Vitamin D is a strong risk marker for cardiovascular (CV) risk factors and diseases (1) and may be negatively associated with CV diseases (2, 3). An elevated low-density lipoprotein level is associated with an increased risk of coronary artery disease (4, 5) and stroke (5) in Japanese patients. Furthermore, low high-density lipoprotein cholesterol (HDL-C) is associated with the risk of developing CAD and stroke, while a high HDL-C decreases this risk, in Japanese men and women (6, 7).

The risk of CAD can be reliably predicted using serum non-high-density lipoprotein cholesterol (non-HDL-C) (8, 9). High serum non-HDL-C levels are associated with a greater risk of CAD (10). Non-fasting and fasting triglycerides (TGs) are predictive of the risk of ischemic CV disease in Japanese men and women (11). Non-fasting serum TG levels predict the incidence of CAD in Japanese men and women (12).

In a cohort study in Japan, the metabolic syndrome was found to be predictive of CAD and ischemic stroke (13) and in a prospective population survey in Japan, casual blood glucose levels predicted CAD and CV disease mortality in a Japanese population (14). Furthermore, type 2 diabetes mellitus was found to be a significant risk factor for both cerebral infarction and CAD (15) and a Japanese cohort study also found that type 2 diabetes mellitus was a significant risk factor for non-embolic ischemic stroke (16).

A modest inverse association between serum 25-hydroxyvitamin D (25(OH)D) levels and the risk of all-cause death among diabetic participants has been shown; indicating a good predictive factor in the community (17).

An inverse and significant association between circulating 25(OH)D levels and the risk of type 2 diabetes mellitus was also found across a broad range of blood 25(OH)D levels in diverse populations (18). Higher serum 25(OH)D levels are thus associated with reduced odds of type 2 diabetes mellitus (19). Type 2 diabetic patients with poor glycemic control have been shown to have lower concentrations of serum 25(OH)D with glycated hemoglobin A1c (HbA1c) being an independent risk factor for low 25(OH)D (20).

Vitamin D deficiency has been associated with higher TC, LDL-C, and TG levels in middle-aged and elderly Chinese individuals (21) with low vitamin D levels being a risk factor for the metabolic syndrome in northern Finland (22). Furthermore, in a previous study, 25(OH)D level was inversely correlated with the LDL/HDL and TG values in Japanese men (23). However, the association between 25(OH)D levels and lipid profiles in Japanese patients with type 2 diabetes mellitus has not been reported. Therefore, the purpose of this study was to evaluate the association between serum 25(OH)D concentrations and lipid profiles in Japanese subjects with type 2 diabetes mellitus.

**MATERIALS AND METHODS**

**Patients.** In this case control study, type 2 diabetic patients attending the Manda Memorial Hospital from March to October 2017 were selected. The exclusion criteria were: having an estimated glomerular flow rate (eGFR) < 30 mL/min, type 1 diabetes mellitus, being
The data were represented as mean±SD (for data with normality) or median (range) (for data with non-normality).

SD: standardized deviation, BMI: body mass index, PG: plasma glucose, Cr: creatinine, eGFR: estimated glomerular filtration rate, uAlb/Cr: urine albumin/creatinine ratio, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GTP: γ-glutamyl transpeptidase, TC: total cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, non-HDL-C: non-high-density lipoprotein cholesterol, L/H: LDL-C/HDL-C, 25(OH)D: 25-hydroxyvitamin D.

Table 1. Patient’s characters (continuous variables).

