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Meta-Analysis
Dental Implants

A systematic review and meta-analysis of pre-clinical studies assessing the effect of nicotine on osseointegration

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Abstract. Nicotine has been associated with vasoconstriction and an impaired cellular healing response. It is therefore likely that nicotine jeopardizes osseointegration. This systematic review and meta-analysis was performed to assess pre-clinical studies on the effect of nicotine on implant osseointegration. Databases were searched up to and including March 2016 for animal/non-human studies using the following Keywords: bone to implant contact; implant; nicotine; osseointegration; bone healing; and new bone formation. In total eight *in vivo* design studies were included and processed for data extraction. Five studies reported no significant influence of nicotine on healing around implants. Quantitative analysis of the effects of nicotine on the osseointegration of dental implants showed a significant difference in bone-to-implant contact between test and control subjects ($Z = -2.49$; $P = 0.014$). From the studies included in the present review; it appears that nicotine has an effect on implant osseointegration.

Key words: bone regeneration; nicotine; implantology; osseointegration.

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Osseointegration plays an important role in the overall success and survival of implants. However, a variety of risk factors such as peri-implant bone quality, bone density, poorly controlled diabetes mellitus, and osteoporosis may jeopardize the outcome of osseointegrated implants.[1] A major risk factor for lack of implant osseointegration that has received considerable attention is tobacco use.[2–6] Numerous studies have assessed the impact of tobacco smoking on peri-implant bone and implant failure.[7–11]

Tobacco smoke is known to contain more than 4000 potentially toxic substances, of which nicotine is reported to be the most detrimental.[12] At the cellular level, nicotine reduces the proliferation of red blood cells, macrophages, and fibroblasts and increases platelet adhesiveness.[13] Macroscopically, this affects healing and tissue perfusion due to micro clot formation in the blood vessels.[13,14] Nicotine also has a sympathomimetic action, stimulating epinephrine and norepinephrine release, which causes vasoconstriction and limits tissue perfusion.[15] Considering these effects, it is likely that nicotine impairs the healing potential at the bone–implant interface. Yamano et al. observed down-regulation of the expression of bone matrix-related genes and a decrease in bone formation around implants in rats receiving nicotine for 8 weeks compared with controls.[16]

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Similarly, Berley et al. showed decreased bone-to-implant contact (BIC) after implant placement in rats receiving nicotine compared with control rats receiving saline.[17] However, controversial results have also been reported from studies using animal models.[17–19] For instance, Soares et al. observed a decrease in bone formation around hydroxyapatite implants placed in the tibia and femurs of rats receiving nicotine compared with control rats receiving water as well as rats receiving alcohol.[20] Pereira et al. demonstrated that nicotine not only increases the synthesis of bone-forming enzymes, but also positively influences the growth and differentiation of osteoblasts.[21] In contrast, Cesar-Neto et al. recorded no difference in the bone healing around titanium implants in rats receiving and not receiving subcutaneous nicotine therapy.[22] On the other hand, Balatsouka et al. reported an increase in bone density from 2 weeks to 4 weeks around implants in rabbits receiving nicotine.[23]

There seems to be a debate over the pathophysiological influence of nicotine on BIC. Therefore, the aim of the present systematic review and meta-analysis was to assess pre-clinical studies that have evaluated the effect of nicotine on osseointegration.

Materials and methods

Focused question

The focused question addressed was the following: What is the effect of nicotine on osseointegration?

Eligibility criteria

The eligibility criteria were (1) original experimental studies (*in vivo* design), (2) inclusion of a control group (osseointegration around implants without nicotine administration), and (3) the intervention: effect of nicotine on osseointegration. Letters to the Editor, review articles, commentaries, case-series, and case reports were excluded.

