The replacement of missing teeth with endosseous implants for the rehabilitation of edentulous or partially edentulous patients has become a standard of care in the past two decades. This significant progress is based on the concept of osseointegration, first described by the two research groups of Bråemark and Schroeder. Fundamental experimental studies demonstrated that titanium implants regularly heal with direct bone-to-implant contact, a process termed osseointegration or functional ankylosis. To achieve and maintain osseointegration, indications and contraindications must be carefully balanced, and proper patient selection is thus a key issue in treatment planning. Contraindications can be divided into local and systemic/medical. In a paper prepared for the second ITI (International Team of Oral Implantology) Consensus Conference, Buser and coworkers proposed to subdivide the general medical/systemic risk factors into two groups:

- Group 1 (very high risk): Patients with serious systemic disease (rheumatoid arthritis, osteomalacia, osteogenesis imperfecta); immunocompromised patients (HIV, immunosuppressive medications); drug abusers (alcohol); noncompliant patients (psychological and mental disorders)

Systemic Conditions and Treatments as Risks for Implant Therapy

Michael M. Bornstein, Dr Med Dent1/Norbert Cionca, Dr Med Dent2/Andrea Mombelli, Prof Dr Med Dent3

Purpose: To evaluate whether systemic diseases with/without systemic medication increase the risk of implant failure and therefore diminish success and survival rates of dental implants. Materials and Methods: A MEDLINE search was undertaken to find human studies reporting implant survival in subjects treated with osseointegrated dental implants who were diagnosed with at least one of 12 systemic diseases. Results: For most conditions, no studies comparing patients with and without the condition in a controlled setting were found. For most systemic diseases there are only case reports or case series demonstrating that implant placement, integration, and function are possible in affected patients. For diabetes, heterogeneity of the material and the method of reporting data precluded a formal meta-analysis. No unequivocal tendency for subjects with diabetes to have higher failure rates emerged. The data from papers reporting on osteoporotic patients were also heterogeneous. The evidence for an association between osteoporosis and implant failure was low. Nevertheless, some reports now tend to focus on the medication used in osteoporotic patients, with oral bisphosphonates considered a potential risk factor for osteonecrosis of the jaws, rather than osteoporosis as a risk factor for implant success and survival on its own. Conclusions: The level of evidence indicative of absolute and relative contraindications for implant therapy due to systemic diseases is low. Studies comparing patients with and without the condition in a controlled setting are sparse. Especially for patients with manifest osteoporosis under an oral regime of bisphosphonates, prospective controlled studies are urgently needed. Int J Oral Maxillofac Implants 2009;24(Suppl):12–27

Key words: bisphosphonates, diabetes, implant failure, osseointegration, osteoporosis, systemic disease
Group 2 (significant risk): Patients with irradiated bone (radiotherapy), severe diabetes (especially type 1), bleeding disorders (hemorrhagic diathesis, drug-induced anticoagulation), heavy smoking habit

Systemic diseases may affect oral tissues by increasing their susceptibility to other diseases or by interfering with healing. In addition, systemic conditions may be treated with medications or other therapies that potentially affect implants and the tissues carrying them. Several authors have identified diseases for which dental implants are not recommended, or are at least questionable, but it often remains unclear on what type of evidence these statements are based.

Patients receiving dental implants generally fall into the first two physical status categories of the Classification System of the American Society of Anesthesiology (ASA): P1, a normal healthy patient; or P2, a patient with mild systemic disease. For very severe and acute medical conditions, calculating the risk of failure in affected subjects seems impossible, simply because patients with such conditions hardly ever receive implants. These patients fall into the ASA physical status categories P3 to P6: patients with severe systemic disease (P3); patients with severe systemic disease that is a constant threat to life (P4); moribund patients who are not expected to survive without an operation (P5); and subjects declared brain dead whose organs may be removed for donor purposes (P6). A recent publication stated that elective dental treatment of patients classified as P4 or higher should ideally be postponed until the patient’s medical condition has stabilized and improved to at least P3.

The purpose of this review was to evaluate the impact of systemic diseases, and/or medications used to treat systemic diseases, on the success of dental implant therapy. The analysis was focused on conditions that are not generally considered to be an absolute contraindication. The role of systemic factors in early failures (ie, during the healing period up to initiation of prosthetic treatment) and late failures (ie, after implant loading) was analyzed.

MATERIALS AND METHODS

Literature “Scoping”

To select the most important key words, a preliminary assessment was made of the potentially relevant literature. This was achieved by “scoping” searches, including searching for existing reviews. Incorporating opinions expressed in seven nonsystematic reviews, a list of systemic diseases suspected of having a negative impact on the success of osseointegration therapy was generated. Severe and acute medical conditions for which implant therapy has always been considered a contraindication (eg, acute infections, severe bronchitis or emphysema, severe anemia, uncontrolled diabetes, uncontrolled hypertension, abnormal liver function, nephritis, severe psychiatric disease, conditions with severe risk of hemorrhage, endocarditis or myocardial infarction) were excluded from the start.

As the present review paper is also an update of the paper published in 2006 by Mombelli and Cionca, key word selection was additionally based on the search terms used in the former publication. The diseases and conditions retained for further analysis were: scleroderma, Sjögren syndrome, neuropsychiatric disorders/Parkinson disease, lichen ruber planus/oral lichen planus, HIV infection, ectodermal dysplasia, long-term immunosuppression after organ transplantation, cardiovascular disease, Crohn disease, diabetes, osteoporosis, oral bisphosphonate medication, and use of radiotherapy for the treatment of oral squamous cell carcinoma (OSCC).

