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Sex-Related Differences in Sitagliptin Treatment in Type 2 Diabetes: Results from the PROLOGUE Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Xilin Wu**
ABCEF 1 **Shiming Zhang**
ABC 2 **Yingzhu Jin**
ABCDEF 3 **Xun Xiao**

1 Department of Cardiology, First Affiliated Hospital of Guangxi University of Science and Technology, Liuzhou, Guangxi, PR China
2 Guiyang Second People's Hospital, Guiyang, Guizhou, PR China
3 Xincheng County People's Hospital, Laibin, Guangxi, PR China

Corresponding Author: Xun Xiao, e-mail: xiaoxun666@aliyun.com

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Conflict of interest: None declared

Background: At present, whether sitagliptin has sex-related differences in effect on atherosclerosis in type 2 diabetes mellitus (T2DM) patients is unknown. The purpose of this study was to investigate whether there is sex-related difference in the effect of sitagliptin on atherosclerosis in T2DM patients.

Material/Methods: In the PROLOGUE trial, 222 patients were allocated to the sitagliptin group and 220 patients were allocated to the conventional group. Carotid artery intima-media thickness (IMT) was assessed at baseline, 12 months, and 24 months.

Results: In male patients, sitagliptin significantly reduced the mean IMT (0.84 ± 0.41 mm vs 1.02 ± 0.67 mm, $P=0.013$) and the maximum IMT (1.14 ± 0.59 mm vs 1.39 ± 0.88 mm, $P=0.016$) in the right internal carotid arteries (ICA) compared to the conventional group at 12 months. Similarly, sitagliptin significantly reduced the maximum IMT (1.09 ± 0.52 mm vs 1.28 ± 0.77 mm, $P=0.049$) in the right ICA compared to the conventional group at 24 months, but no difference was found in the mean IMT in the right ICA between groups at 24 months. In female patients, sitagliptin significantly reduced the mean IMT (1.01 ± 0.47 mm vs 1.23 ± 0.51 mm, $P=0.049$) and the maximum IMT (1.39 ± 0.65 mm vs 1.71 ± 0.77 mm, $P=0.042$) in the right bulb compared to the conventional group at 12 months. However, the group differences were not observed in mean IMT and maximum IMT at 24 months.

Conclusions: Our results suggest that sitagliptin slows the progression of right carotid IMT in male patients. However, more research is needed to validate this finding in female patients.

Keywords: 1,5,5-Triallylbarbituric Acid • 46, XY Sex Reversal 5 • 6q24-Related Transient Neonatal Diabetes Mellitus • Sitagliptin Phosphate

Abbreviations: T2DM – type 2 diabetes mellitus; IMT – intima-media thickness; ICA – internal carotid arteries; CHD – coronary heart disease; IS – ischemic stroke; DPP-4 – Dipeptidyl peptidase-4; GLP-1 – glucagon-like peptide-1; GIP – gastric inhibitory polypeptide; RCT – randomized controlled trial; HbA1c – glycosylated hemoglobin; CCA – common carotid arteries; OR – odds ratio; CI – confidence interval; WC – waist circumference; SDP – systolic blood pressure; DBP – diastolic blood pressure; PR – pulse rate; FPG – fasting plasma glucose; HMWA – high-molecular-weight adiponectin; LD – lactic dehydrogenase; HDL-cholesterol – high-density lipoprotein cholesterol; TG – triglyceride; small LDL-cholesterol – small dense low-density lipoprotein cholesterol; RLP-cholesterol – remnant-like particle cholesterol; MMDLI – malondialdehyde-modified low-density lipoprotein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; BUN – blood urea nitrogen; eGFR – estimated glomerular filtration rate

Trial registration: UMIN000004490

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/938030>

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Background

Atherosclerosis [1-3] is a chronic non-infectious inflammation of the arterial wall. Previous studies have shown that cardiovascular [4,5] and cerebrovascular [6,7] diseases caused by atherosclerosis are some of the leading causes of death in developed and developing countries. In China, atherosclerosis has become one of the main causes of death [8,9]. Atherosclerosis is caused by a variety of factors, including endothelial cell injury, dyslipidemia, diabetes, hypertension, and chronic inflammation. Among these factors, type 2 diabetes mellitus (T2DM) is a critical risk factor for atherosclerosis [10-12]. There is clinical evidence showing higher risk of coronary heart disease (CHD) [13] and ischemic stroke (IS) [14] in T2DM patients than in patients with a single disease. Therefore, the main focus of research has been to determine ways to delay or reduce the degree of atherosclerosis in T2DM patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitor [15,16] is a new therapeutic drug for the treatment of diabetes. It can elevate the activity of endogenous glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), promote the release of insulin by islet B cells, and restrain the excretion of glucagon, thus causing an increase in insulin concentration and a drop in blood glucose. Sitagliptin, one of the inhibitors of DPP-4 inhibitors, has been widely assessed in previous studies [17,18]. However, whether sitagliptin can effectively delay the progression of atherosclerosis in T2DM patients and thus reduce cardiovascular events remains controversial. Some previous studies have found that sitagliptin does not improve the degree of atherosclerosis in T2DM patients [19,20], nor reduce the risk of cardiovascular events [21,22]. On the contrary, some other studies have supported the benefits of sitagliptin in T2DM patients [23-25]. It is likely that these conflicting results are due to sex-related differences, since males and females have different levels of hormone secretion (eg, androgens, estrogens, and progestins), which could potentially impact the effectiveness of sitagliptin treatment in T2DM patients. In addition, there have been no studies reporting sex-related differences in the effect of sitagliptin on carotid artery IMT. Therefore, the objective of our study was to re-analyze the PROLOGUE study, and explore whether sex-related differences impact the effectiveness of sitagliptin treatment in patients with T2DM [19].

