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The role of the immune system in the formation and development of diseases of the oral cavity

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Abstract

Aims: the goals were to clarify immune mechanisms involved in the pathogenesis of oral diseases, as well as to identify biomarkers of disease severity, to assess the impacts of environmental factors on immune responses, and to explore immune-modulating therapeutic interventions.

Study design: a narrative literature review.

Place and Duration of Study: from 2019 to 2022.

Methodology: a narrative review using the keywords "Immune System AND Oral Cavity" identified 15,438 studies on PubMed. Refinement excluded articles published before 2019 or after 2022, and those that were not trials or studies, resulting in a total of 41 articles. Following assessment, 15 only highly relevant articles were included into the review.

Results: This narrative review has explored the involvement of the immune system in the development and progression of oral diseases. The key lessons were shown through the underlying mechanisms consisting of inflammatory mediators in the cases of oral graft-versus-host disease and oral lichen planus and the progression of oral cells cancer. The research uncovered the impact of the immune system on conditions such as periodontitis, highlighting the potential predictive utility of oral biomarkers in diagnosing disease progression and metastasis. Also, the modulation of the immune response was shown to be another possible approach for patient management in oral health field, thereby, facilitating new strategies. As a whole, these findings shed light on the massive body of targeted research into the specific immune pathways. This underscored the necessity for developing interventions that navigate the intricate interplay between the immune system and oral diseases.

Conclusion: The narrative review illustrated that the immune system is dual faced in the oral cavity, being a factor that influences the final outcome without excluding the significance of other factors. It was established that distinct immunological profiles exist for numerous oral disorders, where the factors like IFN-γ and TNF can be taken as biomarkers for diagnosis and therapy.

Keywords: mouth diseases, oral health, inflammation, autoimmune diseases of the mouth, microbial interactions.

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Introduction

The oral cavity, as the initial segment of the digestive tract, facilitates the processes of chewing and tasting, in addition to the breakdown of food within the body. It possesses an extraordinary anatomical shape, especially by its inner structure, the oral mucosa. This layer is constituted by stratified epithelial cells which unlike the monolayer structure with single columnar cells also include multiple layers of squamous epithelial cells covering the lamina

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propria. The thickness of keratin depends on the region or function of the mucosa in the palate, which has exposed surfaces, there is a thick layer of keratin to prevent mechanical damage created by chewing [1, 2].

The oral mucosa, home to over 700 species of commensal organisms, is exposed to frequent inflammatory stimuli. However, acute inflammation is uncommon in healthy individuals due to protective immune mechanisms. The immune privilege has an advantage in mucosa, and these are mediated by the immunosuppressive cytokines and T regulatory cells so as to avoid the responses of the immune system to inert antigens. The immune system is sustained by Waldeyer's ring as well as by numerous lymphoid tissues sites that serve for direct involvement and organisational form of the immune responses, the conservation of mucosal homeostasis [3]. In the oral cavity different types of stratified epithelia are located including the non-keratinized epithelium in the sub-lingual and buccal places and the extremely keratinized epithelium called gingiva. The disparity of the mucosal barrier structure leads to Th17 cells' activation as the result of mechanical blow which mastication causes [4, 5].

The primary issue in periodontal disease, primarily caused by bacterial infections in the oral cavity, manifests as gingival inflammation and periodontitis, both inflammatory conditions. The recognition of the immune and inflammatory mechanisms carried out in these diseases is essential in understanding their etiology. This perception served as the cornerstone for the given research into the immune reactions that instigate and enable the progression of the clinical condition recognized as periodontal disease [6, 7].

Aside from the well-known association of periodontitis with chronic diseases like cardiovascular and neurodegenerative disorders, as well as autoimmune and cancer diseases, epidemiology shows the importance of oral health as a component of overall health and wellness. Interventional studies indicate that the treatment for periodontitis, periodontitis is a chronic condition, can restore the abnormal markers that often accompany these comorbidities. Animal research has led the way to a biologically acceptable mechanism that might cooperate with or make other systemic diseases in these cases, periodontal disease. This paper is about the 'mechanisms of causality' studied through the pathway of systemic inflammation from periodontitis, other oral pathogens, and the way these might interact with cardiovascular disease. The identification of these correlations provides access to new treatment strategy aimed at reducing the risks induced by periodontal disease comorbidities [8].

Periodontitis, as an inflammatory disease, is very harmful to the oral health, which is indirectly related to the general health since it is caused by the bad interaction between plaque and the host's immune system. The disease process is started by activation of innate immunity when pathogens invade the periodontium and interact with the molecules of the periodontal tissue. An exaggerated reaction of this system can culminate in an inflammatory response from which the subsequent destruction of periodontal tissue is reproduced, which then triggers the adaptive immune response [9–11].

