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ORIGINAL ARTICLE

Variations in the eicosapentaenoic acid–arachidonic acid ratio associated with age in acute myocardial infarction patients undergoing primary percutaneous coronary intervention

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Abstract

Acute myocardial infarction (AMI) is a life-threatening disease, and its incidence has been increasing even in the young population. Although a low eicosapentaenoic acid (EPA)–arachidonic acid (AA) ratio is associated with an increased risk of coronary artery disease, the effect of age on EPA/AA ratios in AMI patients remains unclear. This study aimed to clarify the independent polyunsaturated fatty acid (PUFA)-related determinants of age in younger and older AMI patients. A total of 153 consecutive patients who underwent primary percutaneous coronary interventions (PCIs) for de novo AMIs were enrolled in this study. Patients' background data, including PUFA and lipid profiles during PCI, were evaluated retrospectively. The EPA/AA ratio correlated positively with age ($r=0.21$; $P=0.011$) and increased markedly from age 60 years. Patients aged < 60 years ($n=35$) had a lower mean EPA/AA ratio (0.25 ± 0.16) than patients aged ≥ 60 years ($n=118$) (0.38 ± 0.25) ($P<0.001$). The AA level was more dependent on age than on EPA level ($r=-0.34$, $P<0.001$ vs. $r=0.12$, $P=0.16$). The multivariate analysis revealed that a 0.1 EPA/AA ratio increase (odds ratio 1.50; 95% confidence interval 1.09–2.06), body mass index, triglyceride level, and aspirin administration were independently associated with the age stratification of AMI patients. The EPA/AA ratio was higher in younger AMI patients who have undergone primary PCIs than in older patients. Younger population at risk for AMI should be managed with multiple interventions including PUFA profiling.

Keywords Acute myocardial infarction · Coronary artery disease · Eicosapentaenoic acid–arachidonic acid ratio · Percutaneous coronary intervention · Polyunsaturated fatty acids

Introduction

Among patients with coronary artery disease (CAD), acute coronary syndrome (ACS), especially acute myocardial infarction (AMI), is a major health problem worldwide. Predicting and preventing AMI are critically important, because AMI can threaten lives without displaying pre-ischemic symptoms. Statin treatment is indispensable for the secondary prevention of cardiovascular (CV) events in dyslipidemic patients with CAD in the primary revascularization era [1, 2]. However, an AMI can occur despite statins controlling the lipid profiles [3], and interventions to allay the residual risk of CV events are being debated [4].

Low *n*-3 polyunsaturated fatty acid (PUFA)–*n*-6 PUFA ratios, especially the eicosapentaenoic acid (EPA)–arachidonic acid (AA) ratio, correlate with long-term CV events [5]. Consuming fish or fish oil could reduce major cardiac events [6]. The Japan EPA Lipid Intervention

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Study (JELIS) focused on a representative *n*-3/*n*-6 PUFA ratio, and its findings showed that treating dyslipidemic patients with highly purified EPA and statins significantly reduced the incidence of major adverse cardiac events, compared with that observed in patients administered statins alone [7]. Based on this evidence, a low EPA/AA ratio has recently been acknowledged as a potent predictor of adverse cardiac events [8, 9]. AMI was considered to be associated with older people specifically, but recently, the prevalence of AMI among younger patients has increased, even in Asian populations [10], and the westernization of everyday food in Asia may explain this phenomenon. Dietary habits directly influence the EPA/AA ratio, and an upsurge in poor PUFA profiles is evident among younger populations within Asian countries [11].

EPA has strong anti-inflammatory and anti-oxidative properties that suppress atherogenesis [12]. The findings from studies undertaken in Japan show that low EPA/AA ratios are associated with the prevalence of ACS [13, 14]. Furthermore, EPA levels were reported to be predictor of some CV events after ACS. The low EPA level is a risk for incidence of ventricular arrhythmia in the acute phase of AMI [15] and is associated with higher prevalence of CV events after AMI [16]. However, the association between PUFA profiles and age in AMI patients has not been completely elucidated, even though AMI can induce the most severe inflammatory response in CAD. We hypothesized that the EPA/AA ratio varies among AMI patients of different ages, and as an inflammatory marker, its contribution to the onset of AMI varies. Therefore, the aim of this study was to clarify the independent PUFA-related determinants of age in younger and older AMI patients.

Methods

Study design and definitions

We screened 201 consecutive patients who were diagnosed with AMI at a single CV center between January 2010 and August 2013. Of these patients, those who did not undergo primary PCI, those who had undergone repeat PCIs, those whose PUFA data were missing, and those who had been administered EPA during PCI were excluded from the study. Ultimately, 153 de novo AMI patients who had undergone primary PCIs were enrolled in this observational cohort study. AMIs, including ST-segment elevation myocardial infarctions (STEMIs) and non-STEMIs (NSTEMIs), were defined according to the third universal definition of myocardial infarction [17].

