Diabetology International (2019) 10:67–76
https://doi.org/10.1007/s13340-018-0365-z

ORIGINAL ARTICLE

Serum lipid management in patients with type 1 and type 2 diabetes: a hospital-based cohort study

Yukiko Hasegawa[1] · Tomoko Nakagami[1] · Junko Oya[1] · Chisato Isago[1] · Moritoshi Kurita[1] · Yuki Tanaka[1] · Arata Ito[1] · Reika Tsuzura[1] · Naoki Hirota[1] · Junnosuke Miura[1] · Yasuko Uchigata[1]

Received: 6 March 2018 / Accepted: 26 July 2018 / Published online: 28 July 2018
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Abstract

Introduction Serum lipid management is important for patients with diabetes; however, it has not been examined in our specialized diabetes clinic.

Aims The aim of the study was to assess the percentage of patients who did not achieve management targets (MT) for low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), and explore factors related to failure to achieve lipid MT in Japanese patients with type 1 (T1D) and type 2 diabetes (T2D).

Methods This cross-sectional study included 795 patients (35% men) with T1D and 4018 patients (60% men) with T2D attending our diabetes center. MTs for serum lipids were in accordance with the guidelines of the Japan Atherosclerosis Society. Logistic regression analysis was performed to identify factors related to failure to achieve MTs for serum lipids.

Results The percentages of men/women who did not achieve MT for LDL-C were 34.1/31.8% in T1D and 40.5/52.7% in T2D. The corresponding values for TG were 35.1/14.0% in T1D and 50.1/47.9% in T2D, and for HDL-C were 2.5/0% in T1D and 8.6/2.9% in T2D. Increase in body mass index (BMI) and glycated hemoglobin (HbA1c) were significantly and independently associated with failure to achieve lipid MT in patients with T1D and T2D for both sexes.

Conclusions The percentages of our patients who did not achieve serum lipid MT were relatively high in T1D and T2D, and higher HbA1c and BMI were associated with failure to achieve serum lipid MTs. More attention should be paid to lipid management in patients with diabetes especially who have higher HbA1c and BMI in our facility.

Keywords Diabetes mellitus · Management target for serum lipid · LDL-cholesterol · Triglyceride · HDL-cholesterol

Introduction

Dyslipidemia defined either as raised serum low-density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) levels, or decreased serum high-density lipoprotein-cholesterol (HDL-C) level, has been identified as a strong risk factor for cardiovascular disease (CVD) in observational studies in Japan [1–5]. While diabetes is a risk factor for CVD, patients with diabetes often have dyslipidemia, and thus are at a very high risk for CVD.

In intervention studies for patients with diabetes, the Japan Diabetes Complications Study (JDCS), which followed 1771 patients with type 2 diabetes (T2D) for a median of 7.86 years, demonstrated that the risk of CVD increased by 1.6-fold with every 1 mmol/L increase in LDL-C, and by 1.5-fold with every 1 unit increase in standard deviation in TG [6]. The United Kingdom Prospective Diabetes Study (UKPDS), which followed 3055 patients with T2D for a median of 7.9 years, identified LDL-C, HDL-C, and TG as factors contributing to the onset of coronary artery disease [7].

The effect of lowering LDL-C and TG by medical treatment has also been reported. In a meta-analysis of intervention trial of patients with diabetes (1466 of T1D and 17,220 of T2D), LDL-C reduction by statin reduced the risk of myocardial infarction, coronary death, and stroke [8]. A subgroup analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, used to examine the effect of pravastatin on CVD in 2210 Japanese T2D and impaired fasting glucose patients

✉ Tomoko Nakagami
nakagami.dmc@twmu.ac.jp

[1] Diabetes Center, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku, Tokyo 162-8666, Japan

with mild-to-moderate hypercholesterolemia, revealed that pravastatin reduced the risk of CVD with a hazard ratio of 0.68 (95% confidence interval [CI] 0.48–0.96) [9]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, conducted in T2D patients in Australia, New Zealand, and Finland; showed that the incidence of coronary events during the 5-year period did not differ between the two groups receiving 200 mg/day of fenofibrate or placebo, but 24% of risk reduction of non-fatal myocardial infarction was shown in the fenofibrate group [10].

In recent years, CVD has become the leading cause of death instead of end-stage renal failure or acute diabetic complications, among Japanese patients with type 1 diabetes (T1D) [11–13]. Thus, lipid management has assumed important clinical significance not only in patients with T2D but also in those with T1D, in Japan. The management targets (MT) for dyslipidemia in patients with diabetes have been provided in the guidelines of the Japan Diabetes Society (JDS) and the Japan Atherosclerosis Society (JAS) [14, 15]; however, there are relatively few reports discussing the status of lipid MT stratified by the type of diabetes (T1D or T2D). We did not know what proportion of our patients with diabetes had not achieved lipid MT in our specialized diabetes clinic. Thus, the aim of the present study was to assess the proportion of patients with diabetes who had not achieved MT for LDL-C, TG, and HDL-C, and to explore factors related to non-achievement of lipid MT among our patients with T1D and T2D.