The immunity of the oral cavity, in particular, is a complex system of many innate and adaptive resources. Consequently, the host reaction influenced both supra- and subgingival biofilm accumulation can be either protective, maintaining a healthy balance and thus, preserving tissue homeostasis without repeated periodontal destructions to inflamed tissues, or it can become detrimental. In short, the immunological dysregulation may re-arrange the biofilm structure leading to the expansion of the pathogenic bacteria. This transformation amplifies the host immune reaction, establishing the offensive/ defensive cycle continuing tissue destruction and persistence of a chronically altered organism [12, 13].

Cytokines are a molecule composed of proteins that are consisted of the body to maintain tissue homeostasis and inflammatory processes and thus serving as the first players in the body's response to pathogens [14]. These molecules are the interface that allows tissues to enter in a dynamic relationship with the diverse types of lymphocytes and helper cell populations. The immunoinflammatory imbalance, which is a predisposing factor for periodontitis, leads to both local and systemic inflammation. Although many studies analysed the molecular mechanism of periodontitis on disturbance in the humoral system of the body, there is still a lack of comprehensive information on the changes in tissue at the cellular level. By novel pathogenesis mechanisms of periodontitis being investigated and the related molecular abnormalities being traced through the analysis of protein interaction and targeted regulation, this study aimed to disclose new pathogenic mechanisms and the immune related gene abnormalities in order to provide accurate evidence for further clinical treatment [15].

Periodontal disease, a type of disease that is progressive in nature and leads to the loss of the tissues that support the teeth, is the result of a complex interplay between dysbiosis, the increased pathogenic nature of the microbial community, and exaggerated immune response. This activation promotes an iterative loop involving proteolysis, inflammation, and multiplication of harmful microorganisms [16].

A genome-wide association study was undertaken with at least 2 million subjects enrolling as a result. Among the 5 million known markers SNPs (single nucleotide polymorphisms) were identified and assigned only to certain periodontal complex traits - microbial communities and interleukin-1β levels. These SNPs, the genetic variants in the genes modifying the immune response, colonization of microorganisms, and the permeability of epithelial cells as well are a link to different biological mechanisms that despite their claimed pathways lead to similar results of

damage to the periodontium tissue. However, the existence of mutations in the genes coding for inflammasome components, particularly those for IFI16 and AIM, increases the chances of the individual developing severe periodontitis, thus demonstrating that inflammasomes are capable of inducing IL-1β release. The development of personalized treatment approaches in oral health could be achieved by such understanding of human genetic variations [17].

The immune system is definitely the important component of the progression and protection against oral diseases, such as oral cancer whereby sometimes inflammation may be the weapon against tumor development and also be a friend of the tumor growth and metastasis at the same time. The immune response is another factor which comes to play in the interaction of the immune system and the oral microbiome, as have been shown by the studies that immune responses can disrupt the balance of the oral microbiota raising diversity and incidence of oral diseases such as dental caries, periodontitis, and oral cancers. These conditions, pervasive in their occurrence, not only exhibit a high prevalence but also demonstrate a substantial association with chronic systemic illnesses such as cardiovascular disease and diabetes. Research activities in immunology are having a positive effect on providing highly targeted agents that of course, imply greater knowledge of these intricate immune interactions within the mouth. Such awareness can offer interdisciplinary synergy to develop innovative preventive and therapeutic approaches, which will minimize health costs and increase patient well-being through the collaborative efforts of healthcare providers, and eventually, oral and system health interdependence.

Research Problem

Despite recent advancements in dental science, oral diseases continue to pose significant global health challenges. This is due to complicated interrelations between the immune system and the oral microbiome. Immune dysregulation can result in symptoms such as periodontal disease where inflammation due to chronically disorder causes the atrophy of tissues and oral cancers, influenced by immune responses. The autoimmune illnesses such as Sjögren's Syndrome, where the immune system distributes the in health of the salivary glands, underscore the necessity of investigating ways to prevent the immune responses from becoming defective. In addition to that, systemic conditions like diabetes and HIV/AIDS, which highlight the mutuality of oral and general health conditions, can aggravate oral health problems even further. Understanding the role of these mechanisms is crucial for the development of drugs capable of enhancing immunity and promoting overall health.

Research Focus

This narrative review was designed to study and summaries previously conducted investigations on the immune system's participation in etiology and development of oral cavity diseases. It also critically analysed how immune responses are associated with such condition like periodontal disease, oral cancers, autoimmune diseases such as oral lichen planus by immune responses. In addition, it considered the effect of systemic inflammatory disorders and other systemic immunological disorders on oral health, and discourse on possible therapeutic approaches that used the immune system in the treatment and prevention of oral diseases.

