Proinflammatory cytokines in the crevicular fluid of patients with peri-implantitis

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Keywords:
Cytokine
Crevicular fluid
Implant
Inflammation
Peri-implantitis

1. Introduction

Several studies [1–4] have confirmed that dental implants can osseointegrate and remain functionally stable; however, bacterial contamination of the implant may evoke an inflammatory response in a manner similar to that of a patient with periodontitis (inflammatory condition involving the supporting structures of teeth including gingiva and alveolar bone) [5–7]. Peri-implantitis (PI) is an inflammatory condition that affects alveolar bone and soft tissues around implants that may result in the loss of supporting bone [8]. Microbial plaque is considered to be the most important factor in the pathogenesis of periodontitis and PI [9,10]. In early stages of PI, peri-mucositis (a reversible inflammation of the soft tissues surrounding the functional implant) occurs, which if left untreated may progress to PI [11]. PI is usually diagnosed during routine dental visits since it is often asymptomatic in conjunction with periodontal bone loss [12]. Increased clinical pocket depth, gingival bleeding and occasionally suppuration may be indicative of pathology in peri-implant tissues [12]. Studies have reported a high prevalence of PI in patients with periodontitis compared to patients without periodontitis; however, controversy persists in this regard [12–14].

An early and reliable detection of any adverse peri-implant tissue reaction is a requirement for treatment planning in patients treated with endosseous dental implants. The peri-implant crevicular fluid (PICF) is an osmotically mediated inflammatory exudate originating from the vessels of the gingival plexus. Its composition is similar to that of the gingival crevicular fluid (GCF), containing host-derived enzymes and their inhibitors, inflammatory mediators and host-response modifiers and tissue breakdown products [14,15]. PI may modulate periodontal destruction by altering polymorphonuclear leukocyte function and by deregulating cytokine production [16]. A destructive inflammatory cytokine may be described as a cytokine which is induced during an inflammatory response and is associated with the onset and/or progression of the insult. Such proinflammatory cytokines have also been shown to promote osteoclastic activity that may lead to the loss of natural
teeth (in patients with periodontitis) and dental implants (in patients with PI) [17,18]. Thus, analysis of cytokine levels in the PICF may help in detecting inflammatory lesions at an early stage which might be clinically latent. Simultaneously, PICF analysis may also help in monitoring the osseointegration process and the bone response to occlusal loading and infection, thereby improving the long-term success of implants. Standard techniques that have been shown to be reliable and accurate in investigating cytokine levels in PICF include enzyme link immunosorbent assay (ELISA), polymerase chain reaction (PCR) and western blotting [19–33].

Since alveolar bone resorption is a classical feature of PI as well as periodontal disease, particular attention should be paid to the cytokine profiles in the PICF of patients with PI. In this regard, the purpose of this paper was to review the current literature on the cytokine profile in the PICF of patients with PI and to investigate whether specific PICF assays could be useful in the assessment, monitoring and prediction of peri-implant tissue responses.

2. Materials and methods

2.1. Focused question

The addressed focused question was: “What is the proinflammatory cytokine profile in the PICF of patients with PI?”.

2.2. Eligibility criteria

The eligibility criteria were: (1) original research articles; (2) clinical and experimental studies; (3) use of control group; (4) reference list of pertinent original and review studies; (5) use of statistical methods; (6) intervention: patients with and without PI; and (7) articles published only in English-language. Letters to the editor, historic reviews and unpublished articles were excluded.

2.3. Search strategy

The authors searched the MEDLINE/PubMed databases of the National Library of Medicine, Bethesda, Maryland, for appropriate articles addressing the focused question. 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 eligibility criteria. Databases were explored from 1994 up to and including July 2010 using various combinations of the following keywords: “cytokine”, “crevicular fluid”, “implant”, “inflammation”, “peri-implantitis” and “periodontitis”.

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 was performed. The initial search yielded 24 articles. Nine studies, which did not meet the eligibility criteria, were excluded (see Appendix). In total, 15 articles [19–33] were retrieved and processed for data extraction (Table 1).

3. Results

3.1. Characteristics of included studies

All studies [19–33] were performed in humans and were either carried out at universities or healthcare centers. Fourteen case-control studies [19–31,33] and one case-report [32] were included in the present analysis. The numbers of study participants ranged from one female individual to 180 subjects. The participants with PI were aged between 20 and 90 years. The durations for which the implants had remained in situ ranged between at least 7 months to 13.9 years. Smokers were included in three studies [26,28,30]. Cytokine levels in PICF of patients with and without PI were analyzed using ELISA, PCR and western blotting [19–33].

