Synergistic effects of liver fibrosis and sarcopenia on endothelial dysfunction and arterial stiffness in patients with type 2 diabetes

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A B S T R A C T

Aims: To investigate synergistic effects of liver fibrosis evaluated by FibroScan and sarcopenia on endothelial function and arterial stiffness in patients with type 2 diabetes.

Methods: This cross-sectional study evaluated liver fibrosis (LF) and sarcopenia in 115 patients with type 2 diabetes. LF was assessed as the liver stiffness measurement (LSM) in transient elastography (FibroScan) and was defined as an LSM greater than or equal to 8.0 kPa. Sarcopenia was defined as a ratio of appendicular skeletal muscle mass to body mass index of <0.789 in men and <0.512 in women. Endothelial function was measured by reactive hyperemia index (RHI) with tonometry, and arterial stiffness was evaluated by the cardio-ankle vascular index (CAVI). Endothelial dysfunction was defined an RHI value below 1.67, while arterial stiffness was defined a CAVI value above 9.0. Patients were divided into four groups: no LF and no sarcopenia; LF but no sarcopenia; no LF but sarcopenia; and LF and sarcopenia. The composite of endothelial dysfunction of arterial stiffness was defined as an outcome.

Results: In patients with LF, RHI was significantly lower and CAVI was significantly higher than in patients without LF. Furthermore, RHI was significantly lower in patients with sarcopenia than in those without it. Patients with both LF and sarcopenia had the lowest RHI and the highest CAVI and urinary albumin levels. Sarcopenia and HDL cholesterol were independent factor the composite of endothelial dysfunction and arterial stiffness.

Conclusion: LF and sarcopenia are independently associated with endothelial dysfunction and arterial stiffness in patients with type 2 diabetes. Coexistence of LF and sarcopenia may synergistically lead to vascular damage and thus contribute to the high risk of cardiovascular disease in people with type 2 diabetes.

1. Introduction

Type 2 diabetes is well known to be associated with an increased risk of morbidity and mortality from atherosclerotic cardiovascular disease (CVD). Furthermore, it also is known to be a risk factor for the development of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) and liver fibrosis [1]. Approximately 50% to 60% of patients with type 2 diabetes have NAFLD [2]. NAFLD itself, especially liver fibrosis, is a predictor of CVD independently of other traditional risk factors [3,4]. Several studies demonstrated that liver fibrosis is associated with endothelial dysfunction and arterial stiffness [5–7], both of which are predictors of CVD morbidity and mortality. Recently, FibroScan (a transient elastography method) was developed as a means for non-invasively evaluating liver fibrosis by liver stiffness measurement (LSM), which is strongly correlated with the stage of liver fibrosis assessed by concurrent liver biopsy [8].

Sarcopenia is defined as a loss of skeletal muscle mass and muscle strength due to processes associated with both aging and chronic diseases [9]. Compared with people without diabetes, those with the disease were shown to have a threefold higher risk of sarcopenia after adjusting for age [10], indicating that diabetes is closely associated with an increased risk of sarcopenia. Muscle mass or function or both are lost in the early stage of type 2 diabetes, and they decline more significantly with age than in people without diabetes [11]. Sarcopenia also is an important prognostic factor for CVD morbidity and mortality in older people [12].

Because patients with type 2 diabetes often have both NAFLD (with significant fibrosis) and sarcopenia, we hypothesized that when liver
of the sodium-glucose transport protein 2 inhibitor dapagliflozin [13],
of more than 280 g/week for men and 140 g/week for women were
data were collected at baseline. Patients with excess alcohol consump-
tion and arterial stiffness in patients with type 2 diabetes.
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tide-1 receptor agonists; ARB, angiotensin II receptor blocker; ACEI,
sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium glucose
GGT,
creatinine ratio; AST, aspartate aminotransferase; ALT, alanine transaminase;
eGFR, estimated glomerular filtration rate; UACR, urinary albumin
FPG, fasting plasma glucose; Hb, hemoglobin; HDL, high-density lipopro-
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pres-
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2. Methods

2.1. Patient characteristics

We studied 115 consecutive patients with type 2 diabetes who were referred to the diabetes outpatient clinic at the Dokkyo Medical University Hospital for optimization of glycemic control. Although most of the patients had participated in a previous randomized controlled trial of the sodium-glucose transport protein 2 inhibitor dapagliflozin [13], data were collected at baseline. Patients with excess alcohol consumption of more than 280 g/week for men and 140 g/week for women were excluded from the study. Also excluded were patients with liver diseases such as chronic hepatitis B and C, autoimmune hepatitis, and primary biliary cirrhosis.

