Original Paper

Clinical Evaluation of Periodontal Status and IL-6 Gingival Fluid Level in Patients with Sjogren's Syndrome

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ABSTRACT: The objective of the cross-sectional study was to assess periodontal and implant health condition among individuals diagnosed with Sjogren's Syndrome (SS), taking into account the clinical circumstances associated with this patient population. The clinical parameters employed to evaluate the periodontal status of both natural teeth and implants included: periodontal probing depth (PPD) measured at six sites per tooth/implant, clinical attachment level (CAL), bleeding on probing index (BOP), plaque index (PLQ). Gingival crevicular fluid samples were collected for interleukin-16 level evaluation. After clinical and immunological assessment of the study and control groups, the data was centralized, compiled and submitted for statistical analysis. In all four types of assessed periodontal parameters, there were statistically significant differences between the SS patients with no dental implants and the other test (SSi) and control groups (Cni and Ci). Nevertheless, in SS patients with dental implants, plaque levels were similar to that of controls. In addition, other periodontal parameters (PPD, BOP and CAL) were similar in SS patients with dental implants and controls, with no statistically significant difference. The highest GCF IL-6 levels were found in SS patients with no dental implants, the differences to the other study and control groups being statistically significant. In patients with SS and dental implants, there were no statistically significant differences to the other groups. Individuals diagnosed with Sjogren's Syndrome (SS) exhibit a less favorable periodontal condition compared to controls without SS. Notably, SS patients who undergo dental implant procedures demonstrate an improvement in their periodontal status. This highlights the importance of proactive and ongoing dental and periodontal surveillance for SS patients, aiming to decrease the risk of developing periodontal diseases.

KEYWORDS: *Periodontitis, Sjogren's syndrome, periodontal status, dental implants, interleukin-6*

Introduction

Periodontal disease represents a commonly encountered condition within the oral cavity and dental apparatus, attracting increasing attention from both patients and general practitioners [1].

As a result, periodontology has emerged as a prominent specialty within the field of dental medicine [2].

The domain of periodontology is primarily focused on conducting research and acquiring a comprehensive understanding of the pathogenic mechanisms, complementary risk factors, and clinical characteristics associated with periodontal diseases [3].

This knowledge serves as a foundation for providing reliable tools for accurate diagnostic approaches and establishing predictable treatment plans [3].

Periodontitis is characterized as a chronic inflammatory condition that affects the periodontal tissue, encompassing the supporting structures of the teeth, namely the gingiva, alveolar bone, cementum, and periodontal ligament [4].

Progressive breakdown of these tissues ensues, posing the risk of tooth loss if left untreated [4].

The pathogenesis of periodontitis is intricate, with bacterial plaque and its metabolites primarily implicated.

Bacterial colonization on tooth surfaces gives rise to the formation of biofilm, triggering the host's immune response [5].

Subsequent production of inflammatory mediators as a result of the host response can contribute to periodontal tissue destruction when surpassing a threshold level [5].

Clinical manifestations of periodontitis encompass clinical attachment loss, gingival recession, and alveolar bone loss [6].

Given its substantial impact on morbidity and being the leading cause of tooth loss in adults,

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periodontitis represents a notable public health concern [7].

Nonetheless, early detection of symptoms such as gingival redness, swelling, bleeding or halitosis can facilitate timely intervention, thereby preventing disease progression and the emergence of significant clinical consequences through appropriate treatment measures [3].

Periodontal medicine represents a specialized field within periodontology that focuses on exploring the intricate relationship between periodontal disease and overall health outcomes [8].

This discipline endeavors to unravel the pathophysiological mechanisms underlying periodontal disease, elucidate the host's susceptibility to the condition, and comprehend the systemic impact of periodontal disease.

It integrates periodontology, general medicine, and relevant scientific disciplines to provide a comprehensive and holistic approach to patient care [8,9].

Sjögren's syndrome (SS), characterized by chronic autoimmune pathology, is distinguished by the infiltration of lymphocytes into exocrine glands, particularly the lacrimal and salivary glands, leading to diminished secretion of tears and saliva, known as sicca syndrome [10].

The precise etiological underpinnings of Sjögren's syndrome are not entirely understood; however, it is believed to arise from a complex interplay between genetic predisposition and environmental triggers [10].