Material and Methods

We obtained all data analyzed in this study from an open database (datadryad: <https://datadryad.org/stash>). Datadryad is a non-profit database that allows researchers to download the data for free, for the purpose of verifying the accuracy of the results or conducting different statistical analysis based on different research assumptions. For this study, we downloaded

the data from the PROLOGUE trial [19] (Oyama, Jun-ichi et al (2017), Data from: The effect of sitagliptin on carotid artery atherosclerosis in Type 2 Diabetes: the PROLOGUE randomized controlled trial, Dryad, Dataset, <https://doi.org/10.5061/dryad.qt743>). The detailed results of the PROLOGUE study have been described in previous studies [19,25]. In brief, PROLOGUE is a multicenter, prospective, randomized clinical trial conducted in 48 institutions in Japan. The study recruited 463 T2DM patients treated in 48 institutions between June 2011 and September 2012 [19]. The participants were >30 years old, with glycated hemoglobin (HbA1c) ranging from 6.2% to 9.4%. Exclusion criteria were: patients with type 1 diabetes, patients with severe heart failure (NYHA \geq III grade), patients who had been treated with DPP-4 inhibitors and/or GLP-1 analogs, patients with severe renal insufficiency, pregnant patients, and patients without informed consent. Other details of inclusion and exclusion criteria have been described in previous studies [19,25]. Based on the inclusion and exclusion criteria, 442 participants were finally included in the study. The participants were randomly assigned to the sitagliptin group (n=222, 25-100 mg/d) or the conventional group (n=220) in a 1: 1 ratio. The sitagliptin group included 146 male participants and 76 female participants, while the conventional group include 151 male participants and 69 female participants. Since this study was a secondary analysis of a prior study, no informed consent of patients or approval certificate by an ethics committee was necessary.

Endpoints

The primary endpoint of our current study included changes in the mean IMT in the right and the left common carotid arteries (CCA), the mean IMT in the right and the left bulb, the mean IMT in the right and the left internal carotid arteries (ICA), the maximum IMT in the right and the left CCA, the maximum IMT in the right and the left bulb, and the maximum IMT in the right and the left ICA. The primary endpoints were measured by high-resolution carotid ultrasonography at baseline, 12 months, and 24 months by expert sonographers trained in the measurement of carotid IMT, as described in Oyama et al [19]. In addition, all ultrasonic systems were equipped with more than 7.5 MHz linear sensors. The secondary endpoints included weight, waist circumference (WC), systolic blood pressure (SDP), diastolic blood pressure (DBP), pulse rate (PR), HbA1c, fasting plasma glucose (FPG), 1,5-anhydroglucitol, 1,4-anhydro-D-glucitol, high-molecular-weight adiponectin (HMWA), lactic dehydrogenase (LD), high-density lipoprotein cholesterol (HDL-cholesterol), triglyceride (TG), small dense low-density lipoprotein cholesterol (small LDL-cholesterol), remnant-like particle cholesterol (RLP-cholesterol), malondialdehyde-modified low-density lipoprotein (MMDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine, estimated glomerular filtration rate (eGFR), cystatin C, and urinary albumin/creatinine ratio, and were measured at 24 months.

Table 1. Baseline characteristics of male participants.

Characteristic	Sitagliptin group	Conventional group	P-value
N	146	151	
Age, years	68.21±9.22	68.66±9.24	0.670
Height, cm	164.55±6.66	165.06±5.50	0.479
Weight, kg	68.89±10.69	68.04±10.82	0.498
Body mass index, kg/m ²	25.20±3.49	25.10±3.91	0.834
Waist circumference, (cm)	90.98±9.52	89.67±9.71	0.267
Systolic blood pressure, mmHg	130.01±16.22	127.77±15.83	0.231
Diastolic blood pressure, mmHg	73.66±10.34	72.62±11.33	0.409
HbA1c,%	6.54±0.52	6.57±0.52	0.593
Fasting plasma glucose, mmol/l	141.75±44.04	135.86±34.48	0.210
Serum creatinine, μmol/l	0.93±0.22	0.94±0.25	0.649
Estimated glomerular filtration rate, ml/min/1.73 m ²	66.43±16.47	65.91±16.65	0.786
Hypertension, N (%)	121 (82.88%)	116 (76.82%)	0.194
Dyslipidemia, N (%)	105 (71.92%)	99 (65.56%)	0.238
Cerebral infarction, N (%)	11 (7.53%)	17 (11.26%)	0.272
Cerebral hemorrhage, N (%)	2 (1.37%)	1 (0.66%)	0.542
Myocardial infarction, N (%)	39 (26.71%)	49 (32.45%)	0.279
Arrhythmia, N (%)	20 (13.70%)	25 (16.56%)	0.492
Chronic heart failure, N (%)	12 (8.22%)	19 (12.58%)	0.219
Percutaneous coronary intervention, N (%)	45 (30.82%)	51 (33.77%)	0.586
Coronary artery bypass grafting, N (%)	15 (10.27%)	15 (9.93%)	0.923

Statistical Analysis

The Shapiro-Wilk test was used to judge the normality of continuous variables. In this study, we first divided all participants into 2 groups based on sex, and then explored the effect of sitagliptin on carotid atherosclerosis in T2DM patients. We used mean and standard deviations to represent normally distributed continuous variables, and used the independent-samples *t* test or repeated measures variance to compare differences between groups when appropriate. Continuous variables without normal distribution are presented as median (IQ) range, and the Mann-Whitney test or Kruskal Wallis test was used to compare differences between groups. We expressed categorical variables by numbers and percentages, and used the chi-square test to compare differences between groups. We used odds ratios (OR) with 95% confidence interval (CI) to express the difference between groups. *P* value <0.05 was considered statistically significant (2-sided) difference. We used SPSS 24.0 statistical software and R software (version 3.6.2) for statistical analysis.