Methods

Study participants

This cross-sectional study was carried out as a part of the Diabetes Study from the Center of Tokyo Women's Medical University (DIACET), established in October 2012 by the DIACET committee (Chair: Y. Uchigata, Secretary: J. Miura). The DIACET is an ongoing single-center prospective observational cohort study targeting Japanese patients with diabetes visiting the Diabetes Center, Tokyo Women's Medical University Hospital. The primary objectives of the study are to assess whether health conditions, treatment statuses, medications, and comorbidities of patients with diabetes are associated with an increased incidence of all-cause mortality, cardiovascular mortality, and cancer, as well as loss of vision and end-stage renal disease.

Among the participants (1299 patients with T1D [36% men] and 6621 patients with T2D [63% men]) who were registered in the DIACET between October 2013 and January 2014, we excluded patients younger than 18 years ($n = 244$), patients with neither T1D nor T2D, patients with unknown types of diabetes ($n = 261$), and patients for whom information was incomplete ($n = 3209$). Our final cohort consisted of 795 patients with T1D (35% men), and 4018 patients with T2D (60% men). T1D and T2D were diagnosed according to the Position Statement of the American Diabetes Association (ADA) [16], as described below. T1D was defined as absolute insulin deficiency, being prone to ketosis and requiring insulin therapy, in a relatively early period after the diagnosis of diabetes. Serological tests positive for islet cell autoantibodies (ICA), autoantibodies to glutamic acid decarboxylase (GAD) and insulinoma-associated protein-2 (IA-2) were strongly suggestive, but not pathognomonic for the diagnosis of T1D. Other specific types of diabetes and gestational diabetes mellitus were excluded, where the remaining were defined as T2D.

Data collection and definition of dyslipidemia

Data on the type of diabetes, smoking, and alcohol habits were obtained from the DIACET patient questionnaires completed in 2013. Data on height, body weight, glycated hemoglobin (HbA1c) levels, blood pressure, lipid profile, duration of diabetes, use of lipid-lowering agents, and the past history of coronary artery disease (CAD), cerebrovascular disease, cerebral infarction, and chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) were extracted from the patients' clinical records from October 2013 to January 2014. Body mass index (BMI) was calculated by dividing the body weight (kg) by squared height (m).

The MT for LDL-C, TG, and HDL-C were defined according to the guidelines of the JDS and JAS [9, 10]. The MT for LDL-C was defined as serum LDL-C < 120 mg/dL for patients with diabetes or < 100 mg/dL for patients with a history of CAD. The MT for TG was defined as serum TG < 150 mg/dL, and the MT for HDL-C was defined as ≥ 40 mg/dL. As the laboratory data were recorded during a patient's regular clinic visit, serum samples were not always taken in the fasting state.

Serum levels of LDL-C, TG, and HDL-C were measured by direct methods using automatic analyzers, including LABOSPECT008 (Hitachi High-Technologies Clinical Analyzer, Tokyo) and Determiner L LDL-C®, Determiner L TG II® and MetaboLead HDL-C® (KYOWA-Medex, Tokyo). Blood glucose levels were measured using the electrode method (Adams Glu GA1171; Arkray, Kyoto, Japan). HbA1c values were measured using the high-performance liquid chromatography method (Adams A1c HA-8160; Arkray) and are shown as the values (%) assigned by the National Glycohemoglobin Standardization Program.

Statistical analysis

All analyses were reported in men and women, stratified by types of diabetes. Patient baseline characteristics were compared between sexes in T1D and T2D, separately. The percentages of failure to achieve lipid MT for LDL-C (LDL-C $\geq$ 120 mg/dL without history of CAD or LDL-C $\geq$ 100 mg/dL with history of CAD), TG (TG $\geq$ 150 mg/dL) and HDL-C (HDL-C $\leq$ 40 mg/dL) were calculated and compared between sexes in T1D and T2D separately. The same comparison was made for different patterns of lipid abnormalities: LDL-C alone (LDL-C $\geq$ 120 mg/dL without history of CAD or LDL-C $\geq$ 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C $\geq$ 40 mg/dL); TG alone (LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG $\geq$ 150 mg/dL, and HDL-C $\geq$ 40 mg/dL); HDL-C alone (LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C < 40 mg/dL); both LDL-C and TG (LDL-C $\geq$ 120 mg/dL without history of CAD or LDL-C $\geq$ 100 mg/dL with history of CAD, TG $\geq$ 150 mg/dL, and HDL-C $\geq$ 40 mg/dL); both LDL-C and HDL-C (LDL-C $\geq$ 120 mg/dL without history of CAD or LDL-C $\geq$ 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C < 40 mg/dL); both TG and HDL-C (LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG $\geq$ 150 mg/dL, and HDL-C < 40 mg/dL); and all three (LDL-C $\geq$ 120 mg/dL without history of CAD or LDL-C $\geq$ 100 mg/dL with history of CAD, TG $\geq$ 150 mg/dL, and HDL-C < 40 mg/dL).

