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(Citation)
Atherosclerosis,265:312-317

(Issue Date)
2017-10

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90004507

Atherosclerosis 265 (2017) 312–317

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The impact of serum trans fatty acids concentration on plaque vulnerability in patients with coronary artery disease: Assessment via optical coherence tomography

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ARTICLE INFO

Article history:
Received 1 March 2017
Received in revised form
18 June 2017
Accepted 27 June 2017
Available online 28 June 2017

Keywords:
Thin-cap fibroatheroma
Optical coherence tomography
Trans fatty acid

ABSTRACT

Background and aims: Recent epidemiological studies have showed that excessive intake of trans fatty acids (TFA) can be a residual risk for the development of coronary artery disease (CAD) even under medical management, including statins. This study aimed at investigating the association between lipid profile, including serum TFA concentration, and plaque vulnerability using optical coherence tomography (OCT).

Methods: The level of serum elaidic acid, a major TFA component, was measured using gas chromatography in 161 consecutively enrolled patients with CAD under guideline-directed risk factor management. OCT was performed to evaluate morphological features of angiographic intermediate stenosis (30% < diameter of stenosis <70%). OCT data were also used to measure lipid index (LI), defined as mean lipid arc multiplied by lipid length, and determine the presence of thin-cap fibroatheroma (TCFA), defined as a lipid-rich plaque with the smallest fibrous cap thickness <65 μm and the maximal arc >90°.

Results: Among 190 lesions assessed using OCT, 49 TCFAs were detected. In patients with at least one TCFA lesion, levels of elaidic acid (12.9 ± 4.9 *vs.* 10.3 ± 4.3 μmol/L, $p = 0.001$), triglycerides (169 ± 81 *vs.* 130 ± 60 mg/dL, $p = 0.005$), and remnant-like particle cholesterol (10.4 ± 6.5 *vs.* 7.7 ± 4.7 mg/dL, $p = 0.005$) were higher than in those without TCFAs. Generalized estimating equations identified elaidic acid level as the independent risk factor of TCFA. LI had a positive correlation with elaidic acid level ($r = 0.173$, $p = 0.025$).

Conclusions: TFA may affect plaque vulnerability in patients with CAD. Serum TFA concentration may represent another cardiovascular risk factor during conventional risk factor management.

1. Introduction

Trans fatty acids (TFA) are unsaturated fatty acids with at least one double bond in the trans configuration. Epidemiological studies have shown that excessive intake of TFA increases the risk of coronary artery disease (CAD) [1]. Thus, a 2% increase in energy intake from TFA increases the CAD risk by 23% [2]. Accordingly, increased dietary intake of TFA is considered to bear a much higher risk of CAD [3] and increase mortality in patients with CAD [4].

In patients with CAD, coronary plaques may evolve into

Abbreviations: TFA, trans fatty acid; OCT, optical coherence tomography; IVUS, intravascular ultrasound; TCFA, thin cap fibroatheroma; PCI, percutaneous coronary intervention; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; RLP, remnant-like particle; FCT, fibrous cap thickness; LI, lipid index; MLA, minimum lumen area; TLR, targeted lesion revascularization; TVR, targeted vessel revascularization; AMI, acute myocardial infarction; UAP, unstable angina pectoris; MACE, major adverse cardiac event.

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http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.922

vulnerable features that are prone to rupture or rapid progression. A thin-cap fibroatheroma (TCFA) is an atheroma with a thin (<65 μm) overlying fibrous cap heavily infiltrated by macrophages [5], it has been thought to be a main substrate of plaque rupture leading to acute coronary syndrome [6]. TCFAs can be detected with optical coherence tomography (OCT) [7].

Given the major impact of TFA consumption on CAD prevalence, it is reasonable to consider that TFA may modulate plaque morphology and CAD prognosis. Elaidic acid is the trans isomer of oleic acid, which is the main component of TFA from hydrogenated vegetable oils [1,8], which can be used as a measure of intestinally derived lipids since humans cannot synthesize TFA [8]. The aim of this study was to investigate the association between serum elaidic acid and the development of vulnerable lipid-rich plaque, including TCFA, using OCT in patients under management for conventional risk factors of CAD.

