ORIGINAL RESEARCH

Quantitative estimation of Serum Fibrinogen Degradation Product levels in Oral Premalignant and Malignant lesions

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ABSTRACT

Background: A specific association between cancer and the hemostatic system has been recognized for decades. Fibrinogen degradation product (FDP) is one of the factors, which opposes coagulation causing fibrinolysis. The mechanism of fibrinolysis can be used by the malignant cells to facilitate invasion into surrounding tissues and metastases to distant organs by breaking the fibrin barrier. The coagulation cascade also plays an important role in both the formation of tumour stroma and the promotion of hematogenous metastasis. The present study was undertaken to evaluate the serum FDP levels in individuals without any oral lesions and those with oral premalignant and malignant lesions, and determine whether the estimation of the same can be used as an aid in early diagnosis.

Materials & Methods: 25 cases each of Leukoplakia, Oral submucous fibrosis and Oral squamous cell carcinomas (OSCC) and normal control cases were selected. The OSCC cases were staged according to the TNM classification. Diagnosis of all cases was confirmed by histopathological examination. The aspirated serum was then subjected to the Thrombo-Wellco test which was used for the biochemical analysis of FDP.

Results: Increased serum FDP levels were seen corresponding to the stage of the OSCC, but no appreciable difference was noted between the histological grades or in cases of premalignant lesions.

Conclusions: The study demonstrates that FDP levels correlate with the cancer stage and progression. Thus, the estimation of serum FDP levels can be used as a reliable prognostic indicator and as a biologic marker of tumour spread

Key Words: coagulation, fibrinogen degradation product, oral squamous cell carcinoma, tumour marker, fibrinolysis.

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Introduction

Cancer has been described as one of the most alarming health problem facing mankind. It is possibly the most important challenge facing medicine in recent times and consequently the focus of one of the fastest growing areas of fundamental biological research.

Oral cancer is the sixth most common cancer world-wide with more than 90% of all oral cancers being squamous cell carcinoma.[1,2] The prevalence of Oral Squamous Cell Carcinoma (OSCC) is very high in the Indian subcontinent as the risk of developing it is

increased by the very prevalent habits of chewing tobacco, betel quid and areca nut. Also genetic characteristics & environmental factors may predispose to the development of OSCC.

Today a plethora of tumour markers are available which can be used for screening, diagnosis, establishing prognosis, monitoring treatment and for detecting relapse. However most of the tumour markers do not have sufficient sensitivity or specificity for use in screening and cannot be detected in the early stages of malignancy.

Fibrin degradation products(FDP), also known as fibrin split products are fragments of fibrinogen or fibrin which are produced when either of them is broken down by the enzyme plasmin. Thrombin is a powerful proteolytic enzyme and procoagulant compound which activates pro-MMP-2 while fibrinogen is a soluble plasma glycoprotein. Thrombin induces the degradation of fibrinogen to fibrin monomer and forms an extracellular fibrin barrier.[3] The measurement of the degradation products that appear in the serum during malignancy, for the most part is related to the activation of enzyme plasmin. Plasmin is the major fibrinolytic protease which occurs in plasma in the inactive form plasminogen. Plasminogen is activated via cleavage by the tissue plasminogen activator (tPA), prourokinase or urokinase plasminogen activator (uPA). Through a positive feedback mechanism, the plasmin formed on the surface of fibrin cleaves substrate fibrin at specific sites. This leads to a distinct set of fibrin degradation products with different molecular weights.[4-7]

An abnormal fibrinolytic or fibrinogenolytic activity indicated by high levels of FDP in plasma can be found in clinical states, such as eclampsia, postoperative complications, cardiac and renal disorders, hepatic disorders, fibrinolysis, pulmonary embolism, and deep vein thrombosis.

FDP has also been shown to be valuable as a tumour marker in a number of different cancers like ovarian, renal, colorectal, gastrointestinal, breast, urinary bladder and various other malignancies,[8-13] in which the FDP levels have been seen to correlate with cancer occurrence, stage, progression and prognosis.

The present study was undertaken to evaluate the serum levels of FDP in individuals without any oral lesions and those with oral premalignant and malignant lesions, and to determine whether the estimation of these levels can be used as an aid in the early diagnosis of oral malignancies.

