD.

CONCLUSION
NAFLD was detected with CT in 25.2% of the participants. NAFLD was associated with younger age, higher hemoglobin levels, lower HDL cholesterol levels, and an absence of dialysis.

Key Words: Age; Computed tomography; Dialysis; Hemoglobin; Nonalcoholic fatty liver disease; Type 2 diabetes mellitus

Core Tip: Type 2 diabetes mellitus (T2DM) is a risk factor for nonalcoholic fatty liver disease (NAFLD). The prevalence of NAFLD by computed tomography (CT) has been reported in a few studies. The clinical correlates of NAFLD are often ambiguous. We determined the prevalence and clinical correlates of NAFLD determined by CT in a large cohort of patients with T2DM. The prevalence of NAFLD by CT was 25.2%. NAFLD was associated with younger age, higher hemoglobin levels, lower HDL cholesterol levels, and an absence of dialysis.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) frequently coexists with type 2 diabetes mellitus (T2DM). Both synergistically increase adverse outcomes[1,2]. NAFLD, T2DM, and obesity are epidemiologically correlated, but their causal interrelationships remain incompletely understood. Liu *et al*[3] proposed the hypothesis of disease subphenotyping in which genetically-driven NAFLD promotes T2DM and central obesity but protects against overall obesity. In contrast, genetically-driven T2DM and obesity increase the NAFLD risk.

A meta-analysis showed that the prevalence of NAFLD in patients with T2DM was 56% with ultrasonography (US) and proton magnetic resonance spectroscopy (MRI)[4]. The prevalence of NAFLD in patients with T2DM was highest in Europe (68%), but varies widely depending on the population. Three studies from Japan using US reported that the prevalence of NAFLD was 31%, 69%, and 61%[5-7]. The sensitivity of diagnosing NAFLD varies with the method. The prevalence of NAFLD in patients with T2DM detected by computed tomography (CT) was 10% in the United States[8], 22% in Turkey[9], and 27% in Japan[10].

In patients with T2DM, NAFLD is associated with an increased risk of overall death[11] but not with liver-related deaths[8]. Meanwhile, in NAFLD patients, T2DM is associated with advanced liver fibrosis [12] and increased mortality related to liver-related deaths[13]. NAFLD in patients with T2DM is associated with an increased risk of cardiovascular disease[7,9,10,14]. However, some reports have denied this association[8,15-17]. A positive association between NAFLD and nephropathy in patients with T2DM has been reported in some studies[18,19], while others did not find an association[20-22]. The association of NAFLD with cardiovascular risk and chronic kidney disease in the general population was reported to start in childhood[23,24].

We studied the prevalence of NAFLD in patients with T2DM in our hospital using CT and determined the factors associated with NAFLD in patients with T2DM.

MATERIALS AND METHODS

Study population

Data of patients with T2DM were retrieved from the hospital database. There were 724 Japanese diabetic patients who consulted at the Federation of National Public Service Personnel Mutual Aid Associations Meijo Hospital from April 2019 to September 2020. We excluded participants who had chronic hepatitis B (*n* = 6) and C (*n* = 28) infections, no assessment of hepatitis B surface antigen and

hepatitis C virus antibody (*n* = 105), and an alcohol intake ≥ 20 g/d (*n* = 33). We also excluded 115 participants who did not have an abdominal CT examination; thus, 437 participants (269 men and 168 women) were included in the analysis (Figure 1). The mean age was 74 ± 13 years. There were 322 patients treated with oral hypoglycemic agents, 32 with insulin, one with a glucagon-like peptide-1 receptor agonist, and 82 with diet and exercise. All patients had more than a year with T2DM.

The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of Federation of National Public Service Personnel Mutual Aid Associations Meijo Hospital (Approval No. 166). Written informed consent was waived because the data were analyzed anonymously based on information stored in the hospital database.

Abdominal CT examinations

A non-enhanced CT was performed using either a 16-section multidetector scanner (Aquilion 16; Canon Medical Systems, Tochigi, Japan), a 64-section multidetector scanner (Aquilion 64; Canon Medical Systems, Tochigi, Japan), or an 80-section multidetector scanner (Aquilion Prime SP/iEdition; Canon Medical Systems, Tochigi, Japan). The CT indications were to screen for diseases in the chest and abdomen in 430 patients. The CT was performed to investigate liver diseases in seven patients. Nine and three regions of interest were positioned at the liver or spleen, respectively, to avoid macroscopic vessels. Median hepatic or splenic attenuation values were obtained. Hepatic attenuation minus splenic attenuation (CT_{L-s}) less than 1 Hounsfield unit was considered fatty liver[25].

