

Relationship Between Total and Lipid-bound Serum Sialic Acid and Some Tumor Markers

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Abstract

Background: Increased levels of total and lipid-associated sialic acid (TSA and LASA) have been reported in the sera of patients with benign or malignant tumors and also could be regarded as newly important clinical criteria for the diagnosis of cancer. This study has investigated the differences of TSA and LASA contents between cancer patients and healthy individuals and evaluated their correlations between TSA and LASA with some tumor markers in different types of cancer.

Methods: 35 patients with histopathologically confirmed cancers and 32 healthy individuals participated in the study. Tumor markers in serum including CEA, CA15-3, CA19-9 and CA-125 were measured using ELISA. TSA and LASA were quantified using spectrophotometric methods of Erlich and Katopodis respectively and non-parametric tests were used for statistical analysis.

Results: The median (range) obtained for TSA in healthy and cancer patients were 83.6 (59.0-106.2) and 119.5 (84.7-205.8) mg/dl respectively and the difference was statistically significant ($P < 0.001$). The corresponding values for LASA content of serum in healthy and cancer patients were 16.9 (13.3-20.7), and 31.0 (15.0-50.3) mg/dl. Statistical analysis showed significant differences in LASA content between these two groups ($P < 0.001$). A positive correlation coefficient was obtained between TSA, LASA and different tumor markers.

Conclusion: The significant correlation between TSA, LASA and different tumor markers in cancer patients indicated that they could be used as diagnostic criteria. However, due to their lack of specificity, they may support the presence of tumor markers in different malignancies and be helpful in relation to therapy and monitoring of patients.

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Keywords • Sialic acid • tumor markers • cancer

Introduction

Sialic acids are terminal sugar components of the oligosaccharide chains of glycoproteins and glycolipids.¹ Numerous recent studies have addressed themselves to the quantification of serum or plasma sialic acid in various disease states. Significant elevation of total circulating sialic acid has been documented in diabetes and inflammatory diseases.^{2,3} Elevation of serum sialic acid was reported in the

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oral cavity of patients with cervical cancer. It is therefore concluded that this factor can be used for the prognosis and treatment monitoring.^{4,5}

The values of serum total sialic acid (TSA) and lipid-bound or lipid-associated sialic acid (LASA) as tumor markers has been a highly contentious issue for many years.¹ LASA concentration was measured in the serum and plasma of normal individuals, in those with benign disease, and in a large numbers of patients with malignant neoplasms.^{6,7} These studies showed consistent, highly significant increases of LASA levels in cancer patients and suggested that the LASA may prove to be an important new clinical tool for the diagnosis and management of cancer.⁸

In a study carried out on patients with endometrial cancer, it was shown that serum TSA level was significantly higher in cancer patients than in healthy control group.⁹ Hobarth et al. evaluated serum TSA as tumor marker for prostate cancer and compared it with serum prostate specific antigen (PSA). They reported that serum TSA was significantly elevated among cancer patients. They concluded that as sialic acid lacked tumor specificity, it was not helpful in screening for prostate cancer, yet might contribute towards the early detection of tumor progression and metastasis during both therapy and follow-up.¹⁰

Romppanen and co-workers indicated that both benign and malignant breast cancers caused elevation of serum TSA and LASA. However they concluded that these values do not provide reliable classification of undefined breast tumors.¹¹ Another group of researchers showed that elevated LASA in women with breast tumors in absence of family history of breast cancer was due to genetic changes occurring in non-familial breast cancer.¹² A good correlation was found between TSA and CA125 levels in patients with undifferentiated ovarian cancers. It was concluded that total serum sialic acid level reflected the development of malignancy and should be considered as a supportive evidence of tumor marker for the diagnosis of ovarian cancer.¹³

Despite foregoing and several other studies, the diagnostic utility of serum TSA and LASA level has not yet been established. The objective of the present study was to determine whether the elevated TSA and LASA levels found in cancer patients correlate with increasing concentrations of some tumor markers. Another aim of the study was to explore if TSA and LASA could support the presence of tumor markers in different malignancies.

Patients and Methods

Thirty-five patients with different malignancies, referred to Kermanshah Private Clinic, Kermanshah, West of Iran, participated in the study. These included breast (14 females and one male), ovarian (eight females) and gastrointestinal (four females and 6 males). The mean age in breast, ovarian, and gastrointestinal groups were 48±13; 46±18; and 51±15 yrs respectively. All patients were in active phase of the disease and their neoplasia was confirmed histopathologically. Blood samples were taken prior to chemotherapy. Control group comprised of 32 apparently healthy individuals with mean age 49±16 yrs. Blood samples were taken from all subjects in fasting state and serum was separated and kept at -20 °C until used.

Using ELISA (Can Ag EIA, Sweden), tumor markers including CA125, CEA, CA19-9, and CA15-3 were measured in sera of cancer patients. TSA was measured in all samples using spectrophotometric method of Erlich,¹⁴ and sialic acid as standard (Merck Co, Germany). LASA assay was performed spectrophotometrically according to Katopodis method.⁸

Statistical Analysis

Non-parametric Mann-Whitney U test was used to compare the various parameters and P<0.05 was considered as significant. Pearson correlation coefficients were calculated,¹⁵ to show the correlation between parameters.

Table 1: Mean serum tumor marker levels from cancer patients compared with healthy ranges.

