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Review

Smoking and dental implants: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form
3 March 2015
Accepted 5 March 2015
Available online xxx

Keywords:
Dental implants
Smoking
Implant failure rate
Postoperative infection
Marginal bone loss
Meta-analysis

ABSTRACT

Objective: Recent studies implicate smoking as a significant factor in the failure of dental implants. This review aims to test the null hypothesis of no difference in the implant failure rates, risk of postoperative infection, and marginal bone loss for smokers versus non-smokers, against the alternative hypothesis of a difference.
Data: Main search terms used in combination: dental implant, oral implant, smoking, tobacco, nicotine, smoker, and non-smoker.
Sources: An electronic search was undertaken in September/2014 in PubMed/Medline, Web of Science, Cochrane Oral Health Group Trials Register plus hand-searching.
Study selection: Eligibility criteria included clinical human studies, either randomized or not. The search strategy resulted in 1432 publications, of which 107 were eligible, with 19,836 implants placed in smokers, with 1259 failures (6.35%), and 60,464 implants placed in non-smokers, with 1923 failures (3.18%).
Conclusions: The insertion of implants in smokers significantly affected the failure rates, the risk of postoperative infections as well as the marginal bone loss. The results should be interpreted with caution due to the presence of uncontrolled confounding factors in the included studies.
Clinical significance: Smoking is a factor that has the potential to negatively affect healing and the outcome of implant treatment. It is important to perform an updated periodic review to synthesize the clinical research evidence relevant to the matter.

1. Introduction

Q2 Nicotine is the most important constituent among more than 4000 potentially toxic substances in tobacco products. It is the main chemical component responsible for tobacco addiction, appears to mediate the haemodynamic effects of smoking, and has been implicated in the pathogenesis of numerous diseases.[1] Studies have also demonstrated the detrimental effects of smoking on oral health. A clinical study[2] observed that smokers had a higher prevalence of moderate and severe periodontitis and higher prevalence and extent of attachment loss and gingival recession than non-smokers, suggesting poorer periodontal health in smokers. In addition, smokers had a higher number of missing teeth than non-smokers. Concerning the bone-implant interface, the deleterious effects

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http://dx.doi.org/10.1016/j.jdent.2015.03.003
0300-5712/

of tobacco smoke reflects a series of direct and indirect systemic and local effects on bone metabolism.[3] It has been strongly suggested that local exposure of the peri-implant tissues to tobacco products is the main factor leading to an overall increase in implant failure rate in smokers.[4] A recent meta-analysis on the subject[5] observed that smoking was associated with a higher risk of dental implant failure. However, the review was only able to include 33 studies, even though observational retrospective studies were eligible, according to the inclusion criteria. Moreover, the study did not evaluate the effects of smoking on marginal bone loss (MBL) around implants.

The ability to anticipate outcomes is an essential part of risk management in an implant practice. Recognizing conditions that place the patient at a higher risk of failure will allow the surgeon to make informed decisions and refine the treatment plan to optimize the outcome.[6] The use of implant therapy in special populations requires consideration of potential benefits to be gained from the therapy. To better appreciate this potential, we conducted a systematic review and meta-analysis of both prospective and retrospective studies to compare the survival rate of dental implants, postoperative infection, and MBL between smokers and non-smokers. The present meta-analysis included non-randomized studies and performed several sensitivity analyses, in order to verify whether the results were sensitive to restrictions on the data included.

2. Materials and Methods

This study followed the PRISMA statement guidelines.[7] A review protocol does not exist.

2.1. Objective

The purpose of the present review was to test the null hypothesis of no difference in the implant failure rates, postoperative infection, and MBL for smokers or non-smokers, against the alternative hypothesis of a difference. The focused question was elaborated by using the PICO format (participants, interventions, comparisons, and outcomes): in patients undergoing implant placement, are patients who smoke versus those who do not at higher risk for implant failure, postoperative infection, and greater MBL?

2.2. Search Strategies

See appendix-supplementary data.

2.3. Inclusion and Exclusion Criteria

Eligibility criteria included clinical human studies, either randomized or not, providing outcome data for dental implant failure in smokers and non-smokers, in any group of patients (of any age, race, or sex), with no follow-up restrictions There were no time or language restrictions for the publications. For this review, patients smoking a minimum of one cigarette per day were classified as smokers, and implant failure represents the complete loss of the implant. Exclusion criteria were case reports, technical reports, biomechanical studies, finite element analysis (FEA) studies, animal studies, in vitro studies, and review papers.

