The Clinical Significance of Low Serum Arachidonic Acid in Sepsis Patients with Hypoalbuminemia

Junko Yamaguchi, Kosaku Kinoshita, Shingo Ihara, Makoto Furukawa and Atsushi Sakurai

Abstract:

Background & Objectives  Fatty acids (FAs) have various roles in pro-inflammatory and anti-inflammatory functions. Hypoalbuminemia is often observed in sepsis patients. An imbalance among these compounds formed from FAs caused by hypoalbuminemia may be related to increased mortality in sepsis patients. The purpose of this study was to investigate the correlations between serum albumin and FAs in sepsis and the outcome.

Methods and Study Design  This study was an observational investigation. The clinical and laboratory data of sepsis patients were recorded and the Sequential Organ Failure Assessment (SOFA) score was calculated at admission. The serum arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and dihomo-gamma-linolenic acid (DHLA) levels were also measured as FAs. The body mass index (BMI) was used to determine the general nutrition status.

Results  Two hundred sepsis patients were enrolled during the study period. No significant correlations were observed between the BMI and the SOFA score or the serum albumin level at admission. The FA levels of the non-survivors were significantly lower, but there were no significant differences in the EPA/AA levels of the survivors and non-survivors. A low serum albumin level was closely related to low AA (p<0.0001), EPA (p<0.0001), DHA (p=0.0003), and DHLA levels (p<0.0001). A multiple logistic-regression analysis revealed that a high SOFA score (adjusted odds ratio, 1.19; 95% CI, 1.02-1.39, p=0.026) and low AA (adjusted odds ratio, 0.98; 95% CI, 0.978-0.994, p=0.041) were associated with a poor outcome.

Conclusion  A lower AA level was an important determinant of the outcome of patients with sepsis. These findings are consistent with the findings of previous studies, which reported that hypoalbuminemia might alter the AA metabolism in sepsis patients.

Key words: Sepsis, fatty acids, hypoalbuminemia, anti-inflammation, arachidonic acid

Introduction

Lipid peroxidation is a key mediator of oxidative stress under acute inflammation, and is induced by arachidonic acid, which is released from cell membrane phospholipids (1). These fatty acids (FAs) have numerous physiological roles as components of the cell membrane phospholipids, modifiers of protein structure, regulators of gene expression, and precursors for the synthesis of bioactive lipid mediators (2). An increase in plasma peroxidation products from FAs has been reported in patients with acute lung injury and is considered to play an important role in oxidative stress leading to molecular damage to lipids (3). A recent study also demonstrated that the metabolism of arachidonic acid (AA) is markedly reduced in patients with sepsis (4). However, it remains unclear whether the changes in FAs that occur in inflammatory conditions can affect the final outcome.

On the other hand, albumin is well known to have many properties, which include not only oncotic effects, but also antioxidant activity, FA transport, and the stabilization of endothelial integrity (5). Hypoalbuminemia is an important parameter for predicting the outcome of patients with sepsis (6). Albumin mobilizes FAs from vital organs, and these
FAs, such as AA, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and dihomo-gamma-linolenic acid (DHLA), perform pro-inflammatory and anti-inflammatory functions (7). Albumin also contributes to the production of lipid metabolites, which mobilizes FAs and thereby has an anti-inflammatory effect (7, 8). Hence, as albumin is strongly related to FA transport, we hypothesized that the increased mortality in patients with sepsis and hypoalbuminemia may occur because the form of FAs is altered under this condition. The purpose of this study was to investigate the relationship between serum AA and albumin in inflammatory conditions and the correlation with the outcome.

Methods

The present study was approved by the Clinical Research Review Committee of NihoUn University School of Medicine (RK15-100611-15) and was designed as a single-institution prospective observational investigation using our hospital’s patient database. Adult patients who were admitted to the intensive care unit (ICU) of our hospital between July 2011 and March 2013 and who were diagnosed with sepsis were targeted (9). The outcome was evaluated on the 28th day in the ICU or when the patient was discharged or transferred from our hospital.

Peripheral whole blood was collected from patients with sepsis at the time of admission. The patient information and laboratory data that were recorded included age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, white blood cell count (WBC), procalcitonin (PCT), C-reactive protein (CRP), and platelet count (10, 11). In this study the serum FA composition of serum lipid fractions (AA, EPA, DHA, and DHLA) were also measured as FAs. The body mass index (BMI) was used as an indicator of the general nutritional status of the patient. It was calculated by dividing the body weight by the square of body height.