Group	Tumor Marker [median (range)]			
	CEA (range) (µg/L)	CA15-3 (range) (Unit)	CA 125 (range) (Unit/ml)	CA 19-9 (range) (Unit)
Breast	41.8 (0.2-84.3) n=14	34.8 (15.6-300) n=13	51.9 (6.1-329) n=13	26.1 (2.1-65) n=12
Ovarian	10.8 (0.9-46.8) n=9	251 (45-452) n=8	148.6 (5.7-550) n= 8	18.9 (3.5-29) n=7
GIT	5.2 (0.5-70.4) n=9	ND	126.3 (45-235) n= 7	119.5 (12.7-490) n=7
HR	Up to 5	<30	<35	<37

GIT= Gastro intestinal tract; ND: Not determined; HR= Healthy ranges are from manufacturers of the kits

Results

The serum levels of different tumor markers in cancer patients are shown in Table 1 and compared with those of healthy individuals. In all cases the median of the tumor markers levels in cancer patients were higher than the corresponding healthy subjects.

The TSA level (median and range) obtained for healthy individuals and cancer patients were 83.6 (59.0-106.2) mg/dl and 119.5 (84.7-205.7) mg/dl respectively, and the difference between them was statistically significant ($p < 0.001$). The respective values for LASA in sera of healthy and cancer patients were 16.9 (13.3-20.7), and 30.9 (15.0-50.7) and the difference in LASA content between these two groups was statistically significant ($p < 0.001$).

The results of serum levels of TSA and LASA in three cancer groups and those of healthy individuals were shown in Table 2. The data for each cancer group was compared with those of corresponding healthy group. Statistical analysis showed that the serum levels of these values in three cancers were significantly different from those of healthy group ($p < 0.001$).

Table 2: Serum TSA and LASA levels (median) in different cancer groups and healthy individuals.

Group	TSA (range) (mg/dl)	LASA (range) (mg/dl)
Breast	108.0 (95.0-205.7)*	30.6 (21.3-50.7)**
Ovarian	141.3 (84.6-183.1)**	36.0 (15.0-46.7)**
GIT	117.5 (84.6-183.1)**	25.6 (15.0-39.5)**
Healthy	83.7 (59.0-106.2)	16.8 (13.3-20.7)

Data of each group is compared with those of healthy group; * = $P < 0.01$; ** = $P < 0.001$

Table 3 shows the correlation coefficients (r) between measured tumor markers, TSA and LASA including only the data of positive correlation with $r = 0.4$. A positive and significant correlation was observed between LASA, TSA and tumor markers (CA125, CEA, CA15-3, CA19-9) in different cancers studied ($p < 0.01$).

Table 3: Correlation coefficient (r) between TSA and LASA with different tumor markers in studied cancers.

Factor	Ovarian		Breast		GIT	
	CA125	CEA	CA15-3	CEA	CA19-9	
TSA	0.52	0.50	0.59	0.82	0.84	
LASA	0.67	0.50	0.67	0.55	0.77	

Discussion

These data indicated a strong correlation between TSA, LASA, CEA and CA19-9 in GIT cancer. Despite a vast array of molecules found to be associated with cancer, there is still a continuous search for finding out addi-

tional markers with increasing specificity. There is a challenge to diagnostic utility of total and lipid associated serum sialic acid. The data obtained from this study showed that both of these factors rise in cancer patients. Similar results have previously been reported in cholangiocarcinoma,¹⁶ ovarian neoplasia, and malignant melanoma.¹⁷ It has also been reported that TSA and LASA could be used for assessment of response to anticancer treatment in breast cancer patients.¹⁸ Romppanen et al. have shown that TSA and LASA could be useful adjuncts in exclusion, diagnosis and follow up of malignancies in children.¹¹ Increased serum TSA and a significant correlation with serum CA19-9 is reported in cholangiocarcinoma.¹⁹ The result obtained from the present study was consistent with those of another study that showed increased level of TSA and soluble intercellular adhesion molecule-1 (SICAM-1) in patients with colorectal cancer in which the correlation between these two factors became more significant with increasing stage of disease.²⁰ These data were confirmed by the presence of positive correlation between TSA and LASA and some tumor markers.

Different forms of sialic acid including protein bound, lipids associated and total are measured and shown to undergo alteration in different malignancies. Changes in glycosylation of alpha-1-protease inhibitor such as increased sialylation were found in ovarian and breast cancers,²¹ as well as in rheumatoid arthritis and Crohn's disease.²² An increased expression of carbohydrate antigen sialyl Lewis x (slex) was also found in IgG isolated from rheumatoid arthritis.²³ Kongtawelert et al. in their recent study showed that increased serum TSA concentration yielded a high sensitivity, specificity and accuracy for the diagnosis of cholangiocarcinoma.²⁴ They also stated that serum TSA would be a useful marker to differentiate cholangiocarcinoma from hepatocellular carcinoma.²⁴ In our study also positive correlation of both factors with CEA and CA15-3 showed that sialic acid could be used as a tumor marker. In view of sialylation of these tumor markers, such correlation could be predicted. Also the observed positive correlation between CA19-9 with LASA in GIT cancer could be due to the fact that CA19-9 is a sialyl Lewis x blood group antigen.

A limitation in using sialic acid as a tumor marker is that it has an acute phase reactant and most of the proteins that increase in acute phase are sialylated. Therefore, most investigators indicated that sialic acid and LASA could be used in monitoring of cancer patients and follow up after therapy. The determination

of serum TSA would be most useful as an adjunct to diagnosis rather than an early detection and screening tool in virtue of its apparent non-specificity.

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