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Patient-related risk factors for implant therapy. A critique of pertinent literature

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ABSTRACT

Background: Treatment planning for dental implants involves the assessment of patient-related risk factors prior to formulation of a treatment plan. The aim of this review was to assess relevant literature and provide evidence-based information on the successful surgical placement of dental implants.
Methods: An electronic search of Medline, PubMed and the Cochrane Databases of Systematic Reviews was undertaken using a combination of MeSH terms and keywords. A handsearch was also performed and cross-referenced with articles cited in papers selected. The primary study parameter was implant failure.
Results: Forty-three studies were selected based on specific inclusion criteria. Many studies contain confounding variables, numbers in subcategories are often too small for meaningful statistical analysis, and follow-up times vary and are often short-term.
Conclusions: There are many risk factors which the clinician is required to know and understand to advise patients, and consider in planning and treatment provision. Consistent evidence exists to show an increased failure rate with smokers, a history of radiotherapy and local bone quality and quantity. Weaker evidence exists to show a higher incidence of peri-implant disease in patients with a history of periodontitis-related tooth loss. Lack of evidence precludes definitive guidelines for patients with autoimmune disorders where expert opinion recommends caution. Osteoporotic patients show acceptable survival rates; however patients on oral bisphosphonates show a small incidence but high morbidity from osteonecrosis of the jaw. Emerging evidence suggests that there is a correlation between genetic traits and disruption of osseointegration.

Keywords: Surgery, implant, single-tooth restoration, evidence-based, treatment planning.

Abbreviations and acronyms: BMP-4 = bone morphogenetic protein 4; BP = bisphosphonates; CTX = C-terminal telopeptide; HBO = hyperbaric oxygen therapy; INR = International Normal Ratio; MMP-1 = matrix metalloproteinase 1; ONJ = osteonecrosis of the jaws; OR = odds ratio; RCT = randomized control trial; RR = Risk Ratio.

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INTRODUCTION

The successful replacement of teeth with osseointegrated implants is well documented. Schmitt and Zarb[1] reported a 100% survival rate for 27 anterior maxillary implants observed from 1.4 to 6.6 years. Henry *et al.*[2] reported an implant success rate of 96.6% over five years in a multicentre prospective study of 71 implants in the anterior maxilla. Since then, the utilization of dental implant therapy has increased exponentially, together with supporting technological advances. In this article, assessment of the literature related to successful implant placement and patient-related variables will be discussed.

MATERIALS AND METHODS

A search of electronic databases including Medline, PubMed and the Cochrane Databases of Systematic Reviews was undertaken using a combination of MeSH terms and keywords. Keywords used singly or in combination included: dental or oral implant$; success, survival, failure; informed consent, cardiovascular disorder$; anticoagulant$; hypertension; aspirin; diabetes; autoimmune disorder$; osteoporosis; osteonecrosis; bisphosphonate$; radiotherapy; periodont$; smok$, cigar$; jaw or bone (shape or quality or quantity).

Relevant titles and abstracts were identified and examined. Publications were selected for review based

on inclusion criteria and the full article was retrieved. A handsearch was also performed and cross-referenced with articles cited in papers selected.

Articles which fulfilled the following inclusion criteria were selected: (a) written in English in the last 10 years; and (b) published in a peer-reviewed journal, with a preference for systematic reviews and cohort studies. All levels of evidence were considered; however case reports were excluded if less than 10 patients or if less than one year follow-up. The primary study parameter was implant failure.

RESULTS

The broad terms of the search were designed for a high yield to reduce omissions. As a consequence 5908 papers were retrieved, of which the majority were not relevant to the review. For example: (a) passing reference of a risk factor without scientific critique of its role; (b) duplication of papers addressing multiple search terms; and (c) many papers related to less common conditions were case reports of insufficient number or length of follow-up. This resulted in 43 papers selected using the above criteria. For most of the factors potentially affecting implant survival, no studies comparing patients with and without the condition in a controlled trial were identified.

Table 1 summarizes the best available data using the Centre for Evidence-Based Medicine[3] criteria for evidence selection. Of the 10 factors, one paper representing the highest level of evidence of each risk factor was included in the Table.