Study groups

Based on the results from the current study which showed that the EPA/AA ratio increased significantly in subjects aged 60 years compared with that in subjects aged < 50 years, the patients who were ≥ 60 years comprised the older group and those aged < 60 years comprised the younger group (Fig. 1). This study was carried out according to the principles of the Declaration of Helsinki. Our institution's ethics committee approved the study protocol. All patients provided written informed consent that permitted the use of the data from their medical records before they entered the study.

Data evaluation

We evaluated patients' baseline characteristics, including their EPA, AA, dihomo-gamma-linolenic acid (DHLA), and docosahexaenoic acid (DHA) levels; CAD clinical presentations; body mass indexes (BMIs); smoking statuses; histories of hypertension, dyslipidemia, diabetes, PCI, coronary artery bypass grafting, myocardial infarction, peripheral artery disease (PAD), and atrial fibrillation; laboratory data, such as hemoglobin, C-reactive protein (CRP), hemoglobin A1c (HbA1c) levels, and lipid profiles; flow-mediated dilations; and oral medications at the time of the PCI. Hypertension was defined as a systolic blood pressure (BP) > 140 mmHg, a diastolic BP > 90 mmHg, or ongoing treatment of previously diagnosed hypertension with antihypertensive agents. Diabetes was defined as a fasting plasma blood glucose level of ≥ 126 mg/dL, a plasma blood glucose level of ≥ 200 mg/dL at any time, an HbA1c level of ≥ 6.5%, or treatment with antihyperglycemic agents, including insulin. Dyslipidemia was diagnosed if the low-density lipoprotein cholesterol (LDL-C) level was ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) level was < 40 mg/dL, triglyceride (TG) level was ≥ 150 mg/dL, or if the individual was taking antihyperlipidemic medications. A diagnosis of chronic kidney disease (CKD) was based on an estimated glomerular filtration ratio (eGFR) < 60 mL/min.1.73 m^2. PAD was diagnosed if a patient had an ankle-brachial index ≤ 0.80, angiographically defined peripheral arterial stenosis ≥ 75%, or a history of endovascular treatment of ischemic limbs. The groups were compared in relation to the aforementioned parameters.

Statistical analyses

Data are presented as means and standard deviations or numbers and percentages in the tables, and as means and standard errors of the means in the figures. The groups

