



## Similar fatty acid status of plasma lipids in postmenopausal women newly diagnosed with breast cancer and those receiving aromatase inhibitor therapy

Sličan masnokiselinski status kod žena sa novodijagnostikovanim karcinomom dojke i onih koje su na terapiji inhibitorima aromataze

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### Abstract

**Background/Aim.** Dysregulation of fatty acid (FA) metabolism is recognized as a component of malignant transformation in many cancers, including breast cancer (BC), and is often related to disease progression and prognosis. Adjuvant endocrine BC therapy using aromatase inhibitors may also influence FA metabolism. Thus, the aim of our study was to compare plasma total lipids FA status in newly diagnosed postmenopausal patients with BC and in postmenopausal women with BC receiving aromatase inhibitors at least 2 years after completing chemotherapy with healthy women. **Methods.** The study included 17 newly diagnosed postmenopausal BC patients (ND group) and 21 postmenopausal women with BC receiving aromatase inhibitor therapy 2 years after ending chemotherapy (AI group), while a total of 15 apparently healthy women without a family history of BC, comparable in age and body mass index, served as a control group. **Results.** In both patient groups, we found significantly lower levels of vaccenic acid (18:1n-7), alpha-linolenic acid (18:3n-3), gamma-linolenic acid (GLA, 18:3n-6), and docosapenta-

noic acid (22:5n-3), and a significantly higher level of di-homo-gamma-linolenic (20:3n-6), when compared with the control group. On the other hand, a significantly lower level of stearic acid (18:0) was observed only in AI patients, while the level of linoleic acid (18:2n-6) was significantly higher in ND women than in the control group. Reduced estimated activities of D6 and D5 desaturases were found in both patient groups than in the control group. **Conclusion.** Our results indicate that FA profiles of plasma lipids of the newly diagnosed, untreated BC patients are very similar to those of cured BC patients who underwent all sessions of chemotherapy and received aromatase inhibitors for at least two years. Additionally, according to our results, their FA profiles markedly differ from those of healthy women. Therefore, supplementation with omega-3 FA and GLA could have beneficial effects in these patients, and further studies should address the potential clinical benefits of the supplementation.

**Key words:** aromatase inhibitors; antineoplastic agents; breast neoplasms; fatty acids; postmenopause; women.

### Apstrakt

**Uvod/Cilj.** Promene u metabolizmu masnih kiselina prepoznate su kao komponenta maligne transformacije u mnogim različitim vrstama kancera, uključujući i karcinom dojke (KD), a često su povezane sa progresijom i prognozom bolesti. Adjuvantna endokrina terapija KD, korišćenjem inhibitora aromataze, takođe može uticati na metabolizam masnih kiselina (MK). Zbog toga je cilj ovog rada bio da se uporede MK profili iz ukupnih lipida plazme kod žena u menopauzi, a kojima je dijagnostikovano KD, i

onih sa KD koje su na terapiji inhibitorima aromataze najmanje dve godine, sa MK profilima kontrolne grupe. **Metode.** U studiju je bilo uključeno 17 žena sa novodijagnostikovanim KD (ND grupi) i 21 žena sa KD koje su na terapiji inhibitorima aromataze (AI grupi). Kontrolnu grupu je činilo 15 uslovno zdravih žena u menopauzi koje nisu imale porodičnu anamnezu za KD i koje su po godinama i indeksu telesne mase poređene sa bolesnicama. **Rezultati.** Procenat vakkenske (18:1n-7), alfa-linolenske (18:3n-3), gamma-linolenske (18:3n-6) i dokozapentaenske (22:5n-3) kiseline bio je značajno niži, dok je procenat di-homo-gama-

linolenske kiseline (20:3n-6) bio značajno viši, kod obe grupe bolesnica u odnosu na kontrolnu grupu. Sa druge strane, niži nivo stearinske kiseline (18:0) pronašli smo u samo AI grupi, dok je visok nivo linolne kiseline (18:2n-6) utvrđen samo u ND grupi u odnosu na kontrolu. Smanjena procenjena aktivnost D6 i D5 desaturaze nađena je kod obe grupe bolesnica u odnosu na kontrolnu grupu. **Zaključak.** Naši rezultati su pokazali veoma sličan MK profil kod žena sa tek dijagnostikovanim KD i onih koje su na terapiji inhibitorima aroma-

taze najkraće dve godine, ali i da se njihovi MK profili u velikoj meri razlikuju od MK profila kontrolne grupe. Zbog toga, suplementacija n-3 masnim kiselinama i gama linolenskom kiselinom može biti korisna za ove bolesnice, i buduće studije bi mogle ispitivati potencijalnu korist ovih suplemenata.