2.4. Study Selection

The titles and abstracts of all reports identified through the electronic searches were read independently by three authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors.

2.5. Quality Assessment

Quality assessment of the studies was executed according to the Newcastle–Ottawa scale (NOS), which is a quality assessment tool to use when observational studies are also included in systematic reviews.[8] The NOS calculates the study quality on the basis of three major components: selection, comparability, and outcome for cohort studies. It assigns a maximum of four stars for selection, a maximum of two stars for comparability, and a maximum of three stars for outcome. According to that quality scale, a maximum of nine stars/points can be given to a study, and this score represents the highest quality, where six or more points were considered of high quality.

2.6. Data Extraction and Meta-analysis

From the studies included in the final analysis, the following data was extracted (when available): year of publication, study design, unicenter or multicenter study, country, setting (academic, institutional, industry, etc.), number of patients, type of smokers included in the study, patients' age, follow-up, days of antibiotic prophylaxis, mouth rinse, implant healing period, failed and placed implants, postoperative infection, marginal bone loss, implant surface modification, jaws receiving implants (maxilla and/or mandible), type of prosthetic rehabilitation, and opposing dentition. Only one reviewer performed the data extraction. Authors were contacted for possible missing data.

Implant failure and postoperative infection were the dichotomous outcomes measures evaluated. Weighted mean differences were used to construct forest plots of marginal bone loss, a continuous outcome. The statistical unit for all outcomes ('implant failure', 'marginal bone loss', and 'postoperative infection') was the implant. Whenever outcomes of interest were not clearly stated, the data were not used for analysis. The I^2 statistic was used to express the percentage of the total variation across studies due to heterogeneity, with 25% corresponding to low heterogeneity, 50% to moderate, and 75% to high. The inverse variance method was used for random-effects or fixed-effects model. Where statistically significant ($P < 0.10$) heterogeneity is detected, a random-effects model was used to assess the significance of treatment effects. Where no statistically significant heterogeneity was found, analysis was performed using a fixed-effects model.[9] The estimates of relative effect for dichotomous outcomes were expressed in risk ratio (RR) and in mean difference (MD)

Please cite this article in press as: Chrcanovic BR, et al. Smoking and dental implants: A systematic review and meta-analysis. Journal of Dentistry (2015), http://dx.doi.org/10.1016/j.jdent.2015.03.003

in millimetres for continuous outcomes, both with a 95% confidence interval (CI). Only if there were studies with similar comparisons reporting the same outcome measures was meta-analysis to be attempted. In the case where no events (or all events) are observed in both groups, the study provides no information about relative probability of the event and is automatically omitted from the meta-analysis. In this (these) case(s), the term 'not estimable' is shown under the column of RR of the forest plot table.

Sensitivity analysis tests were performed when possible, in order to verify whether the results were sensitive to restrictions on the data included. A funnel plot (plot of effect size versus standard error) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, although the asymmetry may also represent a true relationship between trial size and effect size.[10]

The data were analyzed using the statistical software Review Manager (version 5.3.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

3. Results

3.1. Literature Search

The study selection process is summarized in Fig. 1. The search strategy resulted in 1432 papers. A number of 464 articles were cited in more than one research of terms (duplicates). The three reviewers independently screened the abstracts for those articles related to the focus question. Of the resulted 968 studies, 754 were excluded for not being related to the topic. Additional hand-searching of the reference lists of selected studies yielded 32 additional papers. The full-text reports of the remaining 246 articles led to the exclusion of 139 because they did not meet the inclusion criteria (80 papers did not inform the number of implants and/or failures in each group, 32 review papers, 20 papers not evaluating failures, two same studies published in a different journal, two histologic studies, one earlier follow-up, one gene expression profile study, and one case report paper). Thus, a total of 107 publications were included in the review.

3.2. Description of the Studies

Detailed data of the 107 included studies are listed in Table 1 and 2 (appendix-supplementary data). Four randomized clinical trials (RCT),[11–14] 16 controlled clinical trials (CCT),[15–30] 16 prospective studies,[31–46] and 71 retrospective analyses[47–117] were included in the meta-analysis. Seven CCTs[15–17,22,27,29,30] were controlled for the patients' smoking habit. Four RCTs and nine of the CCTs included here were not controlled for the smoking habit.

