

Plasma fibrinogen degradation products in oral submucous fibrosis

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Abstract

Context: Plasma fibrinogen degradation products (FDPs) and oral submucous fibrosis (OSMF). **Background:** OSMF is a chronic, progressive, scarring disease of multifactorial etiology. Areca nut is found to be the main cause of this disease. But it has been found in the routine clinical practice that some individuals with the habit of areca nut chewing may not show any clinical evidence of OSMF, while some individuals without the habit of areca nut chewing are found to have OSMF. So, there must be some other factors associated with OSMF. Recently, plasma FDPs have been identified as an early indicator of disease in OSMF patients. A systematic review of their role would help to elucidate whether there is an association of these FDPs in the pathogenesis of OSMF or not. **Objective:** To review studies reported in the literature elucidating the role of these plasma FDPs in OSMF. **Materials and Methods:** Articles were searched in PubMed; MEDLINE using appropriate key words like “plasma fibrinogen degradation products” and “oral submucous fibrosis.” Hand search of journals was also performed. Articles were reviewed and analyzed. **Results:** The search strategy revealed nine relevant articles which studied the role of these plasma FDPs in the etiopathogenesis of OSMF and further progression of this disease with the increased clinical grades and the risk of carcinoma, but the exact role of these factors is still obscure. **Conclusion:** The data validate the role of plasma FDPs in the etiopathogenesis of OSMF. Studies with a large sample size are still required to evaluate the definite association between these FDPs and OSMF. It has the advantage of being a noninvasive method to evaluate the stage of OSMF patients, instead of using the invasive techniques like biopsy.

Key words: *Areca nut, fibrinogen degradation products, habit, oral submucous fibrosis, plasma*

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic, progressive, scarring disease that predominantly affects the people of South-East Asian origin.^[1] OSMF is found to be of multifactorial etiology including

excessive chili consumption, genetic susceptibility, autoimmunity, iron and vitamin deficiency,^[2] but it is strongly associated with areca nut chewing and pan masala.^[3] Experiments have shown that ethanolic extracts of areca nut stimulate collagen synthesis in human dermal fibroblasts and also stabilize collagen fibrils and render them resistant to degradation by collagenase leading to fibrosis.^[4] It has been found that some amount of copper is also present in areca nut, which up-regulates collagen production by activating lysyl oxidase that is involved in collagen synthesis and cross linking.^[5] Areca nut is found to be the main cause of OSMF. But it has been found in the routine clinical practice that some individuals with the habit of areca nut chewing may not show any clinical evidence

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of OSMF.^[6] Also, some individuals are found to have OSMF without the habit of areca nut chewing.^[7] So, there must be some other factors associated with OSMF. Recently, plasma fibrinogen degradation products (FDPs) have been identified as an early indicator of disease in OSMF patients.^[2]

FDPs, also termed as fibrin split products, are components of blood that are produced by clot degeneration.^[2] Whenever injury occurs to any blood vessel, thrombin is produced in the first stage of coagulation cascade. In the second stage, fibrinogen, a glycoprotein synthesized by liver, is converted to fibrin which forms a fibrin meshwork. As the site heals, this clot is broken by the enzyme plasminogen which gets converted into plasmin that further splits fibrin resulting in the release of fibrin split products termed as FDPs. Principal FDPs X, Y, A, B, C, D, and E, particularly fragment Y and to a lesser extent fragment X, are known to produce anticoagulant effects. These FDPs are detected only when their plasma levels increase above the normal levels. In normal healthy individuals, plasma FDPs are present in very low concentrations, and thus, they cannot be detected. Excessive FDPs are released in plasma in three main conditions: Disseminated intravascular coagulation, thrombolytic therapy, and primary fibrinolysis.^[8]

Though the plasma FDPs have been found to be associated with OSMF, very few studies in the literature were able to demark their role in the etiopathogenesis of OSMF. The purpose of the systematic review was to determine whether there is any association between these FDPs and OSMF or not.

MATERIALS AND METHODS

Search strategy for identification of studies

Articles were searched and selected for the related topic using Google, PubMed; MEDLINE from 1979 till date. Article search included only those articles published in the English literature.

