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A High Fibrosis-4 Index is Associated with a Reduction in the Estimated Glomerular Filtration Rate in Non-obese Japanese Patients with Type 2 Diabetes Mellitus

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Liver fibrosis is associated with non-alcoholic fatty liver disease (NAFLD), and one of the most important risk factors for NAFLD is type 2 diabetes (T2DM). The Fibrosis-4 (FIB-4) index, a noninvasive liver fibrosis score, has been found to be useful for estimating liver fibrosis. Because individuals with non-obese NAFLD were recently reported to be metabolically unhealthy and have a higher risk of T2DM than individuals with obese NAFLD, we hypothesized that the clinical factors related to a high FIB-4 index would differ between non-obese and obese Japanese T2DM patients. Accordingly, we examined the relationship between clinical factors and the FIB-4 index in non-obese and obese Japanese patients with T2DM. We divided 265 patients into two groups by BMI level—a non-obese group (n = 149) and an obese group (n = 116)—and examined the correlation between the FIB-4 index and clinical parameters. Single regression analysis revealed that a high FIB-4 index was correlated with a reduction in the estimated glomerular filtration rate and hypertension in the non-obese group. Importantly, multiple regression analysis showed that only a reduction in the estimated glomerular filtration rate was significantly associated with a high FIB-4 index in the non-obese group. These results demonstrated that non-obese T2DM patients with a high FIB-4 index might be at risk of kidney dysfunction. Our findings may enable the more appropriate treatment of T2DM patients based on BMI level.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most widespread lifestyle diseases worldwide. The pathogenesis of T2DM is characterized mainly by insulin resistance or pancreatic β-cell failure. As the number of patients with T2DM and obesity has been increasing dramatically worldwide, the number of patients with non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), has also been increasing. Obesity is closely associated with liver fibrosis. However, NAFLD develops even in individuals with a normal body mass index (BMI), which is known as "non-obese NAFLD" (1). The prevalence of non-obese NAFLD varies widely. The reported prevalence of non-obese NAFLD is 12.6% in Japan (2). It is therefore necessary to evaluate liver fibrosis in non-obese patients with T2DM. Although liver biopsy is considered the gold standard for the assessment of liver fibrosis, it has some limitations, including invasiveness, sampling variability, and costs (3), and it may thus be unsuitable for the large-scale screening of liver fibrosis. To overcome these problems, several clinical and biochemical scoring systems that noninvasively predict advanced liver fibrosis have been proposed (4).

The Fibrosis-4 (FIB-4) index, a noninvasive liver fibrosis score, has been reported to be useful for predicting liver fibrosis and monitoring disease activity (5). Recent studies reported that the FIB-4 index was associated with diabetic complications (6, 7). However, the clinical factors associated with a high FIB-4 index in non-obese Japanese patients with T2DM remain unclear. Importantly, the characteristics of non-obese and obese patients can differ because individuals with non-obese NAFLD are metabolically unhealthy and have a higher risk of

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T2DM than do individuals with obese NAFLD (8, 9). Thus, we considered that the clinical factors related to a high FIB-4 index would not be the same in non-obese and obese Japanese T2DM patients.

Accordingly, the objective of the present study was to examine the value of the FIB-4 index and to identify the clinical factors related to a high FIB-4 index in Japanese T2DM patients divided into two groups: a non-obese group and an obese group.

MATERIALS AND METHODS

Patients

We analyzed the data of 265 patients with T2DM (non-obese patients [non-obese group], n = 149; obese patients [obese group], n = 116) from July 2018 to December 2020. All patients were diagnosed as having T2DM according to the criteria of the American Diabetes Association (10): fasting blood glucose >126 mg/dL and glycated hemoglobin (HbA1c) ≥6.5%. They were further subclassified into two groups based on criteria outlined by the Japan Society for the Study of Obesity (11): non-obese (BMI <25) and obese (BMI ≥25). We excluded patients with liver disease (hepatitis B virus-related hepatitis, hepatitis C virus-related hepatitis, alcoholic hepatitis, autoimmune hepatitis), kidney disease (renal cancer, IgA nephropathy), hematologic disease (lymphoma, leukemia, multiple myeloma), or type 1 diabetes. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement when writing the manuscript (12). The patients we analyzed visited Nara Prefecture General Medical Center.

