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Abstract

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A STUDY OF THE PROGNOSTIC ROLE OF SERUM FUCOSE AND FUCOSYL TRANSFERASE IN CANCER OF THE UTERINE CERVIX

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Abstract. Serum fucose levels and fucosyl transferase activities have been designated as nonspecific markers of malignancy, and play an important role in the diagnosis of different types of malignancies. In the present study, attempts were made to determine the prognostic significance of these markers in patients with cancer of the uterine cervix after therapy. It was found that both serum fucose and fucosyl transferase, which were elevated in untreated patients declined significantly in patients responsive to therapy at different follow-up intervals, but not in patients unresponsive to therapy.

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The importance of tumor markers for the detection of malignancies and for determining the magnitude of the disease and its prognosis has prompted much investigation into possible biochemical markers of different types of malignancies.

There is considerable evidence to show that neoplastic transformation is accompanied by a variety of alterations in the cell surface, particularly in the glycoprotein components. Serum fucose, a terminal pentose sugar of the glycoprotein chains, and fucosyl transferase, the enzyme responsible for the transfer of the free fucose moiety to the existing glycoproteins, are detectable in the blood of both normal persons and persons with different types of malignancies. Various studies have shown an increased serum fucose level along with an elevation in the fucosyl transferase activity in a wide spectrum of malignancies (1-5). Thus these two parameters have been indicated as possible nonspecific markers for the early detection of a variety of malignant conditions.

It is also possible that these parameters may be used as markers of treatment responsiveness and in patient follow up studies. In the present work experiments were carried out on patients with carcinoma of the uterine cervix at different intervals after completion of therapy to investigate whether serum fucose levels and fucosyl transferase activity could play an effective role in determining therapeutic efficacy.

MATERIALS AND METHODS

The normal controls in the present study consisted of healthy females in the age group

of twenty-five to fifty. Females with confirmed cases of cervical carcinoma, who had not undergone any previous treatment were selected from the outpatient department of Chittaranjan Cancer Hospital. These patients, who served as untreated controls were in clinical stage II or III and had tumors histologically graded as squamous cell carcinomas of Grade II or III.

Patients who completed a course of radiotherapy and a few who underwent both surgery and radiotherapy were divided into two groups. Group I included those who showed signs of complete tumor regression on completion of treatment and maintained that condition during the entire observation period. Group II consisted of those who showed partial regression and maintained that refractory state during the entire observation period, and those who, after initial regression, showed signs of relapse during the observation period.

Blood was collected and allowed to stand for 4 h to collect the serum. A portion of the serum was stored at -80°C until used for the fucosyl transferase assay.

Changes in the glycoprotein content of the serum were determined by measuring the quantitative changes in glycosyl moieties at the terminal and of the glycoprotein chains. The protein bound serum fucose content of the serum was measured by the method of Dische and Shettle (6). The protein in 0.1 ml of serum was precipitated with 95 % ethanol. The precipitate was dissolved in 1 ml of 0.1 N NaOH, and heated with 4.5 ml conc. H_2SO_4 (6 : 1) for exactly 3 min. After cooling, 0.1 ml of 3 % cysteine reagent was added, and the preparation was kept at room temperature for 60-90 min. Methyl pentose ($20\ \mu\text{g}/\text{ml}$) was used as standard. The optical density was measured at $396\ \mu\text{m}$ and $430\ \mu\text{m}$, in order to correct for nonspecific color development.

The activity of serum fucosyl transferase was determined by measuring the rate of transfer of free fucose moieties to glycoprotein chain. The determination was carried out after the method of Chatterjee *et al.* (7). The standard incubation medium contained 50 mM Tris Hcl (pH 7.0), 2.5 mM EDTA (pH adjusted to 7.0) 0.1 % Triton X, about 0.5 mg ovomucoid as acceptor (Trypsin inhibitor Type II-0, Sigma), $3\ \mu\text{M}$ C^{14} -GDP fucose (specific activity 192.0 mci/m mol, New England Nuclear, Boston, Mass) and serum which contained approximately $50\ \mu\text{g}$ of protein in a total volume of $100\ \mu\text{l}$. After incubation at 37°C for 60 min., the reaction was terminated with 1 % PTA in 0.5 N Hcl. The precipitate was collected on $0.22\ \mu$ Millipore filter (Millipore Corporation, Bedford, Mass), and washed three times with the same medium. The filter were further washed with a 2 : 1 mixture of chloroform-methanol and dried in scintillation vials. Radioactivity was determined after the addition of 10 ml of toluene based fluor. Serum protein was estimated according to the method of Lowry, *et al.* (8). The results were analysed by students 't' test.