The condition exhibits a clear gender predilection, with a female-to-male ratio of 9:1, indicating a higher susceptibility among women [10,11].

Patients diagnosed with Sjögren's syndrome may encounter various oral health complications attributed to xerostomia (dry mouth) resulting from the disorder [12].

These complications include the following [12-14]:

- Dental caries: Xerostomia can elevate the risk of dental caries due to decreased salivary flow, compromising the ability to neutralize acid and flush away bacteria and food particles.

- Oral candidosis: Xerostomia can foster the proliferation of the *Candida* fungus, leading to the development of white, tender patches in the oral cavity known as oral candidosis.

- Mucositis: Individuals with Sjögren's syndrome are susceptible to oral mucositis, characterized by inflammation and ulceration of the mucous membranes.

- Dysgeusia (distorted sense of taste) and dysphagia (difficulty swallowing) [12-14].

According to a recent meta-analysis involving 21 studies and a total of 11,435 participants, Sjögren's syndrome (SS) patients may face an elevated risk of being diagnosed with periodontitis [15].

However, it is important to note that the findings of Yang's meta-analysis indicate significant heterogeneity in the results, implying that a definitive conclusion cannot be drawn at present [15,16].

The existing scientific literature offers varying degrees of evidence suggesting an augmented risk of developing periodontitis in individuals with Sjögren's syndrome [16].

However, it is important to note that there is a lack of consensus among researchers investigating this topic, as opinions and findings differ among authors [16].

Interleukin-6 (IL-6) is a protein molecule that plays a crucial role in the immune system as a pro-inflammatory cytokine [17].

It is produced by various cells in the body, including immune cells, fibroblasts, and endothelial cells [17].

IL-6 acts as a signaling molecule, transmitting messages between cells to regulate immune responses and inflammation [17,18].

IL-6 is involved in several biological processes, including the activation and differentiation of immune cells, such as T cells and B cells [18].

It also stimulates the production of acute-phase proteins by the liver and promotes the growth and differentiation of certain cell types, such as plasma cells [18].

The purpose of the cross-sectional study was to evaluate periodontal and implant health status in patients with Sjögren's Syndrome (SS) and to assess whether their reduced saliva flow could increase the probability of periodontitis or periimplantitis onset, given the particular clinical settings generated by xerostomia.

Materials and Methods

Study Design

The current investigation was carried out subsequent to receiving approval from the Ethics Commission of the University of Medicine and Pharmacy of Craiova (no. 186/2022) and of the Emergency County Hospital Dolj (no. 57095/2022).

The study strictly adhered to the necessary protocols, which included obtaining informed consent from each participating patient.

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Compliance with the European Union's General Data Protection Regulation (GDPR) and the Declaration of Helsinki 1975-2013 was ensured to safeguard data protection and maintain patient privacy.

The design of this cross-sectional study included a clinical stage for the assessment of the dental and periodontal status of the selected patients, combined with the sampling of gingival crevicular fluid (GCF).

Subsequently, an immunological laboratory assessment of GCF IL-6 level was performed.

All generated data (clinical and immunological) was gathered into a database and subjected to statistical analysis.

Patient Selection

The study enrolled 17 patients (14 female and 3 male) diagnosed with SS (no other systemic condition) and 17 sex and aged-matched controls (no SS, no other systemic condition).

The SS patients originated from the Rheumatology Ward of the Emergency County Hospital Dolj, while the controls were selected among the patients addressing the Periodontology Clinic of the University of Medicine and Pharmacy of Craiova.

The selection criteria for the SS patients consisted of: (i) previously diagnosed primary or secondary Sjogren's Syndrome; (ii) absence of additional systemic disease in connection with periodontitis (diabetes, cardiovascular disease).

The following exclusion criteria were applied to all participants in the study (SS patients and controls): (i) edentulism; (ii) active smoking status; (iii) anti-inflammatory or antibiotic medication in the last month prior to GCF sampling.

Two main patient groups were assembled: (i) SS group: 17 patients with SS; (ii) C group: 17 controls.

Afterwards, these two main study groups were further divided according to the patients having previously followed or not dental implant therapy: (i) SSi group: SS patients with dental implants; (ii) Ci group: control patients with dental implants; (iii) SSni group: SS patients with no dental implants; (iv) Cni groups: control patients with no dental implants.