Search methodology

Article search through PubMed and internet sources was done using the following key words: Oral submucous fibrosis, plasma fibrinogen, plasma fibrinogen degradation products, fibrin precipitating factor, areca nut, and carcinoma. Journals evaluating the role of these plasma FDPs in the etiopathogenesis of OSMF were referred for review.

Selection criteria

Published reviews were selected if they met the following criterion: Cross-sectional studies elucidating the role of plasma FDPs in the etiopathogenesis of OSMF and the mechanism by which they exert their role.

Inclusion criteria

- Studies published in English literature
- Studies that evaluated the role of plasma FDPs in the etiopathogenesis of OSMF.

Exclusion criterion

- Studies with missing data that could not be supplied by the study authors.

Data extraction and analysis

A total of nine studies by different authors were selected in this review. The studies were included based on data extraction and analysis of the quality of studies and by exploring publication bias. The primary outcome was to elucidate the role of plasma FDPs in the etiopathogenesis of OSMF and the mechanism by which they exert their role. Potentially relevant articles for systematic review were obtained; data extracted from each article were tabulated and cross checked.

RESULTS

The selected articles were divided into subgroups of author name and year of publication, subject groups, and results, as shown in Table 1.

All the included studies evaluated the presence of plasma FDPs in OSMF patients. Six of the authors found strong positive association of the FDPs in all the subjects of OSMF included in their studies. One author observed that plasma FDPs could be detected in only more than half of the total cases of OSMF. One of the studies indicated that there was no strong association between the FDPs and OSMF.

DISCUSSION

Various studies have been reported in the literature evaluating the association between FDPs and OSMF. Variable results have been reported in all the studies. The reason could be the different methods used to evaluate these products.

In 1979, Pathak^[9] reported the case of a 25-year-old male patient with stage III OSMF and the habit of

Table 1: Summary of studies included in the literature

Author (year)	Subject groups	Result
Pathak (1979)	Group I	25-year-old male patient with stage III OSMF and having the habit of chewing areca nut
	Group II	One control group case
Pathak (1984)	Group I	7 cases of OSMF
	Group II	7 control group cases
Pathak (1984)	Group I	25-year-old male patient with the stage III OSMF and without habit of chewing areca nut
	Group II	One control group case
Koshti and Barpande (2007)	Group I	35 cases of OSMF
	Group II	35 control group cases
Wanjari <i>et al.</i> (2011)	Group I	50 cases of OSMF
	Group II	Areca nut chewer without OSMF
	Group III	50 control group cases
Kiran <i>et al.</i> (2013)	Group I	35 cases of OSMF
	Group II	10 cases with areca nut chewing habit without OSMF
	Group III	10 control group cases
Gharat <i>et al.</i> (2013)	Group I	25 cases of OSMF
	Group II	25 cases of leukoplakia
	Group III	25 cases of OSCC
	Group IV	25 control group cases
Kadani <i>et al.</i> (2014)	Group I	30 cases of OSMF
	Group II	30 control group cases
Gupta <i>et al.</i> (2014)	Group I	35 cases of areca nut chewing with OSMF
	Group II	30 cases of areca nut chewing without OSMF
	Group III	30 control group cases

chewing areca nut, and observed that when the saliva of the patient suffering from OSMF was mixed with the plasma of the same patient and of two other normal control persons and incubated at 37°C, a strong fibrin producing factor (FPF) was detected in the saliva of the OSMF patient. An elevated plasma fibrinogen level was found in the OSMF patient. Precipitable fibrinogen at 37°C and cryoprecipitate containing fibrinogen and IgG were also detected in these patients. He also observed that elevated fibrinogen level and precipitable fibrinogen were found in other cases of OSMF patients too at 37°C and 4°C.

In 1984, Pathak^[10] detected circulating molecules that were immunologically similar to fibrinogen in seven patients suffering from OSMF, as suggested by the hemagglutination inhibition studies using the FDP kit and by paracoagulation tests such as serial dilution protamine tests. According to him, fibrinogen, fibrinogen intermediates, and FDPs deserved further scrutiny, as this might help define the etiology of OSMF which had been obscure at that time.

