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THE SPECTRUM OF BLOOD SERUM LIPIDS IN PATIENTS WITH BREAST CANCER WITHOUT METABOLIC SYNDROME

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The incidence of breast cancer has been increasing recently worldwide. Therefore, the search for the novel techniques for diagnosis and treatment as well as the studies elucidating pathogenetic mechanisms associated with tumorogenesis and delineating the molecular markers useful for diagnostics and monitoring of the disease are the topical issues of the day.

The tumor develops in the setting of the metabolic disorders. In particular, tumor growth is accompanied by the impaired lipid metabolism. Lipids as the constituents of plasma membranes, energy substrate and signal molecules participate actively in neocarcinogenesis.

Metabolic impairments form the basis of metabolic syndrome. In 2005, International Diabetes Federation referred to metabolic syndrome as one of the major problems in modern medicine contributing to the increased total death rate in population. Moreover, metabolic syndrome is associated with increased risk of tumor growth and unfavorable prognosis for cancer patients [1, 2].

In economically developed countries, the prevalence of metabolic syndrome is 25–35%. This figure increases up to 42–45% among the patients aged over 60. And one should take into account that cancer prevalence is also maximal in the persons of the older age group.

The principal symptoms of metabolic syndrome are such as follows:

- Abdominal obesity with waist exceeding 88 cm
- Dyslipidemia with triglycerides >1.69 mmol/L and cholesterol of the high density lipids >1.04 mmol/L
- Hyperglycemia with fasting glucose in the peripheral blood >6.1mmol/L
- Arterial hypertension with arterial blood pressure >130/85 mm Hg/

The presence of at least 3 signs of the 4 listed above allows one to diagnose metabolic syndrome.

The metabolic syndrome with accompanying insulin resistance and dyslipidemia are associated with the increased risk of colorectal cancer, endometrial cancer, gall bladder cancer, prostate cancer, cancer of pancreas and breast cancer [1–4]. At present, the role of many molecular factors of the metabolic syndrome that are pertinent to carcinogenesis has been already clarified, namely insulin, insulin-like growth factor, leptin, tumor necrosis factor, cholesterol, aromatase, etc.

The spectrum of blood serum lipids in the patients with breast cancer in the setting of metabolic syndrome is different from that in the healthy women [4, 5]. The role of the impaired lipid metabolism as the triggers of the molecular mechanisms of neocarcinogenesis has been proven.

The following alterations of the spectrum of blood serum lipids in the patients with breast cancer in the setting of metabolic syndrome have been found out:

There are plenty researches [4–6] devoted to breast cancer in the setting of metabolic syndrome. According to various data, in 20–40% of the patients with breast cancer (setting apart the familial and hereditary breast cancer), the signs of the metabolic syndrome are lacking.

Therefore, we have attempted to study the characteristic features of spectrum of blood serum lipids in the patients with breast cancer without metabolic syndrome and to assess the dynamics of the parameters of the spectrum of blood serum lipids following the cytostatic therapy.

Among 100 patients with breast cancer stage IIB (T2N1M0,T3N0M0) aged 30–60 treated in Kyiv municipal clinical oncological center, 67 patients were with the signs of metabolic syndrome while in 23 patients the metabolic syndrome was not revealed.

23 patients with breast cancer without metabolic syndrome and 13 healthy women were included into the study. The clinical characteristics of patients and controls included in to the study are presented in Table 1.

Table 1. Clinical characteristic of patients with breast cancer without metabolic syndrome and healthy women

Parameter	Control (n=13)	Patients (n=23)
Age (years)	41.3±2.7	44.1±4.7
Body height (cm)	167.1±1.3	165.8±1.1
Body mass (kg)	61.2±3.9	65.3±5.0
Index of body mass (kg/m^2)	23.8±1.1	25.4±1.3
Circumference of abdomen (cm)	70.8±1.6	72.1±2.2
Arterial blood pressure (mm Hg)	118±1.8/70±0.6	115±3.2/9±1.4

The group of patient and the control group were similar according to stated parameters.

In all patients and healthy persons participating in the study, the fasting venous blood was sampled for assaying total cholesterol, triglycerides, and glucose content (Table 2).

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Table 2. Biochemical parameters of blood in the patients with breast cancer without metabolic syndrome and healthy women

Parameter (mmol/L)	Control group (n=13)	Patients (n=23)
Total cholesterol	4.9±0.7	5.2±0.5
Triglycerides	1.5±0.5	1.4±0.7
Glucose	4.4±0.2	4.5±0.3

The biochemical parameters in both groups were within the normal ranges, that coincide with data of other authors [7].

Therefore, in the patients with breast cancer with normal body mass, without abdominal obesity and without arterial hypertension, the blood content of total cholesterol, triglycerides, and glucose do not deviate from the normal values.

Then we assayed the total lipids of blood serum by thin layer chromatography using micromethod of detection. The percent content of phospholipids, di- and triglycerides, and cholesterol esters was assessed. The results are given in Table 3.