Research Aim

1. To clarify how the immune system works in oral diseases.
2. To identify the immune markers that associate with disease intensity and progression of the infection in the oral cavity.
3. To assess the impact of environmental and behavioral factors (like smoking and diet) on the immune responses in the oral cavity.
4. To explore therapeutic interventions that can modulate the immune responses to treat or prevent oral diseases.

Research Questions

1. What specific immune mechanisms are involved in the pathogenesis of oral diseases?
2. Which immune biomarkers correlate with the disease severity and progression in the oral cavity?
3. How do environmental and behavioural factors, such as smoking and diet etc., impact the immune responses in the oral cavity?
4. What therapeutic interventions can modulate the immune responses to treat or prevent oral diseases?

Research Methodology

General Background

The oral cavity represents a complex ecosystem where microbiota, immune responses, and host tissues intricately interact. Given the diverse microbial presence, the immune system plays a pivotal role in maintaining oral health and preventing disease. It acts both as a defender against pathogenic invaders and, paradoxically, as a potential facilitator of pathological conditions when dysregulation occurs.

Diseases of the oral cavity, such as periodontitis, dental caries, oral cancers, and various mucosal conditions, illustrate the outcomes of host-microbe interactions that can shift from symbiotic to pathogenic under certain conditions. The immune system's ability to distinguish between benign and harmful entities, initiating appropriate responses, is central to oral health. Nonetheless, immune dysregulation can result in chronic inflammation, tissue damage, and the perpetuation of disease.

The role of innate and adaptive immunity, including the function of barriers such as saliva and mucosal linings, immune cells (e.g., macrophages, dendritic cells, T cells, B cells), and signaling molecules (e.g., cytokines, chemokines), is crucial in the pathogenesis and progression of oral diseases. Autoimmune responses, for example, are instrumental in conditions like Sjögren's syndrome and oral lichen planus, while hypersensitivity reactions are evident in allergic stomatitis.

This narrative review aimed to explore the dynamic interplay between the immune system and oral diseases, highlighting recent discoveries, theoretical frameworks, and potential therapeutic avenues. By synthesising current research and clinical findings, the review provided a comprehensive understanding of how immune responses, both protective and pathological, shape the landscape of oral health and disease.

Study Design

This was a narrative review of the literature from 2019 to 2022.

Search Strategy

To conduct a narrative review on "The role of the immune system in the formation and development of diseases of the oral cavity," a search was performed using the keywords "Immune System AND Oral Cavity" on PubMed.

Study Selection

Figure 1 shows the selection process. Initially, this search identified 15,438 studies. The selection process involved applying strict criteria to refine the studies: publications outside the 2019 to 2022 date range were excluded, resulting in the removal of 13,480 articles and leaving 1,958 articles for analysis. Next, 878 were excluded for not offering free full text, followed by an additional exclusion of 1,040 studies that were not clinical trials, observational studies, or RCTs, reducing the number to 41 eligible studies. Ultimately, only 15 highly relevant studies were included after a detailed assessment of their relevance and quality, ensuring the review focused on the most scientifically valid and accessible research related to how the immune system influences diseases in the oral cavity.

