Sitagliptin on carotid intima-media thickness in type 2 diabetes and hyperuricemia patients: a subgroup analysis of the PROLOGUE study

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Abstract

Background and Aims: Studies have shown that dipeptidyl peptidase-4 (DDP-4) inhibitors have anti-atherosclerotic effects. However, in the PROLOGUE study, sitagliptin failed to slow the progression of carotid intima-media thickness (CIMT) relative to conventional therapy. We conducted a *post hoc* analysis of the PROLOGUE study and compared the effects of sitagliptin and conventional therapy on changes in CIMT in subgroups with or without hyperuricemia.

Methods: The PROLOGUE study was a randomized controlled trial of 442 patients with type 2 diabetes mellitus (T2DM). Patients were randomized to receive sitagliptin added therapy or conventional therapy. Based on the serum uric acid levels of all study populations in the PROLOGUE study, we divided them into hyperuricemia subgroup ($n = 104$) and non-hyperuricemia subgroup ($n = 331$). The primary outcome was changed in carotid intima-media thickness (CIMT) parameters compared with baseline during the 24 months treatment period.

Results: In the hyperuricemia subgroup, compared with the conventional therapy group, the changes in the mean internal carotid artery (ICA)-IMT and max ICA-IMT at 24 months were significantly lower in the sitagliptin group [−0.233 mm, 95% confidence interval (CI) (−0.419 to 0.046), $p = 0.015$ and −0.325 mm, 95% CI (−0.583 to −0.068), $p = 0.014$], although there was no significant difference in the common carotid artery CIMT.

Conclusion: The results of our analysis indicated that sitagliptin attenuated the progression of CIMT than conventional therapy in T2DM and hyperuricemia patients.

Keywords: hyperuricemia, intima-media thickness, PROLOGUE study, sitagliptin, type 2 diabetes mellitus

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Introduction

Diabetes mellitus (DM) and atherosclerosis are common diseases that collectively threaten the health of all humans. DM is a major risk factor for developing atherosclerosis, and patients with DM have a high risk of developing atherosclerotic cardiovascular disease (CVD).[1,2] CVD is one of the leading causes of death in patients with DM, and patients with DM have a worse prognosis of comorbid CVD.[3] Therefore, it is necessary to identify high-risk groups as early as possible and carry out active and effective interventions such as diet, exercise, and medication to prevent further progress of the cardiovascular disease in diabetic patients and improve their prognosis.

As one of the carotid ultrasound measurements, carotid intima-media thickness (CIMT) is defined as the distance between the lumen-intima and media-adventitia interfaces of a carotid segment.[4] Many longitudinal studies and meta-analysis results have found CIMT to be an independent

predictor of cardiovascular events.[5–10] In patients with DM or impaired glucose tolerance, their CIMT tends to be higher than in healthy individuals.[11] In addition, for DM patients, CIMT has been reported to be one of the predictors of the future development of nonfatal CAD.[12–14]

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor and a hypoglycemic drug.[15] The mechanism of sitagliptin is mainly to prolong the duration of glucagon-like peptide-1 (GLP-1) by inhibiting the activity of DPP-4 to achieve a stable blood glucose level. In addition to glycemic control, several experimental studies have shown that DPP-4 inhibitors also inhibit foam cell formation and atherosclerosis.[16,17] In clinical studies, the anti-atherogenic effect of sitagliptin has also been reported.[18,19] However, several clinical trials have shown that DPP-4 inhibitors do not affect cardiovascular events.[15,20,21] Results from the PROLOGUE study have shown that sitagliptin did not significantly attenuate the progression of CIMT compared with conventional treatment. Therefore, whether DPP-4 inhibitors can alleviate atherosclerosis remains controversial clinically.

Hyperuricemia, similar to diabetes, may be influenced by diet, lifestyle, and genetic factors. In addition, hyperuricemia is also considered an independent risk factor associated with atherosclerosis.[22] Although studies have shown that type 2 DM (T2DM) patients with high uric acid levels have a higher risk of cardiovascular events.[23] But the PROLOGUE study has not demonstrated other clinical benefits of sitagliptin, and whether sitagliptin has different effects on CIMT in T2DM patients with hyperuricemia is unclear. Thus, we conducted this study as a *post hoc* analysis of the PROLOGUE study to examine the hypothesis that the effect of sitagliptin on CIMT may be related to the presence or absence of hyperuricemia.

Materials and methods

Study design

The present study is a *post hoc* analysis based on data available from the PROLOGUE study. This is a 24-month, multicenter, prospective, randomized, open-label, and blind end-point trial conducted between June 2011 and September 2012 (University hospital Medical Information Network Center: ID 000004490).[24] To assess the effect of sitagliptin on CIMT, a total of 463 patients with T2DM were enrolled in the PROLOGUE study during the study period, and all patients were assigned randomly and equally to either sitagliptin supplementation therapy (sitagliptin group) or to the conventional hypoglycemic therapy (conventional group). Inclusion and exclusion criteria are described more extensively elsewhere.[24] Carotid ultrasound parameters were measured for all patients at the beginning of the study and follow-up visits at 12 and 24 months. The primary endpoint was the change in the mean common carotid artery (CCA)-IMT at the 24th month. Other CIMT parameters, including the internal carotid artery- (ICA-)IMT, were secondary endpoints. The study was approved by all participating institutional review boards, and all study participants gave informed consent.[24] The full study protocol can be found in previously published research.[24]

In this *post hoc* analysis, based on previous studies, we defined hyperuricemia as serum uric acid levels $\geqslant$7.0 mg/dl in men and $\geqslant$6.0 mg/dl in women.[25–28] Serum uric acid levels were recorded at the beginning of the study in 435 T2DM patients in the PROLOGUE study, 104 of whom were diagnosed with hyperuricemia and 331 with non-hyperuricemia. After the subgroups were divided, we compared the changes of various parameters including CIMT at 12 and 24 months after treatment in each group.

