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Evaluations of blood lipids, lipid peroxidation and antioxidant enzymes activities in women with uterine tumors

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The research aim was to study alterations in lipid spectrum, lipid peroxidation intensity and fatty acid (FA) spectrum in the blood of women with benign and malignant uterine tumors during the menopausal period. In case of malignant tumor, following changes were observed regarding saturated FAs: decreased myristic (3-fold) and palmitic acid (~1.3 fold) compared to control, but stearic acid was increased (1.13-fold). The decreased ratio between palmitic/stearic acids ($C_{16:0}/C_{18:0}$) by ~1.5-times was noted. In case of unsaturated FAs in malignant tumor samples, there was a decrease in oleic (2.9-fold), linolenic (1.5-fold), eicosatrienoic (3-fold), and arachidonic (1.3-fold) acid compared to control. The increased ratio between stearic/oleic acids ($C_{18:0}/C_{18:1}$) by 3.3-times was noted in malignant cases. Increase in lipid peroxidation intensification was associated with altered lipid spectrum composition (hyperlipidemia, disruption in the exchange rate of phospholipids). There was a negative correlation between lipid peroxidation intensity and phospholipids ($r=-0.96\pm0.04$). Total cholesterol level was higher in malignant cases. Total amount and activities of superoxide dismutase (SOD) and catalase (CAT) were decreased in malignant cases. The negative correlation between total cholesterol and SOD, CAT activities was $r=-0.99\pm0.014$. Amine-containing phospholipids were decreased, but choline-containing phospholipids levels were increased along with the severity of the disease. It is concluded that intensification of lipid peroxidation and alterations in lipid spectrum composition contributes to hyperlipidemia, disruption of phospholipids' exchange rate and hypercholesterolemia. Thus, specific changes in these biochemical parameters can be useful in the differentiation of benign and malignant uterine tumors for menopausal women.

Keywords: Free fatty acids, Lipids, Menopause, Metabolism, Phospholipids, Uterine tumors

The reprogramming of lipid metabolism and signaling pathways is the central aspect of cancer biology. Recent investigations have shown unique regulation of "*de novo"* lipid synthesis in cancer cells [1]. Cancer cells often use new pathways and enzymes to simplify the synthesis of fatty acids, and the newly synthesizsed lipids affect cellular processes, which impact cancer cell proliferation and survival outcomes[1].

Lipids are major structural components of the membrane; therefore, they have the role of biological effectors[2] and regulators[3]. Mainly, they participate in important physiological processes (*viz*., immune responses, hemostasis, the regulation of muscle and blood vessels tonus, and inflammation, *etc*.) and biochemical reactions in the body[4]. Besides, the lipids, as secondary messengers, transmit different signals within the cell[5]. Based on the investigation, they also perform the role of intracellular mediators[6,7].

Accordingly, alteration of lipid metabolism in the body should be responsible for the disruption of cellular apparatus and a series of intracellular interactions that could result in the breaking of homeostasis of the entire organism[8]. Alterations in lipid metabolism have been considered as a significant contributing/provoking factor in the process of tumor growth, proliferation, and metastasis - as they are of significant relevance to the management of therapeutic process[6].

Based on the studies, steroid hormones (especially estrogen) play a leading role in the development of

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uterine body tumors[9]. Mentioned hormones are also actively involved in the regulation of lipid metabolism[10]. Furthermore, it is well known that estrogen has hypercholesterolemic, hypocholesterolemic and hyperphospholipid effects[10]. Findings support that obesity is significantly associated with tumors of the reproductive organs among women[11,12]. It is suggested that obesity is actively involved in the regulation of lipid metabolism[8]. A number of studies indicate that obesity is significantly associated with uterine tumors (72.8% of the uterine tumors develop on the background of obesity)[13,14]. Moreover, abnormal lipid metabolism is linked to tumor development, growth, invasion, and metastasis, making it a possible target for treatment and drug development in this pathway[15].

