Association of Postprandial Hypertriglyceridemia and Carotid Intima-Media Thickness in Patients With Type 2 Diabetes

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OBJECTIVE — Serum triglyceride levels are important in the development of atherosclerosis. Although triglyceride levels are generally increased in the postprandial periods, the association between postprandial triglyceride (pTG) levels and atherosclerosis has not been investigated in diabetic patients. To investigate the role of pTG levels in atherosclerosis, we examined the correlation between pTG levels and carotid intimal-medial thickness (IMT).

RESEARCH DESIGN AND METHODS — Carotid IMT was measured by ultrasonography in 61 patients with type 2 diabetes. Plasma glucose (PG), insulin, total cholesterol, triglycerides, and HDL cholesterol levels were measured after overnight fasting and 4 h after a meal.

RESULTS — Carotid IMT of the patients with fasting hypertriglyceridemia was greater than that of the patients with normal fasting triglyceride (fTG) levels (0.85 ± 0.12 vs. 0.76 ± 0.14 mm; $P = 0.02$). The carotid IMT was increased in the patients with pTG levels >2.27 mmol/l. The normo-normo (NN) and normo-hyper (NH) groups consisted of patients with normal fTG levels but with pTG levels <2.27 and >2.27 mmol/l, respectively. Patients with both hypertriglyceridemia and pTG levels >2.27 mmol/l formed the hyper-hyper (HH) group. Carotid IMT was significantly increased in the NH (0.86 ± 0.13 mm) and HH (0.85 ± 0.12 mm) groups compared with the NN group (0.73 ± 0.13 mm; $P < 0.01$). Although postprandial PG, pTG, and fasting LDL cholesterol levels were all independently correlated with carotid IMT, pTG levels had the strongest statistical influence ($P = 0.002$).

CONCLUSIONS — Postprandial hypertriglyceridemia despite normal fTG levels may be an independent risk factor for early atherosclerosis in type 2 diabetes.

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Abbreviations: CPR, C-peptide immunoreactivity; CVD, cerebrovascular disease; E%, percentage of energy; fTG, fasting triglyceride; HH, hyper-hyper; IHD, ischemic heart disease; IMT, intimal-medial thickness; IRI, immunoreactive insulin; Lp(a), lipoprotein(a); NH, normo-hyper; NN, normo-normo; OHA, oral hypoglycemic agent; PG, plasma glucose; pTG, postprandial triglyceride; TC, total cholesterol; TRL, triglyceride-rich lipoprotein.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Macrovascular disease is a major cause of death in diabetic individuals (1). Because many diabetic individuals have multiple risk factors for atherosclerosis, the relative risks of ischemic heart disease (IHD) and cerebrovascular disease (CVD) are 2- to 4-fold and 2- to 3-fold higher, respectively, than the risk in nondiabetic subjects (1–4).

Although many previous studies have shown that total cholesterol (TC), especially LDL cholesterol, is associated with atherosclerosis, whether hypertriglyceridemia is important as an independent predictor of IHD remains unclear. However, hypertriglyceridemia occurs more frequently in patients with early-onset IHD than does hypercholesterolemia alone, and coronary events are increased in patients with fasting triglyceride (fTG) levels >1.13 mmol/l (5). Furthermore, in patients who received coronary artery bypass grafting, a reduction in triglycerides was found to slow the progression of atherosclerosis in both native arteries and grafts (6,7). A prospective study revealed that hypertriglyceridemia is the independent and highest risk factor for IHD (8). In type 2 diabetes, elevated triglyceride levels may be a better predictor of IHD than elevated LDL cholesterol levels (9,10).

Serum triglyceride levels are generally increased for 3–6 h after a meal (11–13). Once postprandial hypertriglyceridemia occurs, it is exacerbated by the next meal and persists for the entire day. The most common pattern of dyslipidemia in type 2 diabetic patients is elevation of triglyceride levels and a decrease in HDL cholesterol levels. Therefore, measuring postprandial values for evaluation of hypertriglyceridemia in patients with diabetes is important. However, to our knowledge, the association between postprandial triglyceride (pTG) levels and atherosclerosis has not been investigated.

