Daytime Triglyceridemia in Normocholesterolemic Patients With Premature Atherosclerosis and in Their First-Degree Relatives

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Postprandial hypertriglyceridemia tested under metabolic ward conditions with unphysiological high fat loads has been reported in CAD patients and their relatives even in the presence of normal fasting lipids. It is unclear whether this also occurs in the daytime situation. Twenty-seven normocholesterolemic, non-obese and nondiabetic patients with premature coronary artery disease (CAD) and 56 first-degree relatives without CAD measured daytime capillary triglyceride profiles (TGc-AUC) as an estimate of postprandial lipemia. Fasting capillary triglycerides (TGc) were not significantly different between CAD index patients and their relatives (1.68 ± 0.63 and 1.54 ± 0.71 mmol/L, respectively). In contrast, daytime triglyceridemia was significantly higher in CAD patients (30.7 ± 13.6 mmol · h/L) compared to their relatives (24.4 ± 9.4 mmol · h/L) and this was also the case after correction for fasting TGc (7.24 ± 7.41 and 2.79 ± 6.89 mmol · h/L; $P < .05$). The best predictors of TGc-AUC by multiple regression analysis in CAD families were fasting TGc, systolic blood pressure, and high-density lipoprotein cholesterol (HDL-C), which are all components of the metabolic syndrome, explaining 65% of the variation. Since there were no major differences in nutritional intake between index patients and their relatives, this could not explain the differences Daytime triglyceridemia, measured under physiological conditions, is increased in patients with premature atherosclerosis and normal fasting TG levels, when compared to their non-CAD relatives. This study confirms previous observations using standardized oral fat loading tests and underlines the importance of postprandial hyperlipidemia in CAD.

CORONARY ARTERY DISEASE (CAD) is closely associated with a positive family history for CAD, particularly when it presents early in adult life.[1-3] The familial CAD risk has been explained, in part, by familial clustering of risk factors, such as systemic hypertension, high total serum cholesterol, low high-density lipoprotein cholesterol (HDL-C), and high fasting plasma triglycerides (TG).[4,5] In addition, postprandial hyperlipidemia has been linked to atherosclerosis, even in fasting normocholesterolemic subjects,[6-16] which may also determine the familial risk of CAD.[17-19]

Hypertriglyceridemia is highly associated with the metabolic syndrome, which is a clustering of lipid and non-lipid risk factors.[20-23] The involved atherogenic lipid profile consists of high TG, low HDL-C, and small, dense low-density lipoprotein cholesterol (LDL-C). It is accepted that the presence of the metabolic syndrome results in increased risk for premature CAD.[24] Besides genetic factors, central obesity, physical inactivity, and excessive consumption of food are involved in the pathogenesis of the metabolic syndrome.[25,26] Regarding dietary intake, it has been reported that the intake of carbohydrates is the major determinant of daytime triglyceridemia.[27]

Both, fasting and postprandial TG are closely linked to the metabolic syndrome and to dietary intake but it is not known how these factors are related to each other in CAD patients and their relatives. Moreover, most studies have been performed in metabolic wards using an unphysiological amount of fat,[9-17] which does not represent the normal daytime situation. We wanted to investigate the magnitude of postprandial lipemia in real life in index CAD subjects compared to their relatives. For this purpose daytime triglyceridemia, which reflects postprandial lipemia,[26-31] was determined in families with a normocholesterolemic index CAD patient.

MATERIALS AND METHODS

Subjects

Index subjects were 27 CAD patients under medical control, with CAD established by coronary angiography at a young age (males < 55; females < 65 years), who had undergone a percutaneous transluminal coronary angioplasty (PTCA) in the University Medical Center Utrecht (UMC-Utrecht) or the St. Antonius Hospital in Nieuwegein. The mean time that had passed between the onset of CAD and participation to this study was 2 years (range, 1.5 to 2.5 years). Exclusion criteria were the presence of diabetes, body mass index (BMI) greater than 30 kg/m^2, renal and/or liver failure, fasting plasma cholesterol greater than 6.5 mmol/L (off lipid-lowering medication), the presence of apolipoprotein (apo)E2/E2 genotype, use of alcohol (>3 units per day), and a cardiac event or revascularization procedure less than 6 months before the study. All patients had normal exercise tests at the time of investigation and none had limitations of physical activities.

