Summer 8-14-2019

Dental Implant Failure Rate and Marginal Bone Loss in Smokers Compared to Non-Smokers: A Systematic Review and Meta-Analysis

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Dental Implant Failure Rate and Marginal Bone Loss in Smokers Compared to Non-Smokers: A Systematic Review and Meta-Analysis

Abstract

Background: Although dental implant therapy is considered a predictable treatment modality with reported high survival and success rates, biological complications do occur, and a number of risk factors have been involved. Tobacco smoking is related to many health risks affecting general & oral health.

Objectives: The aim of this systematic review and meta-analysis is to test the null hypothesis of no difference in dental implant failure rates and marginal bone loss between smokers and non-smokers with regards to follow-up time.

Search methods: An extensive electronic search was performed in PubMed, Scopus and EBSCOhost Dentistry and Oral Sciences source to identify relevant articles published up to June 2019. The eligibility criteria included randomized and non-randomized clinical trials & prospective & retrospective observational studies. After a thorough selection process, 23 papers were included. The meta-analysis was expressed in terms of the odds ratio (OR) or standardized mean difference (SMD) with a confidence interval (CI) of 95% and the level of statistical significance was set at $P < 0.05$.

Results: There was a statistically significant difference in marginal bone loss favoring the non-smoking group with a SMD of 1.07 (95% CI 0.67–1.48), demonstrating a statistically significant difference in favor of non-smokers ($P$

Author’s conclusion: Based on the results of this review, the null hypothesis is rejected, and that is in agreement with other reports in the literature. Therefore, the clinical recommendation for a period of abstinence from smoking that at least covers the pre-surgical evaluation & initial therapy, definite implant treatment & immediate post-op phases remains to be very relevant.

Degree Type
Thesis

Degree Name
MSOB (Master of Science in Oral Biology)

Primary Advisor
Dr. Joseph Fiorellini DMD, DMSc

Keywords
edentulous, partially edentulous, smoking, tobacco use, dental implants, bone resorption, marginal bone loss, failure rate, cumulative survival rate

Subject Categories
Dentistry | Oral and Maxillofacial Surgery | Periodontics and Periodontology | Prosthodontics and Prosthodontology

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Dental Implant Failure Rate and Marginal Bone Loss in Smokers
Compared to non-Smokers: A Systematic Review and Meta-Analysis

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Thesis

Presented to the Faculty of Penn Dental Medicine in Fulfillment of the Requirements for
the Degree of Master of Science in Oral Biology

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Abstract

**Background:** Although dental implant therapy is considered a predictable treatment modality with reported high survival and success rates, biological complications do occur, and a number of risk factors have been involved. Tobacco smoking is related to many health risks affecting general & oral health.

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**Results:** There was a statistically significant difference in marginal bone loss favoring the non-smoking group with a SMD of 1.07 (95% CI 0.67–1.48), demonstrating a statistically significant difference in favor of non-smokers (P<0.00001). A subgroup analysis in smokers revealed a statistically significant increase in marginal bone loss in the maxillary implants compared to the mandible (P = 0.008) with a SMD of 1.39 (95% CI 0.35–2.42) although with a high level of heterogeneity (I² = 97%; P = 0.0001). A statistically significant difference (P < 0.00001) in implant failure rate in favor of the non-smoking group was also observed, with OR of 2.24 (95% CI 1.90–2.64). Moreover, the subgroup analysis for follow-up time revealed a significant increase in implant failure proportional to the increase in follow-up time (P = 0.05), but with considerable heterogeneity (I²=74.5%).

**Author’s conclusion:** Based on the results of this review, the null hypothesis is rejected, and that is in agreement with other reports in the literature. Therefore, the clinical recommendation for a period of abstinence from smoking that at least covers the pre-surgical evaluation & initial therapy, definite implant treatment & immediate post-op phases remains to be very relevant.

**Keywords:** edentulous, partially edentulous, smoking, tobacco use, dental implants, bone resorption, marginal bone loss, failure rate, cumulative survival rate.
Acknowledgements

I would like to express my deep gratitude to Dr. Jonathan Korostoff, director of the Master of Science in Oral Biology program, Dr. Fiorellini and Dr. Hangorsky for granting me the opportunity to pursue this coursework. I also thank the rest of my thesis committee members and Dr. Paul Hunter for their insightful remarks & continued support. Last but never least, I thank God, my family and friends for being in my life.
Review of pertinent literature

Methods of evidence-based dental practice was introduced to optimize the decision-making processes in diagnosis and treatment planning, and for comprehensive patient information in preparation of diagnostic and therapeutic interventions, particularly before elective procedures. Outcome anticipation is an important aspect of risk management in contemporary implant dentistry. Recognizing the factors that may potentially place the patient receiving dental implant(s) at a higher risk of implant failure or other adverse conditions allows the practitioner to make informed decisions and refine the treatment approach to optimize the results and improve the predictability of successful therapy. As in other topics, RCTs are one of the most reliable sources of information for clinical practice and therefore are the studies preferred for the elaboration of longitudinal studies in implant dentistry. However, the inclusion of longitudinal observational studies, with high number of participants can potentially increase the amount of viable data. The Early longitudinal studies evaluating osseointegrated dental implants showed satisfactory results. Currently, with more than 40 years of scientific evidence, the clinical use of dental implants has been increasing day by day. Nevertheless, few studies have examined follow-up periods for ten years or longer, which is important to enable us to understand the biological aspects of dental implant therapy. Implant-supported prostheses have been shown to have successful long-term outcomes. However, numerous local and systemic factors have been hypothesized to affect implant success to various degrees. Such factors include but are not limited to implant insertion in type III and IV bone qualities, reduced initial stability of the implant, particularly in cases of immediate loading protocol, implant placement in posterior maxilla, radiation therapy sites, drug and alcohol intake, and tobacco smoking. When a cause-effect relationship is being investigated, an accurate definition of the potential cause is
imperative. This is particularly important when the effect is expected to be frequency and dose dependent. In the medical literature, smoking was established to cause a dose-dependent effect on the extent of bone loss and the risk of fracture in long bones.\textsuperscript{167} Surprisingly, however, smaller doses of nicotine have been found to stimulate osteoblastic growth.\textsuperscript{98} Wide variations in the definition of smoking are encountered in the dental literature in terms of smoking duration, number of cigarettes consumed daily, and categorization of previous smokers, and these variations prevent a detailed analysis of the predictability of measure outcomes. Different patient and implant-related confounding factors have been shown to impact the clinical outcomes associated with dental implants, but these factors are not always considered in the included studies. Many studies investigated the correlation between tobacco smoking and adverse implant-related outcomes, some align with the hypothesis that tobacco smoking increases implant failure rate, but others does not reach the same conclusion.\textsuperscript{6,49,120,159} Currently, no consensus has been reached, and no evidence-based guidelines have been generated to help clinicians make informed clinical decisions in utilizing dental implant treatment in tobacco smokers. These shortcomings may be attributed to several factors, like the variability in the design, quality and findings of studies conducted. The considerable heterogeneity among the studies has made direct comparison across studies a difficult task. Therefore, there is a limited number of recent systematic reviews comparing dental implant complications in smokers to non-smokers. Peri-implant mucositis is the most common biological complication associated with dental implants.\textsuperscript{73,144} It is characterized by a reversible inflammatory process, demonstrating a color change and redness and bleeding of the peri-implant mucosa, without presenting signs of bone resorption. Probing of the peri-implant sulcus and identifying signs such as the presence of bleeding or suppuration is important for thorough diagnosis of implant health,\textsuperscript{173} particularly
peri-implant mucositis. Clinically, peri-implant probing depth is influenced by a number of factors, including the depth of implant placement, the level of peri-implant marginal bone, peri-implant soft tissue phenotype and thickness, type of the prosthetic abutment, emergence profile of the prosthetic restoration, the region in which the implant was placed. Probing depths of $\geq 5$ mm must be investigated, as they may be indicative of peri-implant disease. However, peri-implant probing depths were either unreported or reported with wide variations with regard to the exact probing depth value in millimeters or the numbers of sites probed per implant. Therefore, the author elected not to select peri-implant probing depth as an outcome variable in this review.