Review Question and Study Parameters

In patients treated with dental implants, to what extent does a history of scleroderma, Sjögren syndrome, neuropsychiatric disorders/Parkinson disease, oral lichen planus, HIV infection, ectodermal dysplasia, long-term immunosuppression after organ transplantation, cardiovascular disease, Crohn disease, diabetes, osteoporosis, oral bisphosphonates, or irradiated bone due to the treatment of OSCC increase the risk for implant failure?

Implant failure was selected as the primary study parameter, and it was further divided into early and late implant failures.

Search Strategy

Using EndNote X1, 13 MEDLINE searches were conducted based on the process mentioned previously. The search was conducted up to and including March 2008 using the following strategy: implant AND (oral OR dental) AND

1. Scleroderma
2. Sjögren’s syndrome and/or Sjögren
3. Neuropsychiatric disorders and/or Parkinson
4. Lichen planus
5. AIDS or HIV
6. Ectodermal dysplasia
7. Crohn
8. Transplantation
9. Cardiovascular
RESULTS AND DISCUSSION

Scleroderma, Lichen Planus, and Ectodermal Dysplasia

No controlled studies were found for scleroderma, oral lichen planus, or ectodermal dysplasia to demonstrate any positive or negative effects on the outcome of implant therapy. For all three conditions only case reports or case series could be identified.

Scleroderma is defined as a multisystem disorder characterized by inflammatory, vascular, and sclerotic changes of the skin and various internal organs, especially the lungs, heart, and gastrointestinal tract. Typical clinical features in the facial region are a masklike appearance (patients look younger), thinning of the lips, microstomia, radial perioral furrowing, sclerosis of the sublingual ligament, and indurations of the tongue. These symptoms cause the skin of the face and lips as well as the intraoral mucosa to become taut, thereby hindering dental treatment and complicating or even preventing the insertion of dental prostheses. Only five case reports with up to two patients treated with dental implants could be found in the literature. Therefore, the level of evidence for the efficacy of dental implants in these patients is quite low (level 4).

Oral lichen planus (OLP) is a common T-cell–mediated autoimmune disease of unknown cause that affects stratified squamous epithelium virtually exclusively. OLP has been considered a contraindication for the placement of dental implants possibly because of the altered capacity of the oral epithelium to adhere to the titanium surface. In the literature there are only case reports with up to three patients treated, including symptomatic and asymptomatic forms of lichen planus. Nevertheless, OLP is a potentially malignant condition, which in rare cases may result in malignant transformation. Only one case report describing an OSCC originating from OLP in association with dental implants was identified. With the literature available at present (level 4), oral lichen planus as a risk factor for implant surgery and long-term success cannot be properly assessed.

Ectodermal dysplasia (ED) is a hereditary disease characterized by congenital dysplasia of one or more ectodermal structures. Common extra- and intraoral manifestations include defective hair follicles and eyebrows, frontal bossing, nasal bridge depression, protuberant lips, hypo- or anodontia, conical teeth, and generalized spacing. Most search results for ED were case reports demonstrating treatment success with dental implants. A few larger case series report survival and success rates of implants in such patients (Table 1). However, due to the lack of controls, it cannot be determined how these results...
Group 1

Sjögren Syndrome

Sjögren syndrome (SS) is a chronic autoimmune disease affecting the exocrine glands, primarily the salivary and lacrimal glands. At present, the etiology of SS is far from being understood.43 The most common symptoms of SS are extreme tiredness, along with dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Xerostomia can eventually lead to difficulty in swallowing, severe and progressive tooth decay, or oral infections. Currently, there is no cure for SS, and treatment is mainly palliative.44

Literature on implant performance in patients with SS is scarce. There are no controlled studies available, and only one case series study with eight patients included was found (level of evidence 4).45 The eight patients in this study were all women receiving a total of 54 implants (18 in the maxilla, 36 in the mandible) with a machined surface. At abutment connection seven of these implants (12.9%) were found not to be osseointegrated at abutment connection. During the first year of function, two additional implants in the mandible were lost, resulting in an implant-based failure rate of 16.7% (patient-based 50%; four patients out of eight lost at least one implant).

Neuropsychiatric Disorders and/or Parkinson Disease

There is virtually no literature available on implant performance in patients with neuropsychiatric disorders. There are no controlled studies or even case series on defined pathological entities to evaluate implant survival and success rates in these patients (evidence level 4).

AIDS and/or HIV

The introduction of highly active antiretroviral therapy (HAART) for HIV infection has significantly postponed the outbreak of AIDS-defining diseases, reduced the rates of clinically manifested opportunistic infections and oral HIV-associated mucosal lesions, and extended life expectancy considerably.54 Several case reports have demonstrated successful implant-prosthetic rehabilitation of these immunocompromised but immunologically stable patients.55–58 The authors of a recent report conclude that no modification of routine dental treatment is needed in HIV-positive patients, provided that their immune status is stable.59 Optimized oral hygiene, regular recall intervals, screening for HIV-related oral lesions, and detection of hyposalivation/xerostomia are preventive therapies used to treat HAART side effects. Only one study was found that investigated the short-term clinical outcome of implant placement in a group of HIV-positive patients compared to results with an HIV-negative control group.60 In this study, 20 HIV-positive subjects and 9 HIV-negative control patients were followed for 6 months after loading of the implants. The success rates for both groups were 100%; no differences in clinical outcome were noted between the two groups (a level 3b study).