**Cljučne reči:**  
**aromataza, inhibitori; antineoplastici; dojka, neoplazme; masne kiseline; postmenopauza; žene.**

## Introduction

Breast cancer (BC) is one of the most common causes of mortality worldwide and the second leading cause of cancer-related death in women<sup>1</sup>. Numerous factors, such as genetic constitution, immune system function, metabolism, hormone levels, the lack or short duration of breastfeeding, as well as environmental factors, are associated with BC development<sup>2</sup>. Nutritional status, amount and type of dietary fats and obesity, are also linked to the etiology of BC<sup>3,4</sup>.

Almost 70% of all BC are hormone-dependent, and hormones play a key role in the formation and progression of cancer. Some BC produce hormones and/or growth factors, which can act locally to stimulate or inhibit tumor growth. In addition to hormonal status, hormone receptor status is closely related to carcinogenesis. Specifically, the estrogen receptor (ER) plays a critical role in cancerogenesis since estrogen binding to the ER leads to altered expression of genes responsible for cell growth, differentiation, apoptosis, and angiogenesis<sup>5</sup>. In addition, overexpression in human epidermal growth factor receptor-2 (HER-2) leads to enhanced aromatase activity and estrogen production<sup>6</sup>. Accordingly, based on their receptor status, BCs are classified into four subgroups as follows: luminal A ER-positive (ER+) and progesterone receptor (PR) positive (PR+) tumors with luminal HER2 negative (HER2-), luminal B (ER+, PR-, HER2-), HER2 positive (ER-, PR- and HER2+), and basaloid (triple-negative) (ER-, PR-, HER2-) types<sup>7-9</sup>.

BC treatment involves surgery, chemotherapy, radiotherapy, and adjuvant endocrine therapies in some types of BC. Aromatase inhibitor, which profoundly decreases plasma and intratumoral estrogen levels, is used as a standard endocrine treatment for early-stage, hormone receptor-positive BC in postmenopausal women<sup>10,11</sup>. It blocks the final step in estrogen biosynthesis, ie., the bioconversion of androstenedione to estrone, catalyzing by enzyme aromatase<sup>6</sup>. Substantially, a decrease in both circulating plasma estrogens and intratumoral estrogen levels using aromatase inhibitors can lead to a reduction in BC mortality by almost one-third throughout the first 15 years<sup>12</sup>.

The rapid growth and expansion of tumor tissue often leads to a poor blood supply of nutrients but also alters *de novo* synthesis of many macromolecules, including lipids and fatty acids (FA)<sup>13</sup>. Several studies have suggested that the malignant phenotype is characterized by alterations in FA metabolism pathways and the expression of enzymes

included in FA metabolism. Thus, overexpression of FA synthase (FAS), the rate-limiting enzyme in the FA synthesis pathway, has been reported for a variety of cancers, including prostate, liver, ovary, colon, endometrium, and breast<sup>14</sup>. Furthermore, overexpression of stearoyl CoA-desaturase (SCD), responsible for conversion of saturated FA (SFA) to monounsaturated FA (MUFA), is confirmed in HER2+ BC cells<sup>15</sup> and in mucin-1 overexpressing BC cells<sup>16</sup>. Modified activities of these enzymes lead to altered distributions and concentrations of FA in cell membranes. In addition to tumor cells, abnormal FA profile has been shown in plasma in patients with a new diagnosis of pancreatic, non-small-cell lung and stomach or esophageal cancer<sup>17</sup>, bladder cancer<sup>18</sup>, non-Hodgkin's lymphoma<sup>19</sup>, uterine cervical cancer<sup>20</sup>, suggesting that changes in FA metabolism in patients with cancer are systemic<sup>21</sup>.

Besides the tumor itself, cytotoxic chemotherapy in BC patients results in increased oxidative stress and selective depletion of long-chain polyunsaturated fatty acids (PUFA) in plasma and membrane of phospholipids<sup>22,23</sup>, and may limit the endogenous production of long-chain PUFA<sup>24</sup>. Long-term endocrine therapy with aromatase inhibitors, as a systemic treatment for many patients with BC, may also influence lipid metabolism and blood level of some lipoproteins<sup>25</sup>.

