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Significance of Trans Fatty Acids and Omega-3 Fatty Acids in Japanese Men with Coronary Heart Disease

Shinji Koba, Tetsuya Takao, Fumiko Shimizu, Mutsumi Ogawa, Yuuya Yokota, Fumiyoshi Tsunoda, Ken Arai, Toshiro Shinke and Akikazu Takada

Abstract

Trans fatty acids (TFA) are found naturally in ruminant foods (R-TFA) by biohydrogenation in ruminant animals or industrially produced oils (IP-TFA) by partial hydrogenation of vegetable or fish oils. The intake of TFA mainly IP-TFA is associated with an elevated risk of coronary heart disease (CHD), while some prospective cohort studies showed that R-TFA were associated with a lower risk for sudden cardiac death (SCD). Our case-control study showed that *trans*-C18:2 isomers (IP-TFA) were significantly higher, and palmitelaidic acid (R-TFA) levels were lower in patients with acute coronary syndrome (ACS) compared with healthy men. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have different effects on cardiometabolic risk factors. Delta-5 desaturase (D5D) is a key enzyme in the conversion of linoleic acid and alpha-linolenic acid to arachidonic acid (AA) and EPA, respectively. Previous studies reported that low D5D estimated from the ratio of AA to dihomo-gamma linolenic acid predicts the incident cardiovascular disease. In our cross-sectional study with 436 men with ACS, various atherogenic lipid markers such as small dense LDL cholesterol and malondialdehyde-modified LDL were significantly inversely associated with D5D activity. We found that the EPA/AA may be a superior risk marker than DHA/AA in terms of correlation with atherogenic lipid profiles.

Keywords: trans fatty acid, omega-3 fatty acids, delta-5 desaturase, coronary heart disease

1. Introduction

Fatty acids (FA) are biologically active molecules with a wide array of effects [1]. FA are classified as saturated or unsaturated on the basis of the absence or presence of double bonds. Monounsaturated FA (MUFA) have one double bond; polyunsaturated FA (PUFA) have more than one double bond. UFA usually occur in the *cis* configuration, and *trans* FA (TFA) are UFA containing at least one double bond in the *trans* configuration. FA status can be expressed as composition

(each as a percent of total) or as concentration (mass/volume or cell count). PUFA with double bonds starting from the sixth position from the methyl end of FA are termed as omega-6 series and those from the third position as omega-3 series. Both omega-3 and omega-6 long-chain PUFA are particularly important in humans in order to maintain the function of brain and central nervous system. These PUFA are incorporated into the cell membrane. Numerous studies have demonstrated that, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 PUFA which are present in fish oils, protect against coronary heart disease (CHD) [2]. Harris and von Schacky proposed a metric called the "Omega-3 index," which is the content of EPA + DHA in red blood cell (RBC) membranes (expressed as a weight percent of total FA) as a risk factor for death from CHD and especially sudden cardiac death (SCD) [3]. The Omega-3 index is highly responsive to changes in EPA + DHA intake and the levels in RBCs reflect those of other tissues [4]. The Omega-3 index has been used in multiple observational cohort and interventional studies around the world. It has been associated with the lower risk for CHD, SCD, acute coronary syndromes (ACS), all-cause mortality, and other health conditions such as impaired cognitive function, depression, aggressive behaviors, and bipolar disease [4]. EPA and DHA are usually considered as good friends for cardiovascular health, whereas arachidonic acid (AA), omega-6 PUFA, is the most important substrate for the synthesis of the strongest pro-inflammatory eicosanoids. However, in recent years, the complex biochemistry of the eicosanoids, docosanoids, and octadecanoids has become clearer, with some omega-6 PUFA metabolites being pro- and others anti-inflammatory [5, 6]. According to a meta-analysis of prospective cohort studies investigating plasma FA (palmitic, oleic, EPA, DHA, and AA) and CHD outcome, relative risk and 95% of confidence interval (CI) for CHD for these five FAs was, respectively, 1.15 (CI 0.96–1.37), 1.09 (CI 0.97–1.23), 0.78 (CI 0.65–0.94), 0.79 (CI 0.67–0.93), and 0.83 (CI 0.74–0.92), which suggest the statistically significant protective associations with EPA, DHA, and AA [7].

TFA can be found naturally in ruminant foods (R-TFA) by biohydrogenation in ruminant animals or industrially produced oils (IP-TFA) by partial hydrogenation of vegetable or fish oils. TFA were, initially, considered as safe, and partially hydrogenated oils (PHO) were responsible for high intakes in the 1970s to 1980s, when margarines were advocated over butter to reduce SFA intakes [8]. PHO are contained in hard margarine, fatty spreads, and vegetable shortening, deep-fried food, refined vegetable oils such as salad oil, and confectionery made using these products [9]. Since the early 1990s, however, numerous studies have suggested that high TFA intakes may be associated with CHD [10]. Cohort studies and their meta-analyses provide concordant evidence that the intake of TFA mainly IP-TFA is associated with the elevated risk of CHD [9]. In this chapter, we would like to focus on the role of TFA and omega-3 PUFA with special relation on their effects on blood lipids and CHD.

2. IP-TFA and RP-TFA on human health

There is a considerable overlap of TFA in IP-TFA and R-TFA (**Figure 1**) [11]. For fatty acids with 18 carbon atoms, a peak concentration of trans double bonds in IP-TFA is found in position 9, as elaidic acid, while a distinct preference for the double bond in R-TFA is in position 11.

Numerous studies have suggested that IP-TFA increase LDL cholesterol (LDL-C) and lipoprotein (a) [Lp(a)], which is a lipoprotein that promotes atherosclerosis and decrease HDL cholesterol (HDL-C), compared with other FA, whereas the effect on triglyceride is inconsistent [9, 12]. However, the threshold of effects of

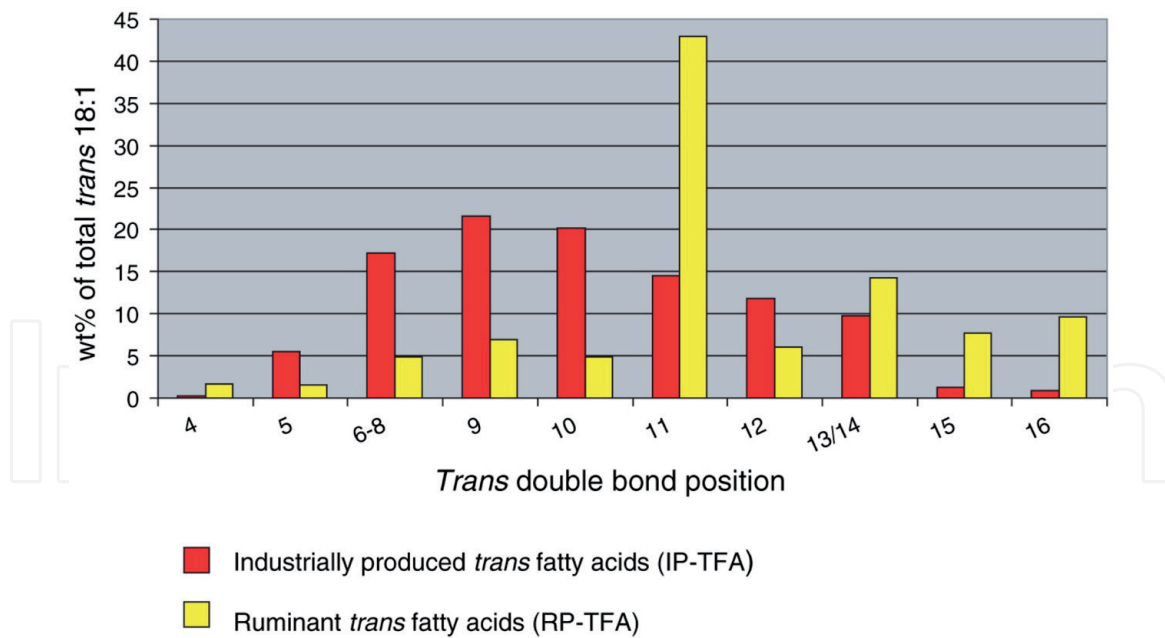


Figure 1. Isomeric distribution of trans-octadecenoic acids in industrially produced and ruminant trans fatty acids (mean wt% of trans-18:1 fatty acids) adapted from [11].