First-degree relatives of the normocholesterolemic CAD patients were asked to participate. On the morning of inclusion blood pressure, weight, length, and waist-to-hip ratio were measured and a fasting blood sample was taken for baseline plasma determinations. Only relatives without CAD were included. Information about subjects' personal and family histories of cardiovascular disease was obtained by a standardized questionnaire. Furthermore, instructions about the TG self-measurements were given. The study protocol was approved by the Human Investigation Review Committees of the UMC-Utrecht and St. Antonius Hospital and informed consent was obtained from all participants.

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TG Self-Measurements

Self-measurement of capillary TG (TGc) was performed with a TG-specific point-of-care testing device (Accutrend GCT, Roche Diagnostics, Mannheim, Germany).[26-30,32,33] Subjects were instructed to wash and dry their hands thoroughly before each measurement. With a lancing device a drop of blood (30 μL) from the finger was obtained, which was applied to the TG test strip in the TG analyzer. Subsequently, TG concentrations were measured by a process of dry chemistry and colorimetry. Participants measured their TGc on 3 different days at the following time points: fasting, before and 3 hours after lunch and dinner, and at bedtime. The results and time points were recorded in a diary and were evaluated with the subjects afterwards. Subjects were requested to refrain from heavy physical activity on the measurement days. Participants did not receive recommendations concerning the frequency and composition of the meals and they were requested to use their regular diet during the study. In case of one or more missing measurements during a day, the data for that particular day were not used for construction of an average daytime TG profile. The mean daytime TG profile was used for statistical analysis.

The measurement range for TGc is 0.80 to 6.86 mmol/L. The Accutrend system detects TG reliably, regardless of the nature of the TG-carrying lipoprotein species (chylomicrons or very-low-density lipoprotein [VLDL] particles).[32] The variation coefficient for repetitive measurements of samples with high TG is 3.3% (6.12 mmol/L) and 5.3% for samples with low TG (1.81 mmol/L).[28,29,33] The biological intra-individual variability of daytime TGc is lower than of fasting TGc, at 15% and 25%, respectively.[28] The correlation coefficient between Accutrend TGc measurements and plasma measurements according to enzymatic methods is 0.94.[28,32] Furthermore, in healthy lean subjects daytime TGc profiles correlate to postprandial lipemia assessed by standardized oral fat loading tests.[29] In addition, daytime triglyceridemia estimated with 6 measurements was not different compared to hourly measurements, suggesting that these time points are representative for the daylong study period.[29]

Dietary Intake

Dietary intake and time of intake were accurately recorded in a diary. Quantities of intake were estimated according to instructions given by a dietician and according to a table with standardized portion sizes.[34] Eventual particularities, like illness, were also recorded. The diaries were evaluated by a trained physician together with each subject individually. Foods consumed were converted into nutrients with a release of the Dutch Nutrient Data Base.[36] Dietary intake was calculated as an average of 3 days. Mean absolute intake and intake as percentage of total energy intake were used for statistical analysis.

Analytical Methods

Fasting blood was collected at inclusion after a 12-hour fast for measurement of lipids, apolipoproteins, insulin, and glucose from plasma. Cholesterol and TG in plasma and HDL-C (obtained after precipitation with dextransulphate/$MgCl_2$) were determined using a Vitros 250 analyzer (Johnson & Johnson, Rochester, NY). Plasma apoB was measured by nephelometry using apoB monoclonal antibodies (Behring Diagnostics NV, Mannheim, Gerany, OSAN 14/15). Plasma glucose was measured by glucose oxidase dry chemistry (Vitros GLU slides) and colorimetry, and insulin was measured by competitive radioimmunoassay with polyclonal antibodies. Homeostasis model assessment (HOMA = glucose · insulin/22.5) was calculated as an overall estimate of insulin sensitivity. LDL-C was calculated using the Friedewald formula.