Although some studies reported impaired serum FA profiles in BC women<sup>2</sup>, literature data are not consistent. Moreover, it is not clear whether and how plasma FA status changes during BC development, after the surgery and chemotherapy, and especially during aromatase inhibitors treatment, when patients are considered cured. Therefore, the aim of our study was to compare plasma total lipids FA status in newly diagnosed postmenopausal patients with BC and in postmenopausal women receiving aromatase inhibitors at least 2 years after completing chemotherapy with the control group.

## Methods

### Subjects

Seventeen newly diagnosed postmenopausal BC patients (ND group), together with 21 postmenopausal women with BC receiving aromatase inhibitor therapy 2 years after the end of chemotherapy (AI group), were included in the study. Patients were recruited from the Department of Hematology at the Military Medical Academy

(MMA) in Belgrade, Serbia, during 2018 and 2019. The clinical diagnosis was histologically proven BC. Immunohistochemical measurement of ER expression was performed at the MMA. All newly diagnosed BC patients were included in this study immediately after the cancer diagnosis and before surgery. Inclusion criteria were postmenopausal women with ER+ and HER-2 negative BC. Additional criteria were the absence of chemo- and/or radiotherapy for the ND group and receiving adjuvant hormone therapy with aromatase inhibitors at least 2 years after the end of chemotherapy for the AI group. Excluding criteria for both groups were a metastatic or locally advanced disease of HER-2 positive, previous stroke or heart attack, presence of significant neurological deficit and consciousness disorder, dementia, presence of other malignancies, thyroid disease, and use of statins. The study protocols were approved by the Ethics Committee of the MMA in accordance with the Declaration of Helsinki and principles of Good Clinical Practice. All participants provided written informed consent at the time of their inclusion in the study. None of the study participants received supplements that may influence lipid and FA metabolism in the 3 months prior to entering the study. Fifteen apparently healthy women without a family history of BC, comparable in age and body mass index (BMI) with patients from the ND and AI groups, served as a control group.

#### Analytical methods

The blood was collected in the morning after 12 h of fasting. Plasma samples were immediately stored at -80 °C

until the determination of FA profiles. Total plasma FA were isolated by Glaser's method with some modifications as previously reported by Nikolić Turnić et al.<sup>26</sup> FA methyl esters were analyzed by gas chromatograph SHIMADZU 2014, which was equipped with capillary column RESTEK Rtx 2330. The temperature program was 140–210°C for 3°/min. Individual FA was identified compared with retention time FA methyl esters commercial standards PUFA-2 (Supelco, Inc., Bellefonte, Pennsylvania, USA). The results are presented as a percentage of total FA<sup>27</sup>. The activities of enzymes involved in long-chain FA syntheses were estimated as we previously described<sup>28</sup>.

#### Statistical analysis

Statistical analysis was performed using the statistical package SPSS 20.0 for Windows. The results are presented as means ± standard deviation (SD). The Shapiro-Wilk's test was used to determine the normality of data distribution. Comparison between groups was assessed with ANOVA test with Tukey's *post hoc* test, for normally distributed variables. Kruskal-Wallis test and Mann-Whitney U test were used for comparisons between non-normally distributed variables. The alpha level for significance was set to  $p < 0.05$ .

#### Results

FA composition of total plasma lipids in the ND group, AI group, and healthy control women are presented in Table 1. Our results indicated significant differences between both groups of BC patients and healthy persons. Thus, a

**Table 1**  
**Fatty acid composition (%) in total plasma lipids in patients with breast cancer and controls**

Fatty acid	ND group	AI group	Control group
16:0	27.87 ± 2.09	28.10 ± 1.86	27.24 ± 1.01
18:0	12.56 ± 0.61	12.42 ± 1.63*	13.58 ± 1.40
SFA	40.43 ± 2.21	40.52 ± 2.01	40.82 ± 1.56
16:1n-7	1.10 ± 0.44	1.40 ± 0.46	1.51 ± 0.52
18:1n-9	12.40 ± 1.31	12.76 ± 2.33	13.19 ± 1.55
18:1n-7	1.31 ± 0.20**	1.39 ± 0.23*	1.60 ± 0.24
MUFA	14.18 ± 1.69	15.55 ± 2.74	16.30 ± 1.58
18:2n-6	27.60 ± 5.51*	25.27 ± 2.94	24.29 ± 2.51
18:3n-6	0.50 ± 0.19**	0.58 ± 0.25**	0.85 ± 0.22
20:3n-6	3.35 ± 1.10**	3.89 ± 0.25***	2.38 ± 0.66
20:4n-6	9.52 ± 3.71	10.34 ± 2.57	11.15 ± 1.87
22:4n-6	0.43 ± 0.42	0.52 ± 0.38	0.46 ± 0.20
n-6 PUFA	41.40 ± 2.83	40.60 ± 3.16	39.13 ± 2.23
18:3n-3	0.21 ± 0.15***	0.18 ± 0.05**	0.44 ± 0.20
20:5n-3	0.41 ± 0.28	0.34 ± 0.26	0.48 ± 0.28
22:5n-3	0.38 ± 0.09**	0.42 ± 0.10**	0.58 ± 0.19
22:6n-3	2.36 ± 0.67	2.38 ± 0.70	2.24 ± 0.82
n-3 PUFA	3.36 ± 0.84	3.33 ± 0.96	3.75 ± 1.12
PUFA	44.76 ± 2.81	43.93 ± 3.52	42.88 ± 1.97
n-6/n-3 ratio	13.31 ± 4.62	13.11 ± 3.71	11.36 ± 3.55