Statistical analysis

Student's t-test was used to analyze differences in continuous variables between two groups. Categorical variables were compared with the Chi-squared or Fisher's exact test. Linear regression was performed to assess the relationship between two variables. Multiple logistic regression was performed to determine the independent factors associated with the presence of NAFLD. *P* values < 0.05 were considered significant. All analyses were performed with StatFlex version 6.0 for Windows (StatFlex, Osaka, Japan).

RESULTS

Fatty liver was detected in 110 of 437 patients (25.2%). It was significantly associated with male gender (*P* = 0.005), younger age (*P* < 0.001), greater height (*P* < 0.001) and weight (*P* < 0.001), higher body mass index (BMI) (*P* < 0.001), blood parameters [higher white blood cell counts (*P* = 0.021) and higher hemoglobin (*P* < 0.001)], altered liver function tests [higher albumin (*P* < 0.001), higher total bilirubin (*P* = 0.015), aspartate aminotransferase (*P* = 0.014), alanine aminotransferase (*P* < 0.001), and gamma glutamyl transpeptidase (*P* < 0.001)], kidney function [lower creatinine (*P* = 0.012) and higher estimated glomerular filtration rate (eGFR) (*P* = 0.004)], metabolic status [higher total cholesterol (*P* = 0.012), lower high density lipoprotein (HDL) cholesterol (*P* = 0.039), higher triglycerides (*P* < 0.001), and higher low density lipoprotein (LDL) cholesterol (*P* = 0.001)], a lower fibrosis-4 (FIB-4) index (*P* = 0.005), and non-hypertensive (*P* = 0.013) and non-dialysis patients (*P* = 0.003) (Table 1). Fatty liver also tended to be associated with higher HbA1c (*P* = 0.066).

Multivariate logistic regression was used to elucidate the independent factors associated with fatty liver. Gender, age, BMI, HbA1c, white blood cell count, hemoglobin, albumin, eGFR, total cholesterol, HDL cholesterol, triglyceride, LDL cholesterol, hypertension, and dialysis therapy were analyzed. Age (*P* < 0.001), hemoglobin level (*P* < 0.001), HDL cholesterol level (*P* = 0.002), and absence of dialysis (*P* = 0.035) were independent factors associated with fatty liver (Table 2).

The patients were stratified according to age, hemoglobin level, and HDL cholesterol level, and the association with fatty liver was assessed. The prevalence of fatty liver significantly decreased with increasing age (*P* < 0.001) (Figure 2A), significantly increased as hemoglobin levels increased (*P* < 0.001) (Figure 2B), and was significantly higher in patients with HDL cholesterol < 70 mg/dL (29.9%) than patients with HDL cholesterol ≥ 70 mg/dL (13.8%) (*P* = 0.012) (Figure 2C).

DISCUSSION

The prevalence of NAFLD in patients with T2DM detected by CT was 25.2%. NAFLD was associated with younger age, higher hemoglobin levels, lower HDL cholesterol levels, and the absence of dialysis.

A previous meta-analysis found that the prevalence of NAFLD in patients with T2DM was 56% with US or proton magnetic resonance spectroscopy[4]. The prevalence of NAFLD in patients with T2DM detected by CT was 10% in the United States[8], 22% in Turkey[9], and 27% in Japan[10]. Lee *et al*[26] reported that the sensitivity of US (92%) for detecting more than 30% hepatic steatosis was higher than CT (64%). The prevalence of NAFLD in this study is comparable to the reported prevalence in patients with T2DM diagnosed by CT in Japan. In a preliminary study of 179 subjects who attended health

