Increased visceral adiposity with normal weight is associated with the prevalence of non-alcoholic fatty liver disease in Japanese patients with type 2 diabetes

Ryotaro Bouchi1*, Takato Takeuchi1†, Momoko Akihisa1, Norihiko Ohara1, Yuiiro Nakano1, Rie Nishitani1, Masanori Murakami1, Tatsuya Fukuda1, Masamichi Fujita1, Isao Minami1, Masatomo Mihara1, Takanobu Yoshimoto1, Yoshihiro Ogawa1‡

1Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, and 2Japan Agency for Medical Research and Development, CREST, Tokyo, Japan

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*Correspondence
Ryotaro Bouchi
Tel.: +81-3-5803-5216
Fax: +81-3-5803-0172
E-mail address: bouchi.mem@tmd.ac.jp

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ABSTRACT

Aims/Introduction: To investigate the impact of increased visceral adiposity with normal weight (OB-VA+) on the prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes.

Materials and Methods: This was a cross-sectional study of 140 Japanese patients with type 2 diabetes (mean age 65 ± 11 year; 44.6% women). Visceral fat area (VFA; cm²) and liver attenuation index (LAI) were assessed by abdominal computed tomography. The patients were divided into four groups by VFA and body mass index (BMI; kg/m²) as follows: BMI <25 kg/m² and VFA <100 cm² (OB-VA-), BMI ≥25 kg/m² and VFA <100 cm² (OB+VA-), BMI <25 kg/m² and VFA ≥100 cm² (OB-VA+), and BMI ≥25 kg/m² and VFA ≥100 cm² (OB+VA+). Multivariate linear regression and logistic regression analysis were carried out to determine the impact of OB-VA+ on LAI.

Results: In the present study, 25.0% were OB-VA+ patients, where the LAI levels were lower (1.09 ± 0.22) than those in OB-VA- patients (1.23 ± 0.15), and were equivalent to those in OB+VA+ patients (1.03 ± 0.26). In multivariate linear regression analysis, OB-VA+ was independently associated with LAI (standardized β=0.212, P=0.014). In multivariate logistic regression analysis, OB-VA+ was a significant predictor of LAI <0.9 (odds ratio 5.88, 95% confidence interval 1.03–33.52, P=0.046).

Conclusions: The present study provides evidence that increased visceral adiposity with normal weight is a strong predictor for the prevalence of non-alcoholic fatty liver disease in Japanese patients with type 2 diabetes.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as excessive lipid accumulation in the liver without a history of excessive alcohol consumption. It is thought to be a hepatic manifestation of the metabolic syndrome1–3. The spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis. The prevalence of NAFLD varies between 10% in West Bengal and 45% in the USA4–6. It is noteworthy that the prevalence of NAFLD in East Asians with a mean body mass index (BMI) <25 kg/m² is relatively high (15–20%), which is roughly equivalent to that in Western countries with a mean BMI of 27–31 kg/m²4. Thus, East Asians with normal BMI are likely to have an increased risk for the progression of NAFLD relative to those with equivalent BMI levels in Western countries.

Interestingly, a recent study from China showed that the prevalence of NAFLD is 18.3% in individuals with BMI <24.0 kg/m² and 72.9% in those with BMI ≥24.0 kg/m², and that non-obese NAFLD is more strongly associated with diabetes than overweight or obese NAFLD9. The authors reported

†These authors contributed equally to this work.

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that non-obese patients with NAFLD have a higher waist circumference (WC), a surrogate marker of visceral adiposity, than those without NAFLD, and suggested that those with increased visceral adiposity and normal BMI are at increased risk for the progression of NAFLD than those with normal visceral adiposity and normal BMI among diabetic patients. In contrast, a previous study from India showed that the number of steatohapatitis and advanced fibrosis is roughly equivalent among non-obese, overweight, and obese NAFLD patients. These observations suggest the importance of evaluating both visceral adiposity and lipid accumulation in the liver in non-obese individuals, as well as in obese individuals.