Morbus Crohn or Crohn Disease

Crohn disease is an idiopathic chronic inflammatory disorder of the gastrointestinal tract that may also involve the oral cavity. The disease process is characterized by recurrent exacerbations and remissions.61 The literature regarding the performance of dental implants in patients with Crohn disease is scarce, with

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of implants placed</th>
<th>Early failures</th>
<th>Late failures</th>
<th>All failures</th>
<th>Implant failures (no.) by location</th>
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<tr>
<td></td>
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<td>Mandible</td>
<td>%Subj</td>
<td>%Impl</td>
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<td>%Subj</td>
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<tr>
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<td>35.7</td>
<td>11.4</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Umberto et al (2007)42</td>
<td>13</td>
<td>51</td>
<td>ND</td>
<td>3</td>
<td>3</td>
<td>ND</td>
</tr>
</tbody>
</table>

%Subj = subject-based rate; %Impl = implant-based rate; Y = years of follow-up after restoration; ND = no data available.
a level of evidence 4. In a retrospective study with observation up to 1 week after second-stage surgery, two of three patients with Crohn disease had implant failures (3 out of 10 inserted implants were lost). The authors speculated that the presence of antibody-antigen complexes might lead to autoimmune inflammatory processes in several parts of the body, including the bone-implant interface. However, in both of these patients with early implant failures, other medical and local risk factors were also present: claustrophobia, smoking, and poor bone quantity.

In a follow-up study, patients treated from 1982 to 2003 were evaluated to assess the influence of systemic and local factors on the occurrence of early implant failures. Crohn disease was significantly related to early implant failure, exhibiting an odds ratio of 7.95 (95% CI of 3.47 to 18.24)—the highest odds ratio of all systemic factors evaluated in the study. Unfortunately, the authors did not provide the exact number of patients with Crohn disease treated or the number of implant failures in these patients.

In a recent prospective study from the same group, the influence of various systemic and local factors on the occurrence of early failures was once more evaluated. This time the implants had a modified, oxidized titanium surface. Between November 2003 and June 2005, 11 of 12 implants placed in patients with Crohn disease integrated successfully. Unfortunately, the authors again did not provide the exact number of patients with Crohn disease treated.

Transplantation (Heart/Liver/Renal Transplant)

Patients receiving transplanted organs generally undergo long-term immunosuppressive therapy, usually consisting of cyclosporine A combined with steroids, which have anti-inflammatory properties. Several animal studies have demonstrated that cyclosporine may negatively influence bone healing around dental implants and may even impair the mechanical retention of dental implants previously integrated in bone. With regard to studies in humans, there is no information available in the literature addressing heart or renal transplantations and the performance of subsequently placed or already present dental implants (evidence level 5). There is one case report describing the placement of two interforaminal implants 6 months after liver transplantation, providing anecdotal evidence of stability 10 years after insertion (evidence level 4).

Cardiovascular

The literature addressing dental implants and their success and failure rates in patients with cardiovascular diseases (CVD) is scarce. In addition, very different pathologies—ranging from recent myocardial infarction to congestive heart failure to atherosclerosis and hypertension—are referred to as CVD. In a preliminary retrospective study with a total of 246 patients receiving dental implants, three different groups were separately analyzed for early implant failures: group I, CVD (39 patients); group II, healthy subjects (98 patients); group III, other systemic disease (109 patients). The patient-based failure rates varied between 12.2% and 13.8% in the three groups, and differences were not statistically significant (evidence level 3b).

One center has published three papers on this subject. The influence of systemic and local factors on implant failure, again only up to 1 week after second-stage surgery, was evaluated in a retrospective analysis of patients receiving implants. CVD was not associated with an increased incidence of early implant failures. In a second retrospective analysis of a much larger patient population, hypertension and cardiac problems also were not significantly related to early implant failure. In a third study, the authors prospectively evaluated the occurrence of early failures of implants with a modified, oxidized titanium surface, again only up to second-stage surgery. Once more, hypertension and cardiac problems were not factors contributing to early implant failure.

A retrospective cohort study including patients consecutively treated with dental implants between 1982 and 2003 revealed that hypertension and cardiac disease were not significant factors associated with implant failure.

Diabetes or Insulin Therapy or Glucose Intolerance

There are two major types of diabetes: Type 1 (previously termed “insulin-dependent”) is caused by an autoimmune reaction destroying the beta cells of the pancreas, leading to insufficient production of insulin. Type 2 (previously termed “non–insulin-dependent”) is viewed as a resistance to insulin in combination with an incapability to produce additional compensatory insulin. Type 2 diabetes, often linked to obesity, is the predominant form, notably in the adult population in need of implant therapy. Diabetes mellitus is associated with various systemic complications, including retinopathy, nephropathy, neuropathy, micro- and macrovascular disturbances, and impaired wound healing. In the oral cavity, xerostomia, caries, and periodontitis have been linked to diabetes mellitus. The increased susceptibility to periodontitis is thought to be due to a negative influence of diabetes on inflammatory mechanisms and apoptosis, resulting in a deregulated host defense, deficits in wound healing, and microvascular problems (for review, see Taylor and coworkers [2004], Graves et al [2006]).
The present authors have analyzed the literature published up to October 2005 in a previous paper. At that time, a search using the terms implant AND (oral OR dental) AND (diabetes OR insulin therapy OR glucose intolerance) yielded 73 articles. The primary screening excluded 60 of these papers because they either did not report results from humans, did not include diabetic subjects, did not deal with osseointegrated implants, or did not quantitatively report failure/success/survival. Scanning the reference lists of the retained studies yielded one additional paper. Furthermore, one MSc thesis found through personal communication was added. A repetition of the same search in April 2008 yielded a limited amount of additional original data published with regard to diabetes: one case report of successful implants in a diabetic patient, one prospective cohort study, and two papers from the same center presenting retrospective data of a patient population that included diabetic subjects.

