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Research article

Up regulation of serum L fucose glycoprotein as a diagnostic biomarker for dysplasia in oral sub mucous fibrosis patients

Sunil Kumar Vaddamanu [a], Ravinder S. Saini [a], Bhavana T. Veerabasavaiah [b], Fahad Hussain Alhamoudi [a], AbdulKhaliq Ali F Alshadidi [a], Antonino Lo Giudice [c,*], Marco Cicciù [c], Giuseppe Minervini [d]

[a] *Department of Dental Technology, College of Applied Medical Sciences, King Khalid University, Saudi Arabia*
[b] *Department of Oral Medical & Radiology, Sri Rajiv Gandhi College of Dental Sciences and Hospital, India*
[c] *Department of Biomedical and Surgical and Biomedical Sciences, Catania University, 95123, Catania, Italy*
[d] *Multidisciplinary Department of Medical-Surgical and Odontostomatological Specialties, University of Campania "Luigi Vanvitelli", 80121, Naples, Italy*

A R T I C L E I N F O

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A B S T R A C T

Glycoproteins, essential for cellular functions, contain monosaccharides like Levo-fucose, crucial for cell communication. Recent research highlights serum L-fucose as a potential biomarker for early detection of malignancies. Typically, serum L-fucose levels are low but rise with malignancy. This study evaluates serum L-fucose as an early biomarker in oral submucous fibrosis (OSMF) patients.

Aim: Assess serum L-fucose's diagnostic potential for dysplasia in OSMF patients.

Objectives: Determine the Association between Serum L Fucose Glycoprotein Levels and Dysplasia in OSF Patients.

Evaluate the Diagnostic Accuracy of Serum L Fucose Glycoprotein as a Biomarker for OSF-Related Dysplasia.

Methodology: Over a span of two years, this study encompassed 80 subjects, aged between 18 and 60 years, who were clinically and histopathologically identified as OSMF patients, with or without dysplastic alterations. From each participant, 5 ml of blood was collected. Following centrifugation to separate the serum, the samples were analyzed to determine the levels of Levo-fucose.

Statistical analysis: Using SPSS (version 17.0), serum L-Fucose levels of the case group were compared to the control group using ANOVA. Frequencies were analyzed with the chi-square test, and Tukey's Test was used for multiple comparisons. Significance was set at $p < 0.01$.

Results: The analysis revealed a statistically significant disparity in the mean serum L-Fucose levels between the two groups ($p < 0.01$). Notably, Group II patients (those with OSMF and dysplasia) exhibited markedly elevated mean serum L-fucose levels.

Conclusion: Elevated serum L-Fucose levels were observed in OSMF patients with dysplasia. Harmful habits, especially gutkha chewing, were linked to Oral Squamous Cell Carcinoma onset. Serum L-fucose can be a reliable marker for evaluating precancerous conditions.

* Corresponding author.
E-mail addresses: snu@kku.edu.sa (S.K. Vaddamanu), rsaini@kku.edu.sa (R.S. Saini), bhavanatv@gmail.com (B.T. Veerabasavaiah), fhali@kku.edu.sa (F.H. Alhamoudi), aalshadidi@kku.edu.sa (A. Ali F Alshadidi), antonino.logiudice@unict.it (A. Lo Giudice), marco.cicciu@unict.it (M. Cicciù), Giuseppe.minervini@unicampania.it (G. Minervini).

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1. Introduction

Oral Submucous Fibrosis (OSMF) is a chronic, progressive precancerous condition characterized by juxta-epithelial fibrosis, predominantly affecting the buccal mucosa, soft palate, retromolar trigone, and facial pillars [1]. At its core, OSMF arises from alterations in collagen deposition—a phenomenon believed to be a cell-mediated immune response triggered by the consumption of areca nut and betel quid. While OSMF is especially prevalent in South Asia, specific ethnic groups, individuals of lower socioeconomic status, and those with nutritional deficiencies are particularly susceptible. Alarmingly, the disorder carries a significant risk of malignant transformation, with rates ranging from 1.5% to 15%. Factors such as age, gender, exposure to risk agents, and duration of disease tracking can influence this transformation. Recent years have witnessed a surge in OSMF incidence due to a myriad of etiological factors, underscoring the imperative for accurate diagnosis and optimal management strategies [1–4].