Materials & Methods

The study group consisted of hundred cases with 25 cases each of leukoplakia, oral submucous fibrosis (OSMF) and oral squamous cell carcinomas (OSCC) along with an equal number of age and sex matched control patients. A detailed case history of each patient was recorded and those with a recent history of ovarian malignancy, renal carcinoma, pre-eclampsia and eclampsia, venous thrombosis, pulmonary embolism, diffuse vasculitis, hepatic disease, females with menorrhagia and in their menstruating period were excluded from this study. Provisional diagnosis of the lesions was made. The OSCC cases were staged according to the TNM classification. All the patients were then subjected to a punch or scalpel biopsy. The diagnosis was then confirmed by histopathological examination. The OSCC cases were further graded by the Bryne's system of classification.

Using all aseptic precautions, 5 ml of venous blood was collected into a dry sterile syringe and then injected through the plug of one of the sample tubes. The blood was immediately mixed by inverting the tube gently several times, where upon the blood clotted firmly. It was then allowed to remain steady and clot at room temperature for 30-60 minutes. After an hour, the blood was centrifuged at 2000 rpm for 10 minutes. The aspirated serum was then used for the biochemical analysis of FDP.

The Thrombo-Wellco test was used for the rapid quantitative determination of serum for the presence of FDP. It is a simple & rapid test in which antisera are raised to highly purified preparations of human fibrinogen fragments D and E. After solid phase absorption to remove antibodies to all other serum proteins, the specific antibody globulins are extracted and used to coat by adsorption a suspension of latex particles in glycine saline buffer. It is designed as a slide agglutination method in which one drop of the sample and one drop of latex suspension are mixed for

a period of two minutes by gentle rocking. An agglutinated pattern at the end of the test period indicates the presence of 2µg/ml FDP or more in the sample under test. By assaying samples of two different dilutions, an approximate FDP value/µg can be determined. The levels were calculated by multiplying the dilution at the end point of the titration by 2. Different dilutions had to be prepared each time to get values in between those obtained by the above mentioned method.

Results

The data was tabulated according to different categories of the lesions and was statistically analyzed. The relationship of serum FDP levels to different premalignant and malignant cases was noted. Mean ± Standard Deviation (Min-Max) and results on categorical measurements are presented in Number (%). Significance was assessed at 5 % level of significance. An analysis of variance (ANOVA) using General Linear model was used to find the significance of study parameters between three or more groups of patients.

The study group consisting of 25 cases each of leukoplakia, OSMF, OSCC and control were tabulated according to age & sex (Table 1 & 2). Comparison of the serum FDP levels in these cases shows a statistically significant rise in the levels in OSCC (Table 3a & 3b). When the mean serum FDP levels in the different histological grades of OSCC were compared, they showed a raise with increase in grades in case of well and moderately differentiated SCC, but the increase was not found to be statistically significant. Since only one case presented a poorly differentiated SCC, it could not be included in the statistical analysis (Table 4a & 4b). The mean serum FDP levels in 25 OSCC patients also showed a statistically significant increase in FDP levels with an increase in the stage of the lesion (Table 5a & 5b)

Table 1: Distribution of cases according to age

Age in years	Control	Leukoplakia	Oral submucous fibrosis	Oral squamous cell carcinoma
17-20	3(12%)	0(0%)	7(28%)	0(0%)
21-30	8(32%)	1(4%)	13(52%)	1(4%)
31-40	7(28%)	2(8%)	2(8%)	1(4%)
41-50	5(20%)	12(48%)	1(4%)	4(16%)
51-60	1(4%)	4(16%)	2(8%)	6(24%)
61-70	1(4%)	4(16%)	0(0%)	12(48%)
>70	0(0%)	2(8%)	0(0%)	1(4%)
Total	25(100%)	25(100%)	25(100%)	25(100%)
Mean ± SD	33.04±11.34	51.04±11.64	27.04±9.75	57.92±10.54

Table 2: Distribution of cases according to Gender

Gender	Control	Leukoplakia	Oral submucous fibrosis	Oral squamous cell carcinoma
Male	17(68.0%)	22(88.0%)	25(100.0%)	22(88.0%)
Female	8(32.0%)	3(12.0%)	0	3(12.0%)
Total	25(100%)	25(100%)	25(100%)	25(100%)

Table 3a: Comparison of FDP levels in Control, Leukoplakia, Oral submucous fibrosis and Oral squamous cell carcinoma patients