| Continuous variable | Mean±SD or median (range) |
|---------------------|---------------------------|
| Age (y)             | 61.4±12.1                 |
| BMI (kg/m²)         | 26.4±16.2                 |
| Duration of DM (y)  | 9 (0.17–41)               |
| HbA1c (%)           | 7.2 (5.5–11.5)            |
| PG (mg/dL)          | 150 (77–416)              |
| Cr (mg/dL)          | 0.83 (0.48–1.74)          |
| eGFR (mL/min)       | 67.2±15.5                 |
| uAlb/Cr (mg/gCr)    | 8.1 (0.6–1,409.8)         |
| ALT (U/L)           | 62 (21–93)                |
| AST (U/L)           | 22 (13–80)                |
| γ-GTP (U/L)         | 29 (10–285)               |
| TC (mg/dL)          | 187.6±30.3                |
| TG (mg/dL)          | 134 (44–1,680)            |
| LDL-C (mg/dL)       | 102.1±26.0                |
| HDL-C (mg/dL)       | 56.5±13.7                 |
| Non-HDL-C (mg/dL)   | 131.2±31.1                |
| L/H                 | 1.8 (0.6–3.9)             |
| 25(OH)D (ng/mL)     | 17.0±6.2                  |

The background variables included age, sex, alcohol consumption, current smoking, timing of blood sampling, BMI, duration of diabetes mellitus (DM), estimated glomerular filtration rate (eGFR), urine albumin/creatinine ratio (uAlb/Cr), HbA1c, plasma glucose (PG), serum creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (γ-GTP) levels, the presence of CAD, history of stroke, and use of insulin, anti-hypertensive agents (AHT agents), statins, fibrates, cholesterol absorption inhibitors (CAI), and eicosapentaenoic acid/docosahexaenoic acid.

25(OH)D levels were measured using a chemiluminescent immunoassay (CLI).

Statistical analysis. All the statistical analyses were performed using EZR, version 1.53 (24). A Kolmogorov-Smirnov test was performed to assess the normality of the data distribution. The data were represented as mean±standard deviations (SDs) (for normally distributed data) or medians (ranges) (for non-normally distributed data). Non-normally distributed continuous variables were log-transformed using 10 as the base.

For the continuous variables, comparisons of 25(OH)D values between the groups were performed using the Student’s t-test (when both groups were more than 30) or the Mann-Whitney U test (when one group was less than 30).

For the continuous variables, the Pearson’s product-moment correlation was used to examine the correlation with 25(OH)D. The duration of DM, and the HbA1c, PG, uAlb/Cr, ALT, AST, γ-GTP, TG, and L/H

Table 2. Patient’s characters (nominal variables).

| Nominal variable       | No (n) | Yes (n) | Yes (%) |
|------------------------|--------|---------|---------|
| Sex (female)           | 178    | 107     | 37.5    |
| Alcohol consumption    | 225    | 57      | 20      |
| Current smoking        | 186    | 99      | 34.7    |
| Sampling timing        |        |         |         |
| (Fast/Postprandial)    | 42     | 243     | 85.3    |
| CAD                    | 264    | 21      | 7.4     |
| Stroke                 | 260    | 25      | 8.8     |
| Insulin use            | 206    | 79      | 27.7    |
| AHT agent              | 176    | 109     | 38.2    |
| Statin                 | 136    | 149     | 52.3    |
| Fibrate                | 266    | 19      | 6.7     |
| CAI                    | 259    | 26      | 9.1     |
| EPA/DHA                | 280    | 5       | 1.8     |

Sex was defined as male=No/female=Yes.
Sampling was defined as Fast=No/Postprandial=Yes.
Sampling: the timing of blood sampling.
CAD: coronary artery disease, AHT: anti-hypertensive, CAI: cholesterol absorption inhibitor, EPA/DHA: eicosapentaenoic acid/docosahexaenoic acid.

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parameters were log-transformed for the analysis.

Multiple linear regression analyses were performed to assess the associations between the serum 25(OH)D concentration (the independent variable) and the lipid profiles (the dependent variables), adjusted for age, sex, BMI, eGFR, insulin use, duration of DM, HbA1c, alcohol consumption, current smoking, and sampling time. The level of statistical significance was set at $p < 0.05$. In addition, correlations were analyzed for 25(OH)D and lipid profiles (TC, TG, LDL-C, HDL-C, non-HDL-C and L/H), and multiple regression analysis was conducted as above (adjust without sex) by gender.

