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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.

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]

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
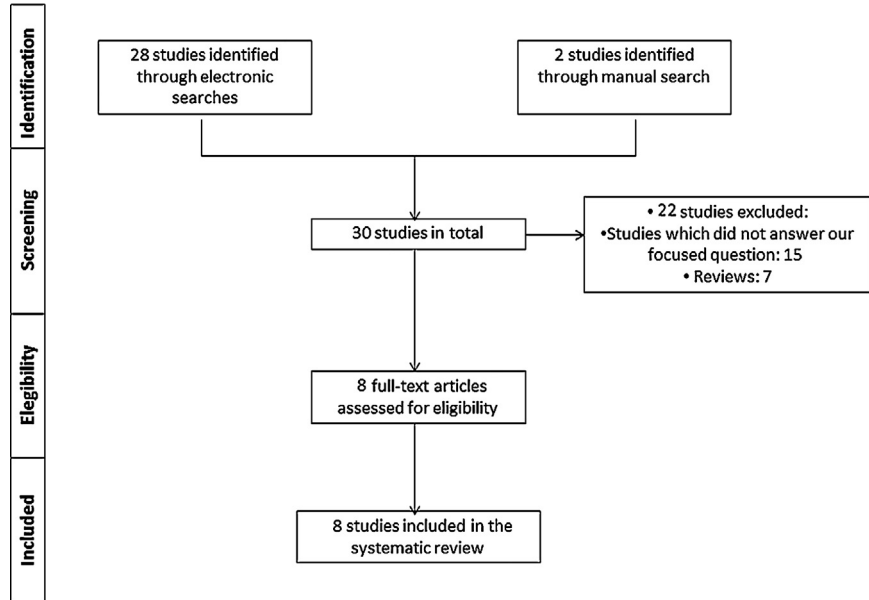

Fig. 1. PRISMA flow chart illustrating the selection of studies.

protocol were screened by . . . 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 hand-searched 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.

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

Q4

of the rats was reported in three studies, and ranged between 4 weeks and 9.2 weeks[16,17,20]; one study did not report the age of the rats.[22] Implants were placed in the tibia in four studies,[18,22,23,26] in the femur in two studies,[16,17] and in both the tibia and femur in two studies.[20,25] The follow-up period in all studies ranged from 14 days to 90 days. Five of the studies used nicotine doses ranging from 0.37 mg/kg to 6 mg/kg.[16,17,20,22,26] Nicotine tartrate was used in three studies at a dose range of 3 µg/kg/min to 6 µg/kg/min.[18,23,25] The nicotine was administered by subcutaneous injection in three studies[20,22,26] and by subcutaneously implanted mini-osmotic pump in five studies[16–18,23,25] (Table 1).

Titanium implants were used in seven studies[16–18,22,23,25,26]; one study used hydroxyapatite implants.[20] Seven studies did not report the number of implants used[16–18,20,22,23,25]; in one study, 128 were used.[26] All studies reported the dimensions of the implants used (diameter × length in millimetres); the dimensions ranged between 1 × 2 mm and 3.75 × 7 mm. Five studies used rough surface titanium implants,[16–18,23,25] one study used both smooth surface and rough surface titanium implants,[26] and one study did not report the type of implant surface.[22] One study used dense hydroxyapatite and porous hydroxyapatite implants (Table 2).[20]

Assessment of osseointegration

The outcome variables measured in the studies were BIC, bone density in implant threads (BD-i), bone density in central bone beds without implants (BD-c), removal torque test (RMT), resonance frequency analysis (RFA), bone volume (BV), bone area (BA), resistance to load, and the expression of bone matrix-related genes. Six studies assessed osseointegration using histomorphometric analysis.[18,20,22,23,25,26] Histology was used to measure new bone formation in five studies.[16,18,20,23,25] One study used micro-computed tomography to assess BIC.[17] Three studies used mechanical tests to evaluate osseointegration[16,17,20] and one used a quantitative reverse transcription polymerase chain reaction (QRT-PCR) to study the expression of bone matrix-related genes.[16]

Main outcomes

Five of the studies did not observe a significant difference in BIC between the control group and the nicotine group.[18,22,23,25,26] Berley et al. noted a significant decrease in BIC in the nicotine group compared with the control group at 4 weeks.[17] Soares et al. reported that BV in the nicotine group and nicotine + alcohol group was lower than that in the control group and alcohol group at 90 days.[20] The resistance to load in this study was higher in the nicotine group compared with the nicotine and alcohol group.[20] Yamano et al. observed comparable bone stiffness between the nicotine and control groups, and lower BIC and down-regulation of expression of bone matrix-related genes in the nicotine group compared to the control group.[16]