Measurement of the intimal-medial thickness (IMT) of the carotid artery by ultrasonography is a noninvasive and quantitative method of evaluating early athero-

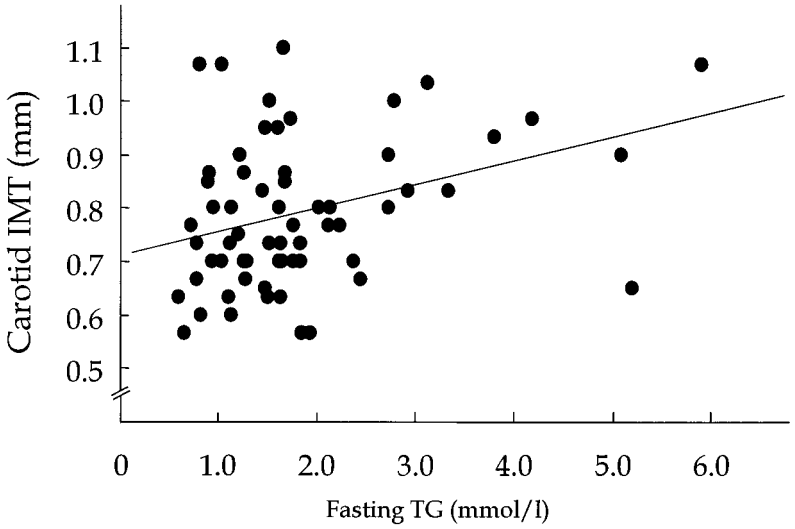

Figure 1—*Correlation between fTG levels and carotid IMT. A positive correlation was evident between the fTG level and carotid IMT (*P = *0.04,* r = *0.27). TG, triglyceride.*

sclerotic changes in the vasculature (14–16). An increase in carotid IMT is associated with an increased risk of CVD or IHD (17). To investigate the role of postprandial hypertriglyceridemia in early atherosclerosis, we examined the correlation between pTG levels and carotid IMT values.

RESEARCH DESIGN AND METHODS

Subjects

A total of 61 patients (21 women and 40 men) with type 2 diabetes 35–69 years of age were recruited. None of the subjects had evidence of CVD or IHD based on a physical examination and electrocardiogram. Smoking habits and a familial history of IHD or CVD were assessed by a questionnaire. The patients with hypertension or hyperlipidemia were being treated with antihypertensive drugs or lipid-lowering therapy. The study was approved by the Saiseikai Kurihashi Hospital Research Ethics Committee, and all subjects gave written informed consent.

Protocol

Blood pressure was measured with a standard mercury sphygmomanometer in the sitting position after resting for at least 15 min. Blood samples were obtained after an overnight fast, and then the patients ate a standard meal that had a total energy of 9 kcal/kg, with 60–65% of this energy (E%) being supplied by carbohydrate, 15–20 E% by protein, and 20 E% by fat after taking insulin or oral hypoglycemic agents (OHAs). Blood samples were taken again 4 h after the meal. Plasma glucose (PG), HbA_{1c}, immunoreactive insulin (IRI), C-peptide immunoreactivity (CPR), TC, triglycerides, and HDL cholesterol were measured by standard laboratory techniques. LDL cholesterol was calculated with Friedewald's formula (18), and lipoprotein(a) [Lp(a)] was measured by radioimmunoassay as described previously (19). We defined an fTG level >1.70 mmol/l as hypertriglyceridemia according to the Japan Atherosclerosis Society (20).

Measurement of carotid IMT

Ultrasonography of the carotid arteries was performed with an echotomography system (SSA-380A; Toshiba, Tokyo) and an electrical linear transducer (midfrequency of 8.0 MHz) as reported previously (14,21). The IMT at the carotid bulb, at the common carotid artery 10 mm proximal to the bulb, and at the internal carotid artery 10 mm distal to the carotid bulb was measured from the leading edge of the first echogenic line to that of the second echogenic line. The first line represented the lumen-intima interface, and the second line represented the collagen-containing upper layer of the adventitia. The mean value was calculated. Obvious plaques were excluded from measurement. The scanning time averaged 30 min, and all images were photographed.

