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REVIEW

Biological Factors Involved in Implant-Anchored Orthodontics and in Prosthetic-Implant Therapy: A Literature Review

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Abstract During the past few years, the application of orthodontic miniscrews and dental implants has been expanded. However, failures have necessitated ongoing investigation of potential risk factors. The aim of this overview was to conduct an assessment of the immunological response following application of cortical temporary anchorage devices—titanium miniscrew implants—in orthodontic patients. A scrupulous search of the database revealed only two matching items; therefore studies evaluating the immune response subsequent to insertion of dental implants were reviewed. Thorough assessment revealed the following as factors associated with dental implant rejection: (1) correlation of the volume of gingival and peri-implant crevicular fluid and the amount of interleukin (IL)-1β with mucosal inflammation, thus serving as a peri-implantitis evaluation index; (2) significantly more frequent marginal bone loss around implants in patients with IL-1B-511 2/2 genotype; (3) humoral response to *Staphylococcus aureus*. However, since there is almost no evidence-based evaluation of the allergic/inflammatory reaction either to orthodontic titanium miniscrews themselves or in adolescents and young adults, who comprise the largest group of orthodontic patients, this issue requires further investigation. It is essential in order to achieve successful, sophisticated and modern treatment of malocclusions.

Keywords Orthodontics · Miniscrew implants · Immunological response

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Introduction

Clinicians and researchers have tried to use endosseous implants as orthodontic anchorage for over half a century. The first successful attempt to move teeth against a stationary screw was published as early as in 1969 by Linkow (1969), although routine application of dental implants for orthodontic purposes in humans began 20 years later (Prosterman et al. 1995; Renouard and Nguyen-Gauffre 1997; Roberts et al. 1984, 1994; Shapiro and Kokich 1988). Together with a certain increase of orthodontists' interest in application of screws, obvious disadvantages have become apparent: the requirement of specific surgical procedures during insertion and removal; the demand for complicated clinical and laboratory procedures to accurately transfer the implant position to cast models and to facilitate safe and precise implant insertion; delayed loading resulting from the waiting period necessary for osseointegration, increasing total treatment time; possible location limited only to edentulous or retromolar areas of the maxilla and mandible; and large dimensions apparently increasing the risk of damage of the adjacent tissues or root injuries. In order to overcome these problems, Kanomi (1997) and Costa et al. (1998) introduced miniscrew implants—temporary anchorage devices (TADs). Their decreased diameter facilitates insertion in almost all sites of the jaws, with no flap surgery required. Osseointegration

does not usually occur; therefore they provide only temporary stationary anchorage (Liou et al. 2004). Consequently there is no 6-month waiting period: immediate loading of TADs apparently decreases total treatment time.

During the past few years, the application of miniscrew implants has been expanded to include a variety of cases that would otherwise require orthognathic surgery, such as correction of deep bite, closure of extraction spaces, correction of canted occlusal plane, alignment of dental midlines, extrusion of impacted canines, extrusion and uprighting of impacted molars, molar intrusion, distalization of either upper molar or lower teeth, en-masse retraction of anterior teeth, molar mesialization, upper third molar alignment, intermaxillary anchorage for the correction of sagittal discrepancies, and correction of vertical skeletal discrepancies (Antoszewska 2007a, b; Papadopoulos 2008; Park and Kwon 2004; Park et al. 2001, 2002).

Despite researchers' efforts, no TAD system has provided a 100% success rate. The occurrence of screw failures has required ongoing investigation of potential risk factors. Since peri-implantitis turned out to be the main cause of screw loosening (Antoszewska et al. 2009; Chen et al. 2007; Cheng et al. 2004; Kuroda et al. 2007; Moon et al. 2008), assessment of factors involved in such inflammation has become crucial to increase TAD stability in orthodontics.

