Associations of Serum Fatty Acids with Serum Lipids Parameters in Ischaemic Stroke Patients

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Abstract

Background: Serum fatty acids (s-FA) are likely associated with serum lipids parameters (s-LP), such as total cholesterol (T-CHO), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG), because fatty acids (FA) are components of lipoproteins. However, little is known about the association of s-FA with s-LP. The aim of our retrospective study was to investigate the association of s-FA with s-LP in Ischaemic stroke patients. **Methods:** We conducted a cross-sectional study of ischaemic stroke patients aged 50 years or older who 1) were admitted to our institution between September 2015 and March 2017 within 24 hours of stroke onset and 2) took blood examination of s-FA levels of palmitic acid (PA), stearic acid (StA), oleic acid (OIA), linoleic acid (LiA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). We evaluated correlation of serum levels or composition percentage (%) of FA with s-LP. **Results:** One hundred ninety-one patients met our inclusive criteria. Their average age was 74.4 years, BMI was 23.4 kg/m², T-CHO was 203.4, LDL-C was 121.7, HDL-C was 58.5 and TG was 116.2 mg/dl. Stepwise linear regression analysis showed that LiA and AA were independent positive factors of T-CHO, AA and LiA% were independent positive factors of LDL-C, AA was an independent positive factor of HDL-C, AA% and LiA% were independent inverse factors of HDL-C, and OIA was an independent positive factor of TG. **Conclusions:** Serum FA had correlation with s-LP in ischaemic stroke patients. The results warrant clinical application of s-FA modification to improve s-LP.

Background

Serum lipids parameters such as total cholesterol (T-CHO), low density lipoprotein (LDL)-cholesterol (LDL-C), high density lipoprotein (HDL)-cholesterol (HDL-C) and triglycerides (TG) are significant factors of atherosclerosis. Lipoproteins, such as chylomicron, very low density lipoprotein (VLDL), LDL and HDL, are composed of triglycerides, cholesterol ester, phospholipids and apoproteins[1, 2]. Fatty acids, such as saturated fatty acids (SFA), n-9 monounsaturated fatty acids (n-9 MUFA), n-6 polyunsaturated fatty acids (n-6 PUFA) and n-3 polyunsaturated fatty acids (n-3 PUFA), are components of phospholipids and triglycerides. Serum fatty acids, therefore, are likely associated with serum lipids parameters and progression of atherosclerosis.

Previous studies have reported that n-3 PUFA may reduce the incidence of coronary heart disease or stroke or the mortality associated with cardiovascular disease[3-7]. By contrast, SFA may increase the risks of these conditions[8], and the effects of n-6 PUFA remain controversial[9]. Previous studies have reported that serum n-6 PUFA was inversely and n-9 MUFA positively correlated with TG [10] and linoleic acid lowers LDL cholesterol without a proportionate displacement of SFA [11]. Serum FA may be associated with the age at ischaemic disease onset [12]. However, little is known about the association of s-FA with s-LP particularly in ischaemic stroke patients. The aim of our retrospective study was to investigate the association of s-FA with s-LP in ischaemic stroke patients.

Methods

We conducted a cross-sectional study of ischaemic stroke patients aged 50 years or older who 1) were admitted to our institution between September 2015 and March 2017 within 24 hours of stroke onset and then 2) underwent blood evaluations of s-LP and s-FA. We excluded patients who used statins, n-3 PUFA supplements or purified EPA drugs, fibrates or ezetimibe at onset. Additionally, we excluded those with a pre-hospital modified Rankin scale (mRS) score of 3 or more and/or a body mass index (BMI) less than 18.5, which was defined as severe disability and/or underweight according to the World Health Organisation (WHO) guidelines, as we determined that possible malnutrition was not appropriate to our investigation.