**RESULTS**

This study enrolled 285 patients with type 2 diabetes mellitus. Patient characteristics and the blood parameters (continuous variables) are presented in Table 1. The mean 25(OH)D concentration was 17.0 ± 6.2. The mean age was 61.4 ± 12.1. The median duration of DM was 9 y (0.17–41 y). The median HbA1c was 7.2 (5.5–11.5). Patient characteristics (nominal variables) are presented in Table 2. Females accounted for 37.5% of
The relationship between the serum 25(OH)D levels and patient characteristics (nominal variables) is shown in Table 3. Significant differences in 25(OH)D values between the groups were observed for sex (p<0.001***). The 25(OH)D levels were significantly lower in women, but the differences were not significant for insulin use, alcohol consumption, current smoking, the timing of sampling, presence of CAD, history of stroke, and use of AHT agent, statin, fibrate, CAI, and EPA/DHA.

The relationships between serum 25(OH)D levels and patient characteristics (continuous variables) are shown in Table 4. The data are presented as Pearson product-moment correlations. The correlation with the 25(OH)D value was significant for the background variables of age (r=0.016*), BMI (r<0.001***), and the duration of DM (r=0.019*). The correlation with the 25(OH)D value was also significant for TG (r<0.001***), and non-HDL-C (r=0.015*).

To investigate whether the serum 25(OH)D concentration was independently related to the blood lipid profiles, multivariate linear regression analyses using blood lipids as the dependent variable were performed and the results are shown in Table 5. Model 1 showed that the
25(OH)D concentration was negatively correlated with the TG level \((p<0.001^{***})\) after adjusting for age, sex, BMI, eGFR, insulin use, and duration of DM. The significance of the correlation between the 25(OH)D concentration and non-HDL-C disappeared in Model 1. In Model 2 (adjusted for the Model 1 characters plus HbA1c), Model 3 (adjusted for the Model 2 characters plus alcohol consumption and current smoking), Model 4 (adjusted for the Model 3 characters plus sampling timing), the associations between 25(OH)D concentrations and TG level were statistically significant \((p<0.01^{**})\).

The association between 25(OH)D concentration and non-HDL-C level was not significant after the adjustments, and although statistically significant before adjustments, the associations between 25(OH)D concentrations and the other lipid profiles (TC, HDL-C, LDL-C, and L/H) were no longer significant after the adjustments.

In statistical analysis by sex, the relationships between serum 25(OH)D levels and lipid profiles are shown in Table 6. The data are presented as Pearson product-moment correlations. The correlation with the 25(OH)D value was significant for TG both in male \((p=0.0018^{**})\) and female \((p<0.001^{***})\) and for HDL-C in male \((p=0.048^*)\).

### DISCUSSION

This case-control study was conducted to examine whether serum 25(OH)D concentrations were associated with circulating lipid profiles in Japanese patients with type 2 diabetes mellitus. Our results showed that the serum 25(OH)D concentrations were inversely correlated with the TG levels, even after controlling for potential confounding factors, such as age, sex, BMI, eGFR, insulin use, and duration of DM, HbA1c, alcohol consumption, current smoking, and sampling timing. By sex, similar results were shown.

Wang et al. showed that the lipid profile (particularly TC and TG) mediated the relationship between 25(OH)D or total 25(OH)D and IFG or type 2 diabetes mellitus in Chinese rural adults \((25)\) and Yu et al. reported that TG and LDL-C were inversely correlated with 25(OH)D concentration in Korean patients with type 2 diabetes mellitus \((26)\). As mentioned above, lipid profiles and 25(OH)D concentrations have been shown to be related in Asian patients with type 2 diabetes mellitus; however, the variables were different.