Results

Baseline Characteristics of Male Participants

Table 1 shows the baseline characteristics and baseline laboratory information for male participants. The average age of participants in the sitagliptin and the conventional group was 68.21±9.22 years and 68.66±9.24 years, respectively. No significant differences were observed in height, weight, SBP, DBP, HbA1c, FPG, serum creatinine, eGFR, mean IMT in the right and the left CCA, mean IMT in the right and the left bulb, mean IMT in the right and the left ICA, maximum IMT in the right and the left CCA, maximum IMT in the right and the left bulb, maximum IMT in the right and the left ICA, plaque area, plaque gray-scale median, and history of medication and diseases between the 2 groups (all *P*>0.05).

Baseline Characteristics of Female Participants

Table 2 shows the baseline characteristics and baseline laboratory information for female participants. The average age of participants in the sitagliptin group and the conventional

Table 2. Baseline characteristics of female participants.

Characteristic	Sitagliptin group	Conventional group	P-value
N	76	69	
Age, years	71.04±9.10	71.35±8.83	0.837
Height, cm	151.23±5.29	150.00±5.70	0.180
Weight, kg	57.95±13.62	55.62±10.46	0.255
Body mass index, kg/m ²	25.15±5.03	24.82±4.68	0.688
Waist circumference, (cm)	86.97±11.68	86.10±11.97	0.876
Systolic blood pressure, mmHg	130.08±14.74	130.88±17.76	0.766
Diastolic blood pressure, mmHg	71.26±11.24	69.67±11.64	0.402
HbA1c,%	6.58±0.53	6.58±0.58	0.981
Fasting plasma glucose, mmol/l	131.49±35.92	133.21±41.93	0.796
Serum creatinine, µmol/l	0.71±0.18	0.69±0.19	0.588
Estimated glomerular filtration rate, ml/min/1.73 m ²	66.49±19.09	68.78±20.79	0.491
Hypertension, N (%)	60 (78.95%)	50 (72.46%)	0.362
Dyslipidemia, N (%)	58 (76.32%)	49 (71.01%)	0.468
Cerebral infarction, N (%)	10 (13.16%)	8 (11.59%)	0.776
Cerebral hemorrhage, N (%)	1 (1.32%)	0 (0.00%)	0.339
Myocardial infarction, N (%)	7 (9.21%)	6 (8.70%)	0.914
Arrhythmia, N (%)	12 (15.79%)	7 (10.14%)	0.314
Chronic heart failure, N (%)	3 (3.95%)	7 (10.14%)	0.141
Percutaneous coronary intervention, N (%)	13 (17.11%)	18 (26.09%)	0.188
Coronary artery bypass grafting, N (%)	4 (5.26%)	1 (1.45%)	0.209

group was 71.04±9.10 years and 71.35±8.83 years, respectively. Similar to male participants, no significant differences were observed in height, weight, SBP, DBP, HbA1c, FPG, serum creatinine, eGFR, mean IMT in the right and the left CCA, mean IMT in the right and the left bulb, mean IMT in the right and the left ICA, maximum IMT in the right and the left CCA, maximum IMT in the right and the left bulb, maximum IMT in the right and the left ICA, plaque area, plaque gray scale median, and history of medication and diseases between the 2 groups (all $P>0.05$).

Comparison of Atherosclerotic Parameters in Male Participants at 12 Months and 24 Months

Our results show that in male patients, sitagliptin significantly reduced mean IMT (0.84±0.41 mm vs 1.02±0.67 mm, group differences: -0.19, -0.34 to -0.04) (Figure 1A) and maximum IMT (1.14±0.59 mm vs 1.39±0.88 mm, group differences: -0.25, -0.45 to -0.05) in the right ICA (Figure 1B) compared to the conventional group at 12 months. Similarly, sitagliptin also significantly reduced maximum IMT in the right ICA (1.09±0.52 mm vs 1.28±0.77 mm, group differences: -0.19, -0.37 to -0.00) (Figure 1C) compared to the conventional group at 24 months, but showed no

difference in the mean IMT in the right ICA between the groups at 24 months. For other atherosclerosis parameters, no difference was found between groups (all $P>0.05$) (Table 3).

Comparison of Atherosclerotic Parameters in Female Participants at 12 Months and 24 Months

For female patients, our results also showed that sitagliptin significantly reduced the mean IMT (1.01±0.47 mm vs 1.23±0.51 mm, $P=0.049$) and the maximum IMT (1.39±0.65 mm vs 1.71±0.77 mm, $P=0.042$) in the right bulb compared to the conventional group at 12 months (Figure 2). However, the difference between these 2 indexes was not significant at 24 months. Similarly, no significant difference was noted for other atherosclerosis indicators (all $P>0.05$) (Table 4).