Data were extracted from 18 articles. Three types of reports were found: (1) case series of diabetic patients treated with implants; (2) cross-sectional, longitudinal, or retrospective evaluations of groups of subjects treated with implants, including some diabetic patients; and (3) one matched control retrospective chart survey (evidence level 3a). Data were extracted from 18 articles.

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Table 2 lists eight papers, each reporting results from multiple diabetic patients treated with implants. One paper is a 1-year interim report of the same patient population presented with a 5-year follow-up in another publication. From the data in these papers, an attempt was made to calculate early, late, and overall failure rates. However, it was noted that due to incomplete follow-up of subjects in these reports, the numbers of subjects and implants available to calculate early and late failure rates do not always correspond (n indicating the number of treated subjects). Thus, estimated overall failure rates are not identical to the sum of early and late failure rates as presented in Table 2.

Because the data compiled in Table 2 were heterogeneous with regard to the length of time the cases were followed, the proportion of implants and subjects monitored throughout the entire period varied, and large parts of sought information were unavailable, a meta-analysis was not possible. Within the limitations of the collected material, the following trends were recognized: (1) more failures in diabetic patients occurred early, and (2) the percentage of diabetic patients experiencing failures seemed to be relatively high, but the percentage of failing implants appeared to lie within the normal range.

Nine studies reported data on failures in cohorts including some diabetic subjects. Specific attribution of failures to the diabetic status was not reported in one of them. The other eight studies are listed in Table 3.

Again heterogeneity of the material and the method of data reporting precluded any further analysis. The diabetic patients in general had well-controlled blood glucose levels, at least before and immediately after implant therapy. No unequivocal tendency for subjects with diabetes to have higher failure rates emerged. However, the largest study reporting early and late failures, the retrospective cohort analysis of Moy and coworkers (2005) already mentioned in the context of CVD, included 48 diabetic and 1,092 nondiabetic patients treated consecutively by one surgeon over a period of 21 years.
This study indicated a statistically significant increase in the relative risk of implant failure with diabetes (RR 2.75, 95% CI: 1.46 to 5.18, P < .05).

The most recent publications were limited to reporting the rate of early failures: 50 implants placed in a cohort of 35 subjects, including 25 patients with diabetes (10 well controlled, 12 moderately controlled, 3 poorly controlled), showed 100% success at the 4-month follow-up.60 No apparent influence of diabetes on 252 implant failures in 178 patients was noted in the retrospective assessment of Alsaadi and coworkers (2007)64 including 2,044 subjects treated with 6,946 implants (only odds ratios reported; case numbers not known). In the recent report of the same group, 14 early failing implants in 14 patients out of 283 subjects treated with 720 implants are reported.65 This data set includes one subject with diabetes type 1, who had an early failure, and reports 4% early failures in patients with diabetes type 2, in comparison to 1.9% in nondiabetic subjects.

At the highest available level of evidence, a group of 15 diabetics, retrospectively identified in a pool of 387 consecutively treated patients, were each matched to two control subjects by age, sex, location of implants (jaw and zone), type of prosthetic restoration, opposing arch, and duration of edentulism.78 In this study, diabetic patients had no increased risk of implant failure and a similar number of prosthetic complications compared to matched nondiabetic controls.

The present review focused on failure. In the recent literature, biological complications not necessarily leading to failure, ie, peri-implant mucositis and peri-implantitis, have become an issue of investigation as well. A cross-sectional survey of 212 subjects with 578 implants included 29 diabetics.93 In diabetic patients, peri-implant mucositis was diagnosed in 59% of the cases and peri-implantitis in 24%. In subjects with no diabetes, the prevalence of mucositis was similar (66%) but peri-implantitis was significantly lower (7%).

Osteoporosis or Osteoporotic

Osteoporosis has been defined as a decrease in bone mass and bone density and an increased risk and/or incidence of fracture. However, it has been noted that subjects without fractures may have also lost a significant amount of bone, while many patients with fractures display levels of bone mass similar to those of control subjects.94,95 Thus, definitions of osteoporosis

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**Table 3 Implant Failures: Studies Including Diabetic (D) and Nondiabetic (non-D) Subjects**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of Implants placed</th>
<th>Early failures</th>
<th>Late failures</th>
<th>All failures</th>
<th>Implant failures (no.) by location</th>
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<td></td>
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<td>Maxilla</td>
<td>Mandible</td>
<td>%Subj</td>
<td>%Impl</td>
<td>Y</td>
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<td>ND</td>
<td>5-10*</td>
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<td>ND</td>
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<td>1.8</td>
<td>ND</td>
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<tr>
<td>Alsaadi et al (2008)</td>
<td>283</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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</tbody>
</table>