Measurement of CIMT

Carotid ultrasonography was performed within 1 month before the start of the study and at follow-up visits at 12 and 24 months after randomization. All ultrasound systems were equipped with linear transducers of more than 7.5 MHz. In each ultrasound laboratory, high-resolution carotid ultrasonography was performed in a blinded fashion by a specialized sonographer trained in CIMT measurement with a standardized imaging protocol.[29] The methods recommended by the Mannheim consensus on carotid IMT were used.[30] Longitudinal B-mode images, perpendicular to the ultrasound beam, with a 4-cm imaging depth, were obtained from the distal CCAs, bulbs, and proximal ICAs on both sides. CCA images were obtained using lateral probe incidence using an external landmark with an original

semicircular protractor developed for this purpose. In measured and calculated IMT, the primary parameter was the change in mean far wall CCA-IMT in the left and right CCAs 10 mm from the bulb. In addition, the maximum IMT of the CCA, the mean of the mean IMTs of the CCA, bulb, and ICA, and the mean of the maximum IMTs of the CCA, bulb, and ICA were measured.

Statistical analysis

For continuous variables that conform to the normal distribution, the mean ± standard deviation (SD) is used to represent and compared using a Student's *t* test. Categorical variables were summarized as frequencies (%) and differences were compared using the chi-square test. To compare changes in uric acid levels at different time points in each treatment group, a repeated-measures analysis of variance was used. We used analysis of covariance, with the corresponding baseline measured parameters as covariates, to assess the baseline adjusted mean of each parameter. In addition, mixed-effect models for repeated measures were used to account for the correlation. Baseline IMT, treatment group, time (months), and interaction between treatment group and time (months) were treated as fixed effects; an unstructured covariate was used to model the covariance of within-subject variability.[31,32] All statistical analyses were conducted using the SPSS Statistics Software for Windows, version 26.0; a two-tailed p value < 0.05 was considered statistically significant.

Results

Baseline clinical variables

Baseline clinical variables were similar between the two subgroups, except that a modestly higher proportion of patients in the hyperuricemia subgroup had a history of kidney disease, cerebral infarction, and chronic heart failure (Table 1). In addition, serum creatinine and blood urea nitrogen, uric acid, non-high-density lipoprotein cholesterol were significantly higher and estimated glomerular filtration rate lower in the hyperuricemia group than in the non-hyperuricemia group (Table 1). Mean CCA-IMT and Max CCA-IMT were significantly higher in the hyperuricemia group than in the non hyperuricemia group (Table 1). Among the different treatment groups, the mean CCA-IMT (0.797 ± 0.145 *versus* 0.835 ± 0.179, $p = 0.035$) and max CCA-IMT (1.013 ± 0.188 *versus* 1.078 ± 0.245, $p = 0.007$) were higher in patients treated with conventional therapy than those with added sitagliptin in the non-hyperuricemia subgroup (Table 1), whereas in the hyperuricemia subgroup, the mean CCA-IMT (0.921 ± 0.186 *versus* 0.835 ± 0.228, $p = 0.038$) was higher in the added sitagliptin group than in the conventional treatment group (Table 1).

Carotid ultrasound parameters and other clinical data at 12 and 24 months

After 24 months of treatment, sitagliptin significantly reduced HbA1c levels in patients with non-hyperuricemia compared with conventional therapy [−0.161 (95% confidence interval (CI) −0.300 to −0.022, $p = 0.023$)] (Table 2). The changes in body mass index, systolic blood pressure, diastolic blood pressure, non-high-density lipoprotein cholesterol, and estimated glomerular filtration rate from baseline to 24 months were not significantly different among the different subgroups (All $p > 0.05$). However, in the hyperuricemia subgroup, the changes in serum creatinine levels were significantly higher in the sitagliptin group at 12 months [0.054, 95% CI (−0.004 to 0.104), $p = 0.036$], and the changes in blood urea nitrogen levels were significantly lower in the sitagliptin group at 24 months [−2.682, 95% CI (−5.334 to 0.031), $p = 0.047$] (Table 2). In addition, there were no change differences in serum uric acid levels between different treatment groups in the hyperuricemia subgroup and the non-hyperuricemia subgroup (Table 2). However, the results of repeated measures analysis of variance showed that the serum uric acid levels of the two treatment groups in the hyperuricemia subgroup were significantly reduced at 12 and 24 months (Figure 1). And in non-hyperuricemia subgroup, serum uric acid levels increased significantly at the 12th month, and then decreased slightly at the 24th month (Figure 1).

