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Influence of local denture-related factors on the inflammatory marker levels in patients with denture stomatitis

Marija Bradić-Vasić[1], Ana Pejčić[2*], Milena Kostić[3], Radmila Obradović[2], Ivan Minić[4], Ivana Stanković[3], Katarina Živadinović[1], Jelena Bašić[5] and Aleksandra Ignjatović[6]

Abstract

Objectives Many denture-related factors have been identified as risk factors for DS, including trauma, nighttime denture wearing, insufficient oral and denture hygiene. The aim of this research was to examine the effects of local denture factors in the oral mucosa and saliva content that occurred after the DS onset.

Materials and methods The study sample comprised 150 adult partial or total denture wearers, 100 of whom were diagnosed with DS, and the remaining 50 had a healthy mucous membrane despite having prosthetic restorations and served as controls. Participants' saliva was tested for the presence of salivary cytokines (IL-1β, TNF-α, and MMP-9) as indicators of inflammation and damage to the oral mucosa.

Results The obtained findings confirmed that local denture-related factors have a major influence on the DS occurrence. Moreover, levels of IL-1β, TNF-α, and MMP-9 inflammatory biomarkers were statistically significantly increased in the DS group.

Conclusion A significant DS frequency was noted in denture-wearing patients in whom a large number of local denture factors was present. As inflammation is more prevalent among denture wearers than in general population, regular examinations are advised to facilitate an early diagnosis and implement adequate therapy, with a focus on inflammation and DS prevention.

Clinical relevance (1) a greater number of exclusively denture factors can damage the oral mucosa; (2) development of inflammation as a basis for denture stomatitis; (3) increase in the concentration of salivary biomarkers of inflammation; (4) indicates the need for further research regarding the key contributors to the development of DS.

Clinical trial number Not applicable.'

Keywords Denture stomatitis, Inflammation, Local denture-related factors, Salivary biomarkers

*Correspondence:
Ana Pejčić
dranapejcic@hotmail.com
[1]Doctoral studies, Periodontology and oral medicine Faculty of Medicine, University of Niš, Niš, Serbia
[2]Department of Periodontology and oral medicine, Clinic for Dental Medicine, Faculty of Medicine, University of Niš, dr Z. Djindjica 81 Blvd, Niš 18000, Serbia
[3]Department for Dental Prosthetics, Clinic for Dental Medicine, Faculty of Medicine, University of Niš, dr Z. Djindjica 81 Blvd, Niš 18000, Serbia
[4]Private dental office •Insta-smile•, Milentijeva Street 25, Niš 18000, Serbia
[5]Research Center for Biomedicine, Faculty of Medicine, University of Niš, dr Z. Djindjica 81 Blvd, Niš 18000, Serbia
[6]Institute of Public Health, Faculty of Medicine, University of Niš, dr Z. Djindjcia 81 Blvd, Niš 18000, Serbia

Introduction

Denture stomatitis (DS) is a term used to describe pathological changes in the oral mucosa. It is the most common complication among removable denture wearers, predominantly affecting the hard palate mucosa in contact with complete or partial dentures [1]. DS occurs more frequently in the maxilla, as upper dentures maintain closer contact with the mucosa, creating favorable conditions for plaque accumulation on the rough surfaces of the prosthesis. It predominantly affects immunocompromised patients, in whom the oral cavity can serve as a reservoir for Candida infections, potentially leading to systemic infection [2].

Denture stomatitis can present in different clinical forms. The most widely used classification is Newton's classification, which categorizes the condition into three types: (1) Type 1 – characterized by pinpoint erythema; (2) Type 2 – diffuse erythema, which is the most common form of DS and (3) Type 3 – hyperplastic nodular reaction of the palatal mucosa [3, 4].

DS is considered to have a multifactorial etiology, involving both systemic and local factors. Local factors include trauma from ill-fitting dentures and infections (primarily *Candida*), while systemic factors are related to reduced host immunity, leading to systemic diseases such as HIV infection, leukemia, radiation therapy, anemia, and prolonged corticosteroid or antibiotic use. Current research suggests that inflammatory processes are more likely to develop due to the synergistic action of multiple factors rather than the influence of a single cause [5, 6].

Several local factors influence the onset and severity of denture stomatitis (DS). Poor denture hygiene and plaque accumulation are primary causes, as rough and porous denture surfaces provide an ideal environment for microbial colonization [2, 7]. *Candida albicans* is frequently implicated in DS due to its ability to adhere to acrylic surfaces and penetrate epithelial layers, leading to persistent inflammation [8, 9].

Mechanical trauma caused by ill-fitting dentures, unstable occlusion, or prolonged wear contributes to mucosal irritation and inflammatory responses [10]. Additionally, nocturnal denture use is associated with an increased risk of DS, as continuous wear reduces the natural cleansing effect of saliva and promotes anaerobic microbial growth [11]. Other prosthetic factors, such as denture age, loss of stability, and inadequate occlusal support, further exacerbate mucosal irritation and increase susceptibility to DS [12].

The oral mucosa in elderly individuals undergoes significant physiological changes [13]. Moreover, it becomes less elastic due to a reduction in elastic fibers and becomes thinner, pale, dry, smooth, and less vascularized. Senile epithelium is also more permeable to various substances and highly susceptible to mechanical damage caused by irritating agents [14].

In addition to local influences, systemic health conditions significantly affect the development and progression of denture stomatitis (DS). Aging is a critical factor, as older individuals experience physiological changes in the oral mucosa, including reduced epithelial thickness, decreased vascularization, and diminished salivary flow, all of which impair mucosal resistance [15]. Diabetes mellitus is strongly associated with DS due to altered immune responses and increased susceptibility to fungal infections [16].