Ever since the first longitudinal studies were conducted to evaluate the clinical performance of implants, various authors have proposed different criteria for classifying implant health and success. Nonetheless, up to the current time, no standardization for this classification has been made in the literature and that leads to considerable difficulty in the interpretation and comparison of data among the available studies. Due to the differences in criteria adopted by different authors, it is not always possible to arrive at an absolute mean value for the success rates in systematic reviews. However, in two systematic reviews by Needleman et al (2012) and Papaspyridakos et al (2012) evaluating the success criteria for implants, the criteria of Albrektsson et al. (1986) were related in around 33.3% ($n = 78$) and 31.7% ($n = 41$) of the studies included, respectively. This demonstrates that these remain to be the most widely accepted criteria at the present time. In longitudinal studies on osseointegrated dental implants, the terms ‘survival’ and ‘success’ are routinely used. However, these terms continue to generate confusion regarding their actual meanings and are frequently used incorrectly. Knowledge and standardization of these terms is necessary to facilitate communication, comparison, and thorough understanding among dental professionals. Studies evaluating success rates in
implant dentistry are complex because of the large number of confounding variables, such as surgical techniques, materials used, and follow-up period. In addition, several criteria have been proposed for the definition of success and the absence of international standardization makes it rather difficult to compare studies. While other authors have argued that a period of 5 years may still be too short to enable reliable information to be obtained, a minimum of 5 years of follow-up is necessary to properly analyze survival and success rates of dental implants. The majority of longitudinal studies evaluated only the survival rate of dental implants, as a quantitative analysis, potentially underestimating the importance of the data with reference to the overall health and quality of the placed implants. The most probable reason for the preference for survival studies appears to be related to easier methodology for that analysis; i.e. the measurement for statistical analysis is done only by counting the implants remaining in situ. Conversely, evaluating dental implant success involves analysis of more complex parameters and criteria and is more directly associated with the health and quality of the implants. Consequently, the statistical differences between the survival and success rates are typically significant. Smoking has been shown to be a primary risk factor for general health and responsible for many serious diseases, as for 90% of all lung cancers, 70% of chronic lung diseases, 80% of myocardial infarctions before the age of 50, and 30% of chronic ischemic heart diseases and strokes. There are an estimated 1.3 billion smokers around the world, and 4.9 million people die from tobacco smoking-related diseases every year (WHO). Besides the general role healthcare professionals play in tobacco smoking cessation and prevention, certain aspects pertaining to modern dental implant practice should be considered in tobacco smokers for thorough patient evaluation before oral surgical procedures and implant treatment planning. While the smoking cessation and sustained abstinence well before oral
surgical procedures should be the ultimate goal, nicotine dependence has proven to be a chronic relapsing disorder and is usually characterized by multiple failed quitting attempts. Nevertheless, a number of studies have suggested that adjunctive measures can possibly minimize the negative effects of tobacco smoking on dental implant survival rates. Abstinence from smoking for one week before and eight weeks post implant placement has been reported to improve the success rate associated with the Branemark implants. Opting for a two-stage placement and delayed loading protocol with may minimize the accumulation of bacterial biofilms and the diffusion of several of the nearly 4000 chemicals contained in cigarette smoke. Placement of dental implant in special populations like tobacco smokers requires consideration of the potential benefits to be gained from the treatment and possible adverse effects. To better appreciate this potential, properly conducted, high-quality systematic reviews and meta-analysis, whenever possible, comparing the survival rate of dental implants, postoperative infection, and peri-implant marginal bone loss (MBL) between smokers and non-smokers are essential to critically summarize the current knowledge and synthesize evidence. Thorough patient information not only about the planned treatment approach and the expected outcomes, but also about risks and risk factors are necessary to support the patient’s decision making before dental implant therapy. Moreover, smoking cessation advice, given in conjunction with dental health information may have a marked effect on smokers’ attitude toward their habit and provide a powerful incentive to reduce or even quit smoking. When placing dental implants in smokers, the peri-operative use of antibiotics as well as additional local potential preventive measures, like using flat instead of high cover screws, should be considered in an attempt to prevent postoperative complications during the healing period.
Recombinant human parathormone (PTH 1-34), which is an anabolic agent approved for the
treatment of patients with osteoporosis that stimulates osteoblast function,\textsuperscript{92} has been reported to
increase bone volume around implants in the presence of cigarette smoke in animals.\textsuperscript{119} It is
strongly suggested that the direct exposure of the peri-implant tissues to tobacco smoke products
is the main factor causing an increase in dental implant failure rate in smokers compared to non-
smokers.\textsuperscript{104} The increased risk of post-surgical wound healing complications\textsuperscript{105,126,127,146} as well
as the risk of peri-implant marginal bone loss and increased implant failure rates\textsuperscript{10,116,121} must be
emphasized. Delayed wound healing has to be anticipated due to deficient collagen synthesis and
production,\textsuperscript{106} reduced peripheral blood circulation and capillary bed perfusion\textsuperscript{115} and
compromised polymorpho-nuclear leucocytes and macrophages functions.\textsuperscript{110,124} Furthermore,
tobacco smoking was indicated as a significant subject-based risk factor for periodontitis in
literature reviews.\textsuperscript{132,139} Although not entirely understood, the long-term chronic effect of
smoking on periodontitis was found to be due to impairment of periodontal tissues vasculature
through vasoconstrictive effects at the end-arterial gingival vessels,\textsuperscript{54} multiple function
deficiencies of fibroblasts and neutrophils and reduced inflammatory response.\textsuperscript{132} Therefore, a
regular and strict recall of smoking patients undergoing implant treatment is important for early
detection of implant complications. The carbon monoxide generated during combustion of
tobacco smoking lowers the oxygen tension in tissues by displacing the oxygen from
hemoglobin.\textsuperscript{117} Nicotine, which has been found in high concentrations in saliva\textsuperscript{101,103} and
crevicular fluid\textsuperscript{84} of smokers has been reported to have a negative impact on bone regenerative
capacity.\textsuperscript{71,161} Furthermore, polymorphonuclear neutrophils viability, opsonization &
phagocytosis are significantly reduced in smokers compared to non-smokers.\textsuperscript{110} Nicotine is the
most significant constituent among more than 4000 potentially harmful substances in tobacco
products. It is the principal chemical component that causes tobacco addiction, appears to mediate the vasoconstrictive effects of tobacco smoking, and involved in the pathogenesis of many diseases.\textsuperscript{80} The exact mechanism by which tobacco smoke affects the osseointegration process remains to be unclear. However, several chemicals found in tobacco smoke have been shown to reduce the vascularity of the peri-implant tissues, and so may compromise the bone healing process.\textsuperscript{132} Approximately 3 mg of nicotine and 20–30 mL of carbon monoxide is inhaled for each cigarette smoked.\textsuperscript{151} Nicotine has been related to increased platelet aggregation and interference with the function of fibroblasts, osteoblasts, red blood cells and macrophages.\textsuperscript{55,81,102,164,169} In addition, carbon monoxide converts hemoglobin into carboxyhemoglobin rather than oxyhemoglobin due to its 200-fold greater affinity for hemoglobin than oxygen. The formation of carboxyhemoglobin decreases oxygen transportation, resulting in reduced tissue oxygenation and hypoxia.\textsuperscript{72,106,117,131,140} Although tobacco smoking is widely accepted as a risk factor for oral health in general,\textsuperscript{54} smoking was considered a risk factor for implant treatment since the first publication on this topic by Bain & Moy (1993).\textsuperscript{3}