Statistical Analysis

Data are given as mean ± SD in tables and mean ± SEM in figures. Daytime TGc profiles were calculated as mean integrated area under the TGc curve (total daytime triglyceridemia; TGc-AUC). Incremental daytime triglyceridemia was calculated as delta TGc-AUC (dTGc-AUC), after correction for fasting TGc. All calculations for TGc-AUCs and diet were performed with averages of 2 or 3 days. Comparisons between both groups were performed with the independent Students' *t* test. In the case of TG, insulin, and HOMA index, calculations were performed after logarithmic transformation; however, untransformed concentrations are shown in text, tables, and figures. Pearson's correlation coefficients (2-tailed) were used to quantify associations between variables. All significantly correlated variables were used as independent variables in stepwise multiple regression analysis with TGc-AUC as the dependent variable. For this analysis, fasting TGc were used as baseline TG instead of plasma TG. For statistical analysis SPSS version 10.0 (SPSS Inc, Chicago, IL) was used. Calculations of TGc-AUCs were performed with GraphPad Prism version 3.0 for Windows (Graph Pad Software, San Diego, CA) using nonlogarithmic transformed TG concentrations. Statistical significance was reached when $P < .05$ (2-sided).

Table 1. General Characteristics of CAD Patients and Their First-Degree Relatives

	CAD Patients* (n = 27)	Relatives (n = 56)
Age (yr)	48 (8)†	41 (12)
Gender (M/F), n	17/10	27/29
BMI (kg/m^2)	25.3 (3.1)	25.2 (4.2)
Waist (cm)	92 (12)	91 (13)
Waist-to-hip ratio	0.93 (0.1)	0.89 (0.11)
Systolic BP (mm Hg)	131 (19)	124 (14)
Diastolic BP (mm Hg)	88 (12)†	82 (8)
Serum glucose (mmol/L)	5.4 (0.4)	5.3 (1.0)
Serum insulin (mU/L)	9.2 (3.9)	9.2 (4.3)
HOMA	2.24 (1.01)	2.27 (1.59)
Total cholesterol (mmol/L)	5.5 (0.7)	5.4 (1.0)
Plasma TG (mmol/L)	1.64 (0.99)†	1.22 (0.53)
HDL-C (mmol/L)	1.12 (0.27)†	1.28 (0.31)
ApoB (g/L)	1.02 (0.22)†	0.91 (0.21)

NOTE. Data are given as mean (±SD).
*CAD index patients were studied off lipid-lowering drugs.
†$P < .05$ compared to relatives.

RESULTS

General Characteristics

Twenty-seven normocholesterolemic CAD patients and 56 first-degree relatives without CAD were included. Of the 79 relatives originally invited to participate in the study, 63 visited our department (80% response). Four relatives from 3 different pedigrees were excluded from the analyses because they had a history of CAD. Three individuals were not able to measure daytime triglyceride profiles. Therefore, data from 56 relatives were available for full analysis. The data of CAD index subjects were obtained off lipid-lowering medication. Ten of 27 patients used beta-blockers. The general characteristics of the patients on and off beta-blockers were compared by a Student's *t* test. We did not find any significant differences for the lipid parameters (data not shown). Table 1 shows the mean baseline characteristics.

