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

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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.

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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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