Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2017.11.009, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
Dental Implants

Influence of involuntary cigarette smoke inhalation on osseointegration: a systematic review and meta-analysis of preclinical studies☆

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F. Javed, S. V. Kellesarian, T. Abduljabbar, A. T. Abduljabbar, Z. Akram, F. Vohra, I. Rahman, G. E. Romanos: Influence of involuntary cigarette smoke inhalation on osseointegration: a systematic review and meta-analysis of preclinical studies. Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx.

Abstract. There are no studies that have systematically reviewed the influence of involuntary cigarette smoke inhalation (ICSI) on the stability of implants. The aim of the present study was to perform a systematic review and meta-analysis of preclinical studies that assessed the influence of involuntary cigarette smoke inhalation ICSI on osseointegration. Indexed databases (PubMed, Google-Scholar, Scopus, EMBASE, and Web of Knowledge) were searched till September 2017. Titles and abstracts of studies identified using the above-described protocol were independently screened by 2 authors. Full-texts of studies judged by title and abstract to be relevant were independently evaluated for the stated eligibility criteria. Nine studies were included. Six studies showed that ICSI compromised bone area contact around implants. In 4 studies, peri-implant bone mineral density was significantly higher in the control group than among subjects exposed to ICSI. For the effects of ICSI on the osseointegration of dental implants, significant differences could be observed for bone-to-implant contact for test subjects in cancellous ($Z = -4.08$, $p < 0.001$) and cortical bone ($Z = -4.31$, $p < 0.001$) respectively. ICSI may negatively influence osseointegration of dental implants. It is imperative to educate patients about the negative effects of passive smoking on dental and systemic health.

Key words: alveolar bone loss; dental implants; osseointegration; tobacco smoke pollution.

Accepted for publication 15 November 2017

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0901-5027/000001+09

Tobacco smoking (TS) is a classical risk factor for periimplant diseases.[1,2] Studies[3–7] have reported that the probability of periodontal and peri-implant alveolar bone loss are significantly higher among tobacco-smokers compared with non-smokers. TS is associated with an increased expression of advanced glycation endproducts (AGEs) and their receptors in the gingival tissue of smokers compared with non-smokers.[8] Interactions between AGEs and their receptors play a significant role in the progression of periodontal and peri-implant disease.[9,10] Moreover, exposure to tobacco smoke exerts a cytotoxic effect on human gingival fibroblasts, thereby decreasing their proliferation and adhesive properties.[11,12]

Interestingly, studies[13–18] have also indicated that involuntary cigarette smoke inhalation (ICSI) (synonyms: passive smoking, secondhand smoking and environmental tobacco smoke [ETS] exposure) is also a risk factor for periodontal and peri-implant diseases. In the study by Erdemir et al.[19], children that were exposed to ETS showed significantly raised levels of cotinine in the gingival crevicular fluid and reduced clinical attachment levels compared with unexposed children[19]. Likewise, in a histological study on Wistar rats, César-Neto et al.[20] investigated the effect of ICSI on healing around titanium screw-shaped implants placed in tibiae. The results showed that percentages of bone-to-implant contact (BIC) and bone area (BA) were significantly decreased around implants placed in rats exposed to tobacco-smoke compared with unexposed rats[20]. Similar results from another study showed that ICSI resulted in poor bone quality around titanium implants placed in rat tibiae[21]. However, in the experimental study by Lima et al.[22], ICSI did not influence BA around implants placed in tibiae of rats.

It seems that ICSI may influence the stability of implants by compromising healing, BIC and peri-implant bone quality. However, to our knowledge from indexed literature, there are no studies that have systematically reviewed the influence of ICSI on the stability of implants. With this background, the aim of the present systematic review and meta-analysis was to assess the influence of ICSI on the stability of implants.

Materials and methods

The present systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23]. The Participants, Interventions, Control, and Outcomes (PICO) format was used to formulate the focused question ''Can ICSI influence stability of implants?''

