Iraqi JMS

Published by Al-Nahrain College of Medicine
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net
Iraqi JMS 2021; Vol. 19(2)

Biochemical Estimation of Total Sialic Acid, Lipid-Bound Sialic Acid and Fucose in Serum Patients with Nasal and Paranasal Sinus Malignancies

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Abstract

Background It is known that measurement of serum total sialic acid (TSA), lipid bound sialic acid (LBSA) and L-Fucose levels may be altered and associated with different types of disease included malignant tumors, therefore, the evaluation of these compounds in serum cancer patients may elucidate the possibility of using this as a diagnostic marker.

Objective To explore the clinical application of TSA, LBSA and L-Fucose serum levels in patients with different site of nasal and para nasal sinus malignancies and compare with a group of healthy controls.

Methods Blood samples obtained from 16 patients with nasal-paranasal sinus malignancies confirmed cases (12 males, 4 females) (age range 45-73 years) and 28 healthy individuals (18 males, 10 females) (age range 38-67 years) participated in this study. Serum TSA and LBSA levels were determined by using colorimetric methods and the serum Fucose level estimation was done based on the method as adopted by Winzler using cysteine reagent.

Results Results showed that serum levels of TSA, LBSA and L-Fucose were significantly higher in cancer patients compared to normal healthy control ($P<0.001$) and more increased in patients with ethmoid and frontal sinuses cancer group.

Conclusion Estimation of TSA, LBSA and L-Fucose is suggestive to be a reliable marker as well as can use an effective diagnostic biomarker of cancer patients.

Keywords Sialic acid, lipid-bound sialic acid, Fucose, nasal, paranasal sinus cancer, spectrophotometer

Citation Mohammed AK, Mahdi NR, Ahmed FS. Biochemical estimation of total sialic acid, lipid-bound sialic acid and fucose in serum patients with nasal and paranasal sinus malignancies. Iraqi JMS. 2021; 19(2): 137-146. doi: 10.22578/IJMS.19.2.2

List of abbreviations: EFSC = Ethmoid and frontal sinuses cancer, LBSA = Lipid bound sialic acid, LWNCC = Lateral wall of the nasal cavity cancer, NCC = Nasal cavity cancer, TSA =Total sialic acid

Introduction

The incidence and mortality rate of cancer is still unacceptably high; this stark fact itself is the strong argument for further research in the field of cancer biology. Immense increase in knowledge of the altered characteristics of malignant cells has shown that cell surface glycoconjugate are considered to be important in relation to cancer because many of the altered properties of cancer cells expressed at the cell surface. Cell surface is transformed during carcinogenesis and is vital for uncontrolled growth and malignant behavior of the neoplastic cells. The only traces of sialofucosyl glycopeptides, which is characteristic of tumor tissue, are found in the serum of healthy subjects, whereas it is found in high concentration in malignant transformed cells [(1)]. Glycoconjugate molecules such as sialic acid and Fucose level are imported constituents of

cell membrane and also reported to be associated with tumor progression [2-7].

Majority of studies have been documented increase levels of glycoprotein in serum/plasma in cancer patients with lung cancer [8], urologic cancer [9], melanoma [10], breast cancer [11], thyroid cancer [12], and liver metastasis [13].

Numerous studies have documented that tumor cells modulate their surface by increasing fucosylation levels (addition of L-Fucose at the terminal end of the oligosaccharide chain) to escape recognition, which contribute to several abnormal characteristics of tumor cells, such as decreased adhesion and uncontrolled tumor growth [14] and found to be a powerful immune modulator as it is distributed in macrophages, which are important for immune function [15].

Alterations in serum Fucose levels had been detected in patients with different types of malignancies [16]. Hence, monitoring serum/tissue Fucose levels could be a promising approach for the early detection, diagnosis, and prognosis of various cancer types.

The present study aimed to evaluate total sialic acid (TSA), lipid bound sialic acid (LBSA) and Fucose as monosaccharide in serum patients suffered from nasal and paranasal sinus cancer patients and their role as a biomarker in diagnosis and compared with normal group.

Methods

A retrospective study of medical records was performed for 16 patients with different site of nasal and paranasal sinus malignancies referred to ear, nose and throat (E.N.T) and Maxillofacial Department in the Basra General Hospital between April 2014 and October 2018 were enrolled in this study. Provisional diagnosis of tumors was made on the basis of clinical examination and was confirmed by biopsy. Ethical approval was not required as this is a retrospective study and clinical date were identified before analysis.