Furthermore, systemic conditions that compromise the immune system, such as HIV infection, leukemia, radiotherapy, and prolonged use of corticosteroids or antibiotics, are linked to a higher incidence of DS [7]. These factors contribute to impaired mucosal defense, allowing for excessive Candida overgrowth and chronic inflammation.

Recent studies have investigated the role of salivary inflammatory biomarkers in denture stomatitis (DS) as potential indicators of disease severity. Cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) play a crucial role in mucosal inflammation by regulating immune responses and mediating tissue damage [17]. IL-1β is primarily released by macrophages and epithelial cells in response to trauma and microbial invasion, promoting further cytokine production and neutrophil recruitment. TNF-α, secreted by macrophages and T cells, increases vascular permeability and inflammatory cell infiltration, contributing to mucosal damage [18].

Matrix metalloproteinase-9 (MMP-9), an enzyme involved in extracellular matrix remodeling, is also implicated in DS. Elevated MMP-9 levels are associated with tissue degradation and inflammation progression, making it a potential marker for assessing DS severity [19].

Understanding the relationship between prosthetic factors and these biomarkers could provide insights into DS pathogenesis and aid in the development of targeted therapeutic strategies [20].

Dentures play a key role in the etiology of denture stomatitis (DS), primarily through mechanical, microbiological, and chemical factors. Poor stability, inadequate hygiene, and material characteristics significantly contribute to the development of inflammation. Understanding these factors can aid in the prevention and treatment of DS through proper denture fabrication, regular hygiene maintenance, and appropriate material selection.

This study is important as it provides deeper insight into the mechanisms of denture stomatitis (DS), where the role of local prosthetic factors in modulating the inflammatory response remains insufficiently explored. Existing studies primarily investigate DS through the lens

of fungal and bacterial infections, while less attention has been given to the direct impact of local prosthetic factors on inflammatory processes. Most research focuses on individual factors (e.g., the microbiological aspect), whereas the complex interactions between local prosthetic factors and the immune response of patients are underexplored. The lack of longitudinal studies further complicates the understanding of how specific factors influence disease progression over time.

Research objective

It is hypothesized that various denture-related factors, including denture hygiene, duration of use, stability, and others, influence the levels of inflammatory biomarkers in the saliva of patients with denture stomatitis (DS). This study aims to contribute to the literature by providing more precise data on the role of local prosthetic factors in the development of inflammation in DS patients. Understanding the causal relationships between denture factors and inflammatory biomarkers may enable the development of personalized approaches in dental therapy, thereby improving patients' quality of life and reducing the incidence of DS-related complications.

The objective of this study is to examine the impact of denture-related factors on the presence and levels of inflammatory and immune responses as potential modifiers of this condition. For this reason, the study will assess the presence and concentration of salivary pro-inflammatory biomarkers (IL-1β, TNF-α) in saliva. Additionally, the presence and salivary levels of MMP-9 will be evaluated, along with its diagnostic significance in DS, as MMP-9 plays a role in extracellular matrix degradation.

Materials and methods

This study was conducted at the Department of Oral Medicine and Periodontology, Clinic for Dental Medicine, Faculty of Medicine, University of Nis.

After all inclusion criteria were met, confirming the patient's eligibility for the study, a detailed verbal and written explanation of the research details, objectives, purpose, and the participant's role was provided. A written document containing the study explanation and informed consent, along with a questionnaire collecting basic participant data, was signed by both the participants and the researchers.

The study included 150 patients wearing either partial or complete dentures. Of these, 100 patients were diagnosed with denture stomatitis, while 50 participants with healthy oral mucosa despite wearing dentures served as the control group. Oral health status assessment was conducted through medical history, clinical oral and dental examination, and biochemical analysis of saliva in all participants.

Prior to the assessment of oral mucosal status, all patients underwent periodontal treatment to eliminate the potential confounding influence of periodontal conditions on inflammatory mediator production.

The examinations were conducted thoroughly and individually for all possible factors to minimize or completely eliminate their effects, as well as to prevent denture stomatitis (DS). To confirm the presence of inflammation and damage to the oral mucosa, an analysis of salivary cytokines, specifically IL-1β, TNF-α, and MMP-9, was performed.

For saliva collection, participants were required to refrain from eating, drinking, and brushing their teeth for one hour before sample collection. Additionally, they were advised to avoid alcohol consumption for 24 h prior to sample collection. Participants arrived at the clinic in the morning. Before sampling, they rinsed their mouths with distilled water to remove debris. Saliva was collected after a 10-minute resting period. During saliva collection, patients were instructed to keep their eyes open and refrain from speaking to prevent mental stimulation of salivary secretion. All samples were collected using the same protocol under identical conditions.

For saliva sample analysis, high-sensitivity commercial ELISA kits were used: (a) IL-1β concentration was determined using the Human IL-1β High Sensitivity ELISA BMS224HS (eBioscience); (b) TNF-α concentration was determined using the Human TNF-α High Sensitivity ELISA BMS223HS (eBioscience); (c) MMP-9 concentration was determined using the Human MMP-9 High Sensitivity ELISA BMS213HS (eBioscience).

The minimal detection limits were defined according to the manufacturer's instructions for the ELISA kits.

The methodology of this study was approved by the Ethics Committee of the Clinic for Dental Medicine, Faculty of Medicine, University of Niš, by decision No. 20/11-2017-6EO, dated October 31, 2019.

Statistical analyses

The data were presented as arithmetic mean and standard deviation or as absolute and relative numbers. The normality of data distribution was tested using the Shapiro-Wilk test. Comparison of continuous variables with a normal data distribution was performed using the t-test. If the data distribution was not normal, the comparison between two groups was conducted using the Mann-Whitney test. Comparison of numerical values between three or more groups was performed using analysis of variance (ANOVA) or the Kruskal-Wallis's test, depending on the data distribution.

Results

Denture wearers predominantly demonstrated that prosthetic factors, including poorly made dentures, unstable dentures, dentures with poor occlusion and retention, and continuous wear, have a significant impact on the development of denture stomatitis (DS).