Statistical analysis

Analysis was performed with the SAS system (SAS Institute, Cary, NC), and data are frequencies or means ± SD. The statistical analysis of triglyceride levels was performed on log-transformed values. Analysis of variance was used to test for statistically significant differences among groups, and the Tukey-Kramer multiple comparison test was applied when appropriate. Correlations were tested by Pearson correlation coefficients and Spearman rank-correlation coefficients. To determine the relationship

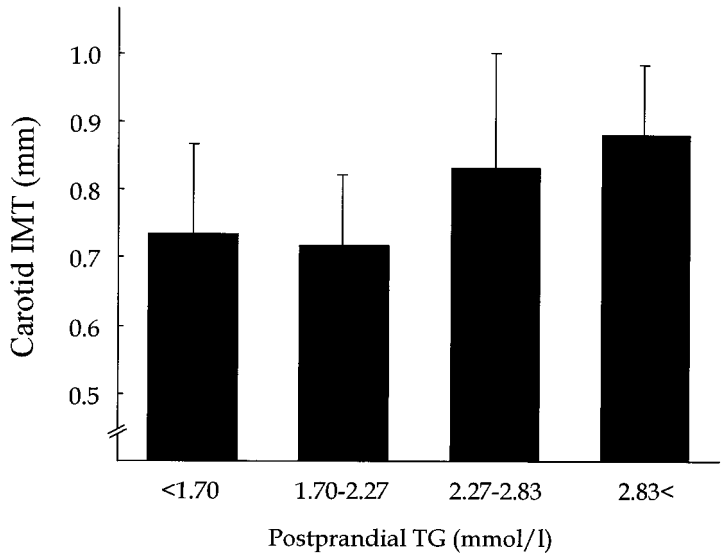

Figure 2—*Association of carotid IMT with different pTG levels in patients with normal fTG levels. In patients with normal fTG levels, carotid IMT tended to increase when pTG levels were >2.27 mmol/l.*

between variables and the carotid IMT, regression coefficients from simple linear regression analysis and standardized partial regression coefficients obtained by a multiple linear regression model with stepwise variable selection were applied. The influence of outliers and the interactions of the final model were examined by regression diagnosis. Two-tailed P values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of all subjects

The mean age was 53.7 ± 7.2 years, and the mean duration of diabetes from initial diagnosis was 7.2 ± 5.8 years. The HbA_{1c} and fasting PG values were 7.3 ± 1.2% and 8.4 ± 2.4 mmol/l, respectively. A total of 35 patients were treated with OHAs, 8 patients were treated with insulin, and 18 patients were treated with medical nutrition therapy alone. A total of 19 patients had diabetic retinopathy (simple retinopathy in 13 subjects, preproliferative retinopathy in 3 subjects, and proliferative retinopathy in 3 subjects). A total of 7 patients had diabetic nephropathy (incipient nephropathy in 5 subjects and overt nephropathy in 2 subjects), but the serum creatinine levels were all within the normal range. A total of 26 patients were treated with antihypertensive drugs (Ca^+ antagonists and ACE inhibitors), mean systolic blood pressure was 134 ± 16 mmHg, and mean diastolic blood pressure was 79 ± 8 mmHg. Fasting TC and LDL cholesterol levels were well controlled by lipid-lowering therapy (HMG-CoA reductase inhibitor alone in 21 subjects, bezafibrate alone in 5 subjects, and their combination in 2 subjects), but the mean fTG level was slightly elevated (1.84 ± 1.12 mmol/l). A total of 12 and 6 patients had hereditary risk factors for IHD and CVD, respectively. Smoking, either currently or in the past, was reported by approximately half of the subjects.

Relationship between fTG levels and carotid IMT

The carotid IMT of patients with fasting hypertriglyceridemia was greater than that of patients with normal fTG levels (0.85 ± 0.12 vs. 0.76 ± 0.14 mm, respectively; P = 0.02). The mean carotid IMT in all patients was 0.79 ± 0.14 mm, and a weak correlation was evident between the fTG level and the carotid IMT (P = 0.04, r = 0.27) (Fig. 1). Although a stronger correlation existed between fTG and carotid IMT in the patients with fasting hypertriglyceridemia (P = 0.02, r = 0.49), no correlation was evident in the patients with normal fTG levels (P = 0.12). Interestingly, almost all of the patients who had fasting hypertriglyceridemia showed an increase in carotid IMT, but carotid IMT ranged widely in the patients with normal fTG levels.

