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ERYTHROCYTE MEMBRANE FATTY ACID COMPOSITION OF DEPRESSIVE PATIENTS

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Research Article

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Abstract

Major depressive disorder (MDD) is a serious affective illness. Eventhough association of some fatty acids and depression is reported, there is no information on composition of total fatty acids in erythrocyte mebranes. The present study was aimed to investigate for a possible relationship between depression and fatty acid composition of erythrocyte membranes. For this purpose, 30 patients diagnosed with major unipolar depression and 30 healthy control groups without any depression symptoms were formed. In these groups, erythrocyte membrane fatty acid composition was detected by Gas Chromatopgraphy. According to our results, unsaturated fatty acid levels in depressive patients were lower than in control group. The level of some fatty acids, especially with 18 to 22 carbon fatty acids, was reduced. The reduction of some fatty acids in erythrocyte mebranes during depression may indicate an alteration or a defect in polyunsaturated fatty acid (PUFA) methabolism in depressive patients.

Key Words: Deppresive patients, Erytrocytes membranes, Fatty acids, Gas Chromatopgraphy

Özet

Majör depresif bozukluk (MDB) ciddi bir duygudurum hastalığıdır. Bazı yağ asitlerinin depresyonla ilişkisi bildirilse de eritrosit zarlarındaki toplam yağ asitlerinin bileşimi hakkında literatürde yeterli bilgi mevcut değildir. Bu çalışma ile depresyon ile eritrosit membranlarının yağ asidi bileşimi arasındaki olası bir ilişkiyi araştırmak amaçlanmıştır. Bu amaçla majör unipolar depresyon tanısı alan 30 hasta ve herhangi bir depresyon belirtisi olmayan 30 sağlıklı kontrol grubu oluşturuldu. Bu gruplarda eritrosit membran yağ asidi kompozisyonu Gaz Kromatografisi ile tespit edildi. Sonuçlarımıza göre depresif hastalarda doymamış yağ asidi düzeyleri kontrol grubuna göre daha düşüktü. Özellikle 18 ila 22 karbonlu yağ asitleri ile bazı yağ asitlerinin seviyesinin düşük olduğu tespit edildi. Depresyon sırasında eritrosit zarlarındaki bazı yağ asitlerinin azalması, depresif hastalarda çoklu doymamış yağ asidi (PUFA) metabolizmasında bir değişikliği veya bir bozukluğu gösterebilir.

Anahtar Kelimeler: Depresyon, Eritrosit membranı, Gaz Kromotografisi, Yağ Asitleri

1. Introduction

Polyunsaturated fatty acids (PUFA) contain two or more carbon-carbon double bonds that are unsaturated with hydrogen atoms. PUFA classified into various groups by their chemical structure in omega-3 and omega-6 fatty acids. The methyl carbon is called the omega "ω" carbon, and the unsaturated fatty acids ω-3 (n-3), ω-6(n-6), depending on the position of the ω carbon where the first double bond is found. (Grosso et al., 2014).

Major depressive disorder (MDD) which is one of the most common mental disorders, is a serious affective illness with an estimated lifetime prevalence of approximately 5% to 11% of the population. (McIntyre and O'Donovan, 2004). In recent years, there has been increasing interest in clinical studies supporting the use of ω − 3 PUFA, one of a kind of polyunsaturated fatty acids, in the treatment of MDD. (Peet and Stokes, 2005).

Various studies have shown that the development of major depression may be associated with changes in the fatty acid composition of lipids. The information obtained from these studies is that the decrease in n-3 fatty acids in the serum may trigger the formation of major depression. In addition, in the light of these studies, a decrease in n-3 fatty acids and a shift in fatty acid balance from n-3 to n-6 were noticed in depressed patients. (Maes et al., 1996; Edwards et al., 1998). It

has been reported that total n-3 fatty acid amounts in the erythrocyte membrane are lower in patients with major depression compared to healthy controls. In these patient groups, disease severity was positively correlated with a ratio of 20:4 n-6 to 20:5 n-3 in serum phospholipids (PL) and red blood cell membranes (Adams et al., 1996). It was determined that n-3 fatty acids, especially 22:6 n-3 levels, were decreased in the red blood cell membranes of depressed patients compared to the healthy control group (Edwards et al., 1998; Peet et al., 1998). These results suggest that abnormal metabolism of n-3 PUFA's may be effective in the development of depression.