Biochemical measurements

Standard methods were used for biochemical analyses of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Platelet counts were measured using an ADVIA® 2120i Hematology System (Siemens; Munich, Germany). HbA1c was analyzed using high-performance liquid chromatography (HLC723-G9; Tosoh Bioscience; Tokyo, Japan). The clinical laboratory of Nara Prefecture General Medical Center performed all laboratory measurements.

Definitions

The FIB-4 index was calculated by Age (year) × AST (IU/L)/(√ALT (IU/L) × Platelet count (10^9/L) (13). A cutoff value of 1.3 or less, which is 90% negative for the progression of liver fibrosis (14), was applied. The estimated glomerular filtration rate (eGFR) was calculated using the following Japanese GFR inference formula: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL) − 1.094 × age (years) − 0.287 (× 0.739 for women) (15). In this study, chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2.

Statistical analysis

An unpaired Student's t-test and Mann–Whitney U test were used for comparisons of parametric data (age, BMI level, HbA1c level, platelet count, and eGFR) and non-parametric data (AST, ALT, and the FIB-4 index) between the obese and non-obese groups. Spearman's correlation model was used to calculate single correlations between the FIB-4 index and sex, BMI level, HbA1c level, eGFR, hypertension, and smoking status. To examine the relationships between the FIB-4 index and some parameters after adjustment for clinical characteristics, multiple linear regression analysis was performed. A regression analysis was adjusted for variables which were not included in the formula, such as sex, eGFR, the FIB-4 index, HbA1c, hypertension and smoking status. All statistical analyses were performed using R 3.5.2 (R Foundation for Statistical Computing; Vienna, Austria). Parametric data are presented as the mean ± standard deviation and non-parametric data are presented as the median (25–75th percentile). $P < 0.05$ was considered to indicate statistical significance.

Ethics approval

The protocol for this research project was approved by the Institutional Review Board of Nara Prefecture General Medical Center (Approval No. 681) on January 14, 2022, and conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained in the form of opt-out on the website of Nara Prefecture General Medical Center.

RESULTS

Table I summarizes patients' characteristics. No significant differences in age, the HbA1c level, platelet count, or eGFR were evident between the obese and non-obese groups. BMI level, AST, and ALT were significantly higher in the obese group than in the non-obese group. In the non-obese group, the percentage of patients who had a FIB-4 index ≥1.3 was 56.3%. In the obese group, the percentage of patients who had a FIB-4 index ≥1.3 was 56.8%. The median FIB-4 index was ≥1.3 in the obese and non-obese groups, and liver fibrosis

risk was present in both groups. Table II shows the types of antidiabetic medication taken in the two groups. Dipeptidyl peptidase (DPP4) inhibitor tended to be used in the non-obese group, whereas metformin was more commonly used in the obese group.

Table I. FIB-4 index and participants' clinical and biochemical parameters (N = 265)

