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S3-guideline "Dental implants in patients with immunodeficiency" – practice-oriented treatment recommendations

Dental implants are an integral part of modern dental, oral and maxillofacial medicine. Apart from rehabilitating the physiological masticatory function and increasing the quality of life, dental implants have a positive influence on the general health condition [31]. For successful treatment, a key prerequisite is the osseous healing of the inserted implants (osseointegration). This strongly depends on an adequately functioning immune system, as it is involved in regulating postoperative wound healing and it has an important modulating effect on the tendency of subsequent peri-implantitis development. In this respect, immunocompromised patients exhibit a particularly higher risk profile.

Given the current demographic development of higher life expectancy and continuously improving health care, it has become apparent that the number of patients displaying immunodeficiency, who wish to be treated with implant-supported restorations, is increasing. Furthermore, due to the ongoing improvement in long-term immunosuppressive therapies, a significant increase in this category of patients can be anticipated in the future [1, 13, 17].

Moreover, in deciding when dental implants are indicated in immunocompromised patients, it must be considered that the patient population is very heterogeneous with varying degrees of immune system impairment. For the dental practice, this means a high degree of uncertainty with respect to the indication for treatment, as well as the associated treatment sequence, which includes preparation, conducting the operative intervention and postoperative aftercare.

For a better overview, the classification of immunodeficiency can be grouped as follows:

1. Primary, congenital immunodeficiency*
2. Secondary, acquired immunodeficiency, e.g. HIV infection**
3. Secondary, drug-induced immunosuppression, e.g. steroids (cortisone)

Autoimmune diseases

Studies performed in the last 10 years corroborate that there is a steady increase in the frequency of autoimmune diseases [17]; at present, their prevalence in Europe and North America is presumed to be as high as 12.5 % [13, 17]. Accordingly, there is reason to suspect that the number of patients with autoimmune diseases, who wish for dental implants, will grow. The mechanisms which underlie the reduction of the body's immunological tolerance to one's own body molecules, and subsequently, to a lowered immune response and to different forms of autoimmune diseases, is not yet fully understood [28]. Socioeconomic, genetic and environmental factors as well as certain types of infections are discussed as being triggering factors for autoimmune reactions.

Autoimmune diseases occur more frequently in women. They represent the predominant group among patients suffering from autoimmune diseases (75 %) [13]. In a systematic review, the influence of autoimmune diseases and their therapy on the survival rates of dental implants was investigated. The outcome revealed a clear trend towards female patients who accounted for 98 % of the patient population. The frequent occurrence of different coexisting autoimmune diseases was also conspicuous; examples include the combination of rheumatoid arthritis and

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* There is insufficient literature on primary immunodeficiency for the purpose of drawing conclusions regarding the influence of the underlying disease on the survival of dental implants. The classification 1) has been included for the scope of completeness.

** Although the underlying disease, diabetes mellitus, also has immunomodulatory influences, it is not included in this guideline. In this context, reference should be made to the Guideline "Dental Implants in Diabetes Mellitus" (AWMF register number 083–025).

Sjögren's syndrome or dermatomyositis as well as oral lichen planus and Sjögren's syndrome.

With regard to the modalities for treating autoimmune diseases such as rheumatoid arthritis, polymyalgia rheumatica, pemphigus vulgaris, scleroderma, Sjögren's syndrome and systemic lupus erythematosus, mainly steroid medication such as prednisone or other glucocorticoid derivatives are used for therapy. Neither the effect of the drug nor the underlying autoimmune disease was found to affect implant survival [8].

In principle, due to the possible risk of malignant transformation of the oral manifestation of the underlying diseases, stringent implant aftercare should be respected. There is evidence to suggest that the very rare peri-implant carcinomas occur with particular frequency in patients with oral lichen planus [22].