TFA may exist in the relationship between TFA and lipid levels, and direct evidence of the dose-response relations were not observed from clinical trials when the dietary intake of TFAs was as low as <3%E [9, 10]. The consumption of TFA is currently decreasing in many countries. The average daily TFA intake of the Japanese is 0.92–0.96 g, or 0.44–0.47%E, which is lower than the <1% target recommended by the World Health Organization [9].

The Seven Countries Study (United States (US), Finland, the Netherlands, Italy, Yugoslavia, Greece, and Japan) that was initiated in 1958 was the first to show true differences in prevalence, incidence, and mortality for CHD among populations with different geographical, ethnic, and cultural characteristics. The study reported that the intake of elaidic acids, the major IP-TFA, was strongly associated with the intake of SFA, serum levels of total cholesterol, and 25-year CHD mortality rates [13]. The cross-sectional study of Japanese patients undergoing coronary angiography (CAG) that was conducted from 2008 to 2012 failed to show the differences in levels of elaidic acid and linoelaidic acids (the two major IP-TFA, although the latter can be formed by frying in nonhydrogenated vegetable oils [14]) between patients with and without CHD [15]. They showed significantly higher elaidic acid levels in younger patients with CHD (≤ 66 years) compared with elder CHD patients and/or patients with metabolic syndrome compared with patients without metabolic syndrome [15]. Their group also reported that serum levels of elaidic acids were significantly higher in CHD patients with vulnerable plaque evaluated by optical coherence tomography compared with those without it (12.9 ± 4.9 vs. 10.3 ± 4.3 $\mu\text{mol/L}$, respectively, $p = 0.001$) [16]. Our case-control study with 66 male patients with ACS and 49 healthy men, which was conducted from 2013 to 2014, has reported that total FA and TFA levels were similar between ACS and control subjects [17]. Palmitelaidic acid, R-TFA, levels were lower in ACS patients, especially in middle-aged ACS patients (0.17 ± 0.06 vs. 0.20 ± 0.06 of total FA, in ACS and control, respectively, $p < 0.01$) (Figure 2). Both proportional and absolute concentrations of palmitelaidic acid were significantly directly associated with HDL-C ($\rho = 0.269$ and $\rho = 0.216$, respectively), EPA + DHA ($\rho = 0.458$ and $\rho = 0.620$, respectively), and EPA + DHA/AA ratios ($\rho = 0.474$ and $\rho = 0.475$, respectively). Linoleic trans isomers (total C18:2 TFA), (IP- or frying-derived TFA)

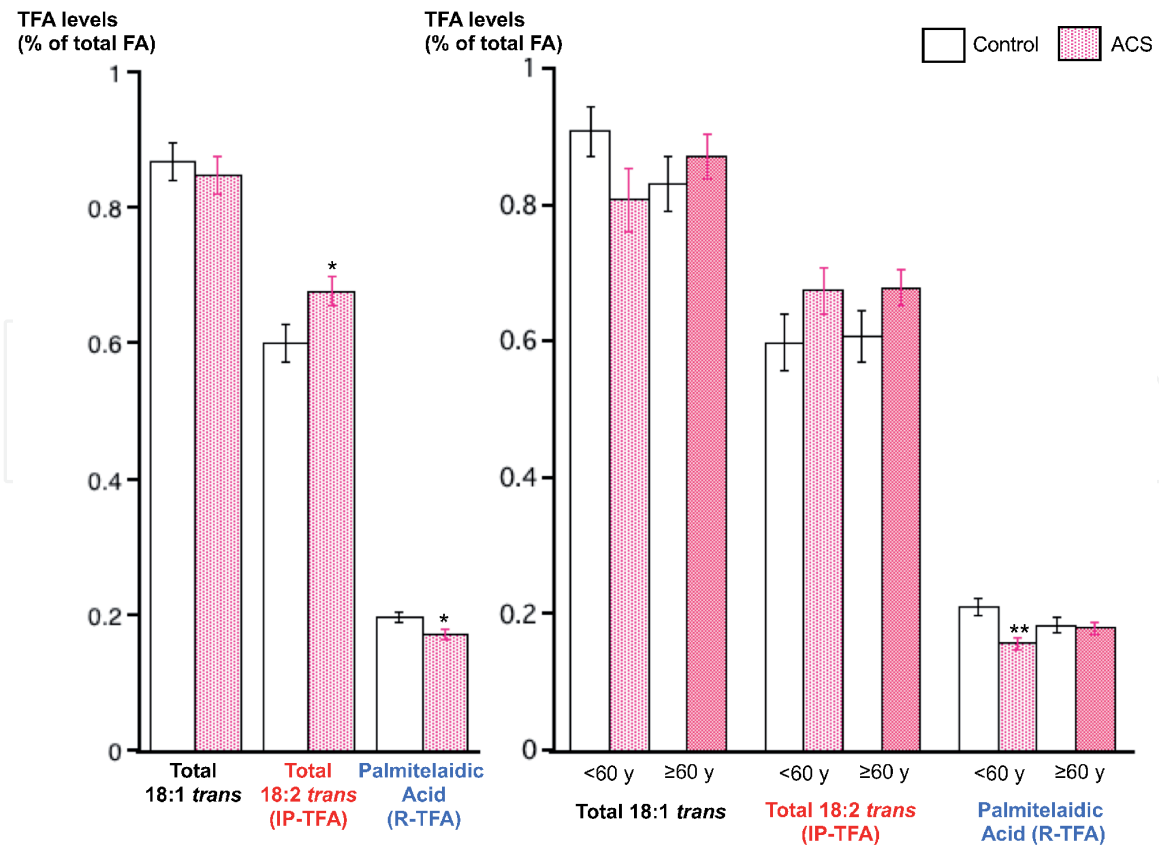


Figure 2.

The comparison of trans fatty acids (TFA) between control and ACS patients. Left panel: comparison in whole subjects and Right panel: comparison separated by age. Data are expressed as mean \pm standard error (SE), and the error bar represents SE. The number of subjects is 49 (<60 years 24; \geq 60 years 25) in control and 67 (<60 years 25; \geq 60 years 42) in ACS. * $P < 0.05$, ** $p < 0.01$ vs. control. Figure was made by Ref. [17].

were significantly higher in ACS patients (0.68 ± 0.17 vs. 0.60 ± 0.20 of total FA, in ACS and control, respectively) (Figure 2). Absolute concentration of *trans*-C18:2 isomers were significantly directly associated with LDL-C and non-HDL-C in ACS men. In conclusion of our case-control study, total *trans*-C18:1 isomers were comparable between ACS and control [17]. Differences between ACS and controls in C18:1 trans varied by specific C18:1 trans species [17]. Palmitelaidic acid (R-TFA) was lower in ACS patients, especially in middle-aged patients. Palmitelaidic acid was significantly directly associated with HDL-C, EPA + DHA, and EPA + DHA/AA ratios [17]. Linoleic trans isomers (IP-TFAs) were higher in ACS.

