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Review Article

Link between Genetic Polymorphisms in Interleukins and Periodontitis in Individuals with Diabetes Mellitus

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ABSTRACT

The connection between interleukin (IL) gene variations and periodontitis in individuals with or without diabetes mellitus (DM) is still uncertain. This review aimed to examine available evidence on whether genetic polymorphisms in interleukins influence periodontitis in patients with and without DM. The guiding question was: "Do IL gene polymorphisms associate with periodontitis in individuals with or without DM?" Original research articles were selected, and relevant databases were systematically searched to compile and summarize the findings. Eight studies met the inclusion criteria and were analyzed. Results were inconsistent: two studies indicated that IL-1B polymorphisms worsen periodontitis in type-2 DM patients, while another two reported minimal or no effect of these polymorphisms. Additionally, two studies found no overlapping susceptibility between IL genes, periodontitis, and type-2 DM. One study highlighted that inadequate oral hygiene, rather than genetic factors, primarily drives periodontitis in both DM and non-DM populations. Notably, seven studies exhibited a high risk of bias. In conclusion, the influence of IL gene polymorphisms on the onset and progression of periodontitis in patients with and without diabetes mellitus remains inconclusive and warrants further investigation.

Keywords: Diabetes mellitus, Interleukin, Periodontitis, Genetic polymorphisms

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Introduction

The interplay between periodontitis and diabetes mellitus (DM) is complex and has been the focus of numerous studies [1, 2]. Persistent hyperglycemia, a hallmark of poorly managed DM and prediabetes, has been identified as a significant contributor to periodontal tissue inflammation and loss of alveolar bone [3–6]. Mechanistically, sustained high blood glucose accelerates the accumulation of advanced glycation end-products (AGEs) in periodontal tissues, which exacerbates clinical indicators of periodontitis such as attachment loss, deeper periodontal pockets, and marginal bone resorption [7–9]. The binding of AGEs to their receptors (RAGEs) promotes oxidative stress, which in turn stimulates the release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) [2, 4, 10]. Hyperglycemia can also activate nuclear factor kappa B (NF-κB), altering gene expression in periodontal fibroblasts and further accelerating tissue degradation [11].

Genetic variations in IL genes have been proposed to influence susceptibility to periodontitis, yet findings remain inconsistent. For instance, Zao and Ronghua [12] reported a negative impact of IL-6 polymorphisms on periodontal health, while Yin *et al*. [13] cautioned that heterogeneity across studies makes definitive conclusions difficult. Investigations into IL gene polymorphisms in the context of DM have produced conflicting evidence [14–19]. A pilot study by Kavitha *et al*. [16] suggested that IL-6 variants may increase the risk of periodontitis in both diabetic and non-diabetic individuals, with similar observations reported by Xiao

et al. [20], Raunio *et al*. [21], and Struch *et al*. [22]. Additionally, in vitro data indicate that IL-10 can help modulate inflammatory responses and mitigate periodontal tissue damage [23].

However, several studies have failed to establish a significant link between IL polymorphisms and periodontitis. López *et al*. [15] found that while IL-1 gene variations were associated with periodontitis, they did not correlate with type-2 DM. Likewise, da Silva *et al*. [24] and Ding *et al*. [25] observed no meaningful association between IL-1A or IL-1RN polymorphisms and periodontitis, though DM was not considered in these populations. Deppe *et al*. [17] highlighted that inadequate oral hygiene, rather than genetic predisposition, is the primary driver of periodontitis progression, whereas Toker *et al*. [26] reported that IL-10 polymorphisms could heighten susceptibility to periodontal disease.

Taken together, the evidence regarding IL gene polymorphisms and their role in periodontitis among patients with and without type-2 DM remains ambiguous. This study aims to systematically review and synthesize indexed data to clarify the association between interleukin polymorphisms and periodontitis in these populations.

Materials and Methods

Research question

This review aimed to determine whether genetic variations in interleukins are linked to periodontitis in individuals with and without type-2 diabetes mellitus.