Diabetes is known to be a strong and independent risk factor for NAFLD. Conversely, NAFLD has been histologically improved by reduction of blood glucose level. Recently, we reported that patients with type 2 diabetes who had visceral fat area (VFA) ≥100 cm² and BMI <25.0 kg/m² (OB[-]VA[+]) were at increased risk for the progression of arterial stiffening as well as those with VFA ≥100 cm² and BMI ≥25.0 kg/m² (OB[+]VA[+])

MATERIALS AND METHODS
Study participants
We enrolled patients with type 2 diabetes who regularly visited Tokyo Medical and Dental University Hospital for the management of diabetes during the period from 1 April 2014 to 31 March 2015. Patients were eligible if they were aged ≥20 years, and their alcohol consumption was <30 g/day for men and <20 g/day for women, based on the epidemiological studies that alcoholic liver disease can occur when the daily alcohol intake exceeds 20 g/day in women and 30 g/day in men. Patients with type 1 diabetes, those with severe renal impairment (with estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m² or renal replacement therapy), pregnant women and those with infectious or malignant diseases were excluded. We also excluded patients who had received hepatotoxic drugs including glucocorticoids, tamoxifen, amiodarone, sodium valproate and methotrexate, and those with other causes of liver diseases, such as viral hepatitis (hepatitis B virus/ hepatitis C virus) and autoimmune liver diseases. In the present study, type 2 diabetes was diagnosed according to the criteria of the Japan Diabetes Society. Urinary albumin and creatinine excretion were measured by the turbidimetric immunoassay and enzymatic method, respectively, in a spot urine collection. GFR was estimated using the following equation for the Japanese, as proposed by the Japanese Society of Nephrology:

\[ \text{GFR} = 194 \times \text{Scr}^{-1.094} \times \text{age}^{-0.287} \]

where SCr stands for serum creatinine in mg/dL, measured by an enzymatic method. BMI was calculated as weight divided by the square of height (kg/m²). Triglycerides-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio was used for the assessment of insulin resistance, because we were unable to determine markers for insulin resistance, such as fasting C-peptide or homeostatic model assessment for insulin resistance. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured by abdominal computed tomography (CT) examination (Aquilion PRIME; Toshiba Medical Systems, Tochigi, Japan). Lipid accumulation in the liver was determined by liver-spleen attenuation index (LAI) in the CT examination as described previously. Briefly, hepatic and splenic attenuation values were measured on non-contrast CT scans by using eight circular region-of-interest (ROI) cursors with a diameter of 1.5 cm in the liver and three ROIs with a diameter of 1.5 cm in the spleen. For the liver, four ROIs were located in each of the right anterior, right posterior, left medial and left lateral segments. In the present study, the ratio of attenuation values in the liver to those in the spleen (LAI) was evaluated as a marker for steatosis in the liver. The LAI was calculated as follows: the mean attenuation value of eight different sites in the liver (two ROIs each in Couinaud hepatic segments, V, VI, VII and VIII) divided by that of three different sites in the spleen (the upper, middle and lower third of the spleen). In the present study, fatty liver disease was diagnosed if LAI was <0.9. According to the definition of obesity and visceral fat obesity in Japan, we used the cut-point of 25.0 kg/m² in BMI for obesity and that of 100 cm² in VFA for visceral fat obesity. We classified the patients into four groups by the cut-off values of BMI and VFA as follows: BMI ≤25 and VFA <100 (OB[-]VA(-)), BMI ≥25 and VFA ≤100 (OB[-]VA[+]), BMI ≥25 and VFA ≥100 (OB[-]VA[+]), and BMI ≥25 and VFA ≥100 (OB[+]VA[+]). The present study complies with the principles laid by the Declaration of Helsinki, and has been approved by the ethics committee of Tokyo Medical and Dental University (No. 2103).

