Fatty acids of erythrocyte membrane in acute pancreatitis patients

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AIM: To evaluate changes in the fatty acid composition of erythrocyte membrane phospholipids during severe and mild acute pancreatitis (AP) of alcoholic and nonalcoholic etiology.

METHODS: All consecutive patients with a diagnosis of AP and onset of the disease within the last 72 h admitted to the Hospital of Lithuanian University of Health Sciences between June and December 2007 were included. According to the Acute Physiology and Chronic Health Evaluation (APACHE II) scale, the patients were subdivided into the mild (APACHE II score < 7, n = 22) and severe (APACHE II score ≥ 7, n = 17) AP groups. Healthy individuals (n = 26) were enrolled as controls. Blood samples were collected from patients on admission to the hospital. Fatty acids (FAs) were extracted from erythrocyte phospholipids and expressed as percentages of the total FAs present in the chromatogram. The concentrations of superoxide dismutase and glutathione peroxidase were measured in erythrocytes.

RESULTS: We found an increase in the percentages of saturated and monounsaturated FAs, a decrease in the percentages of total polyunsaturated FAs (PUFAs) and n-3 PUFAs in erythrocyte membrane phospholipids of AP patients compared with healthy controls. Palmitic (C16:0), palmitoleic (C16:1n7cis), arachidonic (C20:4n6), docosahexaenoic (DHA, C22:6n3), and docosapentaenoic (DPA, C22:5n3) acids were the major contributing factors. A decrease in the peroxidation and unsaturation indexes in AP patients as well as the severe and mild AP groups as compared with controls was observed. The concentrations of antioxidant enzymes in the mild AP group were lower than in the control group. In severe AP of nonalcoholic etiology, the percentages of arachidic (C20:0) and arachidonic (C20:4n6) acids were decreased as compared with the control group. The patients with mild AP of nonalcoholic etiology had the increased percentages of total saturated FAs and gama linoleic acid (C18:3n6) and the decreased percentages of elaidic (C18:1n9t), eicosapentaenoic acid (EPA, C20:5n3), DPA (C22:5n3), DHA (C22:6n3) as well as total and n-3 PUFAs in erythrocyte membrane phospholipids.

CONCLUSION: The composition of FAs in erythrocyte membranes is altered during AP. These changes are likely to be associated with alcohol consumption, inflammatory processes, and oxidative stress.

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Key words: Acute pancreatitis; Alcohol; Fatty acids; Oxidative stress; Systemic inflammatory response syndrome

Core tip: The manuscript by Kuliaviene et al elucidates the changes of fatty acids in erythrocyte membrane phospholipids during acute pancreatitis. Alcohol may influence the increased percentage of saturated and monounsaturated fatty acids of erythrocyte membrane. Fatty acids that are linked with inflammatory processes change differently during severe and mild nonalcoholic acute pancreatitis. The decrease of pro-inflammatory acids is seen in severe acute pancreatitis while anti-inflammatory players decrease during mild acute pancreatitis. The antioxidant enzymes of erythrocytes change in mild but not severe pancreatitis group. Thus the erythrocyte membranes can reflect the inflammatory and oxidative processes of acute pancreatitis.

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INTRODUCTION

Acute pancreatitis (AP) is a sudden inflammation of pancreas. About 20%-30% of patients develop severe forms of the disease manifesting with local and systemic complications. Acute pancreatitis carries an overall mortality rate of 10%-15%
[1,2]. The main causes of death are associated with multiple organ failure and pancreatic infection[3,4]. The initial process of inflammation starts in the pancreas, but no strict correlation between pancreatic necrosis and organ failure has been reported[5]. Systemic inflammatory response is responsible for multiple organ failure and has the most considerable impact on the severity of acute pancreatitis and mortality from this disease[6].