In addition to fatty acids, there are studies with membrane phospholipids in psychiatric disorders. In a study, it was shown that phosphatidylethanolamine levels decreased significantly in these patient groups, while there was a significant increase in sphingomyelin levels. (Keshavan at al., 1992). moreover, Pargerl et al. (1991) observed no change in phosphatidylcholine or phosphatidylethanolamine in their study, but an increase in lysophosphatidylcholine in depressive disorders.

Evidence from epidemiological studies showing a possible link between seafood consumption and a reduced prevalence of depression supports this negative association. Majör depresyonun yaygınlığı, balık tüketimi ile güçlü bir şekilde ters orantılıdır. (Hibbeln,1998). Moreover, Hibbeln (2002) reported that higher concentrations of DHA in mothers' milk and fish consumption predicted lower prevalance rate of depression.On the other hand, Peet et al (1998) found that total ω -3 fatty acid levels were decreased, DHA especially on red blood cell membranes in patients with major depressive disorder (n=15) compared with normal controls (Yoshikawa et al., 2016)

In recent years, there has been great interest in n-3 PUFAs, which are important for the development and function of the central nervous system, and their role in depression. Recent studies suggest that a diet deficient in n-3 PUFAs may subscribe to the development of psychological disorders (Deacon et al., 2017).

Studies have shown that there are significant decreases in red blood cell membrane, docosahexaenoic acid and other n-3 long chain PUFA levels in patients with depression compared to controls. In addition, it has been reported that increased PUFA levels in the red blood cell membrane as a result of diet rich in n-3 PUFA are negatively correlated with the severity of depression. On the other hand, the severity of the disease and eicosapentaenoic acid (EPA; C20:5n-3) levels in erythrocyte phospholipids were negatively correlated in a group of depressed

patients [Adams et al., 1996; Peet et al., 1998). However, there are also studies in the literature that do not show a decrease in n-3 PUFA in depressed patients, unlike healthy subjects. In particular, a few studies showed significant increases in plasma phosphatidylcholine and erythrocyte EPA and DHA levels in depressed patients in contrast to healthy control subjects (Ellis and Sanders, 1977; Fehily et al., 1981).

There are several studies investigating the relationship between fatty acid composition and depressive disorders (Maes et al., 1996; Peet et al., 1998; Maes et al., 1999). According to the results of the study examining the relationship between depressive disorders and fatty acid composition, n-3 PUFA concentrations were found to be lower in depressed patient groups than in healthy controls. Therefore, unlike previous studies, the aim of the present study was to investigate the amounts of all fatty acids in red blood cell membrane of depressive patients comprare to control group and whether these fatty acids may be associated with depression. In this study, the effects of depresion on fatty acid composition of erythrocyte membrane was examined.

2. Material and Methods

2.1. Subjects

In our study, each consisting of 30 people, including two groups of patients and controls have been established. The control group consisted of 24 women and 6 men between 23-65 years old with no symptoms of depression. The control subjects were selected among subjects who did not use non- steroidal anti inflammatory (NSAI) in two-week period applied to Gaziosmanpasa University Medical Faculty Physical Therapy and Rehabilitation and Psychiatry Clinic. The patient group consisted of 23 women and 7 men, between 23-65 years old with diagnosis of major unipolar depression and have not been started any antidepression treatment. The patient group was evaluated by Gaziosmanpasa University Medical Faculty of Psychiatry Clinic. Psychiatric diagnosis were made acoording to Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Both groups consisted of persons who were outpatients. Characteristics of patients and control subjects in Table 1.

Table 1. Characteristics of patients and control subjects.

	Age	Sex (Female/Male)	Pirmer-seconder	Drug use	Ilicited drug use
Depressive patients (n=30)	23-65	23 Female 7 Male	primer	_	_
Control group (n=30)	23-65	24 Female 6 Male	_	_	_

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Gaziosmanpasa University, Faculty of Medicine.