Recent research underscores that the consumption of areca nut emerges as a principal risk factor. This is largely attributed to its affordability, easy accessibility, and the general populace's limited awareness of its carcinogenic potential [2,5–7]. Its consumption predominantly impacts the masticatory lining and the specialized mucosa within the oral cavity, leading to discernible changes in both the function and histological structure of the mucosa. Notably, the buccal mucosa, retromolar trigone, soft palate, and oropharynx are the most adversely affected regions. A hallmark of this condition is the augmented synthesis of collagen by fibroblasts coupled with a diminished degradation rate. This imbalance results in an excessive accumulation of collagen within the tissue [2,8–13].

n its initial stages, OSMF is marked by the emergence of erythema and vesicles. The rupture of these vesicles often results in ulcer formation, subsequently leading to mucosal blanching, fibrosis, and scarring that extends to the underlying muscles. Such pathological changes culminate in trismus, limited tongue mobility, and restricted movement of the soft palate. This compromises the tongue's natural cleansing ability, adversely affecting oral hygiene [5]. Moreover, the restricted mouth opening in OSMF patients hampers nutrient intake, which can further precipitate anemia. Given these debilitating symptoms and their subsequent ramifications, OSMF profoundly impacts a patient's quality of life [14–17].

When detected in its nascent stages, OSMF is treatable through an array of invasive therapeutic modalities. In contrast, advanced cases necessitate a more aggressive treatment strategy. Intriguingly, cells within the premalignant lesion produce an array of biochemical products. Once released into the bloodstream and other body fluids, these products can serve as biomarkers for the lesion [18].

Among the diverse biochemical products associated with OSMF, serum glycoproteins stand out as pivotal biomarkers, particularly in light of alterations observed in conjunction with dysplastic features in premalignant lesions [18–21]. These glycoproteins comprise various forms of monosaccharides, with levo-fucose serving as a terminal sugar. This specific monosaccharide plays a crucial role in cell-to-cell communication, essential for the body's optimal functionality. Levo fucose can be sourced from a range of natural biological products, including 2'-fucosyl lactate and the brown algal polysaccharide, fucoidan. Notably, the fucosylation of glycoproteins, facilitated by the augmented activity of fucosyltransferase, orchestrates several vital biological processes within the human body [19,22,23].

Typically, L-fucose concentrations in serum are relatively low. However, during carcinogenesis, a noticeable elevation in these levels is observed. In the context of neoplasia, elevated fucosylation levels induce alterations in tumor cell surface components. This modification enables tumor cells to evade detection by the body's defensive mechanisms. Consequently, heightened fucosylation is implicated in uncontrolled cellular proliferation, tumor progression, altered cell adhesion, disruptions in cell-to-cell interactions, metastasis, and eventual malignant transformation [19,24–26].

Thus, elucidating the interplay between fucosylation and carcinogenesis is pivotal for the early identification of tumor progression. The primary objective of this study is to discern the correlation between serum L-fucose concentrations and the presence of dysplasia in patients with OSMF.

Aim: Assess serum L-fucose's diagnostic potential for dysplasia in OSMF patients.

Objectives: Determine the Association between Serum L Fucose Glycoprotein Levels and Dysplasia in OSF Patients.

Evaluate the Diagnostic Accuracy of Serum L Fucose Glycoprotein as a Biomarker for OSF-Related Dysplasia.

2. Methodology

This study was undertaken in the Department of Oral Medicine and Radiology at Sri Rajiv Gandhi College of Dental Sciences & Hospital over a span of two years, commencing on February 2019 and concluding in 2022. The study received approval from the Institutional Ethics Committee (Reference No. ECC#2019-04). All participants provided informed consent prior to their inclusion. Comprehensive case histories of 80 subjects were meticulously documented using a structured proforma. The clinical diagnosis of OSMF was carried out employing Kerr's grading system [2]. Subsequently, the 80 OSMF subjects were categorized into two distinct groups.

- Group I -40 OSMF with dysplasia (case).
- Group II - 40 OSMF without dysplasia (control).

Sample size estimation was performed using G Power software (Version 3.1.9.4, Heinrich-Heine Universität Düsseldorf, Germany)& confidence interval of 95%.

