Dental implants in patients affected by systemic diseases

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VERIFIABLE CPD PAPER

PRACTICE

IN BRIEF

- Reviews the available evidence on the success/survival of dental implants in patients affected by systemic diseases.
- Gives practical suggestions to the clinician when possible.
- Provides indications for future studies that will help clarify the effect of systemic diseases on the success of dental implants.

Several systemic diseases (and relative medications) have been reported to impair or in some cases complicate dental implant surgery. In broader terms, when dealing with patients suffering from systemic diseases, the monitoring of the medical condition and of the related post-operative complications is of great importance in order to avoid risks which could jeopardise the health of the patient. In this review, the available evidence on implant survival/success, as well as relevant surgical recommendations in patients affected by systemic diseases, are evaluated and when possible, practical suggestions for the clinician are provided.

INTRODUCTION

Dental implants are a reliable and well-established option for the treatment of complete and partial edentulism and have been associated with high survival rates both in pristine and regenerated bone.[1-4]

One of the key factors for the success of implant therapy is appropriate patient selection,[5,6] which indicates that, like for all surgical procedures, a thorough medical history should be carefully registered together with the assessment of the complexity of the involved surgical site. A number of systemic conditions have been reported to complicate or even contraindicate implant surgery, with different levels of evidence.[7,8] Since the number of medically compromised patients requiring implant surgery is potentially increasing, understanding the effect of any systemic disease (and associated medications) on the surgical procedure and on the final treatment outcome in relation to implants is of paramount importance. This critical review aims to present a summary of the available knowledge on this topic and to provide practical guidelines for patient management.

ABSOLUTE MEDICAL CONTRAINDICATIONS TO DENTAL IMPLANTS

Implant surgery, like any other non-compulsory surgery, must be always carried out within a 'safety regime'.[9] Although the evidence from the literature is limited and mainly anecdotal, Hwang *et al.* described some severe systemic conditions representing an absolute contraindication for implant surgery (and any other elective surgery).[9] These conditions include:

- Recent myocardial infarction or cerebrovascular accident (<6 months)
- Recent valvular prosthesis placement or transplant (<6-12 months)
- High risk of bleeding (INR >3-3.5, platelet count <50,000/mm^3)
- Significant immunosuppression (total white count <1,500-3,000 cells/mm^3)
- Active cancer therapy
- Intravenous bisphosphonate treatment.

In all the aforementioned conditions, implant surgery may not only be at a higher risk of failure, but also the surgical procedure *per se* may jeopardise the general health of the patient and represent a life-threatening event.

In addition to the above, psychiatric disorders should also be carefully evaluated, since they may prevent the patient from properly understanding or accepting the proposed treatment and they are often associated to poor oral hygiene.[9]

MEDICALLY COMPROMISED PATIENTS AND DENTAL IMPLANTS

A number of animal and human studies have been performed in order to investigate the possible influence of common systemic diseases on implant survival/success. However, as highlighted by a recent review,[8] the level of available evidence based on well-recognised evidence-based criteria[10] is overall weak, since most of the data derive from case series or case report studies and only a limited number of RCTs have been published.

BONE DISEASES

Osteoporosis

Osteoporosis is a very common skeletal disease characterised by a reduction in bone density and alterations in the microstructure of bone that lead to an increased risk of fractures.[11] Its prevalence in Europe was estimated to be 27.6 million people in 2010, but this number is expected to rise in the next years.[12] The hypothesis that the impaired bone metabolism in osteoporotic patients can impair bone healing around dental implants and affect osseointegration is biologically plausible but still controversial.

Some evidence of reduction in bone-to-implant contact (BIC) and bone volume per tissue volume (BA) has been reported at eight weeks after implant placement in osteoporotic rat tibias.[13] In addition, in other preclinical studies, reduction of bone mechanical properties,[14,15] formation of impaired extracellular matrix (ECM) and delay of bone healing[16–18] have been shown. However, the use of implants with modified, hydrophilic surfaces treatment has shown to significantly improve dental implant success in osteoporotic animals[19,20] and should be further investigated in future human studies.[21,22] Even though few prospective and retrospective clinical studies indicated that osteoporosis could impair implant success,[5,23–25] a systematic and a critical review on this topic concluded that there is not

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enough evidence to consider osteoporosis as an absolute contraindication for implant placement.[26,27] In clinical practice, when dealing with osteoporotic patients, a careful evaluation of bone density at the implant site should be performed. Osteoporotic bone can be regarded as equivalent to Type IV according to Lekholm and Zarb classification[28] and, according to the limited available evidence, the clinician may also consider to allow a longer healing period for osseointegration before the prostheses' insertion.[29] Currently, immediate loading is not recommended and it is plausible to expect an increased risk of complications in case bone augmentation procedures are required.[30–32]