Variable	All (n = 265)	Obese group (n = 116)	Non-obese group (n = 149)	*P* Value
Male/female sex (n)	175/90	76/40	99/50	0.874
Age (years)	69.4 ± 10.2	68.7 ± 9.6	69.9 ± 10.7	0.381
BMI (kg/m^2)	25.1 ± 4.1	28.9 ± 2.5	22.3 ± 2.3	**<0.001**
HbA1c (%)	8.3 ± 2.9	8.1 ± 1.7	8.5 ± 3.7	0.286
AST (IU/L)	21.0 (16.0–28.0)	22.0 (17.0–31.0)	20.0 (16.0–27.0)	**<0.05**
ALT (IU/L)	21.0 (14.0–33.0)	26.0 (17.0–39.0)	18.0 (13.0–27.0)	**<0.001**
Platelet count (10^9/L)	243.5 ± 86.3	235.0 ± 90.1	249.4 ± 83.1	0.209
FIB-4 index	1.3 (0.9–1.8)	1.3 (0.9–1.7)	1.4 (0.9–1.8)	0.522
eGFR (mL/min/1.73 m^2)	63.5 ± 24.1	61.2 ± 24.1	65.4 ± 24.1	0.162
Hypertension (n)	67	37	30	**<0.05**
Smoking (n)	19	10	9	0.419

Parametric data are shown as the mean ± standard deviation and non-parametric data are shown as the median (25–75th percentile) for all subjects and the obese and non-obese groups. Significant values are in bold. BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate.

Table II. Types of antidiabetic medication taken by patients

Antidiabetic medications	All	Obese group	Non-obese group	*P* value
Sulfonylurea (n)	35	17	18	0.539
Glinide (n)	3	1	2	0.713
Metformin (n)	52	34	18	**<0.001**
Alpha-glucosidase inhibitor (n)	6	2	4	0.602
Thiazolidinedione (n)	7	5	2	0.135
DPP-4 inhibitor (n)	57	18	39	**<0.05**
GLP-1 receptor agonist (n)	13	6	7	0.859
SGLT2 inhibitor (n)	36	17	19	0.653
Insulin (n)	40	14	26	0.224

DPP-4, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

We next performed a single regression analysis to identify the correlation between the FIB-4 index and clinical parameters (sex, HbA1c level, eGFR reduction, hypertension, and smoking status). HbA1c and an eGFR reduction was correlated with the FIB-4 index in the entire patient's population (Table III). In the non-obese group, the FIB-4 index was correlated with an eGFR reduction and hypertension but not with sex, HbA1c level, or smoking status (Table III). On the other hand, a high FIB-4 index was correlated with the HbA1c level in the obese group but not with sex, an eGFR reduction, hypertension, or smoking status (Table III).

Table III. Correlation of the FIB-4 index with clinical parameters

Parameters	All		Non-obese group		Obese group	
	r	*P* value	*r*	*P* value	*r*	*P* value
eGFR	−0.261	**<0.001**	0.391	**<0.001**	0.111	0.237
HbA1c	−0.130	**<0.05**	−0.083	0.343	−0.223	**<0.05**
Hypertension	0.111	0.115	0.260	**<0.05**	−0.047	0.645
Sex	−0.009	0.891	0.005	0.946	−0.036	0.700
Smoking	0.057	0.419	0.039	0.695	0.073	0.470

Significant values are in bold. HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate.

It remained unclear whether the correlation between the FIB-4 index and an eGFR reduction was independent of confounding factors in the non-obese group. In addition, it was also unclear whether the correlation between the FIB-4 index and HbA1c level was independent of confounding factors in the obese group. To examine the independent relationships among confounding factors, we next performed multiple linear regression analysis. The results showed that the correlation between the FIB-4 index and the eGFR reduction was maintained in the non-obese group after adjusting for sex, HbA1c level, hypertension, and smoking status (Table IV). Multiple linear regression analysis in the entire patient's population and obese group revealed that

the correlation between the FIB-4 index and HbA1c level was not independent after adjusting for sex, eGFR, hypertension, and smoking status (Table IV).