Clinical dental and periodontal assessment

The clinical criteria used for the periodontal evaluation of teeth and implants included: periodontal probing depth (PPD, 6 sites of probing of each tooth/implant), clinical attachment level (CAL), bleeding on probing index (BPI) and plaque index (PLQ).

A single, calibrated, clinician performed the periodontal probing using a manual periodontal probe.

The data was gathered on digital periodontal charts, generating individual results per patient, such as mean PPD (mms), mean CAL (mms), PLQ and BPI percentage values (%).

This allowed the diagnosis of periodontitis on stages and grades, or of periimplantitis, where needed.

Gingival Crevicular Fluid Sampling

After the periodontal evaluation, samples of GCF were collected from each patient, with absorbent paper strips inserted into the gingival sulcus of maxillary central incisors and kept inside for 30 seconds (for standardization of method).

The contamination of saliva was prevented by choice of sampling tooth, use of cotton rolls and air suction.

If gingival bleeding occurred during sampling, the paper strip was discarded and the sampling redone.

GCF quantity standardization was performed with the help of a Periotron 8000 device (Oraflow Inc., Smithtown, NY, USA).

Subsequently, the paper strip was stored in a polyethylene microtube with saline buffer solution (PBS) in a refrigerated environment (-8 degrees Celsius), until sampling ending.

IL-6 GCF level assessment

GCF samples were transferred to the Immunology Laboratory of the University of Medicine and Pharmacy of Craiova for enzyme-linked immunosorbent assay (ELISA) quantitative detection of IL-6 levels.

The assay was performed using commercial kits (BMS213-2 Thermo Scientific LSG HU IL-6 COATED ELISA 96T, Waltham, USA, range 0.08-5.0pg/mL), according to the manufacturer's indications and prescribed method.

The optical analyser was set to 450nm wavelength.

Statistical Analysis

After clinical and immunological assessment of study and control groups the data was centralized, compiled and submitted for statistical analysis, using GraphPad Prism 9.2.0 (GraphPad Software, San Diego, CA, USA) and Mann-Whitney test due to the small number of included patients.

The power analysis for our study was performed using G*Power 3.1.9.7, at a 95% confidence level and power factor of 80% for each of the groups.

A two-sided p-value smaller than 0.05 was considered to be statistically significant.

Results

Demographics

No statistical difference was found for demographics and number of teeth/implants (Figure 1).

The median age of the SS patients was 49.7 years, with a total number of 327 existing teeth (19.2 teeth per patient) and 28 dental implants (6 patients with implants, 4.6 implants per patient).

The control group had an average age of 52.4 years, with a total number of 384 teeth (22.5 teeth per control) and a total number of 32 implants (5 controls with implants, 6.4 implants per control).

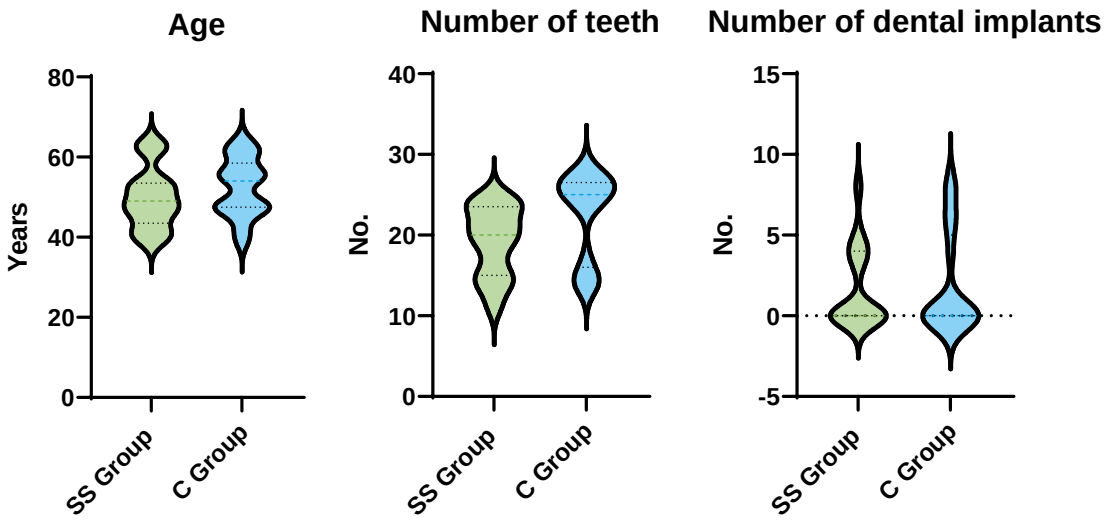

Figure 1. Demographic results: age, number of teeth and dental implants in study and control groups.