RESULTS

The serum fucose values were expressed as mg/100 ml of serum. A total of 17 normal females were studied, and the mean serum fucose value was 18.8 ± 4.22 . In 12 cases of untreated carcinoma of the cervix clinically diagnosed in stage II or III, it was elevated to 23.49 ± 2.55 ($p < 0.05$, in comparison to the normal). However, in the 27 treated patients of Group I, the mean value showed a tendency to decrease at different follow-up intervals, and finally after 5-7 years it came down to 20.5 ± 2.21 ($p < 0.2$, compared to normal controls). In the 26 patients of Group II, however, the value remained elevated even after therapy, and finally at the end of follow-up interval of 5-7 years it remained high at 28.8 ± 5.44 ($p < 0.01$, compared

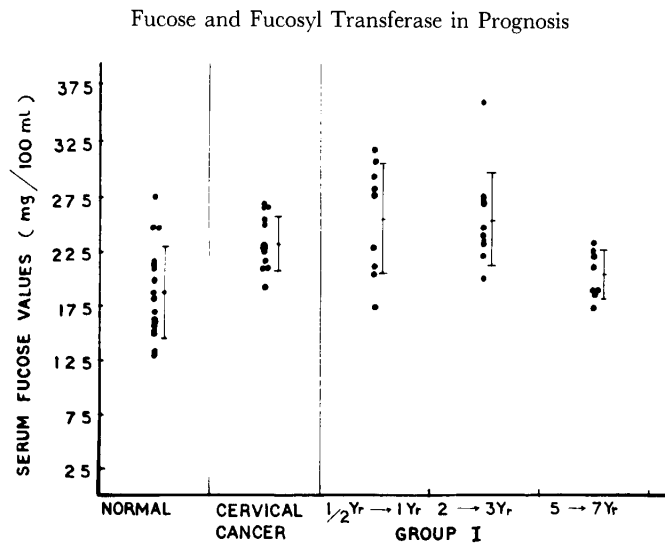


Fig. 1. Serum fucose values expressed as mg/100 ml serum in normal subjects, untreated patients with carcinoma of the cervix and treated patients who were responsive to therapy.

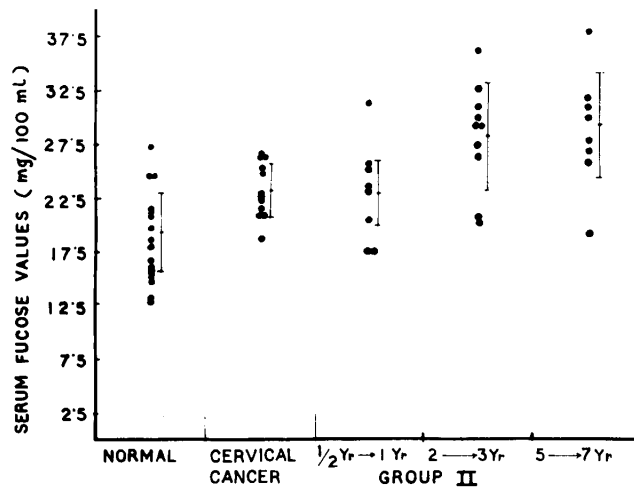


Fig. 2. Serum fucose values expressed as mg/100 ml serum in normal subjects, untreated patients with carcinoma of the cervix and treated patients who did not respond well to therapy.

to normal controls). These results are shown in Figs 1 and 2.

Serum fucosyl transferase activity was expressed as cpm/mg protein/h. In the 10 normal females studied, it was 1013 ± 351.25 . In the 11 cases of untreated carcinoma of the cervix clinically diagnosed in stage II or III, it was 1822 ± 345 ($p < 0.01$, compared to normal controls). In 25 patients belonging to Group I, the fucosyl transferase activity gradually declined and dropped to 1639 ± 460 after a follow-up period of 5-7 years ($p < 0.01$, compared to normal controls). In 25

cases of Group II, the enzyme showed increased activity even after therapy and remained elevated at 2321 ± 690 ($p < 0.01$, compared to normal controls), at the end of follow-up period of 5-7 years. These results are shown in Figs 3 and 4. All of the values are expressed as the mean \pm S.D.