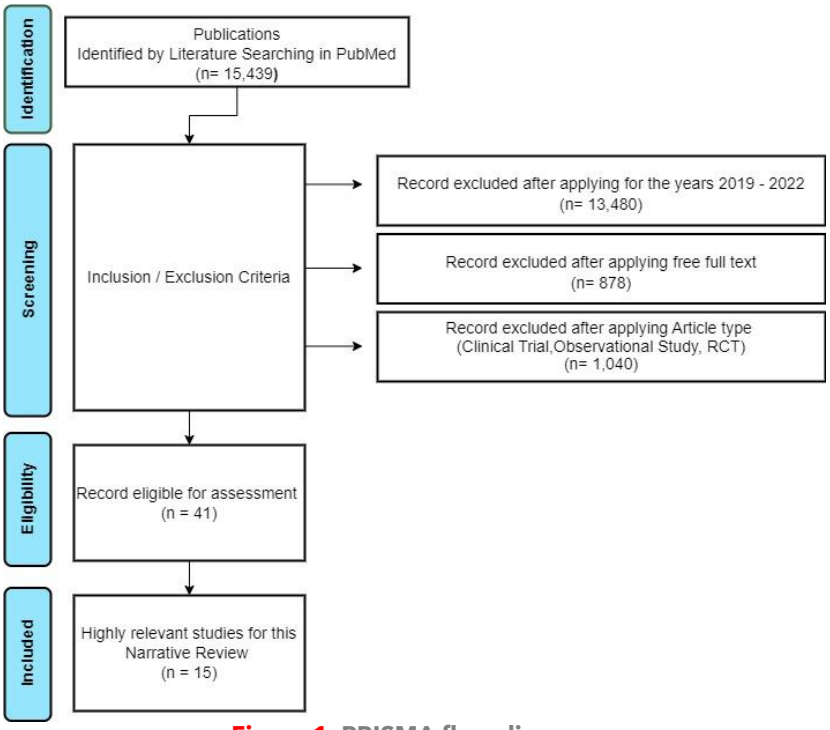

Figure 1. PRISMA flow diagram

Research Results

The narrative review on the role of the immune system in the formation and development of diseases of the oral cavity included several recent studies from 2019 to 2022. Observational studies by Pinto et al. [18] (8 participants, 2022), Dasgupta et al. [19] (122 participants, 2022), Barbieri et al. [20] (28 participants, 2022), Teófilo et al. [21] (60 participants, 2020), Shigeoka et al. [22] (24 participants, 2019), and Bi et al. [23] (57 participants, 2019) provide varied insights into immune responses in oral diseases. Experimental research is represented by Zhao et al. [24] (66 participants, 2022), Liu et al. [25] (12 participants, 2021), Zibandeh et al. [26] (11 participants, 2020), Xiong et al. [27] (10 participants, 2020), and Colares et al. [28] (22 participants, 2019), focusing on specific immune mechanisms. Prospective cohort studies by Piersiala et al. [29] (14 participants, 2021) and Adler et al. [30] (200 participants, 2020), along with retrospective cohort studies by Hung et al. [31] (993 participants, 2021) and Li et al. [32] (65 participants, 2020), additionally, include longitudinal perspectives on how immune factors influence oral health outcomes over time. This collection of studies underscored a robust and growing interest in deciphering the complex interactions between the immune system and oral diseases, ranging from small-scale focused experiments to large-scale observational and cohort studies.

Table 1. Study Characteristics

Author's	Study Design	Sample Size	Publication Year
Pinto et al. 2022 [18]	Observational study	8	2022
Dasgupta et al. 2022[19]	Observational study	122	2022
Barbieri et al. 2022 [20]	Observational study	28	2022
Zhao et al. 2022 [24]	Experimental study	66	2022
Liu et al. 2021 [25]	Experimental study	12	2021
Piersiala et al. 2021 [29]	Prospective cohort study	14	2021
Hung et al. 2021 [31]	Retrospective cohort study	993	2021
Zibandeh et al. 2020 [26]	Experimental study	11	2020
Teófilo et al. 2020 [21]	Observational study	60	2020
Adler et al. 2020 [30]	Prospective cohort study	200	2020
Xiong et al. 2020 [27]	Experimental study	10	2020
Li et al. 2020 [32]	Retrospective cohort study	65	2020
Shigeoka et al. 2019 [22]	Observational study	24	2019
Bi et al. 2019 [23]	Observational study	57	2019

Colares et al. 2019 [28]	Experimental study	22	2019

The narrative review provided a comprehensive overview of the interplay between the immune system and various oral diseases. Some studies illustrated how inflammatory mediators contributed to oral chronic GVHD [18], while other research highlighted the role of immune elements like tumor-infiltrating lymphocytes, PD-1 blockade, and T-cell dysregulation in the development of oral cancers such as HNSCC, OCSCC, and OSCC [19, 20, 25, 27, 29, 31, 32]. Additionally, few studies explored the Th1/Th2 imbalance in oral lichen planus, and while other addressed mast cell density and immunotolerance in conditions like oral epithelial dysplasia and tongue leukoplakia [21, 22, 24]. Studies on chronic periodontitis and tooth sensitivity discussed how T-helper cell polarisation and inflammation impacted these common oral conditions [23, 28]. Furthermore, immune responses to Group A Streptococcus in pharyngitis were examined, and the potential of mesenchymal stem cells in modulating immune responses was investigated, showcasing the diverse implications of immune function in oral health and disease [26, 30].