Variables

The following fatty acids were examined: SFA [lauric acid (LaA)(12:0), myristic acid (MyA)(14:0), palmitic acid (PA)(16:0) and stearic acid (StA)(18:0)], a n-9 MUFA [oleic acid (OIA)(18:1)], n-6 PUFA [linoleic acid (LiA)(18:2) and arachidonic acid (AA)(20:4)] and n-3 PUFA [alpha-linolenic acid (ALA)(18:3), eicosapentaenoic acid (EPA)(20:5) and docosahexaenoic acid (DHA)(22:5)]. LDL-C was calculated using the Friedewald formula: $\text{LDL-C} = \text{T-CHO} - \text{HDL-C} - \text{TG} / 5$. MBP was calculated using the following formula: $\text{DBP} + (\text{SBP} - \text{DBP}) / 3$.

Evaluation

We evaluated correlation among s-FA, correlation between serum concentration levels or composition percentage (%) of FA and s-LP levels.

Statistical analysis

Continuous variables are expressed as means $\pm$ standard deviations (SDs) and were analysed by using simple linear regression analysis and stepwise linear regression analysis. A p value of less than 0.05 was considered statistically significant. We used the JMP software program (version 14.3; SAS Institute, Cary, NC, USA) to perform the statistical analyses.

Results

A total of 463 patients with ischaemic stroke were admitted to our stroke centre during the study period. Among them, 129 patients were excluded from our analysis because of a pre-hospital mRS score of 3 or more, 37 were excluded with a BMI of less than 18.5, 57 were excluded because they did not undergo a serum fatty acid analysis at admission and 49 were excluded for using medication for dyslipidaemia. Finally, 191 patients (Table 1) met our inclusion criteria. The included patients had an average age of 74.4 years and a slight male predominance (63.3%). Regarding stroke subtype, 102 (53.4%) patients experienced lacunar/atherosclerotic, 50 patients (26.2%) experienced cardiogenic stroke, 5 patients (2.6%) experienced TIA and 34 (17.8%) patients' subtype was not determined. The serum levels of T-CHO, LDL-C, HDL-C and TG were 203.4 ± 40.2 mg/dl, 121.2 ± 33.5 mg/dl, 58.5 ± 17.5 mg/dl and 116.2 ± 71.2 mg/dl, respectively (Table 1). Among fatty acids, LiA(18:2 n-6PUFA) had the largest concentration of

810.6 µg/ml and the largest composition of 27.1% and PA(16:0 SFA) had the second concentration of 711.1 µg/ml, the second composition of 23.7% and OIA(18:1 n-9 MUFA) had the third concentration of 641.2 µg/ml and the third composition of 21.3% (Table 1). The total composition of LiA, PA and OIA was 72.1% among s-FA and the three fatty acids occupied most of s-FA in our patients. On the other hand, the composition of AIA (18:3 n-3), EPA (20:5 n-3) and DHA (22:5 n-3) was 0.8, 2.5 and 4.7% (Table 1), respectively. The total composition of the three n-3 PUFA was 8%. Simple linear regression analysis to explain relationship between fatty acids and serum lipids parameters showed that AA had the largest adjusted R² to estimate T-CHO level, LDL-C level and HDL-C level (Table 2), although the adjusted R² was less than 0.5. OIA had the largest adjusted R² of 0.69 and PA had the second adjusted R² (0.62) to estimate TG level (Table 2). Simple linear regression analysis to explain relationship among fatty acids showed that PA (16:0 SFA) had the largest adjusted R² of 0.84 and StA (18:0 SFA) had the second adjusted R² of 0.57 to estimate OIA (18:1 n-9 MUFA), PA (16:0 SFA) and StA (18:0 SFA) had the larger adjusted R² of less than 0.5 to estimate AA (20:4 n-6 PUFA) than LiA (18:2 n-6 PUFA), AIA (18:3 n-3 PUFA) had no correlation with EPA (20:5 n-3 PUFA) and AIA had weak correlation with DHA (22:5 n-3 PUFA), and EPA (20:5 n-3 PUFA) had the largest adjusted R² of 0.52 to estimate DHA (22:5 n-3 PUFA) (Table 3). Stepwise linear regression analysis to find independent determinants of T-CHO showed that the adjusted R² was 0.49 and that LiA (18:2 n-6 PUFA) (Figure) and AA (20:4 n-6 PUFA) were positive determinants and OIA% was a negative determinant (Table 4-1). Stepwise linear regression analysis to find independent determinants of LDL-C showed that the adjusted R² was 0.21 and that AA (20:4 n-6 PUFA) and LiA% were positive determinants (Table 4-2). Stepwise linear regression analysis to find independent determinants of HDL-C showed that the adjusted R² was 0.43 and that AA (20:4 n-6 PUFA) was a positive determinant and AA% and LiA% were negative determinants (Table 4-3). Stepwise linear regression analysis to find independent determinants of TG showed that the adjusted R² was 0.72 and that OIA (18:1 n-9 MUFA), AIA (20:4 n-6 PUFA) and PA% were positive determinants (Table 4-4).