In 1984, Pathak^[11] reported the case of a 25-year-old male suffering from OSMF without any habit of chewing tobacco and areca nut. He was well-built and nourished, except that he was suffering from iron deficiency anemia. Fibrinogen and its degradation products were assayed in a hemagglutination inhibition system using the FDP kit (Wellcome). Plasma fibrinogen level was found to be increased to 800 mg/ml (normal 200–400 mg/ml). FDPs were also found to be elevated. Cryofibrinogen was detected in heat-oxygenated plasma and also in dilute oxylated plasma. No precipitate was detected in the control tubes kept at 37°C. FPF, a factor that had been described previously in routine saliva, was also detected in the saliva collected after parotid duct stimulation.

In 1990, Ghosh *et al.*^[12] also observed significant increase in the mean values of plasma FDP levels with the advancement of stages in oral cancer patients as compared to normal individuals.

In 1992, Phatak^[13] reported in his review that OSMF is a chronic disseminated intravascular coagulation syndrome, in addition to being a local coagulopathy. He also mentioned about the thrombin-like substance termed as FPF in the saliva of patients with OSMF as compared to normal saliva. In the normal saliva, fibrinolytic substances are present.

In 2007, Koshti and Barpande^[2] performed a study on

35 patients of OSMF and found a significant increase of plasma FDP levels with an increase in the clinical grades of OSMF. Comparison with histological grades of OSMF showed an increase in plasma FDP levels with an increase in the histological grade of OSMF, but the increase was not statistically significant. They found that plasma FDP was an early indicator of fibrin deposition. When the plasma FDPs increased, the fibrin deposited also increased. The quantification was based on latex agglutination method used by XL-FDP kit.

In 2011, Wanjari *et al.*^[14] also estimated the presence of FPF in the saliva of OSMF patients. Plasma fibrinogen level increased in the subjects with positive FPF as compared to subjects with negative FPF. Patients with increased plasma fibrinogen level and positive FPF are at greater risk of OSMF as compared to patients with normal fibrinogen level and negative FPF. Their results provide evidence that there is a definite relation between FPF and increased fibrinogen level in OSMF.

In 2013, Kiran *et al.*^[15] conducted a study consisting of 35 cases of areca nut chewers with OSMF, 10 patients with areca nut chewing habit but with apparently normal oral mucosa, and 10 normal patients without any habit (control group). The patients were evaluated for plasma FDP levels. It was observed that all the areca nut chewers with OSMF showed the presence of plasma FDP. However, controls and subjects with the habit but without OSMF did not show FDP in the plasma. It was also noticed that there was not any statistically significant association between the levels of FDPs in various clinical and histological grades of OSMF.

In 2013, Gharat *et al.*^[16] conducted a study comprising 25 cases each of leukoplakia, OSMF, and Oral squamous cell carcinoma, and normal control cases. No significant association was found between the FDPs and premalignant lesions including OSMF. However, increased serum FDP levels were seen corresponding to the stage of the OSCC, but no appreciable difference was noted between the histological grades.

Kadani *et al.*,^[17] in their study on FDPs in 2014, comprising a total of 30 subjects with OSMF and 30 control group subjects observed that out of total 30 cases of OSMF, 14 subjects showed FDP levels above 200 ng/mg and 16 subjects showed negative response to the presence of FDP level. The probable reasons for undetectable FDP levels in some cases could be because of the method employed by the kit to detect FDP levels. Latex agglutination slide test method was

used in their study, which according to previous studies lacked sensitivity to detect minimal rise of FDP levels, resulting in lower sensitivity. Qualitative method of estimation for FDP levels did not show an association between the FDP levels and OSMF. Semi-quantitative method of plasma FDP estimation did not show an association between increased level of FDP and the increase in severity of OSMF.

In 2014, Gupta *et al.*^[18] conducted a study including 35 subjects with OSMF and having the habit of areca nut chewing, 30 subjects having areca nut chewing habit without OSMF, and 30 control group subjects. They observed in their study that plasma FDPs were detected in all the areca nut chewing subjects with OSMF, but could not be detected in the other two groups. Also, it was observed that as the clinical grades of OSMF increased, the levels of plasma FDPs also increased. The quantification was based on the principle of agglutination. The method used by XL-FDP reagent kit could detect FDPs above the level of 200 ng/ml.

