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ORIGINAL RESEARCH

PRE-IMPLANTATION GINGIVAL STATE AS A PREDICTOR OF THE EARLY IMPLANT FAILURE: RETROSPECTIVE CASE-CONTROL STUDY

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ABSTRACT

Background: Dental implantation has emerged as a prominent alternative to traditional dental orthopedic approaches, however predicting and preventing implant failure remains a significant challenge.
Aim: To assess the gingival state at the pre-implantation stage to predict early implant failures in dental implantation patients.
Material and methods: This retrospective case-control study involved 138 patients, of whom 124 were included in the analysis set: ages 35-60, with a bounded edentulous space, satisfactory oral hygiene, and informed consent. Patients with acute inflammation, generalized chronic periodontitis, severe systemic pathology, or smokers were excluded. Gingival biopsies were collected pre-implantation, fixed in formalin, and analyzed using histological and immunohistochemical (IHC) methods. The primary antibodies used included CD3, CD20, TBX21, GATA3, Foxp3, CD68, CD80, and CD163. Statistical analysis was conducted using descriptive statistics, Chi-Square Test, and Mann-Whitney U Test.
Results:During the one-year follow-up, signs of early implant failure were observed in 21 out of 124 patients (16.9%). Histopathological analysis revealed inflammatory changes in 18 out of 103 control group patients (17.5%) and 14 out of 21 case group patients (66.7%) ($P < 0.001$). IHC analysis showed a predominance of CD3+ cells, particularly Th1 cells, and a significant portion of macrophages, mainly from the M2 subpopulation, in the case group. These findings suggest a pro-inflammatory immune response in patients with implant failure.
Conclusion: The pre-implantation gingival state can be a valuable predictor of the early implant failure. A predominance of T-cells, especially Th1 cells, along with a significant presence of macrophages, can indicate a higher risk for developing implant failure due to inflammatory background and affected bone remodelling. Understanding and addressing gingival inflammation before implantation can help minimize complications and improve implant success. Further research is needed to explore these inflammatory mechanisms and develop targeted prevention strategies.

Keywords: gingiva, inflammation, dental implant, periodontal disease, implant failure

INTRODUCTION

Over the past decades, dental implantation has become a prominent alternative to various dental orthopedic approaches. Numerous clinical studies have shown that dentition restoration using implants has a favorable long-term prognosis with high rates of osseointegration[1,2]. However, unresolved issues persist, especially regarding the prediction and prevention of peri-implantitis and implant rejection. Early implant rejection is often linked to factors like alveolar bone quality, surgical trauma, bacterial contamination, and systemic diseases such as diabetes mellitus or metabolic syndrome[3]. A significant factor is a history of periodontitis, which can lead to chronic inflammation in the periodontal tissues and complicate dental implantation. Reactivation of inflammation during surgery can cause peri-implantitis, reducing successful osseointegration [4,5]. Peri-implantitis occurs in about 30% of dental implants and affects up to 20% of patients[6]. Treatment outcomes for peri-implant inflammation are unpredictable, with success rates ranging from 0% to 100% in patients and 75% to 93% in dental implants over 12 months [7]. The search for markers to predict implant failure and peri-implantitis risk and effective adjuvant therapies to prevent complications is crucial. Understanding mechanisms of implant failure is a key to developing early diagnosis criteria. Given the potential link between periodontitis history and implant failure / peri-implantitis, studying gingival characteristics before implantation is of great importance. Therefore, this retrospective study aimed to assess the gingival state at the pre-implantation stage using histopathological and immunophenotyping analysis to predict early implant failure in dental implantation patients.

MATERIALS AND METHODS

Study Design and Participants: This retrospective case-control study was conducted to evaluate the gingival state as a predictor of early implant failure. The study involved analyzing the results of gingival biopsies taken at the pre-implantation stage in the area of the bounded edentulous space. The inclusion criteria were: age between 35 and 60 years; presence of a single or combined bounded edentulous space on the upper or lower jaw (partial absence of teeth [partial secondary adentia]); satisfactory state of oral hygiene; and signed informed consent form. Patients were excluded if they had an acute inflammatory process in the area of surgical intervention, generalized chronic periodontitis, severe systemic pathology, or if they were smokers.