Nevertheless, the impact of consideration of the patient’s status as a smoker or non-smoker in dental implant treatment planning seems to be uncontentroversial, but indistinct. In 1999, a national survey questionnaire to National Health Service (NHS) consultants evaluating their attitudes regarding medical and oral health-related factors considered in patient selection and treatment planning for dental implant placement revealed that, among others, tobacco smoking was one of the most important factors contraindicating dental implant therapy.\textsuperscript{75} Another survey among Finnish dentists to evaluate the relationship of various patient characteristics or possible contraindications for dental implant therapy revealed that more dentists practicing in the public or private sectors recommended implant therapy compared to staff of dental schools in case of
smoking patients. Older dentists (40–49 years) were found to be more in favor of implant
treatment in smoking patients than younger dentists (30–39 years). Therefore, validation of
smoking as a risk factor in treatment decisions may differ among dentists. This impression seems
to be confirmed by different attempts made to quantify the number of cigarettes smoked per day
in different studies. Human and animal studies have showed the deleterious effects of tobacco
smoking on the health of oral tissues. Animal studies have demonstrated that nicotine
inhibits gene expression of several enzymes that play an important role in the regulation of
osteoblast proliferation, differentiation and apoptosis, subsequently affecting bone formation and
remodeling. Furthermore, it was shown that exposure to nicotine has a direct effect on blood
vessels, producing vasoconstriction which decreases blood perfusion and causes low oxygen and
local ischemia. In addition to delivering oxygen and nutrients to tissues, blood circulation
plays an active role in bone formation and remodeling by mediating the interactions between
different bone and vascular cells at different regulatory levels. In a clinical study (AlBandar et
al. 2000), tobacco smokers had a higher prevalence of moderate and severe periodontal disease
with increased attachment loss and gingival recession compared to non-smokers, indicating
worse periodontal conditions in the smokers’ group. Furthermore, smokers had more missing
teeth than non-smokers. Several review articles identified within this literature search confirmed
that smoking is one of the factors related to implant failure by reporting conclusions of several
studies showing that smoking is associated with higher failure rates, complications and altered
peri-implant tissue conditions. A literature review by Klokkevold and Han (2007) suggested that tobacco smoking may be a significant risk factor with an adverse effect on implant
survival and success rates in areas of lower jawbone quality but may not be as significant in sites
with better bone. While a review by Levin and Schwartz-Arad (2005) revealed a significant
association between smoking, peri-implant marginal bone loss, reduced survival rate of implants 
(0.001 < p < 0.05) and the outcome of onlay bone grafts (p < 0.05) as well. In a recent meta-
analysis (Chen et al 2013),78 smoking was associated with an increased risk of dental implant 
failure. However, the analysis did not investigate the effects of tobacco smoking on peri-implant 
MBL. Results from another meta-analysis (Chrcanovic et al. 2015),60 suggested that insertion of 
dental implants in smokers affected implant failure rates, the risk of postoperative infection, and 
peri-implant MBL. It is hypothesized that the increased implant failure rates in tobacco smokers 
are mainly due to smoking effect on osteogenesis and angiogenesis. The commercially available 
titanium used in dental implant manufacturing have a wide range of surface topographies or 
morphologies and chemical and physical properties depending on how it is prepared and 
handled, examples include turned, acid-etched, sandblasted and acid-etched, sandblasted and 
fluoride-modified, and oxidized dental implants.56,57,58 It is known that the surface modifications 
of different dental implant brands influence the osseointegration process.168 A retrospective 
cohort study by Balshe and colleagues (2008)27 reported that smoking was not significantly 
associated with implant failure among the moderately rough surface (anodized) implants, while it 
was associated with implant failure among the group with minimally rough surface implants. 
Despite the large number of implants in this study (n = 4607), the results were not included in the 
upcoming meta-analysis because the number of placed and the number of failed implants were 
not separately reported between smokers and non-smokers. The evidence presented by Balshe et 
al.27 did not meet all requirements to be included in the current meta-analysis, however it is a 
valuable addition to the literature due to the great number of implants investigated. In a more 
recent study by Sayardoust et al. (2013),16 turned implants had more peri-implant MBL and a 
higher incidence of failure in smokers, while oxidized implants showed similar MBL and failure
rates in smokers and non-smokers. Such contrasting results indicate that controversy still exists and that there is a need for additional studies to investigate the long-term outcomes of implants with altered surface characteristics in tobacco smokers. The studies included in the current analysis used implants with several different brands and surface characteristics. In a retrospective study investigating success rates of dental implants placed in grafted maxillary sinuses, Kan et al. (1999) reported a 93.04% success rate in non-smokers and an 82.82% in smokers. In another study by the same authors with a longer follow-up period, the success rate for the non-smokers was 82.7% and for smokers was 65.3%. Therefore, in considering the difference in success rates in smokers and non-smokers for implants placed in loose trabecular bone sites that are followed over a longer period of time, the adverse effect of smoking may become more evident. A longer follow-up period can lead to an increase in the failure rate, particularly if it extended beyond functional loading, because other restorative factors can influence implant failure after loading. This may project an underestimation of actual failures in some clinical studies. However, it is difficult to define what would be considered a short follow-up period to evaluate implant failure rate in smokers. Results from the meta-analysis by Chrcanovic et al. (2015) demonstrated that smoking is associated with increased number of dental implant failures regardless of the type of implant surface topography or modification. Additionally, a higher risk ratio was observed with rough-surface implants compared to turned implants in the smoking group. Nevertheless, there is some contradictory evidence that smoking is associated with older turned implant surfaces but not with modern ones. With regard to the bone-implant interface, the detrimental effects of tobacco smoke have a series of local and systemic influences on bone metabolism. Concerning associations with patients’ tobacco smoking status, peri-implant bone level is known to be associated with implant prognosis. The peri-implant marginal bone around the
implant platform is normally a significant indicator for defining good peri-implant health. Misch et al. (2008) classified the implants with marginal bone loss of <2 mm from the time of initial surgery as successful, while according to Albrektsson and Isidor (1993) an implant is regarded as successful when it presents bone resorption of less than 1.5 mm in the first year after prosthetic loading and 0.2 mm in subsequent years. Other authors have proposed that an implant should present a lower bone resorption than one third of the implant length, regardless of the number of years in function. To date, there is no consensus regarding the quantity of peri-implant marginal bone resorption consistent with time after placement, overall health, and success. In a recent meta-analysis by Alfadda (2018), smokers experienced significantly more implant failure and peri-implant marginal bone loss relative to nonsmokers. These findings are in accordance with those of another review conducted by Moraschini et al. (2016). The greater difference in MBL observed between smokers and nonsmokers in association with aging (~0.02 mm/year) may be explained by a combination of the depleting effect of the tobacco chemicals on bone vascularity and the slow, progressive, age-related phase of bone loss in trabecular and cortical bone. A meta-analysis by Strietzel et al. (2007) on studies in which threaded titanium implants with machined, titanium plasma sprayed (TPS) or Hydroxyapatite (HA)-coated surfaces were predominantly used, revealed a significantly enhanced risk for implant failure among smokers compared to non-smokers. The study compared the implant related odds ratios for implant failure in smokers considering different observation periods. The risk of implant failure for smokers ranged from 2.8 after up to 1 year decreasing to about 2.3 up to 5 years, indicating a higher risk of early implant failure. However, the risk of implant failures in smokers was found to be significantly increased even after 5 years. In an earlier review by Esposito et al. (1998) on studies mainly reporting on threaded implants with a machined surface, i.e.
Branemark implants, the consensus was that smoking has a negative influence on implant survival. Furthermore, a comparison between threaded implants with machined and anodic-oxidized surfaces showed no significant influence of smoking on implant failures for implants with an anodic-oxidized surface. However, it is probably worth noting that studies including more modern implants with micro-structured surfaces like sand blasted and/or acid etched surfaces were scarcely published at that time. In the author’s opinion, whether these implant surfaces indeed significantly improve outcomes in smokers need to be further explored through studies with larger sample sizes reporting data on implant failure rates in relation to smokers and non-smokers. The findings reported by Strietzel et al. (2007) considering the implant-related ORs for implant failures in smokers were remarkably similar to those published in another study by Hinode et al. (2006) who performed a meta-analysis on the effect of smoking on osseointegrated dental implants, based on implant-related data. This review used a subgroup analysis to examine success in the maxilla versus the mandible. Whereas the overall OR for implant failure was 2.17 (95% CI, 1.67–2.83), the OR in the maxilla was 2.06 (95% CI, 1.61–2.65) and in the mandible was 1.32 (95% CI, 0.72–2.40), meaning the odds of failure was double in the maxilla, but statistically insignificant in the mandible. These two systematic reviews represent a small but growing body of evidence indicating implant failure risk is higher in smokers than in nonsmokers, particularly in the maxilla. In a systematic review by Berglundh et al. (2002) analyzing longitudinal studies of up to 5 years, implant survival rate of 97.5% up to the second stage surgery was observed. In the same year, Davarpanah et al. reported a survival rate of 96.5% for 1583 implants placed in different regions of the maxilla and mandible, with a follow-up period of 5 years as well. These results demonstrated a reduction in dental implant survival rate over time during the follow-up period. Simonis et al. (2010) and Carlsson et al.
concluded that there was a larger number of implant losses and higher level of peri-implant marginal bone loss in patients who were smokers. These conclusions are supported by numerous other studies that have analyzed the influence of tobacco smoking on the survival and success of dental implants. A systematic review by Moraschini et al. (2015) revealed a mean survival rate of 94.6% (SD 5.97%) for a total of 7711 implants, with a mean follow-up of 13.4 years. A number of authors from the included studies concluded that bone resorption occurred and was more evident after the first year of prosthetic loading, and in one study (Pikner et al. 2009) it was suggested that implants placed in the mandibular arch tend to present greater marginal bone resorption over the course of time. This review (Moraschini et al. 2015), based on the results of the included studies, presented a mean peri-implant marginal bone loss of 1.3 mm (SD 0.84 mm), and the study that presented the highest mean bone resorption value of 2.67 mm evaluated 316 implants under mandibular overdentures during 12 years of follow-up (van Steenberghe et al. 2001). The results of pertinent studies should be interpreted with caution due to the possible presence of uncontrolled confounding factors and the risk of bias. However, the overall results of most of the recently published studies suggest that placement of dental implants in smokers affects MBL, the incidence of postoperative complications, as well as implant failure rates. In light of the findings of this review, smoking may be associated with significantly increased peri-implant MBL and implant failure rate. Exploring various preventive and interventional measures that can possibly limit the adverse effect of tobacco smoking on implant-related outcomes is highly recommended. Additionally, the potential adverse effects of smoking on treatment outcomes must be explained to the patient before treatment, and the dentists’ clinical decisions should be specific to each case. As the risk of implant failure is generally low, individual practitioners will have to decide what modifications to therapy, if any,
should be employed with their patients. In conclusion, smoking is a significant risk factor for
dental implant therapy. This should be clearly conveyed to the patient before treatment. A strict
recall program throughout the course of the treatment to early detect negative changes in peri-
implant tissues or implant failure is necessary.
Background