In total, 39 publications[16,19,24,25,27–30,32,33,35–37,41,44,45,51,54,59,61,62,64,65,68,70,73–77,82,85,94,99,103,104,111,112,117] clearly defined what kind of smoking patients were included in their studies based on how many cigarettes the patients used to smoke per day.

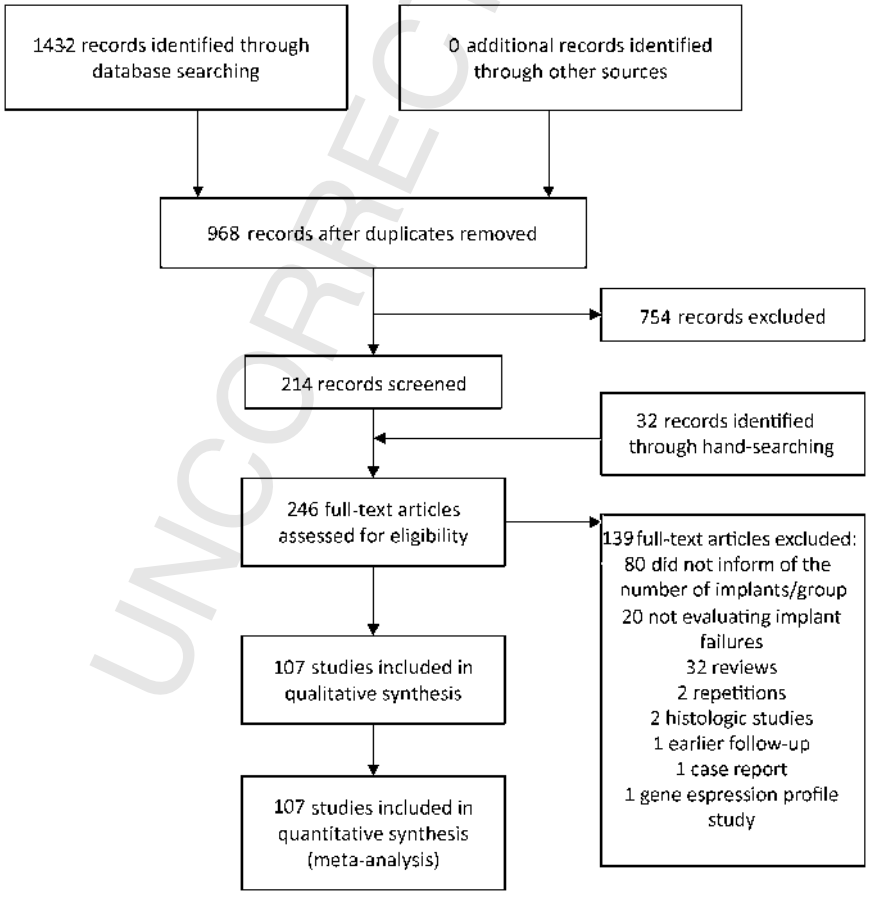

Fig. 1 – Study screening process.

Three studies[13,21,66] included light or heavy smokers 'without distinction', or the patients were classified as non-smokers, former smokers, and current smokers in two studies.[55,67] Only 15 studies[11,13,18,22,29,45,46,55,63,71,81,83,89,107,111] provided information about postoperative infection, with 65 occurrences in a total of 2580 patients receiving 7745 implants. In total, 18 studies[12,14,29,30,39,44,65,74,75,78,91,99,103–106,113,115] provided information about the marginal bone loss separated by groups and with mean values and standard deviation.

From the 107 included studies, three studies[12,14,104] did not provide information about the implant failure rates separately between smokers and non-smokers, reporting information only about the marginal bone loss. From the 104 studies comparing the implant failure rates, a total of 19,836 dental implants were placed in smokers, with 1259 failures (6.35%), and 60,464 implants were placed in non-smokers, with 1923 failures (3.18%). There were no implant failures in five studies.[24,28,94,95,105] In total, 44 studies[11,15,17,20,22,26,30,34,37–39,43,45,47,48,51,57,61,65,67,69,73,74,77,80,81,83,84,87,88,90,93,96,99–103,106,107,110,112,116,117] informed whether there was a statistically significant difference or not between the implant failure rates between smokers and non-smokers, and 17[20,22,26,30,34,39,61,69,73,81,83,88,90,99–101,110] of these studies did not find a statistically significant difference favouring smokers or non-smokers, one[65] found a statistically higher implants failure rate in non-smokers, while the other 26 studies found a statistically higher implants failure rate in smokers.

