

TISSUE TOTAL SIALIC ACID, FIBRONECTIN AND PLASMA FIBRONECTIN, LIPID-BOUND SIALIC ACID LEVELS IN PATIENTS WITH BREAST CANCER

Zeynep Öztürk¹, Hakan EKMEKÇİ¹, Hüseyin Sönmez¹, Hüseyin Baloğlu², Emine KÖKOĞLU¹

MEME KANSERLİ HASTALARDA DOKU TOTAL SİYALİK ASİT, FİBRONEKTİN VE PLASMA FİBRONEKTİN, LİPİDE BAĞLI SİYALİK ASİT DÜZEYLERİ

Özet: Bu çalışmada meme kanserli hastalarda doku total sialik asit, fibronektin ve plazma lipide bağlı sialik asit ve fibronektin düzeyleri tayin edildi. Ortalama doku total sialik asit, plazma ve doku fibronektin ve plazma lipide bağlı sialik asit düzeyleri sırasıyla 18.40±8.88 mg/mg protein, 205.69±46.51 mg/m 23.51±11.60 mg/mg protein ve 27.59±6.79 mg/ml bulundu. Kontrol grubunda ise sırasıyla 10.52±2.44 mg/mg protein, 335.35±92.98 mg/ml, 12.47±5.69 mg/mg protein ve 12.14±3.12 mg/ml bulundu. Kontrol grubuna göre doku total sialik asit düzeyleri anlamlı olarak yüksek bulundu ($p<0.001$). Menopozal durum ve gradeler arasında sialik asit düzeylerinde anlamlı farklılık bulamadık. Meme kanserli hastalarda, doku fibronektin düzeyleri kontrol grubuna göre anlamlı olarak yüksek bulundu ($p<0.001$). Plazma fibronektin düzeyleri, meme kanserli hastalarda kontrol grubuna göre anlamlı olarak düşük bulundu ($p<0.001$). Oysaki lipide bağlı sialik asit düzeyleri meme kanserli hastalarda kontrol grubuna göre anlamlı olarak yüksek bulundu ($p<0.001$).

Anahtar Kelimeler: Fibronektin, lipide bağlı sialik asit, sialik asit, meme kanseri.

Summary: In this study, tissue total sialic acid, fibronectin and plasma fibronectin, lipid-bound sialic acid levels were determined in human breast cancer. The mean tissue sialic acid, plasma and tissue fibronectin and plasma lipid bound sialic acid levels in breast cancer were found to be 18.40±8.88 mg/mg protein, 205.69±46.51 mg/m 23.51±11.60 mg/mg protein and 27.59±6.79 mg/ml, respectively versus 10.52±2.44 mg/mg protein, 335.35±92.98 mg/ml, 12.47±5.69 mg/mg protein and 12.14±3.12 mg/ml in control group. Tissue sialic acid levels were significantly higher than the control group ($p<0.001$). We could not find a significant difference in the levels of sialic acid between the Grades and menapausal status. Tissue fibronectin levels were significantly higher in breast cancer as compared with the control group ($p<0.001$). Plasma fibronectin levels were significantly lower in breast cancer than control group ($p<0.001$). Where as lipid-bound sialic acid levels in breast cancer were found to be significantly higher when compared with the control group ($p<0.001$).

Key Words: Fibronectin, lipid-bound sialic acid, sialic acid, breast cancer.

INTRODUCTION

The usefulness for biochemical tumor markers in clinical oncology is well established and the need for new sensitive and specific tumor markers in detecting malignant disease, staging predicting prognosis and evaluating response to treatment is recognised(1).

N-acetylneuraminic acid (sialic acid), a nine-carbon derivative of N - acetyl mannosamine, is a

component of many glycoproteins and glycolipids in higher animals. The carboxylic acid groups of these sugar derivates are ionized at pH 7(2).

Neoplasm which increased concentration of sialic acid on the tumor cell surface and sialoglycoproteins are shed or secreted by some of these cells which increases in concentration of blood(3,4). Recent studies have shown that a variety of cancers are associated

¹Departman of Biochemistry, Cerrahpaşa Medical Faculty, University of Istanbul

²Departmen of Pathology, Gülhane Military Hospital, Istanbul, Turkey



with changed levels of sialic acid in serum and other biological fluids(5,12).

Sialic acid is located in the outer cell membrane and has a strong negative electrical charge(13). Approximately 98-99.5% of the total sialic acid in serum is bound to glycoproteins. Only a small amount of it is bound to lipids(14).

Several investigators have reported that sialic acid concentrations are related to diagnosis, staging, prognosis and detecting of early recurrence(15,16).