The average age of the examined population was 70.37 ± 7.13 years. It was determined that patients with DS were statistically significantly older compared to the control group participants (72.62 ± 5.96 vs. 65.86 ± 7.20, $p < 0.001$).

There is a significant association between DS and patient age, as the findings indicate that DS occurs more frequently and in more severe forms in older individuals (aged 60 years and above).

The study included 40 male (40%) and 60 female (60%) patients with DS. In the control group, there were 22 males and 28 females. The analysis showed that the groups were balanced in terms of gender distribution ($p = 0.909$). Across all clinical types of DS, female patients were more prevalent.

Local denture-related factors

Stability, occlusion, trauma

Several denture-related factors have been identified as risk factors for the development of DS. These factors include prosthesis stability, occlusion and articulation, as well as trauma.

Good stability was observed in 62.0% of DS patients and 86.0% of participants in the control group ($p = 0.006$). A statistically significant difference in the presence of good stability was found between DS patients and control group participants ($p = 0.005$). Unstable dentures frequently cause traumatic injuries after placement, leading to mucosal inflammation.

Good occlusion was present in 47.0% of DS patients and 80.0% of control group participants ($p < 0.001$). There is a strong correlation between the presence of DS and occlusal discrepancies. A significant difference was recorded between the study group and the control group in terms of the number of occlusal contact points, indicating occlusal errors.

Trauma was observed in 9.0% of DS patients and 4.0% of control group participants ($p = 0.438$). Oral mucosal trauma occurs as an acute response to denture placement. The study revealed a lower prevalence of traumatic lesions, as these changes were quickly resolved after denture placement. More than one-third of the participants reported experiencing erosions after receiving dentures, whereas less than one-fifth of the control group reported the same. After the resolution of trauma-induced erosions, only localized mucosal inflammation remained.

Table 1 IL-1, TNF, and MMP-9 values for the study groups

	Stomatitis protetica	Control group	*p* value
IL-1β – conc. (pg/ml)	162.09 ± 138.53	6.77 ± 4.78	< 0.001
TNF-α – conc. (pg/ml)	36.48 ± 7.40	26.64 ± 3.93	< 0.001
MMP-9 – conc. (ng/ml)	175.58 ± 180.53	14.11 ± 3.3	< 0.001

[1] Mann-Whitney test

Type of dentures

In the studied population, 46.7% of patients wore a partial denture, while 53.3% had a complete denture. No statistically significant difference was found in the type of dentures between the study groups ($p = 0.452$).

Age of dentures

The duration of denture use was categorized into three groups: (1) less than 5 years; (2) 5–10 years and (3) more than 10 years. In the examined population, 20.0% of patients had dentures less than 5 years old, 44.0% had dentures between 5 and 10 years old, and 36.0% had dentures older than 10 years. A statistically significant difference in denture age was observed between the study group and the control group ($p = 0.033$).

Nighttime denture wearing

In the examined population, 36.0% of patients wore their dentures at night—49.0% of DS patients and 10.0% of control group participants. A statistically significant difference was found in the frequency of nighttime denture wearing between the study groups ($p < 0.001$) (Graphs 2).

A highly significant difference was found regarding nighttime denture wearing. Among patients with stomatitis, 49% (49 participants) wore their dentures at night, compared to 51% (51 participants) who did not. Oral lesions associated with denture use were positively correlated with nighttime denture wearing.

Salivary cytokines – interleukins IL-1β, TNF-α, and MMP-9

Saliva samples were collected from all participants in this study to determine the levels of pro-inflammatory cytokines—interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and matrix metalloproteinase-9 (MMP-9). The saliva samples were processed according to the manufacturer's instructions for IL-1β, TNF-α, and MMP-9 quantification.

The results are presented in Tables 1 and 2.

The levels of IL-1β, TNF-α, and MMP-9 were significantly higher in patients with denture stomatitis (DS) compared to the control group ($p < 0.001$ for all) (Table 1).

Since the saliva samples from individuals without denture stomatitis showed inflammatory marker levels within normal ranges, the impact of denture-related factors on these markers was specifically analyzed in individuals with DS.

Table 2 Impact of local Denture-Related factors on inflammatory marker levels in DS patients

Inflammatory markers	Denture factors				*p* value
	Stability				
	Stable	Unstable			p[1]
IL-1β – conc. (pg/ml)	142.36 ± 125.80	194.27 ± 153.44			0.135
TNF-α – conc. (pg/ml)	35.45 ± 6.88	37.53 ± 8.16			0.351
MMP-9 – conc. (ng/ml)	165.66 ± 175.28	191.76 ± 190.04			0.418
	Occlusion				
	Good	Poor			p[1]
IL-1β – conc. (pg/ml)	141.70 ± 135.75	180.17 ± 139.74			0.077
TNF-α – conc. (pg/ml)	34.76 ± 6.63	38.01 ± 7.76			0.009
MMP-9 – conc. (ng/ml)	149.84 ± 155.18	198.41 ± 199.04			0.142
	Trauma				
	Present	Absent			p[1]
IL-1β – conc. (pg/ml)	133.55 ± 171.07	164.91 ± 135.72			0.215
TNF-α – conc. (pg/ml)	38.23 ± 8.94	36.31 ± 7.26			0.567
MMP-9 – conc. (ng/ml)	194.74 ± 221.99	173.69 ± 177.28			0.995
	Type of denture				
	Partial	Total			p[1]
IL-1β – conc. (pg/ml)	131.34 ± 114.19	186.24 ± 151.65			0.101
TNF-α – conc. (pg/ml)	35.21 ± 7.69	37.48 ± 7.08			0.013
MMP-9 – conc. (ng/ml)	159.47 ± 135.79	188.24 ± 209.47			0.679
	Denture age				
	< 5 yrs	5 – 10 yrs	10 + yrs		p[1]
IL-1β – conc. (pg/ml)	118.12 ± 133.78	157.87 ± 142.29	183.40 ± 135.47		0.100
TNF-α – conc. (pg/ml)	34.18 ± 7.38	35.89 ± 7.00	37.95 ± 7.61		0.057
MMP-9 – conc. (ng/ml)	146.84 ± 194.13	152.56 ± 128.69	208.36 ± 212.47		0.166
	Nighttime denture wearing				
	Yes	No			
IL-1β – conc. (pg/ml)	208.98 ± 143.72	117.04 ± 118.08			< 0.001
TNF-α – conc. (pg/ml)	37.92 ± 7.94	35.11 ± 6.62			0.061
MMP-9 – conc. (ng/ml)	226.59 ± 208.34	126.58 ± 133.64			0.002