3.3. *Quality Assessment*

In total, 85 studies were of high quality and 22 were of moderate quality. The scores are summarized in Table 3 (appendix-supplementary data). The moderate quality of some studies is due to four main reasons: (a) the fact that the individuals were not representative from the general population seeking dental implant treatment, (b) the ascertainment of exposure is an issue in retrospective analyses given that this data is collected using questionnaires, (c) short follow-ups, and (d) a considerable number subjects lost to follow-up.

3.4. *Meta-analysis*

In this study, a random-effects model was used to evaluate the implant failure in the comparison between the procedures, since statistically heterogeneity was found ($P < 0.00001$; $I^2 = 51\%$). The insertion of dental implants in smokers statistically affected the implant failure rates ($P < 0.00001$; Fig. 2). A RR of 2.23 (95% CI 1.96–2.53) implies that failures of implants inserted in smokers are 2.23 times likely to happen than failures of implants inserted in non-smokers; i.e. the insertion of implants in smokers increases the risk of implant failure by 123%. The insertion of dental implants in smokers statistically affected the incidence of postoperative infections (RR 2.01, 95% CI 1.09–3.72; $P = 0.03$; heterogeneity: $P = 0.63$; $I^2 = 0\%$, fixed-effects model; and Fig. 3), as well as the marginal bone loss (MD 0.32, 95% CI 0.21–0.43; $P < 0.00001$; heterogeneity: $P < 0.00001$; $I^2 = 95\%$, random-effects model; and Fig. 4).

Since the effect size could differ depending on the insertion of implants in bone areas of different quality, a sensitivity analysis was performed. When only the studies inserting implants in maxillae were pooled, a RR of 2.22 resulted (95% CI 1.63–3.01; heterogeneity: $P = 0.005$; $I^2 = 49\%$, random-effects model; and Fig. 5—appendix-supplementary data), also statistically affecting the implant failure rates ($P < 0.00001$). When only the studies inserting implants in mandibles were pooled, a RR of 2.61 resulted (95% CI 0.92–7.39; heterogeneity: $P = 0.09$; $I^2 = 48\%$, random-effects model; and Fig. 6—appendix-supplementary data), not statistically affecting the implant failure rates ($P = 0.07$).