Eligibility criteria

The inclusion criteria were: (a) original clinical and experimental (animal studies); (b) implant therapy; (c) presence of control group (assessment of implant stability without ICSI exposure); (d) intervention: evaluation of parameters that influence implant stability (BIC, BA, new bone formation [NBF] and/or bone mineral density [BMD]) in subjects with and without ICSI exposure. The exclusion criteria were: (a) qualitative and/or quantitative reviews; (b) laboratory-based investigations (*in vitro* studies); (c) case-reports/case-series; (d) commentaries; (e) letters to the editor and (f) interviews and updates.

Literature search protocol and data extraction.

The international database of Prospectively Registered Systematic Reviews in Health and Social Care and the Cochrane Register of Systematic Reviews were searched in March 2017, and presented no existing reviews assessing the effects of ICSI on implants. In order to identify studies relevant to the focused question, a systematic and structured literature search was conducted by two authors (FJ and SVK) using PubMed (National Library of Medicine, Bethesda), Google-Scholar, Scopus, EMBASE, and Web of Knowledge databases. The databases were searched up to and including September 2017 using different combinations of the following Medical Subject Headings (MeSH) terms: ''alveolar bone loss'', ''dental implants'', ''osseointegration'', and ''tobacco smoke pollution''. Other related non-MeSH terms were used in the search strategy to detect articles discussing bone healing around implants in subjects exposed to cigarette's smoke. These included: ''environmental tobacco smoke''; ''secondhand smoke''; ''smoke inhalation''; ''passive smoking'' and ''healing''. These keywords were used with Boolean operators (OR, AND) to combine the key words mentioned above.

To minimize the potential for reviewer bias, titles and abstracts of studies identified using the above-described protocol were independently screened by 2 authors (FJ and SVK) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. After initial electronic search, references of the identified studies were hand-searched to identify further potentially relevant studies. Any disagreements in the study selection were resolved via discussion and consensus between the authors (FJ and SVK). Cohen's kappa value[24] was used to determine the inter-reviewer reliability. Standardized evaluation forms were used to extract pertinent data from each study including: authors, country and design of the study, animal species, age and gender of study subjects, study groups, number of cigarettes, time of exposure, CSI duration, follow-up, main outcomes, characteristics and location placement of implants. Authors of the studies included were contacted via electronic mail in case data was missing or additional information regarding their studies was required.

Quality assessment

Qualitative analysis has been used to assess data from human clinical studies; however, it has been also reported that is applicable in animal research as well.[25–28] In order to increase the strength of the present study the selected studies underwent a quality assessment following the Animal Research Reporting in Vivo Experiment (ARRIVE) guidelines[29–31] and to a pre-defined grading[32,33] applied to the following 20 specific criteria: (1) Title (concise and accurate); (2) Abstract (summary of background, objectives, methods, main findings and conclusions); (3) Introduction (background objectives, relevance to human biology); (4) Introduction (primary and secondary objectives); (5) Methods (Ethical statement, national and institutional guidelines for the care and use of animals); (6) Methods (study design, steps taken to minimize bias such as allocation concealment, blinding and randomization); (7) Methods (experimental procedure with precise details); (8) Methods (experimental animals details including species, gender, age, weight and source); (9) Methods (housing and husbandry conditions such as, type of cage, light/dark cycle, temperature, access to food and water); (10) Methods (sample size); (11) Methods (allocation of animals to experimental groups, randomization); (12) Methods (experiment outcomes); (13) Methods (statistical analysis); (14) Results (baseline data, health status of animals); (15) Results (number of animals analyzed, reasons for exclusion); (16) Results (outcomes and estimation, results for each analysis); (17) Results (adverse events);

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(18) Discussion (interpretation, scientific implications, study limitations including animal model); (19) Discussion (generalizability and translation, relevance to human biology); and (20) Discussion (funding sources, role of the funders, conflicts of interest).

Each criterion was given a grade following ARRIVE guidelines and recommendations reported previously[29,32,34]. Briefly, items 1, 4, 11, and 14 could have a minimum grade of 0 and a maximum grade of 1 (0 = inaccurate, not concise or not reported; 1 = accurate, concise or reported). Whereas, items 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 15, 16, 17, 18, 19 and 20 could have a minimum grade of 0 and a maximum grade of 2 (0 = clearly inaccurate or not reported; 1 = possibly accurate, unclear or incomplete; 2 = clearly accurate). Maximum score by columns (1–20) were totalized to obtain the quality score by category. According to this a relationship quality score/maximum score generated 3 possible quality coefficients: excellent (0.8–1), average (0.5–0.8) and poor (<0.5).

