Review

Cytokine Profile in the Gingival Crevicular Fluid of Periodontitis Patients With and Without Type 2 Diabetes: A Literature Review

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Background: Periodontitis may occur in patients with and without type 2 diabetes (T2D). It may be hypothesized that the gingival crevicular fluid (GCF) cytokine profile in patients with periodontitis with poorly controlled T2D may differ from the GCF cytokine profile in medically healthy individuals with periodontitis. The aim was to review the cytokine profiles in the GCF of patients with periodontitis with and without T2D.

Methods: Databases were searched from 1988 to August 2011 using different combinations of various keywords. Titles and abstracts of articles that satisfied the eligibility criteria were screened by the authors and checked for agreement. Only articles published in English were included.

Results: Ten studies were included. Two studies reported GCF concentrations of interleukin (IL)-6 to be higher in patients with periodontitis with T2D compared to medically healthy patients with periodontitis. Two studies showed GCF IL-6 levels to be higher in periodontitis with T2D compared to medically healthy subjects without periodontitis. In one study GCF levels of IL-17, IL-23, and interferon-γ were higher in patients with periodontitis with T2D compared to medically healthy patients with periodontitis. In one study, GCF concentrations of IL-8 were significantly higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis. Three studies reported GCF levels of IL-1α to be significantly higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis.

Conclusion: The GCF cytokine profile in patients with and without T2D seems to be governed by the intensity of periodontal inflammation and the role of T2D in this regard is rather secondary. J Periodontol 2012;83:156-161.

KEY WORDS
Cytokines; diabetes mellitus, type 2; gingival crevicular fluid; periodontitis.

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by hematopoietic and non-hematopoietic cells in response to infection, and their primary function is intercellular signaling. An inflammatory cytokine may be described as a cytokine that is induced during an inflammatory response and is associated with the onset or progression of the insult. Studies have demonstrated that patients with periodontitis display higher concentrations of various cytokines including tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-17, IL-23, and matrix metalloproteinase (MMP)-8 and MMP-9 in their GCF. Consequently, analysis of GCF samples may provide valuable information regarding the pathophysiologic processes associated with periodontitis.

Because poorly controlled T2D aggravates periodontitis, it may be hypothesized that the GCF cytokine profile in patients with T2D and periodontitis may also differ from the GCF cytokine profile in medically healthy individuals with periodontitis. The aim of the present literature review is to investigate the cytokine profiles in the GCF of patients with periodontitis with and without T2D.

MATERIALS AND METHODS

Focused Question

The addressed focused question was “Do patients with periodontitis with T2D have a different GCF cytokine profile compared to medically healthy individuals with periodontitis?”

Eligibility Criteria

The selection criteria encompassed the following: 1) original articles; 2) human studies; 3) reference list of original and review studies; 4) use of statistical methods; 5) intervention (cytokine profile in the GCF of patients with periodontitis with and without T2D); and 6) articles published in English. Experimental studies, letters to the editor, historical reviews, and unpublished articles were excluded.

Search Strategy

The authors searched the MEDLINE/PubMed (National Library of Medicine, Bethesda, Maryland), Google Scholar, and Cochrane Library databases for appropriate articles using the following keywords in various combinations: “cytokine,” “type 2 diabetes,” “gingival crevicular fluid,” and “periodontitis.” Databases were explored from 1988 through August 2011. Titles and abstracts of articles that satisfied the eligibility criteria were screened by the authors and checked for agreement. The full text of the articles judged by title and abstract to be relevant were read and independently assessed against the selection protocol. This was followed by hand-searching of the reference lists of original and review studies that were found to be relevant in the previous step and once again, any disagreement between the authors was resolved via discussion.

The studies included in the present review were controlled for confounding parameters including age, smoking, body mass index, medication, and alcohol consumption. Letters to the editor, historic reviews, and unpublished articles were excluded. The initial search yielded 20 articles. Ten studies that did not comply with the selection criteria (as described previously) were excluded (Appendix). In total, 10 studies were included and processed for data extraction (Table 1). Because only a limited number of original studies addressed our focused question, the structure of the present study was customized to mainly summarize the relevant information.

RESULTS

All studies were conducted in humans and were carried out at either universities or health care centers. The age of the study participants ranged between 25 and 69 years. The numbers of patients with periodontitis with T2D ranged between five and 45 individuals. The numbers of patients with periodontitis without T2D ranged between seven and 35 individuals. The age of the study participants ranged between 25 and 69 years. The numbers of patients with periodontitis with T2D ranged between five and 45 individuals. The duration of T2D ranged between 3 and 10 years.