The role of fatty acids (FAs) in the pathogenesis of AP is important but far from being clear. An increase the total serum free FA level is observed during AP[7]. Unsaturated FAs, especially polyunsaturated FAs (PUFAs), are liberated from pancreatic necrotic tissues and are responsible for the disturbance of FA profile in the serum of patients with AP[8]. The increased amount of unsaturated FAs in the necrotic pancreatic tissue and serum during AP is associated with multisystem organ failure and worse outcomes of patients[9]. Moreover, alcohol, an important etiological factor for pancreatitis, has an impact on the FA composition of serum and erythrocyte membrane[10-13]. Surprisingly, during alcohol-induced pancreatitis, the percentage of PUFA is decreased in the serum FA profile in mild and moderate AP as well as chronic pancreatitis[14,15]. These data suggest that alcohol could play a specific role in the pathogenesis of pancreatitis.

FAs of cell membranes are precursors for lipid mediators and play an important role in the process of inflammation and oxidant status[16]. Experimental findings show that n-3 PUFAs may be beneficial in the prevention of oxidative stress-induced inflammation in pancreatitis[17]. Moreover, it influences the histological severity of AP[18,21]. Human studies also indicate likely clinical benefits of enteral feeding rich in n-3 PUFAs in patients with AP[22].

The aim of our study was to evaluate changes in the FA profile of erythrocyte membrane phospholipids and antioxidant enzymes of erythrocytes in patients with severe and mild AP, also of nonalcoholic etiology separately, in comparison with healthy individuals. We believe that erythrocyte membrane phospholipids can better reflect systemic changes caused by oxidative stress and inflammatory response in patients with AP comparing with FAs in serum, which are greatly influenced by necrotic changes in the pancreas and peripancreatic tissues. To our knowledge, no studies examining the FA composition of erythrocyte membrane phospholipids during AP have been carried out.

MATERIALS AND METHODS

Patients

All consecutive patients with a diagnosis of AP and onset of the disease within the last 72 h admitted to the Departments of Surgery and Gastroenterology at the Hospital of Lithuanian University of Health Sciences between June and December 2007 were included in this study. The diagnosis was established based on acute abdominal pain, at least 3-fold elevated levels of serum amylase, and typical radiological findings. According to the Acute Physiology and Chronic Health Evaluation (APACHE II) scale, the patients were subdivided into the mild (APACHE II score < 7, n = 22) and severe (APACHE II score ≥ 7, n = 17) AP groups. Healthy subjects (n = 26) without a past history of pancreatic diseases were enrolled as controls.

Fatty acid and antioxidant analysis

Peripheral blood samples were drawn from patients on admission to the hospital. Plasma and leukocytes were removed after centrifugation. Erythrocytes were washed and centrifuged twice. The samples were stored at -80°C until analysis. The blood samples of the control group were subjected to the same procedure.

FA analysis was performed in the Laboratory for Health Protection Research, National Institute for Public Health and the Environment (The Netherlands), as described previously[23]. Briefly, 200 μL of erythrocytes was taken, and phospholipids were washed with distilled water and extracted with chloroform/methanol (1:1). The chloroform layer was evaporated, and the phospholipids were hydrolyzed and methylated simultaneously.
with BF$_3$/MeOH for 60 min at 100 °C. After extraction with hexane, the methylated FAs (FAME) were separated on a fused silica capillary column using a GC-3900 gas chromatograph with FID detection (Varian Assoc). The baseline separation of more than 50 FAME peaks was accomplished using FAME standards (Sigma) within 57 min. Individual FAs were expressed as percentages of the total FAs present in the chromatogram.

The concentrations of superoxide dismutase (SOD) and glutathione peroxidase (GPs) were measured in erythrocytes on an auto analyzer (LX-20 Pro, Beckman-Coulter, Woerden, Netherlands) with kits from Randox (Ransod and Ransel, Crumlin, United Kingdom).

**Peroxidation and unsaturation index**

The indexes were calculated according to the formulas used by Viviani et al. The peroxidation index (PI) was determined from the percentages of monoenic, dienoic, trienoic, tetraenoic, pentaenoic and hexanoic FAs according to the following formula: PI = [%monoenic × 1 + %dienoic × 2 + %trienoic × 3 + %tetaenoic × 4 + %pentaenoic × 6 + %hexanoic × 8].