Study selection and search strategy

Only original research studies, including clinical and experimental investigations, were considered; publications such as case reports, commentaries, letters, and opinion pieces were excluded. A comprehensive literature search was performed across PubMed, Scopus, Embase, Google Scholar, and Web of Knowledge up to December 2020, without limiting by date or language. The search combined Medical Subject Headings (MeSH) and keywords such as alveolar bone loss, cytokine, type-2 diabetes mellitus, inflammation, interleukin, and periodontitis, using Boolean operators (AND, OR) to capture all relevant studies. Two reviewers independently screened the titles and abstracts for eligibility and subsequently assessed the full texts of selected articles. Reference lists of included studies were also manually reviewed to identify additional relevant research. Any disagreements in selection were resolved through discussion. The review process was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, as depicted in **Figure 1**.

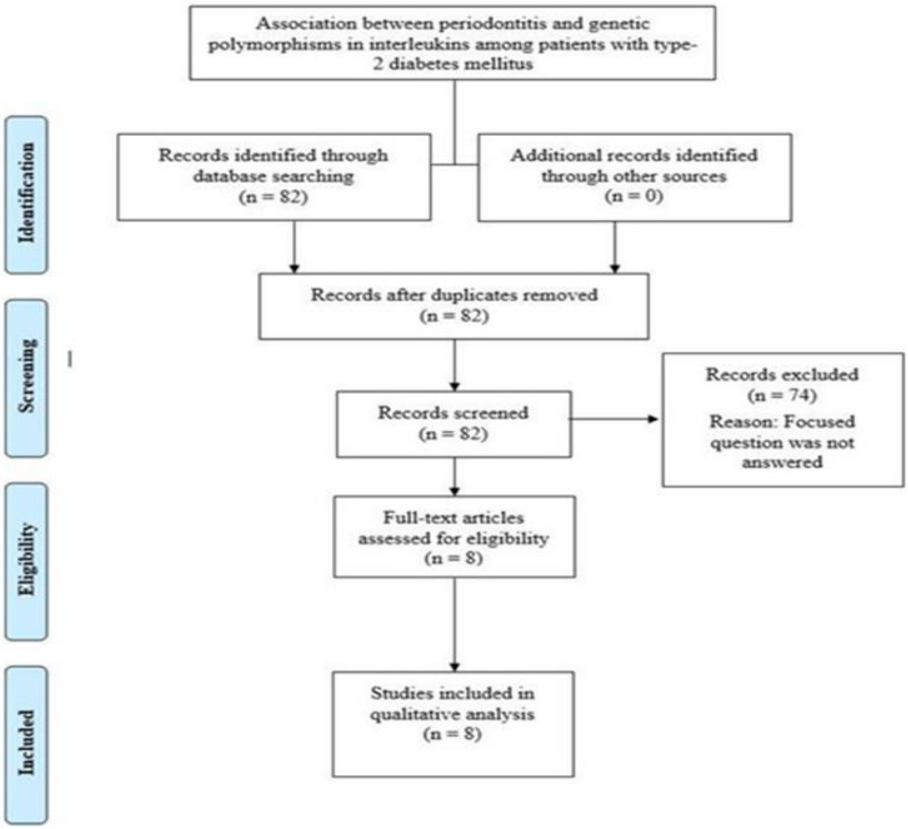

Figure 1. PRISMA flow diagram illustrating the study selection process.

The included studies were evaluated for methodological quality using the Downs and Black checklist [27], where scores of 20 or above indicated good quality, 15–19 fair quality, and below 14 poor quality [27]. A single reviewer conducted the risk of bias assessment for all studies.

Results and Discussion

Characteristics of the selected studies

The initial database search identified 82 potentially relevant articles. After applying the inclusion criteria, 74 articles were excluded, leaving eight studies [14–20, 22] for detailed analysis. Across these studies, periodontitis was defined as the presence of probing depths of 4 mm or more and clinical attachment loss of at least 3 mm affecting 30% or more of examined sites.

Most studies (seven out of eight) [14, 15, 17–20, 22] followed a cross-sectional case-control design, while one study [16] was conducted as a pilot investigation. Seven studies [15–20, 22] included both patients with type-2 diabetes and non-diabetic controls, with and without periodontitis. One study [14] additionally incorporated participants with type-1 diabetes and healthy controls.