%Subj = subject-based rate; %Impl = implant-based rate; Y = years of follow-up; ND = no data available.
*Cumulative (variable time).*
based on reduced bone mass or nonviolent fracture are not perfectly synonymous. In addition, the relationship between skeletal and mandibular or maxillary bone mass is limited. The World Health Organization has established diagnostic criteria for osteoporosis based on bone density measurements determined by dual energy X-ray absorptiometry: A diagnosis of osteoporosis is made if the bone mineral density level is 2.5 standard deviations below that in a mean young population.99

In October 2005, a search using the terms implant AND (oral OR dental) AND (osteoporosis OR osteoporotic) yielded 66 articles. The primary screening excluded 54 of these papers because they either did not report results from humans, did not include subjects with osteoporosis, did not deal with osseointegrated implants, or did not quantitatively report failure/success/survival rates. Three papers were case reports of individual osteoporotic females, all successfully treated with osseointegrated implants.100–102 One paper reported a case of implant failure after therapy with an oral bisphosphonate for osteoporosis.103 In this report, the patient lost all five implants, which had been inserted to retain a fixed hybrid mandibular prosthesis, approximately 2.5 years after insertion. The patient’s initial medical history was significant for osteoporosis, hyperparathyroidism, nephrolithiasis, thyroidectomy, cholecystectomy, hysterectomy, an ankle fracture, and a hip fracture with total hip replacement. Two years after implant placement, therapy for osteoporosis was commenced with etidronate, an oral bisphosphonate known as Didronel. In the following routine appointment, all five implants exhibited massive radiolucency all around the implants. The authors concluded that bisphosphonates should be avoided in patients who have undergone implant placement, and implants should not be placed in patients who require bisphosphonates. This case report is the first article to mention bisphosphonates as a potential risk factor for oral implantology. In light of the current controversy (see next section on bisphosphonates), it is important to note that etidronate is one of the least potent bisphosphonates known today and is administered via an oral route only.

Another paper reported three cases of mandibular fractures following implant placement, two of them in elderly women with advanced mandibular atrophy.104 Sixteen women, all with a diagnosis of osteoporosis (low bone density or the occurrence of low-trauma fractures), were assessed in one retrospective study with regard to the success of implants placed between 6 months and 11 years previously. The reported overall success rate was 97.0% for maxillary implants and 97.3% for mandibular implants.105

The administration of corticosteroids or other endocrinopathies can cause osteoporosis. These drugs are used for a variety of conditions, including, but not limited to, Crohn disease, asthma, pemphigus, and polyarthritis. Cases have been reported in which dental implants were placed, and successfully maintained, under such circumstances.62,106,107

In 2005 a number of papers were published evaluating implant therapy, including subjects with and without a diagnosis of osteoporosis. A repetition of the same search in April 2008 yielded two additional papers in this category. They have already been mentioned previously in the context of CVD and diabetes64,65 and will be discussed below in the context of osteoporosis.

van Steenberge and coworkers63 counted 27 early failures among 1,263 consecutively inserted implants in 399 patients. Two implants were placed in patients diagnosed with osteoporosis and both were a success. In 2007, however, the same center reported a significant association between osteoporosis and early implant failure.64 In a third paper by the same group, none of their 29 implants placed in patients with osteoporosis failed early, whereas 2% of the implants in nonosteoporotic subjects failed.65

Von Wowern and Gottfredsen108 measured changes in mineral content of the mandibular bone in 7 osteoporotic and 11 nonosteoporotic women 5 years after functional loading of their implants. Although no implant failure was observed in any patient, a significant difference was noted in the marginal bone loss between the two groups. One prospective study found no difference in failure rates between women receiving (n = 25) or not receiving (n = 91) hormone replacement therapy (HRT).109 In the study by Moy et al.,73 already discussed in the context of diabetes, postmenopausal hormone replacement therapy (or lack thereof) was also evaluated. Compared to the total of 1,140 patients, the relative risk for implant failure was increased by 2.55 (95% CI: 1.72 to 3.77, P < .05) in the 161 women on HRT. Implant failure rates of postmenopausal women, with or without estrogen replacement therapy, were compared to those of premenopausal women by August and coworkers.110 Postmenopausal women without HRT (n = 168) had the highest maxillary failure rate (13.6%), a rate significantly greater than that of premenopausal women (n = 114) (6.3%). The difference in the maxillary failure rates of HRT-supplemented postmenopausal women (n = 75) (8.1%) and unsupplemented women did not reach statistical significance. Implants placed in the mandible did not show statistically significant differences in the number of failures.

With regard to age, the opposite was found by Dao et al.111 in an informal review of the Toronto implant study patient series (93 women and 36 men, aged 20
to 76 years): The highest failure rates were noted in the youngest age group. The heterogeneity and quality of the data presented in these studies precluded any formal meta-analysis.

Thirty-nine women aged 48 to 70 years, 19 with a densitometric diagnosis of osteoporosis in the lumbar spine and femoral neck and 20 controls with a normal densitometric diagnosis, were compared by Amorim and coworkers. Bone mineral density was measured in the patients and controls by dual-energy x-ray absorptiometry. Eighty-two osseointegrated dental implants were placed in the mandible, 39 of them in the osteoporosis group and 43 in the control group. The loss of one implant (1.2%) could not be attributed to systemic osteoporosis.