Relationship between pTG levels and carotid IMT

In the patients with normal fTG levels, a tendency was evident for the carotid IMT to be greater when the pTG level was >2.27 mmol/l (Fig. 2). According to these results, we classified patients into the following 3 groups. Patients with fTG levels <1.70 mmol/l and pTG levels <2.27 mmol/l formed the normo-normo (NN) (n = 31) group, and the normo-hyper (NH) (n = 11) group consisted of patients with fTG levels <1.70 mmol/l but pTG levels >2.27 mmol/l. The hyper-hyper (HH) (n = 18) group consisted of patients with fTG and pTG levels >1.70 and >2.27 mmol/l, respectively. One patient with fasting hypertriglyceridemia did not belong to any group because his pTG level was <2.27 mmol/l.

Table 1 shows the different clinical characteristics and cardiovascular risk factors for the NN, NH, and HH groups. Fasting CPR as well as postprandial IRI and CPR were higher in the HH group than in the NN group. Fasting TC levels were higher in the HH group than in the NN group, and

Table 1—*Differences in clinical characteristics among the NN, NH, and HH groups*

	NN	NH	HH
n (F/M)	31 (22/9)	11 (7/4)	18 (10/8)
Age (years)	52.5 ± 6.2	54.7 ± 9.1	54.9 ± 7.7
BMI (kg/m^2)	23.5 ± 3.1	25.9 ± 4.1	25 ± 2.5
Systolic blood pressure (mmHg)	130 ± 16	136 ± 16	139 ± 16
Diastolic blood pressure (mmHg)	77 ± 8.5	83 ± 7	80 ± 8
HbA_{1c} (%)	7.5 ± 1.4	7.1 ± 0.7	7.2 ± 1.3
Fasting			
PG (mmol/l)	8.4 ± 2.2	8.1 ± 1.9	8.7 ± 3.2
IRI (pmol/l) (n = 53)	43.8 ± 33.0	43.8 ± 16.8	60.6 ± 46.2
CPR (nmol/l)	0.73 ± 0.30	0.78 ± 0.14	0.99 ± 0.46*
TC (mmol/l)	5.07 ± 0.73	5.74 ± 0.61	5.94 ± 1.15†
Triglycerides (mmol/l)	1.25 ± 0.45	1.41 ± 0.24	3.04 ± 1.24†
HDL cholesterol (mmol/l)	1.37 ± 0.35	1.54 ± 0.31	1.29 ± 0.34
LDL cholesterol (mmol/l)	3.10 ± 0.65	3.56 ± 0.62	3.14 ± 0.95
Postprandial (4-h)			
PG (mmol/l)	8.8 ± 3.3	8.9 ± 1.4	11.3 ± 4.8
IRI (pmol/l) (n = 53)	69.8 ± 52.8	95.4 ± 69.6	244.2 ± 53.0*
CPR (nmol/l)	1.13 ± 0.62	1.61 ± 0.91	2.03 ± 1.21†
TC (mmol/l)	4.81 ± 0.61	5.94 ± 0.73‡	5.76 ± 1.00
Triglycerides (mmol/l)	1.30 ± 0.50	2.96 ± 0.48‡	4.41 ± 2.67†
HDL cholesterol (mmol/l)	1.39 ± 0.34	1.53 ± 0.47	1.23 ± 0.32
LDL cholesterol (mmol/l)	2.84 ± 0.57	3.06 ± 0.83	2.67 ± 1.16
Lp(a)	24.6 ± 21.8	26.4 ± 18.5	44.9 ± 61.4
Smoking	18 (62.1)	3 (27.3)	7 (41.2)
Duration of diabetes (years)	7.8 ± 5.4	4.8 ± 3.4	7.8 ± 7.4
Diabetic retinopathy	13 (43.3)	1 (9.1)	5 (26.3)
Diabetic nephropathy	2 (6.7)	1 (9.1)	4 (21.1)
Therapy (diet/OHA/insulin)	6/20/5	5/5/1	7/10/2
Therapy for hypertension	12 (41.4)	4 (40.0)	10 (52.6)
Therapy for hyperlipidemia	8 (27.6)	8 (80.0)	12 (63.2)
Family history of IHD	2 (7.1)	3 (27.3)	1 (5.9)
Family history of CVD	4 (14.3)	3 (27.3)	5 (29.4)

Data are n, means ± SD, or n (%). NN group, fTG levels <1.70 mmol/l and pTG levels <2.27 mmol/l; NH group, fTG levels <1.70 mmol/l and pTG levels ≥2.27 mmol/l; and HH group, fTG levels ≥1.70 mmol/l and pTG levels ≥2.27 mmol/l. LDL cholesterol was calculated by Friedewald's formula. The statistical analysis of TG levels was performed on log-transformed values. *$P < 0.05$; †$P < 0.01$, NN vs. HH; ‡$P < 0.01$, NN vs. NH.