The lipid peroxidation process also significantly affects lipid metabolism[16]. Notably, activation of free radical processes occurs within pathological processes, including tumor growth[17]. The activation of lipid peroxidation is accompanied by the disruption of the lipid bilayer of the membrane by free radical peroxidation products[17,18], consumption of large amounts of antioxidants and eventually, disruption of the functioning of the antioxidant systems[19]. It is therefore conceivable that all of these processes contribute to the progress of the mentioned disease[20,21].

Besides, it is well established that free fatty acids (FAs) are involved in many cellular processes, such as: i) regulate the action of various enzymes (*e.g.*, phospholipase A2[22], phospholipase D[22]), ii) participate in cell signal transduction[17], iii) regulate the function of ion channels[23] and transcription of genes[24], iv) synthesis of the highly active lipid bioregulators[25] and v) binding of estrogens, glucocorticoids, vitamin D to their receptors[26].

The studies revealed that the specific alterations occur in the composition of FAs during the pathological processes[27], which may be useful predictive and diagnostic markers of the disease. Moreover, according to the recent studies, it is suggested that cancer cells often use alternative ways and enzymes to simplify synthesis of FAs[1].

Taken together, we aimed to study the alterations in lipid spectrum (percentage of the total amount of lipids, total amount of phospholipids, amine- and choline-containing lipids), intensity of lipid peroxidation, activities of antioxidant system enzymes and also alterations in FS (saturated as well as unsaturated) spectrum in the blood of women in menopausal age (45-55 years) with benign (myoma) and malignant tumors (endometrial cancer, stage II) of the uterus.

Materials and Methods

Study Samples

We collected samples from menopausal women with benign and malignant (endometrial cancer, stage II) uterine tumors (15 cases in each group). The age of all subjects ranged between 45-55 years in each group. All patients were recruited in the study groups at their first visit. The control group was consisted of 15 normal healthy women of the same age and approximately the same weight. All subjects belonged to Caucasian race and at the time of recruitment, comorbidities where not described. The disease status and clinical-stage of the disease were determined based on histomorphological and ultrasound examinations of the uterus at the High-Tech Hospital Med Center Ltd, Batumi, Georgia. The study was approved by the independent ethics commission of High-Tech Hospital Med Center Ltd, Batumi, Georgia (*Identification Number: 445466870. September 22, 2018*). Informed consent was obtained from all subjects involved in the study.

Methods

Lipid Extraction Method

This method was based on previously desctribed protocol[28]. Briefly, lipids were separated from the blood through the Folch method, with Patrikeeva's modification[28]. We took 5 mL of blood, added 25 mL chloroform-methanol mixture (1:1 ratio) that would have to wait for 30 min and then separated. We repeated this procedure, and mixed the first and second separated extracts into each other, adding 25 mL chloroform-methanol mixture (2:1) and leaving them for overnight in refrigerator. The next day, we still separated and placed the extract in the separating funnel, adding 0.3N NaCl solution (100 mL extract is added to 20 mL NaCl) and waited for 30 min. After splitting the phases in the separating funnel, we took the lower layer, treated in the solution of Na_2SO_4 (for removing the water). The solution was purified and then evaporated through the vacuum-evaporator. The dry mass of lipids was weighed on analytical scales. The total amount of extracted lipids was dissolved in organic solvent - CCl_4 so that 1 mL of the solution contained 100 micrograms of lipids.

Table 1 — Alterations in lipid levels, lipid peroxidation and activities of antioxidant enzymes in the blood of the women with uterine tumors

Parameter	Control Group	Benign Tumor	Malignant Tumor
Total lipids (mg/mL)	3.3 ± 0.05	4.8 ± 0.14	8.7 ± 0.22
Total phospholipids (mg/mL)	2.5 ± 0.2	2.1 ± 0.15	1.9 ± 0.05
Amino-containing phospholipids	31 ± 2.32	27 ± 1.9	21.7 ± 1.7
Choline-containing phospholipids	34 ± 1.85	44 ± 2.35	63.2 ± 2.9
Total cholesterol (mmol/L)	1.8 ± 0.09	3.5 ± 0.15	6.3 ± 0.29
Superoxides mutase (U/μL)	1 ± 0.2	0.61 ± 0.1	0.17 ± 0.05
Catalase (mcat/mL)	1 ± 0.2	0.72 ± 0.15	0.21 ± 0.06

n=15, number of patients in each group; P< 0.05; The age range of patients was 45- 55 years.