Two publications including a collection of cases with failures and a group of control patients with successful implants analyzed factors associated with implant integration failure. The analysis by Blomqvist et al included 11 patients with severely atrophied maxillary alveolar processes who had lost 43% of implants placed in a one-stage procedure together with sinus-floor bone grafts. Mean relative bone mass density was significantly lower in these subjects than in 11 control subjects, matched for sex and age, who had received the same reconstructive treatment but no grafts. Becker and coworkers compared a case population of 49 individuals who had experienced implant loss to a control population consisting of 49 successful recall patients. The groups had the same gender distribution but were unmatched for age. Ten patients in the test group and 7 in the control group had a history of osteoporosis. Generalized estimating equations were used to evaluate the likelihood of an individual having at least one implant failure. There was no association between bone density assessed at the radius and ulna and the risk of implant failure. The clinical estimation of local bone quality, however, was related to implant failure, suggesting that a simple visual assessment of bone quality at a site considered for implantation may be more informative than bone density measures obtained at peripheral bones.

Based on the results reported above, the evidence for the efficacy of dental implants in patients with osteoporosis is on the level of multiple case-control studies (level 3a).

**Bisphosphonates**

Bisphosphonates reduce or even suppress osteoclast function and can therefore be used in the treatment of various disorders causing abnormal bone resorption. The first type of disorders includes malignancies affecting the bone, such as multiple myeloma and bone metastases of breast and prostate cancer. The second type are nonmalignant bone diseases, the most common of which are osteoporosis and Paget disease. Marx first showed a connection between bisphosphonate cancer therapy and osteonecrosis of the jawbones in 2003. He described 36 cases of osteonecrosis: 80.5% in the mandible, 14% in the maxilla, 5.5% in both jaws simultaneously. All affected subjects were being treated with intravenous bisphosphonates, either pamidronate (brand name Aredia) or zoledronate (Zometa). In 28 of these patients the clinical onset was preceded by a tooth extraction. Since then, numerous centers have reported similar observations, with incidences of osteonecrosis as high as 12% for patients treated with intravenous bisphosphonates.

Today, intravenous bisphosphonate therapy is considered a major risk for jaw necrosis (bisphosphonate-related osteonecrosis of the jaw [BRONJ]). Elective oral surgery, including the insertion of dental implants, is generally contraindicated for subjects on this type of medication.

The risk for BRONJ appears to be much lower for oral than for intravenous drug administration, but appears to increase with the duration of bisphosphonate therapy. Especially oral administration of the potent aminobisphosphonates with N-containing side groups (alendronate/Fosamax; risedronate/Actonel; ibandronate/Boniva or Bonviva) over several years has been associated with BRONJ.

The use of bisphosphonates in the treatment of osteopenia/osteoporosis requires oral administration of much lower dosages than in the context of cancer therapy. The risk for complications of implant therapy in such patients—implant failure or BRONJ—is currently unknown and the subject of controversy.

The present literature search yielded only three clinical studies addressing this issue. As these studies are very different in design, they will be discussed individually without a direct comparison.

In a report from 2006 presenting data from two controlled studies, oral bisphosphonate usage was not associated with osteonecrosis of the jaws. In the first study, the effects of alendronate on alveolar bone loss in patients with moderate or severe periodontal disease were explored using a double-blind placebo-controlled design. Patients were randomized to either 70 mg alendronate or a placebo once weekly for 2 years. No BRONJ was observed in this study. The second study was a parallel-arm controlled study of patients with dental implants receiving oral bisphosphonates (alendronate or risedronate) versus control dental implant patients over the course of at least 3 years. After the observation period, 100% of the implants in the test group and 99.2% of the implants in the control group (no bisphosphonates) were con-
the years 1998 to 2006. 458 of these patients in the United States who received implants in 1998.

The implants were left to heal for 6 weeks before initiation of prosthetic restoration. Patients were followed for 12 to 24 months after implant placement, and hard and soft tissue complications were noted. One patient exhibited exposed bone 1 week after implant insertion. No other postoperative sequelae or complications were noted in any patients, and all implants were classified as successful 12 to 24 months postinsertion. The authors concluded that the incidence of BRONJ after an average of 3.3 years of bisphosphonate intake following implant insertion with or without tooth extraction is minimal, and it is comparable to complication rates in patients without a history of oral bisphosphonate therapy (evidence level 4).

The design of the study mentioned above was criticized in a letter to the editor of the Journal of Periodontology for the following reasons: the mean duration of oral bisphosphonates before implant placement was relatively short; the dosage of alendronate taken by the included patients was low (only four subjects used 70 mg; the remaining patients used 35 mg); and the sample size, with 61 patients, was small.

A retrospective questionnaire was mailed to 1,319 patients in the United States who received implants in the years 1998 to 2006. 458 of these patients returned the questionnaire (34.7%). Anamnestically, 115 patients receiving 468 implants reported that they had been taking oral bisphosphonates at the time. Of these 468 inserted implants, all but 2 integrated. The 115 patients were asked to come for a clinical visit, and 72 patients presented. In these 72 patients, no BRONJ could be diagnosed. The implant failure rate for patients taking oral bisphosphonates was similar to that observed for a healthy control population. The authors therefore concluded that oral bisphosphonates represent no risk factor for osteonecrosis in implant surgery. Nevertheless, they limited this conclusion to a duration of bisphosphonate intake not longer than 3 years and also warned against simultaneous medication with corticosteroids (evidence level 3b).