Quality assessment of studies included was conducted independently by two authors (SVK and FJ) using the above-described tool, and checked for disagreement via discussion among the authors. (Kappa score = 0.90).

Data analysis

In order to answer the focused question, meta-analyses of five studies[20,22,35–37] were conducted for BIC in cancellous bone and cortical bone. The heterogeneity in the treatment difference between control and treatment groups across the studies were assessed by the Q statistic. The random effects meta-analysis model was used to combine the results from different studies.[38] Statistical analyses were carried out by specialized statistical software (MedCalc Software-B-8400 Ostend v 15.11.04, Belgium).

Results

Study selection

One hundred and ninety-nine articles were identified through the initial electronic search. No additional studies were identified via hand-searching. One hundred and eighty studies, which did not answer the focused question and/or were duplicates, were excluded. In the next step, 10 more studies that did not abide by the eligibility criteria were excluded. In total, 9 prospective pre-clinical studies[20–22,35–37,39–41] were included in the present review (Fig. 1). The kappa value for inter-examiner's agreement was 0.86.

Assessment of the study heterogeneity

All the studies[20–22,35–37,39–41] were conducted in Brazil between the year 2002 and 2013. All the studies[20–22,35–37,39–41] were performed in rodents, out of which, 7[20,21,36,37,39–41] and 2[22,35] studies were performed in male and female rats, respectively. Eight studies[20–22,36,37,39–41] assessed the effect of ICSI among healthy animals, and one study[35] assessed the effect of ICSI around implants placed in ovariectomized rats. In all studies[20–22,35–37,39–41], the animals were placed in a chamber and exposed to cigarette smoke. In 8 studies[20–22,35–37,40,41] the animals were intermittently exposed to smoke from 10 cigarettes for 8 minutes. This process was repeated 3 times per day for up to 150 days[20–22,35–37,40,41]. In the study by Andrade et al.[39] the rats in the intervention group were exposed to smoke from 6 cigarettes, once daily for approximately 20–30 minutes.

Four studies[20,21,37,41] exposed the intervention subjects to ICSI for 60 days after implant surgery. In 2 studies[22,35], the rats were exposed to ICSI 60 days before implant placement and continued for 60 days postoperatively. Andrade et al.[39] exposed rats to ICSI for 42 days before implantation and continued for 70 days postoperatively. In two studies[36,40], the subjects were exposed to 3 different ICSI protocols: a) ICSI for 90 days before implant placement and 60 days postoperatively; b) ICSI exposure for 83 days with cessation 7 days before surgery and no resumption postoperatively; c) ICSI exposure for 83 days, with 7 days of CSI cessation prior surgery and CSI resumption 21 days after surgery for 39 days (Table 1).

Implant-related characteristics

All implants were placed in rat tibiae. In 1 study[39] the dimension (diameter × length) of the implant placed was 3 × 3 millimeters; and in 8 studies[20–22,35–37,40,41], implants with dimensions of 2.2 × 4 millimeters were used. In 5 studies[20,35,36,39,40] the implant surface characteristics remains unclear. Rough and smooth surfaced implants were used in 1[22] and 2[21,37] studies, respectively. In the study by Correa et al.[41], smooth surfaced and rough surfaced implants were used (Table 2).

Assessment of osseointegration

All studies[20–22,35–37,39–41] assessed osseointegration using histometric analysis. Seven studies[20,22,35–37,39,41] assessed BA and mineralization around the implants. In 6 studies[20,22,35–37,41], BIC was assessed and BMD was investigated in 5 studies[21,22,35,40,41].