Comparison of Blood Lipid, Blood Glucose, and Other Indexes in Male Participants at 24 Months

Our results found that in male patients, sitagliptin did not remarkably reduce the levels of blood lipids and blood glucose in the diabetic patients compared to the control group. Blood

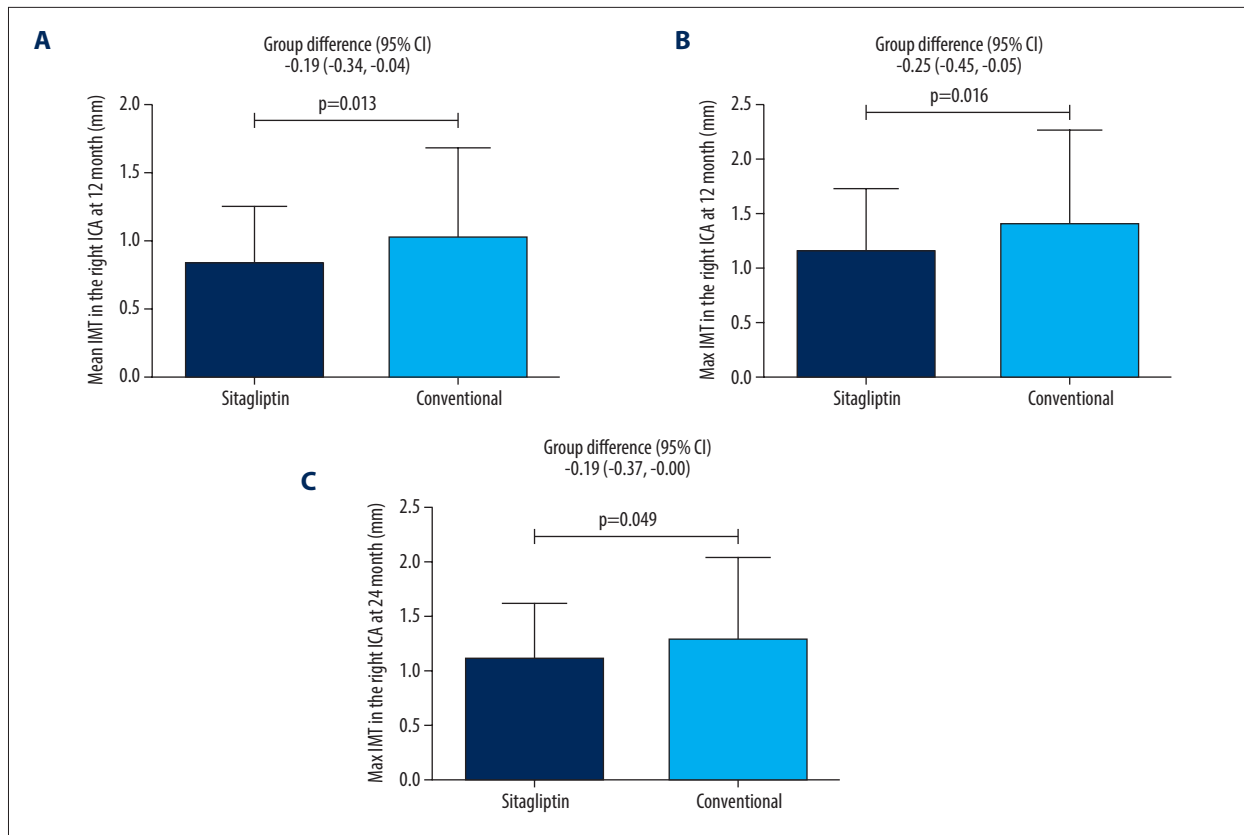


Figure 1. Male patients. (A) Comparison of mean IMT in the right ICA between the 2 groups at 12 months. (B) Comparison of maximum IMT in the right ICA between the 2 groups at 12 months. (C) Comparison of maximum IMT in the right ICA between the 2 groups at 24 months.

Table 3. Comparison of atherosclerotic parameters at baseline, 12 months, and 24 months in male participants.

Variables	Time point	Sitagliptin group	Conventional group	P-value
N		146	151	
Mean IMT in the right CCA, mm	At baseline	0.82±0.19	0.83±0.22	0.567
Mean IMT in the left CCA, mm	At baseline	0.84±0.20	0.87±0.26	0.272
Mean IMT in the right CCA, mm	12 months	0.82±0.19	0.84±0.21	0.666
Mean IMT in the left CCA, mm	12 months	0.85±0.21	0.84±0.20	0.627
Mean IMT in the right CCA, mm	24 months	0.84±0.21	0.84±0.24	0.881
Mean IMT in the left CCA, mm	24 months	0.82±0.18	0.86±0.23	0.149
Mean IMT in the right bulb, mm	At baseline	1.08±0.53	1.17±0.54	0.214
Mean IMT in the left bulb, mm	At baseline	1.11±0.46	1.13±0.48	0.667
Mean IMT in the right bulb, mm	12 months	1.13±0.52	1.20±0.61	0.382
Mean IMT in the left bulb, mm	12 months	1.19±0.58	1.20±0.52	0.856
Mean IMT in the right bulb, mm	24 months	1.11±0.54	1.15±0.56	0.607
Mean IMT in the left bulb, mm	24 months	1.21±0.66	1.15±0.45	0.442
Mean IMT in the right ICA, mm	At baseline	0.87±0.49	0.81±0.36	0.276

Table 3 continued. Comparison of atherosclerotic parameters at baseline, 12 months, and 24 months in male participants.