In all patients, we assessed body weight, body mass index (BMI), total fat mass, and laboratory values, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), low density lipoprotein cholesterol (LDL-cholesterol), platelet count (PLT), and serum creatinine. ALT, AST, and PLT were used to calculate the Fibrosis-4 (FIB-4) index with the following equation: FIB-4 = Age (years) × AST (U/L)/[PLT(109/L) × ALB/2 (U/L)]. Furthermore, serum creatinine was used to calculate the estimated glomerular filtration rate (eGFR).

All participants gave written informed consent. The study was approved by the institutional review board of Dokkyo Medical University and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000022155). The design and primary study results of our original study are reported elsewhere [14].

2.2. Sarcopenia

Body composition was analyzed by bioelectrical impedance analysis with the InBody 720 Analyzer (InBody Japan Inc., Tokyo, Japan) which provides impedance for each segment, including the four limbs and the trunk, by performing multi-frequency measurements to estimate the appendicular skeletal muscle mass (ASM). In this study, the ASM was calculated as the sum of the lean muscle mass in the bilateral upper and lower limbs. We adopted the definition of sarcopenia developed by the National Institutes of Health Sarcopenia Project, which defines sarcopenia as an ASM to BMI ratio (ASM:BM) of < 0.789 in men and < 0.512 in women [15]. In addition, we calculated the skeletal muscle mass index as ASM/height^2 (kg/m^2).

2.3. Liver fibrosis

FibroScan Transient elastography is an ultrasound-based elastography method that allows simultaneous evaluation of hepatic steatosis by measuring the controlled attenuation parameter (CAP) and liver fibrosis by measuring liver stiffness (LSM). LSM is strongly correlated with the stage of liver fibrosis assessed by concurrent liver biopsy [8]. On the basis of meta-analytic findings [16], we assumed the existence of significant liver fibrosis at an LSM value greater than or equal to 8.0 kPa. Furthermore, we defined significant hepatic steatosis as a CAP value greater than or equal to 280 dB/m [17].

2.4. Endothelial function

Endothelial function was evaluated by reactive hyperemia (RH) peripher-al arterial tonometry (PAT) with an EndoPAT2000 system (Itamar Medical, Caesarea, Israel). Participants were assessed in a fasting state in the early morning before taking any medications. Endothelial function was measured as flow-mediated dilation determined with an arterial tonometer on the index fingertip. The RH Index (RHI), which reflects the extent of RH, was automatically calculated by a computerized algorithm with an online system as the ratio of the mean pulse amplitude of the PAT signal over a 1-minute interval starting 1.5 min after cuff deflation in the control arm (C) and study arm (D) to the mean pulse amplitude of the PAT signal over a 2.5-minute interval before cuff inflation in the control arm (A) and study arm (B), i.e., as (C/D)/(A/B). Endothelial dysfunction was defined as an RH value below 1.67 [18,19]. The Framing-ham Heart Study reported that RH is inversely correlated with various cardiovascular risk factors [20].
according to the manufacturer’s recommendations [21]. To assess CAVI, electrocardiogram electrodes were placed on both wrists, a microphone (for phonocardiography) was placed on the sternum, and a blood pressure cuff was wrapped around each of the 4 limbs. CAVI values were automatically calculated with the following equation: \[ \text{CAVI} = \frac{\rho}{\Delta P} \times \ln\left(\frac{P_s}{P_d}\right) \times \text{PWV}^2 + b \]
where \( \rho \) is the blood density; \( P_s \) and \( P_d \) are systolic and diastolic blood pressure, respectively (in mm Hg); and PWV is the pulse wave velocity from the origin of the aorta to the tibial artery at the ankle level. The CAVI was originally derived from the stiffness parameter \( \beta \) [21]. The cutoff values for the CAVI were determined by the Japan Society for Vascular Failure, as follows: normal, <8.0; borderline, 8.0 to 8.9; and abnormal, greater than or equal to 9.0, and the Society uses a CAVI greater than or equal to 9.0 as the cutoff point for the presence of arteriosclerotic vascular disease [19,22].