Statistical analysis
Statistical analysis was carried out using programs available in the SPSS version 21.0 statistical package (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation or geometric mean with 95% confidence interval (CI) as appropriate according to data distribution. Aspartate transaminase (AST), alanine aminotransferase (ALT), triglycerides and urinary albumin-to-creatinine ratio (ACR) were logarithmically transformed because of skewed distributions. Categorical variables are presented as percentage. Differences among the four groups were tested with a one-way ANOVA (continuous vari-
Variables or $\chi^2$-test (categorical variables) followed by Tukey–Kramer methods for the post-hoc analysis. Linear regression and logistic regression analysis with a stepwise procedure were used to assess the cross-sectional association of each manifestation of abdominal (VFA) and the entire bodyweight (BMI) with LAI. The following covariates were incorporated into the analysis: age, sex, duration of diabetes, smoking status, systolic blood pressure, TG/HDL-C ratio, low-density lipoprotein (LDL) cholesterol, HbA1c, urinary ACR, eGFR and the use of oral hypoglycemic agents, insulin, the use of calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and statins. We also underwent a sensitivity analysis to examine the association of BMI and VFA with LAI, using the cut-off of 23.0 kg/m² and 100 cm² in BMI and VFA, respectively, because the World Health Organization, International Association for the Study of Obesity and International Obesity Task Force recommend that the BMI value to denote overweight in Asians should be ≥23.0 kg/m². Differences were considered to be statistically significant at a P-value <0.05.

RESULTS

Characteristics of the study population

A total of 140 Japanese patients with type 2 diabetes (mean age 65 ± 11 year; 44.6% women) were eligible for the present study. In this study, 25.0% of patients (n = 35) were classified as OB(−)VA(+), and 38.6% (n = 54), 10.7% (n = 15), and 25.7% (n = 36) were classified as OB(−)VA(−), OB(+)VA(−) and OB(+)VA(+), respectively. Table 1 shows the demographic characteristics and laboratory data of the study participants. The OB(−)VA(+) patients had higher systolic (P < 0.001) and diastolic blood pressures (P < 0.001), higher BMI (P < 0.001), VFA (P < 0.001) and V/S ratio (P < 0.001) than OB(−)VA(−) patients. Compared with OB(+)VA(−) patients, OB(−)VA(+) patients showed higher systolic blood pressure (P = 0.025), high V/S ratio (P = 0.001) and low BMI (P = 0.009). The OB(−)VA(+) patients were older (P = 0.006), had less visceral adiposity (lower VFA, P < 0.001) with lower BMI (P < 0.001) than those with OB(+)VA(+), although there were no appreciable differences between OB(−)VA(+) and OB(+)VA(+) patients in male predominance, blood pressure, smoking status, and duration of diabetes. The glyceric control as assessed by HbA1c was almost identical among the four groups (P = 0.548). The OB(−)VA(+) patients had significantly higher triglycerides (P = 0.003), LDL cholesterol (P = 0.031), uric acid (P = 0.003) and ALT (P = 0.007) than OB(−)VA(−) patients. The OB(−)VA(−) had significantly lower triglycerides (P < 0.001) and lower urinary ACR (P = 0.008) than OB(+)VA(+) patients. The OB(−)VA(+) patients tended to have a higher TG/HDL-C ratio than those with OB(−)VA(−) (P = 0.068), and TG/HDL-C ratio in those with OB(+)VA(+) was significantly higher than that in OB(−)VA(−) patients (P < 0.001). There were no significant differences in the prevalence of diabetic microvascular complications; retinopathy and albuminuria between OB(+)VA(+) and OB(−)VA(−) patients.

Medications are listed in Table 2. Despite the accumulation of cardiovascular risks, such as high blood pressure, high LDL cholesterol and high VFA (Table 1), OB(−)VA(+) patients were less likely to receive antihypertensive agents including angiotensin receptor blockers, calcium channel blockers, diuretics and statins than those with OB(+)VA(+).

Association of visceral adiposity and BMI with LAI

There was a statistical significance of LAI among the four groups as defined by the whole-body (BMI) and visceral (VFA) adiposity (P < 0.001 by ANOVA; Figure 1). As expected, the OB(+)VA(+) patients showed the lowest LAI among the four groups (1.03 ± 0.26, P < 0.001 vs OB[−]VA[−] patients). The OB(−)VA(+) patients had a significantly lower LAI (1.09 ± 0.22) than those with OB(−)VA(−) (1.23 ± 0.15, P = 0.019). In the multivariate linear regression analysis (Table 3), OB(−)VA(+) was significantly associated with LAI (standardized β = 0.212, P = 0.014) after adjusting for other significant covariates selected in the model, including age (standardized β = 0.289, P = 0.001), smoking status (standardized β = 0.157, P = 0.043) and ALT (standardized β = 0.365, P < 0.001). Patients with OB(+)VA(+) and OB(+)VA(−) were also significantly associated with lower LAI in the multivariate model.