Table 2. Dysregulation of Immune System and Oral Diseases

Author's	Type of Immune Dysregulation	Type of Oral Disease
Pinto et al. 2022 [18]	Upregulation of inflammatory mediators	Oral chronic graft-versus-host disease (oGVHD)
Dasgupta et al. 2022[19]	Tumor-infiltrating lymphocytes	Head neck squamous cell carcinomas (HNSCC)
Barbieri et al. 2022 [20]	Decreased maturation of dendritic cells in smokers	Oral squamous cell carcinoma (OSCC)
Zhao et al. 2022 [24]	Th1/Th2 imbalance	Oral Lichen Planus (OLP)
Liu et al. 2021 [25]	PD-1 blockade in cancer	Oral cavity squamous cell carcinoma (OCSCC)
Piersiala et al. 2021 [29]	Dysregulation of T-cell activation and PD-1 expression in cancer	Oral squamous cell carcinoma (OSCC)
Hung et al. 2021 [31]	Systemic immune-inflammation (expressed through SII)	Oral cavity squamous cell carcinoma (OC-SCC)
Zibandeh et al. 2020 [26]	Overly aggressive T cell responses in CD	study involves Dental Follicle Mesenchymal Stem Cells (DF-MSCs) from healthy individuals
Teófilo et al. 2020 [21]	Lower mast cell density in OSCC	Oral squamous cell carcinoma (OSCC), oral epithelial dysplasia
Adler et al. 2020 [30]	Group A Streptococcus pharyngitis	Pharyngitis
Xiong et al. 2020 [27]	Impact of anti-PD-1 treatment on T-cell subpopulations	Oral cavity squamous cell carcinoma (OCSCC)
Li et al. 2020 [32]	Involvement of tertiary lymphoid structures (TLSs)	Oral cancer
Shigeoka et al. 2019 [22]	Immunotolerance	Tongue leukoplakia
Bi et al. 2019 [23]	T-helper cell polarization	Chronic periodontitis
Colares et al. 2019 [28]	Inflammation	Tooth sensitivity, oxidative tissue damage

The narrative review on "The role of the immune system in the formation and development of diseases of the oral cavity" consolidated findings from various studies, demonstrating the significance of immune biomarkers in diagnosing and understanding the progression of oral diseases. Most of the studies associated cytokines like IFN-γ, TNF, and IL-6 with disease activity and severity [18, 24]. Others examined the surface markers and genetic signatures to link immune response to tumor grade and cancer stage variability [19, 20, 22, 23, 25, 27, 28, 30, 32]. Moreover, immunological markers like PD-1, CD69, and systemic records, being used in disease development and metastasis in OSCC, were being studied [29, 31]. Additional research suggested that components like mast cell tryptase and mesenchymal stem cells played important roles in malignancy progression and immune modulation [21, 26]. Collectively, these findings underscored the complex interplay of immune factors in oral diseases, suggesting potential avenues for targeted diagnostics and therapeutic interventions based on specific immune profiles.

Table 3. Overview of Immune Biomarkers and Their Association with Oral Disease Severity

Author's	Biomarkers of Immune Function	Severity of Oral Disease
Pinto et al. 2022 [18]	IFN-γ, TNF, IL-1β, CCL2, HSP60, HSP90	Active lesions in 2 patients, inactive in 4 patients
Dasgupta et al. 2022[19]	Tumor-infiltrating lymphocytes (TIL), EGFR score	Graded; most cases moderately differentiated
Barbieri et al. 2022 [20]	CD1a+, CD83+	Low-grade and high-grade malignancies
Zhao et al. 2022 [24]	IL-6 and IFN-γ protein expression levels	Non-erosive and erosive forms
Liu et al. 2021 [25]	T cell receptor repertoire diversity, cytolytic T cell signatures, FLT4 mutations, PTEN signature	High-risk, resectable, stage II–IVA
Piersiala et al. 2021 [29]	PD-1, CD69, HLA-DR, CD4, CD8	Varied, including primary and recurrent OSCC with some patients having nodal metastases

Hung et al. 2021 [31]	Systemic Immune-Inflammation Index (SII)	Advanced stages in most patients (87.8% T or N stages)
Zibandeh et al. 2020 [26]	Dental Follicle Mesenchymal Stem Cells (DF-MSCs)	Lymphocyte proliferation, T lymphocyte subsets, cytokine levels (TNF-α, IL-6, IL-10)
Teófilo et al. 2020 [21]	Mast cell tryptase, CD31, CD34	Increased in OSCC (malignant) compared to epithelial dysplasia (pre-malignant) and normal tissue
Adler et al. 2020 [30]	-	Moderate to severe
Xiong et al. 2020 [27]	CD4+, CD8+, IFN-γ, Foxp3, granzyme B	Locoregionally advanced
Li et al. 2020 [32]	IL-7, LTB, CXCL13	Classified based on TLS presence and location; includes different tumor stages and grades
Shigeoka et al. 2019 [22]	CD163+, IL-10, Ki-67, CK13	High degrees of epithelial dysplasia
Bi et al. 2019 [23]	IFN-γ, IL-4, IL-17, IL-10, RANKL, OPG	Severe (in CP group)
Colares et al. 2019 [28]	NOx, H_2O_2, MPO levels	More severe with 35% H2O2