2.6. Outcomes

The main outcome measures of our study were endothelial dysfunction and arterial stiffness, respectively.

We hypothesized that synergistic association of liver fibrosis and sarcopenia with endothelial dysfunction and arterial stiffness. To investigate whether liver fibrosis was associated with endothelial dysfunction and arterial stiffness, we used the cut-off LSM value to divide participants into subgroups with (LSM \( \geq \) 8.0 kPa) or without (LSM < 8.0 kPa) significant liver fibrosis, and to investigate whether sarcopenia was associated with endothelial dysfunction and arterial stiffness, we used the above-mentioned cut-off values for the ASM:BMI ratio to divide participants into subgroups with or without sarcopenia. Then, we used the above definitions to divide patients into 4 groups: group A, no liver fibrosis and no sarcopenia (n = 45); group B, liver fibrosis but no sarcopenia (n = 25); group C, sarcopenia but no liver fibrosis (n = 23); and group D, both liver fibrosis and sarcopenia (n = 14).

We also defined the composite of endothelial dysfunction (RHI < 1.67) and arterial stiffness (CAVI greater than 9.0) as an outcome. Compared with endothelial dysfunction or arterial stiffness alone, combining endothelial dysfunction with endothelial can improve diagnostic sensitivity of vascular damage, since endothelial dysfunction and arterial stiffness are independently involved in development of CVD.

2.7. Statistical analysis

Data are presented as means ± SD or medians and interquartile ranges (IQR). Differences in normally distributed data were assessed by a 1-way analysis of variance with the Newman-Keuls multiple comparison test. For non-normally distributed data, differences between groups were analyzed by the Kruskal-Wallis test with Dunn’s multiple comparison test. Correlations were determined by linear regression analysis or multivariate analysis. Logarithmic transformation of the urinary albumin creatinine ratio was used to render the distribution normal for parametric tests. A \( P \) value of <0.05 was considered statistically significant.

3. Results

The baseline characteristics of the study population are shown in Table 1. The mean age was 59.0 ± 13.8 years; mean BMI, 26.6 ± 4.7; mean CAVI, 8.85 ± 1.45; and mean RHI, 1.72 ± 0.42. Significant fibrosis (F2, LSM \( \geq \) 8.0 kPa) was found in 28.0% of 111 patients (Table 1). A FibroScan failure, defined as the inability to obtain
filtration rate; UACR, urinary albumin creatinine ratio; CAP, controlled arterial stiffness; DBP, diastolic blood pressure; LDL, low-density lipoprotein; FPG, fasting plasma glucose; Hb, hemoglobin; SBP, systolic blood pressure. Our findings expand previous observations by showing a stronger association between liver fibrosis and endothelial dysfunction in people with type 2 diabetes.

We then performed receiver operating characteristic (ROC) curve analysis for detecting the composite of endothelial dysfunction and arterial stiffness in our patients. Analysis of ROC showed that the AUCs for HDL cholesterol and LSM were 0.636 (P = 0.041) and 0.682 (P = 0.006) for detecting the composite of endothelial dysfunction and arterial stiffness, respectively.

4. Discussion

To our knowledge, this is the first study to investigate in patients with type 2 diabetes the synergistic effects of liver fibrosis and sarcopenia on endothelial function and arterial stiffness, both of which are early markers or predictors of CVD. We simultaneously evaluated liver fibrosis and sarcopenia and found that both conditions had significant effects on the RHI and CAVI.

The RHI was significantly lower in patients with liver fibrosis (defined as LSM ≥ 8.0 kPa), indicating that fibrosis is associated with endothelial dysfunction in people with type 2 diabetes. A previous study also found that serum ALT levels are related to impaired conduit vessel vascular endothelial function evaluated by brachial artery flow-mediated dilation in metabolically well-controlled patients with type 2 diabetes [23], and another study showed that the RHI is associated with histological severity of liver fibrosis in people with NAFLD [5].

The CAVI was significantly higher in patients with liver fibrosis than in those without it, indicating that fibrosis is related to increased arterial stiffness in type 2 diabetes. A previous study reported that arterial stiffness is independently associated with LSM on FibroScan in biopsy-proven NAFLD [7]. Furthermore, a prospective study demonstrated that higher arterial stiffness predicted development of advanced liver fibrosis in patients with both type 2 diabetes and NAFLD [24].