Cultures were analyzed by standard microbiological methods at the hospital laboratory. Microbiological samples were obtained from two paired blood cultures, a sputum/nasopharyngeal swab and a urine sample. Isolated microorganisms were identified by Gram staining.

To evaluate the correlations between sepsis severity, causative bacteria, infection sites and each fatty acid, the causative pathogens of sepsis were divided into five groups: Gram-negative bacteria, Gram-positive bacteria, fungi, pathogen not detected (None) by blood culture, and pathogen could not be identified (Non-specific). The infection sites were categorized into the following categories: pulmonary, endocardial (endocarditis), urogenital, abdominal, orthopedic, central nervous system, and various other organs. “Various other organs” included sepsis patients in whom the exact site of infection could not be identified and patients with infections affecting two or more organs.

Patients who received parenteral or enteral nutrition before hospitalization were excluded from this study due to the possibility that this might influence the lipid metabolism.

Statistical analysis

All of the analyses were conducted using the SPSS (Version 22, IBM Statistics, Chicago, IL, USA) and JMP (Version 11.0, SAS Institute, Cary, NC, USA) software programs. The data were presented as the mean (SD) or the number of cases (%). Continuous variables were compared using Student’s t-test or the Mann-Whitney U test as appropriate. The x² test was used to compare categorical variables. Correlations between clinical factors were estimated using the Pearson product-moment correlation coefficient for parametric data, or the Spearman rank test for non-parametric data. The Kruskal-Wallis test was performed for multiple data comparisons of non-parametric data. Post hoc comparisons were performed using Dunn’s method.

The outcome was predicted by a multiple logistic regression analysis using the forced entry method and by calculating the odds ratios and 95% confidence intervals (CIs). The forced entry method was used, with clinical factors that have previously been reported to be related to the outcome included as explanatory variables. Multi-collinearity was assessed using variance inflation factors (12) and detected from the SOFA score and other constituents of the SOFA score (the platelet count, and the creatinine, bilirubin, and GCS values), and metabolites of AA or EPA (DHA or DHLA, and EPA/AA). These variables were not included separately in the multivariate model of the laboratory data on ED. All variables with P values of <0.2 in the bivariate model were included in the multivariate model (a multiple logistic regression analysis).

Finally, any correlations between each fatty acid and albumin were estimated. P values of <0.05 were considered to indicate statistical significance.

Results

Two hundred twenty-eight consecutive sepsis patients were enrolled during the study period. After the exclusion of 11 pediatric patients, 217 patients, whose serum lipid fractions were measured, remained as candidates. Seventeen patients who received parenteral or enteral nutrition before hospitalization were excluded; thus, the final study population included 200 adult patients with sepsis (male, n=115 males; female, n=85).

The average age of the patients was 71.8 years (male, 70.8±14.8 males; female, 73.2±16.0; range, 21-99 years; survivors, 71.2±15.5; non-survivors, 74.2±14.4; p=0.345) and the average BMI was 20.8 (survivors, 20.9±6.2; non-survivors, 20.1±4.6, p=0.601). The age and BMI of the survivors and non-survivors did not differ to a statistically significant extent. Significant differences were observed in the APACHE II score, SOFA score, platelet count, creatinine level, albumin level, acid base balance, heart rate, and body
temperature of the groups. The AA, EPA, DHA, and DHLA levels were also significantly lower in the non-survivors; however, the EPA/AA value did not differ to a statistically significant extent (Table 1).

The causative pathogens of sepsis included Gram-negative bacteria (n=69), Gram-positive bacteria (n=49), fungi (n=10), no pathogen detected by blood culture (n=48) (None), and no identified causative pathogen (n=24) (Non-specific). There were no significant differences in the severity of sepsis or in the causative pathogens (Table 2, upper).

The infection sites were divided into 7 groups (Table 2, bottom). The results of the multiple logistic regression analysis indicated that “various other organs” was an independent factor for a significantly poor outcome in this study (p=0.0159).

The correlation between the FAs and these causative pathogens, namely Gram-negative bacteria, Gram-positive bacteria, fungi and the non-specific group are shown in Table 3. None of the FAs differed to a statistically significant extent. At admission, there were no significant correlations between the BMI and SOFA score (r=-0.0737, p=0.308) or serum albumin (r=0.0474, p=0.517) in the patients of this study. The SOFA score at admission indicated a weak but significant negative correlation with reduced EPA (r=-0.247, p=0.0004), DHA (r=-0.144, p=0.0427), and DHLA (r=-0.214, p=0.002), but no correlation with AA (p=0.106, p=0.136) (Fig. 1).