### Table 7. Multiple regression analysis of the associations between serum 25(OH)D concentrations and lipid parameters.

| Variable  | Model 1’ (Male) | Model 2’ (Male) | Adjusted R² | Model 1’ (Female) | Model 2’ (Female) | Adjusted R² |
|-----------|-----------------|-----------------|-------------|-----------------|-----------------|-------------|
|           | B    | β    | p     | Adjusted R² | B    | β    | p     | Adjusted R² |
| TC        | -0.363 | -0.075 | 0.336 | 0.016 | -0.294 | -0.061 | 0.432 | 0.035 |
| TG        | -0.0076 | -0.187 | 0.014* | 0.096 | -0.0069 | -0.169 | 0.023* | 0.128 |
| LDL-C     | -0.0062 | -0.0015 | 0.984 | 0.012 | 0.046 | 0.011 | 0.885 | 0.026 |
| HDL-C     | 0.206 | 0.100 | 0.182 | 0.098 | 0.190 | 0.092 | 0.221 | 0.100 |
| Non-HDL-C | -0.57 | -0.114 | 0.140 | 0.051 | -0.484 | -0.097 | 0.204 | 0.081 |
| L/H       | -0.0016 | -0.068 | 0.377 | 0.071 | -0.0013 | -0.053 | 0.481 | 0.088 |

B: unstandardized estimated regression coefficients; β: standardized estimated regression coefficients.
Model 1’: adjusted for age, BMI, eGFR, insulin use, duration of DM.
Model 2’: as in Model 1’ plus HbA1c.
Statistical significance *\(p<0.05\), **\(p<0.01\).
In Japanese subjects, TG, L/H, ApoB, and ApoB/ApoA-1 levels were shown to be inversely associated with 25(OH)D concentrations, but only in men (23) and serum 25(OH)D was found to be inversely correlated with higher TC, LDL-C, and TG levels in middle-aged and elderly Chinese individuals (21). Moreover, a cross-sectional study (the VLDL-3 study) showed that a deficiency in serum 25(OH)D was associated with significantly lower HDL-C and higher directly measured LDL-C, intermediate-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, remnant lipoprotein cholesterol, and TG (27).

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes, increased fasting plasma glucose, abdominal obesity, high cholesterol, and high blood pressure; insulin resistance and central obesity are potential risk factors for the metabolic syndrome (28). (International Diabetes Federation. 2006. The IDF consensus worldwide definition of the metabolic syndrome. Available at: http://www.idf.org/webdata/docs/IDF_Metadef_final.pdf). The metabolic syndrome was fund to be inversely associated with the 25(OH)D concentration (29), suggesting that vitamin D status was inversely correlated with the homeostasis model assessment as an index of insulin resistance (HOMA-IR) (30). TG levels have also been correlated with insulin resistance (31).

The relationship between TG and 25(OH)D can be explained by insulin resistance, which is an essential factor in type 2 diabetes mellitus. Thus, it can be suggested that the relationship between TG and 25(OH)D is stronger in patients with type 2 diabetes mellitus and dyslipidemia.

This study had several strengths. First, this study was single-centered and with a focus on a fixed condition. Second, the study was conducted in the same year (2017), and the blood samples were measured using the same method. The 25(OH)D samples were all measured using the CLIA method. Third, this study was conducted under real clinical conditions, and all the patients were included regardless of sampling timing (fasting/postprandial), and both males and females were included. In addition, the association between lipid profile and 25(OH)D in type 2 diabetes was shown by sex.

This study also had several limitations. First, the target population was limited to patients with type 2 diabetes mellitus. Decreased insulin secretion and increased insulin resistance were expected compared to non-diabetic patients. Second, the food intake was not consistent. Fasting and postprandial patients were mixed and inconsistent. Third, this study was case-controlled and retrospective. Fourth, subjects who were taking active vitamin D medication were excluded but vitamin D intake (i.e., food supplements) was not considered in this study because of the lack of data.

Despite these limitations, this study was the first to identify the associations between 25(OH)D and lipid profiles and found that 25(OH)D was inversely associated with TG in Japanese subjects with type 2 diabetes mellitus.

In conclusion, this study revealed that serum 25(OH)D levels are inversely associated with TG levels after adjustment for patient characteristics in Japanese patients with type 2 diabetes mellitus.

Authorship

BH designed the research; BH, TS, and MN performed the research and interpretation of data; BH, TS, and MN were involved in obtaining ethical approval; BH and TS wrote the first draft of the manuscript; and all authors reviewed and edited the manuscript and approved the final version of the manuscript.

Disclosure of state of COI

The authors have no conflicts of interest, financial or otherwise, to disclose.

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