Overall, 33.3% of patients had sarcopenia (Table 1). Body weight, BMI, and total fat mass were significantly higher in patients with sarcopenia than in those without it (Supplementary Table 2). RHI was significantly lower in patients with sarcopenia than in those without it (1.57 ± 0.34 vs 1.80 ± 0.43, respectively; P = 0.0150; Fig. 1C), but CAVI was not different between the two groups.

Table 2 shows the comparison of the 4 groups of patients defined in the methods section above. RHI was significantly lower in group D (both liver fibrosis and sarcopenia) than in group A (no liver fibrosis and no sarcopenia); 1.51 ± 0.31 vs 1.89 ± 0.48, P < 0.01; Fig. 2A) and was lower in group C (sarcopenia but no liver fibrosis) than group A (1.61 ± 0.38 vs 1.89 ± 0.48, P < 0.05; Fig. 2A). In contrast, CAVI was significantly higher in group D than in group A (9.7 ± 1.2 vs 8.6 ± 1.2, P < 0.05; Fig. 2B). In addition, the urinary albumin to creatinine ratio was significantly higher in group D than in the other three groups (Table 2).

We performed multivariate logistic regression analysis for the composite of endothelial dysfunction and arterial stiffness adjustments for all potential confounding factors. As shown in Table 3, only ASM/BMI and HDL-cholesterol were independent factors the composite of endothelial dysfunction and arterial stiffness. This suggests that sarcopenia may be associated strongly with vascular damage in people with type 2 diabetes.

Table 2

|                | No LF/Sarco | LF/No Sarco | No LF/Sarco | LF/Sarco |
|----------------|-------------|-------------|-------------|----------|
| N (M/F)        | 45 (28/17)  | 25 (15/10)  | 23 (13/10)  | 14 (9/5)  |
| Age (years)    | 69.0 ± 13.5 | 59.5 ± 10.5 | 58.8 ± 17.3 | 63.9 ± 12.9 |
| Body weight (kg) | 66.6 ± 14.5 | 72.8 ± 14.5 | 69.3 ± 19.5 | 73.1 ± 11.1 |
| BMI            | 24.6 ± 3.8 | 26.8 ± 3.8 | 28.0 ± 5.6 | 29.1 ± 2.8 |
| Total fat (kg) | 18.2 ± 6.8 | 23.6 ± 7.1 | 26.1 ± 7.1 | 27.1 ± 7.3 |
| Total muscle (kg) | 46.1 ± 10.6 | 48.1 ± 9.5 | 44.0 ± 10.8 | 42.7 ± 9.4 |
| ASM (g)        | 20.2 ± 5.1 | 21.4 ± 4.6 | 18.8 ± 5.5 | 17.5 ± 5.0 |
| ASM/BW (%)     | 30.1 ± 3.6 | 29.9 ± 6.5 | 25.9 ± 13.0 | 23.9 ± 5.6 |
| ASM/BMI (%)    | 0.82 ± 1.17 | 0.81 ± 0.30 | 0.66 ± 0.30 | 0.16 ± 0.30 |
| SMI            | 7.35 ± 1.17 | 7.84 ± 1.17 | 7.35 ± 1.44 | 6.92 ± 1.66 |
| FPG (mg/dl)    | 160 ± 15.7 | 147 ± 5.7 | 151 ± 15.7 | 156 ± 5.7 |
| HbA1c (%)      | 9.2 ± 1.7 | 8.6 ± 1.7 | 9.2 ± 1.9 | 9.0 ± 0.5 |
| LDL-cholesterol (mg/dl) | 112.4 ± 31.7 | 107.9 ± 36.3 | 114.9 ± 31.9 | 92.8 ± 25.4 |
| Triglyceride (mg/dl) | 115 (90.5, 159) | 127 (83, 178) | 138 (88.75, 239.5) | 132.5 (113.5, 178.3) |
| HDL-cholesterol (mg/dl) | 50.3 ± 13.3 | 50.9 ± 17.1 | 48.9 ± 10.8 | 46.2 ± 12.3 |
| eGFR (ml/min/1.73 m²) | 74.0 ± 15.0 | 70.8 ± 18.8 | 81.7 ± 22.5 | 69.5 ± 24.4 |

Data are the mean ± SD or the median and inter-quartile ranges. *P < 0.05, **P < 0.01, ***P < 0.001 vs. Group A; ||P < 0.05, ||P < 0.01, |||P < 0.001 vs. Group B; *P < 0.05, **P < 0.01, ***P < 0.001 vs. Group C.