**Table 1. Characteristics of Septic Patients in the Survival and Non-survival Groups at the Time of Admission.**

| Characteristics                  | All (n=200) | Survivor (n=159) | Non-survivor (n=41) | *p value |
|----------------------------------|------------|----------------|-----------------|---------|
| Number (n) total (n=200)         | 109±47.0   | 115±45.8      | 86.5±44.8       | 0.0006  |
| Age (years)                      | 71.8±15.3  | 71.2±1.2      | 74.2±14.4       | 0.243   |
| Gender (male; %)                 | 115 (57.5%)| 96 (48.0%)    | 19 (9.5%)       |         |
| male vs female                   | 115:85     | 96:63         | 19:22           | 0.105   |
| BMI (kg/m²)                      | 20.8±5.9   | 20.9±6.2      | 20.1±4.6        | 0.601   |
| APACHE II score                  | 20.2±8.0   | 19.3±7.5      | 23.6±9.0        | 0.002   |
| SOFA score                       | 7.0±3.4    | 6.5±3.0       | 9.0±4.0         | <0.001  |
| WBC (×10⁹/μL)                    | 12.2±8.0   | 12.6±8.3      | 10.3±6.7        | 0.110   |
| Platelet (×10⁹/μL)               | 185±99.8   | 193±102       | 155±86.1        | 0.038   |
| Creatinine                       | 2.0±1.9    | 1.9±1.8       | 2.6±2.1         | 0.018   |
| Bilirubin                        | 1.2±1.3    | 1.1±1.2       | 1.4±1.5         | 0.401   |
| CRP (mg/dL)                      | 24.8±42.0  | 26.0±43.1     | 20.4±38.0       | 0.246   |
| Blood pressure                   | 87.0±28.2  | 88.8±28.2     | 79.3±27.1       | 0.074   |
| Temperature (degree)             | 37.1±1.8   | 37.3±1.8      | 36.2±1.6        | 0.001   |

*p value; survival group versus non-survival group

The results are shown in mean±standard deviation.

n: number, BMI: body mass index, BMI is a person’s weight in kilograms divided by the square of height in meters, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA score: Sequential Organ Failure Assessment score, GCS: Glasgow coma scale score, PF: PaO₂/F₉O₂ ratio, PCT: procalcitonin, CRP: C - reactive protein, MAP: mean arterial pressure, HR: heart rate, RR: respiratory rate, WBC: white blood cell

Serum lipid fractions (bracket; reference value)

AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, DHLA: dihomo-gamma-linoleic acid

(p=0.0159).
As Fig. 2 shows, significant positive correlations between AA, EPA, DHA and DHLA, and albumin were evident. A low serum albumin level was closely related to low AA, EPA, DHA, or DHLA levels in this study.

The logistic regression analysis to identify significant predictors of a poor outcome in patients with sepsis revealed that a high SOFA score (adjusted odds ratio 1.25, 95% CI, 1.14-1.40; p<0.0001), low albumin level (adjusted odds ratio 0.42, 95% CI, 0.247-0.693; p=0.0001), and low AA level (adjusted odds ratio 0.98, 95% CI, 0.974-0.993; p=0.0002) were associated with a poor outcome.