Several etiological agents have been found to be responsible for the progression of OSMF. However, areca nut is supposed to be the major causative agent. Various chemicals released by areca nut chewing act as a source of continuous irritation to the oral mucosa. Over a period of time, due to persistent habit, chronic inflammation sets in at the site. Fibrinogen is an acute phase reactant which increases throughout the inflammatory process. In response to inflammation, the body produces more fibrinogen and its degradation products.^[15] Fibrinogen metabolism is related to increased fibrinogen levels, fibrinogen cyroprecipitability, FDPs, and FPF. Based on these four factors, a possible hypothesis regarding the mechanism of OSMF has been described. It states that the parotid saliva contains a coagulant or procoagulant which is designated as FPF. When this FPF interacts with the fibrinous exudates in the oral cavity, it promptly clots the fibrinous exudates. This reaction is accelerated by calcium ion, though it is not entirely calcium dependent. After the formation of clot, the ensuing thrombin perpetuates the process. The fibrinopeptides try to combat inflammation, while FDP counteracts the thrombin-like action of FPF and the thrombin produced in the autocatalytic process.^[11] As no hemorrhagic manifestations are encountered in OSMF, FDPs are labeled as molecules immunologically similar to fibrinogen (MISF).^[10] As the severity of the disease increases, more FPF is produced and, in turn, more FDP is produced. These plasma FDPs are an early indicator of fibrin deposition; increase in

their level with increase in clinical grade suggests that there is increased fibrin deposition in OSMF, thus increasing the severity of the disease.^[2] Also, these FDPs have been detected in various malignant conditions and their level increases with the progression of the disease, which indicates that it can be an early valuable sign in the diagnostic and prognostic evaluation of carcinoma.^[16] As the clinical Grade IV of OSMF is also associated with other potentially malignant disorders or oral carcinoma,^[19] the levels of plasma FDPs can be elevated with the increased severity of disease.

The reference range of FDP levels is less than 10 mcg/ml (conventional units) or less than 10 mg/l (SI units).^[20] An FDP level of more than 40 mg/ml is considered critical.^[21] High levels of these products can cause glomerulosclerosis, cerebral contusion, pulmonary embolism, deep vein thrombosis, liver cirrhosis, disseminated intravascular coagulation, arterial thromboembolism, tachycardia/palpitation, tachypnea/dyspnea, hypotension, acute myocardial infarction, ventricular fibrillation, arteriosclerosis, and related effects. In 1982, Chan *et al.*^[22] reported in their study that the FDPs were increased in diabetic nephropathy leading to fibrin deposition in the endothelial and mesangial regions. Similarly, in 1993, Song *et al.*^[8] also found in their study that FDPs were elevated in various liver diseases, especially cirrhosis of liver, leading to fibrin deposition and thus fibrosis. A study conducted by Whitaker *et al.* in 1984^[23] showed that the mean concentration of FDPs was raised in plasma of patients with pulmonary embolism, deep venous thrombosis, arterial thromboembolism, and disseminated intravascular coagulation, as compared to the normal subjects. Similarly, in 1986, Elms *et al.*^[24] also found in their study that plasma from normal subjects was negative for FDPs using latex agglutination, but positive results were obtained in patients of deep vein thrombosis, pulmonary embolism, or disseminated intravascular coagulation.

Obviously, these plasma FDPs may also produce some systemic effects in the patients with OSMF. Therefore, their association with OSMF patients should be evaluated. They can be used as an early indicator of OSMF. Their detection in the plasma could be used as a diagnostic aid in suspected OSMF cases and it could help to stop the progression of further disease.

CONCLUSION

Studies done by various authors in the literature show that FDPs may be associated in the etiopathogenesis

of OSMF and further progression of this disease to increased clinical grades and the risk of carcinoma, but the exact role of these factors is still obscure. Studies with large sample size are still required to evaluate the definite association between these FDPs and OSMF. This is a noninvasive method to evaluate the stage of OSMF patients, instead of using invasive techniques like biopsy.

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