Medications-related osteonecrosis of the jaws (MRONJ)

A potential issue in osteoporotic patients is the possibility that antiresorptive medications, like bisphosphonates (BP) or denosumab, may interfere with bone turnover at the dental implant interface, reducing implant success and increasing the risk of developing osteonecrosis of the jaws (ONJ).[33,34] BP can be administered either orally (mainly for osteoporosis) or intravenously (mainly for multiple myeloma or other malignant diseases) and have a potent inhibitor effect on osteoclast cells. Denosumab is an antibody against RANK ligand (RANK-L) and therefore inhibits osteoclast function.

Only a few studies have been published on the risk of MRONJ subsequent to dental implant placement, but it is advisable to consider this risk comparable to the one associated with a tooth extraction.[35] There is a general consensus on contraindicating implant surgery in cancer patients treated with intravenous BP,[8] while a systematic review found that in patients taking oral BP for less than five years, neither the short-term (1-4 years) survival of dental implants nor the risk of ONJ seem to be increased.[36] The current evidence shows that the risk of ONJ seems to be higher for intravenous BP than oral BP, but it increases with the duration of the therapy.[37] According to Lazarovici *et al.*,[38] on average ONJ develops 68 months, 16 months and 50 months after implant surgery in patients in therapy with alendronate (os), zoledronic acid (iv) and pamidornate (iv), respectively. In this study, six out of 27 patients developed ONJ within six months from dental implant placement and therefore it was suggested that some cases of ONJ might not be triggered by the surgical trauma caused by implant placement. Furthermore, according to Jacobsen *et al.*,[34] a higher risk of ONJ may be expected after implant placement in the posterior areas of both jaws.

In conclusion, oral BP are not considered a contraindication for implant surgery, but it is important to explain in details the possible risk of complications to the patients. It has been suggested that in order to promote improved implant outcomes and reduce the risk of ONJ, the clinician should reduce the surgical trauma as much as possible, use antibiotic prophylaxis and topical antiseptics.[39] Although there are only limited data on the efficacy of a drug holiday from BP before oral surgical procedures in general, the clinician may consider to discontinue BP two months before and three months after surgery in patients taking this medication for more than four years and also in patients taking BP associated with corticosteroids or anti-angiogenic medications.[35,40] The benefits of stopping treatment with denosumab before implant placement have not been evaluated, although it has been reported that most of the anti-resorptive effect of denosumab disappears within six months.[35]

RHEUMATOID ARTHRITIS AND OTHER LESS COMMON BONE DISEASES

A very limited number of studies have evaluated the effect of other bone diseases on dental implant outcomes. A few case reports reported successful implant treatment in patients with osteogenesis imperfecta[41–45] and ankylosing spondylitis.[46] In a patient affected by osteoporosis and polyarthritis, Eder *et al.*[47] reported a peri-implant bone resorption of 1.38 mm at four years, slightly greater than expected in a healthy subject.

Both case reports[48] and retrospective case series[49] have shown a high success of implants placed in patients with rheumatoid arthritis, however, an increased bone resorption and bleeding can be expected in patients with concomitant connective tissue diseases.[50]

DIABETES MELLITUS

Diabetes mellitus comprises a group of metabolic diseases characterised by hyperglycaemia, as a result of a reduced secretion and/or an impaired action of insulin. Its global prevalence was estimated to be 2.8% in 2000 and is expected to rise to 4.4% in 2030.[51] Type 1 diabetes is an autoimmune disease associated to pancreatic β-cell destruction and therefore requires insulin therapy, while type 2 diabetes is characterised by a relative rather than absolute insulin deficiency and is usually a multi-factorial disease. It has been extensively demonstrated that hyperglycaemia has a negative effect on bone metabolism, usually referred to as diabetic 'osteopathy'. In particular, it has been associated to reduced bone mineral density, increased risk of fractures, reduced bone mechanical properties, impaired endochondral and intramembranous bone formation and impaired microarchitectural quality of bone (for review Retzepi and Donos[52]). Taking all this into consideration, it may be plausible to suggest that diabetes mellitus may impair osseointegration and implant related outcomes. Preclinical studies have shown a negative effect of hyperglycaemia on BIC and implant osseointegration and at the same time have highlighted the importance of glycaemic control.[53–55] The evidence from prospective and retrospective studies supports a positive survival rates of dental implants placed in diabetic patients with good/fair metabolic control, ranging from 85.5 to 100%.[56] Some studies demonstrated higher percentages of early implant failure in diabetic patients compared to late failures[57–59] and an increased risk of peri-implantitis.[60] Although poor metabolic control has been associated to higher implant failures[61], a recent review by Oates *et al.*[62] found that the evidence on the impact of poor metabolic control is still limited. In fact, most of the retrieved studies did not clearly report glycaemic control, which should be assessed through the measurement of glycated haemoglobin HbA1c (53), and they found only two prospective cohort studies and one prospective case series meeting this requirement. In two of these publications, no implant failure was registered over a four-month evaluation period before restoration[63] and after one year of restoration respectively.[64] The third study involved 45 diabetic patients, with 44 of them having HbA1c levels up to 9% (22 well controlled and 22 fairly well controlled) and only one patient with levels over 9% (poorly controlled) and reported a failure rate of 9.1% in poorly controlled diabetic patients along a mean evaluation period of 42.4 months.[65] When combining the fairly well controlled and the poorly controlled patients, the cumulative implant failure rate was 3.9%. The authors concluded that implant therapy could be beneficial even in patients with poor glycaemic control, with appropriate accommodations for delays in osseointegration.