CAD patients were slightly older than the relatives. In addition, index patients were characterized by an increased diastolic

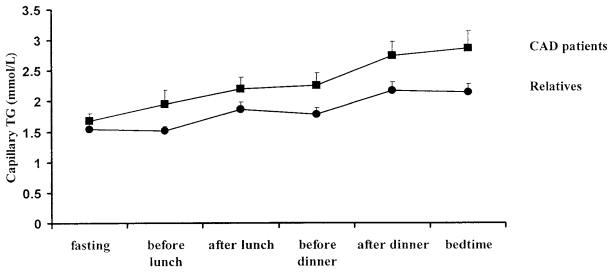

Fig 1. Mean (±SEM) daytime TGc at 6 different time points in CAD patients (■) and first-degree relatives (●).

blood pressure, increased fasting plasma TG levels, lower HDL-C, and increased apoB level compared to the relatives.

At the time of PTCA, 70% of the patients were smokers. At inclusion in this study, still 26% of CAD patients smoked. In the group of relatives, 41% were current smokers.

Daytime TG Profiles

Mean daytime TG profiles are given in Fig 1. Fasting TGc concentrations were similar between CAD patients (1.68 ± 0.63 mmol/L) and relatives (1.54 ± 0.71 mmol/L). There was a progressive increase in TGc concentrations in both groups during the day. The highest TG concentrations were reached at bedtime, namely, 2.86 ± 1.46 mmol/L in CAD patients and 2.14 ± 1.08 mmol/L in relatives ($P < .05$). The total daytime triglyceridemia calculated as TGc-AUC was higher in CAD patients (30.7 ± 13.6 mmol · h/L) compared to relatives (24.4 ± 9.4 mmol · h/L; $P < .05$), although fasting TGc levels were not significantly different (1.68 ± 0.63 mmol/L and 1.54 ± 0.71 mmol/L, respectively; Fig 1). The incremental TGc-AUC (dTGc-AUC) in index subjects (7.24 ± 7.41 mmol · h/L) was significantly higher compared to relatives (2.79 ± 6.89 mmol · h/L; $P < .05$).

Significant bivariate correlations were found between TGc-AUC and fasting TGc, systolic and diastolic blood pressure, HDL-C, apoB, waist circumference, HOMA, and age. Using stepwise multiple regression analysis, fasting TGc (standardized $\beta = 0.66$, $P < .001$), systolic blood pressure (standardized $\beta = 0.24$; $P = .001$), and HDL-C (standardized $\beta = -0.16$; $P = .03$) were the parameters included in the model, explaining 65% of the variation of TGc-AUC.

Dietary Intake

Dietary characteristics are given in Table 2. Total daily energy intake was lower in CAD patients compared to relatives ($P < .05$). The intake of total fat, saturated fat, and monounesterified fatty acids were significantly lower in CAD patients compared to relatives, but for these nutrients the intake as percentage of total energy intake was not significantly different between both groups. No statistically significant correlations were found between TGc-AUC and any of the nutrients shown in Table 2 (data not shown).

DISCUSSION

The present study shows that daytime triglyceridemia is elevated in non-obese, normocholesterolemic index patients with premature CAD compared to their first-degree relatives despite similar fasting TGc. The composition of the daily diet did not influence largely the daytime triglyceridemia, but significant correlations were found with other well-known variables like fasting TG, systolic blood pressure, and HDL-C. The current data confirm previous findings in strictly controlled metabolic ward conditions,[9-17] demonstrating that CAD patients have postprandial hyperlipidemia. We now show that postprandial hyperlipidemia in CAD occurs in a free-living situation when compared to non-CAD relatives sharing the similar diet and environmental conditions.