Discussion

Our results demonstrated that s-FA on admission in acute ischaemic stroke patients aged 50 years or older were correlated with s-LP, such as T-CHO, LDL-C, HDL-C and TG. Linoleic acid (18:2 n-6 PUFA) had a positive correlation with T-CHO. Linoleic acid % had a positive correlation with LDL-C and a negative correlation with HDL-C. Arachidonic acid (20:4 n-6 PUFA) had a positive correlation with T-CHO, LDL-C and HD and arachidonic acid % had a negative correlation with HDL-C. Oleic acid (18:1 n-9 MUFA) had a strong and positive correlation with TG and OIA% had a negative correlation with T-CHO.

Triacylglycerols (i.e., triglycerides), composed of a single glycerol molecule and three fatty acids, constructed dietary lipids. Fatty acids absorbed from the dietary lipids are released into blood and fatty acids synthesized in the liver and fat cells are released into blood, too. High concentration of both PA (16:0 SFA) and OIA (18:1 n-9 MUFA) and the strong correlation of PA (16:0 SFA) with OIA (18:1 n-9 MUFA) suggest metabolic pathway from PA (16:0 SFA) to OIA (18:1 n-9 MUFA) and/or simultaneous ingestion of PA (16:0 SFA) and OIA (18:1 n-9 MUFA) in diet. For example, beef, pork or chicken contains large amounts of OIA (18:1 n-9 MUFA) and PA (16:0 SFA) [13, 14]. Compared to weak correlation of LiA (18:2 n-6 PUFA)

with AA (20:4 n-6 PUFA), StA (18:0 SFA) had a stronger correlation with AA (20:4 n-6 PUFA), suggesting that simultaneous ingestion of both StA (18:0 SFA) and AA (20:4 n-6 PUFA) in diet is superior to metabolic pathway from LiA (18:2 n-6 PUFA) to AA (20:4 n-6 PUFA). Vegetable oils, such as soybean oil, usual sunflower oil, grape seed oil and corn oil, contain large amounts of LiA but little of AA and, for example, pork smoked liver contains moderate amounts of StA and AA [14]. Pork smoked liver is cooked with vegetable oils frequently and then larger amounts of LiA and smaller amounts of StA and AA may be ingested simultaneously. If such food is eaten, too large amounts of LiA (18:2 n-6 PUFA) is not correlated with AA (20:4 n-6 PUFA). The concentration of AIA (18:3 n-3 PUFA) was low and AIA (18:3 n-3 PUFA) had weak correlation with EPA (20:5 n-3 PUFA) and no correlation with DHA (22:5 n-3 PUFA), whereas EPA (20:5 n-3 PUFA) had a strong correlation with DHA (22:5 n-3 PUFA). This suggests that metabolic pathway from AIA (18:3 n-3 PUFA) to EPA (20:5 n-3 PUFA) is weak and metabolic pathway from EPA (20:5 n-3 PUFA) to DHA (22:5 n-3 PUFA) may be stronger or both of EPA and DHA may be ingested simultaneously in diet. For example, raw fish like sardine, mackerel and Japanese horse mackerel contains high concentration of EPA and DHA but does not contain AIA [14].