The narrative review "The Role of the Immune System in the Formation and Development of Diseases of the Oral Cavity" integrated findings on how the immune system impacted oral health. The key observations included the upregulation of inflammatory cytokines in oral graft-versus-host disease Pinto et al. 2022 [18], suppression of mature dendritic cells in smokers Barbieri et al. 2022 [20], and modulation of immune responses through dietary quercetin Zhao et al. 2022 [24]. Liu et al. 2021 [25] noted an increased Treg to Th17 cell ratio, suggesting innate immune resistance, while Piersiala et al. 2021 [29] found heightened activation markers in tumor tissues, indicating a localised aggressive immune response. Decreased mast cell density in oral cancer was reported by Teófilo et al. 2020 [21], and Xiong et al. 2020 [27] discussed increased Treg cells, highlighting complex immune regulation within the oral cavity. The role of tertiary lymphoid structures in chronic inflammation was explored by Li et al. 2020 [32], and Shigeoka et al. 2019 [22] link CD163+ macrophages to immunosuppression. Bi et al. 2019 [23] and Colares et al. 2019 [28] revealed shifts toward pro-inflammatory immune profiles and increased oxidative stress in periodontal disease, respectively. These studies collectively underscored the multifaceted role of immune responses in oral disease progression and provide potential avenues for therapeutic interventions.

Table 4. Immune Response Alterations and Their Implications in Oral Disease Pathogenesis

Author's	Alterations in Oral Immune Responses
Pinto et al. 2022 [18]	Upregulation of inflammatory cytokines and chemokines in oGVHD patients
Barbieri et al. 2022 [20]	Suppression of mature dendritic cells in smokers
Zhao et al. 2022 [24]	Changes in cytokine levels, apoptosis, and T lymphocyte behavior in response to quercetin treatment
Liu et al. 2021 [25]	Increased regulatory T to T helper 17 cell ratio predicting low TCR diversity and innate resistance
Piersiala et al. 2021 [29]	Increased activation markers in tumor tissue compared to lymph nodes and peripheral blood
Teófilo et al. 2020 [21]	Decreased mast cell density in OSCC
Xiong et al. 2020 [27]	Increase in Treg cells among CD4+ cells, varied responses in CD8+ cell subpopulations
Li et al. 2020 [32]	Changes in cytokine and chemokine gene expression associated with TLSs
Shigeoka et al. 2019 [22]	CD163+ macrophages associated with increased IL-10 and immunosuppression
Bi et al. 2019 [23]	Increased Th1 and Th17 cells in CP group; decreased Th2 and Treg cells in CP group compared to PH group
Colares et al. 2019 [28]	Increased oxidative stress, neutrophil content, and altered protein expression associated with inflammation and cell damage

Discussion

The current narrative review highlighted a significant and expanding interest in exploring the complex relationships between the immune system and oral diseases through a variety of research approaches. This encompassed small-scale experiments aimed at understanding specific immune mechanisms to larger observational and longitudinal cohort studies that examined the potential of immune factors affecting the oral health over time. The breadth of study sizes and types provided a diverse understanding of the immune responses involved in oral health and disease dynamics. Expanding on this intricate framework, another narrative review focuses on the impact of microbial dysbiosis on mucosal immune responses and epithelial barriers in several oral mucosal diseases, namely oral candidiasis, oral lichen planus, recurrent aphthous ulcer, oral leukoplakia, and oral squamous cell carcinoma. The results of this review are of critical importance to differentiate the variable microbial affect that differs among various diseases during their respective stages, thereby improving the understanding about the pathogenesis of oral mucosal disease (OMD). Another study emphasised that the changing circumstances of dysbiosis showed the crucial contribution of microbes to the context of the oral disease progression and management [33]. Moreover, another study underlined the complexities generated within the oral cavity, involving the microbiota and the

mechanisms of defense of the oral mucosa. Such investigation emphasised on the functions of mucosa as a protective barrier, the roles played by cells of the immune system, and the stimuli (internal and environmental) that controlled the active immune responses. The implication was that this synergistic activity showed an important gap in the current understanding of the immune response regulation at the oral mucosal barrier. It hinted that a complete comprehension of these host-microorganism associations should be compulsory in solidifying the field of oral health dynamic and delivering specific therapies [34]. Collectively, these reviews and surveys were aimed at providing insights about the immunity and oral health relationship. They underscore the importance of adopting a multifaceted approach in studying the intricate interplay between microbial impacts and immune responses, emphasising its significant value in scientific inquiry. Each of each research line gave an informative aspect to how the system of the immune system and all oral diseases operates creating pathways for new treatment techniques in oral healthcare.