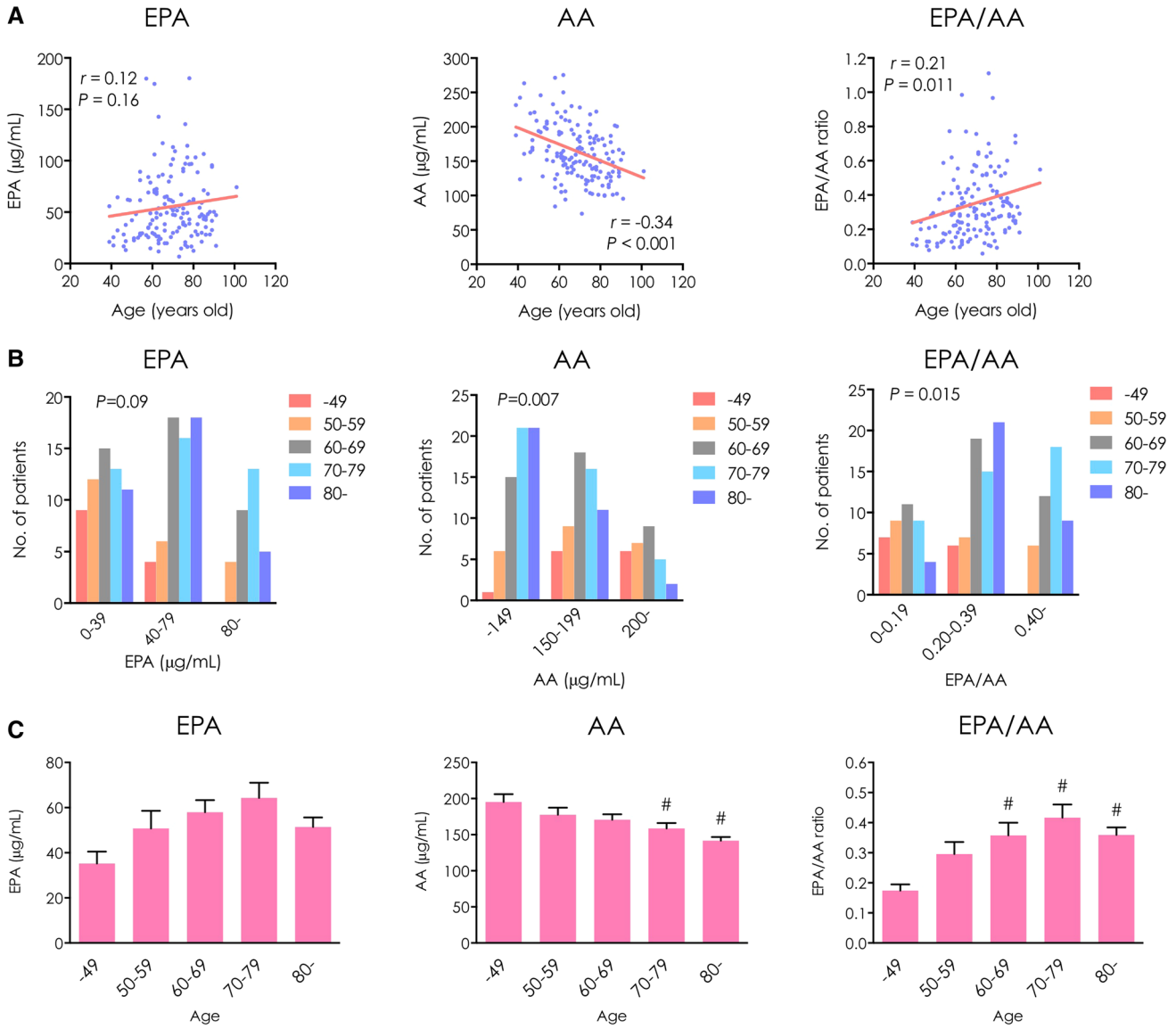

Fig. 1 Polyunsaturated fatty acid (PUFA) profiles in patients classified by age. **a** Association between age and each PUFA profile. **b** PUFA levels classified by age. **c** Distribution of patients who were classified according to age and PUFA profiles. $^{\#}P < 0.05$ versus patients < 50 years old. *AA* arachidonic acid, *EPA* eicosapentaenoic acid

were compared in relation to the continuous variables using independent Student's *t* tests or non-parametric equivalent Mann–Whitney *U* tests. The Kruskal–Wallis test was used to compare the continuous variables among ≥ 3 groups that had been stratified according to age. Tukey's multiple comparison test was applied after the Kruskal–Wallis test to directly compare the differences between two groups. Fisher's exact test for two groups and the Chi squared test for more than two groups were used to compare the categorical variables. Linear regression analysis was performed to determine the correlation coefficients between age and PUFA profiles. The correlations were assessed using Pearson's correlation coefficient. Multiple logistic regression analyses were performed to identify the factors that were independently associated with age of AMI patients. Male sex, BMI, EPA/AA ratio, TG, LDL-C, hemoglobin, and aspirin and statin treatment were used to adjust the multivariable model. Receiver operating characteristic (ROC) curves were plotted and the areas under the curves (AUCs) were determined to compare the relationships between age and *n*-3 PUFA/*n*-6 PUFA ratios. Two-tailed *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using R software version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

There was no correlation between age and the EPA level ($r = 0.12$; $P = 0.16$) (Fig. 1a). The AA level was negatively ($r = -0.34$; $P < 0.001$) and the EPA/AA ratio was positively correlated with age ($r = 0.21$; $P = 0.011$). Dividing the EPA levels into 40 μg/mL increments did not uncover any differences among the age groups in terms of patient distribution. Dividing the AA levels into 50 μg/mL and the EPA/AA ratios into 0.20 increments revealed clear differences in patient distributions among the age groups (Fig. 1b). When the study population was grouped into 10-year age increments, the EPA levels did not differ among the groups ($P = 0.08$); the AA levels decreased in patients aged ≥ 70 years, but the EPA/AA ratio increased significantly in patients aged ≥ 60 years (Fig. 1C) compared with the EPA/AA ratio in patients aged < 50 years.

Given the increase in the EPA/AA ratio at age 60 years, we divided the patients into two groups: those aged < 60 years ($n = 35$) and those aged ≥ 60 years ($n = 118$). Table 1 presents the groups' baseline characteristics. The groups did not differ in relation to the proportions of STEMI and NSTEMI. Patients aged < 60 years had a significantly lower mean EPA concentration (45.0 ± 31.9 μg/mL vs. 58.3 ± 35.7 μg/mL; $P = 0.014$), a significantly lower mean EPA/AA ratio (0.25 ± 0.16 vs. 0.38 ± 0.25; $P < 0.001$), and a higher mean AA level (184.1 ± 44.2 μg/mL vs. 158.1 ± 44.9 μg/mL; $P < 0.001$) than those in patients aged ≥ 60 years (Table 1). The mean DHA levels in the older group and younger group were comparable (131.2 ± 45.2 μg/mL vs. 122.0 ± 49.4 μg/mL; $P = 0.13$), but the mean DHLA level of the younger group (29.7 ± 11.6 μg/mL vs. 41.6 ± 14.0 μg/mL; $P < 0.001$) was significantly higher; therefore, the DHA/DHLA ratio of the younger group was significantly lower than that in the older group(3.24 ± 1.74 vs. 5.08 ± 2.80; $P < 0.001$). Moreover, the EPA/DHLA (1.26 ± 1.23 vs. 2.37 ± 2.47; $P < 0.001$) and DHA/AA (0.68 ± 0.27 vs. 0.85 ± 0.26; $P < 0.001$) ratios in the younger group were lower than those in the older group. The DHLA level and the EPA/DHLA, DHA/AA, and DHA/DHLA ratios showed specific trends in relation to age (Supplemental Figure S1). Dividing the age into 10-year increments did not reveal any associations with the DHA level ($P = 0.63$).