2.2. Blood samples

The blood samples were collected from all subjects after fasting period of 10 hours under standardized conditions in 10 mL tubes with EDTA. The blood samples were then put on ice immediately and centrifuged at 2000 x g at 4 °C for 10 min. Plasma was separated and stored at -20 °C until analyzed.

2.3. Preparation of Erythrocyte packed and extraction of total lipids

After plasma, leucocyte and trombocytes were removed, the erythrocyte fraction was used for preparation of erythrocyte packed. The erythrocyte fraction was washed with 0.9% NaCl for three times to remove leucocyte remnants. Erythrocyte packed of 0.5 mL was counted and expressed as 10 10 mg/cell.

Total lipid extracts of erythrocyte packeds were prepared according to Rose-Oklander method (Rose and Oklander; 1965). 0.5 mL distilled water was added on 0.5 mL of erythrocyte packed. This mixture was hemolized by vortexing and incubated for 15 min. After adding 5.5 mL isopropyl alcohol, tubes were shaked for 15 min and incubated for an hour. Then, 1.5 mL of chloroform was added on erythrocyte packed and incubated. The samples were centrifuged at 4000 rpm for 10 min and supernatant was seperated. For prevent the oxidation, 0.1 g/L of BHT (butylatedhydroxytoluene) was added to each tube. The prepared total lipid extracts were stored at -20 °C.

Following this lipid extraction, the total phospholipid fractions were determined by thin-layer chromatography (TLC).

2.4. Preparation of fatty acid methyl ester

The fatty acids of phospholipid fractions were converted into fatty acid methyl esters by transesterification of fatty acids according to Kim et al method (Kim et al., 2001). The percent levels of methyl esters of fatty acids were determined by temperature programmed capillary Gas Chromatography (Perkin Elmer Clarus Model 500) using a 30 m × 250 µm (L×ID) × 0.2 µm df column Quadrex capiller. Dedector was a flame ionization detector (FID). The injection and detection temperature were set at 260 °C. The starting temperature of the column was 150 °C, which was increased to 240 °C after 1 min at a rate of 2 °C/min. The injection volume was 5 µL. The carrier gas was helium with a flow of 1.5 mL/min. Peak identification was performed by spiking with authentic standards. Peak integration and calculation of the percent composition was performed by computer with Star Chromatography Workstation Version 5.52 software. The results are expressed as percent of total fatty acids.

3. Results

In the present study, the composition of all the fatty acids of erythrocyte membrane in depressive patients has been determined and compared with control group. As summarized in table 2, some fatty acids which in control group, were not seen in depressive patients. Especially this changes was in phosphatidylethanolamine (PE) and sphingomyeline (SM). Although, the 6-22 carbon long fatty acids were detected in all phospholipids, the amount of 16, 18 and 20 C fatty acids were high.

Table 2. The fatty acid composition of major phospholipids in control and patient groups.

Fatty acids	**Control group**					**Depressive group**				
	PE	PS	PC	SM	Total	PE	PS	PC	SM	Total
Capric Acid (C10:0)	5.22	3.99	7.52	25.19	41.92	8.35	5.7	9.83	8.49	32.37
Undecanoic Acid (C11:0)	1.1	0.92	-	4.25	6.27	1.99	1.01	1.44	-	4.44