Table IV. Correlation of the FIB-4 index with clinical characteristics according to multiple linear regression analysis

All					
Characteristic	Regression coefficient β	SE	95% CI		*P* value
			Lower	Upper	
eGFR	–0.006	0.003	–0.012	0.0003	0.062
HbA1c	–0.047	0.037	–0.120	0.026	0.207
Hypertension	–0.160	0.180	–0.517	0.196	0.375
Sex	0.171	0.166	–0.156	0.499	0.302
Smoking	0.050	0.336	–0.615	0.715	0.881
Non-obese Group					
Characteristic	Regression coefficient β	SE	95% CI		*P* value
			Lower	Upper	
eGFR	–0.017	0.005	–0.029	–0.005	**<0.05**
HbA1c	–0.027	0.051	–0.130	0.075	0.600
Hypertension	–0.107	0.287	–0.679	0.464	0.710
Sex	0.460	0.259	–0.055	0.977	0.079
Smoking	0.325	0.577	–0.824	1.475	0.574
Obese Group					
Characteristic	Regression coefficient β	SE	95% CI		*P* value
			Lower	Upper	
eGFR	0.002	0.003	–0.005	0.009	0.520
HbA1c	–0.083	0.052	–0.188	0.021	0.119
Hypertension	–0.271	0.209	–0.688	0.146	0.199
Sex	–0.049	0.197	–0.441	0.343	0.803
Smoking	0.292	0.390	–0.484	1.070	0.455

Significant values are in bold. HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SE, standard error.

The association between the FIB-4 index and an eGFR reduction in the non-obese group might be influenced by the type of antidiabetic medication. To examine whether this association in the non-obese group was affected by the type of antidiabetic medication, we performed multiple linear regression analysis after adjusting for medication type. However, the type of antidiabetic medication had no effect in the non-obese group (Table V).

Table V. Correlation of the FIB-4 index with the type of antidiabetic medication according to multiple linear regression analysis in the non-obese group

Characteristic	Regression coefficient β	SE	95% CI		*P* value
			Lower	Upper	
eGFR	–0.014	0.004	–0.023	–0.005	**<0.05**
Sulfonylurea	0.065	0.323	–0.577	0.707	0.840
Glinide	–0.578	0.866	–2.299	1.142	0.506
Metformin	–0.050	0.306	–0.659	0.558	0.869
Alpha-glucosidase inhibitor	–0.018	0.622	–1.253	1.217	0.976
Thiazolidine	–0.238	0.796	–1.820	1.343	0.765
DPP-4 inhibitor	–0.281	0.253	–0.784	0.222	0.269
GLP-1 receptor agonist	–0.183	0.471	–1.120	0.753	0.698
SGLT2 inhibitor	–0.242	0.322	–0.883	0.398	0.455
insulin	0.088	0.096	–0.103	0.280	0.362

Significant values are in bold. eGFR, estimated glomerular filtration rate; DPP-4, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2; SE, standard error.

DISCUSSION

In this study, we evaluated liver fibrosis using the FIB-4 index in Japanese patients with T2DM. A high FIB-4 index was observed in both non-obese and obese patients with T2DM, suggesting that liver fibrosis was present even in the non-obese T2DM patients. In addition, we performed multiple linear regression analysis. In the non-obese group, the positive relationship between a high FIB-4 index and a reduction in the eGFR was revealed after adjustment for confounding factors. These results suggested that kidney dysfunction might be

specifically associated with liver fibrosis in non-obese patients with T2DM. Previous work showed that the FIB-4 index can predict the onset of CKD in non-diabetic individuals with NAFLD (16) or diabetic patients (7). Previously, Saito et al. (7) reported that high FIB-4 index was independently associated with diabetic kidney disease and proteinuria in Japanese patients with type 2 diabetes, while the significant correlation between high FIB-4 index and decrease of eGFR was not found in their report. In our study, there were the correlation between high FIB-4 index and an eGFR reduction in all group. There are discrepancies between our results and Saito et al. We considered that these discrepancies might be influenced by the difference of eGFR in each population of two studies. Concretely, the value of eGFR in the entire patient's population of our study was low compared to the previous report. Besides, the duration of diabetes was not shown in the previous report. These points may affect the discrepancies between the results of two studies. Another biomarker of liver fibrosis—the AST to ALT ratio—has been linked to an eGFR reduction in European patients with T2DM (17). There might be clinical differences between non-obese and obese patients with T2DM. Thus, our study is the first to show the different associations between a high FIB-4 index and clinical parameters in non-obese and obese patients with T2DM.