Data are presented as a mean ± standard deviation.

ND – new diagnosed group; AI – aromatase inhibitors group;

SFA – saturated fatty acids; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids.

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$  compared to the control group.

significantly lower level of stearic acid (18:0) was observed in AI patients than in the control group. Further, among MUFA, only the levels of vaccenic acid (18:1n-7) were significantly lower in both groups of patients than in the control group.

Among n-6 PUFA, we found a significantly higher level of linoleic acid 18:2n-6 (LA, 18:2n-6) in ND women than in the control group. Furthermore, the level of gamma-linolenic acid (GLA, 18:3n-6) was significantly lower, while the level of di-homo-gamma linolenic acid (DGLA, 20:3n-6) was significantly higher in both patient groups than in the control group (Table 1).

When we compared levels of individual and total n-3 PUFA, we found lower levels of alpha-linolenic acid (ALA, 18:3n-3) and docosapentaenoic acid (DPA, 22:5n-3) in both patient groups than in the controls (Table 1).

As shown in Table 2, there were significant differences between the groups regarding estimated activities of enzymes desaturases. Reduced activities of D6 and D5 desaturases were found in both patient groups compared to the control group.

No differences between ND and AI groups were found in any FA or desaturase/elongase system.

positive association with BC risk in postmenopausal women<sup>16</sup>. Nevertheless, data on the FA composition in total plasma lipids in patients with untreated BC or during/after the therapy is rather sparse. Similar to our results, a reduced level of stearic acid has been found in cancers at different sites<sup>19, 29, 30</sup>. *In vitro* studies demonstrated inhibition of proliferation and induction of apoptosis in BC cells lines by stearic acid<sup>3</sup>. Since stearic acid is considered cardioprotective, a low level of this FA may lead to additional complications in BC patients.

Several authors have found a positive association between oleic acid in plasma and erythrocyte lipids and BC, mostly as a result of overexpression of the genes encoding SCD 18<sup>31, 32</sup>, but there are some studies that showed that MUFA were unrelated to BC<sup>33</sup>. Here we found a lower level of vaccenic acid in both patient groups than in controls, while other MUFA had similar levels in all groups. These results may be due to decreased activity of elongase 5, which is involved in the synthesis of vaccenic from palmitoyl acid<sup>34</sup>.

Among PUFA, we found a significantly higher level of linoleic acid in the ND group than in the control group. Linoleic acid is an essential FA, a precursor of the n-6 PUFA

**Table 2**

**The estimated plasma desaturase and elongase activities in patients with breast cancer and controls**

Desaturase and elongase	ND group	AI group	Control group
18:0/16:0 (elongase)	0.45 ± 0.04	0.44 ± 0.07	0.50 ± 0.06
16:1n-7/16:0 (SCD-16)	0.04 ± 0.02	0.05 ± 0.01	0.06 ± 0.02
18:1n-9/18:0 (SCD-18)	0.98 ± 0.16	1.06 ± 0.30	0.98 ± 0.16
18:3n-6/18:2n-6 (D6 desaturase)	0.02 ± 0.01**	0.02 ± 0.01**	0.04 ± 0.01
20:4n-6/20:3n-6 (D5 desaturase)	3.27 ± 1.87*	2.88 ± 1.08***	5.08 ± 1.69

Data are presented as a mean ± standard deviation.

ND – new diagnosed group; AI – aromatase inhibitor group; SCD – stearyl-CoA desaturase.

\**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001 compared to control group.