Lauric Acid (C12:0)	1.24	0.73	1.59	3.11	6.67	2.09	0.93	2.03	0.98	6.03
Tridecanoic Acid (C13:0)	0.2	0.17	0.54	0.32	1.23	-	0.18	0.31	-	0.49
Cis-10 Pentadecanoic Acid	0.65	0.55	0.73	1.5	3.43	0.76	0.79	0.78	0.79	3.12
Palmitic Acid (C16:0)	0.03	-	0.01	-	0.04	-	0.01	-	-	0.01
Cis-10 Heptadecanoi**c** Acid (C17:1)	-	-	Trace	-	-	0.04	0.24	0.006		0.286
Stearic Acid (C18:0)	0.1	1.2	0.34	0.87	2.51	0.32	1.74	2.27	0.77	5.1
Elaidic Acid (C18:1n9,t)	-	-	Trace	0.61	0.61	3.12	4.04	0.13	2.36	9.65
OleicAcid (C18:1n9,c)	12.62	2.59	11.22	16.4	42.83	-	-	4.54	-	4.54
Linolelaidic Acid (C18:2 n6,t)	0.08	0.04	1.75	2.32	4.19	0.17	0.37	0.04	0.02	0.6
Linoleic Acid (C18:2 n6,c)	5.98	Trace	-	9.1	15.08	-	0.04	-	0.016	0.056
Arachidic Acid (C20:0)	0.05	Trace	-	0.003	0.053	-	-	0.01	-	0.01
Cis-11 eicosenoic Acid(C20:1)	0.23	-	0.06	0.24	0.53	-	0.05	0.02	0.006	0.076
Linolenic Acid (C18:3 n3)	0.18	-	0.17	0.17	0.52	-	0.03	0.16	-	0.19
Heneicosanoic Acid (C21:0)	0.05	-	0.14	0.12	0.31	0.02	0.05	0.02	0.016	0.106
Cis-8,11,14 Eicosatrienoik Acid (C20:3 n6)	-	-	0.006	0.01	0.016	0.1	0.08	-	-	0.18

Erucic Acid (C22:1 n9)	0.4	0.03	0.06	0.06	0.55	0.12	0.02	0.03	0.13	0.3
Cis-11,14,17 Eicosatrienoic Acid (C20:3 n3)	0.03	-	0.016	0.6	0.646	0.03	0.52	0.01	0.07	0.63
Arachidonic Acid (C20:4 n6)	0.003	trace	Trace	0.006	0.009	trace	0.003	trace	Trace	0.003
Tricosanoic Acid (C23:0)	0.03	-	Trace	Trace	0.03	trace	trace	trace	Trace	-
Cis-13,16 Docosadienoic Acid (C22:2)	0.02	-	0.01	0.016	0.046	-	-	0.006	-	0.006
Lignoceric Asit (C24:0)	0.04	0.02	0.14	0.42	0.62	0.09	0.15	0.2	0.07	0.51

As seen in table 2, the capric acid that related were obtained % critical levels. The capric acid was determined at the highest level in both groups. The capric acid in SM was reduced by 60% in patients when compared with the controls. But, it shown an increases in PC, PS, PE in patients. Palmitic acid was not detected in phosphatidylserine (PS) and SM in control group but present in PS only in patient group. Although the stearic acid can be seen in all phospholipids in both groups, it's amount was high in PS and phosphatidylcholine (PC), and low in PE.

The amount of elaidic acid was very high in all phospholipids except PC from patients group according to control group. In contrast, the elaidic acid was extremely low in PC and SM and absent in PS and PE from control group. Linoelaidic acid, a trans fatty acid, was detected in all phospholipis in patients and control group. The amount of this fatty acid was very high level in PC and SM in control group, however it was extremely low in patient group.

Although arachidonic acid was present in all phospholipids both groups, but the amounts of this fatty acid was very low.

Lignoseric acid was determined in the all phospholipids in both groups. But the quantities were close to each other in SM and PE and the maximum amount was detected in PC and PS. Moreover the amount of lignoseric acid in SM from patient group decreased approximately 80% compared to the control group.

Oleic acid was detected in all phospholipids but it was very high in control group. The amount of oleic acid in SM was higher than that of other phospholipids. In patient group, it was detected only in PC but not in other phospholipids. The amount of oleic acid was aproximately % 60 lower in patient group compared to the control.

Linoleic acid was not present in PE and SM and detected as quite low quantities in PC and PS from patient group. This fatty acid was present in all phospholipids except in PC in control group and the values in SM and PE were very high.

Nervonic acid was not detected in none of phospholipids in patient group but it was only in PS in the control group.