Table 3. Content (%) of total lipids in blood serum in the patients with breast cancer without metabolic syndrome and healthy women

Group	Parameters				
	Phospho-lipids	Choles-terol	Diglycer-ides	Triglycer-ides	Cholester-ol esters
Patients	15.9±2.4	23.4±1.9	7.2±1.0	32.7±2.8	20.7±2.1
Controls	18.3±1.8	20.9±1.8	5.0±1.0	24.6±3.6	31.2±3.4

As it can be seen, the content of phospholipids and cholesterol in the patients with breast cancer does not differ from that in the healthy women. Meanwhile, the content of di- and triglycerides in the blood serum of the patients is inferior to that in healthy women; the content of cholesterol esters in the patients is superior to that in healthy women (Fig.1–4).

As to triglycerides representing the energy substrate used in the pathological conditions, one may suggest that the decrease in the content of triglycerides in the blood serum of the patients with breast cancer may be associated with their active utilization by cancer cells.

Although the absolute content of total cholesterol and triglycerides (in mmol/L) in the patients with breast cancer without metabolic syndrome is within the normal range, the redistribution between the components of lipidogram is evident with the increase in cholesterol esters content and decrease in triglyceride content as compared to that in the healthy controls.

The spectrum of the individual phospholipids (lysophosphatidyl choline, sphyngomyelin, phosphatidyl ethanolamine, phosphatidyl inositol) was assessed by thin layer chromatography. The results are given in Table 4.The difference between the parameters under study was insignificant.

Table 4. Content (%) of individual lipids in blood serum in the patients with breast cancer without metabolic syndrome and healthy women

Groups	Parameters				
	Lysophos-phatidyl choline	Sphyngo-myelin	Phospha-tidyl cho-line	Phospha-tidyl etha-nolamine	Phospha-tidyl ino-sitol
Control	10.5±0.7	19.5±1.2	52.0±2.2	11.1±0.3	6.8±1.1
Patients	8.9±0.8	20.0±2.1	58.1±3.5	10.5±2.0	2.3±1.1

All the patients with breast cancer stage IIB without metabolic syndrome were treated with two 21-day courses of neoadjuvant polychemotherapy according to CAF regimen (Doxorubicin, Cyclophosphamide, 5-fluorouracil). Then the analysis of the above biochemical parameters was repeated (Table 5).

Table 5. Content (%) of total lipids in blood serum in the blood serum of patients with breast cancer without metabolic syndrome prior to and after two courses of neoadjuvant polychemotherapy

	Parameters				
	Phospho-lipids	Choles-terol	Diglycer-ides	Triglycer-ides	Cholester-ol esters
Prior to treatment	18.3±1.8	20.9±1.8	5.0±1.0	24.6±3.6	31.2±3.4
After treatment	15.1±2.4	18.3±1.5	4.8±1.3	33.4±5.3	28.5±3.1

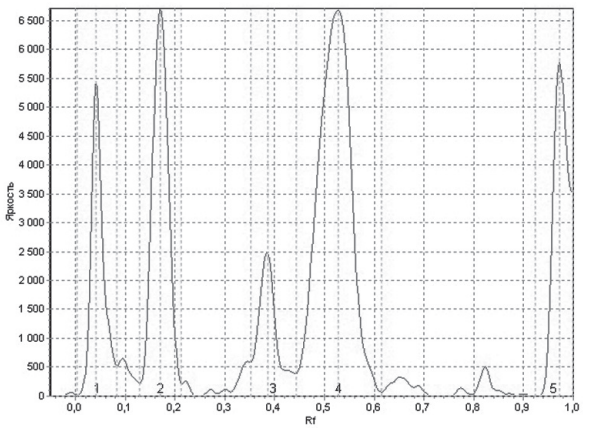

Fig. 1. The spectrum of blood serum lipids of healthy woman FNI, 42 years old.

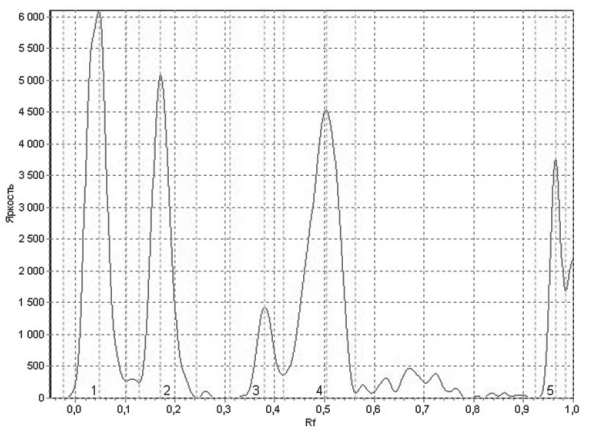

Fig. 2. The spectrum of blood serum lipids of healthy woman YNO, 34 years old

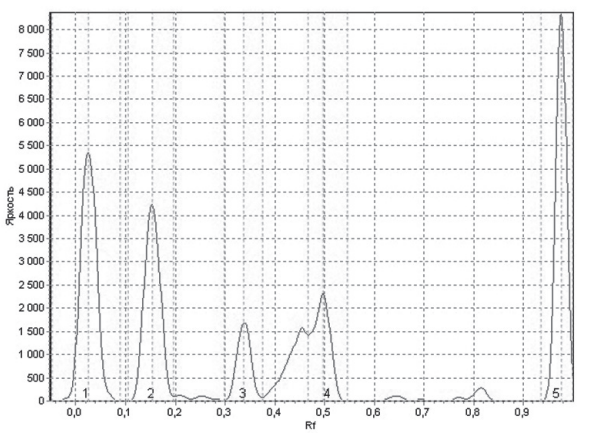

Fig. 3. The spectrum of blood serum lipids of breast cancer patient ZSV, 38 years old