According to the 9th edition of the Glossary of Prosthodontic Terms,95 edentulism is defined as the state of being edentulous, i.e. without natural teeth. It is estimated that 178 million Americans are missing at least one tooth & about 40 million are completely edentulous (ACP).176 The etiology of tooth loss is highly variable, ranging from tooth loss due to dental caries, periodontal disease, trauma or congenital anomalies. Tobacco smoking is a widely spread habit practiced all around the world. In 2016, an estimated 15.5% (37.8 million) of U.S. adults were current cigarette smokers. Of these, 76.1% smoked every day.44 Tobacco smoking is related to many health risks. It affects general and oral health causing increased risk of periodontal disease, dental caries, oral neoplasms and delayed wound healing. It was reported that there is an association between cigarette smoking and dental implant failure.3 The adverse effects of smoking and nicotine on oral soft tissue have also been observed in less-successful regenerative procedures and more gingival recession.138 Higher plaque index (PI) and increased probing depth (PD) have been reported in smokers compared to non-smokers.25 Furthermore, a 5-year retrospective study comparing different dental implants revealed that smokers have more marginal bone loss (MBL) around implants than non-smokers.16

Description of the intervention

The endosteal dental implant: a device placed into the alveolar and/or basal bone of the mandible or maxilla and transecting only one cortical plate.95 It is the most widely used dental implant type in contemporary dentistry. It is composed of an anchorage component, termed the fixture, which, ideally, is within the bone, a retentive component, termed the abutment and a restorative component in the form of a fixed, removable, or fixed-removable implant supported restoration
replacing single or multiple missing teeth and/or associated tissues. Dental implant survival refers to a dental implant that reside in placement site in the dental arch at the time of evaluation, regardless of any disease signs, symptoms, or history of problems. Dental implant success is usually defined by a set of criteria evaluating the condition and function of the implant at the time of evaluation, i.e. whether or not the implant satisfies the functional & esthetic demands. Dental implant failure often refers to loss of osseointegration and implant mobility that warrants removal of the implant.

**How this intervention might work**

Brånemark’s pioneering work on the phenomenon of osseointegration revolutionized the dental implants practice. Osseointegration is the concept that made dental implant therapy possible. It is defined as the direct structural and functional bone-to-implant contact. Successful osseointegration involves a series of biological events that includes inflammation, bone formation and remodeling. Missing tooth/teeth replacement with dental implants represents an invaluable treatment modality in modern dentistry and can preserve healthy natural teeth structure in cases of partial edentulism.

**Why it is important to do this review**

Although dental implant therapy is considered a predictable treatment modality with reported high survival and success rates, biological complications do occur and a number of risk factors have been involved, including the patient’s medical history, smoking habits, jawbone quality, radiation therapy, parafunctional habits, surgeon’s experience and susceptibility to periodontitis. The underlying mechanisms of the detrimental effects of smoking have been studied in vitro and
in vivo in animal and human studies. In vitro studies indicated that nicotine, a component in tobacco smoke, has a negative effect on the osteogenic gene expression in osteoblast cell lines.\textsuperscript{145} Furthermore, nicotine combined with bacterial lipopolysaccharide (LPS) has been shown to stimulate the formation of osteoclast-like cells.\textsuperscript{157} Animal experiments have demonstrated that nicotine attenuates the expression of a wide range of factors involved in the osteogenic differentiation and formation of extracellular matrix and blood vessels.\textsuperscript{171} Additionally, smoking reduces the vascularization of the gingival tissues, impedes the immune response, and promotes a more pathogenic or “dysbiotic” oral microflora.\textsuperscript{112} Although the available evidence highlights the potential biological components affected by smoking, the exact mechanism behind the greater marginal bone loss (MBL) and the higher incidence of implant failure in smokers are not fully understood & need further investigation. Although not an absolute contraindication per se, smoking is considered a risk factor for dental implant failure. Several recommendations were suggested to enhance implant survival in smokers.\textsuperscript{45} However, despite the plethora of the current available literature, confounding factors and inconsistency in reported outcome measures & implant success criteria is not uncommon.

**Objectives**

The aim of this systematic review and meta-analysis is to test the null hypothesis of no difference in dental implant failure rates and marginal bone loss between smokers and non-smokers with regards to follow-up time.
Materials and methods

The methodology of this review was adapted from the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The focus question was stated and categorized according to the PICO format (Population, Intervention, Comparison, and Outcome).

Criteria for considering studies for this review

This review sought prospective and retrospective cohort studies, as well as randomized & non-randomized clinical trials that compared implant failure rates and peri-implant marginal bone loss between smokers and non-smokers. In this review, implant failure was regarded as the total loss of the implant. Only studies published in English were eligible for inclusion.

Types of participants

Study participants are adult subjects, with a minimum age of eighteen years or older, that are tobacco smokers and non-smokers who are fully or partially edentulous and received dental implant(s) re-habilitation to overcome problems with conventional removable complete or partial dentures or for providing alternative treatment options for fixed or fixed-removable implant-supported restorations.

Types of intervention

Surgical placement of a single or multiple titanium endosseous dental implant(s) in one or both jaws to replace a single missing tooth or multiple missing teeth.
Types of outcome measures

The outcome measures investigated in this review are the number of failed implants, comprising the dichotomous or binary outcome variable, and the amount of peri-implant marginal bone loss, as a continuous outcome variable, in smokers & non-smokers.

Exclusion criteria:

Letters to the editor, animal studies, in vitro studies, case series, case reports, commentaries and reviews were all excluded. In addition, articles that did not separately report outcome measures for smokers and non-smokers, included patients with congenital/familial medical conditions or uncontrolled autoimmune or systemic diseases or unbalanced metabolic disorders, included subjects with periodontal disease without prior treatment, or were poorly controlled for confounding variables were excluded. Lastly, any studies that did not obtain ethical approval or written informed consent, included fewer than 10 patients in each group, used short (<6 mm) or zygomatic implants or were not available online were also excluded.