The unsaturation index (UI) is also known as the index of hydrogen deficiency. It was calculated from the number of unsaturated double bonds of each FA: UI = [%monoenic × 1 + %dienoic × 2 + %trienoic × 3 + %tetaenoic × 4 + %pentaenoic × 5 + %hexanoic × 6].

**Ethics**

The study was approved by Kaunas Regional Ethics Committee for Biomedical Research (BE-2-47). All patients and healthy subjects provided written informed consent.

**Statistical analysis**

Statistical analysis was performed using SPSS® for Windows release 14.0 (SPSS, Chicago, IL, United States). The data are presented as mean ± SD. The Mann-Whitney test and one-way and two-way ANOVA tests were applied for analysis of variables. All statistical tests were two sided, and $P < 0.05$ was considered statistically significant.

**RESULTS**

The demographic characteristics of patients and controls are presented in Table 1. There was no difference in the FA composition of membrane phospholipids between men and women in the control group (data not shown).

As shown in Table 2, the percentage of saturated FAs in erythrocyte membrane phospholipids was greater in patients with acute pancreatitis (AP) of alcoholic and nonalcoholic etiology. $P < 0.05$, $P < 0.01$ vs control group.

The percentages of total and n-3 PUFAs were decreased in erythrocyte membrane phospholipids of AP...
patients. This was particularly caused by the decreased percentages of docosahexaenoic (DHA C22:6n3) and docosapentaenoic (DPA C22:5n3) acids. The percentage of arachidonic acid (AA, C20:4n6) was decreased in the patients with AP comparing with the controls, though the percentages of gama-linoleic (C18:3n6) and dihomo gama linoleic (C20:3n6) acids were increased (Table 2).

A decrease of PI and UI in AP patients as well as the severe and mild AP groups compared with the controls was observed. The extent of change in the indexes in the mild AP group was greater than in severe AP group comparing with controls (both compared with controls was observed). Bars represent mean values with standard deviation. The extent of change in the indexes in mild AP was greater than in severe AP patients comparing with controls (\( \mu < 0.05, \mu < 0.01 \) vs control group).

Figure 1 Peroxidation and unsaturation indexes of fatty acids of erythrocyte membrane phospholipids in the acute pancreatitis, severe acute pancreatitis, mild acute pancreatitis, and control groups. A significant decrease of peroxidation index and unsaturation index in acute pancreatitis (AP) patients compared with controls was observed. Bars represent mean values with standard deviation. The extent of change in the indexes in mild AP was greater than in severe AP patients comparing with controls (\( \mu < 0.05, \mu < 0.01 \) vs control group).

DISCUSSION
This study has analyzed the impact of systemic inflammatory response and oxidative stress on the FA composition of erythrocyte membranes and the concentrations of enzymes in patients with AP. The initial generation of ROS and inflammatory events occur in the pancreas, but systemic changes have a crucial impact on the severity and fatal outcomes of AP\(^9\). A better understanding of these systemic processes occurring during AP could help identifying new therapeutic treatment options and escaping undesirable complications or fatal outcomes.

In our study, we found that the FA composition of erythrocyte membrane phospholipids was significantly altered during AP compared with controls mainly because of the increased percentages of saturated and monounsaturated acids, namely palmitic and palmitoleic, and a decreased percentage of PUFAs. Contrary, Sztefko et al\(^5\) found that the proportion of saturated and monounsaturated acids was decreased and the proportion of PUFAs was increased in the serum levels of free FAs in patients with AP. An increase in the percentage of PUFAs in the necrotic pancreatic tissue has also been reported\(^{39}\). On the other hand, in severe sepsis, a similar pathology with systemic inflammatory response syndrome, the lower proportions of PUFAs and the greater proportions of monounsaturated FAs in erythrocyte phospholipids have been documented\(^{39}\). These findings suggest that the FA composition of erythrocyte membrane phospholipids may reflect not only the direct events in the pancreas, but also the systemic response syndrome during AP.