Subsequently, the percentages of patients who failed to achieve MT for lipids were compared between groups with and without history of CAD and between sexes in T1D and T2D separately.

Normally distributed data, presented as the mean ± standard deviation, were compared using the unpaired or paired Student's *t* test. Data not normally distributed were presented as medians and interquartile ranges and compared using the Mann–Whitney *U* test. The frequency and percentage of each categorical variable were reported, and Pearson's Chi-square test or Fisher's exact test was then used for the comparison based on sex.

Logistic regression analysis was performed to calculate odds ratios (ORs) and their 95% confidence intervals (95% CIs) of factors related to failure to achieve MTs for serum lipids. In this model, the condition of failure to achieve MTs for either serum lipids was used as a dependent variable. Independent variables included continuous and categorical variables: the continuous variables were age (1-year increments), duration of diabetes (1-year increments), BMI (1 kg/m^2 increments), and HbA1c level (1% increments); the categorical variables were use of cholesterol-lowering agents (yes vs. no), use of TG-lowering agents (yes vs. no), alcohol [yes (regularly) vs. no], and smoker [yes (past and current) vs. no]. Independent variables that were significant in the univariable model were entered into the multivariable model.

Similarly, logistic regression analysis was performed to assess the sex difference in the percentages of those who failed to achieve lipid MT, independent of age. In this model, sex and age were treated as independent variables.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY), and the differences were considered significant at a two-tailed *p*-value of < 0.05.

Ethical considerations

This study protocol was approved by the Ethics Review Committee of Tokyo Women's Medical University (Approval no. 2481-R2, Approval date: May 31, 2017). All clinical investigations were conducted in accordance with the tenets of the Declaration of Helsinki.

Results

Comparison of characteristics between sex in patients with T1D and T2D

Table 1 shows the comparison of characteristics according to sex in patients with T1D and T2D, separately. In patients with T2D, the means for HbA1c, serum LDL-C and HDL-C levels and the proportion of patients using cholesterol-lowering agents were significantly higher among women than men. In contrast, the proportion of patients using TG-lowering agents was significantly higher among men than women, although the median TG levels were not different between sexes. The proportions of smokers and alcohol drinkers were significantly higher, and the number of the patients who have past history of CAD, cerebrovascular disease, cerebral infarction, and chronic kidney disease were significantly higher among men than women.

In patients with T1D, the mean values for BMI, blood pressure, and TG levels, and the proportion of smokers, alcohol drinkers, and patients using TG-lowering agents were significantly higher among men than women. However, the mean HDL-C level was significantly lower among men than women.

The majority of patients who used cholesterol-lowering agents used statins, regardless of the type of diabetes and sex.

Table 1 Comparison of characteristics according to sex in patients with type 1 and type 2 diabetes

	T1D ($n = 795$)			T2D ($n = 4018$)		
	Men	Women	*p*-values	Men	Women	*p*-values
Number	279	516		2407	1611	
Age (years)	50 ± 15	45 ± 15	< 0.01	65 ± 12	66 ± 12	0.05
Duration of diabetes (years)	19 (10–29)	19 (9–29)	0.58	14 (8–23)	15 (8–23)	0.99
BMI (kg/m^2)	23.2 ± 3.2	22.7 ± 3.4	0.04	24.8 ± 4.0	24.6 ± 4.8	0.30
HbA1c (%)	7.6 ± 1.2	7.8 ± 1.3	0.11	7.3 ± 1.1	7.5 ± 1.3	< 0.01
SBP (mmHg)	133 ± 16	126 ± 18	< 0.01	135 ± 18	135 ± 19	0.40
DBP (mmHg)	78 ± 11	73 ± 10	< 0.01	76 ± 12	73 ± 12	< 0.01
LDL-C (mg/dL)	111 ± 28	109 ± 28	0.59	113 ± 29	123 ± 29	< 0.01
TG (mg/dL)	112 (80–177)	83 (56–118)	< 0.01	150 (103–216)	144 (102–213)	0.13
HDL-C (mg/dL)	71 ± 19	85 ± 20	< 0.01	58 ± 16	66 ± 17	< 0.01
Smoker (%)	23.7	11.2	< 0.01	19.6	6.6	< 0.01
Alcohol (%)	55.6	30.8	< 0.01	50.1	19.0	< 0.01
Use of cholesterol-lowering agents (%)	25.4	18.2	0.02	42.7	54.3	< 0.01
Statins in cholesterol-lowering agents (%)	93.0	94.7	0.65	92.5	93.7	0.30
Use of TG lowering agents (%)	3.2	2.7	0.68	12.1	9.4	0.01
Coronary artery disease (%)	2.9	1.6	0.21	10.7	3.9	< 0.01
Cerebrovascular disease (%)	0.4	0.4	1.00	2.7	1.6	0.01
Cerebral infarction (%)	0.4	0	0.35	1.9	0.6	< 0.01
CKD, eGFR 30–60/< 30 ml/min/1.73 m^2 (%)	13.3/3.2	11.4/3.3	0.75	32.3/6.0	29.2/3.4	< 0.01