2. Patients and methods

2.1. Study population

One hundred sixty-one consecutive patients with CAD, who underwent OCT assessment for native plaque in the Kobe University Hospital from January 2010 to May 2015, were included (Fig. 1A). The inclusion criteria were as follows: 1) a history of percutaneous coronary intervention (PCI); 2) being under guideline-directed medical management; 3) presence of residual intermediate stenosis (diameter: 30–70%) in the native coronary tree. The exclusion criteria were: 1) serum creatinine level >1.5 mg/dL without hemodialysis; 2) anatomy unsuitable for OCT; 3) cardiogenic shock or decompensated heart failure; 4) concomitant inflammatory condition (such as active infection, inflammatory arthritis, or connective tissue disease) or malignancy; and 5) patients who received PCI at the time of follow-up OCT. Written informed consent was obtained from each patient prior to enrollment in this study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Review Committee at Kobe University (Japan).

2.2. Study protocol

On the admission day, blood sample analysis was performed to evaluate levels of creatinine, hemoglobin, glycated hemoglobin (HbA1c), and C-reactive protein (CRP). Levels of elaidic acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), remnant-like particle cholesterol (RLP), and fasting blood sugar (FSB) were measured on day 1 after fasting. Coronary angiography and OCT were performed on day 1. Angiographically intermediate lesions (diameter of stenosis: 30–70%) were evaluated by OCT.

2.3. Measurement of TFA concentration

Serum elaidic acid levels were measured at the Integrated Center for Mass Spectrometry of the Kobe University Graduate School of Medicine. Fatty acid methylation and purification were performed using commercial kits (Nacalai Tesque, Tokyo, Japan) according to the manufacturer's protocols. Nonadecanoic acid (C19:0) was used as an internal standard. Fatty acid methyl esters were analyzed using gas chromatography-mass spectrometry (GC-MS QP2010; Shimadzu, Kyoto, Japan). The capillary column used for fatty acid separation was SP-2650 (length: 100 m, inner diameter: 0.25 mm, membrane thickness: 0.20 μm, Sigma-Aldrich). The column temperature was maintained at 140 °C for 5 min and then increased gradually by 4 °C/min to 240 °C and maintained for 20 min. The sample was injected in the split mode with a split ratio of 1:5. Each fatty acid methyl ester was detected in the selected-ion monitoring mode. All results were normalized to the peak height of the C19:0 internal standard [8].

2.4. OCT imaging

Images were acquired using a commercially available frequency-domain OCT imaging system (ILUMIEN; St. Jude Medical Inc., St Paul, MN, USA). With this system, a 2.7-Fr OCT imaging catheter is advanced distally to the lesion, and automated pullback is initiated in concordance with blood clearance by the injection of contrast media. All images were de-identified and digitally stored.

2.5. OCT analysis

All OCT images were analyzed using an Off-line Review Workstation. The sites selected for analysis were cross-sections with the minimum lumen area and proximal and distal reference cross-sections. The proximal and distal references were defined as the sites with the largest lumen diameter within 10 mm proximally and distally to the regions with the smallest lumen area and before any side branch. Minimum lumen area (MLA) was measured at the site with the smallest lumen area, whereas the reference lumen area was measured at the reference cross-section. Largest reference lumen area was defined as the greater of the proximal and distal reference sites areas. Percent area stenosis was calculated as (largest reference lumen area − MLA)/largest reference lumen area × 100. Lesion length was defined as the region around the MLA where the lumen area was <50% of the largest reference lumen area [9,10].

Lipidic plaque was defined as a diffusely bordered, signal-poor region (lipid pools) (Supplementary Fig. 1) [11]. Lipid arc was measured at 1-mm intervals throughout the length of each lesion, and the values were averaged. Lipid length was also measured on the longitudinal view. Lipid index (LI) was defined as the mean lipid arc multiplied by lipid length [12].

Fibrous cap was defined as a signal-rich homogenous layer overlying a lipid-rich plaque [13]. The thinnest part of the fibrous cap was measured 3 times, and the fibrous cap thickness (FCT) was determined as the average value [14]. TCFA was defined as a lipid-rich plaque (>90°) overlaid with a thin fibrous cap (<65 μm) (Supplementary Fig. 2) [15].

Macrophage infiltration was defined as a high-intensity, signal-rich linear region with sharp attenuation. Microvessel was defined as a no-signal tubuloluminal structure without a connection to the vessel lumen recognized on > consecutive cross-sections. Cholesterol crystals were defined as thin, linear regions of high intensity.