Radiotherapy or Irradiation or Irradiated

With regard to cancer, two aspects need to be considered: the effect of the disease and the effect of its treatment on the tissues containing the implants. The cancer may have been treated before the implants were placed, or treatment may become necessary in subjects who already have implants. Furthermore, implants may be inserted in residual or grafted bone. Due to the heterogeneity of disease conditions, combinations of treatments (radiotherapy and chemotherapy), sequence of events, time of follow-up, and parameters used for assessment, it was decided to analyze the risk factor radiotherapy for dental implant placement in a descriptive manner, with special emphasis on existing systematic reviews. As pointed out in two reviews, several factors may potentially influence success rates in irradiated patients. They include, but are not limited to: the source, dose, and fractionation of irradiation; concomitant therapies (ie, chemotherapy, hyperbaric oxygen therapy); the anatomic region of implantation; and the timing of medical and dental therapies.

In a recent systematic review, the literature from 1990 to 2006 was searched for implant failure rates to compare the outcomes of preimplantation radiotherapy and postimplantation radiotherapy. The authors found similar failure rates for the time points (3.2% versus 5.4%, respectively; evidence level 2c), but cautioned that it was difficult to compare the studies included because of differences in the exact site of implant placement in relation to the region of radiotherapy, in lengths of follow-up periods, in implant systems used, and in the use of prostheses, and because there were other confounding variables, such as systemic disease, smoking, and parafunction. When implants were inserted after radiotherapy, the implant failure rate was lower for the mandible (4.4%) than for the maxilla (17.5%). The authors could not find evidence in the literature to support delaying implant placement after radiotherapy for 6 to 12 months to maximize implant success. No implant failures were found to occur below a radiation dose of 45 Gy.

In a study analyzing the long-term survival rates of 316 dental implants placed in the mandible in 71 patients after radiotherapy and radical surgery, three different groups were evaluated: (1) implants in nonirradiated residual bone, (2) implants in irradiated residual bone, and (3) implants in grafted bone. In this study, the patients were treated with implants after cancer surgery and after receiving a total radiochemotherapy dose of 50 Gy. The survival rates 2, 3, 5, and 8 years after implant insertion were 95%, 94%, 91%, and 75%, respectively. Implants placed in irradiated bone showed significantly lower survival rates than implants in nonirradiated mandibular bone. The survival rates for the three groups com-
pared in this study were 95% (group 1), 72% (group 2), and 54% (group 3). The authors could not show that the amount of time between irradiation and implantation significantly influenced the results.

A retrospective study reported the survival rates of 631 implants inserted in cancer patients over a period of 25 years. This group of irradiated patients was compared to a control group of nonirradiated patients receiving 614 implants at the same clinic during the same period. The mean time of follow-up in this study was 6.3 years, with a range of 0.5 to 23 years. During this period, 147 implants in patients undergoing radiotherapy were lost (23.3%), and 76 implants (12.4%) failed in the control group. High implant failure rates were especially seen after high-dose radiotherapy and a long time after irradiation. Failures occurred in all craniofacial regions, but the greatest risk of implant failures was found for the frontal bone, zygoma, mandible, and nasal maxilla.

In another retrospective study, the survival of dental implants placed in the interferominal region during oral cancer surgery was evaluated in relation to postoperative radiotherapy. In 48 patients with a squamous cell carcinoma of the oral cavity, a total of 139 implants were placed. Of these patients, 21 (with 61 implants) received postoperative radiotherapy with 10 to 68 Gy on the symphysial area, while 27 patients (78 implants) were treated with surgery alone. The average time interval between surgery and the commencement of radiotherapy was 6 weeks. The success rate of the dental implants was 97% in the postoperative irradiated group and 100% in the nonirradiated group. The prosthetic success was lower, irrespective of radiation administration, because in 12 patients a denture could not be fabricated due to death of the patient (7 patients), psychological reasons (4), and loss of an implant (1). The authors concluded that postoperative radiotherapy did not negatively affect the osseointegration of implants placed during oral cancer surgery.

Regarding the papers evaluating multiple local and systemic risk factors for dental implant failure (already mentioned above in the context of Crohn disease, diabetes, osteoporosis, and cardiovascular diseases), radiotherapy was identified by two studies as being a statistically significant variable. The calculated relative risk of failure for implants due to radiation therapy was 2.73 (95% CI 1.10 to 3.77). Two papers did not find a significant association between implant failure and irradiation of the patient due to cancer in the head and neck region.