Patient-related factors

The currently accepted management protocol includes history, clinical examination, special tests, diagnosis, consideration of treatment options, preparation of a treatment plan, delivery of care, review and maintenance. Surgical planning for implant placement should not begin until treatment planning for the complete dentition has been completed. Implant placement is subject to the customary constraints for minor surgical procedures imposed by systemic conditions. The level of evidence to support contraindications for oral implant therapy due to systemic disease is low. No data exist for more severe medical conditions as implant treatment has not been documented in such cases.[4] If the recognized surgical and prosthodontic protocols are followed, a successful outcome is likely if the patient is able to undergo minor oral surgery. However, a range of conditions are believed to be associated with an increased risk of implant failure; either 'early' if they occur before or 'late' if they arise subsequent to implant loading.[4] This understanding has become more arbitrary with the increased use and success of immediate loading protocols.[5]

Informed consent

Informed consent is an essential requirement of all clinical treatment. It is the process of communication between a clinician and a patient in which a patient grants permission for the proposed treatment based on a realistic understanding of the nature of the illness, description of procedure, risks and benefits, and treatment alternatives, including no treatment.[6] Written consent may not necessarily constitute informed consent; however written information is more readily understood and recalled at a later date and provides evidence of consent considerations compared with discussion and verbal consent only. Absence of patient acceptance and agreement with treatment recommendations is a contraindication for treatment. Likewise patients who are unable or unwilling to manage active oral disease or have unrealistic expectations of treatment may not be appropriate candidates for implant therapy.

Cardiovascular disorders

Uncontrolled hypertension, defined as a blood pressure consistently above 160/90 mm Hg, requires stabilization as increased blood pressure places the patient at greater risk of stroke, heart failure, myocardial infarction and renal failure. Around 30% of patients with hypertension remain undiagnosed[7] and nearly 50% of patients on treatment are not controlled.[8] Dental implant surgery may therefore pose a risk with respect to potential adverse cerebrovascular and cardiovascular events. Studies have suggested the use of blood pressure monitoring perioperatively.[7,8] Patients who have suffered a cardiac infarction within the previous six months should not undergo implant surgery and patients with a history of angina should have glyceryl trinitrate tablets or sublingual sprays available when undergoing implant surgery.[9] Moy *et al.*[10] reported on a retrospective analysis of 4680 implants placed in 1140 patients over 21 years. In this analysis, implants were placed by the same oral surgeon and were mostly machined (turned surface) Brånemark implants. Of the 1365 implants placed in patients with coronary artery disease or hypertension, there was no increased risk for implant failure (RR = 1.02, 95% CI 0.58, 1.78).

Antibiotic prophylaxis in accordance with current guidelines and consultation with each patient's cardiologist is necessary for patients with prosthetic heart valves, history of infective endocarditis or complex cyanotic congenital heart disease.

Anticoagulant therapy may cause extended postoperative bleeding and patients taking heparin or

Table 1. Selected studies of best evidence for each patient-related factor

Condition	Best evidence data	Study summary	Outcomes	Comments
Cardiovascular disorders	Moy *et al.* 2005	Level 4 retrospective cohort study of 4680 implants over a 21-year period.	No increased risk for failure (RR = 1.02, 95% CI)	Mostly machined Brånemark implants placed by 1 clinician. Also provides data for a range of medical conditions, smoking, gender and location analysis
Diabetes	Klokkeveld *et al.* 2007 Mombelli, Cionca 2006	Level 3a systematic review of 4 studies Level 3a systematic review of 15 studies	No increased risk for failure (pooled estimates with 95% CI) No increased risk for failure	Studies short-term with small numbers. Only one comparison study. Heterogeneity of studies precluded meta-analysis
Autoimmune disorders	Alsaadi *et al.* 2008	Level 2b prospective cohort study of 283 patients	Tendency to higher failure rate with Crohn's disease ($p < 0.02$)	No definitive trends due to low global failure rate (1.9%) and small cohort size
Osteoporosis	Mombelli, Cionca 2006	Level 3a systematic review of 17 studies	No increased risk for failure	Small sample size studies using modified surgical protocols. Heterogeneity precluded meta-analysis
Bisphosphonates	Ruggiero *et al.* 2009 Mavrokokki *et al.* 2007	Level 5 position paper Level 4 case series	Revised overview 0.09–0.34% ONJ with extraction (oral BPs) 6.7–9.1% ONJ (IV BPs)	Expert opinion emphasizing prevention Postal survey, probable underreporting of cases
Radiotherapy	Ihde *et al.* 2009	Level 3a systematic review of 8 studies	2–3 times greater failure rate in irradiated bone. HBO inconclusive (extrapolated 95% CI)	Poor to medium quality cohort or case series
Periodontitis related tooth loss	Heitz-Mayfield 2008	Review of 4 systematic reviews(2a)	Increased risk for peri-implant disease with a history of periodontitis related tooth loss (extrapolated 95% CI)	Studies generally heterogeneous and short term
Smoking	Strietzel *et al.* 2007	Level 1a systematic review of 35 papers and meta-analysis of 29 studies	Increased risk for implant failure OR 2.25 for smokers, OR 3.61 for smokers with bone augmentation (95% CI)	No distinction for number of cigarettes smoked Higher complications noted. 5 studies showed no significant difference with modified surfaced implants
Implant site	Moy *et al.* 2005	Level 4 retrospective cohort study of 4680 implants over a 21-year period	Failure rate Mn = 4.9% < Mx = 8.2% ($p < 0.001$) Ant Mx = 6.8% < Post Mx = 9.3% ($p < 0.001$) Ant Mn = 2.9% < Post Mn = 5.9% ($p < 0.022$)	Poor jawbone quality and shape associated with increased implant failure
Genetic factors	Alvim-Pereira *et al.* 2008	Level 5 narrative review	Association with implant failure or bone loss noted with some genetic factors	Emerging evidence from small case/control studies