Quality assessment of included studies

In all studies included in the review, the total quality score ranged from 7 to 8. The study issue was focused and the participants were recruited in an acceptable way. The most common shortcomings among all studies were the short-term and incomplete follow-up of the experimental groups and the failure to address confounding factors. Furthermore, as all studies were performed in animals, caution must be practiced when applying the results to the human population. Thus, on average, the quality of these studies on the impact of nicotine on the osseointegration of implants was good; however, limitations in terms of short-term follow-up and a lack of clinical studies limit the clinical applicability of these study outcomes. The quality assessment of the individual papers is summarized in Table 3.

Quantitative analysis

A meta-analysis was performed for the six studies reporting mean and standard deviation values for BIC (Fig. 2).[16,18,22,23,25,26] Heterogeneity was found to be statistically significant for all analyses, therefore the random-effects model was employed ($\chi^2 = 13.18$, df = 5, $P = 0.02$, $I^2 = 62\%$). With regard to the effect of nicotine on the osseointegration of dental implants, a significant difference was observed for BIC between the test and control subjects ($Z = -2.49$, $P = 0.014$) (Fig. 2).

Discussion

This study systematically reviewed the indexed literature to determine the influence of nicotine on osseointegration. It has been reported that nicotine jeopardizes bone by inhibiting neovascularization and osteoblastic differentiation.[27–32] Based on these findings and studies by Saito et al.[27] and Donigan et al.,[28] it was expected that nicotine would have an adverse effect on the osseointegration of implants by promoting peri-implant inflammation. To attain the highest level of evidence, findings of both *in vivo* and *in vitro* studies were included in this systematic review.

Interestingly, 62.5% of the studies reviewed showed no significant influence of nicotine on healing around implants.[18,22,23,25,26] It is therefore tempting to speculate that nicotine does not impair osseointegration. However, there are a number of factors that may have influenced the outcomes of these studies. Primarily, the dosage of nicotine administered varied between the studies, ranging from 0.37 mg/kg to 9 mg/kg. According to Kallala et al., high concentrations of nicotine impair BIC, while low concentrations have a stimulatory effect on bone formation around implants.[33] Therefore, it is difficult to estimate the minimum concentration of nicotine that would jeopardize osseointegration. Interestingly, Daffner et al., in a study on the dose-dependent effect of nicotine on bone healing, suggested that nicotine may not be responsible for the inhibited bone healing observed in smokers.[34] Although nicotine has been implicated as the ingredient responsible for tobacco addiction and vasoconstriction seen in smokers,[35] there are several other potentially toxic chemicals in tobacco smoke that could affect the bone response. Polycyclic hydrocarbons, 7,12-dimethylbenz(a)anthracene, tar, and other components of cigarette smoke have been shown to compromise bone healing in smokers.[36–39] While the authors are by no means suggesting that nicotine may be excluded as a risk factor in bone loss around implants in smokers, it is likely that the higher implant failure rate in smokers is associated with a cascade of interactions between nicotine and other chemicals contained in tobacco smoke.[7,9,40]

The route of administration could be another parameter that mediates the influence of nicotine on BIC. Nicotine in these studies was provided subcutaneously to the animals, either through a pump[16–18,23,25] or as injections.[20,22,26] It is known that the absorption of a drug through the subcutaneous route is slower than the inhalational route.[41] Nicotine administered via inhalation (e.g. in smokers) avoids the first-pass metabolism and achieves higher serum levels in a short duration.[42] Therefore, it is likely that the serum nicotine profile would be different in animals receiving subcutaneous injections compared to

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Table 1. General characteristics of the studies included.