Clinical periodontal status

Regarding the periodontal status of teeth, mean PPD and CAL values were significantly higher in SSni group as compared to controls ($p<0.05$).

Regarding PLQ index, the difference between the SSni group (61%) and the control group (27,4%) was significantly higher, suggesting that reduced saliva flow has a significant impact on plaque accumulation (Figure 2).

Nevertheless, in SS patients with dental implants, plaque levels were similar to that of controls.

In addition, other periodontal parameters (PPD, BOP and CAL) were similar in SS patients with dental implants and controls, with no statistically significant difference.

In all four types of assessed periodontal parameters, there were statistically significant differences between the SS patients with no dental implants (SSni) and the other test (SSi) and control groups (Cni and Ci).

Regarding periodontal and implant disease diagnosis, the prevalence of Stage 1 to 4 periodontitis was significantly higher in the SSni group compared to controls (Stage 1 and 2: 29,4% to 5,8%; Stage 3 and 4: 41,1% to 17,6%).

Peri-implant mucositis was diagnosed in 17,64% of SSi patients and 11,77% controls, with no statistical difference.

Periodontal health was found in 11,77% in SSni group and 64,7% in control group.

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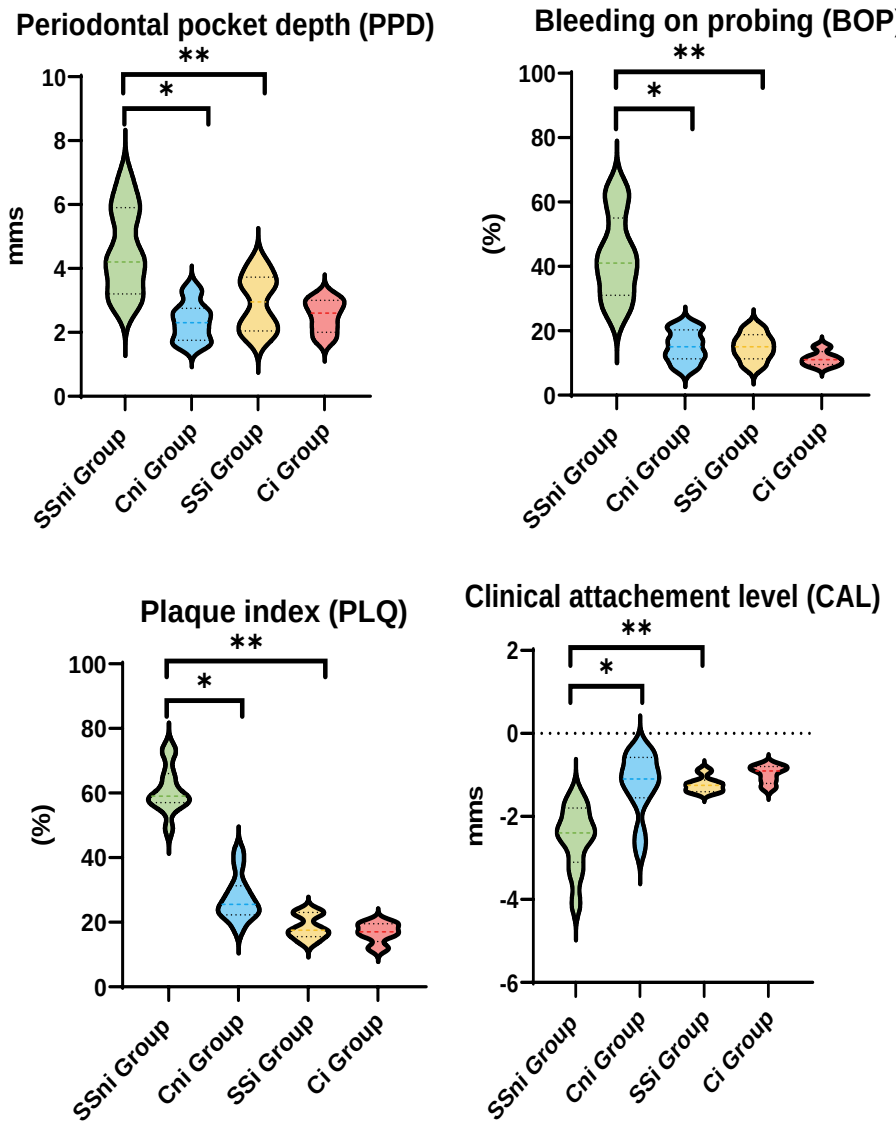