Search methods for identification of studies

Electronic searches

An extensive online search of the following databases was performed to locate relevant articles published up to June 2019: PubMed, Scopus, EBSCOhost Dentistry and Oral Sciences Source. To identify studies eligible for inclusion in this review, detailed search strategies were developed for each of the searched databases. These search terms were based on the search strategy originally developed for Medline (OVID) but revised appropriately for each database in an attempt to maximize the efficiency and effectiveness of the search and increase the number of
results. The search strategies incorporated a combination of MeSH (Medical Subject Heading) terms, controlled vocabulary and free text terms. The search strategies for each database are listed in Table 4.

**Searching other resources**

Citations and cross-referencing were comprehensively utilized to further the identification of studies and peer-reviewed dental journals were hand searched for possible related materials. In addition, grey literature was explored using Google Scholar and OpenGrey, until to June 2019.

**PICO question:** Does smoking increase implant failure rate and peri-implant marginal bone loss in smokers compared to non-smokers?

**P:** tobacco smokers and non-smokers who are fully or partially edentulous

**I:** surgical placement of a single or multiple titanium endosseous dental implant(s) in one or both jaws to replace a single tooth or multiple missing teeth.

**C:** comparison of outcome measures between smokers and non-smokers

**O:** outcome measures of implant failure rate and the extent of peri-implant marginal bone loss

**Critical appraisal & assessment of risk of bias in the included studies**

The Cochrane collaboration's tool for assessing Risk of Bias (RoB) in randomized trials was utilized to assess randomized clinical trials. Quality assessment for non-randomized studies (prospective and retrospective cohort studies) was performed using the Newcastle–Ottawa scale (NOS). For the categories of ‘selection’ and ‘outcome’, studies may obtain a star/point for each item. For the ‘comparability’ category, two stars/points may be awarded. The highest score that
could be assigned to a study according to the NOS was nine stars/points (highest scientific
evidence). Studies scoring six stars/points and above were considered to be of high quality.

**Data extraction**

Customized data extraction sheet were formulated and the following data were extracted from
the included studies (when available): author(s) name(s), publication year, study type, follow-up
period, number, gender and age of the subjects, smoking status & description, number & location
of implants placed, implant brand, surface characterization, size & dimensions, healing period
before loading, marginal bone loss in millimeters +/- standard deviation (SD), implant survival
rate, number of failed and placed implants in smokers & non-smokers, $P$-value for implant
failure rate, and the number of drop-outs.

**Dealing with missing data**

The original investigators were contacted by e-mail in cases of missing or unreported data.

**Statistical analysis**

Dichotomous and continuous variables from the included studies were analyzed through meta-
analysis when the same type of data was assessed by at least two studies. For binary outcomes,
i.e. implant failure, the estimate of the intervention effect was expressed in the form of odds ratio
(OR) with a confidence interval (CI) of 95%. For continuous outcomes, i.e. marginal bone loss,
the average and standard deviation (SD) were used to calculate the standardized mean difference
(SMD) with a 95% CI. The results were pooled using the fixed-effects model (Mantel–Haens-
zel–Peto test) or random-effects model (DerSimonian–Laird test).
**Assessment of heterogeneity**

The I$^2$ statistical test was used to express the percentage of heterogeneity in the studies. Values up to 25% were classified as indicating low heterogeneity, values of 50% as indicating medium heterogeneity, and values of ≥ 70% as indicating high heterogeneity. The results of the random-effects model were validated when significant heterogeneity was observed ($P < 0.10$). The fixed-effects model was considered when low heterogeneity was observed. The level of statistical significance was set at $P < 0.05$. All data were analyzed using the Review Manager software; version 5.2.8 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; 2014).

**Publication bias**

Publication bias was explored graphically through a funnel plot. Asymmetry in the funnel plot may indicate possible publication bias.

**Results**

**Literature search**

The electronic search yielded 379 titles from the selected databases. Additional 22 relevant articles were identified through other resources. After removal of duplicates, the records were screened by reading the title & abstract (& data tables when available). 30 articles were selected for full-text review. Seven studies were excluded (Table 3) after careful analysis, as they did not conform to the eligibility criteria of this review. Therefore, 23 studies; 3 RCTs and 20 observational cohort studies published between 1993 and 2018 were included in the meta-
analysis. The data search and selection process of studies are presented in Figure 1 as a PRISMA flow diagram.

**Fig 1:** PRISMA flow diagram of the screening and article selection process.
Characteristics of the included studies

Eight prospective and twelve retrospective cohort studies and three randomized clinical trials were included. The number of participants in the studies ranged from 32 to 1727 subjects, and the age range was 17 to 88 years. The follow-up period ranged from 6 to 240 months. The number of implants installed in smokers was 7124 and in non-smokers was 19226. The Branemark system (Nobel Biocare) was the most commonly used implant system. Five studies provided definitions for the smoking habits of the participants in terms of quantity or number of years of smoking, while only two studies did not provide definitions for the smoking habits of the patients investigated. Eleven studies reported a statistically significant difference in the average number of implant failures between smokers and non-smokers. The difference was not statistically significant in only one study. The characteristics of the included studies are presented in Table 1.

Quality assessment

The Cochrane RoB tool scores for corresponding randomized controlled trials were included in the forest plot (Figure 2) for the 3 included RCTs. For observational studies, only four studies obtained a score of less than six stars on the NOS. The scores for each study are summarized in Table 2.

Marginal bone loss

14 out of the 23 included studies reported on the analysis of marginal bone loss. All studies performed this analysis via standardized radiographic measurements from the implant platform to the alveolar bone crest. The marginal bone loss in the group of smokers ranged from 0.07 to
4.65 mm, while in the non-smoking group the marginal bone loss ranged from 0.04 to 3.13 mm. The analysis of marginal bone loss was performed using the random-effects model because of the high level of heterogeneity ($I^2 = 98\%; P < 0.00001$). A standardized mean difference (SMD) of 1.07 (95% CI 0.67–1.48) was found, demonstrating a statistically significant difference in favor of non-smokers ($P<0.00001$). Four studies analyzed the marginal bone loss between maxillary and mandibular implants in smokers. Despite the high level of heterogeneity ($I^2 = 97\%; P = 0.00001$), a SMD of 1.39 (95% CI 0.35–2.42) were observed, yielding a statistically significant difference in favor of the mandible ($P < 0.008$). Figure 2 shows Forest plots for marginal bone loss in smokers compared to non-smokers and for MBL in maxilla versus mandible in the smokers’ group.

**Implant failure rate**

Thirteen studies reported on the number of implant failures in smokers versus non-smokers. The average survival rate of implants varied from 84.2% to 97% in the group of smokers, and from 95.2% to 98.8% in the group of non-smokers. The results of the analysis of implant failure were classified into two subgroups according to the follow-up time, i.e. <5 years & $\geq$ 5 years. The fixed-effects model was used for this analysis because of low heterogeneity ($I^2 = 34\%; P < 0.11$). The total odds ratio was 2.24 (95% CI 1.90–2.64), demonstrating a statistically significant difference in favor of the non-smoking group ($P < 0.00001$). The results for follow up subgroups differences demonstrated a significant increase in implant failure with the increase in follow-up time ($P = 0.05$) although with considerable heterogeneity ($I^2=74.5\%$). The overall odds ratio for implant failure rate and the ORs for the subgroup analysis are shown in Figure 3.
**Publication bias:** Analysis of implant failure revealed symmetry of the funnel plot, therefore rejecting the possibility of publication bias (Figure 4).