A multiple logistic-regression analysis was performed to identify the significant predictors of a poor outcome in patients with sepsis. This analysis revealed that a high SOFA score (adjusted odds ratio, 1.19; 95% CI, 1.02-1.39, p=0.026) and a low AA level (adjusted odds ratio, 0.98; 95% CI, 0.978-0.994, p=0.041) were independently associated with a poor outcome. Other independent predictors of a poor outcome, namely the APACHE II score (adjusted odds ratio, 1.00; 95% CI, 0.938-1.073, p=0.934), WBC count (adjusted odds ratio, 0.97; 95% CI, 0.922-1.030, p=0.365), albumin level (adjusted odds ratio, 0.641; 95% CI, 0.328-1.255, p=0.195), pH (adjusted odds ratio, 0.39; 95% CI, 0.015-9.36, p=0.553), lactate level (adjusted odds ratio, 1.06;
EPA/AA ratio between the survivors and non-survivors, and shock, because of the lack of a significant difference in the specific conditions, such as severe sepsis or septic FA generation may be constant and may be accelerated unexpected. DHA performs an anti-inflammatory function. This rate of pro-inflammatory activity, while those of EPA, and prostaglandins, thromboxanes, and leukotrienes, which are precursors for the synthesis of bioactive lipid mediators (2). Interestingly, the AA, EPA, DHA and DHLA values were found to be significantly correlated with hypoalbuminemia in this study. Several studies have reported that omega-3 fatty acids (EPA, or DHA) act as anti-inflammatory agents that may improve outcome in sepsis. Our results indicate that under septic conditions, both the omega-3 and omega-6 fatty acid families were significantly decreased in patients with underlying hypoalbuminemia, and may influence the final outcome in patients with sepsis. The cell membranes of tissues are rich in FAs that have pro-inflammatory and anti-inflammatory effects (7) and are precursors for the synthesis of bioactive lipid mediators (2). Interestingly, the AA, EPA, DHA and DHLA values were found to be significantly correlated with hypoalbuminemia in the non-survivors. AA may accelerate the metabolic activity according to the severity of sepsis or trauma (1). We wondered whether this phenomenon might be related to the severity of inflammation after the metabolism of FAs. If so, the balance between these eicosanoid compounds formed from FAs may play an important role in oxidative tissue injury under aggravated septic conditions in patients with underlying hypoalbuminemia, and may influence the final outcome in patients with sepsis. The cell membranes of tissues are rich in FAs that have pro-inflammatory and anti-inflammatory effects (7) and are precursors for the synthesis of bioactive lipid mediators (2). Interestingly, the AA, EPA, DHA and DHLA values were found to be significantly correlated with hypoalbuminemia in this study. Several studies have reported that omega-3 fatty acids (EPA, or DHA) act as anti-inflammatory agents and that they may improve outcome in sepsis. Our results indicate that under septic conditions, both the omega-3 and omega-6 fatty acid families were significantly decreased in cases of severe sepsis and accompanying hypoalbuminemia. Under physiological conditions albumin could mobilize FAs from the liver and promote anti-inflammatory compounds.

95% CI, 0.962-1.160, p=0.249), and EPA level (adjusted odds ratio, 1.01; 95% CI, 0.986-1.024, p=0.589), showed no correlation.

**Discussion**

The present study revealed that the serum AA, EPA, DHA, and DHLA levels were significantly decreased in the non-survivor group. In particular, a decreased AA level was a significant risk factor for a poor outcome. Decreased AA, EPA, DHA, and DHLA levels were also significantly associated with low albumin, according to the severity of sepsis as estimated by the SOFA score. Previous studies have reported that a low serum albumin level is an independent predictor of the outcome (6, 13-15). The formation of eicosanoids of prostaglandins, thromboxanes, and leukotrienes, which are generated from the metabolized FAs, especially AA, promote pro-inflammatory activity, while those of EPA, and DHA perform an anti-inflammatory function. This rate of FA generation may be constant and may be accelerated under specific conditions, such as severe sepsis or septic shock, because of the lack of a significant difference in the EPA/AA ratio between the survivors and non-survivors, and despite the decrease in the blood values of these 4 lipid fractions in the non-survivors. AA may accelerate the metabolic activity according to the severity of sepsis or trauma (1). We wondered whether this phenomenon might be related to the severity of inflammation after the metabolism of FAs. If so, the balance between these eicosanoid compounds formed from FAs may play an important role in oxidative tissue injury under aggravated septic conditions in patients with underlying hypoalbuminemia, and may influence the final outcome in patients with sepsis. The cell membranes of tissues are rich in FAs that have pro-inflammatory and anti-inflammatory effects (7) and are precursors for the synthesis of bioactive lipid mediators (2). Interestingly, the AA, EPA, DHA and DHLA values were found to be significantly correlated with hypoalbuminemia in this study. Several studies have reported that omega-3 fatty acids (EPA, or DHA) act as anti-inflammatory agents and that they may improve outcome in sepsis. Our results indicate that under septic conditions, both the omega-3 and omega-6 fatty acid families were significantly decreased in cases of severe sepsis and accompanying hypoalbuminemia. Under physiological conditions albumin could mobilize FAs from the liver and promote anti-inflammatory compounds.

**Figure 1.** The correlations among the AA, EPA, DHA, and DHLA values and SOFA score at hospital admission in patients with sepsis. Weak but significant negative correlations were observed among the serum EPA, DHA, and DHLA values and SOFA score; no significant change in AA was observed. All data points (n=200) were obtained from the serum sample at admission. Analyzed by Spearman’s rank test. AA: ρ=-0.106, p=0.136. EPA: ρ=-0.247, p=0.0004. DHA: ρ=-0.144, p=0.0427. DHLA: ρ=-0.214, p=0.0024. AA: arachidonic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, DHLA: dihomogamma-linolenic acid.
such as lipoxins, resolvins, and protectins, which are metabolized from omega-3 fatty acids (7, 16, 17). On the other hand, hypoalbuminemia may reflect a poor nutritional status, and is frequently observed in patients with liver cirrhosis, malnutrition, and sepsis (15, 18, 19). It is also well recognized that hypoalbuminemia is a strong risk factor that predicts a poor outcome (6, 15). In this study, the duration of the patient’s current illness or nutritional background before their hospitalization were not considered, as the BMI, age and gender did not differ to a statistically significant extent between the survivors and non-survivors. The non-survivors showed significantly decreased AA, EPA, DHA, and DHLA levels. These findings, which are related to the lipid metabolism in sepsis patients, are of interest since a poor FA balance may affect the antioxidant protection of the cell membrane (20) and influence the outcome. Further studies that target patients with sepsis to determine the correlation with lipid peroxidation may yield new therapeutic strategies using the omega-3 fatty acids family.