Variables	Time point	Sitagliptin group	Conventional group	P-value
Mean IMT in the left ICA, mm	At baseline	0.78±0.30	0.83±0.42	0.259
Mean IMT in the right ICA, mm	12 months	0.84±0.41	1.02±0.67	0.013
Mean IMT in the left ICA, mm	12 months	0.86±0.43	0.88±0.48	0.858
Mean IMT in the right ICA, mm	24 months	0.80±0.38	0.91±0.57	0.107
Mean IMT in the left ICA, mm	24 months	0.74±0.35	0.79±0.42	0.390
Max IMT in the right CCA, mm	At baseline	1.04±0.25	1.08±0.28	0.223
Max IMT in the left CCA, mm	At baseline	1.07±0.28	1.13±0.37	0.105
Max IMT in the right CCA, mm	12 months	1.03±0.26	1.07±0.27	0.265
Max IMT in the left CCA, mm	12 months	1.08±0.28	1.06±0.28	0.570
Max IMT in the right CCA, mm	24 months	1.05±0.27	1.07±0.29	0.577
Max IMT in the left CCA, mm	24 months	1.06±0.25	1.09±0.32	0.440
Max IMT in the right bulb, mm	At baseline	1.53±0.73	1.63±0.77	0.296
Max IMT in the left bulb, mm	At baseline	1.59±0.69	1.66±0.78	0.450
Max IMT in the right bulb, mm	12 months	1.56±0.72	1.64±0.81	0.459
Max IMT in the left bulb, mm	12 months	1.63±0.80	1.63±0.70	0.976
Max IMT in the right bulb, mm	24 months	1.60±0.73	1.61±0.77	0.927
Max IMT in the left bulb, mm	24 months	1.71±0.84	1.66±0.63	0.568
Max IMT in the right ICA, mm	At baseline	1.16±0.60	1.11±0.53	0.523
Max IMT in the left ICA, mm	At baseline	1.05±0.41	1.12±0.58	0.259
Max IMT in the right ICA, mm	12 months	1.14±0.59	1.39±0.88	0.016
Max IMT in the left ICA, mm	12 months	1.18±0.61	1.23±0.74	0.602
Max IMT in the right ICA, mm	24 months	1.09±0.52	1.28±0.77	0.049
Max IMT in the left ICA, mm	24 months	1.01±0.45	1.10±0.57	0.221
Plaque area, mm ²	At baseline	11.46±6.14	12.85±10.59	0.294
Plaque gray scale median	At baseline	49.94±18.95	52.75±23.45	0.379
Plaque area, mm ²	12 months	12.72±6.00	12.67±5.41	0.968
Plaque area, mm ²	24 months	12.68±6.45	11.32±5.52	0.189
Plaque gray scale median	12 months	59.45±31.73	52.18±18.87	0.312
Plaque gray scale median	24 months	52.15±27.56	53.26±19.64	0.287

lipid and blood glucose-associated indices included high-density lipoprotein cholesterol, triglyceride, small dense low-density lipoprotein cholesterol, remnant-like particle cholesterol, malondialdehyde-modified low-density lipoprotein, HbA1c, and fasting plasma glucose, except for high-molecular-weight adiponectin. Similarly, there were no significant inter-group differences in other indicators, including weight, waist circumference, SBP, DBP, pulse rate, 1,5-anhydroglucitol, 1,4-anhydro-D-glucitol, lactic

dehydrogenase, AST, ALT, BUN, serum creatinine, eGFR, cystatin C, urinary albumin/creatinine ratio, and uric acid (Table 5).

Comparison of Blood Lipid, Blood Glucose, and Other Indexes in Female Participants at 24 Months

Our results demonstrated that sitagliptin significantly improved HbA1c levels in female participants compared to the control

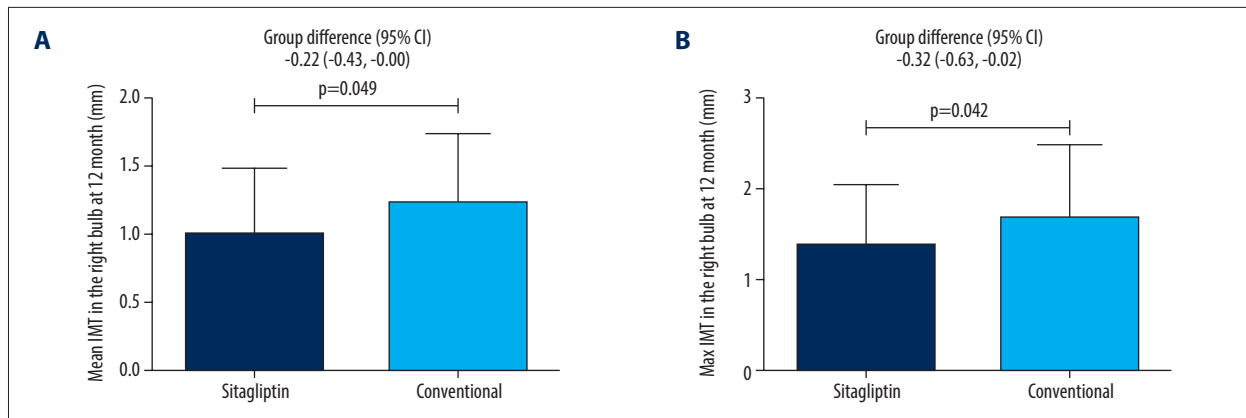


Figure 2. Female patients. **(A)** Comparison of mean IMT in the right bulb between the 2 groups at 12 months. **Figure (B)** Comparison of maximum IMT in the right bulb between the 2 groups at 12 months.

Table 4. Comparison of atherosclerotic parameters at baseline, 12 months, and 24 months in female participants.