Author	Study subjects (*n*)	Mean age (range), years	Study groups: (number of animals) nicotine dose	Duration of nicotine administration		Duration of study	Outcome
				Preoperative	Postoperative		
Nicotine delivery using a subcutaneous injection							
Stefani et al., 2002[26]	32 rabbits	NA (9–12 months)	Control: (8) saline Test 1: (8) 0.37 mg/kg nicotine Test 2: (8) 0.57 mg/kg nicotine Test 3: (8) 0.93 mg/kg nicotine	Not administered	7 days/week	6 weeks	No difference among the 4 groups
Cesar-Neto et al., 2003[22]	45 male rats	NA (NA)	Control 1: (19) control Control 2: (15) CIG Test: (11) 3 mg/kg nicotine	Not administered	Twice daily	60 days	No difference in BIC between control 1 and control 2 and test group
Soares et al., 2010[20]	20 male rats	65 days (NA)	Control 1: (5) water Control 2: (5) alcohol Control 3: (5) alcohol + 1.25 mg/kg nicotine Test: (5) 1.25 mg/kg nicotine	4 weeks	90 days	17 weeks	BV in test group was lower than control 1 and 2
Nicotine delivery using subcutaneous implanted mini-osmotic pump							
Balatsouka et al., 2005[18]	16 female rabbits	NA (9–12 months)	Control: (8) saline Test: (8) 4.5 mg/kg nicotine tartrate	4 weeks and 6 weeks	2 weeks and 4 weeks	8 weeks	No difference between control and test groups
Balatsouka et al., 2005[23]	16 female rabbits	NA (9–12 months)	Control: (8) saline Test: (8) 9 mg/kg nicotine tartrate	4 weeks and 6 weeks	2 weeks and 4 weeks	8 weeks	No difference between control and test groups
Gotfredsen et al., 2009[25]	20 female rabbits	NA (9–12 months)	Control: (10) saline Test: (10) 9 mg/kg nicotine tartrate	24 weeks and 26 weeks	2 weeks and 4 weeks	28 weeks	No difference between control and test groups
Berley et al., 2010[17]	30 male rats	NA (4–6 weeks)	Control: (15) saline Test: (15) 6 mg/kg nicotine	4 weeks	2 weeks and 4 weeks	6 and 8 weeks	Lower rate of BIC (implant push in) at 2 and 4 weeks in test group compared to control group
Yamano et al., 2010[16]	44 male rats	NA (4–6 weeks)[a]	Control: (22) saline Test: (22) 6 mg/kg nicotine	4 weeks	2 weeks and 4 weeks	6 and 8 weeks	BIC lower in test group compared to control

NA, not available; CIG, intermittent cigarette smoke inhalation; BV, bone volume; BIC, bone-to-implant contact.

[a] Implant-free osteotomy (mock surgery) of the same size and depth as the implant dimensions created at the corresponding site in three rats.

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Table 2. Characteristics of the implants included.

Author	Number of implants (n)	Implant dimensions (diameter × length, mm)	Location of implant placement	Implant shape	Implant surface characteristics
Stefani et al.[26]	Titanium (128)	3.75 × 7	Tibia	Screw	Group 1: 64 rough surface Group 2: 64 smooth surface
Cesar-Neto et al.[22]	Titanium (NA)	2.2 × 4	Tibia	Screw	NA
Balatsouka et al.[18]	Titanium (NA)	3.5 × 6	Tibia	NA	Rough surface
Balatsouka et al.[23]	Titanium (NA)	3.5 × 6	Tibia	NA	Rough surface
Gotfredsen et al.[25]	Titanium (NA)	3.5 × 6	Tibia, femur	NA	Rough surface
Berley et al.[17]	Titanium (NA)	1 × 2	Femur	Unthreaded cylindrical	Rough surface
Soares et al.[20]	HAP, HAD	2 × 3	Tibia, femur	Cylindrical	HAP 10–100 mm diameter pores
Yamano et al.[16]	Titanium (NA)	1 × 2	Femur	Unthreaded cylindrical	Rough surface

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NA, not available; HAP, porous hydroxyapatite; HAD, dense hydroxyapatite.

Table 3. Quality assessment of studies included.[a]

Author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total quality score (0–12)
Stefani et al.[26]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Cesar-Neto et al.[22]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Balatsouka et al.[18]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Balatsouka et al.[23]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Gotfredsen et al.[25]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Berley et al.[17]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Soares et al.[20]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8
Yamano et al.[16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Cannot tell	Yes	8

[a] See Materials and methods (Quality assessment) for a description of the items.

humans with a smoking habit. Clinically, the results reported in the studies included here in terms of the bone response to subcutaneous nicotine may have limited application in smokers. However, it is hypothesized that along with the dose of nicotine, the route and frequency of administration, as well as the synergistic effect of nicotine and other chemicals, may affect the marginal bone loss around implants in individuals exposed to different concentrations of nicotine.