Primary outcomes

Results from 6 studies[20,35–37,39,41] and 5 studies[20,35–37,41] showed that ICSI compromised BA and BIC around implants, respectively. In 4 studies[22,35,40,41], peri-implant BMD was significantly higher in the control group compared with the test-group (animals exposed to ICSI). According to Lima et al.[22], ICSI impaired BMD in cortical and cancellous bones, and BIC in cortical bone. In 1 study[21], ICSI was associated with significantly lower cancellous bone density compared with the control group; however, cortical bone density around implants was comparable among unexposed animals and those exposed to ICSI. Andrade et al.[39] reported that ICSI with adjunct coffee consumption jeopardized BA to a significantly greater extent compared with ICSI alone. Carvalho et al.[35] showed that subjects with estrogen deficiency exposed to ICSI presented lower BIC, BMD and NBF levels compared with unexposed ovariectomized rats. One study[22] reported that intermittent doses of parathyroid hormone administration improved BIC and BMD around implants exposed to ICSI. Two studies[36,40] reported that ICSI cessation (temporary and permanent) reverses the deleterious effects of smoke exposure on bone healing around implants.

Quality assessment

None of the studies[20–22,35–37,39–41] reported an adequate method of randomization or method of allocation concealment. Three studies[22,35,41] conducted blinding of examiners with regard to the assessment of osseointegration and/or bone mineralization. In 6 studies[20–22,36,37,39] the number of subjects at baseline and at the final examination was described. Quality assessment of the individual papers is summarized in Table 3.

The total quality score among the included studies ranged from 30 to 33, out of a maximum of 36 points. Eighteen categories were scored as excellent with coefficients between 0.8-1: item 1, title; item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5:

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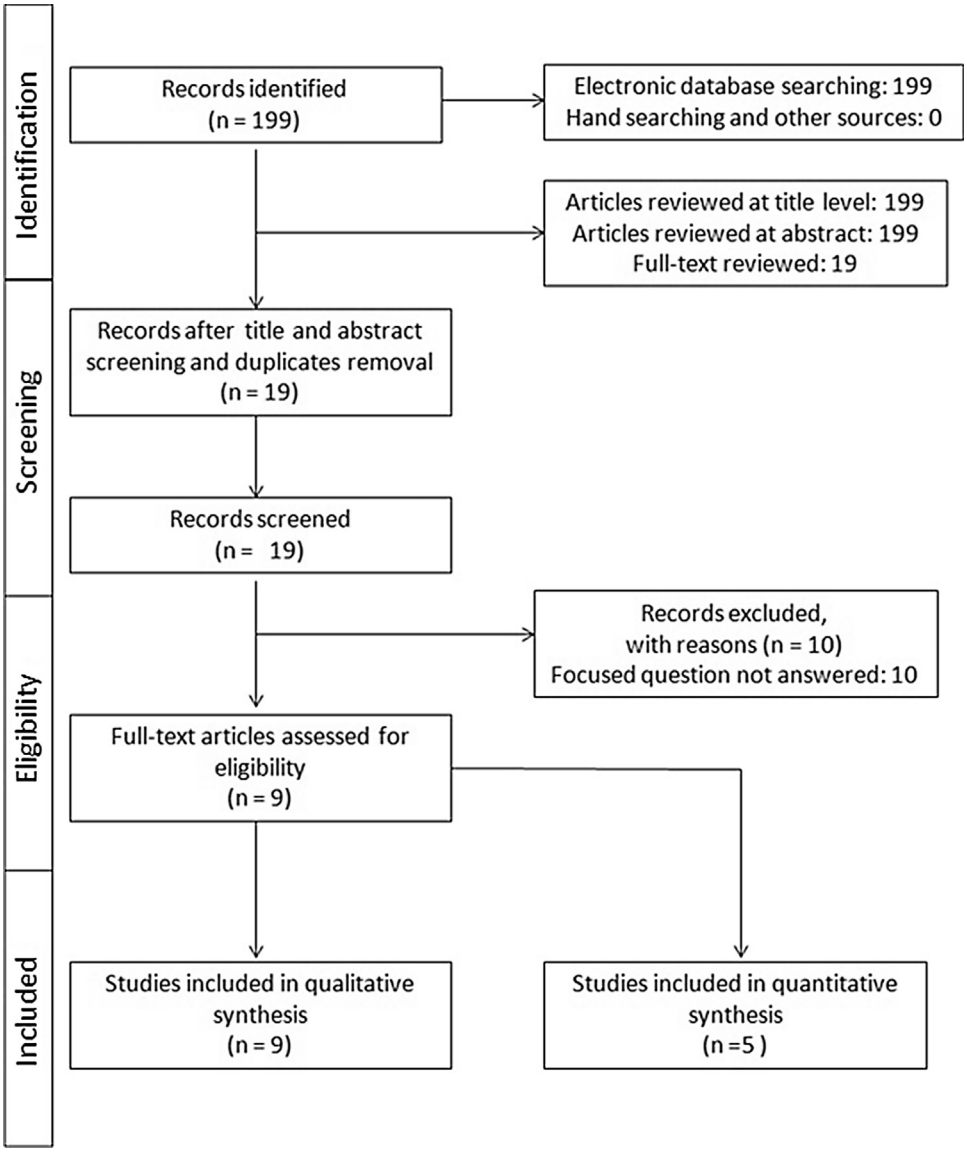