Determination of total amount of phospholipids

The concentration of phospholipids in the total amount of lipids was determined using the method developed at our primary institution[29] as follows: 1 mL of dye was added to the lipids dissolved in 5 mL of CCl_4, and the mixture was incubated in a 60°C water bath for 10 min. The organic phase became blue color, and after the phase separation, we added 1 mL 60% of H_2SO_4 to the organic phase and again incubated in the 60°C water bath for 10 min. We separated the phases, and after 30 min, we determined the optical density of the phospholipid-dye complex in the organic phase at 670 nm wavelength.

Determination of choline-containing phospholipids[30]

We added 5 mL of Dragendorff reagent (preparation method for this reagent is described below), which was prepared just before the experiment, to 5 mL of CCl_4 dissolved lipid solution. The yellow color of the orange-yellow complex was obtained after shaking. We collected the lower layer and measured the optical density at 505 nm wavelength. 1st solution - 1.7 g Bi $(NO_3)_2$ and 100 mL 20% acetic acid. 2nd solution - 10 g KI and 25 mL distillate. Before the experiment, 20 mL of 1st solution was added to 5 mL of 2nd solution and 70 mL of distillate. This solution is called *Dragendorff reagent* (as referred above).

Determination of amino-phospholipids[30]

5 mL of CCl_4 solution that already contained the dissolved lipids was added to 40 mg ninhydrin and incubated in the 60°C water bath for 10 min. We observed a pink colored complex, so we filtered the solution and added a 5 mL $CaCl_2$ solution. We measured the optical density (absorption) of the upper layer at 403 nm wavelength against water.

Determination of total cholesterol

Total amount of cholesterol was assessed by using the colorimetric reagent kit from Human Diagnostics, Germany (Cholesterol liquicolor, complete kit, 10017), according to the manufacturer's instructions.

Determination of fatty acids[31]

Quantitative analysis of fatty acids was performed using high-performance liquid chromatography (HPLC) as described by Fanali *et al*[31].

Determination of lipid peroxidation level

It was determined according to the method described by Uchiyama and Mihara[32]. Briefly, 0.25 mL of homogenate was mixed with 25 μL of 10 mM butylated hydroxytoluene (BHT). Then, 3 mL phosphoric acid (1%) and 1 mL of 0.67% thiobarbituric acid (TBA) were added, and the mixture was incubated at 90°C for 45 min. The absorbance was measured at 535 nm wavelength.

Spectrophotometric methods

These methods were used to assess the activities of superoxide dismutase (SOD) and catalase (CAT) in the blood of the study subjects. Analysis of the enzymes' activities was performed routinely as described by Dubinina *et al*[33] and by Danchenko *et al*[34]. The enzymatic activities were expressed in U/μL and mcat/mL, respectively.

The data obtained were analyzed using the statistical methods in MINITAB (Basic Statistics), and the p-values were analyzed similarly (a p-value of ≤0.05 was considered statistically significant).

Results and Discussion

We observed that the intensity of lipids peroxidation was increased in parallel to the disease aggressiveness in the blood of menopausal women with uterus tumors (Table 1, and Fig. 1.4). The intensity of lipid peroxidation was increased ~1.5-fold in the benign tumor (Fig. 1.4.b.). Tendency of the increase was significantly noted in case of the malignant tumor (~2.2-fold) (Fig. 1.4.c) compared to the control group data (Fig. 1.4.a).