However, it is also important to emphasise that hyperglycaemia may lead to severe complications like macro/micro angiopathy, neuropathy and increased risk of infections, thus a strict glycaemic control before and after implant treatment is highly recommended.[8,66,67] When dealing with diabetic patients, the clinician should consider antibiotic prophylaxis as appropriate and the use of antiseptics pre- and post-operatively to reduce the potential risk of infections.[7,53,66] In addition, these patients should be invited/

counselled to quit smoking and placed in a strict regimen of supportive therapy and maintenance/recall systems in order to optimise the control of oral hygiene and reduce the risk of periodontal and peri-implant infections.[68]

CARDIOVASCULAR DISEASES (CVDs)

The hypothesis of a higher risk of failures in patients with cardiovascular diseases is related to the possibility that the impaired blood supply and the consequent hypoxia may negatively affect the healing process of bone around implants.[69] However, several retrospective studies did not show different implant related clinical outcomes in patients with or without CVDs.[5,70,71]

In this type of patients, Taguchi *et al.*[72] suggested sedation with midazolam and propofol before implant surgery, in order to better stabilise haemodynamics and reduce the stress. Since CVDs include a wide spectrum of pathologies with different levels of severity, it is always important for the dentist to consider issues related to the medical condition of the patient before starting any kind of treatment, especially because patients with CVDs may experience increased bleeding, high blood pressure or even ischaemic attacks during implant surgery.[8] A careful monitoring of these patients and a systematic update of their medication intake is always highly recommended. Whenever indicated and with liaison with the cardiologists, antibiotic prophylaxis may be needed for infective endocarditis prevention.[73]

BLEEDING DISORDERS

Inherited bleeding disorders may increase the risk of haemorrhage during implant surgery, but there is no evidence suggesting that they are a contraindication for implant survival/success. The most common inherited bleeding disorder is von Willebrand's disease, that has an estimated prevalence of 1-2%, while haemophilia A occurs in one in 5,000 live male births and haemophilia B occurs in one in 30,000.[74,75] In patients with inherited bleeding disorders, any elective surgery should be carefully planned and discussed with the haemophilia centre. The following guidelines have been proposed:[76,77]

- Augmentation of the coagulation factor before surgery (and before nerve block). It is recommended that for invasive procedures the coagulation factor reaches a minimum level of 50%
- Peri- and post-operative use of antifibrinolytic agents (oral tranexamic acid and/or 5% tranexamic mouthwash). These should be continued up to seven days post-surgery
- Use local anaesthesia with vasoconstrictor, which should be performed with the slow injection technique and with fine gauge needles
- Use appropriate suturing technique
- Avoid sinus lift and bone grafts
- In order to reduce the risk of local infection and inflammation the clinician is recommended to use topical antiseptics (chlorhexidine or povidone iodine), or antibiotics if the infection is considered to require more than topical measures
- Discuss the use of non-steroidal anti-inflammatory medications with the haemophilia centre, since they may increase the risk of bleeding.