For carotid ultrasound parameters, although there were differences in baseline mean CCA-IMT and max CCA-IMT between sitagliptin and the conventional therapy group in the non-hyperuricemia subgroup (Table 2), there were no significant differences in baseline-adjusted mean CCA-IMT [0.009 mm (95% CI −0.024 to 0.013, $p = 0.578$)] and max CCA-IMT [0.003 mm (95% CI −0.029,

Table 1. Baseline demographics and clinical variables.

Variable	Hyperuricemia (*n* = 104)				Non-hyperuricemia (*n* = 331)			
	All	Sitagliptin (*n* = 56)	Conventional (n = 48)	*p*	All	Sitagliptin (*n* = 163)	Conventional (*n* = 168)	*p*
Age, years	69.790 ± 9.940	70.786 ± 9.685	68.625 ± 10.208	0.271	69.180 ± 8.932	68.61 ± 9.112	69.74 ± 8.745	0.248
Gender (male), *n* (%)	68 (65.4)	34 (60.7)	34 (70.8)	0.280	225 (68.0)	111 (68.1)	114 (67.9)	0.963
Body mass index, kg/m^2	25.449 ± 3.898	25.388 ± 4.126	25.522 ± 3.651	0.863	24.966 ± 4.086	25.235 ± 4.101	24.707 ± 4.066	0.247
Hypertension, *n* (%)	80 (76.9)	46 (82.1)	34 (70.8)	0.172	262 (79.2)	133 (81.6)	129 (76.8)	0.282
Dyslipidemia, *n* (%)	67 (64.4)	39 (69.6)	28 (58.3)	0.230	239 (72.2)	121 (74.2)	118 (70.2)	0.417
Kidney disease, *n* (%)	15 (14.4)	9 (16.1)	6 (12.5)	0.605	21 (6.3)*	9 (5.5)	12 (7.1)	0.545
Cerebral infarction, *n* (%)	17 (16.3)	10 (17.9)	7 (14.6)	0.653	28 (8.5)*	10 (6.1)	18 (10.7)	0.134
Myocardial infarction, *n* (%)	20 (19.2)	10 (17.9)	10 (20.8)	0.701	80 (24.2)	36 (22.1)	44 (26.2)	0.383
Percutaneous coronary intervention, *n* (%)	25 (24.0)	14 (25.0)	11 (22.9)	0.804	101 (30.5)	44 (27.0)	57 (33.9)	0.171
Coronary artery bypass grafting, *n* (%)	8 (7.7)	6 (10.7)	2 (4.2)	0.282	27 (8.2)	13 (8.0)	14 (8.3)	0.905
Chronic heart failure, *n* (%)	18 (17.3)	6 (10.7)	12 (25.0)	0.055	22 (6.6)*	9 (5.5)	13 (7.7)	0.418
Arrhythmia, *n* (%)	20 (19.2)	12 (21.4)	8 (16.7)	0.539	43 (13.0)	20 (12.3)	23 (13.7)	0.701
Systolic blood pressure, mm Hg	128.130 ± 16.424	130.929 ± 16.799	124.854 ± 15.511	0.060	129.730 ± 15.979	129.58 ± 15.429	129.88 ± 16.539	0.865
Diastolic blood pressure, mm Hg	71.160 ± 11.302	73.107 ± 10.23	68.896 ± 12.154	0.058	72.530 ± 11.115	72.67 ± 10.942	72.4 ± 11.312	0.826
HbA1c, percent	6.888 ± 0.567	6.850 ± 0.614	6.932 ± 0.512	0.472	6.976 ± 0.604	6.993 ± 0.651	6.961 ± 0.556	0.637
Fasting plasma glucose, mmol/l	134.830 ± 36.356	135.360 ± 35.810	134.200 ± 37.384	0.876	137.020 ± 40.502	139.23 ± 43.909	134.96 ± 37.06	0.350

(Continued)

Table 1. (Continued)

Variable	Hyperuricemia ($n = 104$)				Non-hyperuricemia ($n = 331$)			
	All	Sitagliptin ($n = 56$)	Conventional ($n = 48$)	p	All	Sitagliptin ($n = 163$)	Conventional ($n = 168$)	p
Serum creatinine, mg/dl	0.970 ± 0.273	0.965 ± 0.282	0.977 ± 0.265	0.827	0.824 ± 0.228*	0.819 ± 0.204	0.829 ± 0.25	0.696
Blood urea nitrogen, mg/dl	19.348 ± 6.367	19.348 ± 6.367	18.531 ± 6.681	0.525	16.755 ± 5.058*	15.902 ± 4.359	16.755 ± 5.058	0.103
Uric acid, mg/dl	7.526 ± 1.149	7.331 ± 0.797	7.753 ± 1.432	0.062	5.188 ± 1.031*	5.245 ± 0.932	5.142 ± 1.120	0.412
Non-HDL cholesterol, mmol/l	126.885 ± 31.982	123.930 ± 30.259	130.148 ± 33.802	0.332	119.890 ± 29.863**	121.845 ± 29.68	118.032 ± 30.008	0.256
Estimated glomerular filtration rate, mL/min/1.73 m^2	58.088 ± 16.949	57.571 ± 17.619	58.691 ± 16.297	0.793	69.246 ± 17.100*	69.278 ± 16.327	69.214 ± 17.871	0.973
Mean CCA-IMT, mm	0.811 ± 0.286	0.921 ± 0.186	0.835 ± 0.228	0.038	0.777 ± 0.299**	0.797 ± 0.145	0.835 ± 0.179	0.035
Max CCA-IMT, mm	1.130 ± 0.419	1.17 ± 0.289	1.069 ± 0.323	0.098	1.042 ± 0.404**	1.013 ± 0.188	1.078 ± 0.245	0.007
Mean bulb-IMT, mm	1.206 ± 0.484	1.255 ± 0.488	1.151 ± 0.48	0.347	1.100 ± 0.410	1.065 ± 0.404	1.131 ± 0.41	0.189
Max bulb-IMT, mm	1.506 ± 0.617	1.535 ± 0.642	1.475 ± 0.598	0.715	1.357 ± 0.515	1.357 ± 0.562	1.358 ± 0.473	0.998
Mean ICA-IMT, mm	0.811 ± 0.286	0.791 ± 0.254	0.832 ± 0.317	0.538	0.777 ± 0.300	0.781 ± 0.279	0.774 ± 0.317	0.846
Max ICA-IMT, mm	1.130 ± 0.419	1.084 ± 0.384	1.175 ± 0.451	0.344	1.042 ± 0.404	1.047 ± 0.36	1.037 ± 0.441	0.849
Plaque area, mm^2	12.571 ± 8.623	12.26 ± 8.654	12.927 ± 8.703	0.744	11.248 ± 8.395	11.034 ± 6.818	11.415 ± 9.477	0.752
Plaque gray scale median	57.306 ± 29.212	57.746 ± 27.154	56.803 ± 31.815	0.892	49.723 ± 18.565*	47.981 ± 19.689	51.086 ± 17.612	0.243