Four studies [25,29,32,33] showed high levels of interleukin (IL)-1 beta (β) in the PICF of implants affected by PI compared to healthy sites; whereas results by Hultin et al. [30] did not report any significant difference in IL-1β levels in sites with and without PI. Two studies [19,21] showed an over-expression of IL-6 and IL-8 in the PICF of implants affected by PI compared to healthy implants. Bordin et al. [21] showed an increased secretion of IL-6, IL-8 and matrix metalloproteinase-1 by fibroblastic cells cultured from sites with PI compared to healthy sites. Six studies [9,10,23–25,27] reported high levels of tumor necrosis factor-alpha (TNF-α) levels in the PICF of sites with PI (test-sites) compared to the healthy (control) sites. Two studies [26,28] reported a positive association between polymorphism of IL-1 gene and PI; whereas the study by Cury et al. [20] showed a negative association between polymorphism of TNF-α and an increased risk of PI.

4. Discussion

A connection between PI and periodontitis has been reported [12,34,13]. Bacterial plaque is a common etiological factor that has been associated with the loss of natural teeth as well as dental implants [10,35,36]. Papioannou et al. [37] reported that patients with high numbers of periodontal pathogens around teeth are at an increased risk of cross-infection with bacteria from periodontal sites to implant sites. Since both PI and periodontitis are inflammatory conditions, it may be hypothesized that this relationship may influence the expression of proinflammatory cytokines in the PICF of the susceptible host. In their study, Mâximo et al. [34] investigated the prevalence of PI in periodontally compromised individuals. The results showed a significant positive relationship between PI and periodontitis [34]. Likewise results from another study [13] also showed PI and implant failure to be more common in patients with periodontitis in comparison to controls (dental implant patients without periodontitis). In contrast, results from the Koldsland study [38] showed PI to be a common manifestation in patients with and without periodontitis. Similar results were reported by Serino and Ström [39] and Wennström et al. [14]. Quirynen et al. reported that periodontally compromised patients can be successfully offered dental implant treatment with periodontal support therapy as an adjunct [40]. Thus, the question “Are patients with periodontitis more susceptible to PI?” remains debatable and further studies are warranted to explore this association.

Several factors [such as underprivileged socioeconomic status (SES), medications [such as antibiotics], poorly-controlled diabetes mellitus (DM), osteoporosis, increasing age, smoking habit, recent periodontal therapy and poor oral hygiene], which are known to influence periodontal inflammation may also play a role in the pathogenesis of PI in the susceptible host [10,38,41,42]. Grossi and Genco [43] proposed that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from lipopolysaccharide and products of periodontopathic organisms may intensify the amount of the advanced glycation end product mediated cytokine response in patients with DM compared to healthy controls. It may therefore be argued that such parameters may also contribute in altering the cytokine levels in the PICF of susceptible hosts. After critically reviewing the pertinent literature, we observed that most of the studies that fulfilled our eligibility criteria were controlled for confounding factors (including those mentioned above). The Mâximo study [34] also reported a negative connection between PI and risk factors including deprived SES, smoking status, gender, age, DM and osteoporosis. On the other hand, results by Laine et al. [26] and Gruica et al. [28] showed that...
Table 1: Characteristics and main results of the studies that fulfilled the eligibility criteria.