Levels of evidence[3] – 1a, systematic review of randomized control trials; 1b, individual RCT (with narrow confidence intervals); 2a, systematic review of cohort studies; 2b, individual cohort study (including low-quality RCT; e.g. <80% follow-up); 2c, outcomes research; ecological studies; 3a, systematic review of case-control studies; 3b, individual case-control study; 4, case-series (and poor-quality cohort and case-control studies); 5, expert opinion without explicit critical appraisal; or based on physiology, bench research or 'proof of principle study'.

warfarin should have an International Normal Ratio (INR) of less than 2.5 immediately preceding surgery. Recent reviews do not recommend ceasing anticoagulant treatment, including aspirin, prior to minor oral surgical procedures, which is comparable with extraction of three teeth. Simple implant placement without soft tissue or bone grafting would be included in this category.[11]

Diabetes

There are two major types of diabetes: Type 1 is caused by an autoimmune reaction destroying the β cells of the pancreas, leading to an insufficient production of insulin; and Type 2 is viewed as a resistance to insulin in combination with an incapacity to produce additional compensatory insulin. Type 2, often linked with obesity, is the predominant form, notably in the adult population presenting for implant therapy.[4]

Surgery should be avoided for poorly controlled diabetics, although diabetes *per se* is not a contraindication to implant therapy. In a retrospective cohort study which included 48 diabetic and 1092 non-diabetic patients, Moy *et al.*[10] reported a statistically significant relative risk for diabetic patients of 2.75

(95% CI 1.46, 5.18). A systematic review (four articles) by Klokkeveld *et al.*[12] showed no significant difference in implant survival rates of Type 2 diabetics (91.7%) vs. non-diabetics (93.2%). However, only one study included a non-diabetic control group. The systematic review by Mombelli *et al.*[4] which analysed data from 15 heterogeneous articles was unable to confirm an unequivocal tendency of diabetics to increased failure, although most studies, with the exception of Moy *et al.*,[10] were short-term or with small patient numbers. In the Mombelli *et al.*[4] analysis, patients were well-controlled with respect to blood glucose levels, before and after implant therapy.

Autoimmune disorders

Autoimmune disorders result from the failure of an organism to recognize its own constituent parts as self, which allows an immune response against its own cells and tissues. Common examples with particular relevance to dentistry include Type 1 diabetes, Crohn's disease, Sjögren's syndrome and rheumatoid arthritis.

A recent study of 270 implants by Alsaadi *et al.*[13] analysed the influence of local and systemic factors on implant failure, up to the stage of abutment connection for 720 implants. This study followed the classical two-stage surgical protocol with only MkIII Brånemark implants with an oxidized surface. The high degree of homogeneity and lack of confounding variables from, for example, occlusal loading or bacterial contamination encountered in a one-stage protocol, provided a strong indication that failures reported were largely due to systemic influences. The failure rate was so low (1.9%) that definitive conclusions could not be made with sufficient statistical power. However, a tendency toward a higher failure rate was noted for patients with Crohn's disease and Type 1 diabetes. A previous published study by the same group recording early implant failures up to abutment connection for 6316 machined implants and 630 TiUnite implants, reported an odds ratio for Crohn's disease of 7.95 (95% CI 3.47, 18.24), being the highest odds ratio of all systemic factors evaluated in this study.[14] Unfortunately, exact numbers of patients treated in both studies were not provided.