The Nurses' Health Study was initiated in 1976 and enrolled 121,799 female registered nurses aged 30–55 years in the United States. TFA content in RBC membrane was measured in 32,826 women from 1989 to 1990. During 6 years of follow-up, 166 incident cases of CHD were ascertained and matched with 327 controls. TFA in RBC membrane was significantly correlated with dietary intake of TFA (correlation coefficient = 0.44, $p < 0.01$). Increases in total TFA, *trans*-C18:1 isomers, and *trans*-C18:2 isomers in RBC membrane were significantly associated with CHD after adjustment of covariates [18]. In the Cardiovascular Health Study, a prospective cohort of older US adults (≥ 65 years), plasma phospholipid TFA was measured in 5888 men and women from 1992 to 1993. Plasma TFA was compared between 214 cases of fatal CHD and 214 matched controls. Neither plasma *trans*-C18:1 isomers nor palmitelaidic acids but linoelaidic acid (*trans*-C18:2 isomers) were significantly associated with fatal CHD [19]. During 31,494 person-years, 1735 total deaths and 639 fatal and nonfatal CHD events occurred. Neither plasma *trans*-C18:1 isomers nor palmitelaidic acids but linoelaidic acid (*trans*-C18:2 isomers) were significantly associated with total mortality mainly due to the cardiovascular disease (CVD) and

increased risk of CHD [20]. Lemaitre et al. measured TFA in RBC membrane in 179 married cases of out-of-hospital primary cardiac arrest between the ages of 25 and 74 years, from 1998 to 1999, and 285 age- and sex-matched controls from the population-based study [21]. Not *trans*-C18:1 isomers but linoelaidic acid (*trans*-C18:2 isomers) were associated with three-fold increase in risk of primary cardiac arrest after adjustment for medical and lifestyle risk factors (odds ratio for interquintile range, 3.1; 95% CI: 1.7–5.4). In the Bergen Coronary Angiography Cohort (BECAC), serum TFA (palmitelaidic acid, an R-TFA; and *trans* C18:1 isomers; primarily IP-TFA) were measured in 1367 Norwegian patients underwent CAG for suspected CHD during 2000–2001 who were followed throughout 2006 [22]. The serum TFA was positively correlated with plasma levels of the NO inhibitor asymmetric dimethylarginine (ADMA). They reported that there are no significant associations between serum TFA and incident acute myocardial infarction (AMI), death from CVD, and all-cause mortality after multivariate adjustments during the median of 5.8 years of follow-up [22].

Lemaitre et al. confirmed a correlation between TFA content (C16:1, C18:1, and C18:2 isomers) in subcutaneous adipose tissue and estimated TFA intake using a self-administered food frequency questionnaire in 51 adult volunteers in 1996 [23]. After adjustment for energy intake, age, and body mass index, the correlation coefficients between total TFA and TFA intake were 0.76 (95% CI: 0.51–0.89) among men and 0.52 (95% CI: 0.17–0.75) among women [23]. A case-control study in the United Kingdom compared TFA (*trans*-C18:1 and C18:2 isomers) in abdominal adipose tissue obtained by necropsy from 66 cases of SCD due to the first episode of CHD ages of <65 years from 1990 to 1991 and by biopsy from 286 healthy age- and sex-matched controls [24]. Not linoelaidic acid (*trans*-C18:2 isomers) but *trans*-oleic acid (*trans*-C18:1 isomers) were unexpectedly inversely associated with SCD. In an international multicenter study in eight European countries and Israel (EURAMIC), adipose tissue aspiration samples were obtained from 671 men with AMI, aged of ≤ 70 years, and 717 men without a history of AMI as control from 1991 to 1992. The *trans*-oleic acid (*trans*-C18:1 isomers) were similar between AMI and controls [25]. A case-control study in Norway compared subcutaneous adipose tissue TFA between 100 patients with the first episode of AMI and 98 population controls, both men and postmenopausal women aged between 45 and 75 years [26]. TFA mainly *trans*-oleic acid (*trans*-C18:1 isomers) was significantly higher in AMI than those in control [26]. A case-control study in Costa Rican population compared adipose tissue TFA between 482 cases aged <75 years with the first episode of nonfatal AMI during 1994 and 482 population controls adjusted for sex, age, and area of residence [27]. Not *trans*-C18:1 isomers but high *trans*-C18:2 isomers were significantly associated with the increased risk of nonfatal AMI [27]. We found that not *trans*-C18:1 isomers but *trans*-C18:2 isomers (IP-TFA) were associated with the increased risk of ACS even in Japan [17] that was in good agreement with previous reports [18–21, 27].

A 2010 survey of the Hawaii-Los Angeles-Hiroshima Study reported that serum elaidic acid concentrations in the native Japanese living in Hiroshima were significantly lower than those in the Japanese-Americans living in Los Angeles [28]. The study reported a significant association between serum levels of elaidic acid and insulin resistance or diabetes among native Japanese [28]. Similarly, our study with Japanese and American older men (> age 50) showed that Japanese men had markedly lower levels of elaidic and linoelaidic acids (IP-TFA) while significantly higher levels of palmitelaidic acids (R-TFA), compared with American men [29].

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study, a prospective cohort study of 3259 Caucasians hospitalized for CAG between 1997 and 2000 in southwestern Germany, was the first to show that higher levels of palmitelaidic

acids (R-TFA) in RBC membranes were associated with the lower risk for SCD during a median of 10 years of follow-up (**Figure 3**) and that three *trans* isomers of C18:2n6 (IP-TFA) were not related to fatal cardiovascular outcomes [30]. Total TFA levels in LURIC patients (mean 0.96%) were much lower than those in US cohorts in the 1990s [31]. According to the TRANSFAIR study, a cross-sectional investigation in eight countries in Europe, TFA intake is below 1%E and 79% of TFA intake was derived from milk and ruminant fat in Germany [32]. Some prospective cohort studies showed that R-TFA were associated with the lower risk for incident diabetes. In the Cardiovascular Health Study, a prospective cohort study comprising elder US adults from 1989 to 1990 from Medicare eligibility lists, plasma phospholipid FA were measured in 3736 adults in 1992 [33]. Higher *trans*-palmitoleate levels were associated with slightly lower adiposity and, independently, with higher HDL-C levels (1.9% across quintiles; $P = 0.040$), lower triglyceride levels (-19.0%; $P < 0.001$), a lower total cholesterol/HDL-C ratio (-4.7%; $P < 0.001$), lower C-reactive protein levels (-13.8%; $P < 0.05$), and lower insulin resistance (-16.7%, $P < 0.001$). *Trans*-palmitoleate was also associated with a substantially lower incidence of diabetes, with multivariate hazard ratios of 0.41 (95% CI, 0.27 to 0.64) and 0.38 (CI, 0.24 to 0.62) in quintiles 4 and 5 versus quintile 1 (P for trend < 0.001) [33]. In the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort of white, black, Hispanic, and Chinese Americans, plasma phospholipid FA and metabolic risk factors were measured in 2000–2002 in 2281 participants free of baseline diabetes [34]. They prospectively assessed the risk of new-onset diabetes (205 cases) from baseline to 2005–2007 [34]. Circulating *trans*-palmitoleate is associated with higher LDL-C but also with lower triglycerides, fasting insulin, blood pressure, and incident diabetes [34]. Large genome-wide association studies have not identified any significant genetic determinants of circulating palmitelaidic acid (C16:1 n7t) levels