A ruptured plaque was defined as a plaque with intimal tearing, disruption, or dissection of the cap (Supplementary Fig. 3). Upon injection of optically transparent crystalloid or radiocontrast media, these defects may have little or no OCT signal and may appear as cavities [9].

Calcification was also recorded when an area contained a signal-poor or heterogeneous region with a sharply delineated border (Supplementary Fig. 4) [9]. Calcification arc was measured at 1-mm intervals throughout the length of each lesion, and the values were averaged. Calcification length was also measured on the longitudinal view. As with LI, calcification index was defined as the mean calcification arc multiplied by the calcification length.

Intracoronary thrombus was defined as a mass (diameter ≥250 μm) attached to the luminal surface or floating within the lumen that had high backscattering and high attenuation (red [red blood cell-rich] thrombus) or that had lower backscattering and low attenuation and was homogeneous (white [platelet-rich]

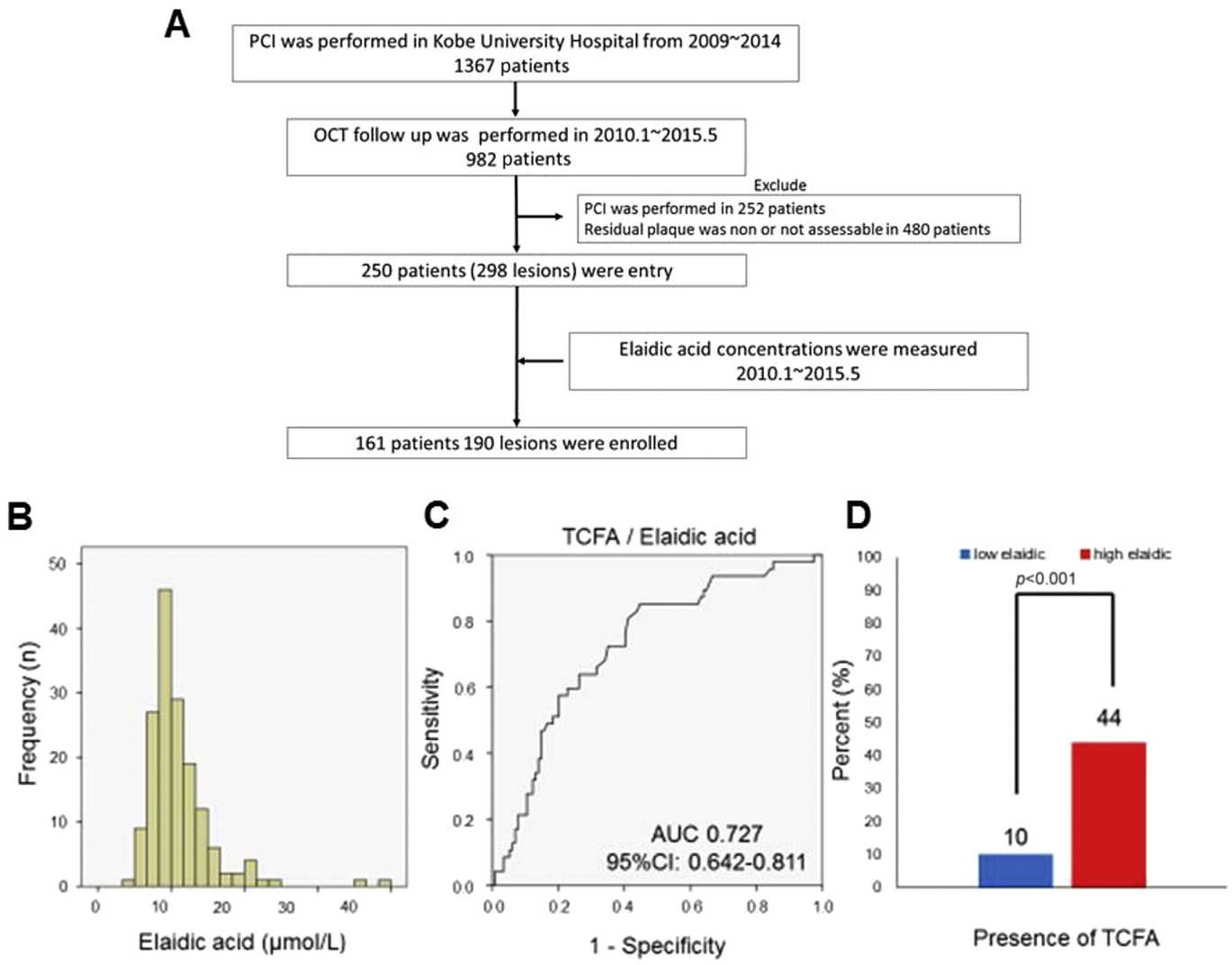

Fig. 1. Elaidic acid level and presence of thin-cap fibroatheroma (TCFA).
(A) Enrollment of study population. (B) Distribution of elaidic acid levels. (C) Receiver operating characteristic curve analysis of elaidic acid level predicting presence of TCFA. (D) Comparison of rates of TCFA presence in groups with elaidic acid levels below ("low elaidic") and above ("high elaidic") the cut-off value.

thrombus) [16].

Lipid arc, lipid length, LI, FCT, and the presence of TCFA were utilized as measures of plaque vulnerability. Inter- and intra-observer agreement in measurements of fibrous cap thickness and TCFA was assessed.

All OCT images were analyzed by 2 independent investigators (YN, HO) blinded to the angiographic and clinical findings using the Off-line Review Workstation. When discordance in terms of qualitative plaque morphology occurred between the observers, a consensus was reached with the assistance of a third investigator (TS). Intra-observer and inter-observer agreement in measurements of fibrous cap thickness was in the acceptable range (intra-class correlation coefficients: intra-observer, 0.977; inter-observer, 0.871), as well as the agreement in the detection of TCFA (intra-observer kappa = 0.904; inter-observer kappa = 0.878).

2.6. Clinical events

Long-term clinical outcome data (mean: 43.6 ± 20.9 months) were obtained from patient records or via telephone interviews. Targeted lesion revascularization (TLR), targeted vascular revascularization (TVR), non-TVR, myocardial infarction (MI), unstable angina pectoris (UAP), cardiac death, and major adverse cardiac events (MACEs) were recorded. MACE was defined as a composite of TLR, TVR, non-TVR, MI, UAP, and cardiac death. Deaths were considered cardiac-related unless an unequivocal non-cardiac cause could be established. MI was considered in cases where cardiac enzyme levels (troponin or myocardial band fraction of creatine kinase) were evaluated.