[1] Mann-Whitney test

The levels of IL-1β, TNF-α, and MMP-9 did not show statistically significant differences concerning denture stability in DS patients ($p = 0.135$, $p = 0.351$, and $p = 0.418$, respectively) (Table 2).

The levels of TNF-α showed a statistically significant difference concerning occlusion in DS patients ($p = 0.009$) (Table 2).

The levels of IL-1β, TNF-α, and MMP-9 did not show statistically significant differences concerning the presence of trauma in DS patients ($p = 0.215$, $p = 0.567$, and $p = 0.995$, respectively) (Table 2).

The levels of TNF-α were significantly higher in DS patients with complete dentures compared to those with partial dentures ($p = 0.013$) (Table 2).

The levels of IL-1β, TNF-α, and MMP-9 did not show statistically significant differences concerning denture age in DS patients ($p = 0.100$, $p = 0.057$, and $p = 0.166$, respectively) (Table 2).

The levels of IL-1β and MMP-9 were significantly higher in DS patients who wore their dentures overnight compared to those who did not ($p < 0.001$ and $p = 0.002$, respectively) (Table 2). Overnight denture wearing did not have a statistically significant effect on TNF-α levels in saliva ($p = 0.061$).

This table presents the relationship between various denture-related factors and the levels of inflammatory markers (IL-1β, TNF-α, and MMP-9) in patients with denture stomatitis (DS). The statistical significance of these associations was evaluated to determine the role of local prosthetic factors in DS pathogenesis.

In the multivariate model, a significant association was found between DS and the presence of trauma (OR = 9.868, $p = 0.017$), increased TNF levels (OR = 1.274, $p < 0.001$), and decreased MMP-9 levels (OR = 0.959, $p = 0.002$) (Table 3).

Discussion

The process of tooth loss is a slowly progressive lifelong process that ultimately leads to edentulism. Today, natural teeth are preserved longer than before, and tooth loss is more associated with older age groups. This is influenced by a combination of oral hygiene habits and

Table 3 The impact of Denture-Related factors and inflammatory markers on DS

DS	B	SE	OR	95% CI		*p*
Type of denture	-0,084	0,583	0,920	0,293	2,884	0,886
Denture age 10+	-0,982	0,677	0,375	0,099	1,413	0,147
Nighttime denture wearing	-0,725	0,857	0,484	0,090	2,599	0,398
Stability	-0,619	0,770	0,538	0,119	2,435	0,421
Oclussion	0,026	0,684	1,026	0,269	3,919	0,970
Trauma	2,289	0,963	9,868	1,496	65,113	0,017
IL-1b (pg/ml)	0,001	0,005	1,001	0,991	1,011	0,818
TNF (pg/ml)	0,242	0,069	1,274	1,113	1,457	0,000
MMP-9 (ng/ml)	-0,042	0,014	0,959	0,934	0,985	0,002
Constant	-6,468	2,325	0,002			0,005

Hosmer-Lemeshow test $p = 0.417$, B– unstandardized regression coefficient, SE– standard error, OR– cross relationship, 95% CI– 95% confidence interval

lifestyle behaviors. The oral cavity, which serves many functions throughout a person's life and is constantly exposed to physical, chemical, and biological agents, has unique significance and deserves greater medical attention in terms of prevention and early diagnosis of any condition. It must be kept in mind that oral health is essential for maintaining a high level of general health [20, 21].

Denture stomatitis is one of the most frequently diagnosed conditions in oral pathology and is associated with dental prostheses. Stomatitis is defined as an inflammatory type of oral mucosal lesion in individuals wearing partial or complete removable dentures, which, if not treated adequately and on time, can progress to a more severe clinical condition. Many factors are linked to this disease, but there is no consensus on a single etiological factor [9, 22]. Wearing partial or complete dentures can lead to various mucosal lesions. In most cases, oral mucosal lesions are inflammatory and reactive in nature [23].

For this reason, there has been increasing interest in recent years in exploring new etiopathogenetic considerations regarding DS. With this objective, the present study aimed to investigate all the listed local etiological factors and their effects to identify the most critical factor in the development of DS and contribute to its prevention [24, 25].

The role of age in DS

Regarding age, the age group with the most significant changes corresponds to individuals aged 60 and above. DS is more frequently observed in older individuals as it is associated with normal degenerative changes occurring throughout life. Wearing dentures and the age of denture wearers are well-known risk factors linked to DS development, as confirmed by this study, aligning with the findings of other authors [26, 27].

According to some studies, oral tissues are susceptible to collagen damage, leading to reduced tissue regeneration. The present study indicates no significant difference between the examined and control groups regarding the average age, which is consistent with the findings of Zissis et al. [28], though conflicting results have also been reported [4]. It was found that patients with DS were statistically significantly older than those in the control group (72.62 ± 5.96 vs. 65.86 ± 7.20, $p < 0.001$).

Although most studies suggest that age is a significant risk factor for DS, some authors have not identified this association. This contradiction may result from different methodological approaches, the presence of other denture-related factors, and individual variations in patients' oral health.