As seen in table 2, 20:3 (ω3,cis) fatty acid was not found in PS in control group and the amount of it in SM was higher than PE and PC. In patient group, amounts of this fatty acid in SM was decreased 9 times compared to control group. Although this fatty acid was not found in PS in control group, it was detected very high amount in PS in patient group.

22:2 (ω6,cis) fatty acid was not detected in PS in control group, it was found only in PC in patient group.

As seen in table 3, 22:6 ω3 fatty acids were detected in all phospholipids in both groups. But the fatty acids in PC and SM of patient group were found in low level compared to control group. Particularly, the fatty acids in SM was decreased 3 times.

Table 3. Comparison of ω3 and ω6 fatty acids of major phospholipids in control and patient groups

Fatty acids	**Control group**					**Depressive group**				
	PE	PS	PC	SM	Total	PE	PS	PC	SM	Total
Linoleic Acid (ω-6)	5.98	_	_	9.1	15.08	_	0.04	_	0.016	0.056
Cis 8,11,14 Eicosatrienoic Acid (ω-6)	_	_	0.006	0.01	0.016	0.1	0.008	_	_	0.18
Arachidonic Acid (ω-6)	0.003	_	_	0.006	0.09	_	0.003	_	_	0.003
Linolenic Acid (ω-3)	0.18	_	0.17	0.17	0.52	_	0.03	0.16	_	0.19

Cis 11,14,17 Eicosatrienoic Acid (ω-3)	0.03	_	0.016	0.6	0.646	0.03	0.52	0.01	0.07	0.63
Cis 4,7,10,13,16,19 Docosahexaenoic acid(C22:6)	0.006	0.18	0.16	0.1	0.446	0.11	0.4	0.12	0.03	0.66

Table 4. shows that the variance analysis results of the glycerophospholipid fractions in both groups.

Table 4. The erythrocyte membrane phospholipid fraction of the control group and the depressed patient group Variance analysis of values and T-test results

Parameters	**N**	**Control group (µg/ml)**	**Patient group (µg/ml)**	**P Value**
PE	30	1.43 ± 0.18	0.91 ± 0.16	P<0.042
PS	30	1.64 ± 0.22	1.31 ± 0.24	P<0.32
PC	30	1.53 ± 0.15	1.18 ± 0.17	P<0.13
SM	30	2.41 ± 0.54	1.02 ± 0.12	**P<0.01***

PE: Phosphatidylethanolamine, PS: Phosphatidylserine, PC: Phosphatidylcholine, SM: Sphingomyelin

* This article was extracted from the master's thesis.

3.2. *Discussion*

The aim of the present study was to investigate the amounts of all fatty acids in red blood cell membrane of depressive patients comprare to control group and whether these fatty acids may be associated with depression.

In our study, the 6-22 carbon long fatty acids were detected in all phospholipids, the amount of 16, 18 and 20 C fatty acids were high. Additionally, total amounts of linolenic acid, cis 11, 14, 17 eicosatrienoic acid, 20:3 ω-3 and DHA which are ω-3 fatty acids were significantly low in depressive patient group compared to control group. The capric acid in SM was significantly reduced in patients when compared with the controls. Stearic acid can be seen in all phospholipids in both groups. The amount of elaidic acid was very high in all phospholipids except PC from patients group according to control group. Therefore our results is parallel to previous studies.

The correlation between depression and omega 3 and/or omega 6 fatty acids on physciatric patients have been studied previously. Edwars et al. (1998) reported that depleted RBC membrane ω-3 fatty acid levels showed a significiant association with the severity of depression, such that the lowest levels were associated with more severe depression. It was reported that high amount of ω-3 fatty acids taken with the diet reduces the severity of depression. Therefore they suggested that there is a strong relationship between ω-3 fatty acids and severity of depression.

Several epidemiological studies support the connection between dietery fish/seafood consumption and depresion frequency. It has reported that there is a significant negative correlation between fish consumption and depression rate around the world. The protective effect of If fish/seafood consumption against the post-partum depression, bipolar disaese and seasonal emotional disorders can be noticed if national seafood consumption is analysed (Logan, 2004).