Intensification of the lipid peroxidation process must be conditioned by activation of oxidation-reduction processes, using the large amounts of

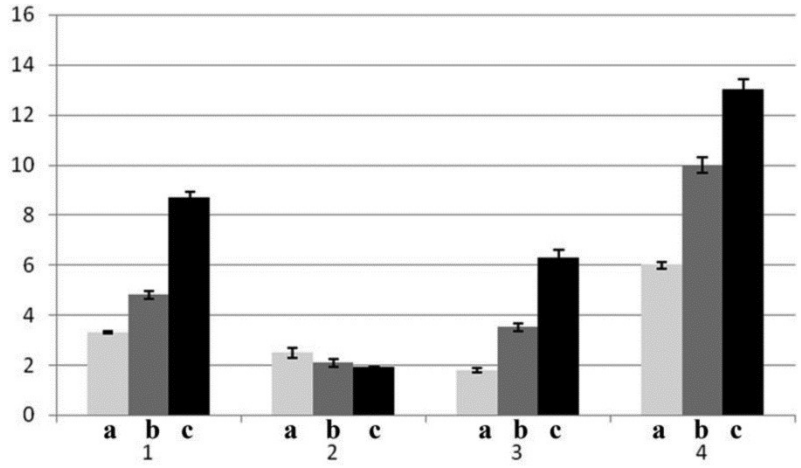


Fig. 1 — The change in lipids amount and alteration in intensity of lipid peroxidation in blood of women (menopause period) with uterine tumors. 1 – Total amount of lipids (mg/mL); 2 – Total amount of phospholipids ((mg/mL); 3 - Total amount of cholesterol (mmol/L); 4 - Lipid peroxidation (μM/L). *a. Control group; b. Benign uterine tumor; c. Malignant uterine cancer group.* n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 45-55 years

antioxidants at the same time[20]. Accordingly, with the reduced antioxidant activity of the organism and the accumulation of free radical oxidation products occurs[16,19,20] (Table 1).

Next, we investigated the alteration of the lipid spectrum within menopausal women with uterine tumors. The analysis shows disruption in blood lipid metabolism (Table 1). Notably, high levels of the total amount of lipids were observed (Fig. 1.1:b.c.) and low levels of the total amount of phospholipids (Fig. 1.2: b.c), compared with the control group data (Fig. 1.1:a, and Fig. 1.2:a). Total amount of blood lipids was increased ~1.5-fold (Fig. 1.1:b) in benign tumor, while in case of endometrial cancer, there was ~ 2.1-fold (Fig. 1.1:c) increase compared with the control group (Fig. 1.1:a).

The results indicating increasement in the amount of total lipids in case of endometrial tumors can be caused on one hand by hormonal imbalance that occurs during the development of pathology (confirming the hormonal basis of hyperlipidemia)[10], and also by enhanced synthesis of triglycerides[33], cholesterol (Table 1) and free FAs on the other hand[35].

We presume that the increased amount of total lipids indicates enhanced lipids biosynthesis during malignant growth. However, it should be noted that, on the background of hyperlipidemia, the total amount of phospholipids is reduced ~1.3-fold (Table 1, and Fig. 1.2.c) compared to the control group (Fig. 1.2.a) in the blood of menopausal women with malignant uterine tumor. As for women

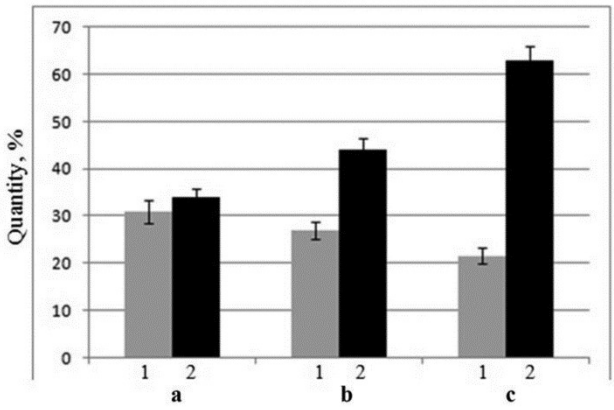


Fig. 2 — The change in percentages of amine-containing and choline-containing phospholipids in total amount of blood lipids of women with uterine tumors. 1 – amount of amine containing phospholipids (%); 2 – amount of choline containing phospholipids (%); *a. Control group; b. Benign uterine tumor; c. Malignant uterine cancer group.* n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 45-55 years