The role of gender in DS

Numerous studies have examined the association between gender and DS, but the findings vary significantly. A smaller number of studies suggest a higher prevalence of DS in men, while the majority indicate a greater occurrence in women [23, 29].

In this study, 40 participants (40%) were male, and 60 (60%) were female. The control group consisted of 22 males and 28 females (Fig. 1). It was determined that the groups were gender-balanced ($p = 0.909$). The reason why women are more prone to developing DS remains unclear [30].

There are partial explanations, such as the role of hormonal deficiencies during menopause, differences in hygiene habits, immune responses, and inconsistent diagnostic criteria. These factors may contribute to mucosal thinning, making it more reactive to the presence of dentures [31, 32]. However, some studies have found no correlation between DS and gender [33, 34].

The role of denture stability, occlusion, and trauma in DS

Several denture-related factors have been identified as risk factors for the development of DS. These factors include denture stability, occlusion, retention, and trauma. In this study, a higher percentage of patients

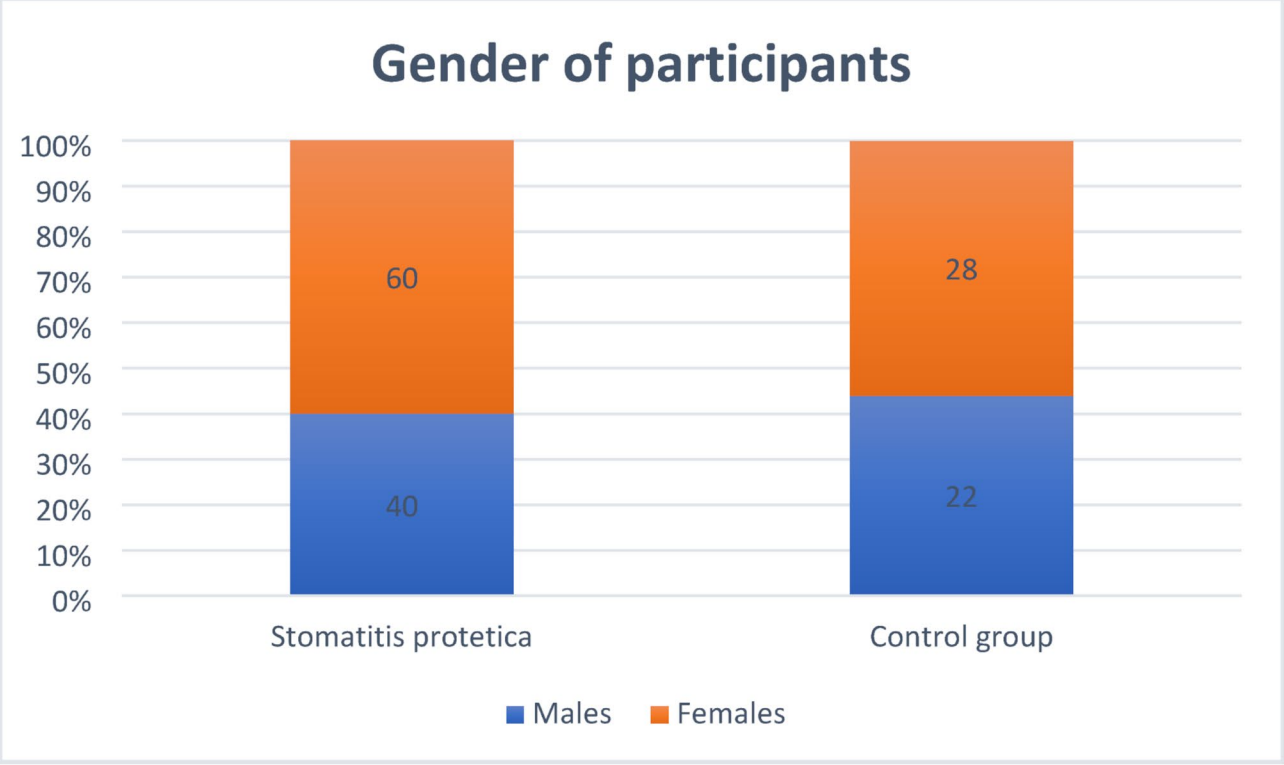

Fig. 1 Gender distribution of the study groups

with DS had unstable dentures compared to the control group of patients without DS. Specifically, good stability was observed in 62% of DS patients and 86% of control group participants. A statistically significant difference was found in denture stability between DS patients and the control group ($p = 0.006$).

Unstable dentures lead to trauma, which can act as a cofactor in creating conditions that allow various pathogens to adhere to and penetrate tissues where inflammation and a proinflammatory response are already present [35].

Good occlusion was observed in 47.0% of DS patients and 80.0% of control group participants ($p < 0.001$). The findings of this study regarding occlusal errors and denture instability align with the results of other authors [36, 37]. Proper occlusion is essential for overall treatment success, as it ensures denture stability. In partial dentures, occlusion tends to be more stable because it is supported by natural teeth and mucosa. If occlusion is poor (i.e., teeth are not in contact—balanced central occlusion in centric relation), it negatively affects both retention and stability [38].

The lack of a statistically significant association between denture stability, trauma, and inflammatory biomarkers highlights the complexity of denture stomatitis. Inflammation cannot be explained solely by the physical properties of dentures. The interaction with microbiological and systemic factors, the adaptive response of the oral mucosa, and methodological limitations of the study may account for this result. Further research with larger sample sizes and longitudinal biomarker monitoring could provide more precise insights into the mechanisms of this process.

Type of denture– partial and complete

In the studied population, 46.7% of patients wore a partial denture, while 53.3% wore a complete denture (Fig. 2). No statistically significant difference was found in the type of denture between the examined groups ($p = 0.452$).