The exclusion criteria for the study were as follows:

- Patients with precancerous lesions or conditions other than OSMF.
- Patients with systemic diseases, including hypertension, diabetes mellitus, liver disease, infectious diseases, inflammatory conditions, and malignancies other than oral cancer.
- Patients with oral lesions not characterized as OSMF.
- Patients who were undergoing, or had completed, chemotherapy or radiotherapy for cancer.
- Immunocompromised individuals.
- Individuals with a history of blood transfusion.
- Patients aged under 18 years.

The study cohort comprised both male and female patients aged between 18 and 60 years, diagnosed with OSMF. The clinical diagnosis was informed by a history of areca nut consumption and the presence of clinical features such as buccal mucosal blanching with a "marble stone appearance", ulceration, burning sensations, restricted mouth opening (trismus), and erythematous areas. Impaired tongue and oral functions, attributed to the formation of fibrous bands, were also considered. Following the selection of an appropriate region within the oral cavity exhibiting erythema or a fibrous band, a biopsy was obtained and dispatched for histopathological verification.

5 ml of blood was drawn from the study subjects. Serum was separated from the blood by centrifugation and used to estimate the levels of Levo-fucose. The samples were then used for the analysis of serum L Fucose levels using ELISA.

To validate an ELISA kit for assessing serum L-Fucose Glycoprotein in Oral Submucous Fibrosis (OSMF) patients, specificity and sensitivity were first ensured by testing with known positive and negative samples, avoiding cross-reactivity. Precision and accuracy were evaluated through repeated measurements of the same samples (intra-assay) and across different runs and operators (inter-assay). A consistent and reproducible standard curve was established for accurate quantification. The kit's performance was verified using human serum samples, confirming its clinical applicability. Inclusion of positive and negative controls in each run, coupled with rigorous data analysis, reinforced the assay's reliability. Comprehensive documentation and adherence to relevant regulatory

Table 1
Values of both groups.

Group 1	Group 2
14.75	16.60
13.52	14.55
14.04	12.98
15.18	33.09
14.84	19.56
12.28	19.95
14.02	15.47
13.03	26.64
13.07	13.49
13.53	21.19
13.29	17.44
14.47	24.49
13.85	19.55
13.27	15.87
13.56	22.21
13.46	24.72
14.51	22.73
12.98	24.03
13.44	18.87
12.39	20.37
10.86	18.66
13.75	20.38
13.94	17.89
12.49	12.87
15.21	23.34
11.85	20.15
13.20	13.40
12.99	24.91
14.54	17.37
14.48	22.65
13.30	26.37
13.50	23.07
12.36	28.63
11.38	15.57
12.85	24.58
13.30	18.60
14.27	17.57
14.24	19.18
12.81	20.65
12.89	22.67

standards were maintained throughout the process, ensuring a thorough and systematic validation.

2.1. Statistical analysis

Data were systematically compiled and entered into Microsoft Excel, from which the mean and standard deviation of serum L-fucose levels for both groups were derived. Subsequent statistical analyses were conducted using SPSS (Statistical Package for Social Sciences, version 17.0). The correlation between serum L-fucose levels and dysplasia in OSMF patients—both with and without dysplasia—was evaluated using a one-way Analysis of Variance (ANOVA). The chi-square test was employed to contrast the frequencies between the two cohorts (Table 5). For multiple and inter-group comparisons, the Tukey HSD Post Hoc test was utilized (Table 4). A p-value of less than 0.001 was deemed to render the results of this study highly significant.

3. Results

This study aimed to ascertain the serum L-fucose levels in OSMF patients, distinguishing between those with and without dysplasia. Participants were categorized into two groups: Group I comprised 40 OSMF patients with dysplasia (cases), while Group II consisted of 40 OSMF patients without dysplasia (controls) (Table 1). The average serum L-fucose levels for Group I and Group II were 13.16 and 22.36, respectively, with standard deviations of 1.871 for Group I and 4.214 for Group II (Table 2). A comparison of the serum L-fucose levels between the two groups, facilitated by a one-way ANOVA, revealed a significantly elevated serum L-fucose level in Group I, with a p-value <0.05, indicative of high significance relative to Group II (Table 3).