Values are shown as medians (interquartile range), means ± standard deviation, or proportions, as appropriate. *p*-values: men versus women, among patients with the same type of diabetes mellitus

T1D type 1 diabetes, *T2D* type 2 diabetes, *BMI* body mass index, *HbA1c* glycated hemoglobin, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein-cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *TG* triglycerides, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

Comparison of percentages of TID and T2D patients who did not achieve lipid MT according to sex

The percentages of men/women who did not achieve MT for LDL-C were 34.1/31.8% in T1D and 40.5/52.7% in T2D. The corresponding values for TG were 35.1/14.0% in T1D and 50.1/47.9% in T2D, and for HDL-C were 2.5/0% in T1D and 8.6/2.9% in T2D (Table 2).

Regardless of the type of diabetes, the percentage of patients who failed to achieve MT for LDL-C alone was significantly higher among women than men, whereas the percentage of those who failed to achieve MT for TG alone was significantly higher among men than women (Table 2). Among patients with T2D, the percentage of failure to achieve MT for HDL-C alone was significantly higher among men than women, while it was very low among patients with T1D for both men and women (Table 2).

The percentage of failure to achieve MT for LDL-C/TG was significantly higher among men than women for patients with T1D, but higher among women than men for patients with T2D (Table 2). The percentage of failure to achieve MT for TG/HDL-C was significantly higher among men than women for patients with T1D and T2D, and that of LDL-C/TG/HDL-C was significantly higher among men than women for patients with T2D (Table 2). These results did not change after adjusting for age.

Comparison of the percentages of patients with T1D and T2D who failed to achieve MT for lipids between the groups with and without history of CAD

In patients with T1D and T2D, the percentages of patients who failed to achieve MT for LDL-C and TG were not significantly different between the group of patients with history of CAD and the group of patients without the history of CAD for both sexes (Table 3). However, the percentage of patients with T2D who failed to achieve MT for HDL-C was significantly higher in the group of patients with history of CAD than in the group of patients without the history of CAD for both sexes (Table 3). Compared by sexes, the percentage of patients with T1D who failed to achieve MT for TG and HDL-C was significantly lower in women than in men among patients without CAD. The percentage

Table 2 Comparison of percentages of failure to achieve lipid MT between sexes among patients with type 1 and type 2 diabetes

Percentage of failure to achieve MT by different pattern of lipid's abnormalities (%)	T1D ($n=795$)			T2D ($n=4018$)		
	Men ($n=279$)	Women ($n=516$)	*p*-values	Men ($n=2407$)	Women ($n=1611$)	*p*-values
LDL-C alone	15.8	22.1	0.03	15.3	22.6	< 0.01
TG alone	15.1	4.3	< 0.01	21.5	16.3	< 0.01
HDL-C alone	0.7	0	0.12	1.7	0.4	< 0.01
Both LDL-C and TG	18.3	9.7	< 0.01	21.9	29.2	< 0.01
Both LDL-C and HDL-C	0	0	–	0.2	0.1	0.49
Both TG and HDL-C	1.8	0	< 0.01	3.6	1.6	< 0.01
LDL-C, TG and HDL-C	0	0	–	3.1	0.8	< 0.01
LDL-C	34.1	31.8	0.52	40.5	52.7	< 0.01
TG	35.1	14.0	< 0.01	50.1	47.9	0.17
HDL-C	2.5	0	< 0.01	8.6	2.9	< 0.01

LDL-C: LDL-C ≥ 120 mg/dL without history of CAD or LDL-C ≥ 100 mg/dL with history of CAD; TG: TG ≥ 150 mg/dL; HDL-C: HDL-C < 40 mg/dL; LDL-C alone: LDL-C ≥ 120 mg/dL without history of CAD or LDL-C ≥ 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C ≥ 40 mg/dL; TG alone: LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG ≥ 150 mg/dL, and HDL-C ≥ 40 mg/dL; HDL-C alone: LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C < 40 mg/dL; Both LDL-C and TG: LDL-C ≥ 120 mg/dL without history of CAD or LDL-C ≥ 100 mg/dL with history of CAD, TG ≥ 150 mg/dL, and HDL-C ≥ 40 mg/dL; both LDL-C and HDL-C: LDL-C ≥ 120 mg/dL without history of CAD or LDL-C ≥ 100 mg/dL with history of CAD, TG < 150 mg/dL, and HDL-C < 40 mg/dL; both TG and HDL-C: LDL-C < 120 mg/dL without history of CAD or LDL-C < 100 mg/dL with history of CAD, TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL; LDL-C, TG and HDL-C: LDL-C ≥ 120 mg/dL without history of CAD or LDL-C ≥ 100 mg/dL with history of CAD, TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL; *p*-values: men versus women, among patients with the same type of diabetes mellitus