Elevated levels of IL-1, TNF-α, and MMP-9 indicate an increased inflammatory response in patients with complete dentures compared to those with partial dentures. These biomarkers can serve as predictors of inflammation and potential alveolar ridge atrophy, highlighting the need for improved patient monitoring and the development of strategies to reduce inflammatory responses associated with denture use.

The role of denture age in DS

Denture age is an important factor, as maintaining hygiene becomes more challenging with prolonged use, and the denture base tends to become more porous over time [28, 39, 40]. Such dentures are considered inadequate, leading to tissue trauma and inflammation,

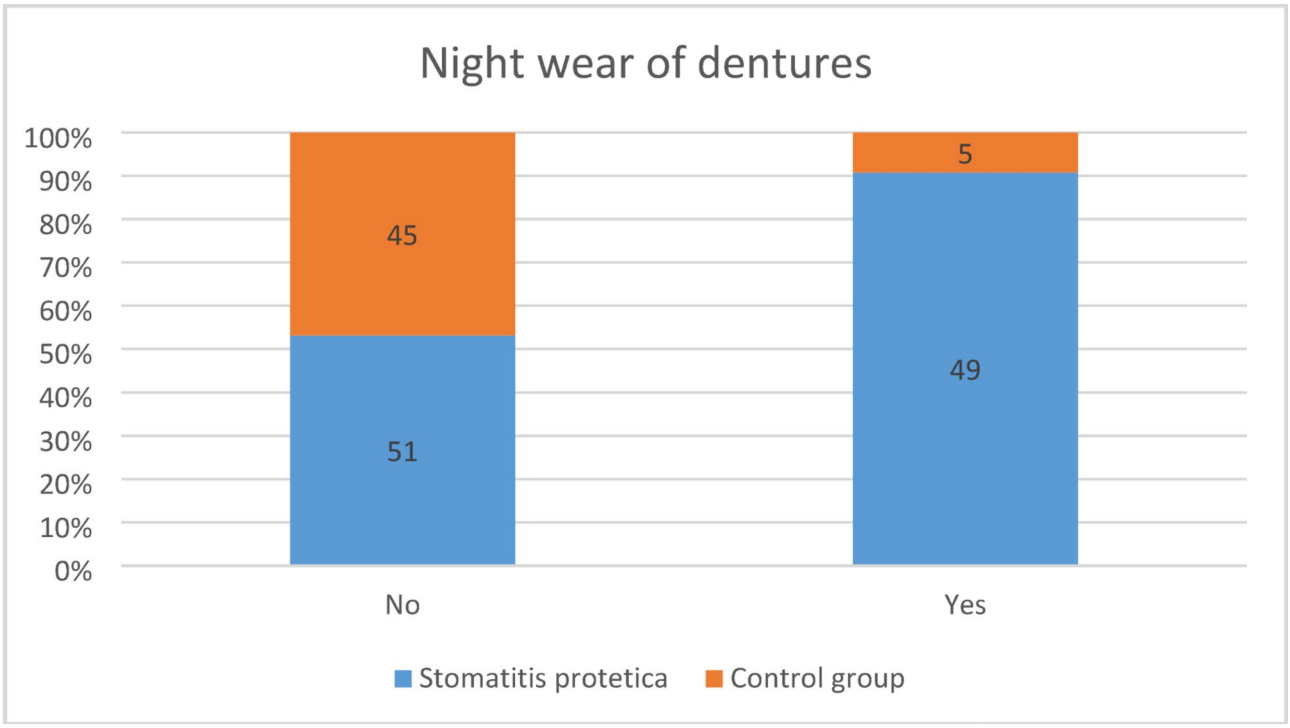

Fig. 2 Nighttime denture wearing per study group

creating favorable conditions for Candida infection [41, 42].

Regarding denture age, this study found a highly significant association between denture age and DS [13]. In the examined population, 20.0% of patients had dentures for less than 5 years, 44.0% had dentures between 5 and 10 years old, and 36.0% had dentures older than 10 years. A statistically significant difference in denture age was observed between the study group and the control group ($p = 0.033$).

The association between denture age and denture stomatitis can be explained by a combination of mechanical, microbiological, and physiological factors. The damage and poor adaptation of older dentures lead to microtrauma of the oral mucosa, while increased material porosity and compromised hygiene promote greater microbial colonization. Combined with the reduced resistance of oral tissues in elderly patients, these factors contribute to a higher risk of inflammatory processes in the oral cavity [43, 44].

Although this study confirms a significant correlation between denture age and DS, conflicting findings in the literature suggest that this relationship is not absolute. Denture age is an important risk factor, but denture hygiene, the frequency of dental check-ups, and individual patient predisposition may play an even greater role.

Future studies should focus on multifactorial analyses to clarify the relative importance of denture age compared to hygiene and microbiological factors, helping to refine recommendations for the optimal lifespan of dentures and the frequency of their replacement.

The role of nighttime denture wearing in DS

Sleeping with dentures is a common habit among many patients. Research has shown that nighttime denture wearing is the most significant risk factor linking oral infections and DS [45]. This occurs because the continuous contact between the denture base and the oral mucosa reduces the protective effect of saliva and prevents mucosal oxygenation [2].

In this study, it was confirmed that nighttime denture wearing has the greatest impact on oral mucosal health. In the examined population, 36.0% of patients wore their dentures overnight, including 49.0% of DS patients and 10.0% of the control group. A statistically significant difference was found in the frequency of nighttime denture wearing between the study groups ($p < 0.001$). The findings of this study suggest that this habit greatly contributes to the development of DS. The results align with previous studies that have identified nighttime denture wearing as a major predisposing factor [46, 47].

The negative impact of wearing dentures overnight arises because the beneficial effects of saliva are diminished in the oral cavity under these conditions. Between the denture base and the palatal mucosa, reduced saliva flow and dynamic pH changes interfere with the natural mechanical cleansing of tissues, further increasing the risk of inflammation and infection [48].