4. Discussion

Oral carcinomas rank as the sixth most prevalent cancer globally, with a staggering 377,130 cases and 177,757 resultant deaths, the majority of which are reported in developing nations. Forecasts from the International Agency for Research on Cancer, under the World Health Organization (IARC–WHO), indicate an unsettling surge in cancer rates, projecting an increase from 10 million to 15 million new cases worldwide. Oropharyngeal cancer constitutes a significant proportion of this global incidence. Notably, oral cancer exhibits a pronounced inclination towards males and populations from lower socioeconomic strata [2,27,28].

Contemporary epidemiological research identifies a multitude of risk factors integral to carcinogenesis. Paramount among these are the consumption of tobacco, both in its smoked and smokeless forms, areca nut, betel quid, exposure to UV radiation, certain viruses, candidiasis, alcohol consumption, genetic predisposition, chronic irritation, and diabetes [29]. A robust association between oropharyngeal cancer and tobacco use is well-documented. Remarkably, smokers face a 5–9 fold elevated risk of developing premalignant oral lesions compared to non-smokers [29,30]. The propensity to develop a secondary malignancy post-primary cancer treatment is predominantly linked to continued tobacco use. It's noteworthy that oral cancer tends to manifest at the site where snuff or chewable tobacco is habitually placed [31–33].

Chewing betel quid and areca nut has been implicated in the onset of oral submucous fibrosis, a chronic, scarring, and progressive premalignant condition. This disorder is characterized by an enhanced deposition of collagen, leading to alterations in the architectural components of the oral mucosa. Notably, this condition possesses a malignant transformation rate of approximately 7.6%. The heightened risk of oral cancer can be largely attributed to the excessive intake of areca nuts. The quintessential composition of betel quid encompasses a blend of slaked lime, areca nut, tobacco, and various sweetening agents, all typically enveloped within a betel leaf [33,34].

Oral submucous fibrosis (OSMF) is recognized as a premalignant phenotype of oral squamous cell carcinoma. Diagnosis fundamentally hinges on clinical manifestations coupled with histopathological scrutiny. Carcinogenesis traditionally unfolds through four cardinal stages: initiation, promotion, progression, and metastasis [35–37].

Normal cells, when exposed to carcinogens, undergo DNA damage and exhibit dysregulated cellular proliferation, survival, differentiation, and DNA repair mechanisms [38–40]. Arecoline, a principal constituent of the areca nut, incites sustained inflammation, growth factor release, augmented collagen deposition, cytokine secretion, and delays in wound healing. Collectively, these alterations elevate the malignant transformation rate of OSMF [35,41–43].

During the promotion phase, OSMF lesions become irreversible due to microenvironmental shifts surrounding the fibrotic tissue. This leads to perturbations in collagen deposition and the promotion of malignant cell growth. The densification of tissue subsequently constricts capillaries, engendering a hypoxic milieu conducive to malignant cell proliferation [44,45]. In the advanced stages of OSMF, the activation of TGF-β fosters carcinogenesis, chemoresistance, and metastasis [46–48]. The engagement of the connective tissue growth factor in OSMF precipitates tumor angiogenesis and the epithelial-mesenchymal transition. TNF-α further stimulates cancer cell growth, invasion, proliferation, and metastasis [49]. Notably, OSMF patients exhibit a markedly elevated infection rate of human

Table 2
Comparison of serum L fucose level in group I and group II OSMF patients.

Groups	N	$\sum x$	Mean	$\sum x^2$	Std. Dev.	Std. Error
Group 1	40	526.7	13.1675	7071.85	1.871	0.2958
Group 2	40	894.7	22.3675	20704.77	4.214	0.6663
Total	**80**	**1421.4**	**17.7675**	**27776.62**		

Table 3
Showing the result of one way ANOVA summary with the f-ratio value is 159.2564. The p-value indicates highly significant. The result is significant at 95% confidence interval.

One way ANOVA Summary					
Source	Degrees of Freedom (DF)	Sum of Squares (SS)	Mean Square (MS)	F-Stat	P-Value
Between Groups	1	1692.8	1692.8	88.45	<0.0001
Within Groups	78	829.0955	10.6294		
Total	79	2521.8955			

Table 4
The Tukey HSD test further supported the ANOVA test, indicating a significant mean difference between Group 1 and Group 2.