MT management targets, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *LDL-C* low-density lipoprotein-cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein-cholesterol

Table 3 Comparison of the percentages of T1D and T2D patients who failed to achieve lipid MT between the groups with and without history of CAD

	T1D			T2D		
	Without prior CAD	With prior CAD	*p*-value	Without prior CAD	With prior CAD	*p*-value
LDL-C						
Men	65.3 (177/271)	87.5 (7/8)	0.19	59.4 (1278/2150)	59.5 (153/257)	0.98
Women	68.7 (349/508)	37.5 (3/8)	0.06	47.3 (732/1548)	47.6 (30/63)	0.96
p-value	0.34	0.04		< 0.01	0.09	
TG						
Men	65.7 (178/271)	37.5 (3/8)	0.10	49.9 (1072/2150)	50.6 (130/257)	0.83
Women	86.4 (439/508)	62.5 (5/8)	0.05	52.5 (812/1548)	44.4 (28/63)	0.21
p-value	< 0.01	0.32		0.12	0.38	
HDL-C						
Men	97.4 (264/271)	100 (8/8)	0.65	91.9 (1975/2150)	86.8 (223/257)	< 0.01
Women	100 (508/508)	100 (8/8)	–	97.3 (1506/1548)	90.5 (57/63)	< 0.01
p-value		–		< 0.01	0.43	

Data indicates proportion (case/number) for each category

MT management targets, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *CAD* coronary artery disease, *LDL-C* low-density lipoprotein-cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein-cholesterol

[a]*p*-value: proportion in the group without prior CAD versus that in the proportion with prior CAD

[b]*p*-value: proportion in the men versus women among the group with (or without) prior CAD

of patients with T2D who failed to achieve MT for LDL-C was significantly lower in men than in women, whereas, MT for HDL-C was significantly lower in women than in men among patients without the history of CAD (Table 3).

Factors related to failure to achieve MT for LDL-C

The univariable logistic regression analysis showed that BMI, HbA1c, and the use of cholesterol-lowering agents were associated with failure to achieve MT for LDL-C in men and women with T1D and T2D (Table 4). Age was associated with failure to achieve MT for LDL-C among women with T1D while age and the duration of diabetes were associated with failure to achieve MT for LDL-C among men and women with T2D.

The multivariable logistic regression analysis showed that increase in BMI and HbA1c were independently associated with failure to achieve MT for LDL-C in both men and women with T1D and T2D while the non-use of cholesterol-lowering agents was independently associated with failure to achieve MT for LDL-C in both men and women with T2D (Table 4).

Factors related to failure to achieve MT for TG

In the univariable logistic regression model (Table 5), BMI in both sexes, and age and HbA1c in women were associated with failure to achieve MT for TG in patients with T1D. Among patients with T2D, age in men and duration of diabetes, BMI, HbA1c, and the use of TG lowering agents in men and women were associated with failure to achieve MT for TG among patients with T2D.

The multivariable logistic regression analysis showed that increase in BMI and HbA1c were independently associated with failure to achieve MT for TG in men with T1D and men and women with T2D, while shorter duration and the use of TG-lowering agents was independently associated with failure to achieve MT for TG in both men and women with T2D (Table 5).

Factors related to failure to achieve MT for HDL-C

In the univariate regression model (Table 6), age in men with T1D and duration of diabetes, BMI, and HbA1c in men with T2D were associated with failure to achieve MT for HDL-C.

The multivariable logistic regression analysis showed that shorter duration of diabetes, higher BMI, and HbA1c in men with T2D were independently associated with failure to achieve MT for HDL-C (Table 6).

