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Mean postprandial triglyceride concentration is an independent risk factor for carotid atherosclerosis in patients with type 2 diabetes

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ABSTRACT

Background: Postprandial hypertriglyceridemia is a risk factor for atherosclerotic disease. However, the postprandial triglyceride (PTG) concentration fluctuates markedly and is poorly reproducible. The aim of this study was to determine whether the mean PTG (mean-PTG) concentration is a risk factor for carotid atherosclerosis in patients with type 2 diabetes.
Methods: We measured the fasting and postprandial lipid concentrations, and the maximum intima-media thickness (max IMT) of carotid arteries by ultrasound in 115 diabetic patients. A carotid plaque was defined as max IMT of >1.0 mm. The mean-PTG concentration was calculated from several PTG concentrations measured on different days during a 1-year follow-up period.
Results: PTG concentrations showed marked intra-individual variability, and ranged from 0.29 to 6.03 mmol/l. Patients with carotid plaques had higher mean-PTG concentrations than those without carotid plaques (1.51 ± 0.57 vs. 1.29 ± 0.47 mmol/l, $p = 0.025$). Neither fasting triglycerides nor one-point PTG concentrations differed between the two groups. Multivariate stepwise logistic regression analysis revealed that the mean-PTG concentration was significantly associated with carotid plaques [OR 1.20 (95% CI, 1.05–1.37), $p = 0.009$], even after adjusting for traditional risk factors including HDL-cholesterol, LDL-cholesterol, age, hypertension, and duration of diabetes.
Conclusions: The mean-PTG concentration is an independent risk factor for carotid atherosclerosis in patients with type 2 diabetes.

1. Introduction

Accumulating evidence suggests that postprandial hypertriglyceridemia is an important risk factor for cardiovascular disease (CVD) in patients with type 2 diabetes. Recent epidemiological studies have shown that the postprandial triglyceride (PTG) concentration is more closely associated with CVD than is the fasting triglyceride (FTG) concentration, which is independent of traditional CVD risk factors [1–4]. Triglyceride-rich lipoproteins (TRLs) are composed of chylomicrons (CM), very low-density lipoproteins (VLDL), and their remnants. Remnant lipoproteins increase in the postprandial state and have greater atherogenicity than their precursors [5–8]. Because hypertriglyceridemia is a common feature in patients with type 2 diabetes, the PTG concentration is likely to be a better predictor of CVD than the FTG concentration in these patients.

Despite its potential usefulness as a diagnostic marker, no clinical guidelines provide a definitive cutoff value for the PTG concentration. The PTG concentration is poorly reproducible and is affected considerably by the meal content and fasting interval [2,9,10]. Most studies evaluated the PTG concentration only once (one-point PTG) or after oral loading with a high-fat diet, which has a much greater fat content than regular meals. Therefore, repeated measurements of PTG might yield a more reliable marker for postprandial dyslipidemia. The aim of this study was to elucidate whether the mean PTG (mean-PTG) concentration is an independent risk factor for carotid atherosclerosis in patients with type 2 diabetes. To assess carotid atherosclerosis, we used carotid ultrasonography because it is a noninvasive and quantitative method and because the extent of carotid atherosclerosis is positively correlated with an increased risk of CVD [11,12].

2. Methods

2.1. Recruitment of study subjects

A total of 177 patients with type 2 diabetes were recruited from those who underwent carotid ultrasonography at Juntendo Tokyo Koto Geriatric Medical Center between April 2007 and March 2009. Type 2 diabetes was defined by the criteria of the Japan Diabetes Society [13]. Patients who received hypoglycemic medications or insulin

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therapy, and/or lipid-lowering medications including statins and fibrates, were eligible. We excluded patients with the following disorders: acute or chronic infections, cancer, liver cirrhosis, biliary tract disease, pancreatitis, chronic kidney disease, endocrine disease, and steroid-induced diabetes. Finally, data for 115 patients were collected and analyzed. The study protocol was approved by the Juntendo Tokyo Koto Geriatric Medical Center Research Ethics Committee.

2.2. Study protocol

In all patients, lipoprotein profiles were determined at 1- to 3-month intervals at the outpatient clinic. As a rule, blood samples were obtained 2 to 4 h after breakfast. However, fasting blood samples were obtained once during the 1-year follow-up period within 4 weeks before/after the ultrasound examination. Fasting and postprandial blood samples were taken on different days. In each patient, all PTG concentrations were used to calculate the mean-PTG concentration, while the PTG concentration measured nearest to the time of ultrasonography was defined as the one-point PTG concentration. The number of measurements of postprandial blood samples for each patient is shown in Supplementary Fig. 1. For subgroup analysis, we calculated the average and standard deviation (SD) of the mean-PTG of 115 patients. The patients were then classified into three groups: Low group [(< average mean-PTG minus 1SD); <0.88 mmol/l (77.5 mg/dl)], Middle group [(average mean-PTG minus 1SD) to (average mean-PTG plus 1SD); 0.88–1.95 mmol/l (77.5–172.5 mg/dl)], and High group [(≥ average mean-PTG plus 1SD); ≥1.95 mmol/l (172.5 mg/dl)].

Anthropometric data and medical history were collected from the medical records. Diabetic retinopathy, nephropathy, and neuropathy were categorized as microvascular complications, while coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease were categorized as macrovascular complications. Smoking status was assessed by a questionnaire. Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, or current use of antihypertensive medications. Dyslipidemia was defined as an FTG of ≥1.69 mmol/l (150 mg/dl), HDL-C of <1.04 mmol/l (40 mg/dl), or LDL-C of ≥3.63 mmol/l (140 mg/dl) according to the guideline of the Japan Atherosclerosis Society [14], or current use of lipid-lowering medications.