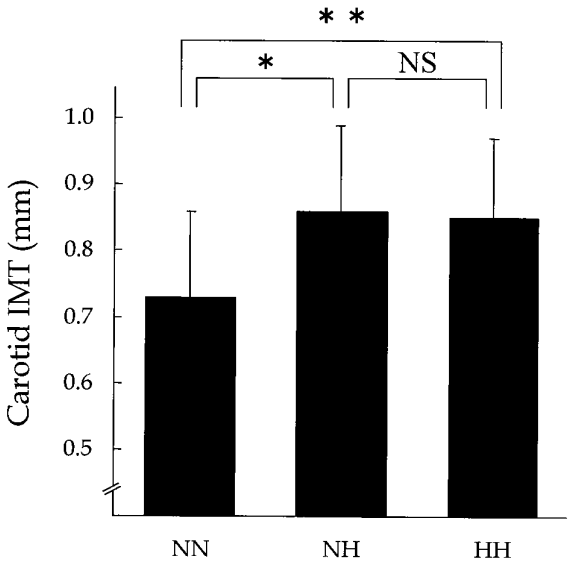

Figure 3—*Comparison of carotid IMT among the NN, NH, and HH groups classified from fTG and pTG levels. The NN group consisted of patients with fTG levels <1.70 mmol/l and pTG levels <2.27 mmol/l. The NH group consisted of patients with fTG levels <1.70 mmol/l and pTG levels >2.27 mmol/l. The HH group consisted of patients with fTG levels >1.70 mmol/l and pTG levels >2.27 mmol/l.* *P $<$ *0.05;* **P $<$ *0.01.*

Table 2—*Multiple linear regression model with stepwise model selection method*

	Univariate		Multivariate	
Variable	Regression coefficient	*P*	Standardized partial regression coefficient	*P*
Age	0.0027	0.280		
BMI	0.0029	0.609		
Systolic blood pressure	0.0004	0.730		
Diastolic blood pressure	0.0010	0.644		
HbA_{1c}	0.0143	0.332		
Fasting				
PG	0.0003	0.443		
IRI (*n* = 57)	0.0011	0.737		
CPR	0.0270	0.123		
TC	0.0014	0.003		
Log triglycerides	0.1897	0.015		
HDL cholesterol	0.0001	0.931		
LDL cholesterol	0.0013	0.043	0.252	0.05
Postprandial (4-h)				
PG	0.0007	0.004	0.307	0.02
IRI (*n* = 57)	0.0005	0.417		
CPR	0.0159	0.012		
TC	0.0016	0.001		
Log triglycerides	0.2300	0.0001	0.414	0.002
HDL cholesterol	−0.0004	0.750		
LDL cholesterol	0.0000	0.962		
Lp(a)	0.0002	0.611		
Smoking	−0.0140	0.712		
Duration of diabetes	−0.0007	0.818		
Therapy for hyperlipidemia	0.0454	0.207		
Family history of IHD	0.0566	0.354		
Family history of CVD	0.0420	0.361		

LDL cholesterol was calculated by Friedewald's formula.

postprandial TC levels were higher in the NH group than in the NN group. However, no differences were evident in LDL cholesterol and HDL cholesterol. Likewise, no statistical differences existed in clinical characteristics (e.g., age, sex, BMI, blood pressure, and duration of diabetes), glycemic control, Lp(a) level, familial history of IHD and CVD, and smoking habits between the groups. A comparison of carotid IMT among the NN, NH, and HH groups is presented in Fig. 3. Carotid IMT was 0.73 ± 0.13 mm in the NN group, 0.86 ± 0.13 mm in the NH group ($P < 0.05$ vs. NN), and 0.85 ± 0.12 mm in the HH group ($P < 0.01$ vs. NN). Interestingly, no difference was evident in carotid IMT between the NH and HH groups.