Procedures: A total of 138 patients met the selection criteria, and 124 (aged 35 to 60 years, 50 women and 74 men) without any systemic diseases, with unilateral/bilateral missing teeth from 2022 to 2024 were included in the analysis set (Figure 1). Clinical and radiological images of the representative case are presented in Figure 2. After obtaining informed consent, a comprehensive assessment of the patients' dental status was performed. Following implant placement, patients were monitored for 1 year (follow-up period). The criteria for early implant failure and/or peri-implantitis development, based on recommendations from the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP), included: implant instability, pain, probing pocket depth (PPD) ≥ 6 mm, presence of bleeding on probing and/or pus discharge upon probing, and radiographic evidence of progressive bone loss around the implant [8]. The final sample size (n = 124) was determined by the total number of eligible patients who met the inclusion and exclusion criteria during the study period and for whom complete clinical and histopathological data were available. While no power analysis was conducted, the observed statistically significant differences between groups suggest that the sample size was adequate to detect meaningful differences in pre-implantation inflammatory markers.

Sample Collection and Histological Analysis: All diagnostic and therapeutic procedures, including biopsies, were conducted from January 2023 to January 2024. All biopsy samples from both case and control groups were collected, processed, and analyzed using identical protocols. Gingival biopsy samples (~2x2 mm) were fixed in neutral buffered 10% formalin for 24 to 48 hours, followed by histological processing. Sections (~3-4 μm) were prepared from paraffin-embedded blocks and stained with hematoxylin and eosin (H&E) for descriptive histological analysis. For immunohistochemical (IHC) analysis, formalin-fixed, paraffin-embedded sections (~4 μm) were stained using a BondMax Semi-automatic Immunohistainer (Leica Biosystems, Germany). The primary antibodies used included CD3, CD20, TBX21 (T-bet), GATA3, Foxp3, CD68, CD80, and CD163 (Affinity Biosciences®). Histological slides were scanned with an Aperio CS2 Histoscanner (Leica Biosystems, Germany) and analyzed using Aperio ImageScope and ImageJ software [9]. Quantitative analysis of immunopositive cells was performed on 3 to 5 high-power fields (HPF) per each slide.

Statistical Analysis: Statistical analysis, including baseline demographic and clinical history data, was conducted using descriptive statistics with Statistica software (Version 10, StatSoft, Inc.). Comparative analyses between the case and control groups were performed using the Chi-Square Test and Mann-Whitney U-Test. Data completeness was ensured during the retrospective review of clinical data and histological assessment. Only patients with fully documented clinical

records and complete histological and immunohistochemical analyses were included in the study. As a result, no imputation methods were required, and all statistical analyses were conducted on complete cases only.

Bias Minimization: To minimize selection bias, strict inclusion and exclusion criteria were applied uniformly to all participants, and patient recruitment was based on pre-defined parameters before implantation. Information bias was reduced by using standardized protocols for sample collection, processing, and immunohistochemical staining, with all analyses performed by trained pathologist blinded to case/control status. Additionally, data analysis was conducted using consistent statistical methods to avoid analytical bias.

Ethical Considerations: The study adhered to the principles of the Declaration of Helsinki and the protocol was approved by the Institutional Ethical Committee (No. AAAA-A20-120061990017-6). To maintain confidentiality, all personal data of patients were anonymized. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case-control studies.