Table 1 Demographics of subjects

Variables	ALL (*n* = 437)	Fatty liver (*n* = 110)	Non-fatty liver (*n* = 327)	*P* value
Gender (Male/Female)	269/168	80/30	189/138	0.005
Age (yr)	74.0 ± 13.0	64.7 ± 13.0	77.1 ± 11.0	< 0.001
Height (cm)	159.4 ± 10.2	163.2 ± 10.0	158.2 ± 9.9	< 0.001
Body weight (kg)	61.3 ± 14.5	70.0 ± 16.6	58.5 ± 12.5	< 0.001
BMI (kg/m^2)	24.0 ± 4.9	26.0 ± 4.7	23.3 ± 4.7	< 0.001
HbA1c (%)	7.0 ± 1.2	7.2 ± 1.2	6.9 ± 1.2	0.066
Blood glucose (mg/dl)	164 ± 80	170 ± 116	161 ± 63	0.297
White blood cells (/μL)	6618 ± 2299	7056 ± 1649	6470 ± 2463	0.021
Hemoglobin (g/dL)	12.6 ± 2.4	14.2 ± 2.1	12.0 ± 2.2	< 0.001
Platelets (10^4/μL)	20.7 ± 7.0	20.4 ± 5.5	20.8 ± 7.4	0.615
Prothrombin time (%)	89.6 ± 22.3	89.2 ± 23.6	89.7 ± 22.1	0.895
Albumin (g/dL)	3.7 ± 0.7	3.9 ± 0.6	3.6 ± 0.6	< 0.001
Total bilirubin (mg/dL)	0.76 ± 0.50	0.86 ± 0.49	0.72 ± 0.49	0.015
ALP (U/L)	266 ± 156	247 ± 80	272 ± 176	0.182
AST (U/L)	25.3 ± 22.8	29.0 ± 20.2	23.0 ± 23.4	0.014
ALT (U/L)	23.5 ± 20.8	35.0 ± 27.4	19.0 ± 16.1	< 0.001
GGT (U/L)	46.2 ± 63.1	68.0 ± 74.4	38.0 ± 56.6	< 0.001
Creatinine (mg/dL)	1.71 ± 2.10	1.27 ± 1.58	1.85 ± 2.22	0.012
eGFR (mL/min)	52.0 ± 29.2	58.9 ± 21.9	49.6 ± 30.9	0.004
Total cholesterol (mg/dL)	181 ± 50	193 ± 64	177 ± 43	0.012
HDL cholesterol (mg/dL)	53 ± 17	50 ± 15	54 ± 17	0.039
Triglyceride (mg/dL)	160 ± 179	228 ± 299	134 ± 87	< 0.001
LDL cholesterol (mg/dL)	101 ± 36	111 ± 40	96 ± 33	0.001
FIB-4 index	2.20 ± 1.56	1.84 ± 1.08	2.32 ± 1.67	0.005
Cirrhosis (%)	8 (1.8)	1 (0.9)	7 (2.1)	0.405
Hepatocellular carcinoma (%)	7 (1.6)	1 (0.9)	6 (1.8)	0.504
Cerebrovascular accident (%)	45 (10)	9 (8.2)	36 (11)	0.399
Cardiovasculart disease (%)	137 (31)	29 (26)	108 (33)	0.193
Dyslipidemia (%)	205 (47)	53 (48)	152 (46)	0.758
Hypertension (%)	270 (62)	57 (51)	213 (65)	0.013
Dialysis (%)	45 (10)	3 (2.7)	42 (12)	0.003

Values are expessed as mean ± SD. Statistical analysis are conducted using the chi-squared test, Fisher's exact test, or Student's *t* test. ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanin aminotransferase; BMI: Body mass index; GGT: Gamma glutamyl transpeptidase; eGFR: Estimated glomelular filtration rate; HDL cholesterol: High density lipoprotein cholesterol; LDL cholesterol: Low density lipoprotein cholesterol; FIB-4 index: Fibrosis-4 index.

screening in our hospital (120 males and 59 females; 53.7 ± 10.8 years), CT detected fatty liver in 40 (22%). Thus, the prevalence of NAFLD in T2DM is higher than in the general population considering older age.

The prevalence of NAFLD significantly decreased with increasing age in this study. In contrast, Targher *et al*[14] reported that the prevalence of NAFLD detected by US in patients with T2DM increased with age; 65% among patients aged 40 to 59 and 75% among those aged 60 and older. The difference in this study compared to Targher's regarding the association of NAFLD and age may be attributed to the difference in the mean age of the participants (74 *vs* 64 years, respectively). By combining Targher's results and this study, it is suggested that the prevalence of NAFLD increases with

Table 2 Multivariate analysis for factors associated with fatty liver

Variables	Odds ratio	95% confidence interval	*P* value
Age	0.945	0.922-0.969	< 0.001
Hemoglobin	1.501	1.278-1.764	< 0.001
HDL cholesterol	0.971	0.953-0.989	0.002
Dialysis	0.109	0.014-0.856	0.035

HDL cholesterol: High density lipoprotein cholesterol.