This review presented in a systematic way the important implication that the immune system played in the many oral diseases. This pinpointed how the immune dysregulation and immune actions like the use of inflammatory mediators, tumor-infiltrating lymphocytes, and T-cell polarisation were respective immunological factors associated with the pathology of the diseases like oral cancers, chronic GVHD, and benign conditions such as oral lichen planus and periodontitis. The multiple studies reported clues at different levels of host immune mechanism underlying the poor oral health, and these findings have indicated possible use of targeted immune modulation as therapeutic interventions for those conditions. This cross-disciplinary connection thus highlighted the necessity for further research into immune therapy approaches in oral disease treatment. Similarly, another review discussed the immune-mediated processes in oral cancers, particularly gingiva-buccal oral squamous cell carcinoma and highlighted in the review points to significant immunosuppression in OSCC-GB, driven by epigenetic changes such as promoter hypomethylation that upregulates immune checkpoint molecules like CD274 and CD80. These findings suggested that targeting immune checkpoints might be an effective strategy for treating this prevalent form of cancer in India. The emphasis on the immune system's involvement in the pathogenesis of OSCC-GB underscored the potential of immunotherapeutic strategies, an area that is currently under-explored and could provide new avenues for treatment. [35]. Furthermore, the review covered the role of the immune system in non-cancerous oral conditions such as oral lichen planus and periodontitis. It discussed a case of a 15-year-old female with a novel CTLA-4 variant, multiple autoimmune conditions, and persistent oral lesions diagnosed as OLP, despite ongoing systemic immunosuppression. This case study from the 2020 CIS Annual Meeting highlighted the complexity of clinical phenotypes associated with the immune dysregulation and the necessity to consider such underlying conditions when diagnosing and managing persistent oral lesions [36,37]. Additionally, the review extends the discussion to the interaction between the oral microbiome and the immune system, emphasising how microbial and host metabolites regulated this interaction. Advances in sequencing technologies have elucidated that in health, there is a symbiotic relationship between the oral microbiome and the immune system, but in disease states such as severe allergies and autoimmune conditions like celiac disease, dysbiosis and mucosal remodeling occur. This can lead to barrier disruption and inflammation, implicating the oral mucosa's significant role in immune responses to allergens and autoimmune triggers [38].

The current narrative review emphasised the core relevance of the immune system in the pathology of oral diseases, particularly via the use of immune biomarkers which were touched on in this paper. It was commenting on the fact that the levels of cytokines and immune surface markers relate to the severity, progression, and staging of oral diseases from mild cases to oral squamous cell carcinoma. These biomarkers become cornerstones for comprehension of the biological mechanisms behind these diseases. Such knowledge would then in turn potentially lead to more authentic diagnostic tools and targeted therapeutics. Collectively, the research showed that the Immune monitoring helps managing oral disorders more effectively, possibly signaling a future treatment where the immune profiles of an individual establish therapy on a more personal level. Additionally, along with the growth of immune biomarkers, studies on oral microbiology and immunology have also changed from a more general to a more focused view which has happened during the last 60 years. The role of bacteria, initially underestimated, is now recognised as crucial in training and influencing the immune system. Advanced "omics" technologies are predicted to further deepen the understanding of the intricate interactions between the host immunity and oral microbiota, paving the way for novel diagnostics and therapeutic strategies [39]. Another study highlighted that the oral microbiota was crucial in health and disease, influencing both oral infections like caries and periodontal diseases and systemic diseases. This review explores the role of oral microbiota in systemic disease, novel diagnostic tools, and therapies like bacterial recolonisation and the host modulation. It highlighted the importance of collaboration between dental and general health specialists to enhance overall patient health[40]. Moreover, salivary molecular analysis presented a promising non-invasive diagnostic approach, particularly for diseases like OSCC. Using more than one hundred prospective salivary biomarkers, which include cytokines that have a pivotal function for both inflammation and tumor kinetics, these biomarkers carry promise not only in diagnostics but also in prognostic and metastasis prediction [41]. Another review emphasises the fact that how the oral microbiota goes beyond strictly defined- oral health and immune responses to the influence of the oral microbiota extends to the systemic diseases such as diabetes mellitus, where in often times periodontal disease, and systemic inflammation are high in individuals who have an altered oral microbial environment. This connection emphasizes the demand for a multi-sectional

approach for the treatment and policy of both oral and systematic health, especially among such risk groups as obesity, hyperlipidemia, and polycystic ovary syndrome [42].