Fig. 1. Article selection flowchart according to PRISMA guidelines.

methods/ethical statement; item 7: experimental procedure; item 8: experimental animals; item 9: housing and husbandry; item 11: allocation; item 12: experimental outcomes; item 13: statistical analysis; item 14: results/baseline data; item 15: number analyzed; item 16: outcome and estimation; 17: adverse events; item 18: discussion/interpretation and scientific implications; item 19: general applicability and relevance; item 20: funding and conflict of interest. Two categories were scored as being of poor quality with coefficients <0.5: item 6: study design and item 10: sample size.

Data pooling

Data pooling was performed for 5 studies[20,22,35–37] reporting means and standard deviations. (1) *BIC for cancellous bone*: For analyses of BIC for cancellous bone, heterogeneity was not found to be statistically significant, therefore random-effects model were employed ($Chi^2 = 6.98$; $df = 4$; ($P = 0.13$); $I^2 = 42.71\%$). For the effects of ICSI on the osseointegration of dental implants, significant differences could be observed for bone-to-implant contact for test subjects (BIC $Z = -4.08$, $p < 0.001$) (Fig. 2).

(2) *BIC for cortical bone*: For analyses of BIC for cortical bone, heterogeneity was not found to be statistically significant, therefore random-effects model were employed ($Chi^2 = 5.74$; $df = 4$; ($P = 0.21$); $I^2 = 30.39\%$). For the effects of ICSI on the osseointegration of dental implants, significant differences could be observed for bone-to-implant contact for test subjects (BIC $Z = -4.31$, $p < 0.001$) (Fig. 3).

Discussion

From the literature reviewed, it may be acknowledged that ICSI negatively influences peri-implant bone parameters, such as BIC and BMD. An explanation in this regard could be associated with the same mechanisms that are associated with periodontal disease among smokers. For example, smoking increases the expression of receptor of AGEs (RAGE) in gingival tissues.[8,9] Moreover, nornicotine (a metabolite of nicotine) has been reported to upregulate RAGE expression in the gingiva of smokers and provoke an inflammatory effect by stimulating the secretion of destructive inflammatory cytokines and

Table 1. Characteristics of the studies included.