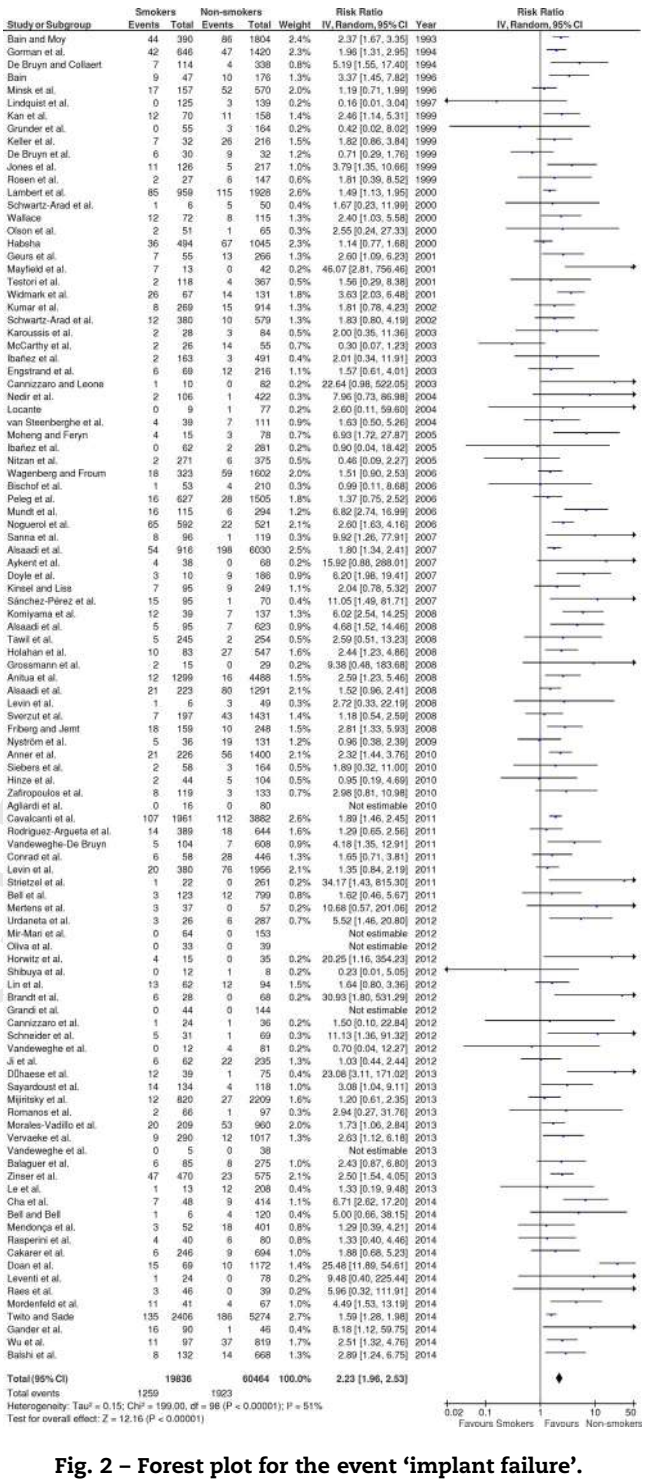

Fig. 2 – Forest plot for the event 'implant failure'.

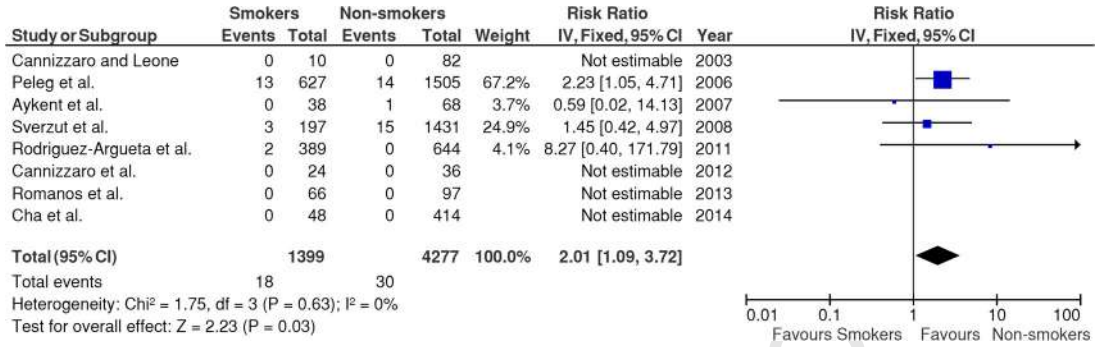

Fig. 3 – Forest plot for the event 'postoperative infection'.