Patients taking anticoagulant (like warfarin) or antiplatelet agents are also at higher risk of haemorrhage during implant surgery. It has been suggested that discontinuing oral anticoagulant therapy (OAT) significantly increases the risk of thromboembolic events and that bridging it with heparin or reducing the dosage may not reduce the risk of thromboembolic events.[78] According to a systematic review of Madrid and Sanz,[78] for minor oral surgery procedures OAT should not be modified, since results from RCTs and CCTs demonstrated that OAT patients (INR 2-4) who did not discontinue their medication did not have a risk of post-operative bleeding higher than those who discontinued the medication. RCTs comparing different haemostatic agents (tranexamic acid mouthrinses, gelatine sponges and fibrin glue) have shown similar results. It is also important to remember that several medications commonly used by dental practitioners (like metronidazole, erythromycin, clarithromycin) may increase the anticoagulant effect of warfarin.[79–83]

MUCOSAL DISEASES

Oral lichen planus (OLP)

OLP is a chronic inflammatory disease, with a prevalence between 0.5 to 2%, that can affect the mucous membranes of the oral cavity, with papular/reticular lesions.[84,85] A few case reports have been published on the use of dental implants in patients affected by OLP, but they all reported positive results, with 100% success rate at 21-36 month follow-up.[86,87] In a retrospective study, Czerninski *et al.*[88] did not find a different success rate of implants placed in 14 patients with OLP and in 15 patients without OLP, however Hernandez *et al.*[89] reported a higher rate of peri-implant mucositis (44.6% of implants) and peri-implantitis (10.7% of implants) in 18 patients affected by OLP that were rehabilitated with 56 implants. Furthermore, it seemed that desquamative gingivitis may be more frequently associated to peri-implant mucositis. Considering the risk, although rare (1%),[90] of malignant transformation of OLP lesions, a long-term monitoring of these patients is highly recommended.

Ectodermal dysplasia

Ectodermal dysplasia comprises a heterogeneous group of genetic disorders with an incidence of one every 100,000 births.[91] It affects ectodermal structures and is associated to hypo/anodontia on both milk and permanent dentitions, impacted teeth, variations in size and shape of teeth, mineralisation disturbances, multiple diastemas and under-developed alveolar ridges.[92] Dental implants have been proposed as an effective treatment both in adults and children affected by this disease.[93] A review of Yap *et al.*[94] reported implant survival rates of 88.5-97.6% and a failure rate at subject level of 16.7-35.7%, with a higher incidence in the upper jaw. Recently, in a consensus paper, it was highlighted that the rehabilitation of children with ectodermal dysplasia needs a multidisciplinary approach and a careful pre-treatment oro-facial assessment.[95] No consensus was reached in relation to the most appropriate age for implant surgery, but the experts agreed that at 7-8 years old dental implants could be placed in the anterior mandible. If there are teeth adjacent to the edentulous area, the dentist needs to wait until growth is completed before placing implants, while if there are no adjacent teeth, the surgery can be performed earlier, but it is likely that the patient will require maxillary advancement once growth is completed.[95]

A few case reports have documented successful dental implant treatment in patients with Papillon Lefevre syndrome, a rare autosomal recessive form of ectodermal dysplasia associated with severe and early onset periodontitis.[96–98]

Epidermolysis bullosa

This defines a group of hereditary diseases of the skin and mucosal membranes characterised by the development of blisters and vesicles as a consequence of minimum trauma. It is estimated to affect approximately eight people per one million population.[99] In these subjects, tooth/implant-supported prostheses are better tolerated then removable dentures, which can easily cause mucosal irritation and blisters.[100] In a recent review, Feijoo *et al.*[101] reported a success rate (% of cases) of 97.7-100% of dental implants in patients with epidermolysis bullosa. Although dental implants may be performed

successfully, the clinician must be aware of the possible complications, such as the development of bleeding blisters due to the surgical trauma.[100,102] In order to reduce the incidence of these unpleasant complications, implant surgery should be performed in an atraumatic way, trying for example to limit irrigation and suction, using small-sized instruments, carefully handling the soft tissues and lubricating the buccal mucosa.[101] Microstomia, often associated to this disease, may limit the access to the oral cavity and prevent the use of implants in the posterior area.[100,102–105]