Alcohol consumption can be associated with the higher percentages of saturated and monounsaturated FAs, such as palmitic and oleic acids, and the lower percentages of PUFAs, especially DHA and arachidonic acid, in serum and membranes\(^{10,13}\). Alcoholics have also been shown to have a disturbed oxidant status of plasma and erythrocyte enzymes\(^{25-28}\). In the study by Khan et al\(^{20}\), the authors showed the increased percentages of saturated palmitic and monounsaturated FAs as well as the decreased percentages of some PUFAs in serum of patients with alcohol-induced AP comparing with alcoholic controls. Moreover, Gabianelli et al\(^{17}\) reported that ethanol can have a direct toxic effect on erythrocyte membranes and antioxidant systems of the cells. These findings indicate that alcohol may have an impact on the FA composition of erythrocyte membrane phospholipids. Thus, the increased percentages of saturated and monounsaturated FAs in our study could partly be explained by etiological factors, most probably alcohol.

To rule out the impact of alcohol and to study the influence of inflammatory and oxidative processes during AP on the phospholipid composition of erythrocyte membranes, we analyzed patients with AP of nonalcoholic etiology. The PUFAs of cell membranes are precursors for prostaglandins and other lipid mediators of inflammatory process\(^{16}\). Arachidonic acid is the main proinflammatory agent. Meanwhile, EPA, DHA, and possibly DPA are precursors for products with anti-inflammatory and proresolving functions\(^{30,31}\). We found that in the severe AP group, the percentage of proinflammatory arachidonic acid was significantly decreased, and
in the mild AP group, a decrease in the percentages of anti-inflammatory players (EPA, DHA, and DPA) was seen as compared with controls. It is now thought that saturated FAs could also be involved in the inflammatory process. We also found a significant increase in the total percentage of saturated FAs in the mild but not severe AP group. Erythrocytes are usually considered to be active players in the inflammatory process, but our study showed that the changes in the percentage of FAs in erythrocyte membrane phospholipids were different during mild and severe AP; therefore, we hypothesize that the composition of erythrocyte membrane phospholipids may reflect the inflammatory processes and the severity of the disease.

Oxidative stress plays a central role in the development of pancreatic inflammation and extra pancreatic complications. The changes of the FA composition of erythrocyte membranes could be affected from “the outside” as PUFAs of erythrocyte membrane phospholipids are extremely sensitive to oxidation. SOD and GPx are important components of enzymatic antioxidant defense. We found that the levels of antioxidant enzymes in erythrocytes were also altered significantly in the mild but not severe AP group comparing with controls. There were significant differences in the PI and the UI mainly because of the different percentage of PUFAs in erythrocyte membrane phospholipids in the severe and mild AP groups comparing with controls. Moreover, there was a significant difference between the severe and mild AP groups. This suggests that oxidative stress might be involved in the changes of the FA composition of erythrocyte membrane phospholipids and systemic inflammatory response.

It was unexpected to find the changes of PI and UI to be more apparent in the mild AP than severe AP group comparing with controls. It is known that systemic response followed by organ failure influences the severity and outcome of AP more than the events in the pancreas itself. The similar phenomenon was also noticed in cytokine expression during mild and severe AP. We hypothesize that these findings could reflect the disproportionate of pro- and anti-inflammatory processes during severe AP possibly associated with oxidative stress. The mechanisms of these processes are still not clear and remain to be elucidated.

The composition of FAs in erythrocyte membranes is altered during AP. These changes are likely to be associated with alcohol intake as an etiological factor for AP, and systemic inflammatory processes and oxidative stress after the onset of the disease could influence the changes.