Maes et al. (1999) reported that there was an increase of major depression associated with of C 20:4 ω-6/C 20:5 ω-3 and reduction in C20:5 ω-3 and C22:5 ω-3 fractions in phospholipids in RBC membranes from depressive patients (Maes et al., 1999). In this study, the amount of 20:4 ω-6 (arachidonic acid, AA) decreased in the erythrocyte membrane of depressive patients compared to control group. Mc Namara et al (2006) report that there is a correlation between schizophrenic symptoms and anormally phospholipid metabolism (Mc Namara et al., 2006). Furthermore, it has been reported that there is a correlation between reduced AA and phospholipid levels in RBC membrane (Nemets et al., 2002).

Su et al. (2003) found that major depression group had high level of DHA after treatment compared to untreated period. Although EPA had many positive effects on patients with schizoprenia (Emsley et al., 2002; Peet and Horrobin, 2002; Peet, 2003). They showed that it had no effect in other studies (Peet, 2003; Fenton et al., 2001).

In 6 of 8 case-control studies observed low ω-3 PUFA and high ω-6 concentradion in depressive patients compared to non-depressive patients. The studies on depression showed that EPA had negative correlation depression severity. Vriese et al. (2003) reported that low DHA and total ω–3 PUFA and high ω–6 / ω–3 PUFA in 10 depressive partients compared to 38 non-depressive controls after pregnancy, on the other hand 20:4 n-6/20:5 n-3 rates were high in major depressive patients in the same study (Vriese et al.,2003). In contrast, Hakkarainen et al. (2004)

reported that dietary ω-3 fatty acids or fish consumption wast not associated with depression (Hakkarainen et al., 2004).

In these studies until now shows that there is a negative correlation between depression and EPA, DHA, ALA and total ω-3 PUFA ftty acids. In our study, ω-3 PUFA fatty acids was found decreased in patients compared to control in accordance with literature. In depressive patients, especially 22:6 n-3 fatty acid levels is decreased. These observations suggest an abnormal n-3 PUFA metabolism in depressive patients.

In a study with elderly depressive patients, there was an increase in %AA and decrease in % DHA compared to controls. It was also observed that there was a significant differences in ω-6/ω-3 PUFA, AA/EPA and AA/DHA ratios. This difference can be changes of ω-6 and ω-3 PUFA (Tiemeier et al., 2003).

The level of 18:1 were high in rats fed with olive oil. For this reason, it was suggested that there is a relation between olive oil diet and increased n9 desaturated activity. Moreover, the desaturated activity was inhibited in rats feeded with n-3 and n-6 PUFA (Escudero et al., 1998).

Gren et al. (2006) found that the concentrations of 18:3 ω-3 and 20:3 ω-3 were lower than controls. They showed that the ratio of 20:5 ω-3(EPA) was lower than 22:6 ω-3 (DHA). In our study, 18:3 ω-3, 20:3 ω-3 and ω-6 fatty acids were found as low level in patient compared to control group.

One of the reason of decreasing n-3 PUFA level in depression is the reduction in the level of zinc, increasing lipid peroxidation and inflamation. It may be responsible for pathophysiological feature of this disease.

Studies on the fatty acids as mentioned above were related to depression and was determined as lower levels in patients group when compared with control group. Moreover, in some of the studies, this reduction cannot be seen and some different results were obtained. In the previous studies above, it was indicated that the reduction in amount of some of fatty acids related to depression may be led by malfunctioning in the PUFA metabolism. The reduction in the amount of phospholipids might cause a reduction in fatty acids with 18-22 carbons especially.

In this study, very important results were obtained with regard to capric acid, undekanoik acid, lauric acid. These three fatty acids in PE, PC, PS in the control group showed a significant decrease. But, These three fatty acids increased a significant levels in patient group. In these fatty acids in SM in patients group when compared with control group was observed very significantly reduction. These observation suggest that there are abnormal fatty acid metabolism in

depression. We suggested that these fatty acids should be taken into account in later studies on depression.

Conflicts of interest

The authors declare that there are no potential conflicts of interest relevant to this article.

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