Statins are commonly used to treat hypercholesterolemia and they can reduce serum T-CHO and LDL-C levels [15]. However, a previous study reported that statins were not able to change s-FA levels [16]. In order to prevent progress of atherosclerosis and ischaemic disease, not only statins but also modification of s-FA may be required. In our patients, the concentration and composition of LiA(18:2 n-6) was the largest and this may be associated with ischaemic stroke. To modify s-FA, it may be effective to reduce LiA% and ingestion of LiA, to increase OIA and OIA% in diet[17] or to increase AIA and AIA% in diet[18]. A previous study reported that, in individuals with peripheral arterial disease, insufficient evidence exists to suggest a beneficial effect of n-3 PUFA supplementation with regard to major adverse cardiac events, need for revascularization or amputation, pain-free walking distance, or quality of life[19]. Not only supplementation of n-3 PUFA but also appropriate daily intake of fatty acids from dietary sources may prevent abnormal increases in the serum levels of TCHO or TG and would thus inhibit the progression of atherosclerosis. Therefore, further prospective study is needed to determine the appropriate levels of SFA (PA and StA), n-9 MUFA (OIA) and n-6 PUFA (LiA and AA) and sufficient levels of n-3 PUFA (EPA and DHA), especially EPA.

Study limitations

Our study had several limitations of note. First, this study included a small number of patients. Moreover, all patients were of East Asian ethnicity and were most likely of Japanese ancestry. In addition to genetic differences attributable to race, our patients likely had different dietary intakes from populations in Western countries. These factors may limit the generalisability of our results. Second, our study design was retrospective and cross-sectional, rather than prospective. Therefore, the appropriate dietary intakes of SFA, MUFA, n-6 PUFA and n-3 PUFA (especially EPA) and consequent serum levels that protect against arteriosclerotic progression could not be confirmed.

Conclusions

Serum fatty acids had correlation with serum lipids parameters in ischaemic stroke patients. The results warrant further clinical application of serum fatty acids modification to improve serum lipids parameters.

Abbreviations

BMI: body mass index, mRS: modified Rankin scale, T-CHO: total cholesterol, VLDL: very low density lipoprotein, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglycerides, FA: fatty acid, s-FA: serum fatty acid, s-LP: serum lipids parameters, SFA: saturated fatty acid, n-9 MUFA: n-9 monounsaturated fatty acid, n-6 PUFA: n-6 polyunsaturated fatty acid, n-3 PUFA: n-3 polyunsaturated fatty acid, LaA: lauric acid, MyA: myristic acid, PA: palmitic acid, StA: stearic acids, OIA: oleic acid, LiA: linoleic acid, AA: arachidonic acid, AIA: alpha-linolenic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, R²: R-square (the coefficient of determination), SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure

Declarations

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institution (Shonan Kamakura General Hospital) and with the 1964 Helsinki Declaration. The institutional (Shonan Kamakura General Hospital) ethics committee approved the access of medical records for our retrospective analysis. Informed consent was not required because of routine medical care, the retrospective design and anonymisation of patient identifiers.

Consent to publish

Not applicable

Availability of data and materials

Raw data can be made available on request to the corresponding author.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors' Contributions

TM had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: TM

Acquisition of data: TM, KY

Interpretation of data and statistical analysis: TM

Drafting the manuscript: TM

Critical revision of the manuscript for important intellectual content: TM

Final approval of the submitted version: TM, KY

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Tables

Due to technical limitations, the tables have been placed in the Supplementary Files section.

Figures

Figure 1

Scatterplot and linear correlation function showing relationship between linoleic acid and T-CHO.

Supplementary Files

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