Data are presented as n (%) or mean ± SD.
*$p < 0.05$, **$p < 0.001$ compared with the overall hyperuricemia group.
CCA, common carotid artery; HbA1c, glycated hemoglobin; HDL, pulmonary endarterectomy; ICA, internal carotid artery; IMT, intima-media thickness; SD, standard deviation.

Table 2. Baseline-adjusted mean and group difference between treatment groups.

Variable	Time point	Hyperuricemia ($n = 104$)			p	Time point	Non-hyperuricemia ($n = 331$)			p
		Baseline-adjusted mean ± SE		Group difference in baseline-adjusted mean (95% CI)			Baseline-adjusted mean ± SE		Group difference in baseline-adjusted mean (95% CI)	
		Sitagliptin ($n = 56$)	Conventional ($n = 48$)				Sitagliptin group ($n = 163$)	Conventional ($n = 168$)		
Body mass index, kg/m^2	12 months	25.442 ± 0.132	25.522 ± 0.148	0.080 (−0.475, 0.315)	0.687	12 months	24.939 ± 0.095	24.844 ± 0.094	0.094 (−0.168, 0.357)	0.480
	24 months	25.346 ± 0.225	25.582 ± 0.251	−0.236 (−0.909, 0.437)	0.486	24 months	24.821 ± 0.108	25.061 ± 0.108	−0.240 (−0.542, 0.062)	0.119
Systolic blood pressure, mm Hg	12 months	127.913 ± 2.450	130.029 ± 2.618	−2.115 (−9.287, 5.057)	0.559	12 months	127.820 ± 1.126	128.589 ± 1.115	−0.769 (−3.887, 2.349)	0.628
	24 months	128.745 ± 2.429	128.062 ± 2.579	0.683 (−6.419, 7.784)	0.849	24 months	129.838 ± 1.289	130.072 ± 1.245	−0.234 (−3.762, 3.294)	0.896
Systolic blood pressure, mm Hg	12 months	70.332 ± 1.774	71.435 ± 1.896	−1.103 (−6.305, 4.100)	0.675	12 months	71.951 ± 0.780	73.351 ± 0.772	−1.400 (−3.561, 0.760)	0.203
	24 months	71.390 ± 1.566	69.161 ± 1.663	2.229 (−2.360, 6.818)	0.337	24 months	73.566 ± 0.806	72.811 ± 0.778	0.755 (−1.450, 2.960)	0.501
HbA1c, percent	12 months	6.470 ± 0.096	6.704 ± 0.103	0.234 (−0.514, 0.047)	0.101	12 months	6.586 ± 0.040	6.648 ± 0.040	−0.062 (−0.173, 0.049)	0.271
	24 months	6.452 ± 0.075	6.548 ± 0.079	−0.096 (−0.315, 0.123)	0.386	24 months	6.588 ± 0.051	6.749 ± 0.049	−0.161 (−0.300, −0.022)	0.023
Fasting plasma glucose, mmol/l	12 months	128.126 ± 5.032	134.557 ± 5.222	−6.432 (−20.869, 8.006)	0.378	12 months	133.699 ± 2.669	129.637 ± 2.576	4.062 (−3.246, 11.369)	0.275
	24 months	124.522 ± 5.058	123.977 ± 5.475	0.545 (−14.321, 15.410)	0.942	24 months	131.466 ± 2.861	132.518 ± 2.725	−1.052 (−8.837, 6.732)	0.790
Serum creatinine, mg/dl	12 months	0.991 ± 0.017	0.937 ± 0.019	0.054 (−0.004, 0.104)	0.036	12 months	0.844 ± 0.008	0.843 ± 0.008	0.001 (−0.022, 0.024)	0.917
	24 months	1.013 ± 0.023	0.968 ± 0.025	0.045 (−0.023, 0.113)	0.190	24 months	0.864 ± 0.014	0.862 ± 0.013	0.002 (−0.035, 0.039)	0.917
Blood urea nitrogen, mg/dl	12 months	18.322 ± 0.600	18.026 ± 0.677	0.297 (−1.509, 2.102)	0.744	12 months	16.789 ± 0.309	17.065 ± 0.308	−0.277 (−1.1.136, 0.583)	0.527
	24 months	18.144 ± 0.905	20.827 ± 0.976	−2.682 (−5.334, 0.031)	0.047	24 months	17.200 ± 0.336	17.009 ± 0.330	0.190 (−0.739, 1.119)	0.687
Uric acid, mg/dl	12 months	7.112 ± 0.193	7.019 ± 0.211	0.092 (−0.480, 0.665)	0.750	12 months	5.476 ± 0.064	5.568 ± 0.064	−0.092 (−0.270, 0.086)	0.309
	24 months	7.090 ± 0.207	6.805 ± 0.227	0.285 (−0.388, 0.907)	0.365	24 months	5.418 ± 0.076	5.523 ± 0.074	−0.105 (−0.313, 0.103)	0.322
Non-HDL cholesterol, mmol/l	12 months	126.343 ± 3.225	133.339 ± 3.427	−6.997 (−16.382, 2.389)	0.142	12 months	115.673 ± 1.859	116.182 ± 1.826	−0.509 (−5.642, 4.624)	0.845
	24 months	121.172 ± 3.569	126.790 ± 3.763	−5.618 (−15.999, 4.763)	0.284	24 months	119.578 ± 2.025	119.575 ± 1.943	0.003 (−5.523, 5.529)	0.999

