Literature Review: The Role of Cytokines in the Oral Cavity of Diabetics

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Abstract:
Diabetes is a chronic inflammation and can affect various organs, one of which is oral health. The oral cavity in diabetic patients has several symptoms, some of them are dry mouth, periodontal disease, gingivitis, and others. The immune system is a very complex body defense, and provides a variety of responses. The response can be through innate or adaptive immunity. Scientific advances have revealed a wealth of information about the numerous types of cytokines that contribute to this response. Cytokines are small protein molecules secreted by cells that have a specific influence on cell contacts and communication. Some researchers explained that there are several mechanisms of action in diabetes such as the role of macrophages, cytokines such as TNF-alpha, IL-1, IL-6, IL-10, and more. Besides that, diabetes can affect the rate of saliva resulting in various changes in other conditions in the oral cavity. Periodontal disease (PD) is one of the risk variables that can rise if the patient has diabetes, and it is the most common oral problem associated with diabetes. microbiome is another aspect that can contribute to changes in cytokine responses as well as other immunological factors. The relationship between diabetes and oral disease demands an increasing need to research to regulate both diseases and contribute to the advancement of oral medicine.

Keywords: diabetes, cytokine, oral diseases.

Introduction
According to the World Health Organization, the prevalence of diabetes has increased in various countries. The number of diabetics has risen in recent decades. The age standard death rate from diabetes increased by 3% between 2019 and 2020. This figure rises by 13% in low-income countries. This is a serious issue and there must be an effort made to assist patients in living a healthy lifestyle. According to the Ministry of Health of the Republic of Indonesia, diabetes prevalence increased in practically all provinces in Indonesia between 2013 and 2018. It has also been stated that up to 25% of diabetics are aware that they have the disease.
Diabetes certainly encounter a variety of health changes. Health education is required, so people would pay greater attention to this. Diabetic can effect in systemic body and also oral cavity. The immune system will activate, and numerous reactions will take place in the body. The World Health Organization describes some of the symptoms that patients may suffer, such as extreme thirst, the urge to urinate more frequently than usual, blurred vision, fatigue, and accidental weight loss. Furthermore, diabetes will almost probably result in various issues that can affect the heart, eyes, kidneys, and nervous system.

A sedentary lifestyle can be one of the triggers that can spur and develop diabetes, especially type 2 diabetes. American Diabetes Association (ADA) reported that the classification of diabetes such as type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes due to autoimmune-cell destruction, usually leading to absolute insulin deficiency, type 2 diabetes due to a progressive loss of adequate b-cell insulin secretion frequently on the background of insulin resistance, and gestational diabetes mellitus and Specific types of diabetes due to other causes, some of cases are diseases of the exocrine pancreas (American Diabetes Association, 2020). Xerostomia, dental caries, gingivitis, periodontal disease, increased susceptibility to oral infections, burning mouth, taste disturbance, and poor wound healing are all common oral symptoms in diabetics patients. Furthermore, some investigations have shown that people who have a poor influence on glucose control have chronic brain issues (Rohani, 2019). This is important and related to the patient’s condition. The immune system of diabetic patients affects cellular systems, such as emotaxis, phagocytosis, and killing of pathogens by monocytes, macrophages, and neutrophils. Rajana (2017) explained that diabetic patients will increase in inflammation condition to chronic. In this review we will describe some immunology reaction in oral cavity of diabetics patients, especially for cytokine.

**Results and Discussion**

**Diabetes and Oral Manifestation**

Diabetic patients’ immunological and metabolic systems are linked to their condition. Other than failure in both central and peripheral immunological tolerance systems contributing to the formation of autoreactive T cells, one hypothesis for Type 1 diabetes is that the beta cell pancreatic islets of patients with T1D become inflamed. Activation of several immune cells are involved in pancreatic beta-cell death through a variety of inflammatory cytokines. Regulatory T cells are defective in this autoimmune disease, while effector T-cells (Teff) participate in the development of type 1 diabetes. The profile of immune B cells also changes during disease progression and macrophages are also critical mediators of islet inflammation due to their direct toxicity on beta-cells by reactive oxygen species (Tsalamandris et al., 2019). Dendritic cells, natural killer cells and natural killer T cells may have a partial role in the process. Some researchers explained that there are several mechanisms of action in diabetes such as the role of macrophages, cytokines such as TNF-alpha, IL-1, IL-6, IL-10, leptin, adiponectin, monocyte chemoattractant protein, angiotensinogen, resistin, chemokines, serum amyloid protein, and many others collectively referred to as adipokines (Rajana, 2017; Tsalamandris et al., 2019).