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┌─────────────────────────────────────┐
│ 724 patients with type 2 diabetes    │
│ mellitus                             │
└─────────────────────────────────────┘
        │         ┌──────────────────────────────┐
        │────────▶│ 6 patients with HBsAg        │
        │         └──────────────────────────────┘
        │         ┌──────────────────────────────┐
        │────────▶│ 28 patients with HCVAb       │
        │         └──────────────────────────────┘
        │         ┌──────────────────────────────┐
        │────────▶│ 105 patients without         │
        │         │ assessment of HBsAg or HCVAb │
        │         └──────────────────────────────┘
        │         ┌──────────────────────────────┐
        │────────▶│ 33 patients with alcoholic   │
        │         │ intake ≥ 20 g/d              │
        │         └──────────────────────────────┘
        ▼
┌─────────────────────────────────────────────┐
│ 552 patients with type 2 diabetes mellitus   │
│ who have none of HBsAg, HCVAb or alcoholic   │
│ intake ≥ 20 g/d                              │
└─────────────────────────────────────────────┘
        │         ┌──────────────────────────────┐
        │────────▶│ 115 patients without         │
        │         │ abdominal CT examination     │
        │         └──────────────────────────────┘
        ▼
┌──────────────────────────────────────────────┐
│ 437 patients with type 2 diabetes mellitus    │
│ and abdominal CT examination, who have none   │
│ of HBsAg, HCVAb or alcoholic intake ≥ 20 g/d  │
└──────────────────────────────────────────────┘
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DOI: 10.4254/wjh.v14.i6.1226 **Copyright** ©The Author(s) 2022.
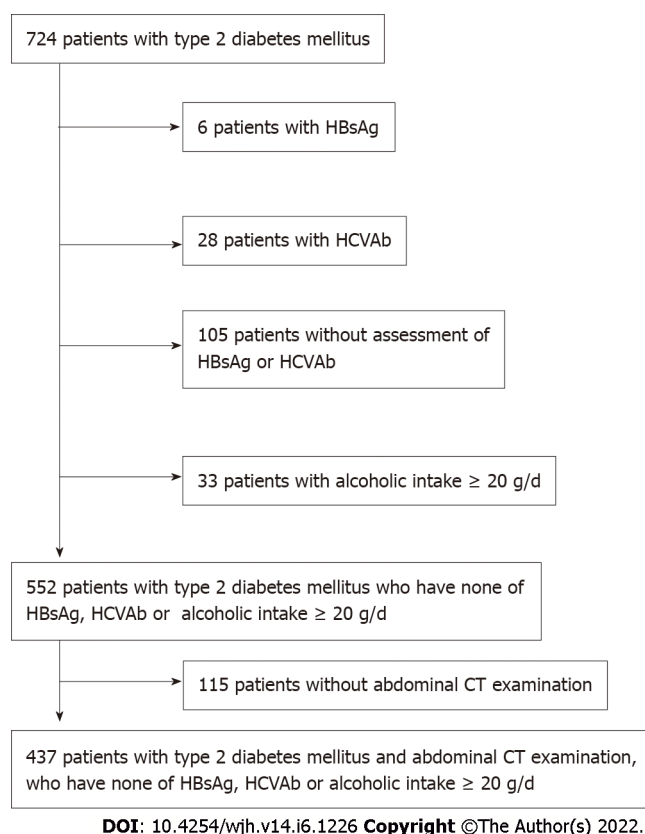
Figure 1 The participants in the present study consisted of 724 Japanese type 2 diabetic patients who consulted at Meijo Hospital from April 2019 to September 2020. We excluded participants who had chronic hepatitis B (*n* = 6) and C (*n* = 28) infection, no assessment of hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (*n* = 105), and alcohol intake ≥ 20 g/d (*n* = 33). We also excluded 115 participants with no abdominal computed tomography examinations. The final analysis included 437 participants (269 men and 168 women). HCVAb: Hepatitis C virus antibody; HBsAg: Hepatitis B surface antigen; CT: Computed tomography.

age until about 60 years (as in Targher's study) and then decreases with age, as shown in this study. An "inverted U curve," in which the prevalence of NAFLD reaches a peak in late adulthood and decreases afterward has been reported in the general population[27-29]. However, a meta-analysis observed a consistent increase in the NAFLD prevalence across all age groups[30].