The role of salivary cytokines (IL-1β, TNF-α, and MMP-9) in DS

The use of new technologies and dental materials in the fabrication of removable prosthetic restorations influences changes in certain biochemical parameters in patients' saliva. For this reason, saliva analysis is increasingly being conducted in patients with dental prosthetic restorations. It has been proven that inflammatory parameters are significantly elevated in the blood of patients who have received dental prosthetic restorations [49, 50, 51]. Therefore, analyzing the biochemical composition of saliva can be particularly important for assessing the risk of disease development, diagnosis, and treatment of various conditions.

As part of the body's immune response, inflammatory mediators are released, enabling the chemotaxis of defensive cells to the site of inflammation. Many researchers have examined various inflammatory mediators in saliva and their roles in DS in patients [52, 53]. The findings of this study suggest that a greater number of exclusively prosthetic factors can damage the oral mucosa and contribute to the inflammation underlying denture stomatitis. Thus, this research highlights the primary role of dentures as foreign bodies, while the presence of other factors may facilitate the penetration of infectious agents that trigger inflammatory changes in the oral cavity.

This study analyzed the biomarkers IL-1β, TNF-α, and MMP-9 to investigate the inflammatory response of the oral mucosa in patients with denture stomatitis. These biomarkers were selected due to their crucial roles in modulating immune response, inflammation progression, and tissue damage. Their detection in saliva allows for non-invasive monitoring of inflammatory processes and may contribute to earlier diagnosis and a better understanding of the pathogenesis of denture stomatitis [54, 55].

IL-1β is one of the key pro-inflammatory cytokines and is considered a marker of acute inflammation. It is secreted by activated macrophages and epithelial cells in response to infections, mechanical irritation, and other harmful stimuli. In the context of denture stomatitis, IL-1β is released in response to microtrauma caused by denture wearing, the presence of microorganisms, and the accumulation of dental plaque. Its elevated concentration in saliva may indicate an early phase of the inflammatory response, making it a useful biomarker for the early detection of inflammatory changes in patients with denture stomatitis [56, 57].

This study demonstrated that the presence of IL-1β indicates that, in patients with DS, although inflammation is present, there are no significant structural changes, as confirmed by findings in individuals without DS [58, 59]. It was determined that IL-1β is present in higher amounts in patients with DS (162.09 ± 138.53 pg/ml). Upon secretion, accumulated IL-1β triggers a series of inflammatory reactions and participates in disease progression. Its production is not continuous but is activated in response to proinflammatory stimuli [60]. This explains the increased concentration of IL-1β in individuals with DS, particularly due to local denture-related factors, while the concentration in individuals without DS remains within reference values (6.77 ± 4.78 pg/ml), as no irritating local denture factors are present.

The results of this study revealed significant differences in IL-1β levels depending on the presence of local denture-related factors (in patients with unstable denture, the IL-1β concentration was 194.27 ± 153.44 pg/ml; in those with poor occlusion it was 180.17 ± 139.74 pg/ml; in those with trauma it was 164.91 ± 135.72 pg/ml; in those wearing total dentures it was 186.24 ± 151.65 pg/ml; in those wearing old dentures it was 183.40 ± 135.47 pg/ml; and was the highest in those wearing dentures at night: 208.98 ± 143.72 pg/ml) (Table 2).

According to some authors, it has been demonstrated that the levels of this interleukin decrease over time with denture use, i.e., as the denture ages [60, 61].

TNF-α is one of the most crucial proinflammatory cytokines involved in the regulation of the mucosal immune response. Its primary function is to initiate the inflammatory reaction by activating other cytokines and recruiting immune cells to the site of inflammation [62]. The analysis of salivary TNF-α can serve as a successful diagnostic and prognostic biomarker for various diseases [63]. In the context of denture stomatitis (DS), an elevated TNF-α level may indicate an active inflammatory response of the mucosa to mechanical, microbial, and immunological stimuli. Additionally, TNF-α may contribute to chronic inflammation, potentially leading to long-term consequences for oral tissue health.

The results obtained in this study confirm that TNF-α may be associated with DS activity, as levels of 36.48 ± 7.40 pg/ml were recorded in the DS group, compared to 26.64 ± 3.93 pg/ml in the control group, with the difference being statistically significant ($p < 0.001$). Therefore, salivary TNF-α levels may serve as indicators of disease activity, given that several studies have reported increased TNF-α levels in saliva among patients with Newton's Type II and Type III DS [64]. However, other studies have found no significant difference between DS patients and healthy controls [65, 66].

Previous research, along with this study, has also demonstrated the presence of TNF-α and other mediators (IL-1) in DS patients [67]. Some studies suggest a statistically significant difference in salivary cytokine (TNF-α) levels between DS patients and those in the control group [51].

Salivary TNF-α levels did not significantly differ among DS patients based on the impact of local denture-related

factors (unstable denture: 37.53 ± 8.16 pg/ml; poor occlusion: 38.01 ± 7.76 pg/ml; trauma: 38.23 ± 8.94 pg/ml; total dentures: 37.48 ± 7.08 pg/ml; old dentures: 37.95 ± 7.61 pg/ml; dentures worn at night: 37.92 ± 7.94 pg/ml; Table 2). A statistically significant presence of TNF-α was observed in cases of poor occlusion in complete denture wearers with DS ($p < 0.013$).

Therefore, the analysis of salivary TNF-α can be a successful diagnostic tool and a potential prognostic marker for DS. The presence of TNF-α in saliva may also serve for monitoring treatment outcomes, as its concentration significantly decreases after successful therapy, as demonstrated by some authors [67, 68]. Variations in the increase of salivary TNF-α levels may indicate prolonged oral inflammation associated with denture use. Some studies have found a significant difference in IL-1β and TNF-α levels between patients with and without DS [69, 70], while others have not [71, 72].