## Discussion

This study investigated possible differences between FA profiles in plasma total lipids in newly diagnosed BC women and women taking aromatase inhibitor during the 2 years after completing BC chemotherapy, and we compared these two groups with apparently healthy women without a family history of BC. Our results showed no differences between the two BC groups, however, there were significant differences when we compared them with the control group. Namely, we found a significantly lower level of stearic acid in the AI group (women who take aromatase inhibitors) than in the control group, while the level of linoleic acid was significantly higher in ND patients than in the controls. In the past two decades, many researchers have been investigating the association between serum or plasma phospholipid FA and BC risk. However, the results are inconsistent. While some authors reported no association between individual SFA in plasma phospholipids and risk of BC<sup>2</sup>, several studies suggested an inverse association between the saturation index and the risk<sup>14, 15</sup>. Moreover, there is evidence that serum total SFA shows a significant

family, and its level in plasma lipids in the healthy population depends on dietary intake. Several prospective epidemiological studies demonstrated no evidence of an association between LA and BC risk<sup>35, 36</sup>, while a significant inverse association has been reported in other studies<sup>15, 33, 37</sup>. On the other hand, a meta-analysis of 12 case-control studies<sup>38</sup> and a cohort study<sup>39</sup> suggests a positive relationship between PUFA intake and BC. Our finding on LA is consistent with Pouchieu et al.<sup>40</sup>, who also found higher plasma levels of LA in BC patients than in healthy women. Furthermore, some investigators suggested that LA is necessary for the growth of some tumors, such as prostate cancer<sup>15</sup>.

In addition, GLA is synthesized from LA. In our study, the level of GLA was significantly lower in both groups of patients than in controls, which is consistent with the results of other authors<sup>40</sup>. The enzyme directly involved in this process is D6 desaturase, and the estimated activity of this enzyme was lower in patients than in the control group. Our results indicate that the synthesis of long-chain PUFA is disturbed in both patient groups. Since GLA has been shown to inhibit the overexpression and hyperactivity of FAS

oncogene, which is closely linked to malignant transformation of mammary cells <sup>41</sup>, these results may suggest poor prognosis for our patients and the need for increased intake of this FA.

Additionally, the level of DGLA (20:3n-6) was significantly higher in both patient groups than in the control group. Similar results have been found in gastric adenocarcinoma <sup>42</sup> and prostate cancer <sup>43</sup>; and some authors have observed inverse associations between DGLA and breast cancer risk. The possible reason for higher levels of DGLA could be decreased activity of D5 desaturase, which converts DGLA into arachidonic acid. Moreover, DGLA is a substrate for cyclooxygenase and lipoxygenase and can be converted by inflammatory cells to prostaglandin E1 (PGE1), which possess both antiinflammatory and antiproliferative properties. PGE1 also inhibits the growth and differentiation of cancer cells <sup>44</sup>, suggesting possibly beneficial effects in our patients.

Omega-3 PUFA are usually low in cancer patients. BC patients in this study had a lower level of essential alpha-linolenic acid and its indirect product docosapentaenoic acid in both patient groups than in controls. A meta-analysis of three prospective cohort studies on circulating FA showed that total n-3 PUFA were associated with decreased BC risk <sup>37</sup>. Also, while animal studies have shown that large amounts of fish oil (n-3 PUFA) in the diet may decrease the incidence and inhibit the growth rate of mammary carcinomas in rodents, some authors found no association between n-3 PUFA and BC risk, suggesting that a beneficial effect of n-3 PUFA on BC development may require a relatively high intake of seafood <sup>40</sup>. Since the control group in this study had low levels of n-3 PUFA as well, the lower levels in BC patients can not be attributed to lower intake,

but rather impaired metabolism. Nevertheless, the obtained results indicate that supplementation with n-3 FA may be beneficial for BC patients.

The weakness of this study is the relatively small number of patients. Nevertheless, these preliminary results suggest that there is a pattern in alterations in FA profiles that should be confirmed in a larger study. Based on these results, dietary interventions studies in BC patients are recommended.

### Conclusion

FA profiles of plasma lipids of newly diagnosed, untreated BC patients are the same as those of cured BC patients who underwent all sessions of chemotherapy and received aromatase inhibitors for at least two years. In addition, their FA profiles markedly differ from those in healthy women. Therefore, supplementation with omega-3 FA and GLA could have beneficial effects in these patients, and further studies should address the potential clinical benefits of the supplementation.

### Conflict of interests

The authors declare that they have no competing interests.

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