As LAI <0.9 indicates definite fatty liver disease with more than 30% of fat deposit in the liver, we next determined the association between OB(−)VA(+) and the prevalence of LAI <0.9. The prevalence of NAFLD defined by LAI <0.9 was 4.2, 8.1, 17.1, and 23.1% in patients with OB(−)VA(−), OB(+)VA(−), OB(−)VA(+) and OB(+)VA(+), respectively (Figure 2; P < 0.001 by ANOVA). In the multivariate logistic regression analysis, OB(−)VA(+) remained significant as a risk factor for LAI <0.9 (OR 5.88, 95% CI 1.03–33.52, P = 0.046). OB(+)VA(−) was also significantly associated with the prevalence of LAI <0.9 (OR 6.79, 95% CI 1.24–36.88, P = 0.027). Other covariates selected for the analysis were age (OR 0.94, 95% CI 0.89–0.99, P = 0.019), log ACR (OR 2.24, 95% CI 0.86–5.84, P = 0.099), and log ALT (OR 14.24, 95% CI 1.46–13.88, P < 0.001) and duration of diabetes (OR 0.89, 95% CI 0.79–0.99, P = 0.040).

We also examined the association of BMI and VFA with LAI, using the cut-off of 23.0 kg/m² and 100 cm² in BMI and VFA, respectively. The LAI levels were 1.21 ± 0.13, 1.19 ± 0.20, 1.06 ± 0.29, and 1.06 ± 0.23 in patients with BMI <23.0 kg/m² and VFA <100 cm² (n = 40), those with BMI ≥23.0 kg/m² and VFA <100 cm² (n = 29), those with BMI <23.0 kg/m² and VFA ≥100 cm² (n = 13), and those with BMI ≥23.0 kg/m² and VFA ≥100 cm² (n = 58), respectively (P < 0.001 by ANOVA). As shown in Table 4, compared with those with BMI <23.0 kg/m² and VFA <100 cm², patients with BMI <23.0 kg/m² and VFA ≥100 cm² had a significantly increased risk for lower LAI; whereas patients with BMI ≥23.0 kg/m² and VFA <100 cm² did not show increased risk for lower LAI.
DISCUSSION

In the present study, although the BMI levels in OB(−)VA(+) patients were comparable with those in OB(+)VA(−) patients, OB(−)VA(+) patients showed more severe cardiometabolic risk profile including high blood pressure, high LDL cholesterol and high uric acid among Japanese patients with type 2 diabetes. Importantly, they were at increased risk for the prevalence of NAFLD, even after adjusting for covariates including age, sex and transaminase. To the best of our knowledge, this is the first study evaluating the impact of OB(−)VA(+) on the prevalence of NAFLD in Japanese patients with type 2 diabetes.

We aimed to investigate the impact of visceral adiposity on hepatic fat accumulation in normal-weight Japanese patients with type 2 diabetes for the following reasons: (i) almost half of the Japanese patients with type 2 diabetes had BMI <25.0 kg/m²; (ii) diabetes is a strong risk factor for the progression of NAFLD including hepatocellular carcinoma; (iii) increased visceral adiposity with normal BMI is relatively common among Japanese patients with type 2 diabetes, and (iv) non-obese people less frequently have an opportunity to be assessed for the cardiometabolic risks and also ectopic fat accumulation, such as fatty liver, than obese people. We examined the clinical features of OB(−)VA(+) patients, and found that they are older and have higher prevalence of LAI <0.9 with higher ALT levels, body mass index <25 kg/m² and visceral adiposity <100 cm²; OB(+)VA(−), body mass index ≥25 kg/m² and visceral adiposity ≥100 cm²; OB(+)VA(−), body mass index ≥25 kg/m² and visceral adiposity ≥100 cm²; SBP, systolic blood pressure; TG, triglycerides; V/S ratio, visceral fat area-to-subcutaneous fat area ratio.