The treatment of autoimmune disease is typically with immunosuppression to decrease the inflammatory response. Patients undergoing systemic steroid therapy may have complications including osteoporosis, delayed wound healing and increased susceptibility to infection. One study showed a slightly lower, but not statistically significant, implant survival rate for patients undergoing steroid therapy. However, the sample sizes were small and subjects were not stratified for medication dose or duration.[10]

Osteoporosis

Osteoporosis has been defined as a decrease in bone mass and bone density and an increased risk and/or incidence of fracture.[4] Frieberg *et al.*[15] conducted a short-term retrospective pilot study of 16 osteoporotic patients where implants were placed with an adapted bone preparation technique to improve initial stability. After extended healing times, favourable success rates were reported (97% maxilla, 97.3% mandible) with no early failures. A systematic review by Mombelli and Cionca[4] included 17 studies reporting data from osteoporotic patients. There was no evidence for a higher failure rate in osteoporotic patients; however the heterogeneity of study design precluded a meta-analysis.

Bisphosphonates

The mode of action of the bisphosphonates (BPs) in bone metabolism is complex and multifactorial. They have a specific affinity for bone and are deposited in newly formed bone close to osteoclasts. Once incorporated, they can persist for up to 10 years. Their action is to directly affect mononuclear activity, the parent cell of osteoclasts. This disrupts osteoclast-mediated bone resorption and increases apoptosis of osteoclasts. This in turn, reduces bone deposition by osteoblasts with a net effect of a reduction in bone resorption and bone turnover. Angiogenesis is reduced by depression of blood flow and a decrease in vascular endothelial growth factor. Inhibition of epithelial keratinocytes combines and results in a reduction in healing capacity.[16]

Osteonecrosis of the jaws (ONJ) is a potential major complication with long-term use of bisphosphonates due to the above actions, rendering exposed bone more susceptible to infection.[17] The impaired bone healing may leave exposed bone uncovered by mucosa resulting in chronic pain, bone loss and in some cases pathologic jaw fracture. In an Australian study, Mavrokokki *et al.*[18] used a postal survey and estimated the risk of ONJ after dental extraction to be 0.09–0.34% with weekly oral alendronate (Fosamax) and 6.7–9.1% with intravenous formulations used for bone malignancy.

Two recent retrospective studies by Bell[19] and Grant[20] of patients prescribed oral bisphosphonates and receiving dental implants showed no sign of ONJ and reported similar success rates to that achieved in non-BP patients. The number of patients included may have been insufficient to detect a significant effect given the small incidence and no differentiation

was made concerning the length of time that the drug had been in use or the cumulative dosage. One study did report that patients on BPs for longer than three years or with concomitant prednisone treatment should consider alternatives to implant treatment.[20]

In a narrative review by Woo *et al.*,[21] the risk for ONJ in patients taking oral bisphosphonates after dental implant surgery was estimated at 1 in 2000 to 8000 patients, dependent on time and dosage, with three years considered a significant time point.

Marx *et al.*[22] reported on 30 consecutive cases of ONJ associated with oral bisphosphonate use. This represents a relatively large group of patients given the low incidence of ONJ patients. However, it is small with respect to statistical validity. The severity of ONJ experienced was related to the length of time the drug had been prescribed, with all patients having exposure of more than three years. A higher incidence was noted with alendronate and co-morbidities of prednisone and/or methotrexate were reported to result in more severe ONJ, more rapidly. The authors proposed a stratification of risk based on the serum C-terminal telopeptide (CTX) test which measures bone turnover. The interpretation of less than 100 pg/mL as high risk, 100–150 pg/mL moderate risk and >150 pg/mL as minimal risk, was proposed as a guide to treatment decisions. A significant improvement in CTX value was shown in every ONJ patient after ceasing the drug for six months, which was more often associated with successful treatment outcome. The same improvement was not seen with ONJ patients undergoing treatment with intravenous bisphosphonates. The conclusions should be interpreted with caution as sample size, qualitative outcome measurement, arbitrary stratification of risk and lack of a control group has low scientific validity.

The discontinuation of bisphosphonate therapy should not be made by the dental practitioner in isolation, but by the prescribing physician in consultation with the dental team. The patient should be made aware of any risks and benefits of discontinuing bisphosphonate medication.[21–23] The American Association of Oral and Maxillofacial Surgeons updated position paper on bisphosphonate-related osteonecrosis of the jaws[23] listed additional risk factors of corticosteroid use, diabetes, smoking, poor oral hygiene and chemotherapy.