Variables	Time point	Sitagliptin group	Conventional group	P-value
N		76	69	
Mean IMT in the right CCA, mm	At baseline	0.83±0.16	0.79±0.15	0.115
Mean IMT in the left CCA, mm	At baseline	0.83±0.20	0.81±0.21	0.624
Mean IMT in the right CCA, mm	12 months	0.81±0.17	0.79±0.15	0.624
Mean IMT in the left CCA, mm	12 months	0.80±0.15	0.82±0.16	0.549
Mean IMT in the right CCA, mm	24 months	0.82±0.19	0.81±0.18	0.748
Mean IMT in the left CCA, mm	24 months	0.81±0.17	0.82±0.20	0.954
Mean IMT in the right bulb, mm	At baseline	1.14±0.66	1.09±0.41	0.621
Mean IMT in the left bulb, mm	At baseline	1.13±0.53	1.04±0.49	0.340
Mean IMT in the right bulb, mm	12 months	1.01±0.47	1.23±0.51	0.049
Mean IMT in the left bulb, mm	12 months	1.24±0.75	1.19±0.59	0.750
Mean IMT in the right bulb, mm	24 months	1.14±0.61	1.17±0.48	0.776
Mean IMT in the left bulb, mm	24 months	1.16±0.64	1.24±0.72	0.592
Mean IMT in the right ICA, mm	At baseline	0.69±0.28	0.73±0.30	0.459
Mean IMT in the left ICA, mm	At baseline	0.69±0.18	0.75±0.42	0.367
Mean IMT in the right ICA, mm	12 months	0.80±0.35	0.83±0.49	0.797
Mean IMT in the left ICA, mm	12 months	0.90±0.46	0.83±0.42	0.497
Mean IMT in the right ICA, mm	24 months	0.70±0.30	0.80±0.57	0.323
Mean IMT in the left ICA, mm	24 months	0.69±0.29	0.80±0.42	0.169
Max IMT in the right CCA, mm	At baseline	1.06±0.21	1.01±0.20	0.129
Max IMT in the left CCA, mm	At baseline	1.05±0.35	1.04±0.26	0.806
Max IMT in the right CCA, mm	12 months	1.01±0.22	1.00±0.22	0.811
Max IMT in the left CCA, mm	12 months	1.02±0.24	1.03±0.22	0.926
Max IMT in the right CCA, mm	24 months	1.06±0.29	1.02±0.23	0.524

Table 4 continued. Comparison of atherosclerotic parameters at baseline, 12 months, and 24 months in female participants.

Variables	Time point	Sitagliptin group	Conventional group	P-value
Max IMT in the left CCA, mm	24 months	1.04±0.25	1.04±0.27	0.989
Max IMT in the right bulb, mm	At baseline	1.62±1.01	1.60±0.65	0.864
Max IMT in the left bulb, mm	At baseline	1.62±0.80	1.49±0.80	0.367
Max IMT in the right bulb, mm	12 months	1.39±0.65	1.71±0.77	0.042
Max IMT in the left bulb, mm	12 months	1.61±0.94	1.66±0.83	0.802
Max IMT in the right bulb, mm	24 months	1.63±0.88	1.71±0.70	0.628
Max IMT in the left bulb, mm	24 months	1.59±0.81	1.71±0.96	0.515
Max IMT in the right ICA, mm	At baseline	0.93±0.40	1.00±0.44	0.374
Max IMT in the left ICA, mm	At baseline	0.92±0.28	0.98±0.53	0.485
Max IMT in the right ICA, mm	12 months	1.05±0.44	1.10±0.58	0.685
Max IMT in the left ICA, mm	12 months	1.20±0.59	1.09±0.50	0.357
Max IMT in the right ICA, mm	24 months	0.94±0.35	1.06±0.72	0.328
Max IMT in the left ICA, mm	24 months	0.97±0.49	1.08±0.57	0.360
Plaque area, mm ²	At baseline	11.17±9.44	9.24±4.31	0.212
Plaque gray scale median	At baseline	52.79±28.26	51.81±17.33	0.842
Plaque area, mm ²	12 months	12.66±9.34	11.73±4.07	0.668
Plaque area, mm ²	24 months	10.86±6.81	10.30±4.05	0.668
Plaque gray scale median	12 months	54.77±40.66	75.57±53.51	0.203
Plaque gray scale median	24 months	43.92±19.10	51.81±19.85	0.096

group (6.52 ± 0.50 vs 6.83 ± 0.82 , $P=0.010$). However, sitagliptin had no impact on blood lipid levels between the groups. Blood lipid-associated indices included high-molecular-weight adiponectin, high-density lipoprotein cholesterol, triglyceride, small dense low-density lipoprotein cholesterol, remnant-like particle cholesterol, and malondialdehyde-modified low-density lipoprotein. Similarly, sitagliptin also had no significant impact on either group for other indicators, including weight, WC, SBP, DBP, pulse rate, FPG, 1,5-anhydroglucitol, 1,4-anhydro-D-glucitol, lactic dehydrogenase, AST, ALT, BUN, serum creatinine, eGFR, cystatin C, urinary albumin/creatinine ratio, and uric acid (Table 6).

Discussion

To the best of our knowledge, our study is the first to analyze a randomized controlled trial to investigate sex-related differences in sitagliptin treatment in carotid atherosclerosis in T2DM patients based on the PROLOGUE trial [19]. The main results of this study are as follows: (1) for male patients, sitagliptin slows the progression of right carotid IMT in male patients at

both 12 and 24 months. However, this effect of sitagliptin appears to be pronounced only in the right ICA, but this influence was not found in other vessels. In terms of blood glucose and blood lipids, sitagliptin only reduced the level of HMWA and had no significant effect on HDL-cholesterol or HbA1c or FPG. (2) For female patients, sitagliptin could also significantly delay the progression of atherosclerosis, but the effect only occurred at 12 months and did not last until 24 months. This effect seemed to be significant only on the right side of the bulb, but this difference was remarkable in other blood vessels. In addition, our results also show that sitagliptin significantly reduced HbA1c levels at 24 months but had no significant effect on blood lipids and renal function.