The ROC curve analysis revealed an EPA/AA ratio cutoff value of 0.31 between the younger and older groups. Comparable AUC values were found for the EPA/AA (AUC 0.70; specificity 80.0%), EPA/DHLA (AUC 0.74; specificity 74.3%), DHA/AA (AUC 0.68; specificity 45.7%), and DHA/DHLA (AUC 0.75; specificity 60.0%) ratios, and of these, the EPA/AA ratio showed the highest level of specificity (Supplemental Figure S2).

Table 1 Patients' characteristics

Variable	Younger group < 60 years $n = 35$	Older group ≥ 60 years $n = 118$	*P* value
Age, years	51.3 ± 6.3	74.1 ± 9.3	< 0.001
Male, *n* (%)	29 (83)	79 (70)	0.09
BMI, kg/m^2	25.7 ± 4.5	23.5 ± 3.1	< 0.001
Current smoker, *n* (%)	18 (51)	32 (27)	0.013
Hypertension, *n* (%)	23 (66)	94 (80)	0.11
Dyslipidemia, *n* (%)	29 (83)	90 (76)	0.49
Diabetes, *n* (%)	13 (37)	52 (44)	0.56
CKD[a], *n* (%)	5 (14)	62 (48)	< 0.001
Maintenance dialysis, *n* (%)	0	3 (3)	–
Prior PCI, *n* (%)	1 (3)	14 (12)	0.19
Prior CABG, *n* (%)	0	6 (5)	–
Prior MI, *n* (%)	3 (9)	15 (13)	0.76
Atrial fibrillation, *n* (%)	1 (3)	9 (8)	0.46
CAD type			> 0.99
STEMI, *n* (%)	29 (83)	98 (83)	
NSTEMI, *n* (%)	6 (17)	20 (17)	
Angiographic findings			
Target vessel			0.65
LAD, *n* (%)	13 (37)	52 (44)	
Circumflex, *n* (%)	7 (20)	17 (14)	
RCA, *n* (%)	15 (43)	40 (39)	
LMT, *n* (%)	0	3 (3)	
Graft, *n* (%)	0	3 (3)	
Multivessel disease, *n* (%)	18 (51)	61 (52)	> 0.99
Type B2/C[b], *n* (%)	24 (69)	75 (64)	0.69
Laboratory data			
Fatty acids			
EPA, μg/mL	45.0 ± 31.9	58.3 ± 35.7	0.014
AA, μg/mL	184.1 ± 44.2	158.1 ± 44.9	< 0.001
DHA, μg/mL	122.0 ± 49.4	131.2 ± 45.2	0.13
DHLA, μg/mL	41.6 ± 14.0	29.7 ± 11.6	< 0.001
EPA/AA ratio	0.25 ± 0.16	0.38 ± 0.25	< 0.001
EPA/DHLA ratio	1.26 ± 1.23	2.37 ± 2.47	< 0.001
DHA/AA ratio	0.68 ± 0.27	0.85 ± 0.26	< 0.001
DHA/DHLA ratio	3.24 ± 1.74	5.08 ± 2.80	< 0.001
Lipids			
Total cholesterol, mg/dL	201.9 ± 50.4	188.7 ± 41.1	0.13
Triglyceride, mg/dL	140.4 ± 88.5	94.1 ± 61.7	< 0.001
HDL-C, mg/dL	46.5 ± 12.1	51.8 ± 14.4	0.01
LDL-C, mg/dL	129.0 ± 49.0	120.4 ± 35.8	0.26
Non-HDL-C, mg/dL	155.4 ± 49.7	137.3 ± 38.9	0.048
LDL/HDL ratio	2.89 ± 1.25	2.46 ± 0.91	0.10
Other laboratory data			
Hemoglobin, g/dL	14.1 ± 1.9	13.0 ± 2.0	0.005
Serum creatinine, mg/dL	0.77 ± 0.18	1.04 ± 0.78	0.068
eGFR, mL/min 1.73 m^2	84.2 ± 22.7	70.2 ± 68.6	< 0.001
HbA1c, %	6.33 ± 1.52	6.30 ± 1.74	0.95
CRP, mg/L	1.03 ± 2.37	1.56 ± 3.50	0.14

Table 1 (continued)

Variable	Younger group <60 years $n=35$	Older group ≥60 years $n=118$	*P* value
FMD, mm	3.67 ± 3.12	3.26 ± 1.50	0.83
Prehospital medication			
Aspirin, *n* (%)	1 (3)	30 (26)	0.002
Clopidogrel, *n* (%)	0	7 (6)	–
Warfarin, *n* (%)	0	4 (3)	–
Beta blockers, *n* (%)	2(6)	14 (12)	0.36
ACEi/ARB, *n* (%)	6 (17)	33 (28)	0.27
CCB, *n* (%)	10 (29)	37 (32)	0.84
Statins, *n* (%)	3 (9)	431 (27)	0.036
Nitrates, *n* (%)	2 (6)	317 (15)	0.25

The data presented are the means and standard deviations or the numbers and percentages