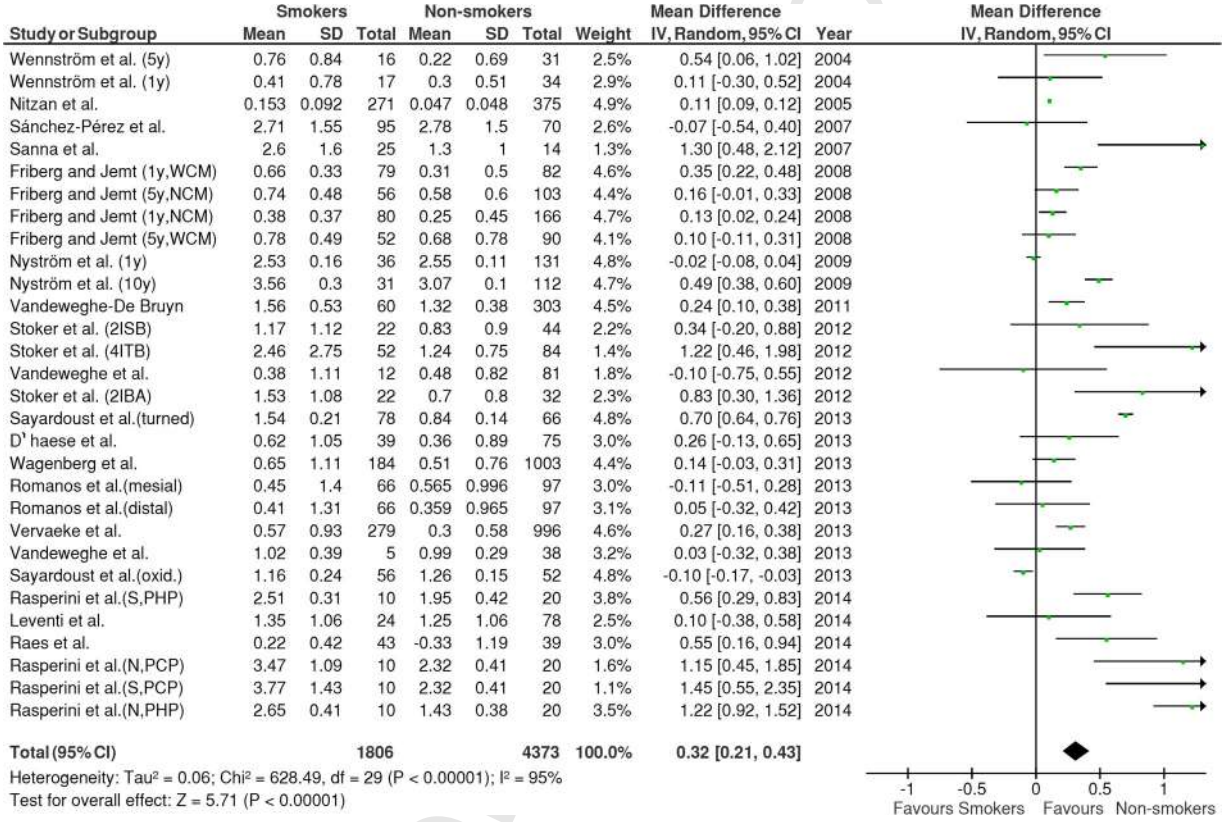

Fig. 4 – Forest plot for the event 'marginal bone loss'.

Other sensitivity analyses were also performed, pooling studies evaluating different implant surface modification processes, there was a statistically significant difference between smokers and non-smokers when the only studies making use of turned implants were pooled (RR 2.17, 95% CI 1.53–3.06, $P < 0.0001$; heterogeneity: $P = 0.001$; $I^2 = 64\%$, random-effects model; and Fig. 7—appendix-supplementary data), acid-etched surface implants (RR 2.07, 95% CI 1.20–3.58, and $P = 0.009$; heterogeneity: $P = 0.50$; $I^2 = 0\%$, fixed-effects model; and Fig. 8—appendix-supplementary data), the same happening to sandblasted and acid-etched surface implants (RR 2.92, 95% CI 1.60–5.34, and $P = 0.0005$; heterogeneity: $P = 0.02$; $I^2 = 50\%$, random-effects model; and Fig. 9—appendix-supplementary data), sandblasted and fluoride-modified surface implants (RR 4.18, 95% CI 2.06–8.50, and $P < 0.0001$; heterogeneity: $P = 0.22$; $I^2 = 32\%$, fixed-effects model; and Fig. 10—appendix-supplementary data), and oxidized surface implants (RR 5.07, 95% CI 2.76–9.30, Q3 $P < 0.00001$; heterogeneity: $P = 0.35$; $I^2 = 10\%$, fixed-effects model; and Fig. 11—appendix-supplementary data).

3.5. *Publication Bias*

The funnel plot for the studies reporting the outcome 'implant failure' did not show a clear asymmetry (Fig. 12), indicating possible absence of publication bias.

4. Discussion

In a meta-analysis, homogeneity implies a mathematical compatibility between the results of each individual trial.

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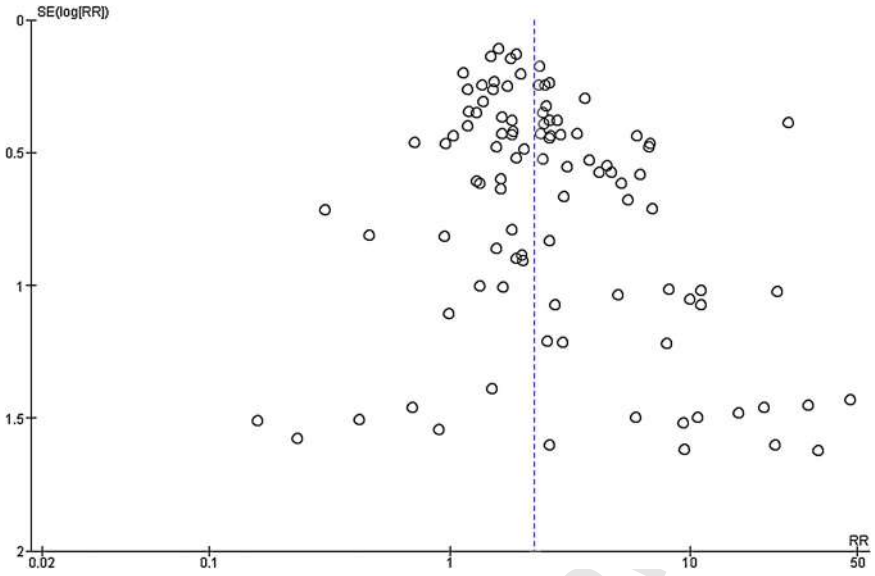