In clinical practice, IMT of the carotid artery is often measured by ultrasonic examination [26,27], which then allows clinicians to predict and estimate the risk of cardiovascular events and stroke and to develop treatment strategies. Previous studies have shown a positive correlation between carotid artery IMT and cardiovascular events [28,29], irrespective of whether the patients have cardiovascular disease or not. In addition,

Table 5. Comparison of blood lipid, blood glucose, and other indexes in male participants at 24 months.

Variables	Time point	Sitagliptin group	Conventional group	P-value
N		146	151	
Weight (kg)	24 months	68.37±10.59	68.46±11.41	0.947
Waist circumference (cm)	24 months	90.24±10.01	90.76±10.77	0.737
Systolic blood pressure (mmHg)	24 months	130.05±16.23	128.87±16.79	0.567
Diastolic blood pressure (mmHg)	24 months	74.07±11.27	72.75±10.19	0.323
Pulse rate (bpm)	24 months	72.11±12.83	70.08±11.07	0.188
HbA1c (%)	24 months	6.58±0.61	6.67±0.63	0.260
Fasting plasma glucose (mg/dL)	24 months	132.81±38.27	130.58±35.52	0.640
1,5-anhydroglucitol,1,4-anhydro-D-glucitol (µg/mL)	24 months	16.22±8.79	16.34±8.61	0.920
High molecular weight adiponectin (µg/mL)	24 months	3.59±3.79	5.08±4.77	0.012
Lactic dehydrogenase (U/L)	24 months	195.60±39.23	209.07±87.72	0.126
High-density lipoprotein cholesterol (mg/dL)	24 months	49.59±13.35	51.21±14.55	0.360
Triglyceride (mg/dL)	24 months	151.25±89.20	132.45±75.07	0.071
Small dense low-density lipoprotein cholesterol (mg/dL)	24 months	35.33±17.10	37.24±20.62	0.462
Remnant-like particle cholesterol (mg/dL)	24 months	5.10±3.90	5.44±5.03	0.586
Malondialdehyde-modified low-density lipoprotein (U/l)	24 months	121.44±36.31	120.69±41.67	0.888
Aspartate aminotransferase (U/l)	24 months	26.26±14.40	27.42±16.70	0.554
Alanine aminotransferase (U/l)	24 months	25.08±16.24	25.27±16.58	0.924
Blood urea nitrogen (mg/dL)	24 months	16.90±5.39	18.41±6.90	0.055
Serum creatinine (mg/dL)	24 months	0.98±0.31	0.98±0.30	0.885
Estimated glomerular filtration rate (ml/min/1.73 m ²)	24 months	63.88±17.55	63.65±17.60	0.915
Cystatin C (mg/dL)	24 months	1.07±0.32	1.07±0.34	0.954
Urinary albumin/creatinine ratio (mg/gCre)	24 months	15.00 (6.15-38.75)	17.00 (7.90-24.80)	0.943
Uric acid (µmol/l)	24 months	6.07±1.20	6.08±1.23	0.949

ultrasonic examination is non-invasive, making it a safe measure to assess cardiovascular events and stroke. For these reasons, the American Heart Association assesses cardiovascular risk by measuring carotid artery IMT, which is an important indicator of cardiovascular risk [30]. The PROLOGUE study [19] measured carotid artery IMT 3 times, and measured multiple arteries, providing enough samples to show statistically significant differences between the groups. Therefore, we had valid reasons to use carotid artery IMT as the primary endpoint in this study.

Previous studies have demonstrated that the use of DPP-4 inhibitors in diabetes patients could significantly reduce the degree of atherosclerosis [23-25] and better control the level of blood glucose [31]. In addition, some clinical trials [32,33] supported the finding that DPP-4 inhibitors have beneficial effects on endothelial function in diabetes patients. However, no prior study looked at the impact of sex-related differences on sitagliptin's effect on atherosclerosis in T2DM patients. In the present study, we compared the effect of sitagliptin on atherosclerosis between male and female diabetes patients. The results showed that sitagliptin delayed the progression of

Table 6. Comparison of blood lipid, blood glucose, and other indexes in female participants at 24 months.

Variables	Time point	Sitagliptin group	Conventional group	P-value
N		76	69	
Weight (kg)	24 months	57.55±14.19	55.71±10.48	0.457
Waist circumference (cm)	24 months	90.26±12.50	86.37±10.48	0.163
Systolic blood pressure (mmHg)	24 months	129.39±15.27	131.53±20.70	0.510
Diastolic blood pressure (mmHg)	24 months	71.77±12.22	70.51±11.97	0.560
Pulse rate (bpm)	24 months	72.42±11.21	72.80±11.05	0.857
HbA1c (%)	24 months	6.52±0.50	6.83±0.82	0.010
Fasting plasma glucose (mg/dL)	24 months	123.68±29.32	128.19±42.40	0.505
1,5-anhydroglucitol,1,4-anhydro-D-glucitol (µg/mL)	24 months	16.95±8.80	14.52±7.94	0.135
High molecular weight adiponectin (µg/mL)	24 months	5.40±3.43	6.09±5.45	0.428
Lactic dehydrogenase (U/L)	24 months	202.46±42.14	215.97±37.76	0.078
High-density lipoprotein cholesterol (mg/dL)	24 months	56.67±12.66	58.30±15.78	0.531
Triglyceride (mg/dL)	24 months	114.25±51.09	130.89±70.05	0.135
Small dense low-density lipoprotein cholesterol (mg/dL)	24 months	30.41±16.28	35.05±18.98	0.174
Remnant-like particle cholesterol (mg/dL)	24 months	4.27±2.34	4.81±3.04	0.305
Malondialdehyde-modified low-density lipoprotein (U/l)	24 months	109.10±35.20	117.49±38.43	0.237
Aspartate aminotransferase (U/l)	24 months	22.92±5.78	24.73±10.26	0.225
Alanine aminotransferase (U/l)	24 months	18.53±6.90	21.68±14.37	0.117
Blood urea nitrogen (mg/dL)	24 months	17.79±5.54	18.06±8.04	0.826
Serum creatinine (mg/dL)	24 months	0.72±0.22	0.71±0.21	0.720
Estimated glomerular filtration rate (ml/min/1.73 m ²)	24 months	65.53±18.99	67.02±20.38	0.675
Cystatin C (mg/L)	24 months	1.09±0.30	0.98±0.23	0.120
Urinary albumin/creatinine ratio (mg/gCre)	24 months	18.05(11.03-29.60)	18.10 (10.68-92.13)	0.441
Uric acid (µmol/l)	24 months	5.28±1.49	5.11±1.69	0.577