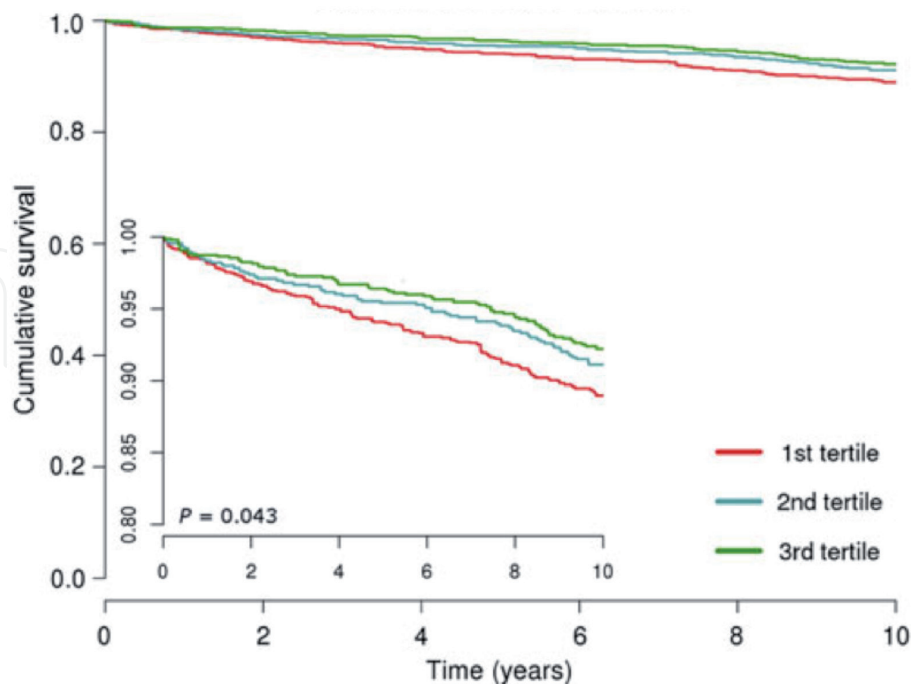


Figure 3.

Adjusted survival curves for sudden cardiac death. Tertiles of palmitelaidic acid (C16:1n7t) were balanced for body mass index, LDL-C, HDL-C, log-Triglyceride, log-fibrinogen, smoking, hypertension, diabetes, lipid-lowering therapy, and estimated glomerular filtration rate by inverse variance weighting. The inset shows the same data on a truncated y axis. Hazard ratios (95% confidence interval) for the second and third tertile compared with the first tertile were 0.82 (0.61–1.12) and 0.67 (0.48–0.93), respectively. The p -value of the robust score test was 0.043. Reproduced from [30].

in RBC or plasma phospholipids [35], suggesting that strong endogenous influences are not present [31].

According to these findings, dietary intake of R-TFA may be cardioprotective, contrary to IP-TFA. Further controlled studies are required to answer the questions how a high amount of R-TFA affects human health.

3. Omega-3 fatty acids and CHD

Numerous studies have demonstrated that omega-3 PUFA protect against CVD, and the ratios of serum levels of EPA and DHA to AA, omega-6 PUFA have been recognized as promising risk markers for CHD [2, 36]. Our case-control study showed that the ACS patients had significantly higher levels of saturated FA, mainly myristic and palmitic acids, and MUFA, mainly oleic acid, and lower levels of omega-3 PUFA, mainly EPA and DHA, and AA, omega-6 PUFA (**Figure 4**) [17]. The Japanese dietary style has markedly changed from the 1960s, and fish to meat ratios in food consumption are decreasing in the younger generation, while the ratios in the Western countries stayed the same or slightly increased [37]. The age profile of the fish/meat >1.0 was ≥ 40 years in 2000, ≥ 50 years in 2005 and 2010, and ≥ 60 years in 2015 in Japan. The EPA plus DHA to AA ratios were significantly lower in ACS patients and were further lower in ACS patients <60 years old (**Figure 4**) [17].

PUFA levels depend on dietary intake, bioavailability, and PUFA metabolism. In the biosynthesis of long chain PUFA from precursor PUFA, the crucial enzymes include elongase and desaturase (**Figure 5**) [38, 39]. Delta-5 desaturase (D5D) and

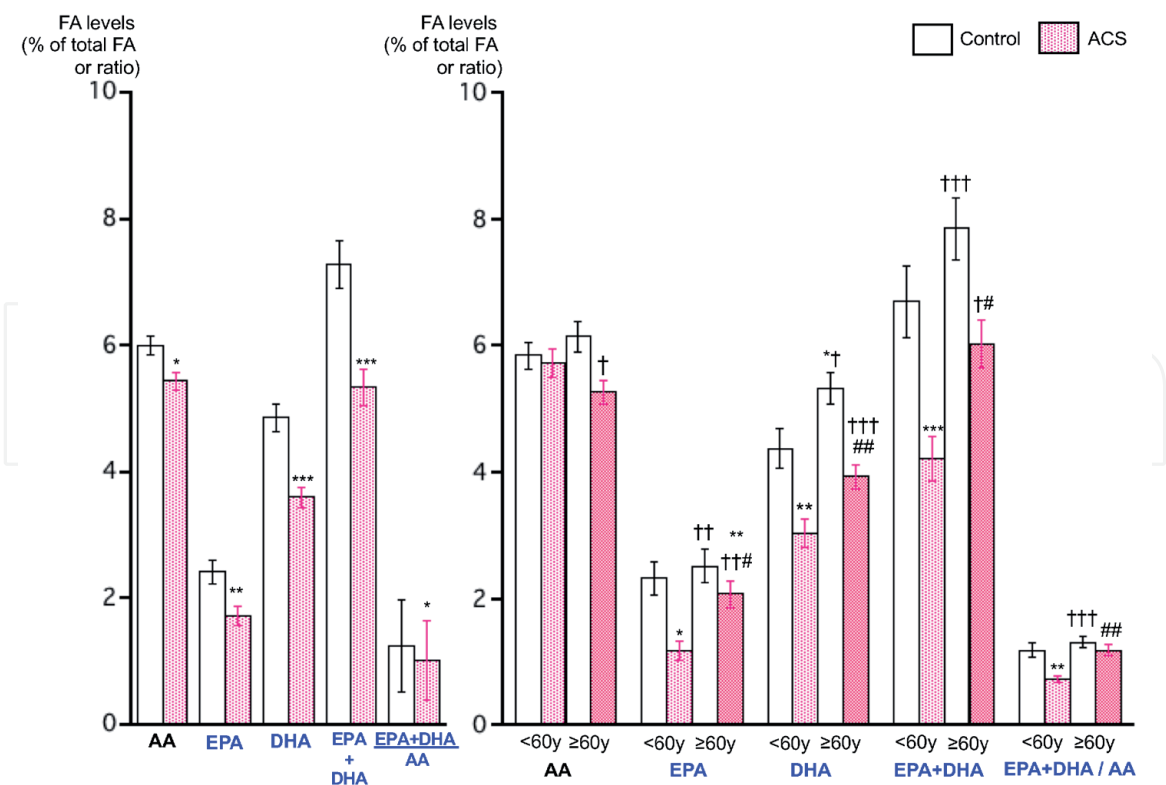


Figure 4. The comparison of trans fatty acids (TFA) between control and ACS patients. Left panel: comparison in whole subjects and Right panel: comparison separated by age. Data are expressed as mean \pm standard error (SE), and the error bar represents SE. The number of subjects is 49 (<60 years 24; ≥ 60 years 25) in control and 67 (<60 years 25; ≥ 60 years 42) in ACS. (A) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. control. (B) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. control <60y; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ vs. ACS <60y; # $p < 0.05$, ## $p < 0.01$ vs. control ≥ 60 years. Figure was made by Ref. [17].