Group 1	Group 2	Mean Difference	Adjusted P-value	Lower Bound	Upper Bound	Reject Null Hypothesis
Group 1	Group 2	6.8638	0.001	5.4108	8.3167	True

Table 5
The Chi-square test was performed on the categorized data and indicated no significant association between the group membership and the categorized value ranges.

Chi-square Statistic	P-value
0.494	0.781

papillomavirus (HPV) relative to the general populace, potentially elucidating the heightened malignancy risk associated with OSMF [50].

For enhancing the early detection of OSMF, several strategies such as the OSMF evaluation index, assessment of single or multiple biomarker expression levels, and the OSMF malignant transformation index can be employed. A synergistic approach combining clinical evaluation with biomarker assays has been identified as the most time-efficient method [51,52].

A neoplasm is characterized as an aberrant tissue mass resulting from the unregulated growth of cells. This growth surpasses the rate of normal cellular proliferation and continues unabatedly even after the initiating stimuli have ceased [53]. As delineated by the International Classification of Diseases (ICD, version 9, categories: [2,54–61], "oral cancer" is essentially synonymous with squamous cell carcinoma (SCC) originating from the oral mucosa. Remarkably, such carcinomas constitute over 90% of all malignancies emerging in the aforementioned anatomical regions [59].

Oral cancer frequently emerges subsequent to precancerous lesions and conditions, including leukoplakia, erythroplakia, lichen planus, and oral submucous fibrosis. Early detection is pivotal in curbing disease progression [37]. Historically, alterations in cell surface glycosylation during the transition from a benign to a malignant cellular state have been postulated. The carbohydrate components of these glycoproteins, released into circulation due to augmented turnover, secretion, or shedding, are lauded for their diagnostic and prognostic potential [19]. The glycoprotein index, gauged via measurements of protein-bound carbohydrates, emerges as a crucial diagnostic tool, aiding in metastasis detection, staging, recurrence risk assessment, and therapeutic evaluation. Notably, among the diverse serum glycoproteins, serum L-fucose stands out as a particularly promising biomarker for dysplasia [62]. Numerous studies have corroborated fucose's efficacy as the optimal monosaccharide in decelerating tumor cell growth. Post-effective cancer therapy, a decline in serum L-fucose levels is observed — a phenomenon consistently reported in the literature. However, for discernible serological changes, extended recall and follow-up durations are imperative [62,63].

Numerous biomarker studies have identified elevated serum L-fucose levels across a spectrum of cancers, encompassing breast cancer, cervical cancer, brain tumors, colorectal adenocarcinomas, leukemia, and melanoma [64–66]. Additionally, elevated serum L-fucose concentrations have been associated with diverse pathological conditions, including osteomalacia, liver cirrhosis, rickets, tuberculosis, depressive disorders, meningitis, and cardiovascular disorders [67]. Given this broad spectrum of associations, it becomes imperative to rule out other malignancies as well as proliferative and degenerative diseases when evaluating serum L-fucose levels in the context of oral cancer [67].

Glycosylation represents the most prevalent post-translational modification observed in proteins. This modification plays a pivotal role in numerous signaling pathways responsible for the oncogenic transformation of cells [18]. The vast diversity in protein structures is attributed to the variations in the sequences and configurations of attached sugar moieties or glycans. Alterations in cellular glycosylation patterns have been intricately linked with various forms of neoplastic transformations. It's noteworthy that mammalian cells predominantly manifest or exert their functionalities via the cell surface [65,66]. There is compelling evidence suggesting that enhanced fucosylation correlates with an upsurge in fucosyltransferase activity. These enzymes, ubiquitously expressed across various tissues, have been found in elevated concentrations in both the serum and tumors of oncology patients. Furthermore, cancerous cells that detach from the primary tumor and enter the circulatory system frequently exhibit an overexpression of fucosylated glycans on their surface [68].

Elevated levels of L-fucose in serum and other bodily fluids can be attributed to the discharge of pre-existing glycoproteins from tissues, a consequence of tissue degradation. Alternatively, this elevation may arise from the augmented synthesis and release of such glycoproteins by neoplastic cells. Numerous studies have posited that tracking serum or tissue L-fucose concentrations might offer a promising avenue for the early identification, diagnosis, and prognostication of various malignancies [68–70].