The patients were divided into the following categories according to American Joint on Cancer Tumor staging based on TNM (T=tumor, N=node invasion. M=metastasis) [17].

Group (1): Nasal cavity cancer (NCC), consist of 6 patients.

Group (2): Lateral wall of the nasal cavity cancer (LWNCC), consist of 6 patients with maxillary sinus.

Group (3): Ethmoid and frontal sinuses cancer (EFSC), this group included 4 patients with intracranial extension.

The diagnosis of these tumors was carried out by E.N.T Maxillofacial Surgeons, moreover, the disease had to be measured in two dimensions by a computed tomographic scan (CTS). Based on incisional biopsy most cases included in this study were adenocarcinoma type, moderately differentiated grade (I) and out of 16 patients 7 had grade (II).

Group (4): Comprised of 28 healthy donors as a healthy person (18 males, 10 females age of 38-67 years). The control was judged to be healthy by reviewing their medical histories and no evidence of disease.

Serum preparation

Whole blood samples were collected from each patient and control and allowed at room temperature for 10 minutes, then centrifuged at 2500 rpm for 20 minutes.

The serum was separated and store at -25°C until analysis.

Estimation of TSA and LBSA

Serum TSA and LBSA values was measured by Svennerholm [18] and Katopoids et al. [19] methods respectively.

Estimation of serum L-Fucose

The serum Fucose assay in all samples using method of Dische and Shettles [20] as adopted by Winzler [21].

Statistical analysis:

The differences among mean serum tumor marker levels found in healthy group and subgroup of patients with cancer were tested using student's test. Sensitivity was calculated as the percentage of individuals in the groups with cancer who had levels of the tumor

markers above the cut-off level (2SD) standard deviation. Specificity was calculated as the percentage of individuals in the cancer groups who had levels of the tumor markers within the normal.

Results

Healthy subjects

Comparison of serum TSA, LBSA and Fucose was done in both sexes; the date showed that mean serum levels of TSA and LBSA in male and female was (78.61±6.69), (73.53±8.42), (27.63±6.6) and (23.98±4.08) mg/dl respectively, while the mean serum level for Fucose was (5.49±0.61) and (5.16±0.96) for male and female respectively. Comparing the TAS, LBSA and Fucose levels show little differences between male and female, so that the total mean average for both sexes was (76.06±7.53). (25.63±5.31) and (5.31±0.61) respectively (Table 1).

Table 1. Comparison of serum TSA, LBSA and Fucose levels for healthy control group

Sex	Serum TSA Mean±SD (mg/dl)	Serum LBSA Mean±SD (mg/dl)	Serum Fucose Mean±SD (mg/dl)
Male (n=18)	78.61±6.69	27.63±5.64	5.49±0.61
Female (n=10)	73.53±8.42	24.98±6.08	5.16±0.96
Total (n=28)	76.06±7.53	26.30±5.84	5.31±0.61

TSA: Total sialic acid, LBSA: Lipid bound sialic acid

Cancer patients

Separate calculations were done for each group of patients to investigate whether the changes in serum TSA, LBSA and Fucose levels of patients are conversely related to the location of cancer.

Date analysis revealed significant differences in serum TSA level in different patients' groups when compared with healthy control (Table 2). In the normal healthy sera sample the overall mean TSA level was found to be (76.06±7.53) mg/dl, while the mean sera levels among those in cancer patients was found to be (91.28±4.67) mg/dl, this increase of 17% was statistically significant (P<0.001). The mean values of TSA levels for patients with NCC and LWNCC was found to be 15% higher than that the healthy controls (P<0.001). On the other hand, the most pronounced changes were found in the level of serum patients with EFSC, this 23% increase was statistically significant as compared with the healthy control (P<0.001).

Table 2. Comparisons of serum TSA for the patients diagnosed as NCC, LWNCC and EFSC with healthy control

Clinical condition	Range (mg/dl)	Mean±SD (mg/dl)	*P* value
Control (n=28)	64.99-87.88	76.06±7.53	-
NCC (n=6)	85.18-99.88	90.87±3.04	P<0.001
LWNCC (n=6)	82.19-98.11	89.19±4.55	P<0.001
EFSC (n=4)	85.12-104.18	93.78±6.48	P<0.001
Total (n=16)	82.19-101.18	91.28±4.67	P<0.001

TSA: Total sialic acid, NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

Table 3 shows the data of mean values of serum LBSA found in patients with malignancies and in healthy controls. Likewise, the mean value of overall serum LBSA level in 16 patients under study was found to be 16% increase than that of healthy control (P<0.001). The most pronounced was found in the levels of serum LBSA for the patients with Ethmoid and frontal sinuses cancer (EFSC), this 18% increase was statistically significant (P<0.001).