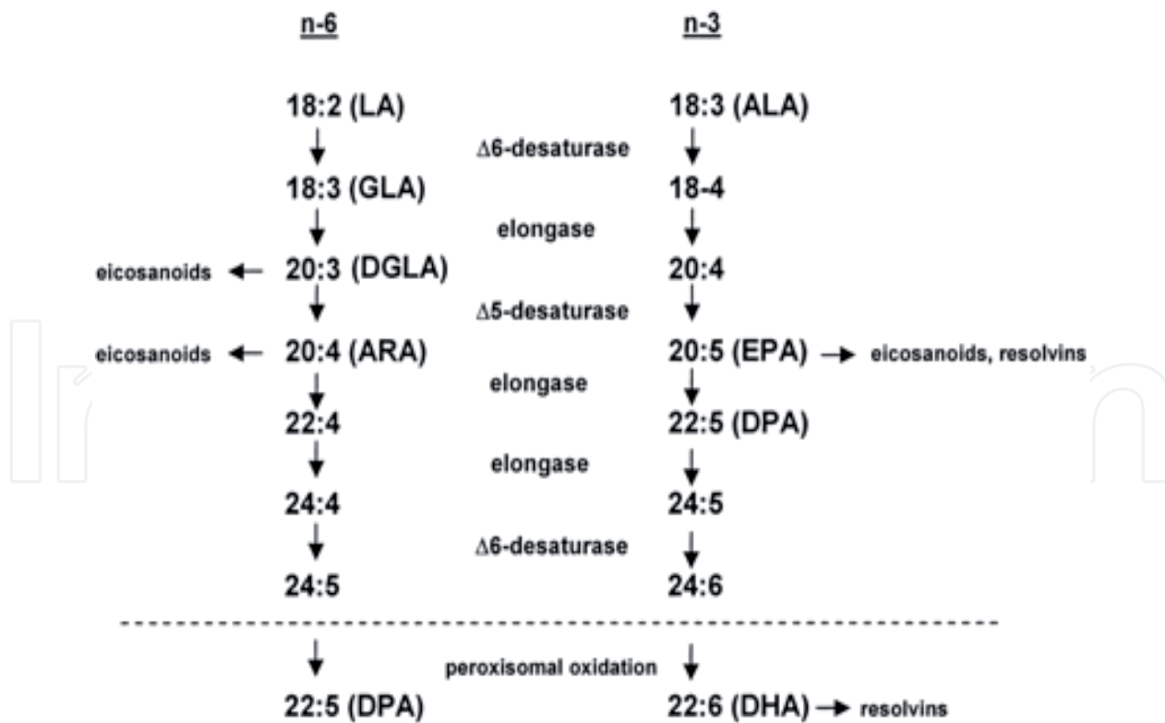


Figure 5. The omega-3 and omega-6 FA metabolism. ALA, α -linolenic acid; ARA, arachidonic acid; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GLA, γ -linolenic acid; LA, linoleic acid. Reproduced Ref. [38].

delta-6 desaturase (D6D) are two key enzymes in the synthesis of long-chain PUFA and are encoded by fatty acid desaturase 1 (FADS1) and FADS2 genes, respectively [39]. Previous studies have reported that the FADS1 gene polymorphism (less function) was associated with an increased CHD risk [40, 41]. D5D is involved in one step in the conversion of linoleic acid (LA, 18:2 n -6) and alpha-linolenic acid (ALA, 18:3 n -3) to AA (20:4 n -6) and EPA (20:5 n -3), respectively, as the sole enzymatic source of endogenous AA and EPA. EPA and DHA are strongly influenced by the dietary intake of pre-formed PUFA, and, while human can readily retroconvert DHA to EPA, the elongation of ALA to EPA and DHA is minimal [38, 42]. However, contrary results have also been very recently reported [43]. The activities of D5D cannot be measured directly; generally, they are conventionally estimated from the ratio of AA to dihomo-gamma linolenic acid (DGLA, 20:3 n -6) [39, 44–46].

In our cross-sectional study with ACS patients alone, PUFA and various lipid markers such as small dense LDL cholesterol (sdLDL-C), malondialdehyde-modified LDL (MDA-LDL), and remnant lipoprotein cholesterol (RL-C) were assessed in 436 men with the first episode of ACS not take any lipid-lowering drugs [47]. Approximately 70% of ACS patients had low EPA/AA (<0.41) or DHA/AA (<0.93) according to the median levels in Japanese general population [48]. Serum levels of LDL-C, apolipoprotein B (apoB), and RL-C were significantly higher in the low EPA/AA or DHA/AA groups, while those of triglycerides and MDA-LDL were significantly higher in the low EPA/AA group alone. Thus, low EPA/AA is associated with more atherogenic lipid biomarkers than low DHA/AA. Patients without any reperfusion at the culprit coronary artery on the initial CAG had significantly lower EPA levels and similar DHA and AA levels compared with the others. The levels of LDL-C, non-HDL-C, triglycerides, sdLDL-C, RL-C, MDA-LDL, and apoB decreased progressively and those of EPA, DHA, and HDL-C increased as D5D increased (**Figure 6**). While large buoyant LDL-C (IbLDL-C) estimated by subtracting the sdLDL-C concentration from the LDL-C concentration, and apoA-1 did not differ among quartiles of D5D. Previous prospective case-control studies