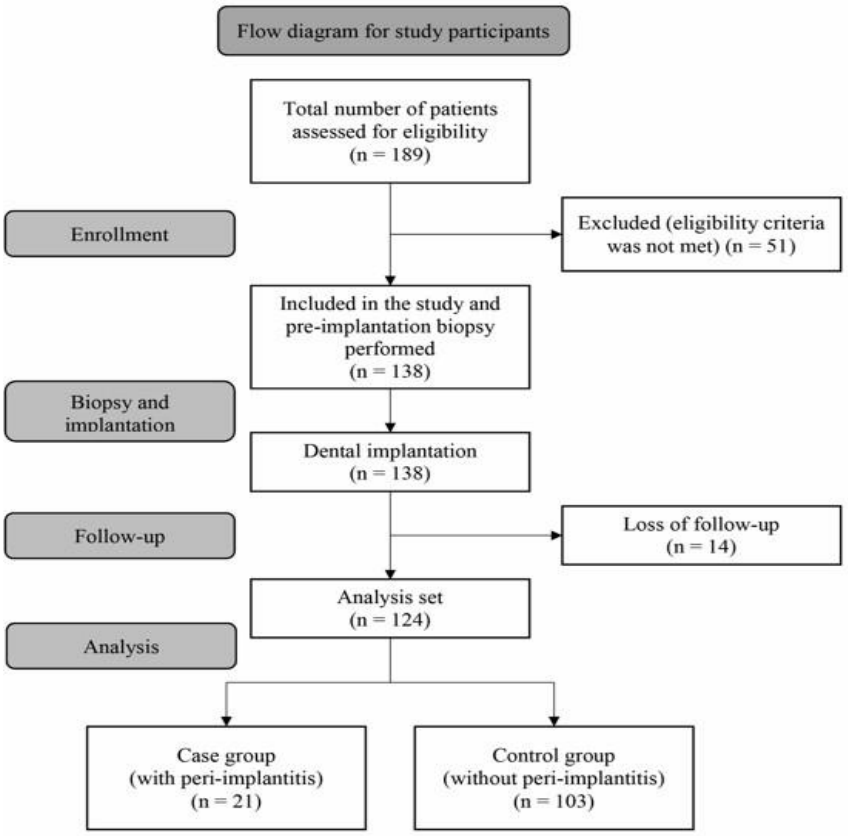


Figure 1 – Flow diagram for study participants

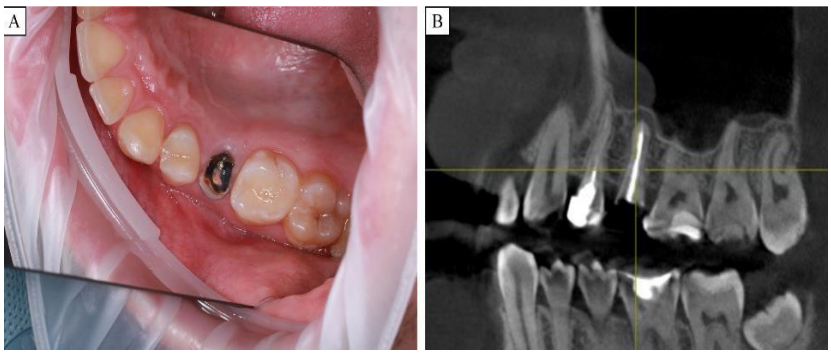


Figure 2. Representative clinical (A) and radiological (B) images before tooth extraction (female, 36 years old). Biopsy was made 2 months after tooth extraction at the pre-implantation stage.

RESULTS

During the 1-year follow-up, signs of implant failure according to clinical and radiological criteria were observed in 21 out of 124 patients (16.9%). The time period from implant placement ranged from 1 to 12 months. A summary of baseline demographic and clinical anamnestic data for patients in the control and case groups is presented in Table 1. Most baseline characteristics were comparable between the groups, except for older age in the case group.

Table 1. Baseline demographic and clinical anamnestic data for patients included in the retrospective study (analysis set)

Baseline demographic and clinical anamnestic parameters	Control group (n = 103)	Case group (n = 21)
Age†	46 [41; 52.5]	55 [47; 59]*
Gender		
Male	61 (59.2%)	13 (61.9%)
Female	42 (40.8%)	8 (38.1%)
Race and ethnicity		
Caucasian	90 (87.4%)	20 (95.2%)
Asian (Crimean Tatars)	13 (12.6%)	1 (4.8%)
Localization of the bounded edentulous space (biopsy area)		
Upper jaw	67 (65.0%)	12 (57.1%)
Lower jaw	36 (35.0%)	9 (42.9%)
Median time since tooth loss (tooth extraction)		
≤ 2 months	23 (22.3%)	5 (23.8%)
≥ 2 months to < 1 year	30 (29.1%)	7 (33.4%)
≥ 1 year to < 2 years	15 (14.6%)	3 (14.3%)
≥ 2 years to < 5 years	25 (24.3%)	4 (19.0%)
≥ 5 years	10 (9.7%)	2 (9.5%)

Notes: † – the data presented as median and values of 1st and 3rd quartiles; * – statistically significant difference vs control group ($p < 0.05$).