atherosclerosis in male patients, with benefits significant at both 12 and 24 months. On the other hand, in female patients, sitagliptin delayed the progression of atherosclerosis, but with benefits only significant at 12 months. The PROLOGUE study [19] found no evidence to support the effectiveness of sitagliptin in delaying atherosclerosis in diabetic patients. However, it should be emphasized that in the PROLOGUE study, the authors did not stratify the study groups based on sex; therefore, the results reflected the effectiveness of sitagliptin in all patients overall. In addition, the PROLOGUE study did not distinguish between changes in left and right carotid atherosclerosis. This

may potentially explain the discrepancies between the results from the PROLOGUE study and our study. Our findings suggest that sitagliptin only significantly benefits the right ICA in male patients and right bulb in female patients. One unanticipated finding was that sitagliptin had different effects on different carotid arteries, which is different from previous studies. In a cohort study [34] of 1414 participants, the authors compared the left and right carotid atherosclerotic plaques and assessed the degree of carotid atherosclerosis using magnetic resonance imaging (MRI). The results showed that the size and composition of the left and the right carotid atherosclerotic plaques

were asymmetrically distributed. Left carotid plaque is prone to intra-plaque bleeding (9.1% vs 5.9%), while right carotid plaque is more prone to calcification (37.4% vs 31.6%). Similarly, Katranas et al [35] also found that the left and the right coronary arteries have significant differences in hemorheology and geometric parameters. Therefore, we speculate that differences in anatomical structures or hemodynamics may also lead to different effects of sitagliptin on different carotid atheroscleroses. Presently, there is no study directly clarifying the difference in carotid artery IMT between males and females treated with sitagliptin. The possible mechanism is that the secretion of estrogen and progesterone in postmenopausal women decreases, thus offsetting the benefits of sitagliptin treatment, but this phenomenon does not exist in men. However, more research is needed to further clarify this hypothesis.

Our study also found that there are sex-specific differences in the effects of sitagliptin on blood glucose and blood lipids. Sitagliptin reduced the level of high-molecular-weight adiponectin in male patients, while it could only reduce HbA1c levels in female patients. No significant differences were observed in weight control, waist circumference, and renal function protection in males or females, which is contrary to the previous results. In a retrospective cohort study [36] of 220 patients with type 2 diabetes, the authors found that weight and HbA1c level decreased significantly after 6 months of sitagliptin treatment. Similarly, Kawasaki et al [37] investigated whether sitagliptin could improve renal function in diabetic patients, and found that the glomerular filtration rate ($\beta=0.20$, $P=0.024$) and blood pressure ($\beta=0.21$, $P=0.016$) were significantly improved after 3 months of sitagliptin treatment. Possible explanations are as follows: (1) the sample size of the PROLOGUE study is relatively larger than that of other studies, providing higher statistical power; (2) the follow-up time of the PROLOGUE study was longer than that of other studies, which produces higher reliability; and (3) the PROLOGUE study was a multicenter randomized controlled trial, suggesting its wide applicability among populations.

Our study has several advantages. First, we explored sex-related differences in sitagliptin treatment in T2DM patients for the first time, and showed that the effect of sitagliptin on atherosclerosis in male T2DM patients is higher than that in female T2DM patients, which suggests that sex-related differences are cause different therapeutic effects. Second, we used the parameters of multiple carotid arteries as the primary

endpoint and found that sitagliptin had different effects on different carotid arteries, which suggests that the appropriate outcome should be selected in clinical research to reduce selection bias. This study also has some shortcomings. First, the research object of this study was a Japanese population. Therefore, whether the conclusions are applicable to other populations still needs to be assessed. Second, based on the current data, we cannot explore the mechanism of sitagliptin only acting on some carotid arteries, nor can we accurately analyze the reasons for the decrease of HbA1c level without significant difference in the degree of atherosclerosis. Third, information on other drugs (eg, antidiabetic drugs, insulin, statin) in the ROLOGUE study is lacking and may potentially affect final conclusions. Fourth, we found a significant difference in age between males and females (68.44 ± 9.22 vs 71.19 ± 8.94 , $P=0.003$). However, it is important to note that the difference in age between male and female was only 2.7 years. Although there was a significant difference in age between males and females, this small difference might not lead to substantial changes in clinical practice. Fifth, we found that sitagliptin significantly improved HbA1c levels in female patients after 24 months, but this phenomenon was not observed in male patients. The possible reason is speculated to be related to the severity of diabetes and the underlying diseases since the participants included in the PROLOGUE Trial basically did not have any diabetes-related diseases and had too many underlying diseases. However, more studies are needed to verify this conclusion.

Conclusions

Our results suggest that sitagliptin slows the progression of right carotid IMT in male patients. However, more studies are needed to confirm this conclusion in female patients.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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