Literature search protocol

Indexed databases (PubMed/Medline, EMBASE, ISI Web of Knowledge, and Google Scholar) were searched up to and including March 2016 for animal/non-human studies using the following Keywords: bone to implant contact; implant; nicotine; osseointegration; bone healing; and new bone formation. Titles and abstracts of studies identified using this protocol were screened by two authors (AG and SVK) and checked for agreement. The full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for compliance with the eligibility criteria. The reference lists of potentially relevant original articles and review articles were handsearched to identify any studies that could have remained unidentified in the previous step. Any disagreement regarding the eligibility was resolved by discussion among the authors. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines flowchart of this process is detailed in Fig. 1.

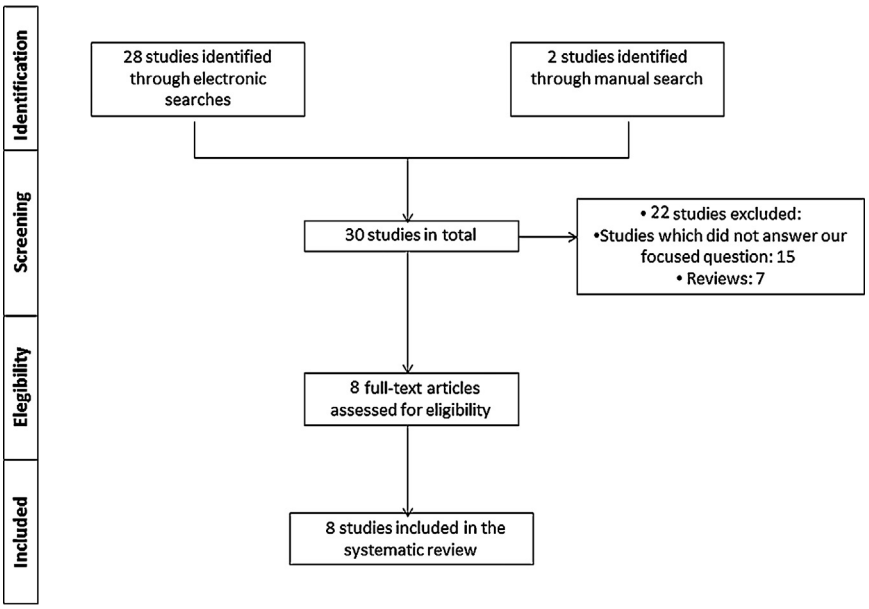

Fig. 1. PRISMA flow chart illustrating the selection of studies.

The initial search yielded 30 studies. Twenty-two studies that did not fulfil the eligibility criteria were excluded. In total, eight original studies were included and processed for data extraction.

Quality assessment

A quality assessment of the studies included was performed in an attempt to increase the strength of the systematic review. The eight studies that were included were assessed for quality against the Critical Appraisal Skills Program (CASP) cohort study checklist.[24] The CASP tool uses a systematic approach based on 12 specific criteria: (1) the study issue is clearly focused; (2) the cohort is recruited in an acceptable way; (3) exposure (nicotine administration) is accurately measured; (4) outcome (osseointegration and/or new bone formation around implants) is accurately measured; (5) confounding factors are addressed; (6) follow-up is long and complete; (7) results are clear; (8) results are precise; (9) results are credible; (10) results can be applied to the local population; (11) results fit with available evidence; (12) there are important clinical implications. A response of either 'yes', 'no', or 'cannot tell', was given for each criterion. A study could have a maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Quantitative analysis

In order to answer the focused question, a meta-analysis was conducted for BIC. The mean differences between the test and control groups were estimated as the effect size measures. Heterogeneity among the studies for each outcome was assessed using Q statistics and the I^2 statistic. Six of the eight studies identified reported overall mean values for BIC and were subjected to meta-analysis.[16,18,22,23,25,26]

Results

Eight studies fulfilled the inclusion criteria and were included for data extraction.[16–18,20,22,23,25,26] Four studies were performed using rabbits[18,23,25,26] (three used female rabbits[18,23,25] and one did not report the sex of the rabbits[26]) and four studies were performed using male rodents.[16,17,20,22] In all four studies performed using rabbits, the rabbits ranged in age from 9 to 12 months.[18,23,25,26] The age