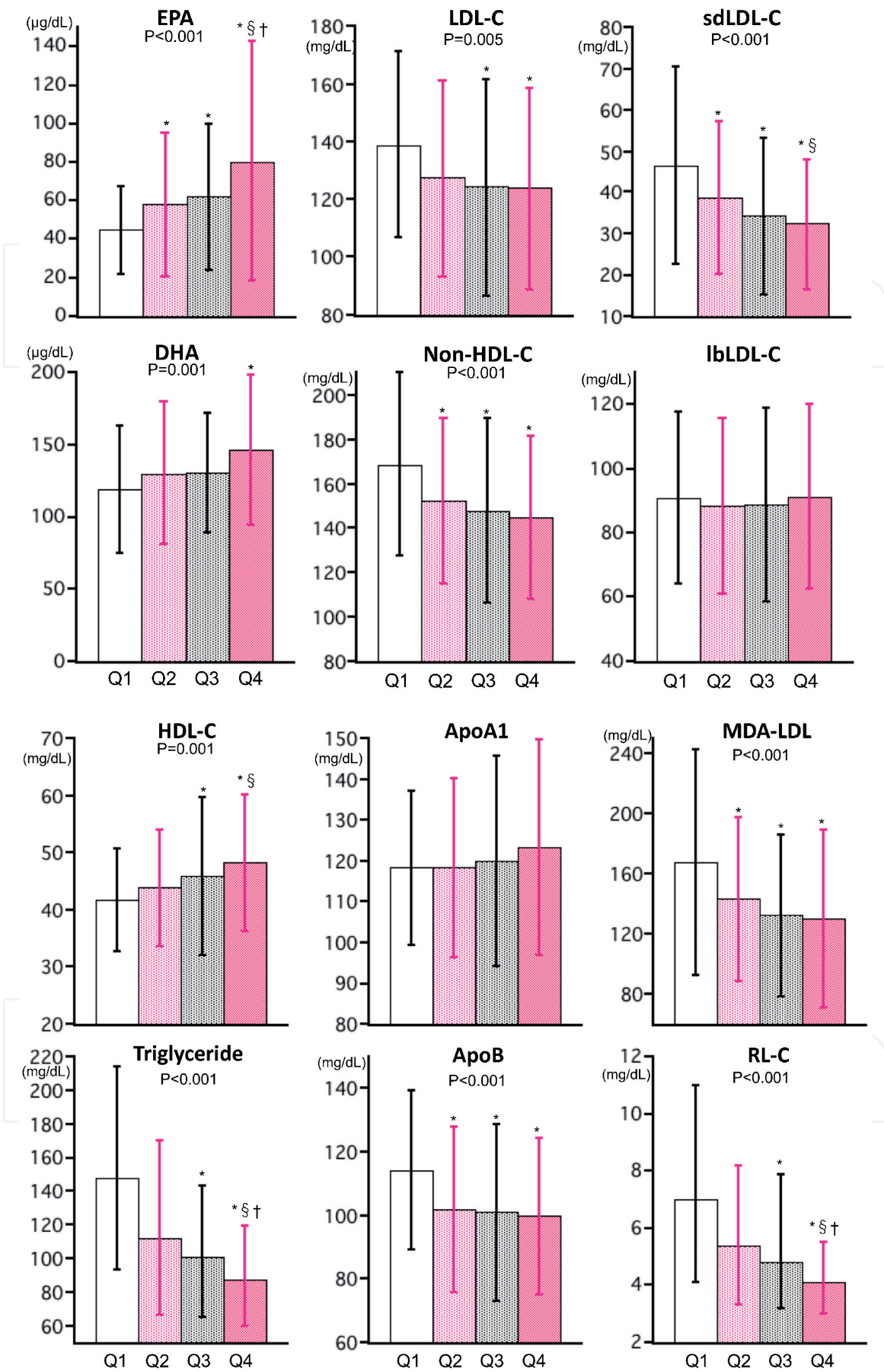


Figure 6. Comparisons of various lipid biomarkers between the quartiles of D5D estimated by AA/DGLA. Data are expressed as means \pm standard deviation, or median (25% and 75% quartiles) (triglyceride and or RL-C). Abbreviations are presented in the main text. Kruskal-Wallis tests and analysis of variance (ANOVA) with Tukey's honest significant difference test was used to identify the differences between the groups. Q1: AA/DGLA < 4.03; Q2: 4.04 \leq AA/DGLA < 5.07; Q3: 5.08 \leq AA/DGLA < 6.29; Q4: AA/DGLA \geq 6.29. * p < 0.05 vs. Q1, § p < 0.05 vs. Q2, † p < 0.05 vs. Q3 using Tukey--Kramer post-hoc test. Figure is made by Ref. [47].

reported that low D5D predict the development of type 2 diabetes [49–51] and the risk of CVD [39]. In a Swedish population-based prospective cohort study of 2009 50-year old men, D5D was reported to have an inverse correlation with CVD mortality over a follow-up of 30 years [52]. The association of lower D5D with accumulation of atherogenic sdLDL, MDA-LDL, and RL-C in our study may provide the association between lower D5D and atherosclerotic CVD.

Previous studies reported that statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, have differential effects on the activities of D5D, D6D, and elongase, and any statins increased AA [53]. It is suggested that EPA/AA may better reflect the residual risk for CHD following statin treatment than DHA / AA. Some previous cross-sectional studies have demonstrated that EPA/AA but not DHA/AA was significantly associated with ACS [54, 55]. A cohort study of CHD patients underwent nonemergency percutaneous coronary intervention (PCI) found that lower EPA/AA (but not lower DHA/AA) was significantly associated with the incidence of major adverse cardiac events [56]. Our study showed that the EPA/AA is a superior risk marker than DHA/AA in terms of correlation with atherogenic lipid profiles in ACS patients.

Multiple studies have demonstrated that EPA and DHA have different effects on cardiometabolic risk factors [57, 58]. Innes and Calder reviewed 18 randomized controlled trials that compare EPA or DHA (>2 g/day and purity ≥90%) and placebo on cardiometabolic risk factors [57]. The study durations were between 4 and 10 weeks. They reported the following results: (1) both EPA and DHA lowered triglycerides with DHA having a greater triglyceride-lowering effects than EPA; (2) while total cholesterol was largely unchanged by EPA and DHA, DHA increased HDL-C, particularly HDL₂ and increased LDL-C and LDL particle size; (3) both EPA and DHA inhibited platelet activity while DHA improved vascular function and lowered heart rate and blood pressure to a greater extent than EPA; and (4)

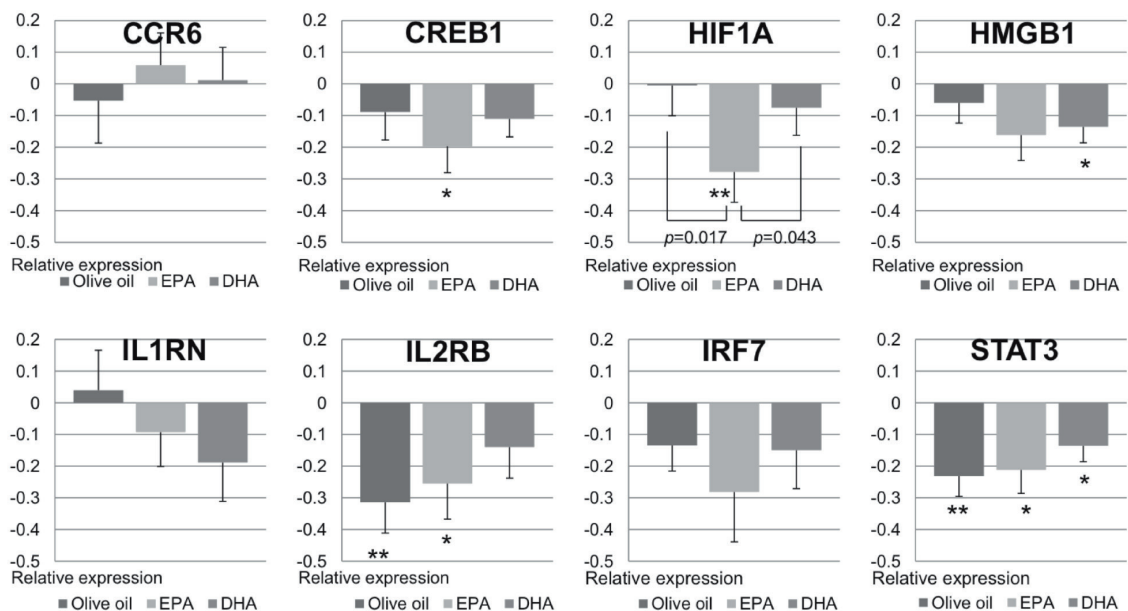


Figure 7.

Relative changes in the expression of specific genes determined by quantitative real-time polymerase chain reaction (Q-PCR) in olive oil, EPA and DHA supplementation groups. Data are expressed as mean ± standard error. Differences within each group were determined by paired t test (** $p < 0.01$, * $p < 0.05$). Brackets indicate differences between two groups as determined with a 2-factor ANOVA with Tukey honestly significant difference correction. CCR6, chemokine (C-C motif) receptor 6; CREB1, cAMP responsive element binding protein 1; HIF1A, hypoxia-inducible factor 1- α ; HMGB1, high mobility group box 1; IL1RN, interleukin 1 receptor antagonist; IL2RB, interleukin 2 receptor, beta; IRF7, interferon regulatory factor 7; STAT3, signal transducer and activator of transcription. Reproduced from [58].

the effects of EPA and DHA on inflammatory markers and glycemic control were inconclusive [57]. Tsunoda et al. assessed the effect of a six-week supplementation with either olive oil (6 g/day), EPA (1.8 g/day), or DHA (1.8 g/day) on gene expression in peripheral blood mononuclear cells in healthy men and postmenopausal women [58]. EPA but not DHA or olive oil significantly affected the gene expression in the interferon signaling, receptor recognition of bacteria and viruses, G protein signaling, glycolysis, glycolytic shunting, S-adenosyl-L-methionine biosynthesis, cAMP-mediated signaling, as well as many other individual genes including hypoxia inducible factor 1 (**Figure 7**) [58]. They concluded that the effects of EPA and DHA were mediated by different pathways in human peripheral blood mononuclear cells and that EPA affected cellular immune responses including the interferon signaling pathway [58].