(Continued)

Table 2. (Continued)

Variable	Time point	Hyperuricemia ($n = 104$)			p	Time point	Non-hyperuricemia ($n = 331$)			p
		Baseline-adjusted mean ± SE		Group difference in baseline-adjusted mean (95% CI)			Baseline-adjusted mean ± SE		Group difference in baseline-adjusted mean (95% CI)	
		Sitagliptin ($n = 56$)	Conventional ($n = 48$)				Sitagliptin group ($n = 163$)	Conventional ($n = 168$)		
Estimated glomerular filtration rate, (ml/min/1.73 m^2)	12 months	57.709 ± 1.026	60.029 ± 1.136	−2.320 (−5.363, 0.724)	0.133	12 months	67.399 ± 0.713	68.074 ± 0.711	−0.675 (−2.656, 1.307)	0.503
	24 months	57.834 ± 1.262	58.725 ± 1.358	−0.892 (−4.583, 2.800)	0.231	24 months	66.245 ± 0.804	66.574 ± 0.782	−0.329 (−2.537, 1.880)	0.770
Mean CCA-IMT, mm	12 months	0.848 ± 0.012	0.860 ± 0.014	−0.012 (−0.050, 0.026)	0.537	12 months	0.825 ± 0.008	0.820 ± 0.008	0.006 (−0.015, 0.027)	0.587
	24 months	0.863 ± 0.012	0.873 ± 0.013	−0.010 (−0.044, 0.025)	0.569	24 months	0.822 ± 0.007	0.827 ± 0.007	0.009 (−0.024, 0.013)	0.578
Max CCA-IMT, mm	12 moths	1.080 ± 0.020	1.067 ± 0.023	0.013 (−0.049, 0.076)	0.676	12 months	1.049 ± 0.012	1.030 ± 0.012	0.019 (−0.014, 0.052)	0.260
	24 months	1.108 ± 0.023	1.076 ± 0.025	0.032 (−0.035, 0.099)	0.347	24 months	1.050 ± 0.012	1.047 ± 0.011	0.003 (−0.029, 0.035)	0.865
Mean bulb-IMT, mm	12 months	1.240 ± 0.051	1.290 ± 0.056	−0.051 (−0.205, 0.103)	0.511	12 months	1.170 ± 0.034	1.172 ± 0.033	−0.001 (−0.096, 0.093)	0.979
	24 months	1.183 ± 0.067	1.285 ± 0.072	0.102 (−0.302, 0.098)	0.313	24 months	1.173 ± 0.031	1.132 ± 0.029	0.041 (−0.043, 0.125)	0.335
Max bulb-IMT, mm	12 months	1.754 ± 0.063	1.710 ± 0.066	0.043 (−0.140, 0.227)	0.637	12 months	1.568 ± 0.042	1.599 ± 0.040	−0.031 (−0.146, 0.084)	0.599
	24 months	1.699 ± 0.066	1.814 ± 0.067	−0.115 (−0.305, 0.074)	0.227	24 months	1.648 ± 0.032	1.623 ± 0.030	0.025 (−0.061, 0.111)	0.567
Mean ICA-IMT, mm	12 months	0.932 ± 0.076	1.068 ± 0.077	−0.136 (−0.353, 0.082)	0.217	12 months	0.902 ± 0.035	0.871 ± 0.034	0.031 (−0.065, 0.128)	0.525
	24 months	0.749 ± 0.066	0.982 ± 0.065	−0.233 (−0.419, 0.046)	0.015	24 months	0.763 ± 0.023	0.799 ± 0.021	−0.036 (−0.098, 0.026)	0.254
Max ICA-IMT, mm	12 months	1.249 ± 0.101	1.406 ± 0.103	−0.156 (−0.447, 0.134)	0.285	12 months	1.218 ± 0.047	1.183 ± 0.045	0.035 (−0.093, 0.162)	0.590
	24 months	1.043 ± 0.092	1.368 ± 0.090	−0.325 (−0.583, −0.068)	0.014	24 months	1.031 ± 0.035	1.095 ± 0.033	−0.064 (−0.158, 0.030)	0.179
Plaque area, mm^2	12 months	13.833 ± 1.157	12.609 ± 1.245	1.224 (−2.220, 4.668)	0.476	12 months	12.290 ± 0.789	12.220 ± 0.665	0.070 (−1.977, 2.117)	0.946
	24 months	12.490 ± 0.959	11.119 ± 0.991	1.371 (−1.391, 4.134)	0.324	24 months	12.165 ± 0.651	10.992 ± 0.566	1.174 (−0.529, 2.877)	0.175
Plaque gray scale median	12 months	54.955 ± 5.889	65.487 ± 6.339	−10.532 (−28.091,7.028)	0.232	12 months	57.501 ± 4.764	57.464 ± 3.975	0.037 (−12.323, 12.397)	0.995
	24 months	51.177 ± 4.145	50.209 ± 4.286	0.968 (−10.975, −12.911)	0.872	24 months	49.316 ± 2.472	54.035 ± 2.148	−4.719 (−11.189, 1.752)	0.152