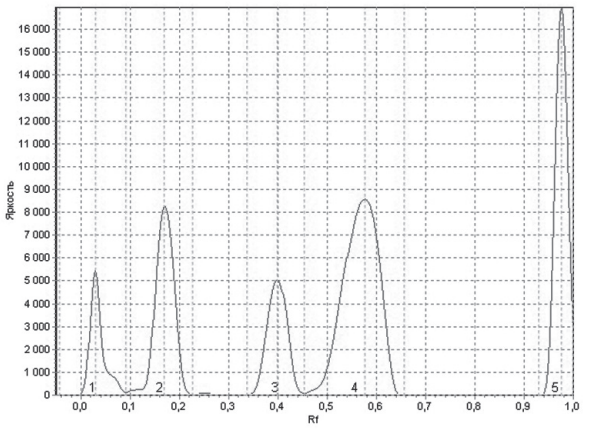

Fig. 4. The spectrum of blood serum lipids of breast cancer patients GNN, 40 years old. 1 — phospholipids, 2 — cholesterol, 3-free fatty acids, 4 — triglycerides, 5 — cholesterol esters

The differences were not statistically significant. The trend to increasing triglyceride content and decreasing content of cholesterol esters and phospholipids was found out.

The dynamics of these parameters in the patients with tumors chemosensitive to chemotherapy was analyzed. The tumor was considered as chemosensitive one when regression exceeded 30% according to mammography findings and pathomorphological response exceeded that of grade II assessed upon the histological study of the resected tumors. The decrease in the content of cholesterol esters and increase in the content of triglycerides was evident in 70% of the patients with tumors chemosensitive to chemotherapy and 26% with resistant tumors. Moreover, in the patients with resistant tumors the level of phospholipids was unchanged or even reduced. In the patients with chemosensitive large tumors, the blood content of phospholipids increased suggesting the destruction of the bulk of chemosensitive cancer cells and the release of phospholipids to the blood circulation.

We have also studied the serum blood content of the individual lipids in the patients with breast cancer prior to and after two courses of neoadjuvant polychemotherapy. The results are given in Table 6.

Table 6. Content (%) of individual lipids in blood serum in the blood serum of patients with breast cancer without metabolic syndrome prior to and after two courses of neoadjuvant polychemotherapy

Groups	Parameters				
	Lysophosphatidyl choline	Sphyngomyelin	Phosphatidyl choline	Phosphatidyl ethanolamine	Phosphatidyl inositol
Prior to treatment	8.9±0.8	20.0±2.1	58.1±3.5	10.5±2.0	2.3±1.1
After treatment	9.8±1.4	23.2±1.8	54.6±2.8	8.5±1.2	3.9±1.3

In general group of the patients, the parameters stated above were not significantly different when assessed prior to the treatment and after two courses of neoadjuvant polychemotherapy. The trend to increasing phosphatidyl inositol content and decreasing content of phosphatidyl choline and phosphatidyl ethanolamine was observed.

In the cases of chemosensitive breast cancer, statistically significant reduction of phosphatidyl ethanolamine was recorded. The content of phosphatidyl inositol was higher in the patients with the chemosensitive tumors (both prior to and after neoadjuvant polychemotherapy).

Phosphatidyl inositol (precursor of inositol triphosphate) does not represent the structural component of plasma membrane. This substance is a signal molecule stimulating a set of metabolic processes related to cell proliferation. The increased blood serum phosphatidyl inositol content in then patients with cancer chemosensitive to the treatment may be considered as indirect evidence of increased proliferative activity of such cancer cells.

Phosphatidyl ethanolamine is classified as canabinoid. These molecules stimulate proliferation affecting the growth receptors of cell membranes. The reasonable explanation of the increased phosphatidyl ethanolamine content is not available in the literature. One may suggest that upon the reduction of the number of cancer cells due to chemotherapy, in the resistant clones the proliferation potential increases. Phosphatidyl ethanolamine may be regarded as the marker of such increased poliferative activity.

Phosphatidyl choline is a product of the cancer cell metabolism. In some studies, the content of phosphatidyl choline is reduced only upon completion of the complex treatment. Therefore, the trend to decreasing content of this substance in the present study does not contradict the results of other authors [5, 8, 9].

In conclusion, our pilot study has confirmed the significance of lipids in carcinogenesis. Breast cancer patients with no obvious metabolic disorder exhibit certain variations in their serum blood lipid spectrum associated with oncologic disease. However, additional immunohistochemical research is required identifying the markers of proliferation in tumor cells in order to confirm our assumptions.

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