Numerous papers have covered various aspects of peri-implant inflammation (Aboyoussef et al. 1998; Berglundh et al. 1992; Donath et al. 1992; Fartash et al. 1997; Paquette et al. 2006; Merritt 1984; Talarico et al. 1997; Toth et al. 1985). Former immunohistologic analysis revealed equal lymphocyte B and T levels, as well as CD4:CD8 ratios, in the vicinity of the implant, either healthy or overtly inflamed gingiva, thus proving that its lesion was a stable, well-controlled response (Seymour et al. 1989). However, since expression of vascular cell adhesion molecules by capillary loops—an early step necessary for leukocyte extravasation and subsequent migration—has turned out to be influenced by local factors (Tonetti et al. 1994), immunization developed after dental implant placement was neither obvious nor linear. As proved in other in vitro studies evaluating the mutual effect of host and foreign body sensitivity, reactions and infections were two aspects of biocompatibility extremely difficult to predict, therefore requiring analysis of the distinguished transmitters and compounds active in the immunological response (Merritt 1984; Toth et al. 1985).

Since biological factors involved in orthodontic and prosthetic therapies based on implants represent a current and very attractive topic, the aim of the present paper was to conduct an assessment of immunological risk factors when using TADs.

Materials and Methods

The PubMed and Cochrane databases were searched for articles in English and Polish, on "miniscrews/mini-implants/miniplates/TADs/titanium screws/skeletal anchorage and immunology/immunological response/antibodies" in human studies (randomized controlled clinical trials, cohort studies, case–control studies, cross-sectional studies) and in vitro research. There were only two items found (Lee et al. 2004; Sari and Uçar 2007). The next database search covered "dental implants/endosseous implants/prosthetic implants and immunology/immunological response/antibodies". Articles published between 1999 and 2009 in dental and medical papers were analyzed. Each article was additionally hand searched for references that may have been missed by the database search. Full text versions of papers were obtained for further analysis.

Results and Discussion

The local balance of reactive and suppressor immune cells, their cytokines and mediators ensures periodontal stability. Bacterial infection induces the host immune response and affects the innate and adaptive immune systems. Proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-12, tumor necrosis factor (TNF)-α and interferon γ, induce tissue destruction (Dinarello 2000; Seymour and Gemmell 2001). Anti-inflammatory cytokines, including IL-1 receptor antagonist, IL-4, IL-10, IL-13 and transforming growth factor (TGF)-β, play a protective role (Opal and DePalo 2000). Recently, the stimulator (the receptor activator of nuclear factor-κB ligand—RANKL) and inhibitor (osteoprotegerin—OPG) of osteoclast differentiation were discovered, confirming the complex molecular interactions in the process of bone resorption in response to bacterial pathogens (Troen 2003).

Some studies focused on the cytokine levels in peri-implant crevicular fluid (Duarte et al. 2009a, b; Sari and Uçar 2007; Schierano et al. 2003, 2008). Sari and Uçar examined the level of pro-inflammatory IL-1β around orthodontic mini-implants during distal movement of the maxillary canines (Sari and Uçar 2007). The study group comprised ten young adults with four premolars extracted. Microscrews were implanted bilaterally in the alveolar bone between the upper second premolars and first molars and served as absolute, skeletal anchorage. The upper canines were designated as the treatment group, the lower ones were used as controls and miniscrews were described as the implant group. The peri-microscrew implant crevicular fluid was analyzed at the beginning of distalization (2 weeks after implantation) after 1, 2 and 7 days, and then on the 14th and 21st day. The level of IL-1β did not change