All variables of interest, including baseline demographic data and immunohistochemical markers, were available for all 124 patients included in the final analysis set. No missing data were recorded for any of the measured clinical or histopathological variables. The most common histopathological findings in the gingival biopsy samples included changes in the stratified squamous epithelium, observed in 76 out of 103 control samples (73.8%) and 16 out of 21 case samples (76.2%) ($p > 0.05$). These changes encompassed hyperkeratosis, dyskeratosis, and parakeratosis. Histological analysis of biopsy samples obtained during the pre-implantation stage revealed pronounced signs of an inflammatory reaction in the gingival connective tissue in 18 out of 103 control group patients (17.5%) and 14 out of 21 case group patients (66.7%) ($P < 0.001$). The inflammatory reaction in the underlying connective tissue was characterized by focal or diffuse inflammatory infiltrate with changes in the microvasculature, including plethora, microthrombi, and small foci of hemorrhages (Figure 3).

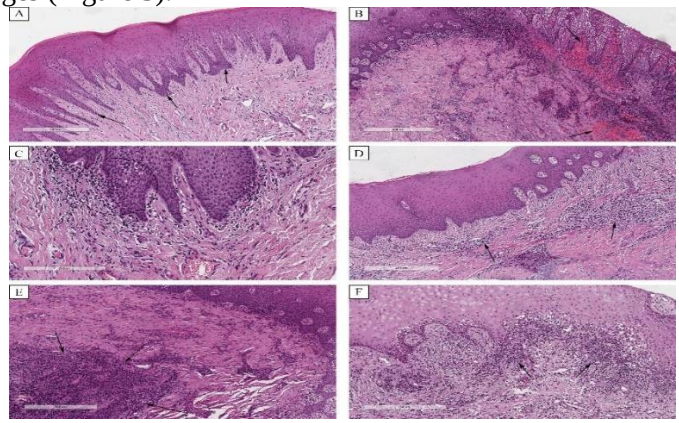
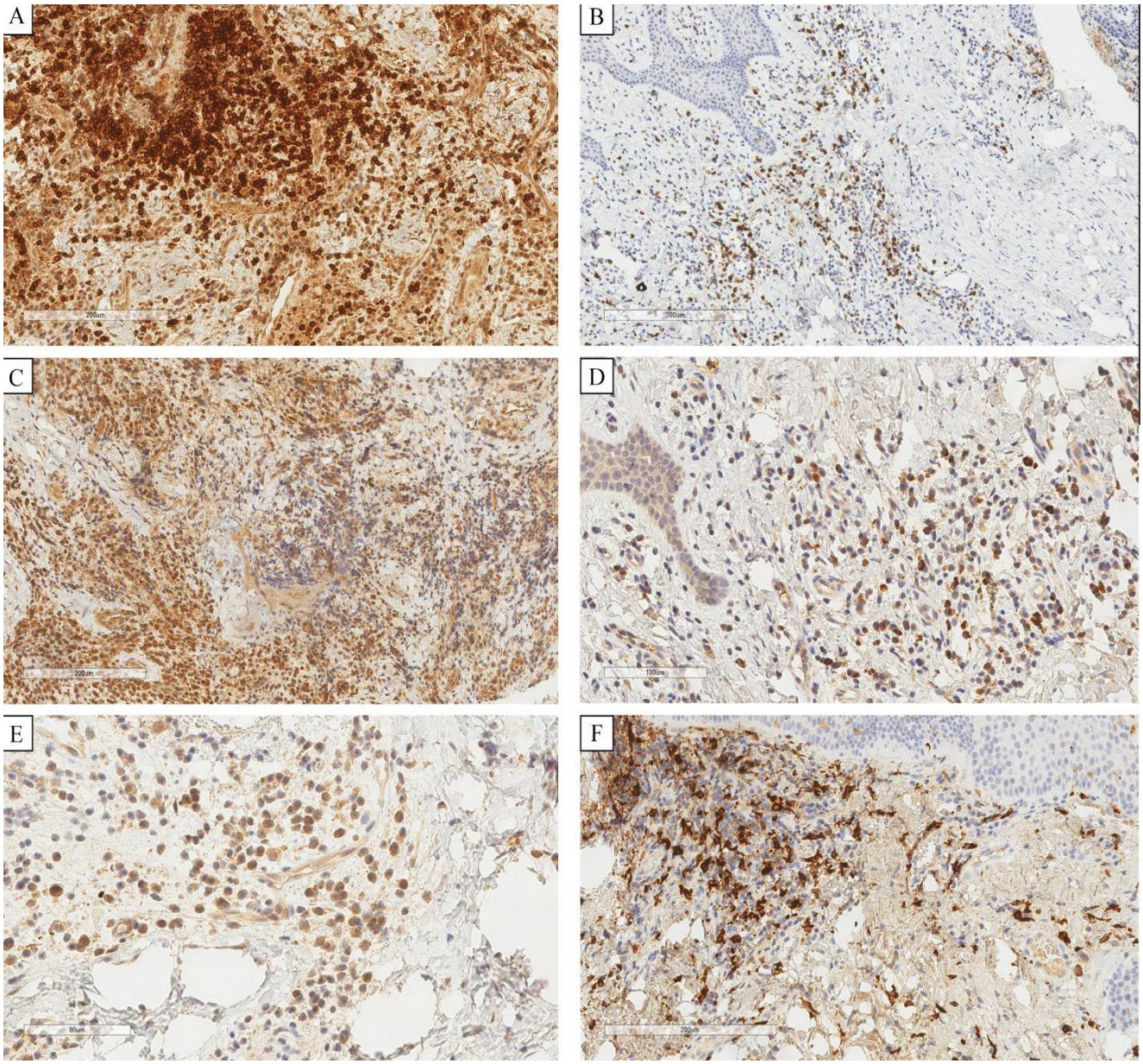