Six of the studies included in the present review reported similar cytokine profiles in patients with periodontitis with and without T2D. Two studies reported GCF concentrations of IL-6 to be higher in patients with periodontitis with T2D compared to medically healthy patients with periodontitis; however, one study showed GCF IL-6 in patients with periodontitis with and without T2D to be similar. In a study by Vieira Ribeiro et al., levels of IL-17, IL-23, and interferon-γ in the GCF were significantly higher in patients with periodontitis with T2D compared to patients without T2D in the same group. Engebretson et al. reported GCF concentrations of IL-8 to be significantly higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis.

DISCUSSION

It is known that patients with diabetes have elevated levels of advanced glycation end products in their serum and gingival tissues that have been associated with a state of enhanced oxidative stress, a potential mechanism for accelerated tissue injury. Studies have reported that advanced glycation end products can interact with specific receptors on gingival cells, thereby stimulating the production of proinflammatory proteins, such as IL-6, IL-1β, and MMP.
<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Patients With Periodontitis and With T2D (n)</th>
<th>Patients With Periodontitis and Without T2D (n)</th>
<th>Cytokines Investigated in Patients With Periodontitis and With and Without T2D</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vieira Ribeiro et al., 2011&lt;sup&gt;1&lt;/sup&gt;</td>
<td>37</td>
<td>20</td>
<td>IL-4, IL-17, IL-23, and IFN-γ</td>
<td>GCF levels of IL-17, IL-23, and IFN-γ were higher in patients with T2D and periodontitis compared to medically healthy individuals with periodontitis. IL-4 levels were reduced in patients with T2D and periodontitis compared to medically healthy individuals with periodontitis.</td>
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<td>Kardeşler et al., 2011&lt;sup&gt;9&lt;/sup&gt;</td>
<td>20</td>
<td>22</td>
<td>IL-6</td>
<td>GCF levels of IL-6 were higher in patients with T2D and periodontitis compared to medically healthy individuals with periodontitis.</td>
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<td>Kardeşler et al., 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>24</td>
<td>25</td>
<td>MMP-8, MMP-13, and TIMP-1</td>
<td>GCF concentrations of MMP-8, MMP-13, and TIMP-1 were similar in patients with periodontitis with and without T2D.</td>
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<tr>
<td>Correa et al., 2008&lt;sup&gt;11&lt;/sup&gt;</td>
<td>23</td>
<td>26</td>
<td>IL-1β, IL-18, MMP-8, and MMP-9</td>
<td>GCF concentrations of IL-1β, IL-18, MMP-8, and MMP-9 were similar in patients with periodontitis with and without T2D.</td>
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<td>Duarte et al., 2007&lt;sup&gt;12&lt;/sup&gt;</td>
<td>20</td>
<td>20</td>
<td>IL-1α, IL-1β, IL-6, IL-8, and IFN-γ</td>
<td>GCF concentrations of IL-1β and IL-8 were similar in patients with periodontitis with and without T2D. GCF levels of IL-6 and IL-1α were higher in patients with T2D and periodontitis compared to medically healthy individuals with periodontitis.</td>
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<td>Navarro-Sanchez et al., 2007&lt;sup&gt;13&lt;/sup&gt;</td>
<td>10</td>
<td>10</td>
<td>IL-1β and TNF-α</td>
<td>Both groups showed significant reductions in GCF levels of IL-1β and TNF-α after periodontal treatment.</td>
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<td>Engebretson et al., 2006&lt;sup&gt;14&lt;/sup&gt;</td>
<td>45</td>
<td>35</td>
<td>IL-8</td>
<td>GCF concentrations of IL-8 were higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis.</td>
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<tr>
<td>Bulut et al., 2001&lt;sup&gt;15&lt;/sup&gt;</td>
<td>17</td>
<td>17</td>
<td>IL-1α</td>
<td>IL-1α levels were higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis.</td>
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<td>Kurtiş et al., 1999&lt;sup&gt;16&lt;/sup&gt;</td>
<td>24</td>
<td>24</td>
<td>IL-6</td>
<td>GCF concentrations of IL-6 were similar in patients with periodontitis with and without T2D.</td>
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<td>Cutler et al., 1999&lt;sup&gt;17&lt;/sup&gt;</td>
<td>5</td>
<td>7</td>
<td>IL-1β</td>
<td>GCF concentrations of IL-1β were similar in patients with periodontitis with and without T2D.</td>
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IFN = interferon; TIMP = tissue inhibitor of metalloproteinases; TNF = tumor necrosis factor.
This suggests that patients with T2D and periodontitis have two chronic inflammatory conditions, each of which may affect the other. In this context, it may be argued that the proinflammatory proteins expressed in the GCF of patients with periodontitis with T2D may also be higher compared to medically healthy patients with periodontitis. Duarte et al.\textsuperscript{12} reported GCF IL-6 levels to be higher in patients with T2D; however, the Kurits study\textsuperscript{16} reported GCF IL-6 levels to be similar between patients with and without T2D. Since IL-6 is actively involved in leukocyte recruitment, apoptosis, and T-cell activation in many chronic inflammatory diseases and several chronic inflammatory disorders,\textsuperscript{21} it seems that an overproduction of IL-6 and IL-1\textalpha\ in the local tissues may be associated with the T2D-associated periodontal destruction induced by the oral biofilm and that IL-8 may not be directly involved in jeopardizing the periodontal tissues. However, Engebretson et al.\textsuperscript{14} reported controversial results to the study by Duarte et al.\textsuperscript{12} by reporting higher levels of IL-8 in the GCF of patients with periodontitis with T2D compared to medically healthy individuals with periodontitis. Because only these two studies\textsuperscript{12,14} that investigated the levels of IL-8 in patients with periodontitis with and without T2D fulfilled our eligibility criteria, the significance of IL-8 in this context remains debatable. Further studies are warranted in this regard. IL-1\beta is also a proinflammatory cytokine that mediates bone destruction by stimulating the formation of collagenase and prostaglandin E.\textsuperscript{22} Three studies\textsuperscript{1,13,17} included in this review showed similar levels of IL-1\beta in patients with periodontitis with and without T2D. This also suggests that the severity of periodontal inflammation mainly governs the expression of proinflammatory cytokines in the GCF regardless of the systemic health status of the patient. The same explanation may be suggested for the raised concentrations of MMP-8 and -9 in the GCF of patients with periodontitis with and without T2D.\textsuperscript{10,11} However, further research is warranted to clarify the association between cytokine expression in patients with periodontitis with and without T2D.