with benign tumors, the total amount of phospholipids in their blood was almost unchanged (Fig. 1.2.b). Furthermore, in case of malignant tumor, the total amount of blood phospholipids was decreased on the background of sharp decrease in the activity of antioxidant enzymes (Table 1, and Fig. 2), accompanied by intensification of lipid peroxidation processes and alterations in the lipid metabolism (Table 1)[12,19]. A negative correlation ($r = -0.96 \pm 0.04$) was established between the intensity of lipid peroxidation and the total amount of phospholipids.

Table 2 — Alterations in the amount (%) of individual fatty acids in the blood of the women with uterine tumors

Fatty acid	Free Fatty acids (%) in Control group	Free Fatty acids (%) in Benign Tumor	Free Fatty acids (%) in Malignant Tumor
Myristic acid, $C_{14:0}$	3.41 ± 0.3	2.26 ± 0.24	1.09 ± 0.18
Palmitic acid, $C_{16:0}$	9.53 ± 1.14	8.72 ± 1.02	7.29 ± 0.69
Stearic acid, $C_{18:0}$	17.78 ± 0.83	18.55 ± 1.03	20.17 ± 1.44
Oleic acid, $C_{18:1}$	2.19 ± 0.26	1.66 ± 0.08	0.76 ± 0.02
linoleic acid, $C_{18:2}$	10.52 ± 0.32	11.9 ± 1.7	16.52± 2.34
Linolenic acid, $C_{18:3}$	21.5 ± 3.05	19.03 ± 2.24	14.84 ± 0.89
Eicosatrienoic acid, $C_{20:3}$	2.84 ± 0.49	2.23 ± 0.2	0.99 ± 0.08
Arachidonic acid, $C_{20:4}$	32.26 ± 3.51	29.89 ± 2.45	25.35 ± 1.62
$C_{16:0}/C_{18:0}$ Ratio	0.54	0.47	0.36
$C_{18:0}/C_{18:1}$ Ratio	8.12	11.17	26.54
$C_{18:2}/C_{20:4}$ Ratio	0.33	0.40	0.65

n=15, number of patients in each study group; $P< 0.05$; The age range of the patients 45-55 years

Next, we investigated the alteration of total cholesterol in the blood of women with uterine tumors because the latter is a structural component of the cell membrane and precursor of steroid hormones[17]. We observed an increase in the amount of cholesterol in parallel to the severity of the disease (Table 1). Notably, in case of benign tumor, the amount of cholesterol was increased ~2-fold (Fig. 1.3b), but ~3.5 fold (Fig. 1.3.c) in case of malignant tumors, compared to the control group (Fig. 1.3.a). A negative correlation was revealed between the decreased activities of antioxidant enzymes and increased cholesterol levels (R = -0.99 ± 0.014).

Based on these observations, we suggest that the sharp increase in cholesterol levels in the blood plasma of women with uterine tumors should be caused by the disruptions in FAs metabolism as well as in the utilization of carbohydrates (that creates good conditions for biosynthesis of triglycerides and cholesterol)[36-38]. Also, the increase in total amount of cholesterol in the blood plasma should be caused by decreased cholesterol esterification process since it is known that cholesterol esterification is reduced in tumors[39].

We then investigated the percentage amount of amino acid-containing phospholipids as well as choline-containing phospholipids. Our analyses showed that the decrease in the amount (%) of amine-containing phospholipids (Table 1, and Fig. 2.1) and the increase in the amount (%) of choline-containing phospholipids in parallel to the severity of the disease, compared to the control group (Fig. 2.2).