Figure 3.Gingival biopsy samples, H&E. (A) Moderate features of hyperkeratosis and acanthosis (arrows) with no inflammatory changes (control group); (B) Pronounced inflammatory reaction with foci of hemorrhages (arrows) (case group); (C) Active migration of lymphocytes into epithelial layer (dotted area) (case group); (D) Moderate mixed lymphohistiocytic inflammatory infiltration (arrows) in superficial layer of gingival connective tissue (case group); (E) Massive focal inflammatory infiltration (arrows) (case group); (F) Massive subepithelial diffuse inflammatory infiltration (arrows) (case group).

Immunohistochemical (IHC) analysis revealed a predominance of CD3+ cells with a strong membrane immunopositive reaction within dense focal or diffuse subepithelial accumulations (Fig. 4A), along with a relatively small to moderate quantity of CD20+ cells (Fig. 4B). The distribution of T-cell subpopulations in the inflammatory infiltrate showed a significant predominance of Th1 cells (TBX21+ cells) (Fig. 4C) and a significantly smaller number of Th2 (GATA3+) and regulatory T-cells (Foxp3+). The mixed cellular infiltrate in biopsy samples also included cells of macrophageal origin (CD68+), constituting approximately one third of the total inflammatory cell population (Fig. 4D). Immunopositive CD68+ cells with pronounced cytoplasmic expression were significantly more prevalent in areas of T-cell infiltration. IHC analysis of the polarization of macrophageal lineage into M1 (CD80+) and M2 (CD163+) cells revealed a uniform predominance of M2 macrophages. IHC expression of the CD80 marker in the inflammatory infiltrate cells was minimal to low, with only isolated clusters of CD80+ cells exhibiting moderate cytoplasmic expression in the deep layers of the gingival connective tissue (Fig. 4E). In contrast, the vast majority of macrophageal cells with typical morphological features were represented by CD163+ cell elements. These cells were localized singly or in groups, in close association with both lymphoid and epithelial cells, and in some cases, even penetrated the basal layers of the epithelium (Fig. 4F).



A quantitative comparison of the IHC analysis results in biopsy samples from the control and case groups is presented in Table 2.

Table 2. Mean number of immunopositive cells per HPF in the control and case groups (analysis set)

Group	CD3	CD20	TBX21	GATA3	Foxp3	CD68	CD80	CD163
Control group (n=103)	15.34 ±3.72	16.23 ±5.50	4.18 ±1.91	1.87 ±0.67	5.92 ±2.30	8.04 ±1.11	1.65 ±0.50	6.13 ±2.69
Case group (n=21)	67.60 ±7.97*	21.03 ±4.55	23.19 ±2.12*	2.19 ±0.40	11.76 ±4.41	19.52 ±3.01*	8.89 ±1.58*	17.39 ±2.92*

Notes: * – statistically significant difference vs control group ($p < 0.05$).