Regarding interleukin gene analysis, three studies [15, 18, 22] focused on IL-1A polymorphisms, four studies [14, 15, 18, 22] examined IL-1B variants, and one study [18] assessed multiple genes, including IL-1A, IL-1B, IL-4, IL-6, and IL-10. Polymerase chain reaction (PCR) was consistently used across all studies to evaluate IL gene polymorphisms **(Table 1)**.

Table 1. Characteristics of Included Studies

Authors	Study Type	Number of Patients	Age Range	Study Groups	Interleukin Polymorphisms Studied	Key Findings
Borilova Linhartova *et al*. [14]	Cross-sectional/ Case-control	1106	30–77 years	Gp-1: Periodontitis patients Gp-2: Type-1 DM patients Gp-3: Periodontitis and type-1 DM patients Gp-4: Type-2 DM patients Gp-5: Periodontitis and type-2 DM patients	IL-1 gene	• IL-1B polymorphism linked to periodontitis. • IL-1RN variant associated with type-1 DM.
López *et al*. [15]	Cross-sectional/ Case-control	544	42–68 years	Gp-1: Periodontitis patients Gp-2: Type-2 DM patients Gp-3: Non-type-2 DM and non-periodontitis patients	IL-1 gene	• IL-1A/1B genotype not linked to type-2 DM. • IL-1 genotype increases periodontitis risk.
Kavitha *et al*. [16]	Case-control	120	Not reported	Gp-1: Periodontitis patients Gp-2: Type-2 DM patients Gp-3: Periodontitis and type-2 DM patients Gp-4: Non-type-2 DM and non-periodontitis patients	IL-6 gene	• IL-6 genotype increases periodontitis risk. • IL-1 genotype not associated with type-2 DM.
Deppe *et al*. [17]	Case-control	104	48–72 years	Gp-1: Type-2 DM patients Gp-2: Non-type-2 DM patients	IL-1 gene	• IL genotypes not linked to periodontitis progression. • Poor oral hygiene better predicts periodontitis in patients with or without type-2 DM.
Cirelli *et al*. [18]	Cross-sectional/ Case-control	894	Not reported	Gp-1: Periodontitis patients Gp-2: Periodontitis patients Gp-3: Type-2 DM patients	IL-1A, IL-1B, IL-4, IL-6, IL-10	• IL-1B genotype less associated with periodontitis and type-2 DM. • IL-4 and IL-6 genotypes more associated with

						periodontitis and type-2 DM.
Petrovic *et al*. [19]	Case-control	Not reported	Not reported	Gp-1: Periodontitis patients Gp-2: Periodontitis and type-2 DM patients Gp-3: Non-type-2 DM and non-periodontitis patients	Not specified	• IL genes showed no cross-susceptibility between periodontitis and type-2 DM.
Xiao *et al*. [20]	Cross-sectional/ Case-control	492	40–87 years	Gp-1: Periodontitis patients Gp-2: Type-2 DM patients Gp-3: Periodontitis and type-2 DM patients Gp-4: Non-type-2 DM and non-periodontitis patients	IL-6 gene	• Lowest IL-6 genotype and C allele frequencies in Gp-3 compared to other groups. • IL-6-572 C allele protects against disease progression.
Struch *et al*. [22]	Cross-sectional/ Case-control	1515	40–60 years	Gp-1: Type-2 DM patients Gp-2: Non-type-2 DM patients	IL-1A/1B haplotype	• IL-1A/1B genotype worsens periodontitis in type-2 DM patients.

Abbreviations: DM, diabetes mellitus; IL, interleukin; Gp, group.

Outcomes

The impact of interleukin gene polymorphisms on periodontitis in type-2 diabetic patients varied across studies. Two investigations [14, 22] found that IL-1B variants intensified periodontal tissue destruction in this group, whereas two other studies [15, 18] suggested that these polymorphisms had minimal or no effect on disease progression. In contrast, findings from Deppe *et al*. [17] and Petrovic *et al*. [19] indicated that IL gene variations do not confer cross-susceptibility between periodontitis and type-2 DM. Regarding IL-1A, López *et al*. [15] observed no significant association with periodontitis progression among diabetic patients, while Struch *et al*. [22] reported a detrimental effect linked to this genotype. Evidence also pointed to certain IL-6 alleles as potentially protective against both periodontitis and DM progression. Importantly, Deppe *et al*. [17] emphasized that poor oral hygiene remains the primary determinant of periodontitis development in both diabetic and non-diabetic individuals, with IL gene polymorphisms playing only a minor role. These findings are summarized in **Table 1**.