Current management is based on expert opinion with an emphasis on prevention. Thorough counselling of each patient on possible risks and sequelae, as well as ongoing careful monitoring, is paramount when considering implant treatment for this group of patients.[16]

Radiotherapy

A recent systematic review by Colella *et al.*[24] showed similar failure rates for implants placed pre-radiotherapy compared with those placed post-radiotherapy – 3.2% and 5.4% respectively. Implant failure rate was significantly higher in the maxilla (17.5%) compared with the mandible (4.4%) with all implant failures occurring within three years after radiotherapy and most within 1 to 12 months. No implant failures were reported when radiation dose was less than 45 Gy.

A long-term study of implant survival in irradiated mandibles showed no statistical difference in post-radiotherapy timing of implant placement in patients receiving 50 Gy of radiotherapy and various forms of reconstructive mandibular grafting.[25] Eight-year implant survival rates were 95% in non-irradiated residual bone, 72% in irradiated residual bone and 54% in grafted bone. The authors suggested the adjunctive use of hyperbaric oxygen therapy (HBO) in the treatment of irradiated patients. Esposito *et al.*[26] in a Cochrane review of HBO and implant treatment failed to show any appreciable clinical benefits. However, the conclusion was based on only one heterogeneous randomized control trial (RCT) of 26 patients, which did not show a statistically significant difference between the two groups.

In a systematic review of animal and human studies, Ihde *et al.*[27] concluded that implants placed in irradiated bone exhibited a 2–3 times greater failure rate compared with non-irradiated bone, with doses above 50 Gy having a higher failure rate. No significant differences in failure rate were found with implants placed at various intervals, either before or after radiotherapy for a clinical recommendation to be made. However, implants placed in the maxilla were at least twice as likely to fail and no specific implant could be recommended based on survival data. HBO therapy was significant for decreasing failure rates in craniofacial implants, but was inconclusive with the use of dental implants based on the studies reviewed.

Periodontitis-related tooth loss

Recent systematic reviews have investigated the risk of peri-implant disease and a history of periodontitis.[28–31] In a systematic review, Schou *et al.*[29] analysed the data from two retrospective cohort studies with 5- and 10-year follow-ups including a total of 33 patients with tooth loss due to periodontitis and 70 patients with non-periodontitis associated tooth loss. There was no significant difference in survival of the superstructure. However, significantly more patients were affected by peri-implantitis (RR = 9, 95% CI 3.94–20.57) after 10 years and significantly increased peri-implant bone loss occurred after five years (95% CI 0.06–0.94) in patients with tooth loss due to periodontitis. The sample size and methods used in these two studies

suggests caution when interpreting the conclusions. Karoussis *et al.*[30] in a critical review of 15 prospective studies found no statistically significant difference in both short- and long-term implant survival between patients with a history of chronic periodontitis and periodontally healthy individuals. However, the short-term studies emphasized a strict individualized maintenance programme following implant placement. Longer-term studies showed an increase in probing depths, peri-implant bone loss and incidence of peri-implantitis. Studies on implants placed in patients with a history of aggressive periodontitis are limited to short-term follow-up. The short-term survival rates appear to be acceptable; long-term results are not available. The authors emphasized the need for more uniformly designed, prospective, controlled long-term studies coupled with a definite need for a universally accepted definition of 'periodontally compromised'. A critical review by Heitz-Mayfield[32] concluded that although the studies on implant therapy in patients with a history of periodontitis-associated tooth loss varied in design, length of follow-up, definition of patient population with respect to periodontal status, outcome measures and supportive periodontal therapy regimens, as well as confounding variables such as smoking and timing of baseline measurements, patients with a history of periodontitis were at greater risk of peri-implant disease. The longest study reviewed was 14 years with many studies of much shorter periods. Longer-term studies may reveal a more significant correlation; however confounding factors such as diabetes and smoking with periodontal disease makes it difficult to determine the effects of periodontitis history alone.

Smoking

Several mechanisms have been proposed by which smoking may effect wound healing: (a) carbon monoxide released by cigarette smoke has a higher affinity for haemoglobin which reduces oxygenation of the healing tissues; (b) nicotine is vasoconstrictive which increases platelet aggregation and adhesiveness and thus further reduces blood flow; (c) the cytotoxic effects on fibroblasts and polymorphonuclear cells additionally disrupt cell repair and defence; and (d) wound healing is impaired leading to a higher complication rate with all surgical procedures.[33] Wound healing is fundamental to the process of osseointegration and smoking is recognized as a risk factor.