**Discussion**

Tobacco smoking is an accepted potential risk factor for general and oral health. Investigating the causes of peri-implant marginal bone loss and implant failure is important for predictable implant therapy. Cigarette smoking has different adverse local and systemic effects. Local effects are mainly due to nicotine and cytotoxic vasoactive substances generated in the combustion of tobacco smoke. Systemically, cigarette smoking negatively affects the cellular immunologic response of neutrophils and production of antibodies. Smoking also influences bone metabolism and turn-over. If local absorption of cigarette smoke products had a definite influence on the failure of implants, this may explain the lower rates of mandibular implant failure in smokers as this area is possibly protected by the tongue and more salivary flow. Several clinical studies have shown that the survival of implants can be affected by tobacco smoking. The smoking habits assessed in this review are based on the patients' acknowledgment in the included studies. However, the quantity and frequency of smoking can be a key factor in determining the predictability of success in dental implants treatment. Only five studies included in this review defined or classified smokers, this is a critical factor for risk assessment, but it’s often overlooked or under-reported. In a meta-analysis, homogeneity implies a mathematical compatibility between the results of each individual trial. Potential biases are likely to be greater for non-randomized studies compared with RCTs, so results should always be interpreted with caution when they are included in reviews and meta-analyses. However, narrowing the inclusion criteria increases homogeneity but also excludes the results of more trials, and thus risks the exclusion of
significant data. This was the reason to include non-randomized studies in the present meta-analysis. This issue is important because meta-analyses are frequently conducted on a limited number of RCTs. In meta-analyses, such as these, adding more information from observational studies may aid in clinical reasoning and establish a more solid foundation for causal inferences. In the present meta-analysis, the statistical unit of analysis for ‘implant failure’ was the implant. It would be technically more correct to adjust for the effect of clustered, correlated observations; however, it is a challenging analytic method and the implant survival is so high that failing to adjust for clustered, correlated observations would have little effect on the estimate and deviation of survival. This systematic review attempted to identify studies comparing the marginal bone loss and implant failure rate between smokers and non-smokers. The search produced observational prospective and retrospective cohort studies and clinical trials. Despite the relatively small number of randomized controlled trials included, the inclusion of a large number of longitudinal observational studies, with large number of participants through a well-defined inclusion and exclusion criteria, in the meta-analysis can potentially increase the amount of information and consolidate the results from the clinical studies. Five different definitions in relation to smoking were reported by the studies, i.e. smoker and non-smoker, smoker and never smoker, low consumption and high consumption, mild smokers and heavy smoker, and one study defined smokers as individuals who smoked half a pack or more of cigarettes a day. The contrast in descriptions and definitions highlights these differences as potential confounding variable. Currently, there is no standardization in the classification of patients regarding the number of cigarettes smoked per day. In addition, other confounding risk factors are known to influence the results by generating publication bias. There is still no consensus in the current evidence regarding the procedures that can minimize the risk of smoking on the health of dental implants.
Two-stage implant placement may decrease the physical contact with tobacco smoke and prevent the accumulation of bacterial biofilms on the implant platform during the healing period, as it is already known that smoking patients tend to have greater bacterial biofilm adhesion. Also, improving the gingival phenotype (increasing the area of keratinized mucosa) in the areas adjacent to implant sites would be a prudent measure. Because tobacco smoking can affect immune function, periodontally susceptible patients may be at a higher risk for dental implant complications, like increased amount of marginal bone loss and implant failure rates. However, a recent meta-analysis that evaluated the interaction between smoking and peri-implantitis concluded that there is low evidence implicating smoking as a risk factor for the development of peri-implant disease. There is a growing evidence in the literature indicating that tobacco smoke ingredients, as nicotine, may delay or inhibit healing after oral surgical procedures. The most accepted theory for the influence of smoking on healing in the oral tissues is the decrease in local blood flow resulting from vasoconstriction, which causes changes in the cell population and the inflammatory process. Results of the present meta-analysis revealed that the marginal bone loss was significantly higher in smokers compared to non-smokers \((P < 0.00001)\). A comparison of the maxillary & mandibular arches revealed a significant difference favoring implants placed in the mandible. \((P < 0.008)\). It is believed that the maxilla is more permeable to the effects of tobacco smoke possibly due to its increased medullary bone content and vascularity compared to the mandible. The bacterial plaque tends to adhere more quickly on the epithelial cells of smokers. This may cause an increase in the incidence of biological complications, such as peri-implant mucositis and peri-implantitis and consequently an increase in the rate of peri-implant marginal bone loss. Limited number of clinical studies have compared implant marginal bone loss between smokers and non-smokers. Bain and Moy (1993)\(^3\) proposed that tobacco smoking
and decreased quality of available jawbone, could negatively affect healing and increase marginal bone loss, mainly in the maxillary arch. The current review analysis results for implant failure rate showed significant increase in failure rate in smokers compared to non-smokers ($P < 0.00001$). Additionally, the follow-up subgroups comparison revealed that implant failure rate increased with the increase in follow-up time ($P = 0.05$). However, considerable heterogeneity ($I^2=74.5\%$) was observed.

**Suggestions for future research**

A larger number of high-quality longitudinal studies, preferably be RCTs, with a follow-up period of at least 5 years evaluating the clinical performance of implants with emphasis on reporting outcomes for smokers and non-smokers individually, and possibly including implants with various surface characterizations and/or modifications, should be conducted in accordance with the guidelines available in the Consolidated Standards of Reporting Trials (CONSORT) statements.\textsuperscript{128} There should be standardization of the success criteria, thereby facilitating communication and comparison of the reported data. Aesthetics is a fundamental factor in dental implant therapy. In spite of this, no success criteria adopted by the studies in this review touched on the individual aesthetic criteria, such as the angle and positioning of the implants and the natural profile of peri-implant soft tissues. Aesthetic outcomes must be part of the evaluation of implant success. Lastly, with the growing popularity of electronic cigarettes and other similar devices, it might be worth-while looking into data generated by evaluation of dental implants placed in individuals who use these devices.
Conclusion

