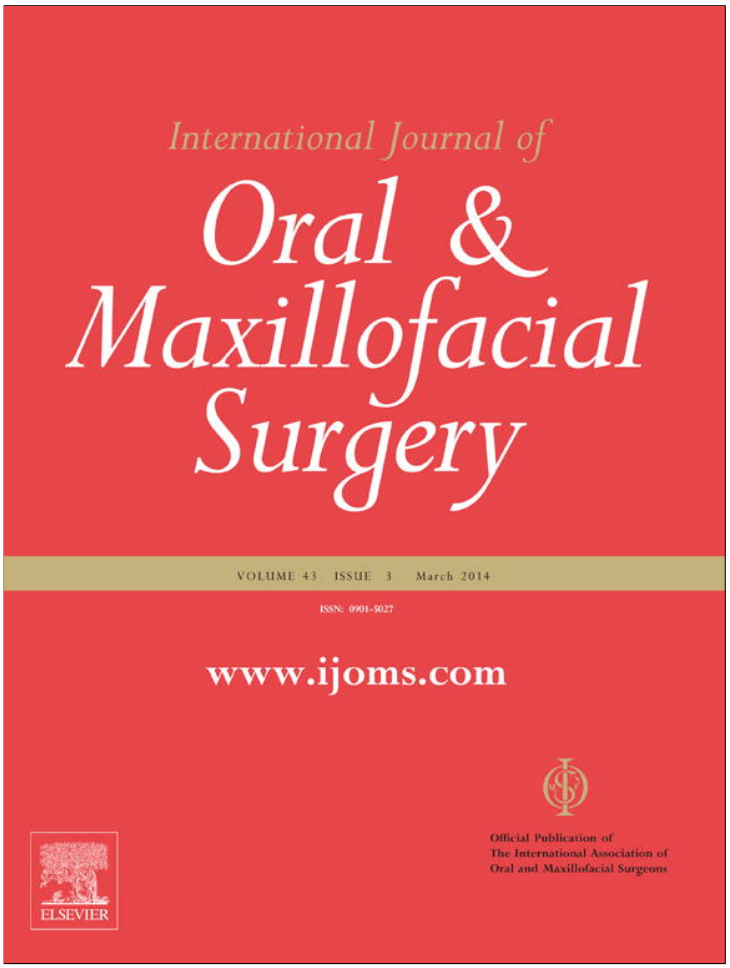

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Systematic Review
Dental Implants

Systemic risk factors for peri-implant bone loss: a systematic review and meta-analysis

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Abstract. The aim of this study was to determine the influence of patient-related systemic risk factors (systemic disease, genetic traits, chronic drug or alcohol consumption, and smoking status) on peri-implant bone loss at least 1 year after implant installation and prosthetic loading. An electronic search was performed of MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials up to January 2012. One thousand seven hundred and sixty-three studies were identified. After applying a three-stage screening process, 17 articles were included in the qualitative analysis, but only 13 in the quantitative analysis, since smoking was a common exposure. The meta-analysis of these 13 studies (478 smokers and 1207 non-smokers) revealed a high level of heterogeneity and that smoking increases the annual rate of bone loss by 0.164 mm/year. Exposure to smoking had a harmful effect on peri-implant bone loss. However, the level of evidence for oral implant therapy in patients with systemic conditions is very low. Future studies should be improved in order to provide more robust data for clinical application.

Keywords: bone loss; risk factors; meta-analysis; systemic diseases; smoking; dental implants.

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The achievement of osseointegration is a biological concept already adopted in implant dentistry.[1] The long-term maintenance of bone around an osseointegrated implant is paramount to clinical success, and peri-implant bone remodelling has commonly been expressed in terms of survival rates.[2,3] It is believed that several factors may affect peri-implant bone resorption: local, surgical, implant, post-restorative, and patient-related risk factors, which include systemic diseases, genetic traits, chronic drug or alcohol consumption, and smoking status. Nevertheless, there is uncertainty around some factors. As an example, the results of a number of in vitro studies that aimed to investigate the association between specific interleukin 1 (IL-1) gene polymorphisms and peri-implant diseases were unclear[4]; this later generated further methodological problems.[5] On the other hand, other factors have been identified as a risk. It has been observed that smokers have a higher risk of dental implant failure than non-smokers,[6–8] with an increased risk for patients with a history of treated periodontitis.[2]

Diabetes is considered a relative contraindication for dental implant treatment. The success rates improve by 85–95% with the eradication of co-morbidities (poor oral hygiene, cigarette smoking, and periodontitis), stabilization of glycaemic control (glycated haemoglobin (HbA1c) around 7%), and preventive measures against infection.[9] Implant failure in patients using oral/intravenous bisphosphonates to treat osteoporosis is a subject that remains controversial. In a recent systematic review, only two out of 10 selected papers demonstrated a negative