Moy *et al.*[10] reported a success rate for non-smokers of 91% compared with 80% for smokers. Using a stepwise regression analysis, the relative risk factor (RR) of 1.56 (95% CI 1.03, 2.36) made smoking a significant variable for implant failure. Most failures occurred in the first year following implant placement. There were twice as many implant failures in the maxilla compared with the mandible for patients who smoke. While patient numbers in this study were high, the numbers in some of the confounding variable groups were small, and the statistical power was low. The overall success rate was high, consistent with success rates generally reported. However, small percentage differences may be affected by 'outlier' values rather than being a definite trend. Data reported by a single operator presents a difficulty in extrapolating the results for success or failure for another operator. In favour of this data is that the protocol was consistent with machined Brånemark implants and two-stage surgery with delayed loading. More recent developments with differing implant designs and surface treatments, single stage placement, immediate placement and shortened time to loading introduce variables which prevent meta-analysis.

A narrative review by Levin *et al.*[33] with extrapolation of data from their own studies compared success rates of implants and augmentation procedures in smokers and non-smokers. The authors also compared a history of smoking from a patient questionnaire, and found no statistical difference compared with patients who had never smoked. As a result, a smoking cessation programme was recommended but without definitive guidelines. Implant survival was statistically different with non-smokers overall survival rate of 97.1% and smokers 87.8%. Onlay bone grafting showed a higher major complication rate of 33% with smokers compared with non-smokers of 7.7%. Interestingly, sinus-lift procedures showed no difference in complication rate.

A 9–14 year long-term retrospective study of 1057 machined Brånemark implants by Roos-Jansåker *et al.*[34] showed a survival rate of 94% in non-smokers and 88% in smokers. The data were not statistically significant due to small numbers and the clustering of failures within a few patients. The high loss to follow-up of 26% undermines statistical validity. However, a significant relationship was noted with periodontitis. Smoking is well known to be a significant risk factor for periodontitis and given that the two often occur together, analysis of these two variables to provide sufficient statistical power to determine a relative risk profile for each, requires large numbers, given the low failure rate of dental implants.

De Luca *et al.*[35] reported on a long-term retrospective study of 1852 consecutive machined Brånemark implants. The mean follow-up was five years with 84% available for examination and the failure rate for non-smokers was 13.3% and smokers 23.1%. The failure rate was statistically significantly greater as cigarette numbers increased. Smokers at the time of implant surgery had a 1.69 (95% CI) times higher incidence of early implant failure compared with patients who had never smoked or who had stopped smoking at

least one week before implant surgery. Thus, data indicated that some of the effects of smoking can be minimized and this is in keeping with an earlier study by Bain.[36]

In this prospective study,[36] 233 consecutive machined Brånemark implants were placed in 78 patients by a single operator. All smokers were encouraged to stop smoking completely one week before implant placement. It was reported that smokers who followed this advice had a failure rate of 11.76% which was not statistically different from non-smokers (5.68%), even though in the group which stopped smoking, three out of the four failures were clustered in one 70-year-old female. This patient had been a heavy smoker for more than 50 years and was treated with short implants, which were placed in type 4 bone.

Smokers who did not stop had a statistically significantly higher failure rate of 38.46%. The one-week cessation protocol was chosen from a medical model suggesting significant blood flow improvement within one week. Although the numbers in this study are low, it nevertheless presents valuable data when advising patients of the benefits of smoking cessation.

While suggesting a tendency for similar survival rates with the cessation protocol, the De Luca *et al.*[35] study did show that individuals with a positive smoking history had a significantly higher late implant failure (23.08%) compared with patients who had never smoked or had a history of light smoking (13.33%). The authors concluded that while a smoking history may not interfere with wound healing in establishing osseointegration, a positive smoking history was associated with failure to maintain established osseointegration. Smoking has been associated with a reduction in bone density, particularly in the maxilla, consistent with the generally higher failure rates observed with maxillary implants in such patients.[10,33,35–37]

A meta-analysis by Hinode *et al.*[37] with strict inclusion criteria on 19 case-control or cohort studies, assessed the relationship with odds ratios (OR). Study heterogeneity, sensitivity and publication bias were controlled by applying statistical models, and the overall OR for smoking in the 19 studies was significant at 2.17 (95% CI 1.67–2.83). Seven studies considered smoking and implant location, where the OR was significant for the maxilla (2.06 95% CI, 1.61–2.65), but not significant for the mandible (1.32 95% CI, 0.72–2.4).