Figure 2. Clinical parameters results: PPD, BOP, PLQ and CAL levels in study groups (SSni, SSi) and control groups (Cni, Ci), *, **-statistically significant difference.

IL-6 GCF levels

The highest GCF IL-6 levels were found in the SSni group, the differences to the other study and control groups being statistically significant (Figure 3).

In patients with SS and dental implants, there were no statistically significant differences to the other groups.

In the SSni group, the GCF IL-6 levels expressed a positive moderate correlation with CAL levels (r=0.56), while in the Cni group, a moderate negative correlation (r=-0.66) was found between GCF IL-6 levels and PLQ (Figure 4).

In SS patients with dental implants (SSi), the GCF IL-6 levels expressed a moderate negative correlation with PLQ levels (r=-0.50), while in control Ci group, the correlations of the GCF IL-6 levels and the clinical parameters were weak (Figure 5).

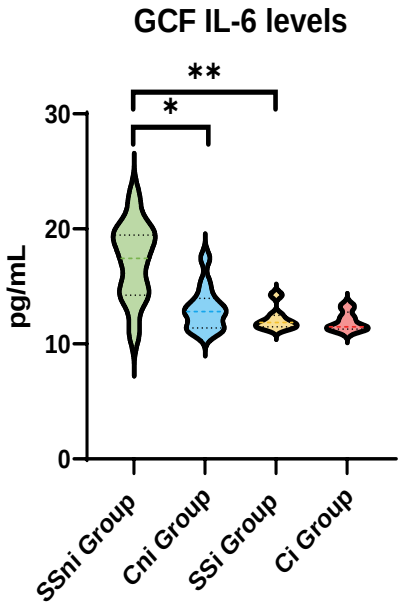

*Figure 3. GCF IL-6 levels in study groups (SSni, SSi) and control groups (Cni, Ci) *, ** - statistically significant difference.*

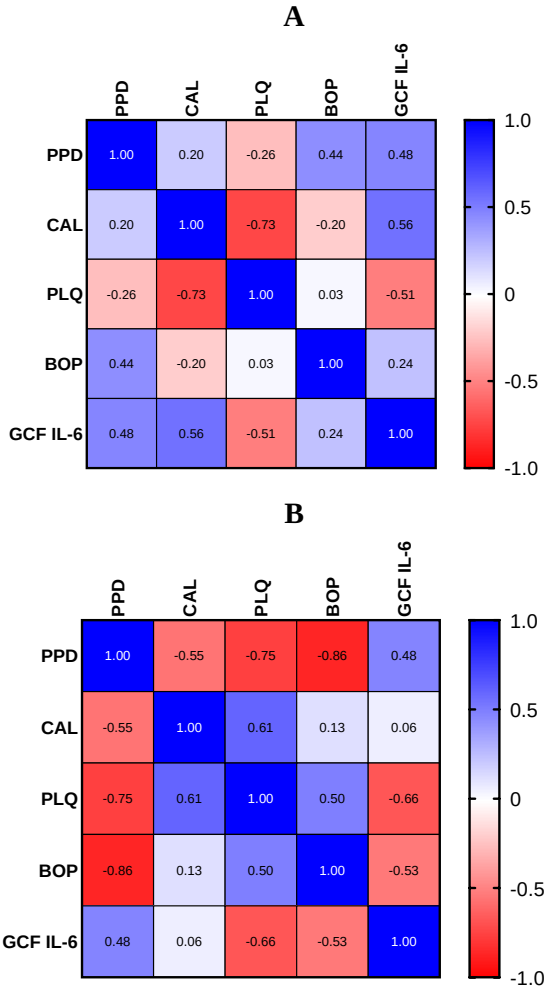

Figure 4. Correlation matrix for GCF IL-6 levels and clinical parameters in patients with no dental implants A: SSni group, B: Cni group.