Fibronectin, is a high molecular weight glycoprotein (440 kd) composed of two similar polypeptide chains that are connected by two disulfide bonds (17). It is localized in the extracellular matrix of various cell types (17,18) and has been implicated functionally in the regulation of several processes, including adhesion, differentiation motility and transformation (19,20).

Fibronectin can bind to the cell surface and has other binding sites to recognize the collagen molecule and other connective components. Therefore fibronectin is believed to be involved in the interaction of cells with the extracellular matrix (21).

It was shown that plasma fibronectin undergoes modification in cancer and in a variety of pathological conditions.

In breast cancer, plasma fibronectin has been shown to be significantly increased (22,23,24), unchanged or decreased (24).

The aim of the present study, was to determine the tissue total sialic acid levels, plasma and tissue fibronectin and plasma lipid-bound sialic acid levels in breast cancer.

MATERIAL AND METHODS

Twenty-seven women aged 25 to 78 years were included in the study. Tumor tissue samples were obtained from the Department of General Surgery immediately after surgical intervention. Macroscopi-

cally homogenous pieces of the tumor were selected and samples were sent to the Department of Pathology for identification.

According to the pathological analysis, tumor tissues were divided in to groups: 15 tumors with Grade I-II and 12 tumors with Grade III. Normal breast tissues were obtained from the healthy zone of the breast tissues of 14 patients with breast cancer.

Twenty-three women aged 25 to 78 years were used in the other part of the study. All had breast cancer and their peripheral blood samples were obtained before surgical intervention. Normal peripheral blood samples were obtained from thirty clinical healthy women ranging in 27 to 82 years. All patients group were also classified according to their menopausal situation: seven subjects with pre, nine subjects with para and seven subjects with post menopause.

Tumor and normal tissues samples were homogenized in phosphate buffer (pH 7.4) at 4°C forming a 10% (w/v) homogenate. Homogenization was performed with a tissue grinder which had been fitted with a teflon pestle at a speed at 1000 rpm for 10 mins.

Tissue total sialic acid determined from the supernatant by the thiobarbituric acid method described by Warren (25). Total proteins were assayed by the Lowry procedure (26) and the results are given in μg sialic acid per mg protein.

Citrated plasma samples for fibronectin and lipid-bound sialic acid determination were obtained from all patients and controls. The plasmas were stored in several small aliquats at -70°C till assayed.

Tissue and plasma fibronectin and lipid-bound sialic acid levels were determined by the turbidimetric immunoassay (Boehringer Mannheim) and the method described by Katopodis(27), respectively.

The mean tissue sialic acid plasma and tissue fibronectin and lipid-bound sialic acid levels in cancerous and control groups were compared by commonly used statistical techniques for the comparison of

sample means (Student's t test). Significance (p) values equal to or less than 0.05 were considered significant. For correlation analysis, Pearson correlation was used.

RESULTS

The mean tissue sialic acid levels in patients with breast cancer and controls are summarized in Table I. The mean tissue sialic acid concentration for patients with breast cancer were 18.40 ± 8.88 $\mu\text{g}/\text{mg}$ protein and for noncancerous tissues were 10.52 ± 2.44 $\mu\text{g}/\text{mg}$ protein respectively.

Table I : The mean tissue total sialic acid levels in breast cancer and non cancerous group

Group	n	Tissue total sialic acid ($\mu\text{g}/\text{mg}$ -protein)
Breast cancer	27	$18.40 \pm 8.88^*$
Control	14	10.52 ± 2.44

* $p < 0.001$

Tissue sialic acid levels were significantly higher in patients with breast cancer than non cancerous tissues group.

Also we couldn't find a significant difference in the levels of sialic acid between Grade I-II and III, pre and para, para and post, pre and post menopause groups.

The mean plasma fibronectin and lipid-bound sialic acid levels are summarized in Table II. Plasma fibronectin levels in breast cancer were found to be significantly lower than control group ($p < 0.001$). On the otherhand, plasma lipid-bound sialic acid levels were significantly higher in breast cancer than control group ($p < 0.001$).

Table II : The mean plasma fibronectin and lipid-bound sialic acid levels in breast and noncancerous group

Group	n	Plasma fibronectin ($\mu\text{g}/\text{ml}$) ($X \pm SD$)	Plasma lipid-Bound sialic acid ($\mu\text{g}/\text{ml}$) ($X \pm SD$)
Breast cancer	23	$205.69 \pm 46.51^*$	$27.59 \pm 6.79^*$
Control	30	335.35 ± 92.98	12.14 ± 3.12

* $p < 0.001$

The mean tissue fibronectin levels in cancerous and noncancerous tissue group summarized in table III. Tissue fibronectin levels in breast cancer were found to be significantly higher than control group ($p < 0.001$).