Discussion

This cross-sectional observational study showed that the percentage of failure to achieve MT for LDL-C, TG, and HDL-C according to JAS guideline were approximately 30–50, 15–50, and 0–10, respectively, among our patients

Table 4 Unadjusted and adjusted odds ratios and their 95% confidence intervals for factors associated with failure to achieve management target for LDL-C, stratified by sex and type of diabetes

	T1D				T2D			
	Men		Women		Men		Women	
	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values
Univariable model								
Age (1 year)	0.99 (0.97–1.01)	0.24	1.03 (1.02–1.05)	< 0.01	0.98 (0.98–0.99)	< 0.01	0.99 (0.98–0.99)	< 0.01
Duration of diabetes (1 year)	0.99 (0.97–1.01)	0.19	1.01 (0.99–1.03)	0.29	0.98 (0.97–0.99)	< 0.01	0.98 (0.97–0.99)	< 0.01
BMI (1 kg/m^2)	1.22 (1.12–1.33)	< 0.01	1.09 (1.03–1.15)	< 0.01	1.05 (1.03–1.08)	< 0.01	1.03 (1.01–1.05)	0.01
HbA1c (1%)	1.53 (1.22–1.92)	< 0.01	1.38 (1.19–1.60)	< 0.01	1.20 (1.11–1.29)	< 0.01	1.14 (1.05–1.24)	< 0.01
Use of cholesterol-lowering agents (yes)	2.05 (1.18–3.56)	0.01	1.88 (1.19–2.97)	< 0.01	0.78 (0.66–0.92)	< 0.01	0.60 (0.49–0.73)	< 0.01
Multivariable model								
Age (1 year)	–	–	1.03 (1.02–1.05)	< 0.01	0.99 (0.99–1.00)	0.12	1.00 (0.99–1.01)	0.84
Duration of diabetes (1 year)	–	–	–	–	0.98 (0.97–0.99)	< 0.01	0.98 (0.97–0.99)	< 0.01
BMI (1 kg/m^2)	1.19 (1.09–1.30)	< 0.01	1.07 (1.01–1.13)	0.02	1.03 (1.01–1.06)	0.01	1.02 (0.99–1.04)	0.16
HbA1c (1%)	1.42 (1.12–1.80)	< 0.01	1.36 (1.17–1.57)	< 0.01	1.20 (1.11–1.30)	< 0.01	1.17 (1.07–1.28)	< 0.01
Use of cholesterol-lowering agents (yes)	1.71 (0.95–3.07)	0.08	1.19 (0.72–1.97)	0.50	0.74 (0.63–0.88)	< 0.01	0.58 (0.48–0.72)	< 0.01

T1D type 1 diabetes, *T2D* type 2 diabetes, *ORs* odds ratios, *CIs* confidence intervals, *DM* diabetes mellitus, *BMI* body mass index, *HbA1c* glycated hemoglobin

Table 5 Unadjusted and adjusted odds ratios and their 95% confidence intervals for factors associated with failure to achieve MT for TG, stratified by sex and type of diabetes

	T1D				T2D			
	Men		Women		Men		Women	
	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values
Univariable model								
Age (1 year)	1.00 (0.99–1.02)	0.60	1.03 (1.01–1.05)	0.01	0.98 (0.97–0.98)	< 0.01	0.99 (0.99–1.00)	0.12
Duration (1 year)	1.00 (0.98–1.02)	0.64	1.00 (0.98–1.03)	0.70	0.98 (0.97–0.99)	< 0.01	0.99 (0.98–0.99)	0.01
BMI (1 kg/m^2)	1.25 (1.14–1.37)	< 0.01	1.15 (1.07–1.23)	< 0.01	1.15 (1.12–1.17)	< 0.01	1.09 (1.07–1.12)	< 0.01
HbA1c (1%)	1.13 (0.91–1.39)	0.27	1.44 (1.21–1.71)	< 0.01	1.34 (1.24–1.45)	< 0.01	1.37 (1.26–1.49)	< 0.01
Use of TG lowering agents (yes)	3.87 (0.95–15.83)	0.06	0.47 (0.06–3.63)	0.47	1.76 (1.36–2.26)	< 0.01	2.95 (2.05–4.25)	< 0.01
Multivariable model								
Age (1 year)	–		1.03 (1.01–1.05)	< 0.01	0.99 (0.99–1.00)	0.12	–	
Duration (1 year)	–		–		0.98 (0.98–0.99)	< 0.01	0.98 (0.97–0.99)	< 0.01
BMI (1 kg/m^2)	1.25 (1.14–1.37)	< 0.01	1.13 (1.05–1.21)	< 0.01	1.11 (1.09–1.14)	< 0.01	1.07 (1.04–1.09)	< 0.01
HbA1c (1%)	–		1.44 (1.20–1.72)	< 0.01	1.26 (1.16–1.37)	< 0.00	1.32 (1.21–1.45)	< 0.01
Use of TG lowering agents (yes)	–	–	–	–	1.65 (1.27–2.15)	< 0.01	3.15 (2.16–4.58)	< 0.01

T1D type 1 diabetes, *T2D* type 2 diabetes, *ORs* odds ratios, *CIs* confidence intervals, *BMI* body mass index, *HbA1c* glycated hemoglobin, *TG* triglycerides

Table 6 Unadjusted and adjusted odds ratios and their 95% confidence intervals for factors associated with failure to achieve MT for HDL-C, stratified by sex and type of diabetes