Periodontal disease (PD) is one of the risk variables that can rise if the patient has diabetes, and it is the most common oral problem associated with diabetes. PD is a chronic infectious illness produced by gram-negative bacteria, and there is an imbalance in the oral cavity between inflammation, infection, and immunology. This chronic infection can affect the gingiva and cause alveolar bone destruction and tissue attachment loss to the teeth, which can be caused by microbial plaque components that can induce the initial infiltration of inflammatory cells such as lymphocytes, macrophages, and polymorphonuclear leukocytes. In this cases serum levels of inflammatory mediators such as Interleukin 6 (IL-6), fibrinogen, and C-reactive protein (CRP).
was increase (Pucher & Stewart, 2004). Xerostomia and diabetes significantly correlated with blood glucose level in saliva. Increased salivary glucose promotes proliferation and colonization of bacteria in the oral cavity. In addition, glucose can be a medium for the development of Candidiasis and reduce the activity of neutrophils (Mauri-Obradors et al., 2017). Xerostomia is one of the symptoms in diabetic patients with dry mouth conditions due to a decrease in the rate of saliva. In controlled type 2 DM patients, xerostomia can also occur, as a result of the slow decrease in antidiabetic drug levels in the salivary glands resulting in drug accumulation (Molania et al., 2017). In table 1 we can show some studies that associated with diabetes and immunology reaction.

![Figure 1. Diabetes and oral diseases](Image)

### Table 1. Cytokine reaction in oral cavity of diabetes

<table>
<thead>
<tr>
<th>Authors</th>
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<tbody>
<tr>
<td>Huabin Luo et al. 2022</td>
<td>Oral Health, Diabetes, and Inflammation: Effects of Oral Hygiene Behaviour</td>
<td>Diabetics patients with and without significant tooth loss (STL) negatively associated with flossing, t STL was associated with higher CRP levels and also STL was associated with higher systemic inflammation (Luo et al., 2022).</td>
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<tr>
<td>E Xiao et al, 2017</td>
<td>Diabetes Enhances IL-17 Expression and Alters the Oral Microbiome to Increase Its Pathogenicity</td>
<td>The level of inflammation can be seen from the presence of periodontal bone loss. Diabetic rats will have increased mRNA levels of inflammatory cytokines. IL-17 is the biggest factor in the increase of inflammatory mediators. In addition, diabetes can cause an increase in the number of neutrophils (Xiao et al., 2017).</td>
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<tr>
<td>Atefe Halimi et al., 2022</td>
<td>The relation between serum levels of interleukin 10 and interferon-gamma with oral candidiasis in type 2 diabetes mellitus patients</td>
<td>122 participants, including 73.77% and 26.22% male, there was an increase in interleukin 10 and a decrease in IFN-γ which could increase oral candidiasis. The presence of oral candidiasis is not associated with HbA1c and FBS levels (Halimi et al., 2022).</td>
</tr>
<tr>
<td>Victor M. Martnez-Aguilar et al., 2019</td>
<td>Quantification of TNF-α in Patients with Periodontitis and Type 2 Diabetes</td>
<td>Analysis for periodontal conditions that No differences in TNF-α concentration were found between groups. A Spearman test identified a weak but significant negative</td>
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### Salivary disorders could be associated with a poor quality of life and could increase caries and oral infections in DM patients, particularly when there has been dehydration and inadequate blood glucose control (An et al., 2018). Some of cytokine can contribute to inflammation in diabetes. Cytokines are low molecular weight glycoproteins secreted into the blood by many types of immune and non-immune cells, where they regulate many aspects of immune responses and inflammatory reactions via autocrine, paracrine, and endocrine effects (Nussrat & Ad’hiah, 2023). In some research member of interleukin especially IL-1, IL-6, IL-12, IL-17 associated with diabetes. Tumor Necrosis Factor (TNF-α) is produced by macrophage / monocyte during inflammation. TNF-α has a role of protection and defense from any infection like virus, microbe and also parasite. TNF-α, IL-1, and IL-8 are pro-inflammatory cytokines secreted by activated macrophages that aid in phagocytosis and improve the T-cell immune response. Bacteria or bacterial products in the blood produce systemic inflammation, which is characterized by macrophage activation in the reticuloendothelial system, leukocytosis, cytokine release, and hypotension (Jang et al., 2021).