2.7. Statistical analysis

All statistical analyses were performed with SPSS Statistics 23.0 (IBM Corp., Somers, New York, USA). Categorical variables are expressed as numbers and percentage. Continuous variables are expressed as means ± standard deviations (SDs). Data were analyzed on a per-patient basis for clinical characteristics and on a per-stenosis basis for lesion morphology. Continuous variables were compared using an independent sample *t*-test. Pearson's Chi-square test was used to compare categorical variables. $p < 0.05$ was considered to indicate a statistically significant difference. Generalized estimating equations (GEE) were used to assess the effect of a

set of factors on TCFA. To evaluate collinearity between variables, we estimated the variance inflation factor (VIF). Univariate regression analysis was used to identify potential factors among patient characteristics, medications, and laboratory variables ($p < 0.05$). To evaluate collinearity between variables, we estimated the variance inflation factor (VIF). A VIF exceeding 10 indicated a strong possibility of collinearity, whereas a VIF >5 indicated a possibly of collinearity. Non-parametric Spearman's correlation test was used to evaluate associations between continuous variables. The sample size was estimated by analyzing results of a previous case-control study [17], in which TCFAs were detected in 21.6% of residual lesions after PCI by IVUS. We assumed that TCFAs would be detected in 36% of individuals in the high TFA group and 15% of individuals in the low TFA group. This would result in a 5% significance level at 80% probability for a sample size of 161 patients. To assess the inter-observer and intra-observer variability, results were compared using the kappa test of concordance for categorical data and intra-class correlation coefficients for continuous data. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Baseline patient characteristics

The baseline patient characteristics, medications, and laboratory data on admission are shown in Table 1. The study population was under adequate risk factor management, with 80% of the subjects receiving statin therapy. The average LDL-C level was 92 ± 27 mg/dL, and the average HbA1c level was 6.39 ± 1.00%. The distribution of elaidic acid level is shown in Fig. 1B. The maximum, minimum, and average serum levels of elaidic acid were 38.81 μmol/L, 4.91 μmol/L, and 11.04 ± 4.61 μmol/L, respectively.

3.2. Plaque characteristics obtained by OCT examination

A total of 190 intermediate stenosis lesions were identified in 161 patients. The plaque characteristics are shown in Table 2. Among the 190 lesions, 49 TCFAs were detected. Forty-seven patients (29%) had at least one TCFA.