These authors commented on the study of Bain *et al.*[38] in which modified surface implants were compared with machined implants. This study reported on a meta-analysis of three prospective multicentre studies using machined 3i implants and six prospective multicentre studies using 3i Osseotite implants. Each was performed using a standardized surgical protocol in a two-stage manner and implants were unloaded for 4–6 months. Groups were checked for imbalance with respect to baseline variables such as bone quality and quantity, location and patient variables. All treatment indications were included for analysis and follow-up over three years accounted for over 99% of implants. No significant difference was found for smoking in the machined group (92.8% non-smoking, 93.5% smoking) or in the Osseotite group (98.4% non-smoking, 98.7% smoking). However, there was a significant difference in success rates between the two surfaces. These findings contradicted previous studies concerning machined implants. The authors provided weak explanation for this outcome and proposed that the smokers, on average, may have been lighter smokers and there may be a difference between heavy smokers. The specific number of cigarettes consumed was not a variable in this study.

The superior performance of modified implant surfaces is consistent with a smaller randomized open-ended clinical trial by Rocci *et al.*[39] In this study, a comparison between 55 Brånemark machined implants and 66 Brånemark oxidized surface implants of an exact macroscopic design were used for immediate loading of a fixed dental prosthesis in the posterior mandible. The success rates for the machined implant was 85.5% and the oxidized surface implant 95.5%. The machined surface implants showed a significantly higher failure rate for smokers and type 4 bone.[40] Conversely, the oxidized surface implant showed no significant difference despite this group having higher numbers of smokers and type 4 bone. Hinode *et al.*[37] recommended that further research was needed to clarify the influence of surface modification; this is important as neither study is long-term and, as proposed by DeLuca *et al.*,[35] smoking may have a significant effect on the maintenance of osseointegration.

A systematic review by Strietzel *et al.*[41] of 35 papers and a meta-analysis of 29 papers compared the statistical analysis of biological complications or implant failure among smokers and non-smokers. The meta-analysis indicated a significantly greater risk for implant failure among smokers (OR 2.25 95% CI 1.96–2.59), compared with non-smokers and for smokers receiving implants with bone augmentation, an OR of 3.61 (95% CI 2.26–5.77). Five studies reported no significant impact of smoking on implant success with particle blasted, acid-etched or anodic oxidized surfaced implants. The systematic review also indicated a significantly greater risk for biologic complications with smokers. Eleven studies showed a significantly greater degree of peri-implant bone loss in smokers compared with non-smokers, although in surface-modified implants, this correlation was not found. A regular and strict recall maintenance programme was suggested for smokers, although no distinction in this review was made for the

number of cigarettes smoked due to the heterogeneity of smoking classifications. Some studies classified 'light' smokers as less than 20 cigarettes per day, whereas other studies classified more than 10 per day as 'heavy'. Patients' individual medical history was also considered pertinent as an additional variable to a history of smoking – risk factors such as diabetes mellitus, post-menopausal women undergoing hormone replacement therapy, osteoporosis and hypothyroidism have been implicated in exacerbating the smoking risk factor.

Implant site

Herrmann *et al.*[42] assessed the influence of individual patient characteristics or combinations of these as potential prognostic factors for implant failure by using prospectively collected patient data. Early implant failure was reported in 3.7% of patients and the most significant patient-related factors were jawbone shape (D and E) and jawbone quality (type 4) according to Lekholm and Zarb.[40] Furthermore, a combination of low bone density and deficient bone volume present a significant association with implant failure. Three per cent of the patient cohort presented with jawbone shapes D and E and jawbone quality type 4, and approximately 65% of these patients experienced implant failure. Moy *et al.*[10] retrospectively analysed 4680 implants placed in 1140 patients over a 21-year period. Overall implant failure was reported to be almost twice as frequent for implants placed in the maxilla (8.16%), than in the mandible (4.93%). Failures in the posterior maxilla (9.26%) were higher than the anterior maxilla (6.75%) and the posterior mandible showed a higher failure rate (5.89%) than the anterior mandible (2.89%).

Local anatomy

A detailed knowledge of orofacial anatomy is essential for implant treatment. Local structures that may affect placement of implants include: the nasal floor; nasopalatine canal; maxillary sinus; mental nerve; and inferior alveolar nerve. Concavities on the lingual aspect of the mandible may lead to perforations during surgical preparation. Trauma to the sublingual and/or submental arteries may result in significant bleeding, swelling and in some cases life-threatening situations. Reports of airway incompetency after mandibular implant surgery[43,44] and anatomical studies of this area[45] provide a salutary reminder for sufficient radiographic investigation and adequate flap elevation.