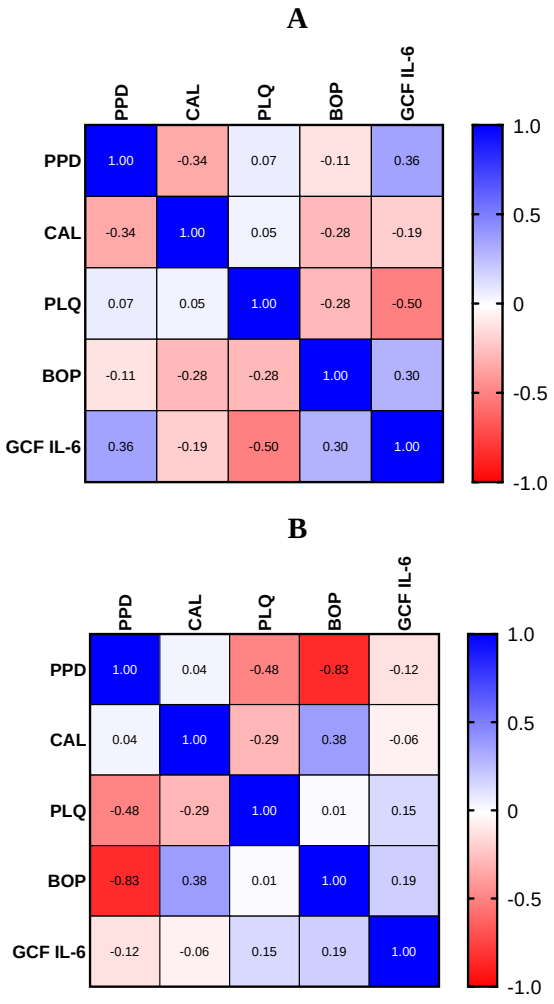

Figure 5. Correlation matrix for GCF IL-6 levels and clinical parameters in patients with dental implants A: SSi group, B: Ci group.

Discussion

Although the topic of increased risked of periodontitis in patients with SS has been previously approached by fellow researchers, a homogenous opinion couldn't be reached, as highlighted by recent systematic reviews on the matter [15,16].

Thus, we decided to adopt a novel approach on the subject and divide the SS patients according to the presence of dental implants.

Any patient receiving dental implants should previously follow a rigorous preparation for the insertion of the implants, mainly focusing on the efficient and stable reduction of dental biofilm [19].

This often implies the adoption of professional mechanical dental plaque removal, treatment of dental carries and elimination of other local elements that could increase the retention of dental biofilm (such as old dental bridges or fillings) [19,20].

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In addition, patients that are to receive dental implants need to adopt rigorous at-home oral health instructions, that should lead to a good reduction of biofilm accumulation and to an improvement of their oral health status [20].

After the reduction of biofilm accumulation and consequent gingival inflammation, the patient is ready to undergo oral dental implant insertion surgery.

This increases the chances of implant therapy success on the long term and a predictable result of the implant-supported prosthesis [21].

Given these premises, we considered that SS patients with dental implants most likely have followed this protocol and they were under constant monitoring by their dental team.

Moreover, the study of dental implants in SS patients has revealed that implant therapy is completely advisable in SS patients, offering acceptable success rates, comparable to healthy controls and that the majority of SS patients that have received dental implants were satisfied with the result and would certainly recommend this type of dental treatment to other [22,23].

Thus, the design of our study would generate results revealing that, even if, having an initial baseline negative oral health status, in the scenario of receiving dental implants and the proper pre-operative and post-operative care that this therapy requires, SS patients would be able to correct their oral health status and improve it close to that of non-SS patients.

In other words, the oral and periodontal health drawbacks generated by SS would be surpassed by proper professional and domestic dental care.

In our study, the periodontal status of SSni patients was significantly different to that of SSi patients and healthy controls.

The dental plaque levels (PLQ) were significantly higher in the SSni group (61%), compared to controls (27,4%), the difference being statistically significant.

In other studies, patients with SS also exhibited elevated dental biofilms levels [24,25].

This is mainly caused by the reduced salivary flow, which disrupts the normal self-cleaning capabilities of saliva and favours the accumulation of large food debrides, the first step of the development of dental biofilm.