significantly during the tooth movement in the implant and control group, whereas the level in the treatment group was significantly increased after 1 and 2 days. Schierano et al. (2003, 2008) assessed the influence of dental implants on pro- and anti-inflammatory cytokine profiles in 11 edentulous patients (mean age 61.4 years), rehabilitated with titanium-implant-retained overdentures. TGF-β1 mRNA levels increased immediately after treatment and transcript accumulation for IL-10 increased after 4 months and decreased dramatically thereafter. The clinical, histomorphometric and immunologic analysis after 12 months showed no inflammation of the peri-implant tissues in 91% of the patients. The authors suggested that the newly described TGF-β and/or IL-10 secreted by regulatory T cells/T helper-3 cells may populate the local implant site and affect the gingival microenvironment and immune response. Schierano et al. also examined the levels of TNF-α, TGF-β2 and IL-1β in gingival and peri-implant crevicular fluid before and after de novo plaque accumulation. They designed a split-mouth study—25 patients (mean age 53 $\pm$ 14 years) rehabilitated with prosthetic implants. On the basis of obtained data, the authors concluded that the volume of gingival and peri-implant crevicular fluid and the amount of IL-1β are correlated with mucosal inflammation and may serve as an index for evaluation of the inflammatory process. Duarte et al. (2009a, b) evaluated the effect of anti-infective mechanical therapy (chemical conditioning, lasers, air-powered abrasive, plastic and resin curets, systemic/local antimicrobials and/or regenerative techniques) on clinical parameters and levels of IL-4, -10, -12, TNF-α, RANKL and OPG in the peri-implant crevicular fluid. They found that the anti-infective treatment may locally influence the levels of TNF-α and the OPG/RANKL ratio and improve the clinical indices around peri-implant tissue. Another study designed by the same researchers assessed the relationship between differential expression of cytokines and the severity of peri-implantitis, evaluating IL-12, IL-4, IL-10, TNF-α, RANKL and OPG levels based on peri-implant soft tissue biopsies in 48 patients totally or partially edentulous, treated with dental implants. The material was divided into: the healthy implant group, mucositis, initial and severe peri-implantitis. The authors found that the level of IL-12 and TNF-α were correlated with the severity of peri-implant disease. The healthy implant group presented the highest values of IL-4 and OPG/RANKL ratio as well as the lowest values of IL-10. The severe peri-implantitis sites group presented the lowest OPG/RANKL ratio. Duarte et al. (2009a, b) suggested that inflammatory and osteoclastogenesis-related factors may affect the onset and severity of peri-implantitis.

Polish researchers (Pietruski et al. 2001) innovatively evaluated the levels of pro-inflammatory interleukins IL-1, IL-6 and IL-8 in the blood, not in the peri-implant crevicular fluid. Pietruski et al. collected the blood for analysis with the ELISA method three times: prior to implantation, 4 day and 4 months after the surgery before implant exposure. The material consisted of ten patients (aged 27–52.4), subjected to implantation procedures, without clinical symptoms of oral inflammation. The serum concentrations of IL-1 were similar during the three consecutive measurements. The second examination revealed significant increase of IL-6 and IL-8, which expressed local inflammation provoked by tissue damage. After four months the levels of IL-6 and IL-8 were close to initial values.

Polymorphisms of the IL-1 gene are supposed to be involved in the increased susceptibility to some diseases, for instance: chronic periodontitis, rheumatoid arthritis and external apical root resorption during orthodontic tooth movement (Bastos Lages et al. 2009; McDevitt et al. 2000; Tolusso et al. 2006). Some studies concentrated on the issue of the relationship between this gene polymorphism and risk factors for dental implant failure (Lachmann et al. 2007; Lin et al. 2007; Rogers et al. 2002; Shimpuku et al. 2003). Rogers et al. (2002) observed no association between IL-1A-889 and IL-1B+3953 alleles or the composite genotype and the failure of dental implants. Lachmann et al. (2007) found that composite genotype (IL-1A-889 and IL-1B+3954) had only a small influence on the immune response, but they suggested that the methodology used could have affected the results. In contrast, Shimpuku et al. (2003) and Lin et al. (2007) reported a relationship between polymorphisms of the IL-1 gene and marginal bone loss around dental implants. Shimpuku et al. (2003) performed a case–control study—the material consisted of 39 Japanese patients (mean age 55.1 $\pm$ 9.4 years) who underwent implantation in the maxilla and/or mandible. The authors suggested that the polymorphisms of the IL-1B+3954 and IL-1A-889 genes could be related to bone loss after connection of the abutments. The researchers observed significantly more frequent occurrence of marginal bone loss around implants in the group with IL-1B-511 2/2 genotype, in comparison to IL-1B-511 1/1 or 1/2 genotypes. Furthermore, the authors found that the IL-1B-511 gene could serve as a genetic marker associated with non-infectious loss of the alveolar bone before connection of the abutments. Similar conclusions were drawn by Lin et al. (2007). They examined the polymorphisms of IL-1 genes in 59 patients (mean age 42.77 years) with 143 dental implants. The patients were divided into two groups: with one or more marginal bone resorption around dental implants exceeding 0.5 mm and with bone loss $<$0.5 mm. In the first group the frequency of IL-1B-511 2/2 was significantly increased.