Despite recent advancements in oncological treatments, the prognosis and outcomes for oral squamous cell carcinoma (OSCC) remain suboptimal. A significant factor contributing to this challenge is the late-stage diagnosis of the neoplasm, often when the tumor has already reached an advanced stage. This delay precludes timely interventions that could arrest tumor progression at its inception [68]. Therefore, strategies facilitating early detection of OSCC are paramount, as they can substantially reduce morbidity and mortality rates, enhancing survival outcomes.

The transition of potentially malignant lesions into overt carcinomas is not readily discernible through clinical examinations or histopathological assessments alone. In this context, biomarkers emerge as invaluable tools [69,70]. Biomarkers are specific substances, either released by the host in response to the tumor or directly by the tumor cells, detectable in the bloodstream, saliva, and other bodily fluids. Their presence can signal cancer progression, enabling timely therapeutic interventions before malignant transformation occurs.

Inflammatory reactions, both primary and secondary, can exacerbate the tumor burden, leading to fluctuations in serum L-fucose levels. Notably, some studies have observed a decline in serum L-fucose levels post-treatment during subsequent follow-ups [70,71]. Moreover, a handful of research endeavors have posited that serum L-fucose may serve as a potential biomarker for diagnosing dysplastic manifestations of OSCC.

Elevated serum L-fucose levels can be indicative of heightened tissue destruction and tumor proliferation. Rai et al. [70] in their investigation on oral cancer posited that the surge in serum L-fucose levels might be attributed to the systemic metabolic impact of oral cancer. Similarly, Shelter et al. suggested that the rise in serum L-fucose levels is a consequence of tissue degradation and the augmented proliferation of normal tissue [71].

The present study was undertaken to assess the diagnostic efficacy of serum L-fucose as a potential biomarker for oral submucous fibrosis (OSMF) with or without dysplasia. This research was conducted in the Department of Oral Medicine and Radiology. For the quantification of serum L-fucose levels, a commercially available Human L-fucose Kinase (FUK) ELISA Kit was employed.

Lifestyle habits, particularly in the context of malignancies, are of paramount importance. Brad W. Neville et al., in their 2002 study, delved into the etiological factors underpinning oral precancerous lesions and oral cancer. Their findings underscored that habits like smoking and tobacco consumption stand as primary risk determinants for the onset of dysplastic alterations in the oral cavity. Furthermore, the duration of exposure to these carcinogens plays a pivotal role in the severity of the precancerous lesion. An extended exposure invariably exacerbates the severity of the lesion [72].

In the investigation, levels of Levo fucose, a glycoprotein, were assessed in two distinct groups: OSMF patients with dysplasia (Group I) and those without dysplasia (Group II). Each group comprised 40 subjects, totaling 80 participants. Findings revealed a statistically significant disparity in fucose levels between the two groups. Group I consisted of 24 males and 16 females, while Group II had 30 males and 10 females. A robust correlation was discerned between habits and the dysplastic features linked to OSMF. Notably, OSMF with dysplasia exhibited a higher predilection in males, attributed to habits like smoking (42%), chewing gutkha and betel nut (56%), and alcohol consumption combined with betel nut chewing (17%). These habits were more prevalent in male participants compared to females. Thus, observations underscore that male patients with habits of gutkha & betel quid consumption, smoking, and concurrent alcohol and betel nut intake are at an elevated risk for malignancy [73]. The habit-related findings from this study align with research by Lingappa Ashok et al., 2015 [73], Kumar et al., 2015 [74], and Azadeh et al., 2012 [75].

Serum L-fucose estimation stands out as a minimally invasive, straightforward, and cost-efficient method. The results from the current investigation indicate a pronounced correlation in serum L-fucose levels. The mean serum L-fucose levels were recorded at 13.16 mg/dl for Group I and 22.36 mg/dl for Group II. Notably, the mean fucose level in Group II was significantly elevated compared to Group I. The mean fucose levels derived from both groups in this study closely mirrored those from the research conducted by Khan et al., in 2019 [76]. Based on the biomarker values related to serum L-fucose levels in this study, a significant trend ($P < 0.01$) was observed with the progression of OSMF (C) (Table 2).