### Table 3 Percentages of fatty acids

| Nonalcoholic | Severe AP       | Mild AP       | Control        |
|--------------|-----------------|---------------|----------------|
| C20:0        | 0.32 ± 0.09 a   | 0.39 ± 0.09 a | 0.40 ± 0.06 a  |
| C20:4n6      | 12.89 ± 0.83 a  | 13.09 ± 1.40 a| 13.64 ± 0.99 a |
| SFA          | 43.53 ± 1.29 a  | 44.54 ± 1.86 a| 43.34 ± 0.90 a |
| C18:3n6      | 0.04 ± 0.02 a   | 0.05 ± 0.02 a | 0.03 ± 0.01 a  |
| C18:1n9t     | 0.13 ± 0.04 a   | 0.12 ± 0.07 a | 0.16 ± 0.04 a  |
| C20:5n3      | 1.03 ± 0.56 a   | 0.67 ± 0.18 a | 1.02 ± 0.4 a   |
| C22:5n3      | 2.28 ± 0.22 a   | 2.10 ± 0.36 a | 2.39 ± 0.29 a  |
| C22:6n3      | 5.29 ± 1.02 a   | 4.24 ± 1.05 a | 5.89 ± 0.81 a  |
| n-3 PUFA     | 8.76 ± 1.73 a   | 7.14 ± 1.45 a | 9.45 ± 1.30 a  |
| Total PUFA   | 36.87 ± 1.62 a  | 34.91 ± 2.26 a| 37.34 ± 1.30 a |
| SOD          | 385.37 ± 21.37 a| 314.90 ± 86.04 a| 384.88 ± 42.21 |
| GPx          | 12557.07 ± 2836.06 a| 9370.85 ± 2196.13 a| 11649.09 ± 1844.75 a |
| PI           | 138.49 ± 10.34 a| 128.14 ± 10.74 a| 146.19 ± 7.08 a |
| UI           | 156.67 ± 7.26 a | 148.99 ± 8.04 a| 161.70 ± 4.90 a |

Results are presented as mean ± SD. Percentages of fatty acids in erythrocyte membrane phospholipids, peroxidation and unsaturation indexes, and concentrations of superoxide dismutase (SOD, μmol/mL) and glutathione peroxidase (GPx, U/L) in patients with acute pancreatitis (AP) of nonalcoholic etiology. aP < 0.05 comparing mild and severe AP; aP < 0.01 vs control group. PUFA: Polyunsaturated fatty acids; SFA: Saturated fatty acids.

**COMMENTS**

**Background**

Acute pancreatitis carries an overall mortality rate of 10%-15%. Systemic inflammatory response has the most considerable impact on the severity of acute pancreatitis and mortality from this disease. Fatty acids of cell membranes are precursors for lipid mediators and play an important role in the process of inflammation and oxidant status. Erythrocyte membrane phospholipids can reflect systemic changes caused by oxidative stress and inflammatory response in patients with acute pancreatitis.

**Research frontiers**

The role of fatty acids in the pathogenesis of acute pancreatitis is important but far from being clear. Fatty acids are the components of membrane phospholipids. They are responsible for inflammatory and oxidative processes. Free fatty acids in serum are associated with necrotic lesions in the pancreas and peripancreatic tissues. Moreover, alcohol, an important etiological factor for pancreatitis, has an impact on the fatty acid composition of serum and erythrocyte membranes.

**Innovations and breakthroughs**

The earlier studies of alterations in the fatty acid composition during acute pancreatitis mainly investigated the fatty acid composition in serum that is greatly influenced by necrotic changes in the pancreas and peripancreatic tissues. Authors believe that erythrocyte membrane phospholipids can better reflect systemic changes caused by oxidative stress and inflammatory response as well as alcohol impact in patients with acute pancreatitis. To the knowledge, no studies examining the fatty acid composition of membranes during acute pan-
Applications
This study elucidates the pathogenesis of acute pancreatitis, especially the systemic and oxidative processes that are of high importance in the severity of acute pancreatitis and mortality from this disease.

Terminology
Fatty acids are the components of phospholipids that form the lipid bilayers of cell membranes. Fatty acids of membranes are precursors for lipid mediators of inflammatory response syndrome. Oxidative stress is a disturbance of the pro-oxidant-antioxidant balance in favor of the former, leading to potential damage, and is associated with many chronic and acute inflammatory conditions.

Peer review
This study evaluates changes in fatty acids of erythrocyte membrane phospholipids during mild and severe acute pancreatitis, of alcohol and non-alcohol etiology. The study is a prospective one and Acute Physiology and Chronic Health Evaluation II score was used to classify patients into mild (n = 22 patients) and severe (n = 17 patients). Some 26 healthy individuals were enrolled as control.

This is a well conducted prospective study, and to my knowledge this is the first study that examines the fatty acid profile of the erythrocyte membrane in acute pancreatitis.

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