Special role of Crohn's disease

The chronic inflammatory bowel disease, Crohn's disease, predominantly affects the gastrointestinal tract, although a direct influence on the oral mucosa can also occur. The autoimmune inflammatory reactions are triggered by antigen-antibody complexes and this is why immunosuppressive and anti-inflammatory drugs are part of the treatment spectrum.

Pertaining to the therapy of patients with dental implants and Crohn's disease, a correlation was observed between implant loss and Crohn's disease in studies investigating early implant failure [2, 3, 30]. These results were statistically supported by further studies performed in 2007 and 2008. The basis for the cumulative incidence of early implant loss in Crohn's disease patients is controversially debated in the scientific community. Thus far, it has been shown that the osseointegration of dental implants can be influenced by antigen-antibody complexes due to autoimmune reactions in the area of bone-implant contact [26]. Moreover, malnourishment, which frequently occurs in the course of Crohn's disease, may also lead to inadequate bone healing around dental implants [9].

HIV

In the last 30 years, the HIV infection and the subsequent Acquired Immune Deficiency Syndrome (AIDS) has developed from being an epidemic with a devastating deterioration of patient's health, to being a stable, chronic disease thanks to current therapeutic management. Consequently, there is an increasing number of patients at different stages of the disease who wish for implant-based dental rehabilitation.

Compared to healthy patients, both HIV-seropositive patients with a CD4 cell count > 200 cells/µl and severely immunocompromised patients with a CD4 count of less than 200 cells/µl showed no significant differences after implant insertion with regard to the healing reaction, infection rate or postoperative complications. In addition, higher rates of implant loss were not observed [6, 16, 18]. Consequently, there was no evidence of a direct relationship between the risk of postoperative infections after implant treatment and the CD4 count [10, 20, 29].

In 75 % of the studies which were analyzed, different forms of antibiotic therapy were used for implant surgery. The prophylactic administration of antibiotics had no influence on the risk of postoperative infections, but it was shown to reduce the risk of implant failure [5, 15]. In summary, in a systematic review, antibiotic therapy was identified as one of the key factors which influences the analysis of dental implant osseointegration in HIV-positive patients [4].

Chemotherapy

Chemotherapy still constitutes one of the main pillars of modern cancer treatment. To date, the number of approved antineoplastic drugs is continuously growing due to the diversification of drugs which target specific types of cancer. Therefore, it is difficult to thoroughly investigate the mechanisms by which chemotherapeutic agents exert their biological effects on dental implants. For this reason, few studies have explored the potential effect of chemotherapeutic agents on osseointegration in spite of the fact that it is one of the most important parameters for successful implant therapy.

For already existing implants, there is evidence to suggest that chemotherapy can have a variety of negative effects such as mucositis, painful peri-implant infections as well as systemic effects such as fever and sepsis. However, these reported side effects have been observed primarily in blade and subperiosteal implants, which are hardly used nowadays [14]. Due to the fact that chemotherapy is associated with serious underlying diseases, there is a need for rigorous risk stratification involving an interdisciplinary approach; thus, close cooperation with the oncologist in charge of therapy is recommended.

Immunosuppresion after organ transplantation

The number of organ transplant recipients is increasing in tandem with medical progress. As a general rule, oral and maxillofacial infectious foci should be surgically operated prior to organ transplantation in order to reduce the rate of postoperative infection. After successful transplantation, patients who have had multiple tooth extractions before transplantation often require the functional rehabilitation of their masticatory functions [24, 27]. It is not uncommon for dental practitioners and oral and maxillofacial surgeons who are performing the treatment to be addressed with the patient's expressed wish for implant-supported prosthetic restorations.

In numerous studies, no demonstrable effect of the various post-transplantation protocols and their respective immunosuppression regimes, which use steroid and immunomodulating drugs (tacrolimus, sirolimus, cyclosporine and mycophenolate), could be shown on the implant survival rate.

The lack of randomized controlled trials limits the ability to draw conclusions. Nevertheless, no constraints for treatment with dental implants could be identified based on the results of the abovementioned studies.