We implicate that the reduction in the percentage amount of amine-containing phospholipids may be due to the reason that amino-containing phospholipids are highly prone to modification by reactive oxygen species (ROS) as readily oxidizing substrates. This phenomenon should contribute to the increased formation of choline-containing phospholipids from amino-containing phospholipids (Phosphatidylserine → phosphatidylethanolamine→ phosphatidylcholine)[40]. Also, another explanation can be the overexpression of the coding gene of enzyme – Choline kinase α (ChoKα)[41], which is a cytosolic enzyme that catalyses the ATP-dependent phosphorylation of choline to generate phosphocholine (PCho) as the first step in the Kennedy pathway[41].

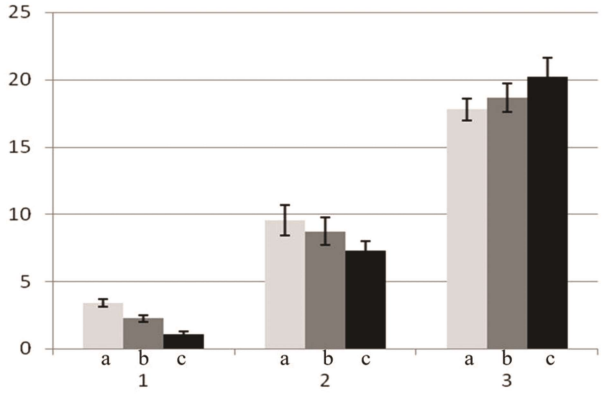


Fig. 3 — Total amount of individual saturated fatty acids in blood of women with uterine tumors. 1. Myristic acid; 2. Palmitic acid; 3. Stearic acid. *a. Control group; b. Benign uterine tumor; c. Malignant uterine cancer group.* n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 45-55 years

Thus, we hypothesize that sharp intensification of lipid peroxidation processes, which leads to the activation of phospholipases, should result in enhanced hydrolysis of phospholipids[42]. One of the outcomes can also be the inhibition of phospholipids' biosynthesis, since the biosynthesis of phospholipids (from lisophospholipids and free FAs) is disrupted[40])

and the FA spectrum is altered[43] (as the latter is reflected in our studies).

In our study, in the case of malignant uterine tumor (endometrial cancer), on the background of lipid peroxidation intensification, the sharp changes in lipid spectrum took place, which are demonstrated by the following alterations: increased hyperlipidemia, disruption in phospholipid metabolism and hypercholesterolemia. These changes are relatively less obvious in the case of benign uterine body tumor (myoma). Together these observations indicate on significant role of lipid metabolism in the development and pathogenesis of uterine cancer (endometrial cancer).

Next, we assessed the alterations in the amount of saturated FAs (*viz*., myristic**,** palmitic and stearic acids), as well as unsaturated FAs (*viz*., oleic, linolic, linolenic, eicosatrienoic and arachidonic acids) in the blood of the women with uterine tumors. We found reduction in the amount (%) of myristic acid in case of uterine tumors ($C_{14:0}$) in parallel to the aggreaviation of the pathology. Notably, the amout of the myristic acid was reduced ~1.5-fold in the case of bening tumors (Table 2, and Fig. 3.1b), but there was ~3-fold reduction in the amount of myristic acid (Fig. 3.1c) in malignant tumors compared to the control group data (Fig. 3.1.a). Sharp decrease in the percentage amount of myristic acid in malignant tumor must be conditioned by the activation of myristoylation processes of oncoproteins[18], which facilitates insertion of oncoproteins in the structure of plasma membrane - and thus performing their specific actions[44].