Fig. 12 – Funnel plot for the studies reporting the outcome event 'implant failure'.

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.[10] However, narrowing the inclusion criteria increases homogeneity but also excludes the results of more trials, and thus risks the exclusion of significant data.[118] This was the reason to include non-randomized studies in the present meta-analysis. The 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.[118]

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.[119]

The results of the present study suggest that the insertion of dental implants in smokers affects implant failure rates, the risk of postoperative infection, and the MBL. The increase of implant failure rates due to smoking is hypothesized to be related mainly to the effect of smoking in osteogenesis and angiogenesis. It was shown[120] that nicotine inhibited the gene expression of several enzymes that play an important role in the regulation of osteoblast proliferation, differentiation, and apoptosis, with subsequent important effects on bone formation and remodelling.[121] Moreover, it was demonstrated[122] that nicotine exposure has direct effects on blood vessels, producing vasoconstriction and systemic venoconstriction, which decreases blood perfusion and causes low oxygen and ischaemia.[123] Besides carrying oxygen and nutrients to bone tissue, blood flow plays an active role in bone formation and remodelling by mediating the interactions among osteoblasts, osteocytes, osteoclasts, and vascular cells at a variety of levels.[124]

Furthermore, sensitivity analysis suggests that smoking significantly affects the survival of implants inserted only in the maxilla. The lack of statistical significance for the mandible is surprising but is most likely explained by the limited number of studies[16,24,28,34,35] reporting implant survival for smokers and non-smokers exclusively in the inferior jaw. A previous review[125] on the subject suggested that smoking may be a significant risk factor with an adverse effect on implant survival and success in areas of loose trabecular bone, but may not be as significant for good bone sites. It is important to stress that caution is required when sensitivity analyses are performed, because both type I and type II errors are likely given the multiple testing and the subgrouping. Moreover, these studies were never designed for showing these effects, and thus all the findings are presumably heavily biased.

Concerning the subgroup analyses for the different surfaces, sensitivity analyses suggest that smoking significantly affects the survival of implants submitted to any surface modification here reviewed (turned, acid-etched, sandblasted and acid-etched, sandblasted and fluoride-modified, and oxidized). The fact is that titanium with different surface modifications shows a wide range of chemical and physical properties, and surface topographies or morphologies, depending on how they are prepared and handled.[126–128] It is known that the surface properties of dental implants, such as topography and chemistry are relevant for the osseointegration process and may influence the results.[129] It seems evident from our results (Figs. 7–11) that smoking is associated with increased number of failures irrespective of the type of implant surface being investigated. Moreover, a higher risk ratio was observed for implants with roughened surfaces in comparison with turned implants in smokers. Having said this, there is some contradictory evidence published that smoking mainly is associated with older turned implant surfaces but not with more modern ones. Balshe et al.[130] observed that smoking was not identified as significantly

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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. Even though Balshe et al.'s paper[130] presented a great number of implants in their study ($n = 4607$), the results were not included in the present meta-analysis because the number of implants placed and the number of failures were not reported separately between smokers and non-smokers. The evidence presented by Balshe et al.[130] did not fulfil all requirements to be included in the meta-analysis, but is nevertheless an important contribution since a great number of implants are being investigated. More recently, Sayardoust et al.[103] showed that turned implants failed more frequently and lost more marginal bone in smokers, and that oxidized implants showed similar failure rates and bone loss in smokers and never-smokers. These contrasting results between the present meta-analysis and previous studies indicate that controversy still exists and that there is a need for more studies to evaluate the long-term outcome of implants with altered surface characteristics in smokers.[125] The studies included here made use of implants with several different brands and surface treatments.