3.3. Associations between TCFA and clinical and laboratory variables

All patients were divided into two groups according to the presence of at least one TCFA (TCFA(+) group and TCFA(−) group). There were no significant differences between the two groups in patient characteristics. According to the Chi-square test, the TCFA(+) group had significantly higher average levels of TG, RLP-C, and elaidic acid than the TCFA(−) group. There was no significant difference in LDL-C level (Table 3).

Univariate and multivariate analyses were performed to identify independent risk factors for the presence of TCFA (Table 4). The univariate regression analysis revealed significant associations with elaidic acid, TG, and RLP-C levels ($p < 0.05$). The estimated VIFs for elaidic acid *vs.* TG and RLP-C were 1.23 and 1.14, respectively, whereas the VIF for TG *vs.* RLP-C was 7.26. Since there was a possibility of collinearity between TG and RLP-C, we excluded RLP-C from the multivariate model. For all lesions, elaidic acid level was the independent predictor of TCFA after adjusting for TG, although the *p*-value did not reach the level of statistical significance. ($p = 0.088$).

Receiver operating characteristic (ROC) analysis revealed the best cut-off point for the serum level of elaidic acid to predict the presence of TCFA of 9.55 μmol/L, with 85.1% sensitivity and 55.3% specificity (area under curve: 0.727, $p < 0.001$) (Fig. 1C).

The study population was then divided into two groups according to the above cut-off value, with 71 patients assigned to the low elaidic acid group and the remaining 90 patients to the high elaidic acid group. The rate of presence of TCFA was 10% in the low elaidic acid group and 44% in the high elaidic acid group ($p < 0.001$). TCFAs were detected significantly more often among lesions from the high elaidic acid group (Fig. 1D). Clinical follow-up data revealed a significantly higher incidence of TVR in the high elaidic

Table 1
Patient characteristics and plaque morphology.

Patient characteristics	
Variables	n = 161
Patient characteristics	
Age, (years)	68 ± 10.4
Sex, male, n (%)	105 (65)
BMI	25.3 ± 4.9
Coronary risk factors	
Hypertension, n (%)	126 (78)
Dyslipidemia, n (%)	119 (74)
Diabetes, n (%)	84 (52)
Smoking, n (%)	98 (61)
Family history, n (%)	35 (22)
Medication	
Statins, n (%)	129 (80)
Ezetimibe, n (%)	7 (4)
EPA, n (%)	11 (7)
Laboratory data	
Cr, mg/dL	1.14 ± 1.2
Hb, mg/dL	13.3 ± 1.7
CRP, mg/dL	0.14 ± 0.36
FBS, mg/dL	109 ± 34.0
HbA1c, %	6.39 ± 1.0
Total cholesterol, mg/dL	160 ± 32
LDL-C, mg/dL	92 ± 27
HDL-C, mg/dL	48 ± 16
TG, mg/dL	141 ± 69
RLP-C, mg/dL	8.5 ± 5.4
Elaidic acid, μmol/L	11.0 ± 4.6
Plaque morphology by OCT	
Variables	n = 190
Minimum lumen area (mm^2)	3.6 ± 2.4
Proximal reference lumen area (mm^2)	6.3 ± 2.9
Distal reference lumen area (mm^2)	4.7 ± 2.7
Largest reference lumen area (mm^2)	7.9 ± 3.5
Percent area stenosis (%)	49 ± 21
Lesion length (mm)	10.8 ± 6.9
Lipid-rich plaque, n (%)	143 (76)
TCFA, n (%)	49 (25)
Ruptured plaque, n (%)	3 (2)
Lipid length (mm)	7.0 ± 5.5
Lipid max arc (°)	175 ± 82
Lipid mean arc (°)	120 ± 55
Lipid index	1049 ± 912
Fibrous cap thickness (mm)	0.11 ± 0.05
Calcified plaque, n (%)	115 (62)
Calcium length (mm)	5.0 ± 5.3
Calcium mean arc (°)	84 ± 62
Calcification index	507 ± 936
Macrophage infiltration	110 (58)
Microvessels	32 (17)
Cholesterol crystals	8 (4)

BMI, body mass index; EPA, eicosapentaenoic acid; CRP, C-reactive protein; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; RLP-C, remnant-like particle cholesterol; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma.
Values are presented as mean ± SD or absolute numbers (%).