	T1D				T2D			
	Men		Women		Men		Women	
	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values	ORs (95% CIs)	*p*-values
Univariable model								
Age (1 year)	1.07 (1.02–1.13)	0.01	–	–	0.99 (0.98–1.00)	0.09	1.01 (0.99–1.03)	0.48
Duration (1 year)	0.99 (0.94–1.06)	0.93	–	–	0.98 (0.97–0.99)	0.02	1.01 (0.99–1.04)	0.32
BMI (1 kg/m^2)	1.17 (0.96–1.42)	0.11	–	–	1.08 (1.05–1.12)	< 0.01	1.03 (0.97–1.08)	0.36
HbA1c (1%)	0.50 (0.21–1.19)	0.12	–	–	1.22 (1.09–1.37)	< 0.01	1.08 (0.87–1.33)	0.49
Multivariable model								
Age (1 year)	1.07 (1.02–1.13)	0.01	–	–			–	–
Duration (1 year)	–	–	–	–	0.99 (0.97–0.99)	0.04	–	–
BMI (1 kg/m^2)	–	–	–	–	1.06 (1.03–1.10)	< 0.01	–	–
HbA1c (1%)	–	–	–	–	1.16 (1.03–1.31)	0.01	–	–

T1D type 1 diabetes, *T2D* type 2 diabetes, *ORs* odds ratios, *CIs* confidence intervals, *BMI* body mass index, *HbA1c* glycated hemoglobin, *TG* triglycerides

with T1D and T2D. Increases in BMI and HbA1c levels were significantly and independently associated with failure to achieve lipid MT among men and women with T1D and T2D. The observational data of Japanese patients with diabetes showed that dyslipidemia was a significant risk factor for CVD [1–5]. However, there has been no intervention trial for lipids targeted at Japanese patients with diabetes. Thus, the current management target of lipids in Japanese patients with diabetes is consensus-based, and is important at clinical settings.

The Japan Diabetes Complication and its Prevention prospective (JDCP) study is an ongoing observational study collecting data from 464 Japanese hospitals (including our facility) to investigate the management of Japanese patients with diabetes [17, 18]. In the JDCP study, approximately 70 and 60% of patients with T1D and T2D, respectively, were found to have LDL-C levels < 120 mg/dL, more than 90% in each group had HDL-C level ≥ 40 mg/dL, and 90 and 75%, respectively, had TG levels < 150 mg/dL. Patients' characteristics in the present study were similar to those of the JDCP study, but the proportion of patients with TG level < 150 mg/dL in the present study was particularly lower than the JDCP study. In these studies, laboratory tests were not always conducted on serum samples obtained in a fasted state; hence, this might have influenced the results.

Since T1D and T2D have different etiologies and pathophysiologies, MT for serum lipids was not stratified by type of diabetes according to the guidelines by different organizations [14, 15, 19]. This may be because the majority (92%) of patients with diabetes in the randomized controlled trial (RCT) for lipids had T2D [20] and data was yet to be analyzed by type of diabetes.

Recently, the importance of evaluation of individualized risk of CVD and comprehensive management of CVD risk factors have been emphasized [21–24]. In particular, age is an important risk factor for CVD. The Japanese Elderly Intervention Trial (J-EDIT) [25], which included 993 elderly patients with T2D aged 65–85 years (mean 71 years), with 16% of patients having the history of coronary events, showed that non HDL-C increased the risk of stroke, diabetes-related mortality, and total events. Furthermore, the study showed that LDL-C lowering therapy by atorvastatin reduced the incidence of CVD and diabetes-related events [26]. Thus, lipid control is important for the prevention of CVD in elderly patients with T2D. However, thus far, no large-scale RCT that examined the effectiveness of lipid lowering therapy on primary prevention of CVD has targeted Japanese late-stage elderly patients (over 75 years) with T1D or T2D. In addition, although women are at a lower risk of CVD than men [27], there is inadequate evidence about sex differences in the risk of CVD for patients over 75 years. For these reasons, the use of lipid lowering therapy in elderly patients with diabetes occurs at the discretion of the attending physician depending on individual risk; and this might have influenced our results.

Serum lipid levels change with age; total cholesterol and LDL-C levels are higher in men than in women up to the age of 40 years, and then they are higher in women than in men. Serum TG levels are higher in men than in women, but it rapidly increases after the age of 50 years in women [28]. The levels of female hormones drop rapidly after menopause, and could account for this difference. In this study, the proportion of postmenopausal women was greater in T2D (mean age, 66 years) than T1D (mean age, 45 years). This may reflect the result that older age was independently associated with the failure to achieve MT for serum lipids in women with T1D.

It would be of interest to note that the percentages of patients who failed to achieve the lipids MT were not different between the two groups with or without the history of CAD except for HDL-C in T2D (Table 3). This suggests insufficient lipid control in our patients with both diabetes and history of CAD.