AA arachidonic acid, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CKD* chronic kidney disease, *CRP* C-reactive protein, *DHA* docosahexaenoic acid, *DHLA* dihomo-gamma-linolenic acid, *eGFR* estimated glomerular filtration rate, *EPA* eicosapentaenoic acid, *FMD* flow-mediated dilation, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein-cholesterol, *LAD* left anterior descending artery, *LDL-C* low-density lipoprotein cholesterol, *LMT* left main trunk, *MI* myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *RCA* right coronary artery, *STEMI* ST-segment elevation myocardial infarction

[a]Estimated glomerular filtration rate <60 mL/min 1.73 m^2

[b]American College of Cardiology/American Heart Association classification

Significantly, more patients in the younger group were current smokers compared with those in the older group. Moreover, the younger group had a higher BMI, higher TG, non-HDL-C, and hemoglobin levels, and a higher eGFR than those in the older group. The older group had a significantly higher CKD rate and a higher HDL-C level than the younger group. The groups did not differ in their mean LDL-C level (129.0 ± 49.0 mg/dL vs. 120.4 ± 35.8 mg/dL; $P=0.26$). Therefore, the younger group had more atherosclerosis risk factors, but fewer comorbidities than the older group. Compared with the younger group, oral medications, including aspirin and statins, were administered more frequently to the older group, which reflected the higher prevalence of comorbidities among the older patients (Table 1).

Given their statistical significance in the univariate analysis, male sex, BMI, EPA/AA ratio, TG and hemoglobin levels, and aspirin and statin use were selected as covariates for the multivariate analysis. The multivariate analysis revealed that a 0.1 increase in the EPA/AA ratio [odds ratio (OR) 1.50; 95% confidence interval (CI) 1.09–2.06], BMI (OR 0.85; 95% CI 0.73–0.99), log TG level (OR 0.88; 95% CI 0.01–0.75), and aspirin administration (OR 12.3; 95% CI 1.39–108) were independently associated with age stratification of AMI patients. Given the potent associations between EPA and DHA ($r=0.68$; 95% CI 0.58–0.76) and AA and DHLA ($r=0.44$; 95% CI 0.36–0.56) in this study, DHA and DHLA were not included in the multivariate analysis (Supplemental Figure S3).

Discussion

This study mainly showed that the EPA/AA ratio increased from age 60 years among AMI patients and this ratio might have an age-associated cutoff value. This finding was corroborated by the results of the multivariate analysis, which revealed that the EPA/AA ratio was independently associated with age stratification of AMI patients. To our knowledge, this is the first study that has focused on PUFA profiles in AMI patients to clarify the effect of the EPA/AA ratio on the onset of AMI.

In the primary PCI era, the AMI prognosis has improved, but the age-adjusted ACS incidence has increased in the last 30 years [10]. Since an AMI can occur with or without preischemic symptoms, there is often little scope for a prophylactic intervention. Although the most notable biomarker is LDL-C, this is not universal. To detect the residual risks, numerous biomarkers have been investigated, particularly those that represent chronic inflammation, including fibrinogen [18], plasminogen activator inhibitor [19], platelet aggregation [20], lipoprotein (a) [21], and high-sensitivity CRP [22]. In those biomarkers, the EPA/AA ratio showed evidence related to ACS and ages. The EPA/AA ratio is negatively associated with clinical profiles of ACS [23] and the severity of ischemic heart disease in STEMI patients [24]. Yanagisawa et al. evaluated 200 healthy individuals who lived in an urban area and stated that the serum EPA/AA ratio increased stepwise with age [25]. Serikawa et al. focused on the associations between ACS risk factors and age, and showed that a low EPA/AA ratio in CAD patients was a common risk factor associated with ACS in young adult and middle-aged patients [26]. Yagi et al. found that a low EPA/AA ratio was associated with the early onset of ACS [27]. Our study involved 153 AMI patients who underwent primary PCI and found that the EPA/AA ratio increased at age 60 years. Our study's findings indicated that the EPA/AA ratio was associated with an early AMI onset and that age 60 years was a clear cutoff point related to the EPA/AA ratio in AMI patients.

In this study, the EPA level was not associated with age, but the AA level and the EPA/AA ratio were significantly associated with age, which suggested that the AA level was more dependent on age than EPA or EPA/AA ratio in AMI patients. The westernized food custom might influence

this AA increase and cause the increase in the incidence of AMI in the younger population. Meat is abundant in AA, and previous studies have shown that excessive AA intake induce thrombogenicity [28, 29]. Hence, higher meat intake in the younger group might have influenced the differences between the patient groups. Higher AA may result in elevated thromboxane A2 levels and enhance platelet aggregation. Therefore, intensive anti-platelet therapy (e.g., prolonged dual anti-platelet therapy) could be the effective treatment [30, 31]. However, these agents have bleeding risks associated with their inhibitory effects on the thromboxane A2 and ADP pathways [32]. Regarding primary prevention for young AMI population, the net benefit of intensive anti-platelet therapy might be unclear because of the bleeding risks. In contrast, administering EPA stabilizes vulnerable plaques before rupture in coronary arteries [33, 34], so that EPA could be useful for primary prevention without major complication. The younger group who had poor PUFA profiles could be affected by continuous systemic inflammation that increases the vulnerability of coronary plaques. Therefore, reducing AA intake and simultaneous EPA supplementation could have a synergistic effect. Considering the net benefit, tailored choices would be warranted.