Authors et al. (Country)	Study subjects (Age)	Study groups	Number of cigarettes (Time of exposition)	CSI duration	Follow up in days	Outcome
Cesar-Neto et al.[20] (Brazil)	45 male rats (NA)	Group 1: 19 control Group 2: 15 ICSI Group 3: 11 SQ nicotine	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine	60 days after SX	60	ICSI group presented significantly lower BIC and BA compared with controls
Nociti et al.[21] (Brazil)	40 male rats (NA)	Group 1: 20 Control Group 2: 20 ICSI	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine	60 days after SX	60	ICSI group presented comparable BIC but significantly lower BA compared with controls
Lima et al.[22] (Brazil)	48 female rats (NA)	Group 1: 15 Control Group 2: 16 CSI Group 3: 17 ICSI + PTH	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine 16.5 mg tar 15.2 mg CO	60 days before and 60 days after SX	120	ICSI compromised BIC in cortical but not in cancellous bone. PTH supplementation improved BIC in cortical and cancellous bone.
Carvalho et al.[35] (Brazil)	45 female rats (30-days-old)	Group 1: 15 OVX Group 2: 15 control (sham) Group 3: 15 OVX + ICSI	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine	60 days before and 60 days after SX	120	ICSI + OVX group presented significantly lower BIC, BA and BMD compared with controls
Cesar-Neto et al.[36] (Brazil)	69 male rats (NA)	Group 1: 16 Control Group 2: 17 ICSI Group 3: 16 cessation of ICSI 7 days prior SX Group 4: 20 cessation of ICSI 7 days prior surgery and resumption 21 days after	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine 16.5 mg tar 15.2 mg CO	Group 2: 90 days prior and 60 days after SX Group 3: 83 days prior SX Group 4: 83 days prior and 39 days after SX	150	Uninterrupted ICSI group presented significantly lower BMD compared to control and smoking cessation groups
Nociti et al.[37] (Brazil)	32 male rats (NA)	Group 1: 18 Control Group 2: 14 ICSI	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine	60 days after SX	60	ICSI group presented comparable cortical BMD but significantly lower cancellous BMD compared to control groups
Andrade et al.[39] (Brazil)	20 male rats (40-days-old)	Group 1: 5 Control Group 2: 5 Coffee Group 3: 5 ICSI Group 4: 5 Coffee + ICSI	6 cigarettes (20–30 minutes, once a day) 1.3 mg nicotine 16.5 mg tar 15.2 mg CO	42 days prior and 70 days after SX	112	ICSI group presented significantly lower BA compared with controls
Cesar-Neto et al.[40] (Brazil)	66 male rats (NA)	Group 1: 16 Control Group 2: 17 ICSI Group 3: 17 cessation of ICSI 7 days prior SX Group 4: 16 cessation of ICSI 7 days prior surgery and resumption 21 days after	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine 16.5 mg tar 15.2 mg CO	Group 2: 90 days prior and 60 days after SX Group 3: 83 days prior SX Group 4: 83 days prior and 39 days after SX	150	Uninterrupted ICSI group presented significantly lower BIC and BA compared to control and smoking cessation groups
Correa et al.[41] (Brazil)	22 male rats (NA)	Group 1: 11 Control Group 2: 11 ICSI	10 cigarettes (8 minutes, 3 times a day) 1.3 mg nicotine	60 days after SX	60	ICSI group presented significantly lower BIC, BA and BMD compared with controls

ICSI: involuntary cigarette smoke inhalation; CO: carbon monoxide; OVX: ovariectomized; SQ: subcutaneous; SX: surgery; PTH: parathyroid hormone; BIC: bone-to-implant contact; BA: bone area; BMD: bone mineral density.

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Table 2. Characteristics of the implants used amongst the studies included.

Authors et al.	Implant material (Number of implants)	Implant dimensions D × L (in mm)	Location of implant placement	Implant features	Implant surface characteristics
Cesar-Neto et al.[20]	Ti (NA)	2.2 × 4	Tibia	Screw	NA
Nociti et al.[21]	Ti (NA)	2.2 × 4	Tibia	Screw	Smooth
Lima et al.[22]	Ti (NA)	2.2 × 4	Tibia	Screw	Rough (SB)
Carvalho et al.[35]	Ti (NA)	2.2 × 4	Tibia	Screw	NA
Cesar-Neto et al.[36]	Ti (NA)	2.2 × 4	Tibia	Screw	NA
Nociti et al.[37]	Ti (NA)	2.2 × 4	Tibia	Screw	Smooth
Andrade et al.[39]	Dense hydroxyapatite (NA)	3 × 3	Tibia	NA	NA
Cesar-Neto et al.[40]	Ti (NA)	2.2 × 4	Tibia	Screw	NA
Correa et al.[41]	Ti (NA)	2.2 × 4	Tibia	Screw	Smooth Rough (SB)

NA: Not available; Ti: titanium; SB: surface blasted.