In light of the results of this review, tobacco smokers have a higher risk of biological dental implant complications compared to non-smokers. A statistically significant difference ($P < 0.00001$) in peri-implant marginal bone loss was found between the smoking group and the non-smoking group, in favor of the non-smoking group with a standardized mean difference (SMD) of 1.07 (95% CI 0.67–1.48). Marginal bone loss in smokers was increased in the maxilla compared to the mandible with a SMD of 1.39 (95% CI 0.35–2.42) revealing a statistically significant difference in favor of the mandible ($P < 0.008$). The total odds ratio for implant failure rate was 2.24 (95% CI 1.9–2.64), demonstrating a statistically significant difference in favor of non-smokers ($P < 0.00001$). The results for follow up subgroups differences demonstrated a significant increase in implant failure with the increase in follow-up time ($P = 0.05$) although with considerable heterogeneity ($I^2=74.5\%$). Therefore, tobacco smoking patients must be encouraged to quit smoking or at least decrease consumption. Although causality between the measured parameters cannot be assessed with absolute certainty in observational studies, the outcomes of the current investigation indicate that there is a connection between tobacco smoking and increased peri-implant marginal bone loss and implant failure. So, for patients who actively smoke, as in other periodontal & oral surgical procedures, the clinical recommendation for a period of abstinence that at least covers the pre-surgical evaluation, initial therapy, definite implant treatment & immediate post-op phases remain to be very relevant. Therefore, taking into consideration the disparate outcome measures employed to assess dental implant performance and within the limitations of this systematic review, the null hypothesis is rejected, and the alternative hypothesis is accepted, which is in agreement with other related meta-analyses reported elsewhere in the literature.
<table>
<thead>
<tr>
<th>Author &amp; year of publication</th>
<th>Study type</th>
<th>Follow-up period in months (mean or range)</th>
<th>No. of subjects</th>
<th>No. per group</th>
<th>Age range Mean</th>
<th>Smoking definition</th>
<th>Smoking definition</th>
<th>Implant brand &amp; Surface</th>
<th>Implant dimensions</th>
<th>Healing Period for loading (months)</th>
<th>Marginal bone loss (mm) (mean +/- SD)</th>
<th>Implant survival rate (%)</th>
<th>Failed/placed implants in each group</th>
<th>P-value (for implant failure rate)</th>
<th>Drop-outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bain 1993</td>
<td>Retrospective 72</td>
<td>13–85 55.1 229 M/311 F</td>
<td>540 NR NR</td>
<td>Smoker and non-smoker</td>
<td>2194</td>
<td>Branemark Machined</td>
<td>NR x 7,10, 13,15,18,20 3(mandible)</td>
<td>NR</td>
<td>&lt;0.001</td>
<td>S:88.7 NS:95.2</td>
<td>S:44/390 NS:86/1804</td>
<td>NR</td>
<td>NR</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lindquist 1997</td>
<td>Retrospective 120</td>
<td>(33-64) M: 13 F: 32</td>
<td>45 S:21 NS: 24</td>
<td>Smoker and non-smoker</td>
<td>266</td>
<td>Branemark NRx10</td>
<td>4</td>
<td>S: 1.3 +/- 0.55 NS:0.65 +/- 0.2</td>
<td>NR</td>
<td>S:NR/125 NS:2/139</td>
<td>&lt;0.001</td>
<td>NR</td>
<td>1</td>
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<tr>
<td>Kumar 2002</td>
<td>Prospective 18</td>
<td>NR NR NR</td>
<td>461 S:72 NS: 389 NR</td>
<td>Smoker consisted of patients who smoked half a pack or more cigarettes a day</td>
<td>1183</td>
<td>Straumann Rough</td>
<td>NR</td>
<td>1 to 3</td>
<td>S:97 NS:98.3</td>
<td>S:8/269 NS:15/914</td>
<td>&lt;0.05</td>
<td>NR</td>
<td>NR</td>
<td>0.05</td>
<td></td>
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<tr>
<td>Schwartz-Arad 2002</td>
<td>Prospective 36</td>
<td>18–67 48 NR</td>
<td>261 S:89 NS: 172 NR</td>
<td>Non-smokers; mild smokers (upto10 cigarettes/day); heavy smokers (&gt;10 cigarettes/day)</td>
<td>959</td>
<td>NR NR NR</td>
<td>NR</td>
<td>NR</td>
<td>S:96 NS:98</td>
<td>S:15/380 NS: 12/579</td>
<td>&lt;0.05</td>
<td>NR</td>
<td>NR</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Wennstrom 2004</td>
<td>RCT</td>
<td>NR 59.5 NR</td>
<td>52 S: 17 NS: 34</td>
<td>Smoker and non-smoker</td>
<td>149 S: NR NS: NR</td>
<td>Astra Tech (screw-shaped,self-tapping)</td>
<td>NR</td>
<td>NR</td>
<td>S: 0.41 +/- 0.69 NS: 0.30 +/- 0.84</td>
<td>97.3</td>
<td>S: NR NS: NR</td>
<td>NR/50 NR/99</td>
<td>NR</td>
<td>NR</td>
<td>0.05</td>
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**Table 1 cont'd: characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>S: NS (%)</th>
<th>NR</th>
<th>Smoker and non-smoker</th>
<th>Screw type</th>
<th>S: NS +/- NS: +/- 0.12</th>
<th>NR</th>
<th>NR</th>
<th>S: NS +/- NS: +/- 0.12</th>
<th>NR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galindo-Moreno 2005</td>
<td>Prospective</td>
<td>185</td>
<td>63/122</td>
<td>NR</td>
<td>Non-smokers; mild smokers (upto 10 cigarettes/day); heavy smokers (&gt;10 cigarettes/day)</td>
<td>Biotech Rough</td>
<td>0.45 +/- 0.18</td>
<td>NR</td>
<td>NR</td>
<td>0.42 +/- 0.12</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nitzan 2005</td>
<td>Prospective</td>
<td>161</td>
<td>59/102</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>S: NR NS: NR</td>
<td>0.15 +/- 0.09</td>
<td>NR</td>
<td>NR</td>
<td>0.09 +/- 0.04</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DeLuca 2006</td>
<td>Prospective</td>
<td>389</td>
<td>285/104</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>S: 285 NS: 1045</td>
<td>0.07 +/- 0.26</td>
<td>NR</td>
<td>NR</td>
<td>0.04 +/- 0.12</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DeLuca &amp; Zarb 2006</td>
<td>Prospective</td>
<td>200</td>
<td>54/146</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>S: 646 NR</td>
<td>0.24 +/- 0.49</td>
<td>NR</td>
<td>NR</td>
<td>0.09 +/- 0.32</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Herzberg 2006</td>
<td>Prospective</td>
<td>60</td>
<td>21/39</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>S: NR NS: NR</td>
<td>2.41 +/- 1.46</td>
<td>NR</td>
<td>NR</td>
<td>3.13 +/- 1.59</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sanchez-Perez 2007</td>
<td>Retrospective</td>
<td>66</td>
<td>40/26</td>
<td>NR</td>
<td>Non-smokers; light smokers (&lt;10 cigarettes/day); moderate smokers (10–20 cigarettes/day); heavy smokers (&gt;20 cigarettes/day)</td>
<td>Biotech Rough</td>
<td>96.6 +/- 97.1</td>
<td>S: 15/95 NS: 1/70</td>
<td>0.5994</td>
<td>&lt;0.001</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Sverzut 2008</td>
<td>Retrospective</td>
<td>650</td>
<td>76/574</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>S: 1628 NR</td>
<td>96.6 +/- 97.1</td>
<td>S: 7/197 NS: 43/1431</td>
<td>0.5994</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anner 2010</td>
<td>Retrospective</td>
<td>475</td>
<td>63/114</td>
<td>NR</td>
<td>Light smokers (&lt;10 cigarettes/day); moderate smokers (10–20 cigarettes/day); heavy smokers (&gt;20 cigarettes/day)</td>
<td>Biotech Rough</td>
<td>1626 NR</td>
<td>S: 21/226 NS: 56/1400</td>
<td>0.0006</td>
<td>17</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 cont'd:
<p>| Study            | Type      | Sample Size | Gender Distribution | Characteristics | Smoker Status | Implant Brands | Success Rate | p Value | NBR | MBR | SBR | NBR | MBR | SBR | NBR | MBR | SBR | NBR | MBR | SBR | NBR | MBR | SBR |
|------------------|-----------|-------------|---------------------|-----------------|---------------|----------------|---------------|----------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Vandeweghe 2011  | Retrospective 60 | 329 NS:288 | M:141 F:188 | Smoker and non-smoker | 712 | Southern Implants Rough | 3.5, 3.75,4,4.3, 5, 6x8.5, 10,10.5, 11.5, 12,13,13.5, 15, 16.5,18 | NR | S:1.56+/−0.53 NS:1.32+/−0.38 | S:95.2 NS:98.8 | S: 5/104 NS: 7/608 | 0.007 |
| Stoker 2012      | RCT 99.6 | 94 NS:59 | M:28 F:66 | Smoker &amp; never smoker | 256 | ITI/Bonefit dental implants TPS | NR | 3 | S: 1.72+/−1.65 NS: 0.92+/−0.8 | 96.5% | 10/256 S:NR/96 NS:NR/160 | NR | 16 |
| Vervaeke 2012    | Retrospective 24 | 300 NS:235 | M:114 F:186 | Smoker and non-smoker | 1093 | NR | NR | 3.5, 4,4.5,5x8, 9, 11,13,15,17 | NR | S:0.53+/−0.92 NS:0.29+/−0.54 | S:96.7 NS:98.7 | S:8/244 NS:11/849 | 0.025 |
| Sayardoust 2013  | Retrospective 60 | 80 NS:40 | M:38 M:42 | Smoker and non-smoker | 80 | Branemark; Nobel Biocare Rough | NR | 3 to 4 | S: 1.39+/−1.57 NS: 1.01+/−1.09 | S:89.6 NS:96.9 | S:4/40 NS:1/40 | &lt;0.05 | 0 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Implantation</th>
<th>Duration</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Roughness</th>
<th>Duration</th>
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<td>Cha 2014</td>
<td>Prospective cohort</td>
<td>161 S: 18 NS: 143</td>
<td>NR</td>
<td>Smoker and non-smoker</td>
<td>462 S: 48 NS: 414</td>
<td>Implantium</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>96.53 S: 85.42 NS: 97.83</td>
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<tr>
<td>Sayardoust 2017b</td>
<td>RCT 3</td>
<td>32 S:16 NS:16</td>
<td>61.8 M:17 F: 15</td>
<td>Smokers: an average of &gt;10 cigarettes/day for &gt;10 years &amp; non-smokers</td>
<td>96 Max:67 Mand: 29</td>
<td>Bränemark, Nobel Biocare Machined, oxidized, &amp; laser-modified</td>
<td>NR</td>
<td>3</td>
<td>S: 2.5+/−0.11 NS: 2.1+/−0.06</td>
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<tr>
<td>Al-Aali 2018</td>
<td>Retrospective</td>
<td>56 S: 29 NS: 27</td>
<td>35-51 45 NR</td>
<td>Smoker &amp; never smoker</td>
<td>177 Max:100 Mand:77</td>
<td>NR Rough</td>
<td>4.1x10-14 NR</td>
<td>S: 4.65+/−0.68 NS: 1.8+/−0.33</td>
<td>NR</td>
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Table 1 cont'd: characteristics of included studies
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<tr>
<th>Authors (Years)</th>
<th>Selection</th>
<th>Outcome</th>
<th>Assesssment of outcome</th>
<th>Was follow-up long enough for outcomes to occur?</th>
<th>Adequacy of follow-up of cohorts</th>
<th>Total 9/9</th>
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<td>Bain (1993)</td>
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<td>*</td>
<td>*0</td>
<td>*</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
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<tr>
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<td>*</td>
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<td>*</td>
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<tr>
<td>Vervaekje (2012)</td>
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<td>*</td>
<td>*</td>
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**Table 2:** Newcastle-Ottawa Scale quality assessment for cohort studies
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Smokers</th>
<th>Non-Smokers</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
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<tr>
<td>Haas 1996</td>
<td>2.7</td>
<td>1.87</td>
<td>366</td>
<td>1.58</td>
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<td>Lindquist 1997</td>
<td>1.3</td>
<td>0.55</td>
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<tr>
<td>Wennstrom 2004</td>
<td>0.41</td>
<td>0.84</td>
<td>50</td>
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<tr>
<td>Galindo-Moreno 2005</td>
<td>0.45</td>
<td>0.18</td>
<td>175</td>
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<tr>
<td>Nitzan 2005</td>
<td>0.15</td>
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<tr>
<td>DeLuca &amp; Zarb 2006</td>
<td>0.07</td>
<td>0.26</td>
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<tr>
<td>Herzberg 2006</td>
<td>0.24</td>
<td>0.49</td>
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<td>0.09</td>
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<tr>
<td>Sanchez-Perez 2007</td>
<td>2.41</td>
<td>1.46</td>
<td>95</td>
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<td>Stoker 2011</td>
<td>1.72</td>
<td>1.65</td>
<td>96</td>
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<tr>
<td>Vandeweghe 2011</td>
<td>1.56</td>
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<td>Vervaek 2012</td>
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<td>Sayardoust 2013</td>
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<td>Sayardoust 2017b</td>
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<td>2.1</td>
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<tr>
<td>Al-Aali 2018</td>
<td>4.65</td>
<td>0.68</td>
<td>86</td>
<td>1.8</td>
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</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maxillary</th>
<th>Mandibular</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
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<tbody>
<tr>
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<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
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<td>Haas 1996</td>
<td>1.95</td>
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<td>Vandeweghe 2011</td>
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<td>Vervaek 2012</td>
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<td>1.07</td>
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<tr>
<td>Al-Aali 2018</td>
<td>4.9</td>
<td>0.93</td>
<td>49</td>
<td>1.6</td>
</tr>
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</table>