The EPA/AA ratio of the younger group is lower than that of older group among the general population in a Japanese urban area (< 35 y-o; 0.26 ± 0.17, 35 to < 45; 0.29 ± 0.13, 45 to < 55 0.43 ± 0.23, 55 to < 65 0.58 ± 0.25, > 65 0.68 ± 0.22) [25], which mainly suggested that the differences in EPA/AA ratio between younger and older AMI groups were not specific. However, the EPA/AA level of the younger group (0.25 ± 0.16) appeared to be further lower than that of the same study [25] and the all-age population in the Hisayama study (median 0.41; interquartile range 0.29–0.59) [5], which is a historical record. The EPA/AA ratio of the younger AMI population is absolutely lower than that of the general younger population and older AMI population. Furthermore, the younger AMI patients in this study had a higher BMI, higher TG level, and a lower aspirin administration rate, as well as a lower EPA/AA ratio. While the BMI and TG level genuinely differed between the younger and the older individuals, the difference in relation to aspirin administration may indicate that the AMIs represented the younger patients' first ischemic insults. In other words, physicians should prevent the younger population from having their first ischemic attack through multiple prophylactic strategies. The EPA/AA ratio could be one of the targets.

Other investigators have concluded that the EPA/AA ratio, but not the DHA/AA ratio, was negatively associated with ACS [13, 35]. The current study showed a higher DHLA level and a lower DHA/AA ratio in the younger group compared with those in the older group. However, the EPA and AA levels were significantly associated with the DHA and DHLA levels, respectively, and the EPA level differed markedly between the age groups rather than the DHA level. Therefore, supplementing younger people's diets with EPA could be preferred. In the lipid section, no significant differences in LDL-C level were found between the younger and older groups. This could be attributed to the LDL-C level that largely depends on an individual's metabolic capacity, while the PUFA levels are defined by food intake [36]. In addition, in this study, the LDL-C level was comparable with that in the Hisayama study population (mean 125 mg/dL; interquartile range 103–149 mg/dL) [37], even if only 9% of the younger patients in our study were administered with statins. The evidence supporting statin therapy for primary prevention is controversial; therefore, statin pretreatment is not widespread compared with statin use for secondary prevention [38]. The findings from this study suggest that there is little scope for intervention for the management of lipid profiles of younger AMI patients.

Limitations

This study had several limitations. First, the retrospective design, small sample size, potential effects of race, and study location can influence the results. Second, as this cross-sectional study could not confirm the causal relation, the study to investigate whether EPA supplementation could prevent the younger population from having AMI prospectively is warranted in the future. Third, we had no data on the food intake of the studied population, although dietary habit including fish intake influences the EPA/AA level. Fourth, the cutoff value for age that defined the younger and older populations was based on the present study's results. Accordingly, an age of 60 years might not be applicable to other populations as a cutoff point. Fifth, we used EPA and AA to represent *n*-3 and *n*-6 PUFAs, respectively, and other PUFA profiles were not evaluated as confounding factors.

Conclusion

The EPA/AA ratio was increased among AMI patients aged 60 years. The EPA/AA ratio, but not the lipid profile, correlated with the age stratification. Younger population at risk of AMI should be managed using multiple strategies including PUFA profiling.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest to declare.