Table 2
Associations between TCFA and patient characteristics.

Patient characteristics *vs.* presence of TCFA			
Variables	TCFA(+) (n = 47)	TCFA(−) (n = 114)	*p*-value
Patient characteristics			
Age, (years)	69.6 ± 10.5[a]	67.9 ± 10.5	0.337
Sex, male, n (%)	27 (57)	78 (68)	0.184
BMI	25.5 ± 3.6	25.3 ± 5.3	0.822
Coronary risk factors			
Hypertension, n (%)	38 (81)	88 (77)	0.609
Dyslipidemia, n (%)	33 (70)	86 (75)	0.492
Diabetes, n (%)	23 (49)	61 (54)	0.597
Smoking, n (%)	26 (55)	72 (63)	0.354
Family history, n (%)	9 (19)	26 (23)	0.642
Medications			
Statins, n (%)	37 (79)	92 (81)	0.775
Ezetimibe, n (%)	3 (6)	4 (4)	0.333
EPA, n (%)	6 (13)	5 (4)	0.063
Laboratory data			
Cr, mg/dL	1.03 ± 0.54	1.19 ± 1.33	0.420
Hb, mg/dL	13.4 ± 1.9	13.3 ± 1.6	0.771
CRP, mg/dL	0.19 ± 0.52	0.11 ± 0.27	0.263
FBS, mg/dL	115 ± 43	106 ± 29	0.187
HbA1c, %	6.5 ± 1.0	6.3 ± 1.0	0.319
Total cholesterol, mg/dL	167 ± 38	159 ± 29	0.147
LDL-C, mg/dL	92 ± 33	92 ± 25	0.889
HDL-C, mg/dL	50 ± 19	48 ± 14	0.450
TG, mg/dL	169 ± 81	130 ± 60	0.005
RLP-C, mg/dL	10.4 ± 6.5	7.7 ± 4.7	0.005
Elaidic acid, μmol/L	12.9 ± 4.9	10.3 ± 4.3	0.001

Logistic regression analysis of risk factors of TCFA						
Variables	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*- value
Elaidic acid	1.14	1.009–1.278	0.035	1.12	0.984–1.287	0.088
TG	1.01	1.001–1.012	0.027			
RLP-C	1.07	1.006–1.146	0.032			

TCFA, thin cap fibroatheroma; HbA1c, glycated hemoglobin; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; RLP-C, remnant-like particle cholesterol; FBS, fasting blood sugar; CI, confidence interval; OR, odds ratio.
[a] Values are presented as mean ± SD or absolute numbers (%).

Table 3
Associations between elaidic acid concentration and cardiac events.

Variables	High elaidic acid (n = 90)	Low elaidic acid (n = 71)	*p*-value
TLR, n (%)	4 (4)[a]	1 (1)	0.266
TVR, n (%)	16 (18)	4 (6)	0.022
Non-TVR, n (%)	16 (18)	12 (17)	0.884
AMI, n (%)	4 (4)	2 (3)	0.458
UAP, n (%)	6 (7)	2 (3)	0.230
Cardiac death, n (%)	1 (1)	0 (0)	0.559
MACE, n (%)	28 (31)	16 (23)	0.225

TLR, targeted lesion revascularization; TVR, targeted vessel revascularization; AMI, acute myocardial infarction; UAP, unstable angina pectoris; MACE, major adverse cardiac event.
[a] Values are presented as absolute numbers (%).

acid group (Table 3).

3.4. Associations between elaidic acid level and OCT variables

Relationships between elaidic acid level and OCT variables associated with lipid plaque were tested by non-parametric Spearman's correlation test (Table 4). The following OCT parameters were correlated with elaidic acid level: FCT (Spearman's correlation coefficient (r) = -0.320, $p < 0.000$), lipid maximum arc (r = 0.153, $p = 0.046$), lipid mean arc (r = 0.237, $p = 0.002$), LI (r = 0.173, $p = 0.025$), macrophage infiltration (r = 0.223, $p = 0.002$), and cholesterol crystals (r = 0.242, $p = 0.001$). These results showed that elaidic acid level was associated with plaque volume and fibrous cap thickness, which are discriminators of plaque vulnerability.

Table 4
Relationships between elaidic acid level and lipid plaque variables determined by OCT evaluated with Spearman's correlation test.