FDP level	Control	Leukoplakia	Oral submucous fibrosis	Oral squamous cell carcinoma
Min-Max	3.00-8.00	3.00-8.00	3.00-8.00	8.00-256.0
Mean ± SD	5.88±1.59	6.16±1.40	6.08±1.59	74.68±65.53
95%CI	5.22-6.54	5.58-6.74	5.43-6.73	47.63-101.73

Discussion

Over the years researchers have established a strong association between malignant cell growth and the coagulation and fibrinolysis system.[14] Fibrin plays an important role in cancer pathophysiology by contributing to tumour growth and to processes that lead to tumour invasion and metastasization by formation of a protective fibrin shield on malignant

Table 3b: Comparison of FDP levels in Control, Leukoplakia, Oral submucous fibrosis and Oral squamous cell carcinoma patients

FDP level	Difference	P value
Leukoplakia with control	0.28	1.000
Oral submucous fibrosis with control	0.20	1.000
Oral squamous cell carcinoma with control	68.80	<0.001**

Table 4a: Comparison of FDP levels in different histological grades of Oral squamous cell carcinoma

FDP level	Well differentiated OSCC	Moderately differentiated OSCC	Poorly differentiated OSCC
Min-Max	8.00-136.00	11.00-160.00	-
Mean ± SD	61.50±53.99	78.37±58.04	256.00
95%CI	32.73-90.27	29.85-126.89	-

OSCC – Oral Squamous Cell Carcinoma

Table 4b: Comparison of FDP levels of different histological grades of OSCC with each other

FDP level	Difference	P value
Well differentiated OSCC v/s control	55.62	<0.001**
Moderately differentiated OSCC v/s control	72.49	<0.001**
Well differentiated OSCC v/s Moderately differentiated OSCC	16.60	0.988

OSCC – Oral Squamous Cell Carcinoma

Table 5a: Comparison of FDP levels in different stages of Oral squamous cell carcinoma

FDP level	Stage I OSCC	Stage II OSCC	Stage III OSCC	Stage IV OSCC
Min-Max	8.0-11.0	14.00-48.00	98.00-132.00	96.00-256.00
Mean ± SD	9.80±1.30	26.25±11.03	112.50±14.55	144.75±48.94
95%CI	8.19-11.42	17.02-35.47	89.35-135.85	103.83-185.66

OSCC – Oral Squamous Cell Carcinoma

Table 5b: Comparison of FDP levels in different stages of Oral Squamous cell carcinoma with each other

FDP level	Difference	P value
Stage I OSCC v/s Control	3.92	0.937
Stage II OSCC v/s Control	20.37	<0.001**
Stage III OSCC v/s Control	106.62	<0.001**
Stage IV OSCC v/s Control	138.87	<0.001**
Stage I OSCC v/s Stage II OSCC	16.45	0.999
Stage I OSCC v/s Stage III OSCC	102.70	0.002**
Stage I OSCC v/s Stage IV OSCC	134.95	<0.001**
Stage II OSCC v/s Stage III OSCC	86.25	0.007**
Stage II OSCC v/s Stage IV OSCC	118.50	<0.001**
Stage III OSCC v/s Stage IV OSCC	32.25	0.916

OSCC – Oral Squamous Cell Carcinoma

tumour cells, which makes tumour cells resistant to endogenous defence mechanisms.[15,16] The fibrin matrices promote the migration of various cell types