Various explanations can be posed regarding the similarity in cytokine expression in the GCF of patients with periodontitis with and without T2D. Because severe periodontitis is a risk-factor of diabetes in undiagnosed individuals,\textsuperscript{23-25} the possibility of these purported medically healthy individuals to be in a prediabetic state cannot be ignored. Likewise, it is also notable that the medically healthy individuals in the included studies were in their fourth decade of life, the age group in which T2D is usually diagnosed.\textsuperscript{26} Thus, it is possible that the similarity in GCF cytokine profiles in patients with periodontitis with and without T2D could be associated with the presence of latent systemic conditions in the otherwise medically healthy individuals. This may also suggest that the balance between proinflammatory and anti-inflammatory mediators in periodontal tissues of medically healthy subjects may be shifted toward a hyper-proinflammatory state that could exacerbate the host response against pathogens and periodontal destruction. Results by Javed et al.\textsuperscript{2} demonstrated that individuals with well-controlled T2D and medically healthy individuals exhibit significantly better periodontal health statuses compared to patients with poorly controlled T2D. It may therefore be hypothesized that the pattern of periodontal inflammation in medically healthy individuals with a devastated periodontal health status may also be similar to that of individuals with poorly controlled T2D. Studies\textsuperscript{27,28} reported that the severity of periodontitis in patients with T2D is positively associated with the duration of T2D. It may therefore be hypothesized that patients with periodontitis with a long-standing history of T2D may experience more severe periodontal inflammatory conditions compared to patients with periodontitis with a shorter medical history of T2D and medically healthy subjects; this may in turn influence the GCF cytokine levels in these groups. From the literature reviewed, it seems that the duration of T2D does not significantly influence the GCF cytokine profiles in patients with periodontitis with and without T2D.

Within the limits of the present review, it is concluded that the severity of the periodontal inflammatory...
response chiefly modulates the cytokine gradient in patients with and without T2D.

ACKNOWLEDGMENT

The authors report no conflicts of interest related to this study.

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Submitted April 5, 2011; accepted for publication May 21, 2011.

APPENDIX:

LIST OF EXCLUDED STUDIES. MAIN REASON FOR EXCLUSION IS SHOWN IN BRACKETS