reactive oxygen species; which directly cause destruction of the periodontal tissues.[9] Furthermore, the vasoconstrictive effects of nicotine increase platelet adhesiveness, increases the risk of microvascular occlusion and causes tissue ischemia.[42] It is hypothesized that the same mechanisms may jeopardize healing and repair around dental implants among individuals exposed to ETS. This hypothesis supports the study by Twito and Sade[6] in which, a statistically significant association was found between ETS exposure and implant survival rate. The result showed that the risk of implant failure was 2.3 times higher among those exposed to ETS compared with individuals who were not exposed to ETS.[6] Nevertheless, it is imperative to interpret these results with caution as the data was collected qualitatively (exposure versus non-exposure) and a quantitative indication to the exposure to ETS remained unaddressed. Furthermore, it has been showed *in vitro* that direct exposure of tobacco smoke induces cellular fibrosis.[43,44] This suggests that direct exposure to nicotine jeopardize tissues, and might be an explanation of the increased occurrence of oral soft tissue fibrosis. It is noteworthy that in the present systematic review and meta-analysis there was a state of compromised healing around implants placed in the long bones of animals exposed to ETS. This suggests that besides having a negative impact locally, nicotine (and its metabolites) exhibits the potential to enter the circulation and jeopardizes healing on general.

It is pertinent to note that all studies[20–22,35–37,39–41] that fulfilled our eligibility criteria were experimental and were performed in animal models. In this context, it may be challenging to extrapolate these results into a clinical setting. In a clinical scenario, there are a several factors that may affect stability of dental implants besides ETS exposure; which encompass bone quality, jaw location (maxilla versus mandible), type of prosthesis (removable versus fixed), para-functional habits (such as bruxism), and systemic factors, such as

Table 3. Quality assessment according ARRIVE guidelines of the included studies.

Studies	Items																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	T
Cesar-Neto et al.[20]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	33
Nociti et al.[21]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	33
Lima et al.[22]	0	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	31
Carvalho et al.[35]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	33
Cesar-Neto et al.[36]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	1	2	2	2	2	2	32
Nociti et al.[37]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	33
Andrade et al.[39]	1	2	1	1	2	0	2	2	2	0	0	2	2	1	2	2	2	2	2	2	30
Cesar-Neto et al.[40]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	2	2	2	2	2	2	33
Correa et al.[42]	1	2	2	1	2	1	2	2	2	0	1	2	2	1	1	2	2	2	2	2	32
Category score (quality obtained)	8	18	17	9	18	8	18	18	18	0	8	18	18	9	16	18	18	18	18	18	
Maximum score by category (quality expected)	9	18	18	9	18	18	18	18	18	18	9	18	18	9	18	18	18	18	18	18	
Quality coefficients	0.88	1	0.94	1	1	0.44	1	1	1	0	0.88	1	1	1	0.88	1	1	1	1	1	

***Item 1*: title; *item 2:* abstract; *item 3:* introduction/background; *item 4:* introduction/objectives; *item 5:* methods/ethical statement; *item 6:* study design; *item 7:* experimental procedure; *item 8:* experimental animals; *item 9:* housing and husbandry; *item 10:* sample size; *item 11:* allocation; *item 12:* experimental outcomes; *item 13:* statistical analysis; *item 14:* results/baseline data; *item 15:* number analyzed; *item 16:* outcome and estimation; *item 17:* adverse events; *item 18:* discussion/interpretation and scientific implications; *item 19:* general applicability and relevance; *item 20:* funding and conflict of interest. *T:* represents the total score obtained by each manuscript (maximum 36 points).**

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Study or Subgroup	ICSI			Control			Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Carvalho et al.[35]	31.01	18.15	15	58.14	12.13	15	-1.71 [-2.56, -0.85]
Cesar-Neto et al.[20]	25.55	13.34	15	36.67	7.11	19	-1.05 [-1.78, -0.31]
Cesar-Neto et al.[40]	33.21	12.51	17	42.70	10.78	16	-0.79 [-1.51, -0.07]
Lima et al.[22]	50.75	9.41	16	55.31	6.85	15	-0.53 [-1.26, 0.19]
Correa et al.[41]	25.55	13.34	20	30.88	9.74	20	-0.44 [-1.08, 0.18]
Total			**83**			**85**	**-0.86 [-1.283, -0.44]**

Test for heterogeneity: Chi² = 6.98; df = 4; (P = 0.13); I² = 42.71%
Test for overall effect: Z = -4.08; (P <0.001)

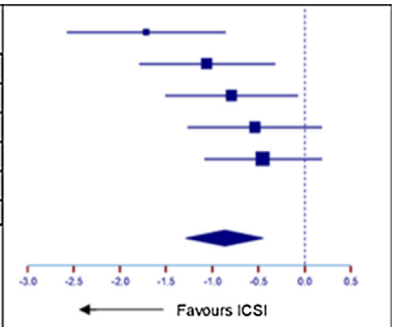

Fig. 2. Forest plots presenting mean difference of bone-to-implant contact in cancellous bone between effect of involuntary cigarette smoke inhalation (test groups) and without smoke (control groups).