Assessment of bias

Evaluation of methodological quality revealed that seven of the eight studies [14–16, 18–20, 22] carried a high risk of bias. Only the study by Deppe *et al*. [17] demonstrated a low risk of bias, highlighting its relatively stronger reliability among the included research **(Table 2)**.

Table 2. Risk of bias assessment using the Downs and Black [27] tool.

Author *et al.*	Reporting (Range: 2–12)	External Validity (Range: 0–2)	Bias (Range: 0–6)	Confounding (Range: 1–6)	Power (Range: 0–1)	Total	Final Assessment
Borilova Linhartova *et al*. [**14**]	4	1	0	2	0	7	High
López *et al*. [**15**]	6	1	2	3	0	12	High
Kavitha *et al*. [**16**]	4	1	2	2	0	9	High
Deppe *et al*. [**17**]	8	4	4	5	1	22	Low
Cirelli *et al*. [**18**]	5	1	1	0	0	7	High
Petrovic *et al*. [**19**]	4	1	2	2	0	9	High
Xiao *et al*. [**20**]	5	1	1	2	0	9	High
Struch *et al*. [**22**]	3	1	1	2	0	7	High

The present study sought to examine indexed literature investigating the contribution of IL gene polymorphisms to the development and progression of periodontitis in patients with and without type-2

diabetes mellitus (DM). Although a systematic review and meta-analysis were attempted, numerous methodological limitations within the included studies impeded both quantitative and qualitative analyses. In systematic reviews, clearly defined patient, intervention/exposure, control, and outcome criteria (PICO/PECO) are crucial [28, 29]; however, the reviewed studies displayed considerable variation in these parameters. For instance, Deppe *et al*. [17] and Struch *et al*. [22] categorized participants simply into two groups—those with and without type-2 DM—whereas Borilova Linhartova *et al*. [14], López *et al*. [15], and Kavitha *et al*. [16] employed multiple subgroup classifications, including systemically healthy and diabetic patients with and without periodontitis. Such heterogeneity complicated standardization of patient and control groups according to PICO/PECO protocols.

The relationship between IL gene polymorphisms and periodontitis remains inconsistent. Borilova Linhartova *et al*. [14] suggested that the IL-1B∗T allele may be protective against periodontitis, yet da Silva *et al*. [24] reported that Caucasian carriers of the T allele had a 1.25-fold higher risk compared to C allele carriers. These discrepancies indicate that genetic polymorphisms alone cannot fully explain periodontitis progression. Deppe *et al*. [17] highlighted that impaired routine oral hygiene in patients with type-2 DM is significantly associated with disease advancement. Studies have also shown that unstimulated salivary flow is markedly reduced below the normal threshold of 0.2 mL/min in poorly controlled DM and prediabetes [30–33], promoting biofilm accumulation on supra- and sub-gingival surfaces and exposing periodontal tissues to pathogens such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, and Enterococcus species [34].

Persistent hyperglycemia, typical of poorly managed type-1 and type-2 DM and prediabetes, also contributes to oxidative stress [3, 5, 10, 35], disrupts normal bone turnover [36], and increases advanced glycation end-product (AGE) formation, which impairs osseous remodeling and delays healing [37–40]. Nevertheless, patients maintaining optimal glycemic control can exhibit periodontal health comparable to systemically healthy individuals without periodontitis [6, 33, 41]. These observations suggest that poor oral hygiene and pathogenic microbial presence are primary drivers of periodontitis in both diabetic and non-diabetic patients, whereas IL gene polymorphisms play a secondary role. Indeed, under controlled glycemic conditions, the impact of IL polymorphisms appears substantially diminished [6]. Collectively, these findings underscore the need for further well-designed, adequately powered studies to clarify the interplay between genetics, glycemic control, and periodontal disease progression.

It is also important to note that approximately 88% of the included studies carried a high risk of bias, and only one study [17] performed a prior sample-size estimation among the eight analyzed [14–20, 22], which further emphasizes the need for cautious interpretation of their findings.

Conclusion

The influence of IL gene polymorphisms on the development and progression of periodontitis in patients with and without DM remains inconclusive.

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