<table>
<thead>
<tr>
<th>Authors year</th>
<th>Aim/s</th>
<th>Study design</th>
<th>Total subjects</th>
<th>Patients with peri-implantitis (n, mean age/age range in years)</th>
<th>Duration of implants in situ</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venza et al. [19]</td>
<td>To assess whether T2D alters the expression of inflammatory mediators in sites with PI</td>
<td>Case-control</td>
<td>135</td>
<td>65/62.1/60–65</td>
<td>At least 2 years</td>
<td>TNF-α, IL-6 and IL-8 were over-expressed in sites affected by PI; T2D affects the expression of TNF-α, IL-6 and IL-8</td>
</tr>
<tr>
<td>Cury et al. [20]</td>
<td>To assess the relationship between a specific polymorphism in the TNF-α gene and PI</td>
<td>Case-control</td>
<td>90</td>
<td>49/51.1/20–77</td>
<td>At least 6 months</td>
<td>Polymorphism TNF-α was not associated with an increased risk for PI</td>
</tr>
<tr>
<td>Bordin et al. [21]</td>
<td>To assess the role of granulation tissue fibroblasts in PI with respect to (a) cytokine release in the PICF (b) secretion of constitutive factors promoting migration/survival of infiltrates into osseointegrated sites</td>
<td>Case-control</td>
<td>16 Biopsies</td>
<td>8 Biopsies (NA/NA)</td>
<td>At least 4 years</td>
<td>Fibroblasts showed a reduced secretion of the collagen inducer TGF-β1 and tissue inhibitor of metalloproteinase-1. Secretions of IL-6, IL-8, MMP-1 and VEGF were increased in these cells compared to healthy fibroblasts</td>
</tr>
<tr>
<td>de Mendonça et al. [22]</td>
<td>To assess the effects of a surgical anti-infective mechanical therapy for PI on TNF-α levels and clinical parameters and at 12 months post-therapy</td>
<td>Case series</td>
<td>10</td>
<td>10/62.3/52–77</td>
<td>At least 5.2 years</td>
<td>At 3 and 12 months, the anti-infective therapy resulted in a significant decrease in TNF-α levels with improvements in clinical parameters (including plaque index, gingival bleeding, probing depth and clinical attachment levels)</td>
</tr>
<tr>
<td>Duarte et al. [23]</td>
<td>To assess the expressions of IL-4, IL-10, IL-12, TNF-α, RANKL and OPG in sites exhibiting initial and severe PI</td>
<td>Clinical</td>
<td>48</td>
<td>48/Initial PI:56.4/37–73 severe PI:59.4 (37–73)</td>
<td>At least 4 years</td>
<td>IL-12 and TNF-α were higher in sites with severe PI compared to sites with initial PI. IL-4 and OPG levels were higher in healthy sites followed by sited with initial and severe PI. Highest OPG/RANKL ratio was observed in healthy implant sites and the lowest in sites with severe PI</td>
</tr>
<tr>
<td>Duarte et al. [24]</td>
<td>To compare the levels of cytokines between PI and healthy sites after mechanical anti-infective therapies</td>
<td>Clinical</td>
<td>35</td>
<td>15/53.4/27–77</td>
<td>At least 1 year</td>
<td>TNF-α levels were significantly reduced for implants with PI and achieved the same level as the controls at 3 months after mechanical anti-infective therapies</td>
</tr>
<tr>
<td>Lachmann et al. [25]</td>
<td>To assess the levels of IL-1β, PAI-2, and PGE2 in the PICF of patients with PI compared to patients with healthy oral implants</td>
<td>Case-control</td>
<td>29</td>
<td>11/59.9/63–74</td>
<td>13.9 years</td>
<td>PAI-2 levels were positively related to IL-1β and PGE2 levels in patients with PI</td>
</tr>
<tr>
<td>Laine et al. [26]</td>
<td>To assess the role of IL-1 gene polymorphisms in patients with PI</td>
<td>Case-control</td>
<td>12,076% Smokers</td>
<td>71/68/32–88</td>
<td>At least 2 years</td>
<td>IL-1 gene polymorphism was associated with PI and may represent a risk factor for the inflammatory disorder</td>
</tr>
<tr>
<td>Konttinen et al. [27]</td>
<td>To investigate the cytokines around loosening dental implants</td>
<td>Case-control</td>
<td>30</td>
<td>10/64.4/55–77</td>
<td>NA</td>
<td>TNF-α was the most common cytokine isolated from patients with PI</td>
</tr>
<tr>
<td>Gruica et al. [28]</td>
<td>To assess the impact of the IL-1 genotype and smoking on the development and prognosis of complications in dental implants</td>
<td>Case-control</td>
<td>18029.4% Smokers</td>
<td>51 Implants (NA/25–90)</td>
<td>At least 8 years</td>
<td>IL-1 genotype and heavy smoking status (at least 20 cigarettes per day) were significantly associated with biologic implant complications including PI</td>
</tr>
<tr>
<td>Murata et al. [29]</td>
<td>To analyze the PICF levels of IL-1β in patients with PI</td>
<td>Case-control</td>
<td>16</td>
<td>4/56/36–66</td>
<td>At least 9 months</td>
<td>TNF-α levels in PICF were significantly higher from PI sites compared to sites without PI</td>
</tr>
<tr>
<td>Hultin et al. [30]</td>
<td>To assess the inflammatory host-response around implants in patients with PI</td>
<td>Case-control</td>
<td>36</td>
<td>17/41% Smokers (62.8/55–69)</td>
<td>At least 6.7 years</td>
<td>There was no significant difference in levels of IL-1β in sites with and without PI</td>
</tr>
<tr>
<td>Aboyoussef et al. [31]</td>
<td>To assess PGE2 levels in PICF of patients with dental implants</td>
<td>Case-control</td>
<td>48 Implants'</td>
<td>NA/NA/NA</td>
<td>NA</td>
<td>PGE2 levels in PICF were higher in dental implants with higher plaque index, gingival bleeding and probing depth in contrast to the control implants</td>
</tr>
<tr>
<td>Curtis et al. [32]</td>
<td>To analyze the PICF around two failing dental implants</td>
<td>Case-report</td>
<td>One female</td>
<td>1/55 years</td>
<td>At least 1.5 years</td>
<td>PICF levels of IL-1β provided an objective measure of the peri-implant health and the effectiveness of treatment for PI</td>
</tr>
<tr>
<td>Panagakos et al. [33]</td>
<td>To compare the proinflammatory cytokines between healthy implants and those affected by PI</td>
<td>Case-control</td>
<td>13</td>
<td>NA/NA/NA</td>
<td>At least 7 months</td>
<td>IL-1β levels in PICF of implants sites affected by PI compared to control (healthy) sites</td>
</tr>
</tbody>
</table>