All patients received diet therapy based on treatment guidelines for diabetes recommended by the Japan Diabetes Society, and underwent nutritional guidance by a registered dietician before the 1-year follow-up period. The content of diet therapy was as follows: a total energy was calculated by standard body weight

Table 1
Patients' characteristics and laboratory data according to mean-PTG level.

	Low	Middle	High	*p*-value
N	17	76	22	
Age (years)	67.0 ± 7.9	64.2 ± 9.6	60.5 ± 10.9	0.10
Men	7 (41)	43 (57)	10 (45)	0.42
BMI (kg/m^2)	23.7 ± 3.1	25.0 ± 3.7	24.6 ± 3.0	0.35
Waist circumference (cm)	86.3 ± 7.0	88.0 ± 9.9	87.3 ± 9.4	0.79
Hypertension	11 (65)	47 (62)	14 (64)	1.0
Systolic BP (mmHg)	133 ± 15	133 ± 13	131 ± 12	0.88
Diastolic BP (mmHg)	81 ± 10	79 ± 9	79 ± 9	0.67
Dyslipidemia	11 (65)	63 (83)	22 (100)**†	0.007
Duration of diabetes (years)	8.5 ± 7.3	9.7 ± 6.3	11.7 ± 7.0	0.30
Micro-/macrovascular complications	6 (35)/2 (12)	37 (49)/23 (30)	11 (50)/10 (45)	0.64/0.07
Current smoker[a]	5 (33)	27 (42)	12 (55)	0.44
Medications				
ACE inhibitors or ARBs	3 (18)	22 (29)	5 (23)	0.67
Calcium channel blockers	3 (18)	15 (20)	8 (36)	0.27
β-Blockers/diuretics	0 (0)/0 (0)	1 (1)/2 (3)	1 (5)/2 (9)	0.57
Statins/fibrates	4 (24)/1 (6)	22 (29)/3 (4)	10 (45)/1 (5)	0.27/0.82
Oral hypoglycemic agents/insulin	14 (82)/1 (6)	61 (80)/4 (5)	20 (91)/4 (18)	0.57/0.14
Fasting data				
FPG (mmol/l)	7.6 ± 2.2	7.7 ± 2.5	8.3 ± 2.7	0.60
A1C (%)	7.8 ± 1.7	7.4 ± 1.2	8.2 ± 2.0	0.31
Insulin (pmol/l)[b]	25 ± 13	49 ± 39**	68 ± 86**	<0.001
HOMA-IR[b]	1.2 ± 0.7	2.6 ± 3.0**	4.4 ± 7.7**	0.003
FTG (mmol/l)	0.75 ± 0.22	1.20 ± 0.37**	2.01 ± 0.54**‡	<0.001
TC (mmol/l)	4.86 ± 0.91	5.28 ± 0.85	5.66 ± 1.13*	0.028
HDL-C (mmol/l)	1.62 ± 0.31	1.35 ± 0.33**	1.22 ± 0.24**	<0.001
LDL-C (mmol/l)[c]	2.89 ± 0.80	3.39 ± 0.69	3.51 ± 1.05	0.07
ApoB (g/l)	0.82 ± 0.20	1.00 ± 0.18**	1.14 ± 0.25**†	<0.001
ApoCIII (g/l)	0.07 ± 0.02	0.09 ± 0.02	0.12 ± 0.03**‡	<0.001
ApoE (g/l)	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01*†	0.013
RLP-C (mmol/l)	0.08 ± 0.03	0.11 ± 0.04*	0.16 ± 0.07**‡	<0.001
FFA (mmol/l)	0.66 ± 0.20	0.49 ± 0.20**	0.54 ± 0.20	0.001
hs-CRP (mg/l)	0.27 (0.20–3.00)	0.71 (0.33–1.74)	1.31 (0.61–3.62)	0.05
Postprandial data				
One-point PTG (mmol/l)	0.77 ± 0.20	1.26 ± 0.47**	2.40 ± 0.87**‡	<0.001
Mean-PTG (mmol/l)	0.75 ± 0.12	1.31 ± 0.29**	2.27 ± 0.29**‡	<0.001

Data are expressed as *n* (%), mean ± SD, or median (interquartile).
The Low group was defined as a mean-PTG of <0.88 (mean − 1SD) mmol/l, the Middle group as a mean-PTG of 0.88–1.95 (mean ± 1 SD) mmol/l, and the High group as a mean-PTG of >1.95 (mean + 1SD) mmol/l.
BP, blood pressure; FPG, fasting plasma glucose; FTG, fasting triglyceride; PTG, postprandial triglyceride.
$^{*}p < 0.05$, $^{**}p < 0.01$ vs. Low; $^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$ vs. Middle.
[a] Smoking status data were missing for 2 subjects in the Low group and for 11 subjects in the Middle group.
[b] We excluded 9 patients from the analysis (1 from the Low group, 4 from the Middle group, and 4 from the High group) because they were treated with insulin. HOMA-IR, as a marker of insulin resistance, was calculated using the formula: FPG (mg/dl) × fasting insulin (μU/ml) / 405.
[c] LDL-C was calculated by the Friedewald formula. In all samples, FTG concentrations were <4.52 mmol/l (400 mg/dl).