Implant surgery should only be performed after consultation with the transplant physician in charge,

especially with regard to prophylactic/prolonged antibiotic therapy.

The practice-oriented treatment recommendations and checklist for risk stratification for indicating and managing dental implant treatment in immunocompromised patients is based on the current S3-guideline „Dental implants in patients with immunodeficiency".

Practice-oriented treatment recommendations

1. Indications

The medical status of the patient at the time of indication has a significant influence on the success rate of implant treatment. Conversely, it must also be ensured that the planned implant therapy does not endanger the patient's health [12]. Thus, before indicating implant treatment, the individual risk for implant loss and complications should first be assessed in all patients displaying an autoimmune disease, immunodeficiency, or who are under immunosuppression.

Primarily, an acute status of the underlying disease as well as any local or systemic contraindications should first be excluded. Further treatment planning should ideally include interdisciplinary cooperation (internists, rheumatologists, or other specialist disciplines).

2. Preoperative pre-treatment and diagnostics

In order to reduce the risk of infection and eliminate existing foci of infection, any necessary surgical interventions should be performed before implant surgery. Wound healing can provide an initial insight into the function of the immune system.

In addition to radiological diagnostics, the reported clinical findings should be included for the purpose of risk assessment, as they may provide possible clues regarding compromised soft tissue healing, bone remodeling or rates of bone regeneration. The prosthetic evaluation (prognosis of the remaining dentition, benefits of abutment augmentation or mucosal load reduction) is performed in the same manner as for healthy patients.

3. Implant prognosis

Literature data indicates that there are no relevant differences between patients with and without immunosuppression based on a follow-up period of at least 24 months. An exception to this are patients suffering from Crohn's disease.

4. Necessity of augmentation

Jaw bone augmentation is accompanied by increased demands on the bony recipient tissue. In cases of immunosuppression or immunodeficiency, it can be assumed that there is a less than adequate systemic immune response of the recipient tissue during wound healing [11, 21, 23].

5. Informing the patient

As part of routine patient education before planning any type of implant-based treatment, immunocompromised patients should be informed about the individual risks of disease-related complications (e.g. poorer implant prognosis in patients with Crohn's disease) and implant loss. Additionally, patients should be well-informed about the importance of follow-up care, which is adapted and structured according to their individual risk, and any potential follow-up costs.

6. Perioperative management

The low complication rates/ implant loss risks observed in the studies were all attained from patients undergoing perioperative systemic antibiotic prophylaxis.

7. Implant insertion

Submucosal and transmucosal healing are both possible. A recommendation regarding which type of healing is preferable cannot be derived from literature. Since the rates of bone remodeling and bone regeneration are reduced under immunosuppressive therapy, immediate or early loading must be critically appraised; this is also true for immediate implant insertion.

8. Prosthetic treatment

With regard to prosthetic treatment adapted to immunocompromised or immunosuppressed patients, no reliable data can be found in literature. Given the increased demands on the peri-implant soft tissue because of an inadequately functioning immune system, prosthetic designs which facilitate good oral hygiene and, if necessary, mucosal load relief should be pursued.

9. Follow-up care

An essential aspect for successful long-term implant therapy is regular follow-up care. In patients with immunodeficiency, the required follow-up care should be individually determined and consider the underlying disease, while being performed on a regular basis. It is advisable to provide patients with additional follow-up care during acute phases of immunodeficiency.

Checklist for risk stratification (low risk profile):

- phase of the underlying disease (chronic or inactive)
- stably adjusted immunosuppressive medication
- adequate oral hygiene
- focal infections are treated before implant surgery
- clinical and radiological examination reveals normal healing of hard and soft tissues
- bone augmentation is not necessary before implant surgery
- perioperative systemic antibiotic prophylaxis
- conventional loading (> 2 months healing period)
- features that facilitate good oral hygiene are integrated into prosthetic design
- follow-up care is adapted and structured according to the patient's specific risk

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