The results of the present study have to be interpreted with caution because of its limitations. First of all, all confounding factors may have affected the long-term outcomes and not just the fact that implants were placed in smokers or non-smokers, and the impact of these variables on the implant survival rate, postoperative infection, and marginal bone loss[131–138] is difficult to estimate if these confounding factors are not identified separately between the two different procedures in order to perform a meta-regression analysis. The studies included here have a considerable number of confounding factors, and most of the studies, if not all, did not inform how many implant were inserted and survived/lost in several different conditions. The use of grafting in some studies is a confounding risk factor, as well as the insertion of some or all implants in fresh extraction sockets, the insertion of implants in different locations, different healing periods, different prosthetic configurations, type of opposing dentition, different implant angulation ranges, splinting of the implants, and the presence of bruxers, or diabetics patients. The dose effect of smoking is another important consideration. There is evidence to suggest that smoking may have a dose-related effect on osseointegration.[70] Unfortunately, not all studies included here reported the quantity of cigarettes smoked per day, and almost none reported the number of years those patients have smoked. The real fact is that individual patients sometimes present with more than one risk factor, and groups of patients are typically heterogeneous with respect to risk factors and susceptibilities so the specific effect of an individual risk factor could be isolated neither for individual studies nor for the present review. This is understandable and expected because study populations are typically representative of normal populations with various risk factors.[125] To precisely assess the effect of a risk factor on implant outcomes, it would be ideal to eliminate all other risk factors from the study population. Not only does the coexistence of multiple risk factors within a study population create an inability to assess the specific effect of one individual risk factor, but there is a possibility that certain risk factors together may be more detrimental than the individual risk factors alone.[125] The lack of control of the confounding factors limited the potential to draw robust conclusions. Second, most of the included studies had a retrospective design, and the nature of a retrospective study inherently results in flaws. These problems were manifested by the gaps in information and incomplete records. Furthermore, all data rely on the accuracy of the original examination and documentation. Items may have been excluded in the initial examination or not recorded in the medical chart.[139–141] In a retrospective study, it is difficult to assess the adverse effects of smoking on the prognosis of implants purely on the basis of implant failure because of the multifactorial genesis of implant failure.[6] Third, much of the research in the field is limited by small cohort size and short follow-up periods. It is important to stress that some publications included in this review have a short-term follow-up period, of up to 3 years. In a 12-month follow-up study, Kan et al.[51] reported a 93.04% success for non-smokers and an 82.82% success for smokers. In a second study by the authors,[142] but now with a 60-month follow-up, the success rate for the non-smokers was 82.7% and for smokers was 65.3%. Thus, if one considers the difference in success rates for smokers and non-smokers with implants placed in loose trabecular bone sites that are followed over a longer period of time, the adverse effect of smoking may be more evident. A longer follow-up period can lead to an increase in the failure rate, especially if it extended beyond functional loading, because other prosthetic factors can influence implant failure from that point onward. This might have led to an underestimation of actual failures in some studies. However, it is hard to define what it would be considered as a short follow-up period to evaluate implant failures in smokers. Fourth, the criteria for the classification of patients as 'smokers' and 'non-smokers' were not always reported by the included studies, which probably resulted in a poor homogeneity of the study group. Fifth, most included studies are characterized by a low level of specificity, where the assessment of smoking as a complicating factor for dental implants was seldom the main focus of the investigation.

5. Conclusion

The results of the present review should be interpreted with caution due to the presence of uncontrolled confounding factors in the included studies. Within the limitations of the existing investigations, the results of the present study suggest that the insertion of dental implants in smokers affects the implant failure rates, the incidence of postoperative infections, as well as the marginal bone loss.

Acknowledgements

This work was supported by CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico–Brazil. The authors would like to thank Dr. Rodolfo Gianserra, for having sent us his article, Mrs. Angela Ruban, who provided us some missing information about Dr. Devorah Schwartz-Arad's article, Dr. Derk Siebers, Dr. James S. Hodges, Dr. Ronen Ofec, Dr. David

Schneider, and Dr. Swati Ahuja, who provided us some missing information about their studies, and Dr. Torsten Jemt, Dr. Miguel de Araújo Nobre, and Dr. Francesco Guido Mangano, who replied our e-mail, even though it was not possible for them to provide us the missing information.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdent.2015.03.003.

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Please cite this article in press as: Chrcanovic BR, et al. Smoking and dental implants: A systematic review and meta-analysis. Journal of Dentistry (2015), http://dx.doi.org/10.1016/j.jdent.2015.03.003