Genetic factors

Implant failure is a complex, multifactorial process and the observed repetitive failure in some individuals questions the role of host susceptibility. The clustering of implant failures in some individuals and the observation of recurrence of implant loss, suggests the existence of genetic risk factors.[46] The most commonly studied functional polymorphism for dental implant failure are variations of the interleukin-1 (IL-1) gene cluster exhibiting pro-inflammatory and bone resorbing properties. Evidence of association in periodontal disease has been found, but not with implant failure. In a retrospective study, Gruica *et al.*[47] showed increased peri-implant bone loss when IL-1 gene polymorphism and smoking were combined. This synergistic effect was also reported by Jansson *et al.*[48] and indicates that further research with larger patient groups using a multifactorial analysis is warranted. Correlations with implant failure have been associated with polymorphisms of matrix metalloproteinase 1 (MMP-1),[49] with bone morphogenetic protein 4 (BMP-4)[50] and calcitonin receptor gene[51] associated with marginal bone loss prior to implant loading. Despite promising advances, the number, identity and specific role of regulatory factors that lead to successful osseointegration and its maintenance, are still largely unknown.[46] Genetic studies will hopefully identify the pathophysiology of implant failure and provide viable tools for screening, prevention and maintenance of osseointegration.

Combined risk factors

Very few studies have analysed the effect of multiple risk factors on implant survival. However, many patients, particularly the elderly, have chronic systemic disease, smoking history and polypharmacy that may not be independent of each other. At this stage, stratification of risk for individual patients must largely be made on a case-by-case basis by the treating clinician, taking into consideration known risk factors. The synergistic effect of a combination of factors, which may not be considered significant when analysed singly, may be so when occurring together.

CONCLUSIONS

Current literature has been assessed concerning risk factors for single tooth implants. Most study conclusions are by association with many confounding variables; the numbers in subcategories are often too small for meaningful statistical comparison and follow-up times vary and are often short-term. There are many potential risk factors and the clinician is required to have a comprehensive knowledge and understanding of these factors and to discuss them with each patient and consider them in treatment planning and treatment provision. Despite these requirements, implant

rehabilitation is a successful and predictable treatment for the majority of patients.

There is evidence from long-term trials to indicate that in patients with hypertension and other cardiovascular disorders, if they are able to undergo minor oral surgery, there is no increased risk of implant failure.

Inconclusive evidence exists that diabetic patients have a higher failure rate as most studies are short-term and have insufficient patient numbers. One long-term study showed a higher relative risk[10] and uncontrolled diabetic patients should not be treated.

Evidence is lacking for recommendations on implant treatment for patients with other autoimmune disorders. Expert opinion papers recommend treatment of these patients with a delayed approach and increased healing times before loading.

Studies reporting on osteoporosis were heterogeneous and short term, and showed reasonable success with osteoporotic patients treated with adapted bone preparation and extended healing times.

Bisphosphonate therapy guidance is largely from expert opinion. The incidence of ONJ is low; however morbidity is high. The evidence base is poor with the emphasis on prevention and further research is required before an accurate risk profile can be developed for individual patients.

The evidence for radiotherapy as a significant risk factor is strong; however the evidence for the use of HBO in decreasing failure rates is inconclusive.

Weak evidence exists that a history of periodontitis-related tooth loss is associated with an increase in peri-implant disease.

Higher quality evidence supports higher failure rates in smokers, especially in the maxilla and shows higher complications with smoking and bone augmentation. Weak evidence indicates a greater marginal bone loss in smokers and a higher complication rate with increasing tobacco use. Good evidence exists to show a low overall failure rate such that smokers should not necessarily be denied implant treatment, but should be apprised of the increased complication rate. There is emerging evidence to suggest that modified surface implants reduce these risks comparable to non-smokers but more research is required. In light of the many smoking-related illnesses, as health care professionals, dental practitioners should encourage all smoking patients to stop.

Good evidence is available to show that implant site is a prognostic factor. A higher failure rate is associated with poor quality bone. Data indicate that the higher rate in the maxilla is almost twice that of the mandible. Posterior sites have a higher failure rate than anterior sites.

A detailed knowledge of orofacial anatomy is essential for implant treatment.

Emerging evidence suggests that there is a correlation between genetic traits and disruption of osseointegration. The number, identity and role of regulatory factors that lead to successful osseointegration and its maintenance are still largely unknown.

Negligible evidence is available on the synergistic effect of multiple risk factors. Therefore, risk must be assessed on a case-by-case basis by individual clinicians.

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