Nonfasting TG may be better predictors of CAD than fasting TG, as has been reported earlier.[8] Postprandial triglyceridemia is traditionally tested in metabolic wards as a response to high amounts of fat. However, atherosclerosis is a continuous process, which develops under daily circumstances, influenced by both genetic and environmental factors. In our laboratory, therefore, a novel method has been introduced for the evaluation of postprandial lipemia using repeated capillary self-measurements in an out-of-hospital situation.[26-30] Daytime triglyceridemia (TGc-AUC) is based on 6 TGc measurements, which are easily measured in an ambulant setting in contrast to plasma TG measurements. Daytime triglyceridemia reflects the TG load to which a subject is exposed during the day and correlates well to postprandial triglyceridemia.[29]

Since it is well known that postprandial triglyceridemia is closely associated to fasting TG levels, to features of the metabolic syndrome and to dietary intake, we were interested to what degree daytime triglyceridemia was dependent on these factors in a group of non-obese CAD patients and their first-degree relatives. It should be noted that fasting plasma TG were higher in CAD patients than in their relatives, which suggests a disturbance in the metabolism of TG-rich lipoproteins. Fasting TG may already suffice to detect patients with disturbed postprandial lipemia.[30]

Table 2. Mean Daily Intake in CAD Patients and First-Degree Relatives

	CAD Patients (n = 27)	Relatives (n = 56)
Total daily energy (kJ)	8451 (2122)*	9476 (1981)
Total fat (g)	74.8 (23.2)*	86.6 (25.3)
%TEI†	33.6 (5.4)	34.5 (6.5)
Saturated fat (g)	26.1 (7.8)*	31.4 (9.8)
%TEI	11.8 (2.3)	12.5 (2.8)
MUFA (g)	27.4 (8.8)*	33.8 (11.9)
%TEI	12.3 (2.2)	13.4 (3.7)
PUFA (g)	14.8 (6.8)	15.8 (4.9)
%TEI	6.6 (2.3)	6.4 (1.7)
Carbohydrates (g)	224.2 (65.2)	246.8 (59.4)
%TEI	45.1 (6.2)	44.5 (6.4)
Protein (g)	88.1 (21.9)	95.8 (21.4)
%TEI	18.0 (2.9)	17.4 (2.9)
Alcohol (g)	12.3 (14.0)	13.9 (20.0)
%TEI	4.2 (4.9)	4.2 (5.7)
Cholesterol (mg)	163.1 (66.6)	195.8 (85.8)

NOTE. Data are given as mean (±SD).

Abbreviations: %TEI, percentage of total energy intake; MUFA, monounesterified fatty acids; PUFA, poly unesterified fatty acids.

*$P < .05$ compared to relatives.

Fasting TG levels were strongly associated to daytime triglyceridemia, which is in concordance with earlier studies.[27-33] Fasting TG, systolic blood pressure, and HDL-C levels, all of which are features of the metabolic syndrome, were the best predictors of daytime triglyceridemia in both groups. Insulin sensitivity, as expressed by fasting insulin or HOMA levels, could not explain the differences in daytime triglyceridemia, possibly due to the limited number of subjects.

It is widely accepted that fasting TG are the single best predictors of postprandial lipemia.[28-31] However, the mean fasting TGc level was not statistically different between these normocholesterolemic CAD index patients and their relatives in contrast to the different fasting plasma TG. Fasting TGc were measured after a shorter period of fasting (8 to 10 hours) and not after a 12 hour overnight fast as was the case for plasma TG. In addition, the difference between fasting TGc and plasma TG may be explained by the fact that both measurements were performed on different days and TG are known to be highly variable within individuals.[31,35,36] Finally, fasting plasma TG were measured only once, whereas fasting TGc were measured on different days, which may have reduced the variability.

Self-reported dietary fat intake was lower in CAD patients compared to their relatives. However, incremental triglyceridemia is associated to the intake of carbohydrates and not to fat intake.[27] In addition, dietary intake was not correlated to daytime triglyceridemia and could therefore not explain the differences in TGc-AUC in patients and relatives, in this study. The importance of the diet on postprandial lipemia has been established by several investigators and also by our group using a similar methodology as described here.[27-29]

Daytime triglyceridemia, measured under physiological conditions, is increased in patients with premature atherosclerosis and normal fasting TG levels, when compared to their non-CAD relatives. This study confirms previous observations using standardized oral fat loading tests and underlines the importance of postprandial hyperlipidemia in CAD.

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