References

1. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists C (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366:1267–1278
2. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, Treating to New Targets I (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352:1425–1435
3. Sachdeva A, Cannon CP, Deedwania PC, Labresh KA, Smith SC Jr, Dai D, Hernandez A, Fonarow GC (2009) Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J 157(111–117):e112
4. Alagona P Jr (2009) Beyond LDL cholesterol: the role of elevated triglycerides and low HDL cholesterol in residual CVD risk remaining after statin therapy. Am J Manag Care 15:S65–S73
5. Ninomiya T, Nagata M, Hata J, Hirakawa Y, Ozawa M, Yoshida D, Ohara T, Kishimoto H, Mukai N, Fukuhara M, Kitazono T, Kiyohara Y (2013) Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: the Hisayama Study. Atherosclerosis 231:261–267
6. Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB (1997) Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 336:1046–1053
7. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPAlisI (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369:1090–1098
8. Ohnishi H, Saito Y (2013) Eicosapentaenoic acid (EPA) reduces cardiovascular events: relationship with the EPA/arachidonic acid ratio. J Atheroscler Thromb 20:861–877
9. Harris WS, Poston WC, Haddock CK (2007) Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. Atherosclerosis 193:1–10
10. Takii T, Yasuda S, Takahashi J, Ito K, Shiba N, Shirato K, Shimokawa H, Investigators M-AS (2010) Trends in acute myocardial infarction incidence and mortality over 30 years in Japan: report from the MIYAGI-AMI Registry Study. Circ J 74:93–100
11. Morimoto A, Nishimura R, Suzuki N, Matsudaira T, Taki K, Tsujino D, Miyashita Y, Ebara F, Ishikawa S, Tajima N (2008) Low prevalence of metabolic syndrome and its components in rural Japan. Tohoku J Exp Med 216:69–75
12. Arita M, Clish CB, Serhan CN (2005) The contributions of aspirin and microbial oxygenase to the biosynthesis of anti-inflammatory resolvins: novel oxygenase products from omega-3 polyunsaturated fatty acids. Biochem Biophys Res Commun 338:149–157
13. Nishizaki Y, Shimada K, Tani S, Ogawa T, Ando J, Takahashi M, Yamamoto M, Shinozaki T, Miyauchi K, Nagao K, Hirayama A, Yoshimura M, Komuro I, Nagai R, Daida H (2014) Significance of imbalance in the ratio of serum n-3 to n-6 polyunsaturated fatty acids in patients with acute coronary syndrome. Am J Cardiol 113:441–445
14. Nishizaki Y, Shimada K, Tani S, Ogawa T, Ando J, Takahashi M, Yamamoto M, Shinozaki T, Miyazaki T, Miyauchi K, Nagao K, Hirayama A, Yoshimura M, Komuro I, Nagai R, Daida H (2016) Association between the docosahexaenoic acid to arachidonic acid ratio and acute coronary syndrome: a multicenter observational study. BMC Cardiovasc Disord 16:143
15. Endo T, Tomita H, Higuma T, Abe N, Kushibiki M, Saitoh S, Yamada M, Yokota T, Echizen T, Yokoyama H, Tateyama S, Suzuki A, Ishida Y, Murakami K, Osanai T, Okumura K (2014) Low serum eicosapentaenoic acid level is a risk for ventricular arrhythmia in patients with acute myocardial infarction: a possible link to J-waves. Heart Vessels 29:847–854
16. Ueeda M, Doumei T, Takaya Y, Ohnishi N, Takaishi A, Hirohata S, Miyoshi T, Shinohata R, Usui S, Kusachi S (2011) Association of serum levels of arachidonic acid and eicosapentaenoic acid with prevalence of major adverse cardiac events after acute myocardial infarction. Heart Vessels 26:145–152
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESCAAHAWHFTFftUDoMI, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S (2012) Third universal definition of myocardial infarction. Circulation 126:2020–2035
18. Fibrinogen Studies C, Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, Kostis JB, Wilson AC, Folsom AR, Wu K, Benderly M, Goldbourt U, Willeit J, Kiechl S, Yarnell JW, Sweetnam PM, Elwood PC, Cushman M, Psaty BM, Tracy RP, Tybjaerg-Hansen A, Haverkate F, de Maat MP, Fowkes FG, Lee AJ, Smith FB, Salomaa V, Harald K, Rasi R, Vahtera E, Jousilahti P, Pekkanen J, D'Agostino R, Kannel WB, Wilson PW, Tofler G, Arocha-Pinango CL, Rodriguez-Larralde A, Nagy E, Mijares M, Espinosa R, Rodriquez-Roa E, Ryder E, Diez-Ewald MP, Campos G, Fernandez V, Torres E, Marchioli R, Valagussa F, Rosengren A, Wilhelmsen L, Lappas G, Eriksson H, Cremer P, Nagel D, Curb JD, Rodriguez B, Yano K, Salonen JT, Nyyssonen K, Tuomainen TP, Hedblad B, Lind P, Loewel H, Koenig W, Meade TW, Cooper JA, De Stavola B, Knottenbelt C, Miller GJ, Cooper JA, Bauer KA, Rosenberg RD, Sato S, Kitamura A, Naito Y, Palosuo T, Ducimetiere P, Amouyel P, Arveiler D, Evans AE, Ferrieres J, Juhan-Vague I, Bingham A, Schulte H, Assmann G, Cantin B, Lamarche B, Despres JP, Dagenais GR, Tunstall-Pedoe H, Woodward M, Ben-Shlomo Y, Davey Smith G, Palmieri V, Yeh JL, Rudnicka A, Ridker P, Rodeghiero F, Tosetto A, Shepherd J, Ford I, Robertson M, Brunner E, Shipley M, Feskens EJ, Kromhout D, Dickinson A, Ireland B, Juzwishin K, Kaptoge S, Lewington S, Memon A, Sarwar N, Walker M, Wheeler J, White I, Wood A (2005) Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. JAMA 294:1799–1809
19. Juhan-Vague I, Morange P, Christine Alessi M (1999) Fibrinolytic function and coronary risk. Curr Cardiol Rep 1:119–124
20. Trip MD, Cats VM, van Capelle FJ, Vreeken J (1990) Platelet hyperreactivity and prognosis in survivors of myocardial infarction. N Engl J Med 322:1549–1554
21. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgozoglu L, Tybjaerg-Hansen A, European Atherosclerosis Society Consensus P (2010) Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 31:2844–2853
22. Karadeniz M, Duran M, Akyel A, Yarlioglues M, Ocek AH, Celik IE, Kilic A, Yalcin AA, Ergun G, Murat SN (2015) High sensitive