BMI, body mass index; ASM, appendicular skeletal muscle mass; SM, skeletal muscle mass index; FPG, fasting plasma glucose; HB, hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, γ-glutamyltransferase; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; CAP, controlled attention parameter; LSM, liver stiffness measurement; CVD, cardiovascular disease.

10 valid measurements in a single patient, occurred in 5 participants. Body weight, BMI, total fat mass, AST, GGT, and the FIB-4 index were significantly higher in patients with liver fibrosis than in those without it (Supplementary Table 1). LDL-cholesterol and eGFR were significantly lower in patients with liver fibrosis than in those without it (Supplementary Table 1), as was RHI (1.57 ± 0.27 vs 1.78 ± 0.45, respectively; P = 0.0218; Fig. 1A), but CAP (Supplementary Table 1) and CAVI (9.42 ± 0.96 vs 8.73 ± 1.16, P = 0.0215; Fig. 1B) were significantly higher in those with than in those without fibrosis.
vascular events, including coronary artery disease or ischemic stroke, between sarcopenia and arterial stiffness in our study, a previous study also reported a relationship between frailty/sarcopenia and endothelial dysfunction in patients with type 2 diabetes. A previous study demonstrated that concurrent sarcopenia and NAFLD conferred a two-fold higher risk of mortality [29]. Sarcopenia and NAFLD with fibrosis share some pathophysiology, such as insulin resistance, inflammation, and increased oxidative stress [30]. Taken together, these results show that sarcopenia and NAFLD additively increase mortality, suggesting that risk stratification would be helpful in predicting mortality in people with type 2 diabetes.

We also found that, among the four subgroups, urinary albumin excretion was highest in patients with both liver fibrosis and sarcopenia. Albuminuria is not only a predictor of progressive diabetic kidney disease but also a marker of endothelial dysfunction. A prospective study demonstrated that low-grade albuminuria may be an independent risk factor for NAFLD with significant fibrosis in patients with type 2 diabetes [31], suggesting that albuminuria may be a possible marker of adverse development of NAFLD with fibrosis. On the other hand, a cross-sectional study reported that sarcopenia itself was associated with an increased risk of albuminuria independent of hypertension, diabetes, and metabolic syndrome [32], suggesting that liver fibrosis and sarcopenia have a synergistic effect on the increased risk of albuminuria. Taken together, findings indicate that concurrent liver fibrosis and sarcopenia synergistically affect urinary albumin excretion, thus contributing to the high risk of CVD and diabetic kidney disease in people with type 2 diabetes.

The present study has several limitations. First, the cross-sectional design did not allow us to prove the existence of a causal relationship between liver fibrosis and/or sarcopenia and vascular damage. Second, the number of participants was small, so we need to repeat the study in a larger number of participants to confirm our findings. Third, we did not perform liver biopsy to confirm liver fibrosis. However, although liver biopsy is the gold standard for assessing liver fibrosis, accumulating evidence suggests that transient elastography with FibroScan is strongly correlated with the stage of liver fibrosis assessed by concurrent liver biopsy [8]. Nevertheless, it is still recommended that clinical studies include liver biopsy to validate their results. The final limitation is a lack of data on gait speed or grip strength, which provide a functional measure of sarcopenia, because measurement of muscle mass does not provide information on muscle quality.

In conclusion, liver fibrosis and sarcopenia are independently associated with endothelial dysfunction and arterial stiffness in patients with type 2 diabetes. Furthermore, coexistence of liver fibrosis and sarcopenia may synergistically lead to vascular damage and thus contribute to the high risk of cardiovascular disease in people with type 2 diabetes.

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Author contributions.
HK, HK, MK, YI, and SS contributed to the study design, data collection, and drafting of the manuscript; TT and IU contributed to the discussion and reviewed the manuscript; IU reviewed and edited the manuscript; and TJ and YA researched the data and wrote, reviewed, and edited the manuscript.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material
Supplementary data to this article can be found online at https://doi.org/10.1161/JAHA.2022.101071.

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