4. Conclusion

IP-TFA intake (estimated from plasma levels) is low in Japan, and accordingly, there is a little difference in IP-TFA levels between Japanese ACS patients and healthy controls. However, a certain IP-TFA is associated with the increased risk of CHD even in Japan. Although it is not clear whether R-TFA are cardioprotective or not, the ACS patients, especially middle-aged patients showed significantly lower levels of R-TFA and omega-3 FA. Although average EPA and DHA levels in Japan are much higher than in the United States [59], still higher levels of the marine omega-3 PUFA are associated with the lower cardiovascular disease risk. However, the Japanese dietary style has changed markedly in the younger generation since 1990 [37, 60]. The lack of fish intake and excessive oils and meat and poultry intakes have been recognized in subjects <60 years old in the present Japanese. Decreased biosynthesis of long-chain PUFA and imbalance of omega-3 and omega-6 FA are clearly associated with atherogenic lipid profiles in Japanese ACS patients. Multiple studies have demonstrated that EPA and DHA have different effects on cardio-metabolic risk factors. The EPA/AA may be a superior risk marker than DHA/AA in terms of correlation with atherogenic lipid profiles in clinical practice.

Abbreviations

AA	arachidonic acid
ACS	acute coronary syndromes
AMI	acute myocardial infarction
apoA1	apolipoprotein A1
apoB	apolipoprotein B
CAG	coronary angiography
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DGLA	dihomo-gamma linolenic acid
DHA	docosahexaenoic acid
D5D	Delta-5 desaturase
D6D	delta-6 desaturase
EPA	eicosapentaenoic acid
FA	Fatty acids
FADS	fatty acid desaturase
HDL-C	HDL cholesterol

HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme
lbLDL-C	large buoyant LDL-C
LDL-C	LDL cholesterol
Lp(a)	lipoprotein(a)
MDA-LDL	malondialdehyde-modified LDL
MUFA	Monounsaturated fatty acid
PCI	percutaneous coronary intervention
PHO	partially hydrogenated oils
PUFA	Polyunsaturated fatty acid
RBC	red blood cell
RL-C	remnant lipoprotein cholesterol
RTD	ruminant trans fatty acid
sdLDL-C	small dense LDL cholesterol
SCD	sudden cardiac death
TFA	<i>trans</i> fatty acid

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References

- [1] Baum S, Kris Etherton P, Willett W, Lichtenstein A, Rudel L, Maki K, et al. Fatty acids in cardiovascular health and disease: A comprehensive update. *Journal of Clinical Lipidology*. 2012;**6**:216-234
- [2] Superko HR, Superko SM, Nasir K, Agatston A, Garrett BC. Omega-3 fatty acid blood levels: Clinical significance and controversy. *Circulation*. 2013;**128**:2154-2161
- [3] Harris WS, Von Schacky C. The Omega-3 index: A new risk factor for death from coronary heart disease? *Preventive Medicine*. 2004;**39**:212-220
- [4] Harris WS. The Omega-6:Omega-3 ratio: A critical appraisal and possible successor. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2018;**132**:34-40
- [5] Harris W, Shearer G. Omega-6 fatty acids and cardiovascular disease: Friend, not foe? *Circulation*. 2014;**130**:1562-1564
- [6] Sala A, Proschak E, Steinhilber D, Rovati GE. Two-pronged approach to anti-inflammatory therapy through the modulation of the arachidonic acid cascade. *Biochemical Pharmacology*. 2018;**158**:161-173
- [7] Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis. *Annals of Internal Medicine*. 2014;**160**:398-406
- [8] Lichtenstein AH. Dietary trans fatty acids and cardiovascular disease risk: Past and present. *Current Atherosclerosis Reports*. 2014;**16**:433
- [9] Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, et al. Japan atherosclerosis society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *Journal of Atherosclerosis and Thrombosis*. 2018;**25**:846-984
- [10] Liska DJ, Cook CM, Wang DD, Gaine PC, Baer DJ. Trans fatty acids and cholesterol levels: An evidence map of the available science. *Food and Chemical Toxicology*. 2016;**98**:269-281
- [11] Stender S, Astrup A, Dyerberg J. Ruminant and industrially produced trans fatty acids: Health aspects. *Food & Nutrition Research*. 2008;**52**
- [12] Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *The New England Journal of Medicine*. 1990;**323**:439-445
- [13] Adachi H. Trans fatty acid and coronary artery disease- lessons from seven countries study. *Circulation Journal*. 2015;**79**:1902-1903
- [14] Sebedio JL, Chardigny JM. Physiological effects of trans and cyclic fatty acids. In: Perkins EG, editor. *Deep Frying*. Chapter 9. 1996. pp. 183-209
- [15] Mori K, Ishida T, Yasuda T, Hasokawa M, et al. Serum trans-fatty acid concentration is elevated in young patients with coronary artery disease in Japan. *Circulation Journal*. 2015;**79**:2017-2025
- [16] Nagasawa Y, Shinke T, Toh R, Ishida T, et al. The impact of serum trans fatty acids concentration on plaque vulnerability in patients with coronary artery disease: Assessment via optical coherence tomography. *Atherosclerosis*. 2017;**265**:312-317
- [17] Koba S, Takao T, Shimizu F, Ogawa M, et al. Comparison of plasma levels of different species of trans fatty

- acids in Japanese male patients with acute coronary syndrome versus healthy men. *Atherosclerosis*. 2019;**284**:173-180
- [18] Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, et al. A prospective study of trans fatty acids in erythrocytes and risk of coronary heart disease. *Circulation*. 2007;**115**:1858-1865
- [19] Lemaitre RN, King IB, Mozaffarian D, Sotoodehnia N, Rea TD, Kuller LH, et al. Plasma phospholipid trans fatty acids, fatal ischemic heart disease, and sudden cardiac death in older adults: The cardiovascular health study. *Circulation*. 2006;**114**:209-215
- [20] Wang Q, Imamura F, Lemaitre RN, Rimm EB, Wang M, King IB, et al. Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: The cardiovascular health study. *Journal of the American Heart Association*. 2014;**3**
- [21] Lemaitre RN, King IB, Raghunathan TE, et al. Cell membrane trans-fatty acids and the risk of primary cardiac arrest. *Circulation*. 2002;**105**:697-701
- [22] Borgeraas H, Hertel JK, Seifert R, Berge RK, Bohov P, Ueland PM, et al. Serum trans fatty acids, asymmetric dimethylarginine and risk of acute myocardial infarction and mortality in patients with suspected coronary heart disease: A prospective cohort study. *Lipids in Health and Disease*. 2016;**15**:38
- [23] Lemaitre RN, King IB, Patterson RE, Psaty BM, Kestlin M, Heckbert SR. Assessment of trans-fatty acid intake with a food frequency questionnaire and validation with adipose tissue levels of trans-fatty acids. *American Journal of Epidemiology*. 1998;**148**:1085-1093
- [24] Roberts TL, Wood DA, Riemersma RA, Gallagher PJ, Lampe FC. Trans isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. *Lancet*. 1995;**345**:278-282
- [25] Aro A, Kardinaal AF, Salminen I, Kark JD, et al. Adipose tissue isomeric trans fatty acids and risk of myocardial infarction in nine countries: The EURAMIC study. *Lancet*. 1995;**345**:273-278
- [26] Pedersen JI, Ringstad J, Almendingen K, Haugen TS, Stensvold I, Thelle DS. Adipose tissue fatty acids and risk of myocardial infarction—A case-control study. *European Journal of Clinical Nutrition*. 2000;**54**:618-625
- [27] Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H. High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults. *The Journal of Nutrition*. 2003;**133**:1186-1191
- [28] Itcho K, Yoshii Y, Ohno H, Oki K, Shinohara M, et al. Association between serum elaidic acid concentration and insulin resistance in two Japanese cohorts with different lifestyles. *Journal of Atherosclerosis and Thrombosis*. 2017;**24**:1206-1214
- [29] Takada A, Shimizu F, Ishii Y, Ogawa M, Takao T, Koba S, et al. Plasma fatty acid composition in men over 50 in the USA and Japan. *Food and Nutrition Sciences*. 2018;**9**:703-710
- [30] Kleber ME, Delgado GE, Lorkowski S, Marz W, von Schacky C. Trans-fatty acids and mortality in patients referred for coronary angiography: The Ludwigshafen risk and cardiovascular health study. *European Heart Journal*. 2016;**37**:1072-1078
- [31] Mozaffarian D. Natural trans fat, dairy fat, partially hydrogenated oils, and cardiometabolic health: The