Poor nutritional status is more common in older people[31]. Age-related changes in appetite, health problems, and social problems predispose older adults to less food intake. Poor nutritional status in older people is also common in patients with T2DM[32]. The decreasing prevalence of NAFLD with age shown in the present study may be attributed to poor nutritional status. Age significantly negatively correlated with BMI in this study (*r* = −0.32, *P* < 0.001, data not shown). A high BMI is associated with NAFLD[28] and a low BMI is associated with poor nutritional status[33]. BMI was associated with NAFLD in this study by univariate analysis but not by multivariate analysis.

In this study, lower hemoglobin values were associated with a lower prevalence of NAFLD. Anemia is common in the elderly and an indicator of poor nutritional status[34]. Therefore, the lower prevalence of NAFLD in patients with lower hemoglobin values may be attributed to the poor nutritional status of these patients. Hemoglobin values also significantly positively correlated with BMI (*r* = 0.21, *P* < 0.001, data not shown).

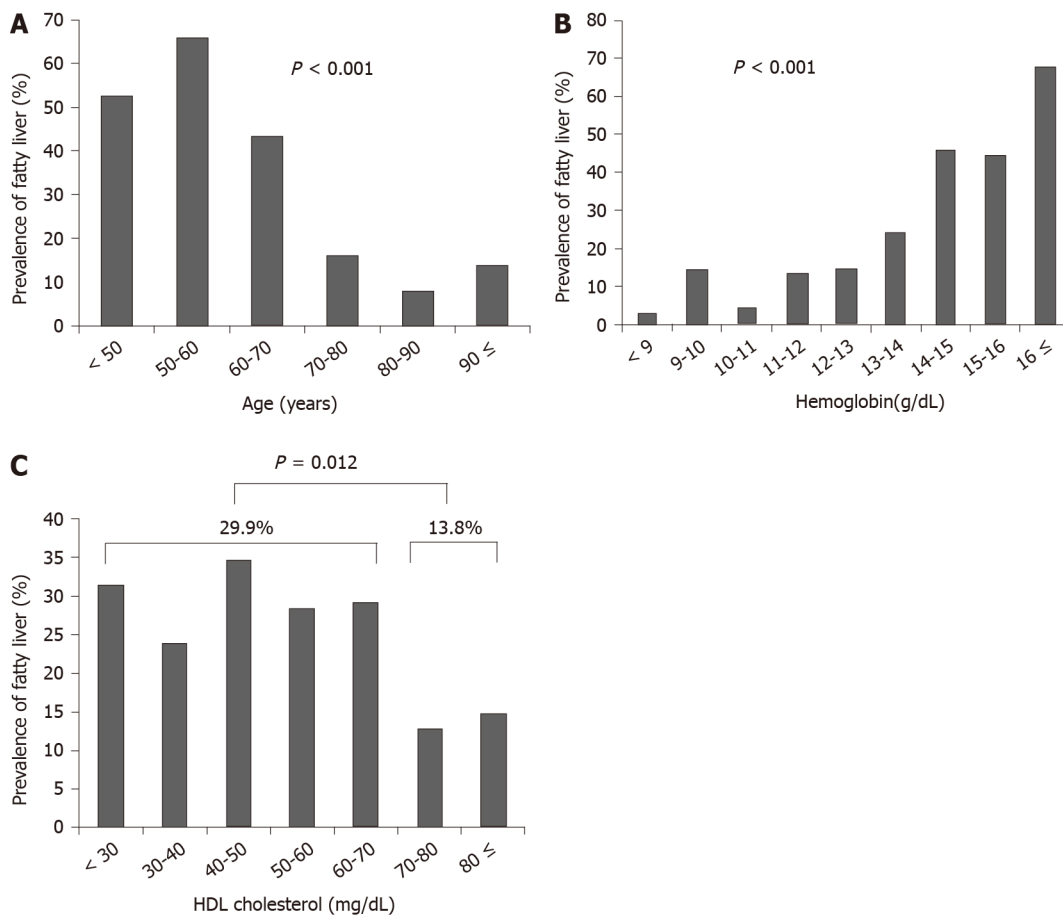**DOI**: 10.4254/wjh.v14.i6.1226 **Copyright** ©The Author(s) 2022.