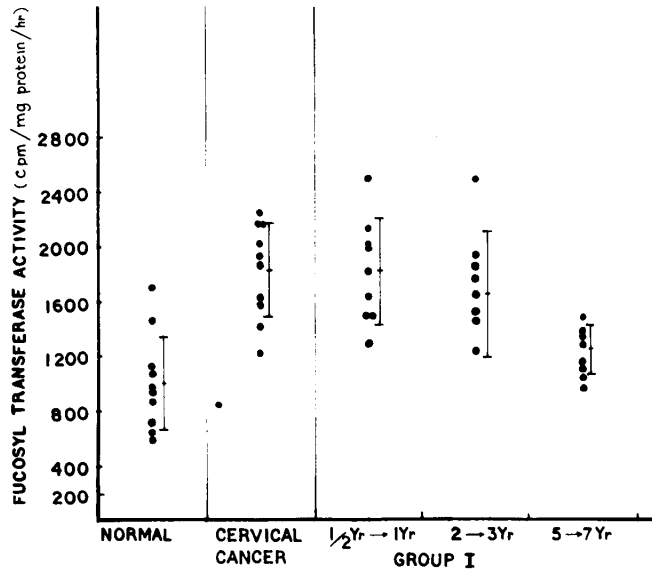


Fig. 3. Serum fucosyl transferase activity expressed as cpm/mg protein/h in normal subjects, untreated patients with carcinoma of the cervix and treated patients who were responsive to therapy.

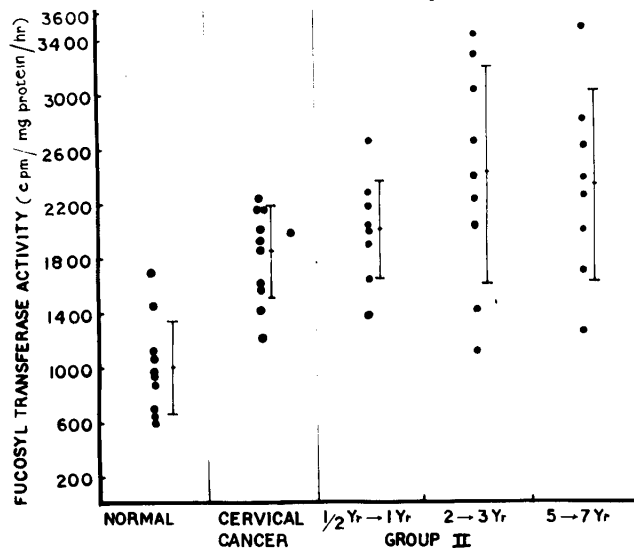


Fig. 4. Serum fucosyl transferase activity expressed as cpm/mg protein/h in normal subjects, untreated patients with carcinoma of the cervix and treated patients who did not respond well to therapy.

DISCUSSION

The changed specificity of glycosyl transferase during malignant transformations is often reflected by the altered level of carbohydrate moieties on the cell surfaces. Higher activity of the fucosyl transferase in the tumor may result in faster completion and secretion of the tumor associated glycoproteins (9-11).

In our previous investigation, it was found that both the serum fucose and fucosyl transferase levels were considerably elevated in untreated patients with different types of confirmed malignancies, showing the importance of determining these levels in the detection of malignancies (5).

In the patients who responded well to therapy and were apparently free from the disease both the serum fucose and fucosyl transferase values showed a significant decline during follow-up intervals of 5-7 years after completion of therapy. This result shows that with the arrest of the diseased condition, the high levels decrease towards the normal values. Different picture was observed in patients who exhibited only a marginal response to therapy or had a relapse after an initial response. Both the serum fucose and fucosyl transferase values remained elevated during the follow-up period. Though a partial response to treatment was achieved in a few of these cases, the transferase levels did not undergo any significant changes. It has been reported that a similar correlation exists between estimated tumor volume and the level of serum galactosyl transferase, another member of the glycosyl transferase group of enzymes. Ovarian cancer patients with large tumors tended to have high enzyme levels, and those with small ones, low values. Patients in remission, with no clinical evidence of disease, had enzyme values in the normal range (12).

All these data suggest that determination of serum fucose levels and fucosyl transferase activity in cervical cancer patients might be of value in evaluating patients who are undergoing therapy as well as in determining the effect of the therapy. The results throw a new light on the prognostic role of serum fucose levels and fucosyl transferase activity in cervical cancer cases with respect to therapy, but further scrutiny is necessary for wider clinical application to other types of malignancies.

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