Our analysis revealed that palmitic acid ($C_{16:0}$) percentage did not substantially change in benign uterine tumors (Fig. 3.2.b), but in malignant tumors it is decreased by ~1.3-fold (Fig. 3.2.c) as compared to control group (Table 2, and Fig. 3.2.a). The amount of stearic acid ($C_{18:0}$) was high in all the study groups as compared to other saturated ($C_{14:0}$; $C_{16:0}$) fatty acids, studied by us. Based on our analysis, the percentage of stearic acid ($C_{18:0}$) in benign tumor (Fig. 3.3.b) slightly differs from the same index of the control group (Fig. 3.3.a). As for malignant tumors, the percentage of stearic acid ($C_{18:0}$) increased by ~1.13-fold. Increased percentage amount of stearic acid in case of uterine tumors and other types of tumors has also been confirmed by other studies in peer-reviewed literature[45,46].

We implicate that the increasing amount of stearic acid can be caused by the activation of distinct enzymes that are involved in the biosynthesis of FAs and in conversion of palmitic acid into stearic acid[24]. Therefore, as a result, the percentage of stearic acid increased and palmitic acid decreased. Accordingly, these changes contribute to the reduction of palmitic/stearic acids ($C_{16:0}/C_{18:0}$) ratio, which is confirmed by our research investigations.

Our data demonstrates that the mentioned ratio within menopausal women with uterine tumors is decreased (~1.5-fold) compared to the control group, whereas there was little-to-no alterations in case of benign tumor (Table 2). Thus, among the saturated fatty acids, there was decrease in the percentage amount of palmitic and myristic acids in all the study groups; however, stearic acid revealed some increasing tendency.

Next, we investigated the levels of following unsaturated fatty acids: oleic acid, linoleic acid, linolenic acid, eicosatrienoic acid, and arachidonic acid. Our analyses showed that the percentage amount of oleic acid ($C_{18:1}$) was decreased in parallel with aggressiveness of the disease. It was sharply decreased (~2,9-fold) in case of malignant tumor (Table 2, and Fig. 4.1.c) as compared to the control group (Fig. 4.1.a).

As for the linoleic acid ($C_{18:2}$), our analysis shows that the percentage amount of linoleic acid slightly increases (~1.1-fold) in benign tumors (Table 2, and Fig. 4.2.b) and ~1.6 fold (Fig. 4.2.c) in malignant tumor as compared to control group (Fig. 4.1.a). However, it should be noted that according to another group, increased linoleic acid does not contribute and/or even reduces the risk of developing breast cancer[47]. It is notable that the increasing tendency of linoleic acid amount on the background of increased stearic acid, may be caused by the disruption in regulation of lipids, especially by alterations in phospholipids biosynthesis, which is reflected in our findings.

In case of linolenic acid, percentage amount of the fatty acid was decreased (Table 2, and Fig. 4.3.b, and Fig. 4.3.c). This alteration was more obvious in case of malignant tumor (~1.5 fold decrease) (Fig. 4.3.c). Reduction in the percentage amount of linolenic and oleic acids within menopausal women with malignant tumors can be conditioned on one hand by the changes in the activities of the enzymes that are involved in fatty acid synthesis[48] and by sharp increase in the lipid peroxidation intensity on the other (Table 1). It is known that the mentioned FAs