Table III : The mean tissue fibronectin levels in breast cancer and noncancerous groups

Group	n	Tissue fibronectin ($\mu\text{g}/\text{mg}$ -protein)
Breast cancer	31	$23.51 \pm 11.60^*$
Control	10	12.47 ± 5.69

* $p < 0.001$

We could not find a significant difference in Total sialic acid, Fibronectin and lipid-bound sialic acid values between Grade I-II and Grade II, pre and para, pre and post, post and para menopause groups ($p > 0.05$). There was no correlation between total sialic acid fibronectin and lipid-bound sialic acid levels in breast cancer.

DISCUSSION

Identification of the reliable biological tumor markers or substance associated with neoplasia that can be used detection, staging and evaluation of therapy is the goal of many investigators.

Various glycoproteins and glycolipids may prove to be tumor markers(28), since cell surfaces and membrane components play a prominent role in neoplastic behavior(29,30,31,32).

Sialic acid (N-acetylneuraminic acid) is an aldehyde, which is located in the outer cell membrane, as part of glycoproteins, glycolipids and polysaccharides.

Increased levels of glycolipid-bound sialic acid in the serum of mice and humans with mammary carcinoma and also serum glycoproteins in the cancer suggest that measurement of total serum and/or LSA might be useful markers of malignancy(33,34).

Warren et al(32) as well as others observed that only traces of tumor characteristic sialo - focusyl



glycopeptides are found in the serum of healthy subjects while it is found in high concentrations in malignant transformed cells.

In several clinical studies(35,36,37,38) it has been shown that one of the most important changes in sialic acid metabolism of malignant cells was the increasing activity of sialyltransferase.

Several groups have evaluated fibronectin in experimental models and in patients with breast cancer. Mosher and Williams (45) found elevated plasma fibronectin concentrations in a small group of metastatic breast cancer patients, however they found decreased levels in severely ill patients with cancer and, particularly, in patients with disseminated intravascular coagulation. Also elevated fibronectin levels were reported in the plasma of patients with breast cancer by other researchers (22,23). Whereas in dogs with mammary gland neoplasia, plasma fibronectin concentration has been found to be increased, unchanged or decreased as compared with normals (24,41).

Our findings indicate that sialic acid levels in cancerous tissues are higher than those in non cancerous breast tissue. These findings are in agreement with the findings of other researches. However, there was no difference in tissue sialic acid levels between the Grades.

In our previous study, we found the levels of plasma fibronectin are decreased in various types of human brain tumors(14). Also plasma fibronectin level has been found to be lowered in patients with squamous cell carcinoma of the head and neck (46), chronic lymphocytic leukemia and small-cell carcinoma of the lung(48). Our findings in the present study are in agreement with above data.

It has been demonstrated the presence of an elastase-type protease in mammary cancer extracts(15). This type of enzyme was shown to fragment plasma fibronectin, which was shown to be very sensitive to elastase-type proteases.

It has been also shown that proteolytic activity increases in transformed cells and tumor extracts(51,52). The decreased levels of plasma fibronectin may be due to an increase in the preteolytic activity.

Histochemical, chemical and immunologic evidence either supports or directly indicates that sialoglycoproteins become attached to the surface of tumor cells, they effect adherence, cohesion and antigenic expression. Changes in the serum sialoglycoproteins that profile malignancies are shared by other disease states, but interactions of malignant cell with increased or abnormal sialoglycoproteins to be different(1,4).

Elevations of serum sialic acid as reflected by serum total N-acetyl-neuraminic acid (NANA) concentrations have been reported in various types of cancers. At present, sialic acid measurements along with CEA and AFP are used as a marker in cancer diagnosis and follow up. Total and lipid-bound sialic acid measurements are nonspecific criteria for cancer detection. However, various investigators have suggested that total and in particular lipid-bound sialic acid may be a valuable biochemical marker in detecting metastases, staging of disease, indicating the risk for recurrence and evaluating therapeutic response(39,40,42,43,44).

In this study, we found the levels of plasma lipid-bound sialic acid tissue total sialic acid and tissue fibronectin levels are elevated in patients with breast cancer as compared to control noncancerous group. And we found plasma fibronectin levels are decreased in patients with breast cancer as compared with the non cancerous group.

In conclusion, we report that both fibronectin, lipid-bound sialic acid and total sialic acid found in the outer cell membrane are changed in the plasma of patients with breast cancer when compared with the noncancerous group. They may be useful marker for

human breast cancer but can not be used as a criterion for identifying tumour types.

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