MMP-9 belongs to a family of enzymes responsible for the degradation of extracellular matrix components, including collagen and elastin. MMP-9 functions as a mediator of tissue damage and has recently received more attention due to its role in the disintegration of the basement membrane and extracellular matrix through direct collagen degradation. Its activation plays a key role in tissue remodeling as well as in the progression of inflammatory processes. Elevated levels of MMP-9 in the saliva of patients with denture stomatitis may indicate active oral tissue degradation due to chronic inflammation induced by denture wearing [8, 23, 55]. This biomarker is particularly significant as it can serve as an indicator of tissue damage and inflammation progression, providing a better understanding of the pathogenesis of denture stomatitis and its potential complications.

The results show a significant difference in MMP-9 levels between the DS group and the non-DS group (175.58 ± 180.53 vs. 14.11 ± 3.3).

Salivary samples in this study were collected from individuals with DS, suggesting that the primary source of salivary MMPs is the ongoing inflammation of the oral mucosa in these patients. In the control group, MMP levels were notably low (14.11 ± 3.3). Salivary MMP-9 levels can vary in healthy individuals depending on age and oral health status, as demonstrated in the non-DS patient group in this study.

These findings align with other similar studies that have examined these proinflammatory cytokines in oral epithelial cells infected with various pathogenic agents [73–75]. These studies have shown that salivary marker levels can serve as indicators of disease activity, such as DS, since a significant increase in MMP-9 levels is directly correlated with the clinical severity of DS.

This study demonstrated significantly higher concentrations of MMP-9 in DS patients compared to the control group regarding the presence of local prosthetic factors (stability: 191.76 ± 190.04 ng/ml; occlusion: 198.41 ± 199.04 ng/ml; old dentures: 208.36 ± 190.04 ng/ml; nocturnal denture wearing: 226.59 ± 208.34 ng/ml vs. controls: 14.11 ± 3.3 ng/ml).

Thus, these markers indicate inflammatory changes in DS patients. Accordingly, MMPs and their inhibitors could be assessed as tools for distinguishing between health and disease states, while the modulation of their molecular processing and activity could be explored for the development of effective therapies [76].

Here are the results of the logistic regression analysis, assessing the impact of various factors on the presence of denture stomatitis (DS). Key findings are that the trauma has a significant positive effect on DS (OR = 9.868, $p = 0.017$), meaning that patients with trauma are nearly 10 times more likely to develop DS. TNF-α is also significantly associated with DS (OR = 1.274, $p < 0.001$), indicating that an increase in TNF-α levels raises the risk of DS.

MMP-9 has a negative effect (OR = 0.959, $p = 0.002$), suggesting that higher MMP-9 levels may be linked to a reduced risk of DS. Other factors did not show a statistically significant association with DS ($p > 0.05$).

Studies have shown that salivary inflammatory markers, including IL-1β, TNF-α, and MMP-9, are interrelated in patients with DS and may have significant potential for monitoring oral health and assessing the inflammatory and proteolytic status in DS patients [60, 69, 74–76].

Biomarkers that provide prognostic information can be valuable for evaluating the presence of current and past disease; however, they do not offer complete predictability of the disease's future course. DS can influence biomarkers locally within the oral cavity. A weak but significant positive correlation between these analyzed biomarkers and clinical variables was observed in the DS group, particularly in individuals who wear dentures overnight (Table 2). These findings emphasize the importance of considering, on one hand, the impact of oral health status when analyzing salivary inflammatory biomarker levels and, on the other hand, the role of reducing local DS-associated factors in preventing inflammation of the oral mucosa.

Many factors that contribute to oral mucosal inflammation in DS patients can be modified to reduce the inflammatory response. However, residual inflammation may pose a risk for disease progression due to unknown reasons. The inflammatory condition cannot be resolved if the patient remains exposed to harmful stimuli. A comparison between DS patients and healthy controls demonstrated that exposure to local prosthetic factors leads to a significant increase in inflammatory marker levels compared to control group patients.

Conclusion

The source of inflammation in denture stomatitis (DS) remains a subject of debate and a priority for numerous studies. The findings of this study suggest that a significant number of prosthetic-related factors can damage the oral mucosa and contribute to the onset of inflammation, which underlies denture stomatitis. The observed increase in salivary inflammatory biomarker concentrations highlights the need for further research into the existing risk factors for DS development.

Given the high prevalence of inflammation among denture wearers, it is advisable to schedule regular check-ups for patients to ensure early diagnosis and appropriate treatment. Emphasis should be placed on preventive measures and the prevention of denture stomatitis, as timely intervention may help mitigate disease progression.

Abbreviations

SP	Stomatitis protetica
IL-1β	Interleukin 1β
TNF-α	Tumor necrosis factor α
MMP-9	Matrix-metalloproteinase-9

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Author contributions

M.BV. and A.P. wrote the main manusript; M.K. read and review the paper; R.O. did original draft preparation; I.S. and K.Ž. did a literature review; J.B did immunological analyses; I.M. prepared tables and charts; A.I. did the statistical analysis. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by M.BV. and A.P. The first draft of the manuscript was written by M.BV. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from [prof. dr Ana Pejcic and dr Marija Bradic-Vasic] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [prof. dr Ana Pejcic and dr Marija Bradic-Vasic].

Declarations

Ethics approval and consent to participate

The provisions of the Declaration of Helsinki were respected, given that the study is retrospective and that patient saliva samples were used, which were taken after verbally informing the patients about the research and their verbal and signed informed consent. The research protocol was both performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and approved by the Ethics Committee of the Clinic for Dental Medicine, Faculty of Medicine, Nis (decision No. 20/11-2017-6EO, dated 31.10. 2019). A written consent form, containing a detailed study description and a sociodemographic questionnaire, was signed by the participants and the researchers by hand.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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