Due to the limited sample size and the retrospective nature of the study, multivariable adjustment was not performed. However, unadjusted group comparisons showed robust significance (e.g., CD3+ cells: 67.60 ± 7.97 in cases vs. 15.34 ± 3.72 in controls, $p < 0.05$). Age was noted to differ between groups and may represent a potential confounder. No categorization of continuous variables was performed; thus, category boundaries were not applicable.

DISCUSSION

The presented data, including descriptive histological analysis and results of immunohistochemical (IHC) studies, expand the existing understanding of the condition of the gingiva in areas of the bounded edentulous space at the pre-implantation stage. Among other identified histopathological changes, special attention should be paid to biopsy samples characterized by varying degrees of inflammatory changes in the underlying gingival connective tissue, which helped identify key players in the intercellular interaction system under persistent periodontal damage conditions.

Baseline demographic and clinical anamnestic data were generally similar between the control and case groups. In the case group, analysis showed that in 12 out of 21 cases (57.1%), tooth loss occurred ≤ 1 year ago, which may be crucial in the persistence of gingival inflammatory changes given a history of compromised periodontal tissues. Additionally, in 7 out of 21 cases (33.3%), tooth loss occurred between 1 to 5 years ago, and in 2 cases (9.5%) more than 5 years ago, indicating the possibility of prolonged inflammatory reaction persistence.

The most notable observation was the significantly greater number of gingival inflammatory reactions identified in the study groups (18 out of 103 in the control group [17.5%] and 14 out of 21 in the case group [66.7%]). Statistically significant immunophenotypic differences between the groups included an increase in T-cells (CD3+), mainly due to Th1 cells, as well as macrophages (including M1 and M2 macrophages). The presented morphological criteria using biopsy samples at the pre-implantation stage can be regarded as possible predictors of complicated dental implantation and the development of early implant failure. However, the reason for the presence of inflammatory changes in the gingival biopsies remains unclear and requires further investigation.

Direct comparison of the obtained results with other studies is limited due to the lack of morphological studies based on biopsy material from the edentulous area at the pre-implantation stage. However, the identified morphological features, with a predominance of mixed lymphohistiocytic infiltrate in the gingival connective tissue, support a chronic inflammatory process comparable to chronic periodontitis. The predominance of T-cells (CD3+) in the inflammatory infiltrate is consistent with other studies of periodontal tissues in various subpopulations [10]. These data align with the accepted concept of the leading role of T-cells in local immune responses against dysbiosis in periodontal tissues [11,12], suggesting similar mechanisms in the persistence of inflammation after tooth extraction. Additionally, the significant predominance of Th1 cells (TBX21+), with relatively few Treg cells and almost no Th2 cells, indicates a predominantly pro-inflammatory immune response in the studied gingival biopsy samples. This observation is supported by both experimental and clinical studies demonstrating the leading role of Th1 cells as orchestrators of the proinflammatory response [13, 14]. However, Th17 cells, considered significant in periodontal tissue damage development, were not studied in this analysis [15].

Regarding the B-cell component, which was invariably present in all cases with inflammatory infiltrate, available data indicate it as an unfavorable prognostic factor for further periodontal tissue damage and alveolar bone resorption. Experimental studies have shown that the B-cell component mostly mediates osteoclast activation [16, 17] through TNFα and RANKL expression [18,19]. B-cells may also act as antigen-presenting cells, mediating immune response induction even without traditional antigen-presenting cells like macrophages or dendritic cells [20]. This is supported by clinical studies showing increased CD20+ cells in inflammatory infiltrate during aggressive chronic periodontitis [21].

Macrophageal cells (CD68+) were a constant component of the mixed inflammatory infiltrate, comprising up to one third of the total cell population in the samples.

Notably, the polarization of macrophageal subpopulations showed a significant quantitative predominance and more pronounced IHC expression of the M2 macrophageal marker (CD163+). This diversion of subpopulations is a key factor in periodontal tissue damage progression due to different modalities of pro- and anti-inflammatory cytokine secretion, including IL-1β and various metalloproteinases. M1 macrophages primarily act as pro-inflammatory agents, while M2 macrophages contribute to inflammation resolution, tissue regeneration, and remodeling [22]. The predominance of the M2 subpopulation (CD163+) in the biopsy samples aligns with the concept of chronic inflammation persistence in gums after tooth loss, acting as a balancing factor against pro-inflammatory Th1 cells. These findings are consistent with clinical studies of gingival biopsies from patients with gingivitis and periodontitis, showing a shift towards the M1 subpopulation (CD80+) as periodontal tissue damage progresses [23]. Similar results were shown in the study by Galárraga-Vinueza et al. (2021), demonstrating the significant role of the M1 inflammatory phenotype in peri-implantitis progression [24]. However, these findings should be interpreted cautiously, considering the lack of absolute specificity of IHC markers and the possibility of co-expression and transdifferentiation of cell subpopulations.