Ludwigshafen risk and cardiovascular health study. *European Heart Journal*. 2016;**37**:1079-1081

[32] Hulshof KF, van Erp-Baart MA, Anttolainen M, et al. Intake of fatty acids in western Europe with emphasis on trans fatty acids: The TRANSFAIR study. *European Journal of Clinical Nutrition*. 1999;**53**:143-157

[33] Mozaffarian D, Cao H, King IB, Lemaitre RN, Song X, Siscovick DS, et al. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: A cohort study. *Annals of Internal Medicine*. 2010;**153**:790-799

[34] Mozaffarian D, de Oliveira Otto MC, et al. Trans-Palmitoleic acid, other dairy fat biomarkers, and incident diabetes: The multi-ethnic study of atherosclerosis (MESA). *The American Journal of Clinical Nutrition*. 2013;**97**:854-861

[35] Mozaffarian D, Kabagambe EK, Johnson CO, Lemaitre RN, et al. Genetic loci associated with circulating phospholipid trans fatty acids: A meta-analysis of genome-wide association studies from the CHARGE Consortium. *The American Journal of Clinical Nutrition*. 2015;**101**:398-406

[36] Watanabe Y, Tatsuno I. Omega-3 polyunsaturated fatty acids for cardiovascular diseases: Present, past and future. *Expert Review of Clinical Pharmacology*. 2017;**10**:865-873

[37] Yokoyama S. Beneficial effect of retuning to “Japan diet” for the Japanese. *Journal of Atherosclerosis and Thrombosis*. 2019;**26**:1-2

[38] Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *The American Journal of Clinical Nutrition*. 2006;**83**:1467S-1476S

[39] Tosi F, Sartori F, Guarini P, Olivieri O, Martinelli N. Delta-5 and delta-6 desaturases: Crucial enzymes in polyunsaturated fatty acid-related pathways with pleiotropic influences in health and disease. *Advances in Experimental Medicine and Biology*. 2014;**824**:61-81

[40] Lv X, Zhang Y, Rao S, Qiu J, Wang M, Luo X, et al. Joint effects of genetic variants in multiple loci on the risk of coronary artery disease in Chinese Han subjects. *Circulation Journal*. 2012;**76**:1987-1992

[41] Liu F, Li Z, Lv X, Ma J. Dietary n-3 polyunsaturated fatty acid intakes modify the effect of genetic variation in fatty acid desaturase 1 on coronary artery disease. *PLoS One*. 2015;**10**:e0121255

[42] Oscarsson J, Hurt Camejo E. Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and their mechanisms of action on apolipoprotein B-containing lipoproteins in humans: A review. *Lipids in Health and Disease*. 2017;**16**:149-149

[43] Metherel A, Irfan M, Klingel S, Mutch D, Bazinet R. Compound-specific isotope analysis reveals no retroconversion of DHA to EPA but substantial conversion of EPA to DHA following supplementation: A randomized control trial. *American Journal of Clinical Nutrition*. 2019;**110**:823-831

[44] Ebbesson SOE, Voruganti V, Higgins P, et al. Fatty acids linked to cardiovascular mortality are associated with risk factors. *International Journal of Circumpolar Health*. 2015;**74**:28055

[45] Harris WS, Luo J, Pottala JV, Margolis KL, et al. Red blood cell fatty acids and incident diabetes mellitus in the women's health initiative memory study. *PLoS One*. 2016;**11**:e0147894

- [46] Tsurutani Y, Inoue K, Sugisawa C, Saito J, Omura M, Nishikawa T. Increased serum Dihomo-gamma-linolenic acid levels are associated with obesity, body fat accumulation, and insulin resistance in Japanese patients with type 2 diabetes. *Internal Medicine*. 2018;**57**:2929-2935
- [47] Arai K, Koba S, Yokota Y, Tsunoda F, Tsujita H, et al. Delta-5 desaturase activity, and lipid profiles in men with acute coronary syndrome. *Journal of Atherosclerosis and Thrombosis*. 2020. DOI: 10.5551/jat.55780. Online ahead of print
- [48] Ninomiya T, Nagata M, Hata J, Hirakawa Y, et al. Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: The Hisayama study. *Atherosclerosis (Amsterdam)*. 2013;**231**:261-267
- [49] Hodge A, English D, O'Dea K, Sinclair A, et al. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: Interpreting the role of linoleic acid. *American Journal of Clinical Nutrition*. 2007;**86**:189-197
- [50] Krachler B, Norberg M, Eriksson JW, et al. Fatty acid profile of the erythrocyte membrane preceding development of type 2 diabetes mellitus. *Nutrition, Metabolism, and Cardiovascular Diseases*. 2008;**18**:503-510
- [51] Kröger J, Schulze M. Recent insights into the relation of $\Delta 5$ desaturase and $\Delta 6$ desaturase activity to the development of type 2 diabetes. *Current Opinion in Lipidology*. 2012;**23**:4-10
- [52] Warensjö E, Sundström J, Vessby B, Cederholm T, Risérus U. Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: A population-based prospective study. *American Journal of Clinical Nutrition*. 2008;**88**:203-209
- [53] Bird JK, Calder PC, Eggersdorfer M. The role of n-3 long chain polyunsaturated fatty acids in cardiovascular disease prevention, and interactions with statins. *Nutrients*. 2018;**10**(6):775. DOI: 10.3390/nu10060775
- [54] Nishizaki Y, Shimada K, Tani S, Ogawa T, et al. Significance of imbalance in the ratio of serum n-3 to n-6 polyunsaturated fatty acids in patients with acute coronary syndrome. *The American Journal of Cardiology*. 2014;**113**:441-445
- [55] Iwamatsu K, Abe S, Nishida H, Kageyama M, Nasuno T, Sakuma M, et al. Which has the stronger impact on coronary artery disease, eicosapentaenoic acid or docosahexaenoic acid? *Hypertension Research*. 2016;**39**:272-275
- [56] Domei T, Yokoi H, Kuramitsu S, Soga Y, et al. Ratio of serum n-3 to n-6 polyunsaturated fatty acids and the incidence of major adverse cardiac events in patients undergoing percutaneous coronary intervention. *Circulation Journal*. 2012;**76**:423-429
- [57] Innes JK, Calder PC. The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: A systematic review. *International Journal of Molecular Sciences*. 2018;**19**
- [58] Tsunoda F, Lamon-Fava S, Asztalos BF, et al. Effects of oral eicosapentaenoic acid versus docosahexaenoic acid on human peripheral blood mononuclear cell gene expression. *Atherosclerosis*. 2015;**241**:400-408
- [59] Sekikawa A, Curb JD, Ueshima H, El-Saed A, Kadowaki T, et al. Marine-derived n-3 fatty acids and

atherosclerosis in Japanese, Japanese-American, and white men: A cross-sectional study. *Journal of the American College of Cardiology*. 2008;52:417-424

[60] Shijo Y, Maruyama C, Nakamura E, Nakano R, et al. Japan diet intake changes serum phospholipid fatty acid compositions in middle-aged men: A pilot study. *Journal of Atherosclerosis and Thrombosis*. 2019;26:3-13

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