It is pertinent to mention that there was a marked variation in the follow-up duration of the studies. Although the duration of the studies ranged from 6 weeks to 28 weeks, the follow-up period after implant placement was 4 weeks in approximately 60% of studies included in the present systematic review.[16–18,23,25,26] Berglundh et al. showed that at 4 weeks the tissue regeneration around implants is mainly immature woven bone.[43] Healing is completed at 6 weeks to 3 months after implant placement, with the transformation of woven bone into lamellar bone.[43] It is hypothesized that the precise effects of nicotine around implants would require long-term follow-up after implant placement. From a clinical perspective, the duration of a nicotine habit, daily frequency of nicotine consumption, and the patient's oral hygiene status may all be interrelated to cause an effect of bone loss.

The timing of nicotine administration (pre and/or post implant placement) is another parameter that could influence BIC. Two studies administered nicotine only after implant placement,[22,26] while in the remaining six studies, nicotine was administered in both the pre-surgical and post-surgical period.[16–18,20,23,25]

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Study	Test Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Random, 95% CI
Yamano et al.[15]	59.4	13	22	70.9	9.2	22	-1.00 [-1.64, -0.36]
Balatsouka et al.[17]	51.3	6.7	8	57.6	6.9	8	-0.87 [-1.94, 0.19]
Cesar-Nato et al.[21]	33.13	8.87	11	32.99	10.3	34	-0.01 [-0.67, 0.70]
Balatsouka et al.[22]	51.7	15.3	8	49.6	8.7	8	0.16 [-0.85, 1.17]
Gotfredsen et al.[24]	44.5	10.9	10	52.3	8.6	10	-0.75 [-1.69, 0.17]
Stefanie et al.[25]	45.54	3.06	24	55.6	11	8	-1.64 [-2.56, -0.73]
Total			83			90	-0.67 [-1.21, -0.14]

Test for heterogeneity: Chi^2 = 13.18; df = 5; (P = 0.02); I^2 = 62%
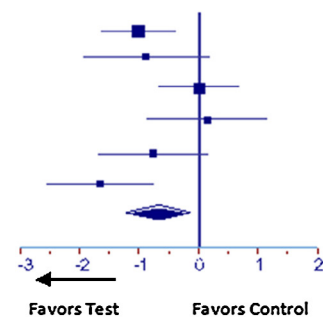Test for overall effect: Z = -2.49; (P = 0.014)

Fig. 2. Forest plot presenting the mean difference (MD) for bone-to-implant contact (effect of osseointegration) between the test groups (with nicotine) and control groups (without nicotine).

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Again the duration of nicotine administration did not exceed 4 weeks in most studies.[16–18,23,25,26] Hollinger et al. showed that the adverse effects of nicotine on bone healing were more severe in the late healing period than immediately after surgery.[44] It is possible that, in the early healing phase, sufficient concentrations of endogenous cells and signalling factors promote bone formation regardless of the presence of nicotine. It has been suggested that when bone regeneration exhausts the local supply of growth factors and cells, an adequate blood supply to the healing site would be needed for their replenishment.[44] It has also been suggested that nicotine causes peripheral vasoconstriction[45] and down-regulates osteoblastic activity,[46–48] which could contribute to implant failure in humans. Perhaps if these studies had used longer durations of nicotine supplementation, possibly 6 weeks or greater, there may have been some difference in the BIC between the study and control animals.[18,22,23,25,26]

The implants in the studies included were placed in dense cortical bone (tibia and femur) of the animals. The mandible has more cortical bone compared to the maxilla, which has more trabecular bone.[49] It is reasoned that BIC would be greater in dense cortical bone than in trabecular bone. Jaffin and Berman showed significantly lower success rates for implants placed in bones with a thin cortex and poorer medullary strength compared to implants placed in dense cortical bone.[49] Therefore, the results of these studies have questionable application to implants placed in the oral cavity, where, not only the difference in bone quality within the maxilla and mandible, but also the effect of local factors such as oral hygiene status, may influence osseointegration. Hence, from a clinical standpoint the outcomes of these studies should be interpreted with caution.

From the studies included in the present review, it appears that nicotine has an effect on implant osseointegration. From a clinical perspective, the detrimental effects of tobacco smoking (which results in the intake of a variety of toxic components) on osseointegration cannot be disregarded.

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Competing interests

None declared.

Ethical approval

Not applicable.

Patient consent

Not applicable.

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