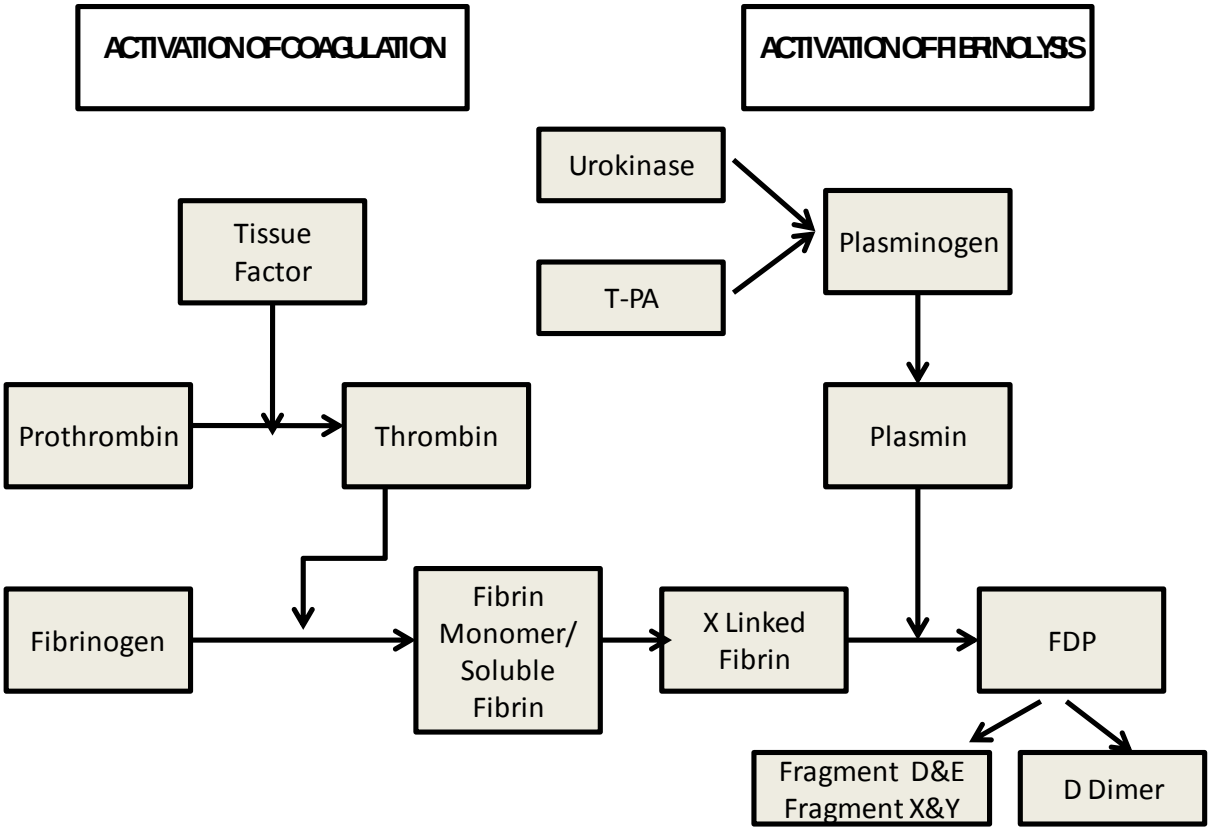

Fig. 1: Formation of Fibrinogen Degradation products by activation of the Fibrinolytic and Coagulation

like transformed cells, endothelial cells, macrophages, and fibroblasts and also promotes neovascularization, thus facilitating tumour stroma formation by mechanisms that are similar to wound repair.[17]

Cancer has been known to elevate FDP levels through two pathways - The Coagulation and Fibrinolysis pathways. It causes elevated levels of both tissue factor (TF) [18,19] and the urokinase-type plasminogen activator (u-PA).[20,21] The TF pathway alters the extrinsic coagulation system by causing an activation of thrombin. Thrombin converts fibrinogen to fibrin. On the other hand, the u-PA pathway activates plasmin by catalyzing its inactive precursor plasminogen into functional plasmin. The type of FDP produced will be different depending upon which of the two substrates is digested by plasmin. When fibrinogen is the substrate for plasmin, 'Fragments D and E' are the end products with 'Fragments X and Y' as intermediate products in this digestion. When fibrin is the substrate 'D-dimer' is the end product (Figure 1).

In cancer patients either the coagulation pathway or the fibrinolysis pathway are activated alone separately, or both are activated simultaneously. The TF pathway plays an important role in formation of the vascular niche for tumor initiating cancer stem cells, through its procoagulant and signalling effects.[22] Coagulation may be increased due to elevated levels of tissue factor. Deregulation of the coagulation system has important adverse affects on cancer patients because the coagulation system plays dual roles in homeostasis and immunity.[23] Alternatively, the process of fibrinolysis is vital in the formation and growth of tumours. Fibrinolysis must occur to release cells from their site of origin, allowing neoplastic cell growth. Thus cancer-related thrombosis represents a complex imbalance of coagulation and fibrinolysis, the processes of formation and deactivation of fibrin, respectively.[24]

The presence of FDP in serum is an indirect marker of coagulation activation followed by reactive thrombolysis. The procoagulant factors in various types of cancer lead to constitutive activation of the coagulation cascade with resultant thrombin generation followed by fibrin formation.