Table 1 | Clinical data of patients with type 2 diabetes

| Visceral adiposity | VFA < 100 cm² | VFA ≥ 100 cm² | P-value* |
|--------------------|---------------|---------------|----------|
| Total adiposity    |               |               |          |
| OB(−)VA(−) (n = 54) |               |               |          |
| VFA (cm²)          | 61 ± 25       | 83 ± 11       |          |
| SFA (cm²)          | 103 ± 61      | 147 ± 32      |          |
| V/S ratio          | 0.77 ± 0.45   | 0.61 ± 0.22   |          |
| Age (year)         | 68 ± 10       | 64 ± 13       |          |
| Sex (% male)       | 48            | 33            |          |
| BMI (kg/m²)        | 203.2 ± 22    | 25.7 ± 05     |          |
| SBP (mmHg)         | 116 ± 13      | 120 ± 7       |          |
| DBP (mmHg)         | 66 ± 11       | 69 ± 8        |          |
| Current smoker (%) | 27            | 16            |          |
| Duration of DM (year) | 8 ± 8       | 3 ± 2         | 0.087    |
| HbA1c (mmol/mol [%]) | 51 ± 14 [7.2 ± 1.1] | 49 ± 8 [6.8 ± 0.4] | 0.548    |
| Triglycerides (mmol/L) | 0.98 (0.85–1.14) | 1.49 (1.14–1.94) | 0.001    |
| HDL-C (mmol/L)     | 1.50 ± 0.57   | 1.47 ± 0.44   | 0.548    |
| TG/HDL-C ratio     | 0.91 (0.65–1.29) | 1.14 (0.85–1.61) | 0.001    |
| LDL-C (mmol/L)     | 2.48 ± 0.83   | 3.10 ± 1.06   | 0.001    |
| UA (μmol/L)        | 280 ± 77      | 238 ± 101     | 0.211    |
| eGFR (ml/min/1.73 m²) | 69.5 ± 21.9 | 68.8 ± 23.8 | 0.001    |
| Log ACR (mg/g)     | 24 (20–38)   | 22 (12–30)   | 0.001    |
| PDR (%)            | 4             | 0             | 0.049    |
| AST (U/L)          | 24 (22–26)   | 22 (13–24)   | 0.013    |
| ALT (U/L)          | 19 (17–21)   | 17 (12–20)   | 0.001    |
| γ-GTP (U/L)        | 24 (21–33)   | 28 (14–31)   | 0.001    |

Data are expressed as mean ± standard deviation, geometric mean (95% confidence interval) or percentage. *One-way ANOVA or chi-square-test. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OB(−)VA(−), body mass index <25 kg/m² and visceral adiposity <100 cm²; OB(+)VA(−), body mass index ≥25 kg/m² and VFA <100 cm²; OB(−)VA(−), body mass index <25 kg/m² and visceral adiposity ≥100 cm²; OB(+)VA(−), body mass index ≥25 kg/m² and visceral adiposity ≥100 cm²; SBP, systolic blood pressure; TG, triglycerides; V/S ratio, visceral fat area-to-subcutaneous fat area ratio.
We used the TG/HDL-C ratio as a marker for insulin resistance; however, its association with NAFLD was not statistically significant in the present study. Direct measures of insulin resistance, such as fasting C-peptide or homeostatic model assessment for insulin resistance, are required in future studies.

A recent large-scale cross-sectional study showed that abdominal adiposity and liver fat deposition are positively associated with a deteriorated cardiometabolic risk profile in multi-ethnicities including white people, African Caribbean black people, Hispanics, East Asians and Southeast Asians. It is noteworthy that East Asians had the most deleterious abdominal fat distribution and accumulation. Japanese men are likely to have a greater percentage of body fat than Australians at any given BMI value. A previous study from the USA and Japan also showed that despite a lower mean BMI, Japanese men have higher liver fat content than non-Hispanic white men. These studies support the hypothesis that Japanese people have less fat storage capacity, especially in subcutaneous adipose tissue, which might explain the ethnic difference in predisposition to NAFLD. Indeed, in the present study, OB(−)VA(−) patients had the highest V/S ratio among the four groups, and the LAI levels in OB(−)VA(−) patients were roughly equivalent to those in OB(+)VA(+) patients. These observations suggest that OB(−)VA(+) patients have a lower capacity to accumulate an excess of energy in the subcutaneous adipose tissue; therefore, liver fat deposition could progress regardless of its less visceral adiposity than that in OB(+)VA(+) patients. Our data support a strong link between visceral adiposity and hepatic fat deposition in