Data are presented as n (%) or mean ± SD.
CCA, common carotid artery; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ICA, internal carotid artery; IMT, intima-media thickness; SD, standard deviation.

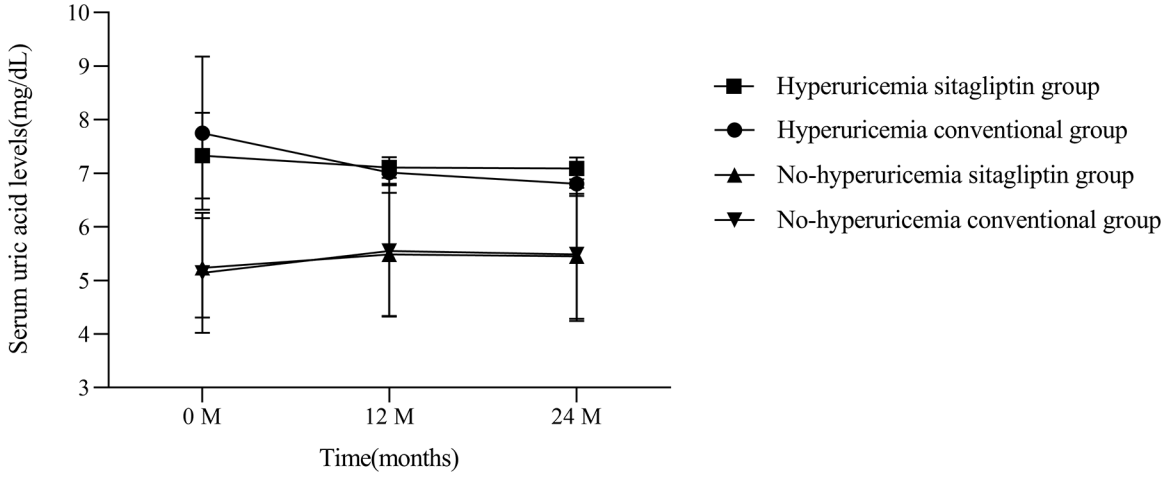

Figure 1. Serum uric acid levels of hyperuricemia and non-hyperuricemia subgroups during treatment.

0.035, $p=0.865$)] at 24 months (Table 2). In the hyperuricemia subgroup, CCA-IMT did not show a difference after 24 months of treatment. But for the mean and max ICA-IMT, the changes at the 24th month in the sitagliptin group were significantly lower than that in the conventional therapy group [−0.325 mm, 95% CI (−0.583, −0.068), $p=0.014$ and −0.233 mm, 95% CI (−0.419, 0.046), $p=0.015$] (Table 2). Similar results were obtained in the adjusted mixed effects model (Supplemental Tables S1 and S2). In addition, the analysis of covariance model, which included treatment group, age, gender, baseline IMT, systolic blood pressure, and administration of statins, produced similar results to the mixed effects model (Supplemental Table S3).

Use of antidiabetic and other agents

There was no significant difference in the baseline frequency of non-investigational hypoglycemic drugs other than glinide (Table 3). In each conventional therapy group, the added use of sulfonylureas, metformin, alpha-glucosidase inhibitors, and thiazolidinediones increased over the 24-month observation period. Whereas in each sitagliptin treatment group, the use of other drugs did not increase except for metformin (Table 3). Compared with the non-hyperuricemia subgroup, no one in the hyperuricemia subgroup had taken fibrates (Table 3). For the use of angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor, no subgroups changed significantly during the 24-month observation period (Table 3).