Besides the problem of implant failure, the risk of induction of osteoradionecrosis is always present. Esser and Wagner reported that in their group of 64 patients rehabilitated with a total of 249 implants (71 IMZ and 178 Brånemark implants) in the irradiated maxilla and mandible, osteoradionecrosis occurred in 2 patients in the mandible, and necrosis of soft tissues in the floor of the mouth occurred in 3 patients following implant placement. Osteoradionecrosis resulted in continuity defects of the mandible and loss of the implants in the region. Some authors even state that this severe complication may be underreported in the literature. To minimize the risk of osteoradionecrosis due to implant placement in irradiated bone and to improve survival and success rates of implants inserted in irradiated jawbones, hyperbaric oxygen (HBO) therapy has been advocated. The rationale for the use of HBO therapy is based on its effect on osteogenesis through stimulation of capillary ingrowth, fibroblastic proliferation, collagen synthesis, and capillary angiogenesis. Therefore, HBO has been recommended for all elective surgery in irradiated tissues, for the prevention and treatment of osteoradionecrosis, and to improve osseointegration of implants inserted in patients undergoing radiotherapy. Nevertheless, the use of HBO in irradiated patients remains controversial in the literature, with some authors considering it ineffective. In a recent systematic review from the Cochrane collaboration, Esposito and coworkers compared the success, morbidity, patient satisfaction, and cost effectiveness of dental implant treatment performed with and without HBO in irradiated patients (evidence level 1b). After screening of the eligible studies, only one randomized controlled clinical trial was identified. In this study, endosseous implants were placed in the anterior part of the mandible either under antibiotic prophylaxis alone (13 patients) or under antibiotic prophylaxis combined with pre- and postsurgery HBO treatment (13 patients). In the HBO group 85.2% of implants survived, and in the non-HBO group 93.3% survived. Interestingly, osteoradionecrosis developed in one patient in the HBO group only. In their systematic review, Esposito and coworkers concluded that HBO therapy in irradiated patients requiring dental implants may not offer any evident clinical benefits.

**Combined Risk Factors**

When discussing the impact of various medical conditions on implant failure, it is necessary to keep in mind that recorded data may be interrelated. Potential risk factors, particularly those found more frequently in older adults in general—systemic chronic diseases, medications taken on a long-term basis, reduced salivary flow—may not be independent of each other. On the other hand, one single factor alone may not influence the risk measurably, whereas a combination of multiple independent factors may
have a significant impact. This is supported by retrospective investigations showing, for example, that the combination of specific interleukin-1 gene polymorphisms and smoking could be associated with peri-implant bone loss, whereas only one of these factors alone is not.\textsuperscript{152–154} Established risk factors for osteoporosis include advanced age, smoking, and alcohol consumption, steroid therapy, inadequate calcium intake, genetic predisposition, and menopause.

There have been attempts in recent years to analyze several factors jointly. Ekfeldt and coworkers\textsuperscript{155} recorded age, gender, smoking habits, alcohol and other drug abuse, as well as medical conditions such as diabetes, osteoporosis, cytostatic treatment or radiotherapy, impaired immune defense, psychological disorders, and bruxism in 27 subjects with multiple implant failures and 27 matched controls. Patients in the failure group had less favorable bone conditions (bone volume) in general, and bruxism was noted only in this group. But this group also included more subjects with signs of addiction to alcohol, narcotics, and tobacco. In addition, this group also included one subject under cortisone treatment, one with uncontrolled diabetes mellitus, and two psychologically stressed individuals. In the retrospective study of Moy and coworkers,\textsuperscript{73} the database of 1,140 implant patients, including 170 with implant failures, was subjected to multiple regression analysis to explore predictors of the number of failed implants per patient. Using this approach, the variables sex, age, implant location, smoking, hypertension, coronary artery disease, asthma, diabetes, steroids, chemotherapy, head and neck radiation therapy, and postmenopausal HRT were evaluated. The only variables identified as having significant predictive value for implant failure were location in the maxillary arch, diabetes, smoking, and head and neck irradiation.

Observations made in case series can reflect cohort effects; for example, results specific to the generation studied that may not be seen in subsequent generations. There may be differences in dental status and dental awareness (today’s young generation may reach old age with more and better maintained teeth), changes in dietary patterns and in the use and abuse of substances (based on availability, preferences, and the awareness of side effects), and changes in general health conditions (as environmental hazards shift and new therapies and pharmaceutical products become available). These may account for many differences that we ascribe to aging.\textsuperscript{156} It remains to be investigated which changes observed in older subjects today are truly a consequence of the physiological aging process (and not due to other extraneous factors), and thus can be expected to occur in future generations as well.

**CONCLUSIONS**

On the basis of the data found in the literature, the following can be concluded:

**General Conclusions**

The level of evidence indicating absolute and relative contraindications for oral implant therapy due to systemic conditions and treatments is low. Many conditions have been listed as potential risk factors, but studies comparing patients with and without the condition in a controlled setting are sparse. In general, the available literature is restricted to case reports and case series.

The problem of positive publication bias exists in case reports and smaller case series.

No data exist for the more severe medical conditions, simply because implant therapy has not been documented.

**Specific Conclusions**

Based on the published literature it is not possible to distinguish between subtypes of systemic diseases such as diabetes type 1 and 2 or primary and secondary osteoporosis.

The supposition that subjects with diabetes tend to have higher failure rates is equivocal. The only available matched-control retrospective survey indicated no increased risk of failure. The largest study, a retrospective cohort analysis of patients with type 2 diabetes treated by one clinician, indicated a statistically significant increase in the relative risk of implant failure with diabetes.

The density of peripheral bone, as currently used for the diagnosis of osteoporosis, showed only a weak association with the risk of implant failure in two case-control studies.

For bisphosphonate therapy and implant surgery, the duration, route, and the dosage of the medication, as well as the type of bisphosphonate are reported to play an important role in potential bisphosphate-related osteonecrosis of the jaws. There are not enough data to estimate the risk for oral bisphosphonates in the context of implant therapy, with only one prospective and two retrospective clinical studies available.

A systematic review of implants placed before and after radiotherapy reported failure rates of between 0% and 12.6% for a follow-up period up to 12 years. Osteoradionecrosis following implant placement has been reported in the literature. A recent systematic review found no beneficial effect of hyperbaric oxygen therapy.
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