HEAD AND NECK CANCER PATIENTS

Neck and head cancers are often aggressive and may require mutilating resective surgeries, which result in evident bone defects and edentulous areas that are extremely challenging to rehabilitate. The use of bone grafts and implant-based prostheses are often the only/best way to rehabilitate these patients.[106] Radiotherapy, which is performed in 60-80% of the patients affected by head and neck cancer,[107] reduces cellular and vascular growth and therefore may significantly impair osseointegration of dental implants and increase the risk of complications (for example, osteoradionecrosis).[108,109] Both animal and human studies have shown an increased risk of implant failure (up to 12 times) in irradiated patients.[110] In a recent systematic review, Chambrone *et al.*[111] reported a mean implant survival rate ranging from 46.3 to 98% and an increased implant failure risk (RR 2.74) in irradiated patients, in particular in the maxilla (RR 5.96). Radiotherapy seems to have both early and late effects; the early effects affect mainly salivary glands, skin and oral mucosa, while the late effects involve bone changes and may lead to demineralisation, fibrosis, increased susceptibility to infection and avascular necrosis.[109] Several studies reported that hyperbaric oxygen therapy (HBOT) could significantly increase implant success and reduce unpleasant complications like osteoradionecrosis.[107,112–114] However, two recent systematic reviews found that there is no evidence that HBOT can reduce implant failure and that better designed studies are needed to clarify the real benefit of HBOT on the survival rates of implants in irradiated jaws.[111,115] In order to increase the implant success in these patients, a few precautions have been suggested,[8,116] such as antimicrobial prophylaxis and strict surgical asepsis, and it has been recommended to wait nine months after radiotherapy before performing implant surgery. The total radiation dose should be kept under 50 Gy to reduce the risk of osseointegration failure, but in case of higher doses, the clinician may consider to use HBOT.[116] A few case series reported no negative effect of chemotherapy on dental implant success.[117,118]

AIDS AND IMMUNOCOMPROMISED PATIENTS

A good immune response is important for wound healing, therefore it is reasonable to speculate that immunocompromised patients may be at higher risk of implant failure. The available literature on implant success in HIV positive patients is limited, however dental implants have been associated to positive short-term outcomes in these patients[119–122] and Strietzel *et al.*[123] concluded that no modification of routine dental treatment should be done, provided the immune status is stable. In a pilot study, Oliveira *et al.*[124] compared the 12-month implant success in 25 HIV positive patients treated with different anti-retroviral regimens and they obtained positive outcomes regardless the therapy, the CD4 T cell count and the viral load levels. However, the long-term predictability of dental implants in HIV positive patients has not been clarified yet and it is considered prudent to carry out implant surgery only when CD4 rates are high and when patients are on anti-retroviral therapy.[8] No specific cut-off for CD4 cells has been proposed to preclude surgery, however when their level is under 400 cells/mm,^{3} the risk of infections, especially from *Candida*, is significantly increased.[9]

Similar consideration and attention should be given to all patients taking immunosuppressants, for example for a transplant. Although some animal studies have shown that cyclosporine causes impairment in bone quality and bone healing around implants and in their mechanical retention,[125–128] case series and case reports have documented successful implant rehabilitations in patients that underwent organ transplantation.[129–131]

In conclusion, no evidence exists that immunodeficiency is a contraindication for dental implants, however the medical condition should be investigated and the clinician should consider antibiotic prophylaxis and topic antiseptics (chlorexidine) to reduce the risk of infections, following communication with the relevant physician.

SJÖGREN'S SYNDROME

Sjögren's syndrome is an autoimmune disease affecting the function of exocrine glands, including salivary glands. The consequent xerostomia creates difficulties in swallowing and possible taste alterations and therefore should be taken into serious consideration by clinicians for any kind of dental treatment, including dental implants. Due to the difficulties of these patients in wearing removable dentures, implant-based rehabilitation may be considered as the treatment of choice. Electro-stimulating devices reported positive outcomes in the management of xerostomia and Ami *et al.*[132] published a successful case report of an electrostimulating device fixed on a dental implant. A few studies investigated the long-term success of dental implants in patients with Sjögren's syndrome, reporting a success of 88.4-100% at 2-13 years.[133–135] Although there is no evident contraindication to implant surgery in these patients, the severity of the medical condition should be carefully considered, especially in secondary forms associated with rheumatoid arthritis, where limitations of movements and manual skills may reduce the efficacy of oral hygiene procedures.[93]

GENERAL CLINICAL RECOMMENDATIONS AND CONCLUSIONS

The evidence on the effect of systemic diseases on dental implant success is limited. This does not mean that systemic factors do not play a role in the success of dental implant treatments, but that future larger prospective studies should be carried out to improve the available knowledge and provide more robust evidence. Only a few severe conditions have been indicated as absolute contraindications for implants (and for elective surgeries in general), however this should not be perceived that in less 'life-threatening' conditions the dentist can consider dental implants as a risk-free procedure. The clinician must always balance the advantages and disadvantages of the surgical procedures and treatment modalities, communicate with the relevant physician/specialist, and take into consideration that in some occasions non-surgical options can be equally well tolerated/accepted, with fewer chances of complications. When dealing with systemic diseases that can potentially reduce dental implant related outcomes and the healing potential of the patients, it is also important to identify and address modifiable risk factors for implant failure (such as, smoking, poor oral hygiene) and adopt more strict follow-up regimens.

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