Discussion

This study found that sitagliptin treatment significantly inhibited the progression of mean and max ICA-IMT in the hyperuricemia subgroup. However, in the non-hyperuricemia subgroup, sitagliptin treatment did not have to alleviate CIMT compared with conventional therapy. In addition, for CCA-IMT at 12 and 24 months, there was no significant difference between the treatment groups in each subgroup. Although most studies on CIMT are focused on mean CCA-IMT, the Mannheim Carotid Intima-Media Thickness and Plaque Consensus recommends that IMT and plaque measurements including maximum or mean IMT, plaque thickness, area and volume, and plaque score may all be used as imaging outcomes in research.[30] In addition, results from several studies, including the Framingham offspring cohort study, have found that max ICA-IMT is more predictive of CVD risk than mean CCA-IMT.[8,33,34] ICA-IMT may reflect the presence of focal plaques and may be more representative of exposure to cardiovascular risk factors. These findings may suggest that ICA-IMT, especially the max ICA-IMT, is an appropriate screening point for CVD risk stratification.[35] In our results, at the 24-month follow up, sitagliptin treatment significantly improved the progression of mean and max ICA-IMT in hyperuricemia subgroup compared with conventional treatment. This suggests that patients with T2DM and hyperuricemia could benefit from sitagliptin treatment.

Hyperuricemia and metabolism, especially human purine metabolism, are closely related and

Table 3. Frequency of the use of antidiabetic and other agents.

Variable	Time point	Hyperuricemia ($n = 104$)		p value	Non-hyperuricemia ($n = 331$)		p value
		Sitagliptin group (%)	Conventional (%)		Sitagliptin group (%)	Conventional (%)	
Sulfonylurea	Baseline	8 (14.3)	12 (25.0)	0.167	48 (29.4)	39 (23.2)	0.198
	12 months	5 (10.2)	12 (27.9)	0.029	35 (21.5)	53 (31.5)	0.091
	24 months	4 (8.7)	11 (27.5)	0.022	32 (19.6)	49 (29.2)	0.131
Metformin	Baseline	6 (10.7)	5 (10.4)	0.961	26 (16.0)	27 (16.1)	0.976
	12 months	9 (18.4)	10 (23.3)	0.563	29 (19.1)	57 (36.8)	0.001
	24 months	9 (19.6)	9 (22.5)	0.739	33 (23.1)	57 (38.0)	0.006
α-Glucosidase inhibitor	Baseline	18 (32.1)	16 (33.3)	0.897	53 (32.5)	49 (29.2)	0.509
	12 months	10 (20.4)	21 (48.8)	0.004	43 (28.3)	62 (40.0)	0.031
	24 months	9 (19.6)	19 (47.5)	0.006	36 (25.2)	60 (40.0)	0.007
Thiazolidinedione	Baseline	11 (19.6)	8 (16.7)	0.695	41 (25.2)	44 (26.2)	0.829
	12 months	7 (14.3)	10 (23.3)	0.269	32 (21.1)	53 (34.2)	0.010
	24 months	7 (15.2)	11 (27.5)	0.163	30 (21.0)	50 (33.3)	0.018
Glinide	Baseline	2 (3.6)	4 (8.3)	0.411	5 (3.1)	15 (8.9)	0.025
	12 months	1 (2.0)	7 (16.3)	0.023	3 (2.0)	18 (11.6)	0.001
	24 months	1 (2.2)	4 (10.0)	0.179	2 (1.4)	17 (11.3)	0.001
Statin	Baseline	40 (71.4)	28 (58.3)	0.162	127 (77.9)	131 (78.0)	0.989
	12 months	34 (69.4)	23 (53.5)	0.117	115 (75.7)	118 (76.1)	0.923
	24 months	33 (71.7)	21 (52.5)	0.066	107 (74.8)	112 (74.7)	0.975
Fibrate	Baseline	0	0	–	3 (1.8)	3 (1.8)	0.970
	12 months	0	0	–	3 (2.0)	3 (1.9)	0.981
	24 months	0	0	–	3 (2.1)	3 (2.0)	0.953
Angiotensin II receptor blocker	Baseline	35 (62.5)	24 (50.0)	0.200	95 (58.3)	86 (51.2)	0.195
	12 months	31 (63.3)	21 (48.8)	0.164	87 (57.2)	82 (52.9)	0.445
	24 months	32 (69.6)	20 (50.0)	0.064	83 (58.0)	78 (52.0)	0.299
Angiotensin-converting enzyme inhibitor	Baseline	7 (12.5)	7 (14.6)	0.756	19 (11.7)	28 (16.7)	0.192
	12 months	4 (8.2)	6 (14.0)	0.506	19 (12.5)	25 (16.1)	0.364
	24 months	4 (8.7)	6 (15.0)	0.504	15 (10.5)	24 (16.0)	0.165

Data are presented as *n* (%).

often occur simultaneously with type 2 diabetes and metabolic syndrome.[36] T2DM and hyperuricemia have been identified as an important risk factor for atherosclerosis.[11,22] However, whether sitagliptin treatment affects CIMT in T2DM patients with hyperuricemia has not been revealed. Although many clinical studies have shown that serum uric acid levels are correlated with CIMT, a marker of subclinical atherosclerosis, few studies have been conducted in patients with T2DM.[37] Of the 442 study population in the PROLOGUE study, 68 men and 36 women were identified as hyperuricemia patients at baseline, accounting for nearly a quarter of the total. On the one hand, it confirms the previous statement that hyperuricemia often occurs concurrently with T2DM. On the other hand, it also reminds us that more attention and specific treatment should be given to this group of patients. Although the PROLOGUE study has not found that sitagliptin has an effect on the progression of atherosclerosis in patients with T2DM. But if this benefit can be found in T2DM patients with hyperuricemia, it may bring new evidence for sitagliptin in preventing the progression of atherosclerosis. At the same time, this is also important from a health economics perspective, as it means that the use of sitagliptin will slow down the progress of ICA-IMT in nearly a quarter of patients with T2DM.