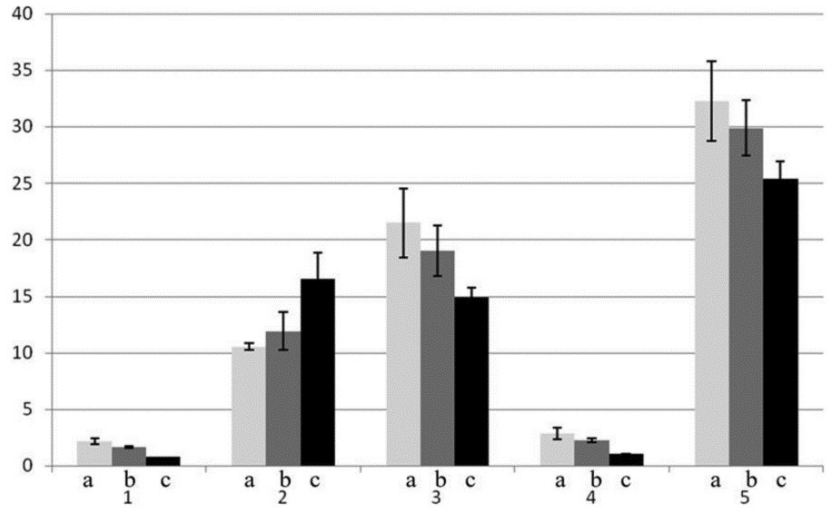


Fig. 4 — Total amount of individual unsaturated fatty acids in blood of the women with uterine tumors. 1. Oleic acid; 2. Linolic acid; 3. Linolenic acid; 4. eicosatrienoic acid; 5. Arachidonic acid. a – *Control group*; b – *Benign uterine tumor*; c - *Malignant uterine cancer group;* n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 45-55 years

are good substrates for lipids peroxidation process, since they are involved in free-radical oxidation reactions and eventually contribute to the formation of high toxic products, *i.e*., lipid peroxides[18].

We also investigated the alteration in the percentage amount of eicosatrienoic acid and arachidonic acids within uterine tumors. Our data revealed that the percentage amount of eicosatrienoic acid ($C_{20:3}$) was sharply decreased in malignant uterine tumors by ~3-fold (Table 2, and Fig. 4.4.c) as compared to the control group (Fig. 4.4.a). It is notable that the amount of eicosatrienoic acid was not substantially altered in benign tumors (Fig. 4.4.b). As for the arachidonic acid, its percentage amount did not alter in benign tumors (Fig. 4.5.b), but it was decreased in malignant tumor by ~1.3 fold (Table 2, and Fig. 4.5.c) as compared to the control group (Fig. 4.5.a). We observed a sharp decrease in eicosatrienoic acid in case of malignant tumor (~1.3-fold). This phenomenon may be caused by the alterations in the biosynthesis of eicosatrienoic acid, which is demonstrated with the decreased amount of this fatty acid (and in the increased amount of linoleic acid) (Fig. 4.2c). It is well known that a high level of linoleic acid inhibits the biosynthesis of eicosatrienoic acid from oleic acid[49], and these changes are also confirmed with our results.

The reduction in the amount of arachidonic acid ($C_{20:4}$) in case of malignant tumors (~1.3-folds) (Table 2) in parallel with increasing linoleic acid amount, may be caused by active biosynthesis of prostaglandins and inhibition of the enzyme (*i.e*., Δ^5 desaturase)[50], that showed the increased ratio of linoleic/arachidonic acids ($C_{18:2}/C_{20:4}$). According to our observations, the mentioned ratio was increased ~2.3-fold in case of menopausal women with malignant tumors (Table 2).

Thus, in the blood of the menopausal women with uterine benign tumors, the levels of saturated and unsaturated FAs was altered slightly to none. Significant alterations occurred with both saturated and unsaturated fatty acids in the women with malignant uterine tumors, which indicates on an enhancement of fatty acid metabolism, or indicates a shift of energy metabolism from carbohydrate utilization towards the preferencial utilization of lipids and fatty acids[48].

Thus, we implicate that excessive utilization of fatty acids should increase the biosynthesis of triglycerides and very low-density lipoproteins in the liver, which results in increased levels of low-density lipoproteins and cholesterol in blood[15]. The observed changes in our study indicate about significant disruptions in blood lipids metabolism in menopausal women with malignant uterine tumor. It can be suggested that tumor cells use alternative pathways and enzymes to enhance the synthesis of fatty acids that contribute to the proliferation and survival of tumor cells[21]. Thus, specific changes in these biochemical parameters can be useful in the differentiation of benign and malignant uterine tumors for menopausal women.

Conclusion

In this study, intensification of lipid peroxidation and alterations in lipid spectrum composition revealed hyperlipidemia, disruption of phospholipids' exchange rate and hypercholesterolemia. Thus, we advocate those specific changes in the evaluated biochemical parameters can be useful in the differentiation of benign and malignant uterine tumors for menopausal women.

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Conflict of interests

All authors declare no conflicts of interest.

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