This review offered a thorough understanding of the intricacies of the immune interactions particular to the oral cavity, highlighting the importance of these immune mechanisms in the pathogenesis of the oral diseases. The review evoked the fact that these responses might stand on either side, representing defense or exemination of oral conditions. This study observed that immune activity in the oral region tends to be finely balanced, with disruptions in this equilibrium, such as those caused by smoking or dietary habits, posing a risk for infection. This explanation brought about the reflection of the inherent possibility of ensuring the immune pathways to be one of the therapeutic strategies. Through the utilisation of these pathways upon which they act, it is possible to form novel interventions that switch on and off the immune response against oral health thus preventing any disease outbreaks. Furthermore, the review focuses on the role of interleukins in oral and systemic disorders salivary cytokines as non-invasive biomarkers. The fact that it only requires saliva renders this methodology more suitable, particularly for applications involving children and settings with limited resources. This makes it highly applicable to serious health conditions such as cancer, HIV, and tuberculosis, among others [43]. Additionally, the review addressed the subject of the immune dynamics of oral cavity through investigating specific cytokines, such as IFN-γ, TNF-α, and IL-1β, regulating the immunoregulatory function of human periodontal ligament stem cells (hPDLSCs). These cells are involved in the mechanism of the proliferation and apoptosis of allogenic CD4+ T lymphocytes, and thus, can lead to immune response to infection. The results indicated that cytokines like IFN-γ and IL-1β directly target hPDLSCs signaling pathways and mediators to cause a significant change on CD4+T cell responses, demonstrating that the cytokines perform this function in a very selective way [44]. Also, another study dealt with the immune responses towards oral microorganisms and systemic ones, pointing out the off-balance immunological systems caused by the gut dysbiosis. By doing that, on one hand, it brings about the diseases while on the other hand, it makes the disease progress at a faster rate [45].

Conclusions

1. The review underscored the dual role of the immune system as a key player in the oral cavity, which might bring the immune system under control or could also drive inflammation under the oral diseases condition. This is underscored by the evidence, emphasizing the importance of understanding the inner workings of the immune system to develop more effective strategies for controlling diseases.

2. It was revealed that some individuals had their unique immune profiles for oral diseases like oral cancer, periodontitis, and oral lichen planus that were so distinct. These profiles display an up-regulation of inflammatory mediators found in oral chronic GVHD, TILs observed in oral cancers, and Th1/Th2 imbalances seen in oral lichen planus.

3. The study established the fact that certain cytokines and immune cells can legitimately be used as biomarkers disease-detection and disease-progression prediction. These refers to the IFN-γ, TNF, and IL-6 which are related to the diseases' activity and severity.

4. The awareness of the narrow processes of the immune dysregulation presents a possibility for targeting a specific therapy. For instance, the modulating regulation of T-helper could use also immunosuppressants or use of mesenchymal stem cells to control the immune response seems to be a very good solution.

5. The insights from prospective and retrospective cohort studies are invaluable for comprehending the long-term effects of immunity on oral health outcomes. It's essential to closely monitor individuals across their sleep, wakefulness, and circadian rhythm cycles over extended periods to develop and implement suitable long-term management strategies.

Implications

1. The understanding of the specific mechanisms of the immune system involved in various oral diseases will draw attention to the quest for more effective and targeted therapies. Such as the P-D1 targeted therapy in oral cancers or the Th17 and Tr increase or decrease in immune-mediated oral disorders might be effective.

2. The detection of a salivary biomarker through a non-invasive way can create an opportunity for diagnostics of people in resource-limited areas which apply asymptomatic screening and require diagnosis methods. Early diagnosis and effective treatment could ultimately stem from such an approach.

3. Encouragement in regulatory systems could offer insights into how lifestyle factors such as smoking, and diet influence the immune response in the oral realm. Therefore, the policies organized to prevent this are built on this information.

4. The varied immune responses observed from different studies could be another indication that customise therapy approaches may be possible for oral diseases. Modifying the therapies considering every patient's immune system would strengthen their effect and minimise the side effects.

5. The findings create a regulatory avenue for new clinical trials aimed at exploring the potential utility of immunotherapy and diagnostic tools. It could also be meant for the realisation of the same extent of studies, the level of diversity in the populations and finally, generalization of results entirely.

In summary, this literature review delved into the amassed evidence suggesting that the immune system plays a significant role in the development of oral disorders. This paves the way for further investigations and clinical intervention programs aimed at improving oral health.

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Conflicts of Interest

There is no conflict of interest, related to this study.

Institutional Review Board Statement

Not Applicable

Informed Consent Statement

Not Applicable

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