Study or Subgroup	ICSI			Control			Random, 95% CI
	Mean	SD	Total	Mean	SD	Total	
Carvalho et al.[35]	43.59	21.53	15	62.95	4.84	15	-1.21 [-2.00, -0.41]
Cesar-Neto et al.[20]	41.39	15.64	15	55.60	11.00	19	-1.04 [-1.78, -0.31]
Cesar-Neto et al.[36]	48.84	11.36	17	55.34	14.57	16	-0.49 [-1.19, 2.17]
Lima et al.[22]	60.40	7.77	16	68.43	4.54	15	-1.21 [-2.00, -0.43]
Nociti et al.[37]	41.39	15.64	20	46.35	12.55	20	-0.34 [-0.97, 0.28]
Total			**83**			**85**	**-0.82 [-1.19, -0.44]**

Test for heterogeneity: Chi² = 5.74; df = 4; (P = 0.21); I² = 30.39%
Test for overall effect: Z = -4.31; (P <0.001)

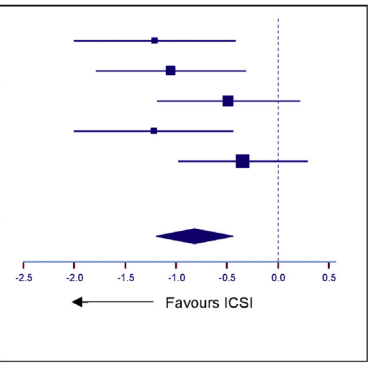

Fig. 3. Forest plots presenting mean difference of bone-to-implant contact in cortical bone between effect of involuntary cigarette smoke inhalation (test groups) and without smoke (control groups).

osteoporosis, poorly-controlled diabetes mellitus and patients undergoing radiation therapy.[45–50] It is therefore postulated these factors play a more critical role in jeopardizing osseointegration and implant success/survival than merely ETS exposure. It is also noteworthy that among the studies[20–22,35–37,39–41] assessed, nearly 44% studies[21,22,37,41] reported the daily frequency of ICSI among animals (3 times daily); however, there were no studies that compared the effect of varying frequency of ETS exposure on osseointegration. Hence, from a clinical perspective, it is hypothesized that individuals that are exposed to ETS several times a day for prolonged durations experience peri-implant soft and hard tissue complications (peri-implant mucositis and peri-implantitis, respectively) more often compare with individuals that have a shorter frequency and duration of ETS exposure. However, further studies are needed in this regard.

It is emphasized that besides documenting a detailed medical, dental and smoking history, clinicians should be encouraged to document a history of ETS exposure among patients undergoing dental therapy (particularly periodontal and peri-implant therapies). Moreover, it is recommended that patients should be educated about the detrimental effects of ETS exposure on overall health and not merely TS.

In conclusion, based upon the preclinical results reported in this systematic review and meta-analysis, it is concluded that ETS exposure may negatively influence osseointegration of dental implants. It is imperative to educate patients about the negative effects of passive smoking on dental and systemic health; however, further well-designed prospective clinical trials are needed to justify the detrimental effects of ETS exposure on the success and survival of dental implants.

Funding

Deanship of Scientific Research at King Saud University for its funding of this prolific research group (PRG-1437-38).

Competing interests

The authors declare no competing interests.

Ethical approval

No ethical approval needed for this study.

Patient consent

Not required.

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Please cite this article in press as: Javed F, et al. Influence of involuntary cigarette smoke inhalation on osseointegration: a systematic review and meta-analysis of preclinical studies, *Int J Oral Maxillofac Surg* (2017), https://doi.org/10.1016/j.ijom.2017.11.009

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Please cite this article in press as: Javed F, et al. Influence of involuntary cigarette smoke inhalation on osseointegration: a systematic review and meta-analysis of preclinical studies, *Int J Oral Maxillofac Surg* (2017), https://doi.org/10.1016/j.ijom.2017.11.009