In diabetes and infection patients, inflammatory cytokines cause regulated alterations in the host's internal milieu. Some investigations revealed that cytokines are constitutively created, that environmental stresses other than microorganisms boost their synthesis, and that they modulate "normal" physiological processes. Beginning at the 6-h time point, *E. coli* significantly raised pro inflammatory cytokine levels such as interleukin (IL)-1, IL-6, tumor necrosis factor- and brain IL-1 (Setyawan, 2006). Several research have focused on TNF-α and IL-1β as the most commonly discussed cytokines. In the presence of inflammation, these cytokines rise with periodontitis. IL-1β recruits inflammatory cells promotes PMN priming / degranulation and increases inflammatory mediators. TNF-α is a significant marker of apoptosis and production of IL-6 (Iacopino, 2001). Lian Sun et al. (2010) reported that 3 months after periodontal intervention, serum of adiponectin levels were increased than those without periodontal intervention, while CRP, IL-6 and TNF-a

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<td>Patients with diabetes have level of C3 increase. C3 level related to the upregulation of inflammatory cytokines including interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-α) and decline of the bone volume density (Li et al., 2020)</td>
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<td>The levels of IL-1β, sIL-6R and CPT in gingival crevicular fluid of deepest PPD in patients with diabetes with periodontitis is higher that patients with periodontitis but without diabetes. Levels of CPT-induced IL-1β, IL-6, sIL-6R production in THP-1 macrophages cultured with NG or HG conditions (Lew et al., 2018).</td>
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significantly decreased in both impaired glucose tolerance and T2DM without macrovascular disease. And in this study reported that HbAlc levels in T2DM patients were improved at 3 months after periodontal invention. Same with wound healing in hard or soft tissue, cytokine can contribute in this case. The oral mucosa is covered by stratified squamous epithelium, containing fibroblasts, collagens, and capillaries beneath the epithelium. Hemostasis, inflammation, cell proliferation, and remodeling are all part of the wound healing process. Aside from EGF, numerous additional growth factors such as insulin-like growth factor (IGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), and nerve growth factor (NGF) produced near the wound stimulate healing (Abiko & Selimovic, 2010). In both T1DM and T2DM models, diabetic animals' oral mucosal lesions heal more slowly than normoglycemic controls. Contributing factors have been demonstrated to represent both the direct effect of high glucose levels as well as the indirect effects of increased inflammation, high levels of advanced glycation endproducts (AGEs), and increased generation of reactive oxygen species (ROS). Diabetes slows healing by reducing keratinocyte migration, the production of growth factors by a variety of cell types including keratinocytes, and interfering with a variety of cellular functions such as cellular proliferation and differentiation, as well as the expression of genes required for the formation of soft connective tissue and bone matrix (Ko et al., 2021).

There are many other factors that can be studied further regarding the immunological reactions in diabetic patients, especially in the oral cavity. Such as the response of the microbiome which plays a natural role and can even provide a natural response to changes in the immune system of the oral cavity. Toll-like receptors (TLRs) are fundamental to innate immunity, and it appears that they play an important role in disease development and pathogenesis (zv et al., 2016). According to Nackiewicz et al., contact between TLR2/6 and its associated ligands activates macrophages and causes the production of IL-1 and IL-6, which are pro-inflammatory cytokines that contribute to islet inflammation (Nackiewicz et al., 2014).

**Conclusion**

Diabetes can damage many organs, including the oral cavity. The immune system will aid in maintaining the body's homeostasis. Diabetes develops in settings of chronic inflammation, therefore cytokines contribute to and play a part in the body's maintenance. The oral cavity, which is undoubtedly influenced by microbiome conditions, may also have a role in the development of this disease in the oral cavity.

**Conflict of interests**

No conflict of interest.

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Nussrat, S. W., & Ad’hiah, A. H. (2023). Interleukin-39 is a novel cytokine associated with type 2 diabetes mellitus and positively
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https://doi.org/10.20473/j.djmkg.v39.i1.p19-23