CRP level is associated with intermediate and high syntax score in patients with acute coronary syndrome. Int Heart J 56:377–380
23. Tani S, Nagao K, Hirayama A (2015) Association of atherosclerosis-related markers and its relationship to n-3 polyunsaturated fatty acids levels with a prevalence of coronary artery disease in an urban area in Japan. Heart Vessels 30:9–19
24. Shimada T, Kadota K, Eguchi H, Osakada K, Kuwayama A, Ohya M, Miura K, Amano H, Kubo S, Ozaki M, Hyodo Y, Yoshino M, Miyake K, Kawase Y, Ohashi N, Otsuru S, Tasaka H, Habara S, Tada T, Tanaka H, Maruo T, Fuku Y, Katoh H, Fujii S, Goto T, Mitsudo K (2017) Relationship between n-3 Polyunsaturated Fatty Acids and Extent of Vessel Disease in Patients with ST Elevation Myocardial Infarction. Int Heart J 58:868–873
25. Yanagisawa N, Shimada K, Miyazaki T, Kume A, Kitamura Y, Ichikawa R, Ohmura H, Kiyanagi T, Hiki M, Fukao K, Sumiyoshi K, Hirose K, Matsumori R, Takizawa H, Fujii K, Mokuno H, Inoue N, Daida H (2010) Polyunsaturated fatty acid levels of serum and red blood cells in apparently healthy Japanese subjects living in an urban area. J Atheroscler Thromb 17:285–294
26. Serikawa T, Miura S, Okabe M, Hongo H, Tokutome M, Yoshikawa T, Takesue K, Adachi S, Osaka K, Matsukawa R, Yanagi D, Nozoe M, Kozai T, Hironaga K, Saku K, Yamamoto Y (2014) Ratio of eicosapentaenoic acid to arachidonic acid is a critical risk factor for acute coronary syndrome in middle-aged older patients as well as younger adult patients. J Cardiol 63:35–40
27. Yagi S, Aihara K, Fukuda D, Takashima A, Bando M, Hara T, Nishimoto S, Ise T, Kusunose K, Yamaguchi K, Tobiume T, Iwase T, Yamada H, Soeki T, Wakatsuki T, Shimabukuro M, Akaike M, Sata M (2015) Reduced ratio of eicosapentaenoic acid and docosahexaenoic acid to arachidonic acid is associated with early onset of acute coronary syndrome. Nutr J 14:111
28. Nelson GJ, Kelley DS, Emken EA, Phinney SD, Kyle D, Ferretti A (1997) A human dietary arachidonic acid supplementation study conducted in a metabolic research unit: rationale and design. Lipids 32:415–420
29. Kusumoto A, Ishikura Y, Kawashima H, Kiso Y, Takai S, Miyazaki M (2007) Effects of arachidonate-enriched triacylglycerol supplementation on serum fatty acids and platelet aggregation in healthy male subjects with a fish diet. Br J Nutr 98:626–635
30. Canadian Cardiovascular S, American Academy of Family P, American College of C, American Heart A, Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr, Anbe DT, Kushner FG, Ornato JP, Pearle DL, Sloan MA, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW (2008) 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 51:210–247
31. Meadows TA, Bhatt DL (2007) Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 100:1261–1275
32. Fintel DJ (2012) Oral antiplatelet therapy for atherothrombotic disease: overview of current and emerging treatment options. Vasc Health Risk Manag 8:77–89
33. Nozue T, Yamamoto S, Tohyama S, Fukui K, Umezawa S, Onishi Y, Kunishima T, Sato A, Nozato T, Miyake S, Takeyama Y, Morino Y, Yamauchi T, Muramatsu T, Hibi K, Terashima M, Michishita I (2013) Comparison of effects of serum n-3 to n-6 polyunsaturated fatty acid ratios on coronary atherosclerosis in patients treated with pitavastatin or pravastatin undergoing percutaneous coronary intervention. Am J Cardiol 111:1570–1575
34. Watanabe T, Ando K, Daidoji H, Otaki Y, Sugawara S, Matsui M, Ikeno E, Hirono O, Miyawaki H, Yashiro Y, Nishiyama S, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Kubota I, Investigators Cs (2017) A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. J Cardiol 70:537–544
35. Sakamoto A, Saotome M, Hosoya N, Kageyama S, Yoshizaki T, Takeuchi R, Murata K, Nawada R, Onodera T, Takizawa A, Satoh H, Hayashi H (2016) Aberrant serum polyunsaturated fatty acids profile is relevant with acute coronary syndrome. Heart Vessels 31:1209–1217
36. Stark AH, Crawford MA, Reifen R (2008) Update on alpha-linolenic acid. Nutr Rev 66:326–332
37. Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, Tanizaki Y, Ibayashi S, Iida M, Kiyohara Y (2009) LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. Stroke 40:382–388
38. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators I-I (2015) Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 372:2387–2397

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