Table 3. Comparisons of serum LBSA for the patients diagnosed as NCC, LWNCC and EFSC with healthy control

Clinical condition	Range (mg/dl)	Mean±SD (mg/dl)	*P* value
Control (n=28)	16.99-33.88	26.30±5.84	-
NCC (n=6)	29.55-39.89	34.23±5.15	P<0.001
LWNCC (n=6)	32.29-42.22	35.04±3.51	P<0.001
EFSC (n=4)	31.62-46.61	41.44±5.97	P<0.001
Total (n=16)	29.55-46.61	36.91±4.86	P<0.001

LBSA: Lipid bound sialic acid, NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

Table 4 shows mean±SD values of serum TSA and LBSA in histopathological grade I and II in malignancies patients. Significant differences in values of serum TSA and LBSA in grade I and grade II when compared with healthy group and the increase of mean value of TSA with stage of malignancy was more prominent than LBSA.

Table 4. Comparison of TSA and LBSA levels within different histopathological grades of patients diagnosed as NCC, LWNCC, EFSC and healthy control

Group	TSA mean±SD (mg/dl)	LBSA mean±SD (mg/dl)
Control (n=29)	76.06±7.53	26.30 ±5.84
NCC		
Grade (I) (n=4)	86.17± 2.65	32.03±2.21
Grade (II) (n=2)	98.74± 0.81	38.22±1.66
LWNCC		
Grade (I) (n=5)	84.80±1.85	35.03±0.92
Grade (II) (n=1)	98.20	42.22
EFSC		
Grade (I) (n=1)	85.12	31.62
Grade (II) (n=3)	97.04±2.31	45.30±0.16

TSA: Total sialic acid, LBSA: Lipid bound sialic acid, NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

Sensitivity of the TSA is shown in (Figures 1 and 2). The magnitude of the sensitivity TSA is varied between 16% for patients with LWNCC one case of 6 and 75% for patients with EFSC three cases of 4 have elevated levels above cut-off level for the healthy controls plus 2SD

(91.12 mg/dl), while the value reach to 33% for the patients with NCC (two cases of 6), this increase in sensitivity might have contributed to the reflection type of tumor and disease stage.

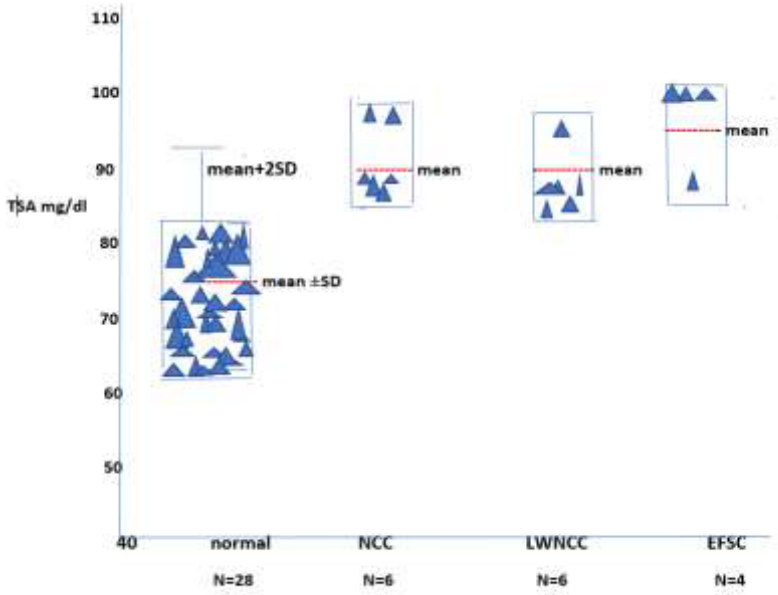

Figure 1. Levels of TSA in serum from healthy control and cancer patient. NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

Figure 2. Sensitivity of TSA in cancer patients. Group (1): Nasal cavity cancer (NCC). Group (2): lateral wall of the nasal cavity cancer (LWNCC). Group (3): Ethmoid and frontal sinuses cancer (EFSC)

To assess the alteration in sensitivity of the LBSA separate calculation was done and show in (Figures 3 and 4). Nevertheless, only one of 6 cases of NCC, three of 6 cases of LWNCC and

three of 4 cases of EFSC are just above 2SD (37.99 mg/ml). It is obvious from the results that the extent of increased sensitivity varied between 17% for cases with NCC and 75% with cases with EFSC, in contrast the value reach 50% for LWNSC cases.