In this investigation, Group 2 patients exhibited a marked increase in serum L-fucose levels compared to healthy controls. This observation aligns with findings from studies by Parwani et al., in 2011 [76], Elango et al., in 2001 [77], and Kumar et al., in 2015 [74], all of which reported a significant surge in serum L-fucose levels in cancer patients relative to control groups. A consistent upward trend in serum L-fucose levels was observed, correlating with the progression and severity of potentially malignant disorders and cancer [78].

Research led by Poojary et al. [79] elucidated that the escalation in serum L-fucose levels in precancerous and cancerous conditions can be attributed to factors such as tissue inflammation, the stage and severity of the lesion, carcinogen consumption, and the duration of the lesion. The findings from this study mirrored these observations, with elevated serum L-fucose levels attributed to analogous risk factors. The data garnered from this investigation aligns with studies on other malignancies, including breast, colon, and lung cancers. In these studies, mean serum L-fucose levels were recorded at 20.56 ± 0.96 mg% for malignant tumors and 12.35 ± 1.26 mg% for benign tumors [80].

The outcomes from this study underscore a correlation between serum L-fucose levels and dysplasia in OSMF patients, a conclusion that resonates with findings from other research endeavors on similar subjects [80–84]. Validating the importance of serum L-fucose levels as an indicator for the progression of OSMF to overt carcinoma hinges on definitive diagnosis and the advancement trajectory of OSMF. Regularly monitoring serum L-fucose levels emerges as a promising strategy for the early detection, intervention, and prognosis of various cancers and premalignant conditions afflicting the oral cavity.

4.1. Clinical implication

This study's discovery that elevated serum L fucose levels indicate Oral Submucous Fibrosis (OSMF) and potential progression to oral squamous cell carcinoma (OSCC) is clinically pivotal. It offers a non-invasive, early detection method, enhancing patient prognosis. Clinicians can use this biomarker for risk assessment, monitoring disease progression, and personalizing treatment strategies, enriching the diagnostic toolkit in oral medicine.

4.2. Practical implications

The findings have significant practical implications in oral healthcare. Incorporating serum L fucose assessments into routine screenings could enable early OSMF detection, particularly in susceptible groups, leading to timely and precise treatments. This research lays groundwork for new therapeutic developments and highlights the importance of educating oral health professionals about biomarkers' role in disease management, promoting a preventative approach in oral healthcare.

5. Conclusion

The study conclusively demonstrates that elevated serum L fucose levels correlate with dysplasia in Oral Submucous Fibrosis (OSMF) patients, indicating its potential as an early malignancy biomarker. This pivotal finding paves the way for enhanced patient outcomes through timely interventions, potentially reducing OSMF-related morbidity and mortality. The results advocate for advanced clinical trials to validate and optimize such biomarkers, aiding clinicians in developing precise treatment modalities to mitigate OSMF progression and improve patient quality of life.

6. Limitation of the study

The manuscript notes key limitations: its focus on Oral Submucous Fibrosis (OSMF) limits generalizability, a small sample size restricts biomarker robustness, and the absence of post-treatment serum L fucose assessments limits understanding of its prognostic value. Additionally, not correlating serum L fucose with histological stages hampers specificity and sensitivity insights. These points emphasize the need for broader research.

Ethics approval

The study received approval from the Institutional Ethics Committee (Reference No. ECC#2019-04).

Consent to participate

All participants provided informed consent prior to their inclusion.

Consent to publish

All authors agreed with the content and that all gave explicit consent to submit.

Data availability statement

Data are available upon request to the corresponding author.

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CRediT authorship contribution statement

Sunil Kumar Vaddamanu: Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ravinder S. Saini:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bhavana T. Veerabasavaiah:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fahad Hussain Alhamoudi:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **AbdulKhaliq Ali F Alshadidi:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Antonino Lo Giudice:** Validation. **Marco Cicciù:** Methodology. **Giuseppe Minervini:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Abbreviations

OSMF	Oral Submucous Fibrosis
TGF	Transforming Growth Factor
TNF	Tumor Necrosis Factor
HPV	Human Papillomavirus
OSCC	Oral Squamous Cell Carcinoma
ELISA	Enzyme Linked Immunosorbent Assay
FUK	Fucose Kinase

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