Consequently, even with a good two times per day brushing habit, patients with SS are confronted with an increased accumulation of plaque deposits, between the two regular dental brushing moments [26].

Thus, the accumulation and maturation of dental plaque leads to the development of biofilm, which is cause of gingival and periodontal inflammation.

An early indicator of gingival inflammation is gingival bleeding on probing (BOP), which in SSni patients was significantly more elevated than in controls (43% to 15,1%).

This increase in gingival bleeding in SS patients was also highlighted by other studies [27].

If left untreated, ideally from first signs of gingival bleeding, periodontal disease increases its extent and severity, leading to periodontal pocket formation and loss of gingival attachment.

SSni patients exhibited significantly increased periodontal pocket depth (PPD) and gingival attachment loss (CAL), compared to controls, suggesting the development of a more severe and extended periodontitis than in controls.

Thus, more SSni patients were diagnosed with Stage 3 or 4 periodontitis (41,1%) than controls (17,6%).

Given the negative change of key periodontal parameters in SS patients (such as increased CAL) [28], other similar studies have concluded that there is a 2.2 times increased risk of periodontitis in patients with SS [29].

The clinical assessment was significantly different for the SS patients with dental implants. In these patients, we found significantly lower values for all assessed parameters (PLQ, BOP, PPD and CAL) than in SS patients with no dental implants.

This significant decrease suggests that, as hypothesized, the oral and periodontal health of SS patients had much improved when being closely monitored and cared after, as in the case of patients that are to follow implant therapy.

Studies focusing on dental implants in SS patients have shown that bone level surrounding implants is stable, despite the lower salivary flow and that the therapy led to a significant improvement of the patient's life quality, by reestablishing their normal masticatory and physiognomic functions [30].

With only 3% complication rate of dental implants in SS patients [22], this therapy is highly recommended, the majority of SS patients receiving the implants being completely satisfied with the result [23].

In addition to these benefits, the assessed periodontal parameters were no longer statistically different between SS patients with dental implants and controls, suggesting a normalization of their periodontal status and improvement of periodontal health, close to that of the general population.

The GCF IL-6 levels were highest in the SSni group, the differences to the other groups being statically different.

In the SS group with dental implants, the clinical improvement of the periodontal status was also highlighted by the immunological evaluation of the GCF IL-6 level, which was not statistically different to that of the control groups.

Thus, the clinical reduction of the periodontal inflammation is generated by the normalization of the GCF IL-6 level.

This finding is significant as IL-6 is a key pro-inflammatory marker for the onset and evolution of periodontitis, controlling bone resorption mechanism by osteoclast activation [31].

IL-6 has also implications in the pathogenic process of SS, as elevated levels of this cytokine have been found in saliva samples of primary SS patients [31].

Our results are also supported by other papers, suggesting that as an end-stage effector cytokine, IL-6 could mediate the pathogenic association between SS and periodontitis [32].

In this aspect, IL-6 GCF levels exhibited moderate correlations with PLQ and PPD levels in patients with periodontitis and SS, suggesting a cause-effect relationship between high biofilm accumulation, IL-6 mediated inflammation and periodontal pocket formation [33].

Thus, GCF IL-6 levels could be useful tool for monitoring the evolution of periodontal inflammatory reaction in patients with SS [31].

Despite the encouraging output, our study was limited by the relatively small sample size and lack of follow-up.

Given the short time span available for the implementation of this study and the numerous exclusion criteria required in order to isolate the population of SS patients as best as possible, the sample size was reduced.

This was also generated by the requirement of implant therapy, which currently is still considered to be expensive and not widely available to the general population and particularly to patients with SS.

As patients with SS could also be confronted with other health problems, dental and periodontal issues could be easily overseen and generate low addressability of these patients to dental healthcare providers.

Nevertheless, our paper brings significant elements of novelty to the field and an innovative approach to the matter, by comparing SS patients with and without dental implants.

From our knowledge, this is the first study of its kind to this moment and it could open a new direction of research, while in the future dental implantology becomes more accessible to a wider part of the population.

Conclusions

Patients with SS show a less favorable periodontal status than controls without SS.

An improvement of periodontal status has been observed in SS patients receiving dental implants.

This illustrates the need of active and continuous dental and periodontal monitoring of SS patients, in order to reduce the risk of periodontal disease onset.

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Conflict of interests

None to declare.

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