The mechanisms underlying the association of liver fibrosis with kidney dysfunction in non-obese patients with T2DM are still unknown. The FIB-4 index calculated with the formula by Vallet-Pichard et al. (13) can increase either with aging and an increase in the AST to ALT ratio or with a decrease in the platelet count. Therefore, the FIB-4 index might be influenced by age, the change in the AST to ALT ratio, or the platelet count. In this study, age and platelet count might not have affected our results because they did not significantly differ between the non-obese and obese groups. However, the AST to ALT ratio tended to be increased in the non-obese group compared with the obese group (Table I). It has been suggested that metabolic disorder inducing kidney dysfunction, which affects the AST to ALT ratio, might be related to a high FIB-4 index. On the other hand, the causal relationship between high the FIB-4 index and the onset of CKD has been reported. Impaired glucose tolerance, diabetes, hypertension, insulin resistance, plasma inflammatory factors, all of which are associated with NAFLD/NASH were reported as important factors for development of CKD in non-diabetic patients (18). Moreover, the lower plasma insulin-like growth factor-1 (IGF-1) levels may contribute to an eGFR reduction in individuals with advanced liver fibrosis (18). Another study showed that the various mechanisms including the development of arteriosclerosis, liver-derived inflammatory mediators, hepatorenal syndrome, and insulin resistance might be related to the onset of CKD in diabetic patients with high FIB-4 index (7). These mechanisms may be the potential underlying causes or reasons for the association between the FIB-4 index and an eGFR reduction among non-obese Japanese T2DM patients. Further research focusing on non-obese individuals with T2DM is needed.

Better pharmacological treatments for non-obese patients with liver fibrosis risk are also necessary. Glucagon-like peptide-1 (GLP-1) analogue, a therapeutic agent often used for the treatment of T2DM, inhibits hepatic steatosis and inflammation in non-obese mice (19). Another study revealed the specific beneficial effects of GLP-1 analogue on individuals with lean NASH through an improvement in hepatic inflammation (20). GLP-1 analogues have protective roles in maintain renal function in T2DM patients (21). The potential beneficial effects of metformin on NAFLD were also written in several articles (22). However, metformin may be contraindicated in diabetic patients with renal dysfunction. Thus, because we showed an association between liver fibrosis and kidney dysfunction in non-obese T2DM patients with liver fibrosis, GLP-1 analogue might be more useful in patients with non-obese NAFLD to protect against liver fibrosis and kidney dysfunction.

This study has several limitations. First, we could not accurately evaluate liver fibrosis by performing liver biopsy, so we could not identify the presence of NAFLD/NASH in the two groups. Second, due to the retrospective nature of the study, our findings reflect only an association with the prevalence of kidney dysfunction and cannot explain the association between a high FIB-4 index and the incidence of CKD. Third, we classified patients using criteria outlined not by the World Health Organization but by the Japan Society for the Study of Obesity. It might be valid to use stricter criteria in this study because individuals with obesity with a BMI <30 have an increased risk of T2DM (23). Our results are reflective of a Japanese population, and we could not explore the discrepancy between Japanese and European populations.

Recently, NAFLD has been renamed Metabolic dysfunction-associated fatty liver disease (MAFLD) (24). MAFLD is well described as a condition with a background of metabolic abnormalities, such as type 2 diabetes mellitus. In future studies, we would like to further investigate the relationship between the pathogenesis of diabetes and "MAFLD." In the present study, we showed that a high FIB-4 index is associated with a reduction in eGFR among non-obese Japanese patients with T2DM. Our results may help to elucidate the pathogenesis of non-obese T2DM patients with liver fibrosis risk and enable the more appropriate treatment of diabetes and liver fibrosis based on BMI level.

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