Figure 2 The patients were stratified according to age, hemoglobin level, and high-density lipoprotein cholesterol level, and the association with fatty liver was assessed. A: The prevalence of fatty liver significantly decreased with age (P < 0.001); B: The prevalence of fatty liver significantly increased as hemoglobin increased (P < 0.001); C: The prevalence of fatty liver was significantly higher in patients with high-density lipoprotein cholesterol of < 70 mg/dL (29.9%) than those with HDL cholesterol ≥ 70 mg/dL (13.8%) (P = 0.012). HDL: High-density lipoprotein

Higher HDL cholesterol values were associated with a lower prevalence of NAFLD. This association between HDL cholesterol and NAFLD has previously been reported[28].

Dialysis treatment was associated with a lower prevalence of NAFLD. Diabetic nephropathy affects approximately 25% of patients with T2DM and is the leading cause of renal failure. Two studies reported that NAFLD is inversely associated with nephropathy in patients with T2DM, similar to this study[20,21]; however, some studies have reported a positive or no association[18,19,22]. The difference in the studied populations may cause this discrepancy. When the study population was not limited to patients with T2DM, a meta-analysis showed a positive association between NAFLD and chronic kidney disease[35]. However, in patients with T2DM, this association is still ambiguous.

This study did not find an association between NAFLD and cardiovascular disease. This association has been previously reported[7,9,10,14]; however, other studies deny it[8,15-17]. Higher HDL cholesterol values associated with a lower prevalence of NAFLD in this study reduce the risk of cardiovascular disease[36]. Thus a follow-up study may reveal an association between NAFLD and cardiovascular disease.

In this study, the number of patients with cirrhosis or hepatocellular carcinoma (HCC) was small, and cirrhosis and HCC were not associated with NAFLD. In a follow-up study of patients with T2DM (mean, 10.9 years), Adams *et al*[11] reported that 5 of 116 patients with NAFLD and none of 221 patients without NAFLD died from liver-related causes. Dunn *et al*[8] reported that NAFLD was not associated with liver-related outcomes (transplant, HCC, or encephalopathy) in patients with T2DM in a five-year retrospective cohort study. Further studies are needed to assess these associations.

There are three limitations to this study. First, it is a cross-sectional study. There may be a question of whether NAFLD decreases with age. Poor nutritional status in older people may be one reason why NAFLD decreases with age. It is also possible that we assessed a certain subpopulation of T2DM with a low risk of NAFLD and survival until older age, while the patients with a high risk of NAFLD dropped out until older age because of complications. Thus, the temporal association of NAFLD with the factors assessed in this study has to be clarified by prospective cohort studies. Second, fatty liver was diagnosed by CT in this study. The sensitivity of MRI, US, and CT for detecting a fatty liver of 5% or higher is 77%-

80%, 53%-62%, and 50% compared with liver biopsy[37]. However, a liver biopsy is invasive and has a risk of severe complications. Thus noninvasive modalities, such as US, CT, and MRI, have been commonly used to detect fatty liver. MRI is expensive and scarce. The disadvantage of US is its subjective nature. The high liver iron content increases CT Hounsfield units and may obliterate the diagnosis of fatty liver. However, CT is widely available in Japan, and the diagnosis is objective. Thus, CT is a promising modality for diagnosing fatty liver. Third, the present study was performed in a single hospital. The prevalence found has to be reevaluated in multicenter studies.

CONCLUSION

The prevalence of NAFLD in patients with T2DM detected by CT was 25.2%. NAFLD was associated with age, hemoglobin level, HDL cholesterol level, and the absence of dialysis treatment.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes mellitus (T2DM) is an established risk factor for the development of nonalcoholic fatty liver disease (NAFLD). Both synergistically increase adverse outcomes.

Research motivation

The prevalence of NAFLD assessed by computed tomography (CT) was reported only in a few studies. The clinical correlates of NAFLD are often ambiguous.

Research objectives

To determine the prevalence and clinical correlates of NAFLD assessed by CT in a large cohort of T2DM patients.

Research methods

Four hundred thirty-seven participants with T2DM who consulted at Meijo Hospital from April 2019 to September 2020 and underwent CT were assessed.

Research results

The prevalence of NAFLD as detected by CT was 25.2% in T2DM patients, and NAFLD was associated with a younger age, higher hemoglobin levels, lower high density lipoprotein cholesterol levels, and absence of dialysis treatment.

Research conclusions

The prevalence of NAFLD in T2DM is higher than in the general population considering older age and decreases with age.

Research perspectives

The association of NAFLD with age has to be clarified by prospective cohort studies.

FOOTNOTES

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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