Taken together, the pro-inflammatory nature of the local immune response, with a predominance of Th1 cells, a significant portion of B-cells, and a shift towards less tolerogenic dendritic cells, raises the question of the need for highly informative markers, including morphological markers based on biopsy, to predict the risks of developing dental implantation complications. The presence of inflammation in gingival tissue may act as a significant risk factor for peri-implantitis. Despite the fact that in 12 out of 21 cases tooth loss occurred less than 1 year ago, indicating the persistence of gingival inflammatory changes, the time factor may not be crucial. Clinical studies have shown statistically significant differences in dental implantation complications, implant survival, and alveolar bone atrophy between patients with and without a history of periodontitis [25, 26]. This study suggests the potential for persistent gingival inflammation after tooth extraction and local periodontitis and highlights the need for further research to understand local immune response patterns, identify prognostic factors, and adjust management tactics to minimize dental implantation complications.

This study has several limitations that should be acknowledged. First, its retrospective case-control design limits the ability to establish causal relationships between pre-implantation gingival inflammation and the development of early implant failure.

Second, the relatively small number of patients in the case group (n = 21) may limit the generalizability of the findings and reduce statistical power for subgroup analyses. Third, potential confounding variables, such as undiagnosed systemic inflammatory conditions, variations in oral hygiene practices over time, and dietary habits, were not assessed. Additionally, while immunohistochemical analysis provided insights into the local immune cell composition, other important immune pathways, such as Th17-mediated responses, were not evaluated and may play a role in peri-implant osteointegration and inflammatory response. Finally, long-term follow-up beyond 12 months was not conducted, and the temporal persistence of the observed inflammatory markers remains unknown.

The findings of this study should be interpreted with caution regarding generalisability. The sample included patients with specific inclusion criteria (e.g., non-smokers, with no severe systemic diseases), which may not reflect the broader population undergoing dental implantation. Furthermore, the relatively small number of cases (n = 21) limits the ability to generalize results across different clinical contexts or populations with varying risk factors. Despite these limitations, the immunohistochemical markers identified may have broader relevance and should be validated in larger, more diverse prospective cohorts.

CONCLUSION

Based on the results of this retrospective case-control study, it was revealed that the persistence of gingival inflammation at the pre-implantation stage is significantly more common among patients who develop early implant failure. When comparing the study groups, possible predictors include the predominance of T-cells, particularly a shift towards pro-inflammatory Th1 cells, with fewer Treg cells and almost no Th2 cells. The mixed inflammatory infiltrate also featured a significant portion of macrophages, primarily from the M2 subpopulation.

The pre-implantation gingival state can be considered a valuable predictor of early implant failure. Understanding and addressing the inflammatory status of the gingiva before dental implantation can help minimize complications and enhance the longevity and success of dental implants. Further research is warranted to explore the mechanisms underlying these inflammatory processes and to develop targeted strategies for prevention and management.

DECLARATIONS

Authors' contributions

SIZ and IGR conceived and designed the study. ASK and OAN enrolled patients and performed diagnostic and treatment procedures. MAK conducted the descriptive histological and immunohistochemical analyses. ASK, OAN, SKS, and MAK analyzed the data and edited the

manuscript. ASK, OAN, IGR, and MAK wrote the article. All authors read, reviewed, and approved the final manuscript before submission.

Acknowledgement

None

Ethics

The study adhered to the principles of the Declaration of Helsinki and the protocol was approved by the Institutional Ethical Committee (No. AAAA-A20-120061990017-6). To maintain confidentiality, all personal data of patients were anonymized.

Data Availability Statement

The data used and/or analyzed during the current study are available from the corresponding author.

Source of funding

None

Conflict of interest

The authors have no conflicts of interest to declare.

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