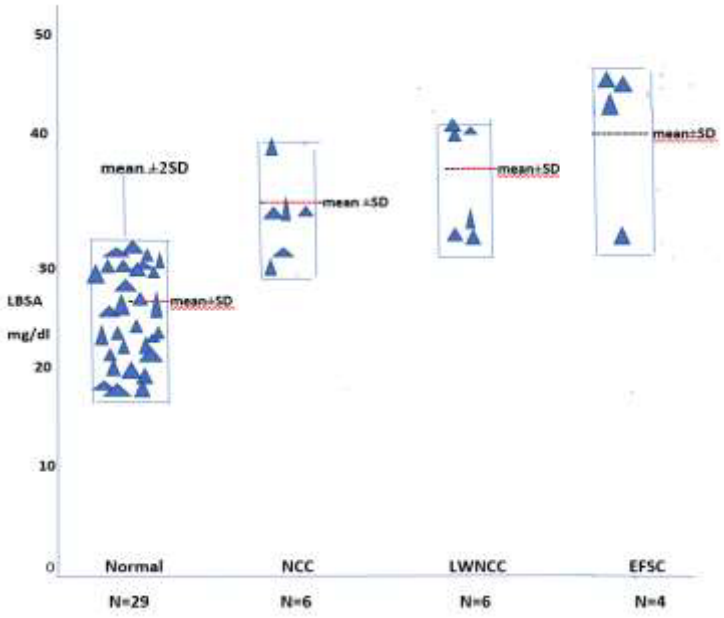

Figure 3. Levels of LBSA in serum from healthy control and cancer patient. NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

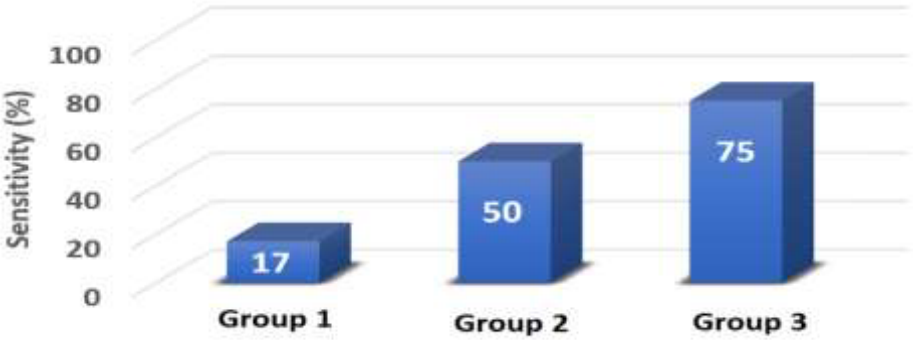

Figure 4. Sensitivity of LBSA in cancer patients. Group (1): Nasal cavity cancer (NCC). Group (2): lateral wall of the nasal cavity cancer (LWNCC). Group (3): Ethmoid and frontal sinuses cancer (EFSC)

The specificity of serum TSA and LPSA are considered in Table 5. Using 87.88 and 33.88 mg/dl as the upper limits of normal for TSA and LPSA respectively.

As can be seen, there were numerous causes of abnormal TSA and LBSA levels and each subgroup had at least one patient with an abnormal serum level of TSA and LBSA

respectively. Over all 25% of these patients had normal TSA and LBSA levels, but the numbers of patients in individual subgroups are too small to define the characteristics of specific malignant.

Table 5. Specificity of the TSA and LBSA test for the patients diagnosed as NCC, LWNCC and EFSC

Clinical condition	No. of cases with normal TSA values	No. of cases with normal LBSA values
NCC (n=6)	2	3
LWNCC (n=6)	1	1
EFSC (n=4)	1	-
Total (n=16)	4	4

NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

A comparison of the overall serum Fucose levels between healthy controls and the various group of cancer patients (Table 6), showed the mean value of serum L-Fucose levels of healthy controls to be 5.49 mg/dl and in various group cancer patients had 17.72 mg/dl, this 32% increase was statistically significant as compared with the healthy control (P<0.001).