An increase in blood peroxidation products from FAs has reported in acute lung injury and acute respiratory distress syndrome (ARDS) patients and oxidative stress is thought to lead to molecular damage to lipids (3, 21). Previous in vivo studies have demonstrated that rabbits that received tumor necrosis factor (TNF)-alpha developed hypoalbuminemia (22), and that endothelial cells treated with TNF-alpha showed decreased FA levels (23). Taken together, these findings may indicate that a circulating inflammatory cytokine, such as TNF-alpha can induce hypoalbuminemia in patients with sepsis and FA deficiency, thereby leading to the decreased mobilization of FAs from the liver.

Sepsis-induced hypoalbuminemia, which is caused by various pathophysiological mechanisms, leads to the exacerbation of septic conditions (15, 19). In the inflammatory setting, changes in vascular permeability increase the transcapillary loss of albumin, accelerating deterioration to hypoalbuminemia (24-26). Hypoalbuminemia may also develop as a result of decreased albumin synthesis due to inflammatory cytokines such as interleukin-1 (IL-1) (27), 6 (IL-6) and TNF-alpha (24). Metabolites of omega-3 fatty acid reduce the infiltration of leukocytes, which has an anti-inflammatory effect (7, 8). Serum albumin can function as a binding protein of long-chain FAs, which are transported to vital organs (28) and, as a result, may be related to the overall outcome when the anti-inflammatory effect of the omega-3 fatty acid family is reduced.

Although albumin has a high-affinity binding of AA to the protein and extraction of AA from the cell membrane (29), the exact role of the correlation between albumin and arachidonic acid, and other FAs in sepsis patients is still
unclear. In an in vitro study, Mayer et al. reported that long-chain polyunsaturated FAs, such as AA (4), EPA, DHA and DHLA, decreased the production from human endothelial cells in the presence of TNF-alpha due to inflammatory reactions (23). These interactions between albumin and AA could play a role in the regulation of vascular permeability (30). If albumin and AA are reduced in response to the severity of sepsis, the change in vascular permeability may progress during sepsis, leading to the transcapillary loss of albumin and acceleration to hypoalbuminemia.

We hypothesize that decreased AA may indicate severe inflammation, and the accelerated reduction of albumin, which is mainly caused by a reduction of hepatic synthesis, increases the leakage into the interstitial compartment, and causes persistent catabolism during sepsis (15, 24).

This study is associated with some limitations. A major limitation is that the data were only obtained once, at the time of admission. Detailed information on the nutritional conditions of the patients, which may affect the blood lipid levels (i.e., blood triglyceride or cholesterol), and the duration of illness before hospitalization, were not analyzed. However, because there was no significant difference in the BMI values of the survivors and non-survivors it is unlikely that there were significant differences in this area. The mean BMI (20.8±5.8) in this study group was low, and no significant differences were seen among the BMI, SOFA, and serum albumin values at the time of admission. The next step is to analyze and clarify the clinical significance of FAs, albumin and the outcome of the sepsis patients over time because these parameters may change substantially. Second, the precise mechanism leading to low AA, EPA, DHA, or DHLA in patients with hypoalbuminemia remains unclear. Cyclooxygenase is the key regulatory enzyme in the metabolism of AA. A recent report demonstrated the significant reduction of AA and cyclooxygenase-dependent metabolites in sepsis (4), presumably at the level of transcription; thus, a cyclooxygenase-dependent feedback regulation mechanism may be involved (29). Further studies are required to fully explore the complex roles of FAs in the setting of hypoalbuminemia after sepsis.

**Conclusion**

Low AA is a potential risk factor for a poor outcome in patients with sepsis. Decreased AA levels were also significantly associated with low albumin levels according to the severity of sepsis, as estimated by the SOFA score. These findings are consistent with previous studies which reported that hypoalbuminemia might alter the AA metabolism of sepsis patients.

The authors state that they have no Conflict of Interest (COI).

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