Variables	r	*p*-value
Minimum lumen area (mm^2)	−0.220	0.774
Percent area stenosis (%)	−0.030	0.693
Lipid length (mm)	0.085	0.262
Lipid max arc (°)	0.153	0.046
Lipid mean arc (°)	0.237	0.002
Lipid index	0.173	0.025
Fibrous cap thickness (mm)	−0.320	<0.001
Macrophage infiltration	0.223	0.002
Microvessels	0.076	0.297
Cholesterol crystals	0.242	0.001

OCT, optical coherence tomography.

4. Discussion

TFA are known to affect lipoprotein metabolism. They worsen plasma lipid profile by increasing LDL-C and TG levels and reducing the level of HDL-C [18,19]. Beyond the lipid profile, it has been postulated that TFA are associated with systemic inflammation and endothelial dysfunction [20,21].

In this study population, LDL-C, HDL-C, HbA1c, and CRP levels were efficiently controlled, with no significant differences between the TCFA and non-TCFA groups. In contrast, the levels of exogenously derived lipids such as TG, RLP-C, and elaidic acid were significantly higher in the TCFA group than in the non-TCFA group. This suggests that exogenously derived lipids may carry a residual risk in secondary prevention. In agreement, our multivariate analysis identified elaidic acid level as an independent risk factor of TCFA. TFA are a component of TG and phospholipids in remnant lipoprotein particles, and the serum TFA level correlates with the exogenous lipid levels [8]. In this context, the present findings suggest that elaidic acid directly impacts the formation of TCFA irrespectively of serum LDL-C and TG levels. The OCT analysis showed that elaidic acid level correlated with FCT, lipid max arc, lipid mean arc, and LI. These parameters are discriminators of plaque vulnerability. Elaidic acid may contribute to an increased plaque instability.

The “beyond lipids effects” of TFA may be related to its role in the arterial wall. During inflammatory processes, macrophages and foam cells in the arterial wall secrete pro-inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which increase local inflammation and contribute to lesion progression. Vulnerable plaques have thinner fibrous caps, resulting in heavy infiltration by macrophages and reduced smooth muscle cells configuration and extracellular matrix synthesis. Several hypotheses explain these changes. Kondo et al. [22] suggested that TFA affect toll-like receptors 2/4, activating nuclear factor-kappa B (NF-κB). This signal induces inflammatory response and thrombogenic processes. In the endothelial cells, TFA activate NF-κB and impair NO production, which leads to increased levels of IL-6 and reactive oxygen species [23]. Progression of atherosclerosis is also

accelerated by apoptosis of endothelial cells, whose early and late stages have been suggested to be stimulated by elaidic acid in a dose-dependent manner [24]. These mechanisms may increase the vulnerability of lipid plaques.

Our findings suggest that elaidic acid participates in plaque destabilization. Although this speculation requires validation, it is likely that elaidic acid level may be an indicator of plaque vulnerability.

This study has several limitations. First, this was a cross-sectional study rather than a prospective study with longitudinal follow-up. It is unknown whether the relationship between TFA level and plaque vulnerability is causal. Second, culprit lesions were not included in this study. Finally, we did not investigate whether elaidic acid levels predict clinical outcomes and whether TCFA could lead to ACS. Future longitudinal and prospective studies are needed to address these issues.

In conclusion, serum level of elaidic acid was associated with the presence of TCFA in patients with CAD receiving conventional lipid-lowering therapy. Excessive intake of TFA may represent a residual risk for CAD development, making TFA a novel therapeutic target for secondary prevention.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

This work was supported by Grants-In-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (project ID: 14470510) and by Grants-in-Aid from the Cabinet Office Food Safety Commission of Japan.

Author contribution

Yoshinori Nagasawa designed the study, collected data, analyzed data, and wrote the manuscript. Toshiro Shinke, Tatsuro Ishida, and Ryuji Toh provided technical support, designed the study, wrote the manuscript, and supervised the study. Hiromasa Otake and Tomofumi Takaya provided technical support. Daisuke Sugiyama provided statistical support. Takayosi Toba, Masaru Kuroda, Hachidai Takahashi, Daisuke Terashita, Natsuko Tahara, Yuto Shinkura, Kenzo Uzu, Daiji Kashiwagi, Koji Kuroda, Yuichiro Nagano, Hiroyuki Yamamoto, Kenichi Yanaka, and Yoshiro Tsukiyama collected data. Ken-ichi Hirata provided logistic support, designed and supervised the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.922.

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