progression of NAFLD. We used the TG/HDL-C ratio as a marker for insulin resistance; however, its association with NAFLD was not statistically significant in the present study. Direct measures of insulin resistance, such as fasting C-peptide or homeostatic model assessment for insulin resistance, are required in future studies.
Table 3 | Linear regression analyses for independent factors associated with liver attenuation index in patients with type 2 diabetes

| Covariates | Standardized β | P-values |
|------------|----------------|----------|
| BMI ≥ 100 kg/m² and VFA ≥ 100 cm² | -0.166 | 0.061 |
| Age | -0.273 | 0.004 |
| Current smoking | -0.426 | <0.001 |

Table 4 | Linear regression analysis for independent factors associated with liver attenuation index in patients with type 2 diabetes using cut-off levels of body mass index at 23.0 kg/m² and visceral fat area at 100 cm²

| Covariates | Standardized β | P-values |
|------------|----------------|----------|
| BMI ≥ 100 kg/m² and VFA ≥ 100 cm² | 0.031 | 0.734 |
| Age | -0.188 | 0.045 |
| Current smoking | -0.248 | <0.001 |

Covariates: age, sex, systolic blood pressure, duration of diabetes, current smoking, glycated hemoglobin, low-density lipoprotein cholesterol, triglycerides-to-high-density lipoprotein cholesterol ratio, ALT, alanine aminotransferase; estimated glomerular filtration rate, albuminuria, the use of insulin, oral hypoglycemic agents, renin–angiotensin system blockers and statins. BMI, body mass index; VFA, visceral fat area.

Figure 2 | Prevalence of liver attenuation index <0.9 in patients with type 2 diabetes according to the categories of adiposity. Blue, visceral fat area (VFA) <100 cm² and body mass index (BMI) <25 kg/m²; green, VFA ≥100 cm² and BMI ≥25 kg/m²; red, VFA ≥100 cm² and BMI ≥25 kg/m²; brown, VFA >100 cm² and BMI ≥25 kg/m². P < 0.001 by ANOVA.

Japanese patients with type 2 diabetes, irrespective of BMI levels. Further studies are required to longitudinally investigate whether OB(−)VA(+) patients with diabetes are at increased risk for NAFLD in multi-ethnicities.

The limitations of the present study deserve comment. First, it is impossible to infer causality because of the cross-sectional design of this study. Second, the severity of hepatic steatosis can be accurately determined radiologically only when there is moderate or severe fatty infiltration of the liver. Thus, some patients with mild NAFLD might be misclassified as non-NAFLD by LAI. In addition, we were unable to determine the histological analysis of the liver. Third, we were unable to obtain the information on diet and exercise, both of which might affect body fat accumulation and skeletal muscle mass. Fourth, body fat distribution is different between men and women, and it would be of great interest to separately investigate the association of VFA and BMI with hepatic liver deposition. However, we were unfortunately unable to carry out the analysis, because the sample size was small for the analysis. Fifth, the study population was socially homogeneous, because this study was hospital-based; generalization of our findings might be limited. Finally, non-diabetic individuals were not enrolled. Further longitudinal studies are required to clarify the impact of visceral adiposity with normal weight on the progression of NAFLD in non-diabetic subjects.

It is important to identify high-risk individuals for NAFLD among patients with type 2 diabetes, because NAFLD and diabetes could interactively worsen both conditions and are strong risk factors for mortality. In the present study, it is noteworthy that the prescription rates of angiotensin receptor blockers, calcium channel blockers, diuretics and statins in OB(−) VA(+) patients were lower than those in OB(+)VA(+) patients, probably indicating that the OB(−)VA(+) patients have insufficient opportunities for the management of cardiometabolic risk factors including hypertension and dyslipidemia because of their...
normal BMI level, although the risks for NAFLD in OB(−)VA(+) patients are almost similar to those in OB(+)VA(+) patients, as well as the association of OB(−)VA(+) and OB(+)VA(+) with atherosclerosis. We therefore propose that visceral adiposity should be directly evaluated for the management of NAFLD among non-obese patients with type 2 diabetes as well as obese patients.

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DISCLOSURE
The authors declare no conflict of interest.

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