In our patients with T2D, the use of cholesterol-lowering agents decreased the OR of failure to achieve MT for LDL-C. Therefore, these agents may be good therapeutic options for patients complicated with high LDL-C. Statins have side effects such as muscle pain and weakness; hence, there is concern about statin intolerance [29]. Although past studies showed that there is little concern about decreasing physical activities due to statin [4, 30]; however, statin's side effects might have resulted in decreased adherence and increased failure to achieve MT for LDL-C, in our study.

On the other hand, the use of TG-lowering agents increased the OR of failure to achieve MT for TG in patients with T2D. This suggests that current TG-lowering regimens were insufficient for patients with T2D, though this was a cross-sectional study and the number of patients who failed to achieve MT for TG who were taking TG lowering agents were very low (0–15%).

In the current study, the percentages of patients who failed to achieve MT for LDL-C/TG were quite high, but few patients were taking both cholesterol- and TG-lowering agents. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study showed that in male patients and patients with high TG and low HDL-C levels, a significant CVD risk reduction was shown by the combined use of statins and fenofibrate [31]. Combination of statins and fibrate may be useful for patients without chronic kidney disease, who have failed to achieve MT for LDL-C/TG.

As expected, an increase in HbA1c or BMI was associated with failure to achieve MT for LDL-C and TG in almost all patients, and for HDL-C in male patients with T2D. In our study, the mean BMI of patients with T1D was within the normal range. The Japan Diabetes Clinical Data Management Study Group reported that the prevalence of overweight and obesity in patients with T1D was less than that in the normal Japanese population [32]. However, the mean BMI of patients with T1D increases year by year [33]. Obesity leads to insulin resistance and deterioration of blood glucose control, suggesting the possibility of complication with dyslipidemia. These data indicate the need for careful monitoring of body weight in daily clinical practice in patients with both T1D and T2D.

Several limitations of this study should be noted. First, this cross-sectional study dealt with the data of Japanese patients from a single facility; thus, the findings should be interpreted with caution. Second, laboratory data were not always obtained from fasting serum samples. However, it is impractical to record fasting data for all patients in the clinical setting. Epidemiologic data from Japan showed that high TG, recorded randomly, is an independent risk factor for CVD [34]. Patients with diabetes often display postprandial hyperlipidemia, and this is a risk factor for CVD [35]. Non-HDL-C, which represents the cholesterol concentration in TG-rich lipoprotein containing ApoB, without the influence of diet [36], is a stronger risk factor for CVD than LDL-C [37]. However, total cholesterol was not measured in our study; thus, we could not assess non-HDL-C. Third, JAS guideline was revised in 2017, and MT for LDL-C is considered to be < 70 mg/dL for patients with history of CAD, complicated with non-cardiogenic cerebral infarction, peripheral artery disease, metabolic syndrome, smoking, CKD, and any other risk factors [38]. However, we did not have data on waist circumference and the history of non-cardiogenic cerebral infarction, peripheral artery disease, and any other risk factors listed in the revised JAS guideline, therefore, we could not analyze the percentages of patients whose LDL-C target were < 70 mg/dL. Fourth, we were unable to exclude secondary causes of hyperlipidemia such as hypothyroidism, nephrotic syndrome, steroid therapy, or familial hypercholesterolemia. These might have influenced the results. Nevertheless, high level of serum lipid is one of the strongest risk factors for atherosclerosis and CVD, irrespective of whether it is primary or secondary. Fifth, physicians' awareness and adherence with the guidelines and patients' adherence to their treatment might have influenced our results. However, we could not examine these factors in this study. Further research will be needed. Nevertheless, we will use our findings to improve the quality of patients' care in our clinic.

Conclusion

The percentage of failure to achieve MT for LDL-C, TG, and HDL-C were relatively high: approximately 30–50, 15–50, and 0–10%, respectively, among our patients with T1D and T2D. Increase in BMI and HbA1c level was independently associated with failure to achieve serum lipid MTs in patients with T1 and T2D for both sexes. Our findings highlight the need for more attention to lipid management especially in patients with diabetes who had higher HbA1c levels and BMI in our facility.

Acknowledgements The authors express their deep appreciation to the DIACET participants, and to the staff of the Department of Medicine and Ophthalmology, Diabetes Center, Tokyo Women's Medical University School of Medicine.

Compliance with ethical standards

Conflicts of interest The Diabetes Center of the Tokyo Women's Medical University is supported through unrestricted research funding from Alcon, Astellas, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eizai, Eli Lilly, Kowa, Kyowa Hakko Kirin, Mitsubishi Tanabe, MSD, Nipro, Novartis, Novo Nordisk, Ono, Otsuka, Pfizer, Sanofi, Sumitomo Dainippon, Takeda, and Terumo.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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