IL: interleukin; MMP: matrix metalloproteinase; OPC: osteoprotegerin; PAI-2: plasminogen activator systems' inhibitor-2; PGE2: prostaglandin E2; PI: peri-implantitis; PICF: peri-implant crevicular fluid; RANKL: receptor activator of nuclear factor-kappa B ligand; T2D: type 2 diabetes; TNF-α: tumor necrosis factor-alpha; TGF-β1: transforming growth factor beta-1; VEGF: vascular endothelial growth factor; NA: not available.

Numbers of study subjects was unclear.
polymorphism of IL-1 gene was associated with the pathophysiology of PI. Based on the results from the present study, there seems to be insufficient evidence to support or refute an association of smoking between the IL-1 genotype status and PI.

It has been suggested that the rate of periodontal bone loss in patients with PI increases with time and follows a non-linear progression pattern [44]. It seems that dental implants that have been in situ over longer durations are more susceptible to PI; hence it may be hypothesized their PICF may express higher cytokine concentrations in comparison to recently inserted dental implants. From the literature reviewed, we did not observe any relationship between duration for which the implant remained in situ and expression of cytokines in the PICF of patients with PI. For example, PI patients in studies by Panagakos et al. [33], Murata et al. [29] and Gruica et al. [28] expressed high levels of proinflammatory cytokines in the PICF; however the durations for which the implants had been in situ were 7, 9 months and 8 years, respectively. Further studies are needed to investigate the impact of duration of implant carriage and expressions of cytokine levels in patients with PI.

Since PI is usually latent in early stages, cytokine analysis in the PICF of susceptible individuals may serve as a valuable analytical tool. Standard techniques such as ELISA, PCR and western blotting have been shown to provide reliable and accurate results in this regard [19–34,13,35–37]. For example a lower osteoprotegerin-receptor activator of nuclear factor-kappa ratio with increased levels of other cytokines including IL-6, IL-8 and IL-1β in the PICF may signal peri-implant tissue inflammation. The authors of the present review suggest that such techniques could yield valuable information regarding the occurrence and prognosis of PI in susceptible individuals such as those with a history of periodontitis.

5. Conclusions

Raised levels of proinflammatory cytokines are exhibited in the PICF of patients with PI. Monitoring cytokine levels in the PICF may help in the early detection of inflammatory conditions that may not be clinically apparent. Regular follow-up visits and other supportive therapies, such as oral hygiene maintenance should also be considered as an inevitable requirement for patients with PI.

Conflict of interest and financial disclosure

The authors declare that they have no conflicts of interest and there were no external sources of funding for the present study.

Appendix A

List of excluded studies. Main reason for exclusion is shown in parenthesis.


References