Total (95% CI) 323 423 100.0% 1.39 [0.35, 2.42]

Figure 2: Forest plots for MBL in smokers vs non-smokers and for MBL in maxilla vs mandible in smokers. Also, the Cochrane RoB tool assessment scores for the 3 included RCTs.
### Figure 3: Forest plot for implant failure rate in smokers vs non-smokers with subgroup analysis for follow up time.
Fig 5: Funnel plot for the studies reporting the outcome measure: implant failure rate.
<table>
<thead>
<tr>
<th>Author (year): Title</th>
<th>Type</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aglietta (2010): A 10-year retrospective analysis of marginal bone-level changes around implants in periodontally healthy and periodontally compromised tobacco smokers</td>
<td>Retrospective</td>
<td>Did not individually report MBL levels or the total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers.</td>
</tr>
<tr>
<td>Al Amri (2017): Comparison of Peri-Implant Soft Tissue Parameters and Crestal Bone Loss Around Immediately Loaded and Delayed Loaded Implants in Smokers and Non- Smokers: 5-Year Follow-Up Results</td>
<td>Retrospective</td>
<td>Standard deviation for the mean total CBL (crestal bone loss) for smokers and non-smokers is not reported. Though can be estimated through some calculations, its usually inaccurate and can increase heterogeneity in the results. The total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers are not reported. Attempted to contact the corresponding author by e-mail but received no reply.</td>
</tr>
<tr>
<td>Ata-Ali (2016): Impact of heavy smoking on the clinical, microbiological and immunological parameters of patients with dental implants: a prospective cross-sectional study</td>
<td>Prospective</td>
<td>Did not individually report MBL levels or the number of failed/placed implants in smokers versus non-smokers. Microbiological sampling of the peri-implant sulcus fluid is the main focus of the study.</td>
</tr>
<tr>
<td>Balshe (2008): The effects of smoking on the survival of smooth and rough surface dental implants</td>
<td>Retrospective</td>
<td>Did not individually report MBL levels or the number of failed/placed implants in smokers versus non-smokers. The study focused on smooth versus rough implant surface comparison.</td>
</tr>
<tr>
<td>Baqain (2012): Early dental implant failure: risk factors</td>
<td>Prospective</td>
<td>Of the 15/399 failed/placed implants, the study did not report how many were placed in smokers and non-smokers. Attempted to contact the corresponding author by e-mail but received no reply.</td>
</tr>
<tr>
<td>Sun (2016): Effect of Heavy Smoking on Dental Implants Placed in Male Patients Posterior Mandibles: A Prospective Clinical Study</td>
<td>Prospective</td>
<td>The distribution of the implants placed (n=45) among the heavy smokers and non-smokers is not reported. Also, the study evaluated only 1 implant per patient. The osteogenic jaw bone sampling is the main focus of the study.</td>
</tr>
<tr>
<td>Uribarri (2017): Bone Remodeling around Implants Placed in Augmented Sinuses in Patients with and without History of Periodontitis</td>
<td>Prospective</td>
<td>The total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers are not reported. The MEAN MBL+/− SD in smokers and non-smokers at the end of the follow up period is not reported. Attempted to contact the corresponding author by e-mail but received no reply.</td>
</tr>
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</table>

Table 3: excluded studies and reason(s) for exclusion.
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<th>Search strategies</th>
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<tbody>
<tr>
<td>((((((jaw, edentulous[MeSH Terms]) OR jaw, edentulous, partially[MeSH Terms]) OR smoking[MeSH Terms]) OR cigarette smoking[MeSH Terms])) AND (((((dental implant[MeSH Terms]) OR dental implants[MeSH Terms]) OR dental implantation[MeSH Terms]) OR dental implantation, endosseous[MeSH Terms]) OR endosseous dental implantation[MeSH Terms]) OR osseointegrated dental implantation[MeSH Terms]) AND ((smokers) OR nonsmokers)) AND (((((((((bone resorption[MeSH Terms]) OR dental implant bone resorption) OR alveolar bone loss[MeSH Terms]) OR marginal bone loss) OR dental implant bone loss) OR dental implant bone loss) OR periodontal pocket[MeSH Terms]) OR dental implant probing depth) OR peri-implant bone loss OR peri-implant tissue health) OR survival rates[MeSH Terms]) OR cumulative survival rates[MeSH Terms]) OR dental implant survival)</td>
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</tr>
<tr>
<td>Scopus</td>
<td>Results</td>
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</tr>
<tr>
<td>Smoking OR cigarette smoking AND dental implants OR dental implantation OR endosseous dental implants OR osseointegrated dental implants AND marginal bone loss OR bone resorption OR dental implant bone resorption or dental implant bone loss or dental implant probing depth or peri-implant bone loss</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>EBSCOhost Dentistry &amp; Oral Sciences</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>Smoking AND dental implant complications OR marginal bone loss OR implant failure rate</td>
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<td>379</td>
<td>Total</td>
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</tr>
</tbody>
</table>

Table 4: the final Boolean search keywords utilized in different electronic databases. Last search update June 1st, 2019.
References

Included studies:


Excluded studies:


**Additional references:**


Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI), 4(1), 1-8.