The highest level of serum Fucose was found in serum with EFSC, this 37% increase compared with normal controls was statistically significant (P<0.001).

Table 6. Comparisons of serum level of Fucose for the patients diagnosed as NCC, LWNCC and EFSC with healthy control

Clinical condition	Range (mg/dl)	Mean±SD (mg/dl)	*P* value
Control (n=28)	4.21-7.88	5.49±0.93	-
NCC (n=6)	4.96-8.32	6.08±1.80	P<0.001
LWNCC (n=6)	5.11-9.60	6.90±2.55	P<0.001
EFSC (n=4)	8.20-12.30	8.16±3.08	P<0.001
Total (n=16)	4.96-12.30	8.02±3.47	P<0.001

NCC: Nasal cavity cancer, LWNCC: Lateral wall of the nasal cavity cancer, EFSC: Ethmoid and frontal sinuses cancer

Discussion

Modified glycoproteins and glycolipids, which presents major structural component of cell surface glycoconjugates undergoes alteration on neoplastic transformation change in surface enzymes have been associated with malignant transformation of a cell, which may contribute to the aberrant cell-cell interactions, cell-matrix adhesion, cell-cell recognition, antigenicity, and tumor progression. As a result of released glycoconjugates into the circulation through increased turnover, secretion and or shedding from malignant cells leading these glycoproteins and glycolipids elevation in biological fluids [4].

In the early tumor progression, the tumor cells have got different surface characteristics and the glycoprotein on the cell membrane would be change on the certain degree and the activity of glycosyltransferases in the cells

would be enhanced [22]. Then, the sialic acid was overexpressed that acted as specific terminal glycan of glycoproteins [23]. Excessive secretion of sialic acid sialylated tumor cells and helped it evade the monitoring and killing of immune system [24,25].

The present study demonstrates that serum TSA and LBSA are higher in cancer patients suffered from nasal and para nasal sinus malignancies as compared to healthy control and the results obtained from the present study was consistent with those of another study that showed increased level of sialic acid form in patients with pancreatic cancer [26], prostate cancer and Bone metastases [27], stomach cancer [3], bladder cancer [4] and oral squamous cell carcinoma [28].

Glycosylation is involved in a variety of biological phenomenon including birth, differentiation, growth, inflammation and play a critical role during malignant transformation [29]. Among different types of oligosaccharides, Fucose is one of the important carbohydrates in oligosaccharide chain. This fucosylation is mainly found in glycoprotein and glycolipids of living beings. Hence, altered fucosylation of glycoproteins is the most representative types of glycan‐related cancer biomarker [30].

The present study revealed significantly higher concentration of L-Fucose in overall among serum cancer patients as compared to healthy controls. Moreover, elevated levels of serum L-Fucose have been in different group of malignancy such as breast cancer [31], leukoplakia and oral cancer patients [32,33], oral squamous cell carcinoma [34] as well as brain tumors [35].

The reason for elevated serum glycoprotein levels in malignancies has not been clearly established, but various views have been put forward by several researchers, wherein they have reported that elevation above the normal level reflects the process of tissue destruction at the site and release of preformed glycoprotein from the tissue or it may be due to local synthesis and release of glycoprotein by the tumor cells or increased glycoprotein levels in diseases are, in whole or in part, associated with tissue proliferation rather than tissue destruction [36] or it may be due to overproduction of glycoprotein or due to polymerization of the ground substance of the connective tissue at the site of tumor invasion with release of solubilized component into the circulation [37].

In conclusions, the combined estimations of serum TSA, LBSA and L-Fucose levels may be used as an additional tool for clinical assessment for cancer detection as well as may be used as a biomarker in the diagnosis of different malignant disease. The limitation of the present study was the small sample patients' size and can be overcome by expanding to a large sample scale for further investigation and can be used as an effective parameter in screening, diagnosis, monitoring of nasal and paranasal sinus malignancies.

Acknowledgement

Thanks to Laboratory Staff in the Blood Collection Unit in Basra General Hospital and College of Al-Hikma University for their cooperation in accomplishing this study.

Author contribution

Dr. Mohammed: put the research plan and writing the manuscript. Dr. Mahdi: did the sampling and lab works and Dr Ahmed did the statistical treatments.

Conflict of interest

Authors declare no conflict of interest.

Funding

This study was financially supported by Al-Hikma University College, Medical Laboratories Techniques.

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Received Jan. 12th 2021
Accepted May 10th 2021