Some authors concentrated on the microbiological findings in failing dental implants (Kronstrom et al. 2000; Leonhardt et al. 1999). Leonhardt et al. (1999) compared

subgingival bacterial samples from 2 groups of patients: 37 with progressive marginal bone loss larger than 3 implant threads and 51 without clinical and radiographic signs of disease. For implants with peri-implantitis putative periodontal pathogens, such as *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *nigrescens*, were found in 60% of the cases, whereas microorganisms not primarily related to periodontal pathogens—*Staphylococcus* spp., *Candida* spp. and enterics—were detected in 55%. Kronstrom et al. (2000) applied the ELISA test to detect serum IgG antibody titers and avidity to *Staphylococcus aureus*, *Streptococcus intermedius*, *Actinomyces viscosus*, *P. gingivalis* and *Bacteroides forsythus* in two groups of patients: with failing and successful titanium dental implants. In the latter group the serum IgG antibody titers to *S. aureus* were significantly increased and higher serum IgG antibody avidity to *B. forsythus* and *P. gingivalis* was observed. The authors stated that infections caused by bacteria such as *S. aureus* and *B. forsythus* could enhance a cytokine response leading to an exaggerated inflammatory response and the start of osteolysis and loss of osseointegration in patients who present a low titer response to infections. The humoral immunity factors relative to these pathogens could be responsible for dental implant failure, and serum IgG antibody titers should be assessed.

Some authors concentrated on the issue of differential inflammatory macrophage response to titanium-based particles (Revell 2008; Valles et al. 2006, 2008). Histological analysis of the peri-prosthetic tissues obtained from mobile implants revealed the presence of granulomatous membrane consisting of macrophages, giant cells, lymphocytes, fibroblasts and wear particles (Ingham and Fisher 2005). Valles et al. (2006, 2008) designed two in vitro studies, in which they evaluated the biocompatibility of wear particles—titanium and rutile—in a co-culture model with differentiated THP-1 cells/osteoblasts and primary macrophages. The authors examined the ability of wear debris to modulate the release of pro-inflammatory cytokines from macrophages and soluble factors involved in bone turnover. The authors observed higher levels of TNF-α, IL-6 and IL-1β after incubation with titanium-based particles, compared with rutile. They also suggested that interactions between osteoblasts and particles can regulate the extent of the response started by macrophages.

Conclusions

Since implantation is an invasive procedure it obviously stimulates the host immune system to secrete inflammatory mediators, possibly jeopardizing primary implant stability. Based on the presented literature review it may be stated that immunological risk factors of failure of dental implants widely used in contemporary orthodontics/dentistry have been carefully and constantly investigated, thus establishing the following potentially useful markers:

- levels of cytokines (especially IL-1β) in the peri-implant crevicular fluid as an index for evaluation of the inflammatory process;
- IL-1 gene polymorphism as a genetic factor associated with non-infectious marginal bone loss around the implant;
- serum IgG titers to various oral pathogens, for example *S. aureus* and *B. forsythus*.

However, the immune response to cortical TADs—miniscrew implants designed especially for orthodontic purposes—remains unexamined. There is almost no evidence-based evaluation of the allergic/inflammatory reaction either to orthodontic titanium miniscrews themselves or in adolescents and young adults, who comprise the largest group of orthodontic patients. Such a scientific niche doubtless requires an effort to establish and evaluate markers in the crevicular fluid and blood of orthodontic patients with miniscrew implants. Possible correlation of the immune response and prime instability of cortical TADs may help to improve control of risk factors responsible for premature loss of orthodontic miniscrew implants essential in sophisticated and modern treatment of malocclusions.

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