In the present study no appreciable increase was observed in the serum FDP levels in premalignant lesions like leukoplakia and OSMF, but a significant increase was seen in cases of OSCC. The increase in oral malignancies was seen to correlate directly with the clinical stage of the malignancy, however no significant correlation was found with the histological grading of the lesion.

The demonstration of abnormal amounts of FDP in cases of malignancy suggests that intravascular fibrin deposition and fibrinolysis are occurring. According to the TNM staging system, the values seen in Stage II, III & IV are significantly higher. This denotes that the levels of serum FDP increase with the increased progression of the disease and that tumour activation and fibrinolysis appear to be related to the pathology of tumour spread, with increased fibrinolysis seen in cases of metastases.[25] It may also give an indication of an early but more malignant form of cancer in which microinvasion, thrombus formation, fibrin deposition and secondary fibrinolysis might already have started.

Our results have been in agreement with the findings of similar researches.[26-28] Ghosh M et al in1990 demonstrated high levels of serum FDP in 50 patients with OSCC prior to any kind of treatment. Their study showed significantly increased mean FDP values with the advancement of the stage of oral cancer. [29]

The hematogenous spread of tumour is related to both shedding as well as the lodgment of cells. The shedding of tumour cells depends on the tumour size as also on the local factors in the tumour. Plasmin plays an important role in tumour cell adhesiveness. An increased release of tumour cells might, however, also be of consequence of the lysis of intravascular thrombi with increased shedding of cells. The incidence and the number of metastases is not only dependent on the number of tumour cells released from the transplanted tumour, but also on the properties of these cells, which lodge them in the capillaries for further spread. All the factors in the tumour cells and in the vascular endothelium which favour arrest, the attachment and the endothelial penetration of tumour cells increase the chances of metastases formation.

Astedt et al in 1971 postulated that the tumour itself contains some proteolytic enzymes capable of causing degradation of fibrin or fibrinogen. Unlike oral malignancies, there are no proteolytic enzymes present in premalignancies, because of absence of a tumour mass. This might explain the insignificant changes seen in premalignancies.[30]

Coagulation disorders in the rapidly growing cancer population may appear as a consequence of tumour growth, chemotherapy, radiotherapy or due to the surgical trauma.[31] Observation of various treatment options in patients with thromboembolic disease and cancer as well as attempts to use anticoagulants and/or therapies modulating the fibrinolytic system as anti-neoplastic strategies have yielded exciting results.[31,32] This data indicate that anticoagulant therapy, and specifically low molecular weight heparin therapy,[33] is likely to have anti-neoplastic effects; and that their use in addition to chemotherapy will probably improve outcome of tumour treatment in certain types of cancer. These anticoagulants while representing an attractive anticancer therapy, may offer a better control of cancer progression.

However, the body of clinical data is still relatively small and the question whether or not the coagulation and/or fibrinolysis system can be routinely considered as therapeutic targets in cancer patients is yet to be answered.

Conclusion

Accurate prediction of survival is difficult but critically important. Involvement of lymph nodes and the presence of distant metastases can worsen the prognosis of the patient. In the present study, a definite relationship is seen to exist between the serum levels of FDP and the stage of OSCC and the levels are seen to correlate directly with the spread of the lesion to the regional lymph nodes and distant metastases. Estimation of serum FDP levels can thus be used to screen cases of oral malignancy, though neither as a strong arbiter nor as a distinct diagnostic stage. With current advances in imaging like FDG – PET, microinvasion can be detected at an early stage and cancer can be staged more accurately. Thus FDP levels can be used as an auxiliary investigation, which may act as an adjunct to diagnosis, as a reliable prognostic indicator and as an adjunct to TNM classification, thus leading to earlier detection of risk patients, and the

mode of treatment can be decided based on the presence and absence of metastases.

No appreciable changes in the FDP levels were noticed in the premalignant lesions like leukoplakia and OSMF nor were there any relationship noted between the different histological grades of OSCC.

Since the number of patients in the above study was limited, further work is needed in this field to conclusively determine the relationship of serum FDP levels and OSCC. Also additional studies related to the relationship of the final FDP products to cancer are also required.

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