In univariate analysis, fasting TC, LDL cholesterol, and fTG levels as well as postprandial PG, CPR, TC, and pTG levels were associated with carotid IMT, but no correlation was evident with HDL cholesterol. In contrast, multivariate analysis demonstrated that postprandial PG, pTG, and fasting LDL cholesterol levels were independently correlated with carotid IMT (Table 2). Among these factors, pTG levels had the strongest influence on carotid IMT (P = 0.002, standardized partial regression coefficient 0.414).

CONCLUSIONS —

Our chief observations in the present study were that carotid IMT was increased in patients with postprandial hypertriglyceridemia despite normal fTG levels, and the pTG levels showed the strongest influence on carotid IMT.

Correlation between the fTG levels and carotid IMT remains controversial (13, 22–24). Karpe et al. (12) reported that fTG levels were not correlated with carotid IMT, but pTG levels were strongly associated with carotid IMT in healthy subjects. Our study showed that, although a positive correlation existed between fTG levels and carotid IMT in the patients with fasting hypertriglyceridemia, no correlation existed in the patients who had normal fTG levels. Interestingly, carotid IMT increased in the patients with postprandial hypertriglyceridemia despite normal fTG levels. Furthermore, pTG levels were more strongly and independently correlated with carotid IMT than fTG levels. We also found a tendency for carotid IMT to be increased in patients with pTG levels >2.27 mmol/l. Some reports have suggested that pTG levels are associated with atherosclerosis, although the clinical definition of post-

prandial hypertriglyceridemia remains unclear. Although no evidence exists of any threshold of pTG levels for atherosclerosis, our results imply that pTG levels >2.27 mmol/l may be regarded as postprandial hypertriglyceridemia.

Many drugs affect plasma lipid levels and the extent of postprandial lipemia. Lipid-lowering drug are obvious, but antihypertensive drugs as well as OHAs and insulin affect plasma lipid levels. In our study, many patients were taking some kinds of drugs, especially the 46% of patients who were treated with lipid-lowering drugs. However, no difference was evident in carotid IMT between patients treated with lipid-lowering drugs and others ($P = 0.21$), and these drugs did not correlate with carotid IMT in multivariate analysis ($P = 0.68$). In a compulsory investigation with lipid-lowering drugs in multivariate analysis, the *P* value for pTG levels correlated with carotid IMT was similar, and carotid IMT was a strong influencing factor (data not shown). Therefore, reducing pTG levels regardless of lipid-lowering drugs is important.

Histopathological evidence has been obtained that cholesterol accumulates in atherosclerotic plaques (25,26). On the other hand, chylomicrons and VLDL cholesterol were generally thought to be too large to infiltrate the arterial wall. However, triglyceride-rich lipoproteins (TRLs) produced from chylomicrons and VLDL cholesterol were considered to have an atherogenic effect in vivo (27,28). Furthermore, a recent report found undegraded VLDL cholesterol and intermediate-density lipoprotein cholesterol in atherosclerotic plaques (29). Larger TRLs may undergo hydrolysis to smaller particles on the arterial surface before entering the intima, and smaller TRLs may undergo further hydrolysis in the intima. Possible cellular pathways for the uptake of TRL by macrophages have been described in vitro (30,31). These TRLs can deliver 5 times as much cholesterol to macrophages as LDL cholesterol, which is why TRLs are regarded as being strongly atherogenic, and triglyceride levels may be a marker of this risk factor for atherosclerosis.

Contrary to some previous studies, age was not correlated with carotid IMT in our study. This may be a reflection of the small age range of our patients (especially younger patients) or the small population of our subjects.

In most previous studies, subjects received a high-fat test meal with a total of 700–1,000 kcal/kg and 60 E% from fat (11–13). However, when the fat content in a test meal increased from 25 to 45%, pTG levels only increased by 10% (32). This result implies that a special test meal is not necessary for the evaluation of postprandial hypertriglyceridemia. Because we wanted to investigate whether pTG levels were associated with atherosclerosis in normal daily life, we gave our subjects a test meal that resembled their daily diets.

In conclusion, postprandial hypertriglyceridemia, despite normal fTG levels, may be an independent risk factor for early atherosclerosis in type 2 diabetes. Postprandial hypertriglyceridemia >2.27 mmol/l may be atherogenic. Evaluating not only fTG levels but also pTG levels during clinical assessment of patients with type 2 diabetes is important.

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