Several studies have reported an association between hyperuricemia and various factors associated with atherosclerosis, such as oxidative stress, inflammation, and endothelial cell dysfunction. Hyperuricemia should be considered as a cause of atherosclerosis rather than a consequence of subclinical atherosclerosis.[38–42] Some clinical studies have also shown a positive correlation between serum uric acid levels and CIMT.[43,44] Uric acid can promote low-density lipoprotein oxidation, and the oxidation of low-density lipoprotein is considered to be an important process in the formation of atherosclerotic plaques.[39,45] Hyperuricemia is also closely related to endothelial cell dysfunction, and its mechanism is achieved by interleukin-1, interleukin -6, and tumor necrosis factor-alpha, as well as some chemokines and adhesion molecules, which have important links with the inflammatory mechanism of atherosclerosis.[46–48] In the present *post hoc* analysis, the results of our analysis also indicate that the hyperuricemia subgroup had higher baseline CIMT parameters than the non-hyperuricemia subgroup.

The results of this work suggest that sitagliptin treatment is beneficial in preventing the progression of CIMT in T2DM and hyperuricemia patients. For patients without hyperuricemia, sitagliptin treatment did not bring this benefit. Blood glucose levels have an effect on CIMT in patients with T2DM. Despite the 24-month observation period, the use of various hypoglycemic agents, including sulfonylureas, metformin, alpha-glucosidase inhibitors, thiazolidinediones, glinide, and others, varied between the different treatment groups in the two subgroups. However, in the PROLOGUE study, the majority of patients achieved good glycemic control. More interestingly, there was less use of other types of hypoglycemic agents in the sitagliptin treatment group than in the conventional treatment group in both subgroups. Meanwhile, there were no differences in the use of other medications, including angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and statins, between the treatment groups during the 24-month observation period. Therefore, we have reason to believe that the addition of sitagliptin plays the most important role in inhibiting the progression of CIMT. In this *post hoc* analysis, sitagliptin treatment was also found to significantly increase serum creatinine levels at 12 months in the hyperuricemia subgroup, consistent with some previous clinical research findings.[49] And, at 24 months, sitagliptin treatment significantly reduced blood urea nitrogen levels compared with the conventional treatment group. Both sitagliptin and conventional therapy reduced serum uric acid levels at 24 months in the two subgroups, although there was no difference between the two treatment groups. Differently, this benefit of sitagliptin has not been found in some clinical studies, and some studies have found that DPP-4 inhibitors may even cause increased serum uric acid levels in patients with T2DM.[50] In the present *post hoc* analysis, the hyperuricemia group had a higher proportion of comorbid kidney disease as well as higher serum creatinine and urea nitrogen levels. Several studies have shown that urea nitrogen and creatinine levels are associated with CIMT thickening.[51,52] Previous experimental studies have confirmed that sitagliptin can reduce serum creatinine and urea nitrogen levels in diabetic nephropathy rats.[53] And in an adenine-induced rat kidney disease model, sitagliptin also can reduce serum urea and creatinine levels.[54] Therefore, we speculate that the effect of

sitagliptin in inhibiting CIMT progression may be attributable partly to its role in reducing urea nitrogen and creatinine levels. The efficacy of sitagliptin may be related to its anti-inflammatory and antioxidant effects, which can reduce oxidative stress levels and increase catalase activity.[54,55]

Our research has some limitations. First, the present study was not a pre-specified sub-analysis of the PROLOGUE study, and the CONSORT statement could not be compliant,[56] though the data still come from a peer-reviewed randomized controlled trial. Meanwhile, *post hoc* sample size calculation was not recommended according to a previous suggestion,[57–59] so was not included. Secondly, the number of patients in this study was small, and some data are missing, such as lack of information on the use of antiplatelet agents. Thirdly, although the basic drug therapies are the same in this *post hoc* analysis, antidiabetics, anti-hyperlipidemic drugs, and antihypertensive drugs may affect the progress of CIMT, and a more rigorous clinical trial will be necessary in future.

Conclusion

Our present sub-group analysis from the PROLOGUE study demonstrated that patients with T2DM and hyperuricemia in the sitagliptin group obtained better anti-atherosclerotic effects compared with a conventional therapy group. However, considering that this study was a *post hoc* analysis, it would be premature to conclude that sitagliptin treatment significantly inhibits CIMT progression. Our findings need to be interpreted carefully, which may provide clues to the population of possible benefit subgroups, suggesting possible hypotheses worth testing for further additional studies, but not as clinical evidence. Large-scale and well-designed studies are needed to confirm our findings.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Trial registration

The PROLOGUE study is registered in University Hospital Medical Information Network Clinical Trials Registry, which is a nonprofit organization in Japan, and meets the requirements of the International Committee of Medical Journal Editors. URL: https://www.umin.ac.jp/ctr/ Unique Identifier: UMIN000004490.

Data availability statement

All data are available on Dryad Digital Repository *via*: (https://doi.org/10.5061/dryad.qt743).

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Supplemental material

Supplemental material for this article is available online.

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