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impact of bisphosphonates on implant success.[3] Moreover, no scientific data are available to sufficiently support any specific treatment protocol for the management of bisphosphonate-related osteonecrosis of the jaws (BRONJ).[10] Finally, although the ravages of cancer therapy are well-known, implants can osseointegrate and remain functionally stable in oral cancer patients who have undergone radiotherapy and chemotherapy.[11]

Nevertheless, the current goals of implant therapy include long-term function, the capability to maintain good oral hygiene at home (even in posterior areas of the oral cavity), and overall aesthetics. In cases of implant survival, it is very important to address how much bone is lost over time radiographically. Furthermore, there is a lack of results on peri-implant soft tissue outcomes (bleeding on probing, plaque index, gingival recession, and width of keratinized tissues).

The aim of the present study was to review, in a systematic manner, the influence of systemic risk factors on peri-implant bone loss.

Materials and methods

Study protocol

The recommendations of the PRISMA statement[12] were followed for the review process.

Focused question

The question in focus was 'In patients undergoing dental implant treatment, what is the influence of systemic risk factors (systemic disease, genetic traits, chronic drug or alcohol consumption, and smoking status) on the occurrence of peri-implant bone loss at least 1 year after implant installation and prosthetic loading?'

Eligibility criteria

The following inclusion criteria were applied: (1) English language publications; (2) randomized controlled clinical trials, controlled clinical trials, cohort studies, case–control studies, and case series with at least five patients (in order to include as many studies as possible); (3) human subjects presenting systemic risk factors (systemic disease, genetic traits, chronic drug or alcohol consumption, and smoking status); (4) intervention involving dental implants and/or immediate loading of dental implants; (5) studies reporting on radiographic peri-implant bone level changes assessed by means of intraoral or panoramic X-rays; and (6) follow-up of at least 1 year after implant placement and prosthetic loading (to avoid the risk of false-positive measurements of peri-implant bone loss due to bone remodelling in the first 3–6 months after implant placement, or early implant loss due to surgical procedures).

The following were exclusion criteria: (1) letters, reviews, and unpublished data; (2) patients with acute medical conditions that could contraindicate implant therapy (acute infection, severe bronchitis or emphysema, severe anaemia, uncontrolled diabetes, uncontrolled hypertension, abnormal liver function, nephritis, severe psychiatric disease, conditions with a severe risk of haemorrhage, endocarditis, and myocardial infarction); and (3) studies reporting only implant failure, survival, and/or success rates.

Study selection

Information sources and the search strategy are available in the Supplementary Material, available online.

A three-stage screening process was performed independently by two reviewers (MC and PHOR). Initially, all titles were screened to eliminate non-related publications and reviews. During the second stage, all selected abstracts were analyzed and the full-text articles were consequently retrieved. Then, all reference lists of the selected studies, relevant reviews, and studies from the 'grey literature' were screened for additional papers that might meet the eligibility criteria of this systematic review. In the third stage, selected articles were analyzed. Any disagreements between the two reviewers were resolved after additional discussion with a third reviewer (LC). The inter-reviewer reliability of the data extraction was calculated by determining the percentage of agreement and the correlation coefficient (kappa, 5% level of significance). In addition, study authors were contacted for incomplete or missing data when necessary.

Heterogeneity of the outcome

In order to evaluate the heterogeneity of the outcome between the selected studies, the following factors were recorded: (1) study design; (2) duration of follow-up; (3) number, mean age (range), and gender of subjects; (4) numbers and types of dental implants; (5) type of prosthetic unit; (6) systemic risk factor affecting the study population; (7) measurement of bone level changes (in mm); and (8) peri-implant soft tissue outcomes (bleeding on probing, plaque index, gingival recession, and width of keratinized tissues).

Risk of bias

Two reviewers (MC and PHOR) assessed the methodological quality using the forms 'quality assessment of a cohort study' and 'quality assessment of a randomized clinical trial', combining the proposed criteria of the MOOSE statement,[13] STROBE statement,[14] and PRISMA.[12] These two validity tools consist of eight and nine items, respectively, which have to be scored with a plus, a minus, or a question mark. In accordance with Telleman et al.,[15] it was decided that studies scoring four or more plusses were methodologically acceptable. The two observers, who were blinded to the author, institute, and journal, independently generated a score for the articles. Any disagreement was resolved with a third reviewer (LC).

Data analysis and synthesis

The meta-analysis was based on the DerSimonian and Laird method. The weighted mean difference (WMD) was expressed for bone loss under a randomized effects model. WMD estimations were accompanied by the 95% confidence interval (95% CI) of the standard error and the *P*-value of the distinction of a null effect of the smoking factor (WMD = 0) for the solution of the meta-analysis, including the statistical value of association Q_A. The statistical Q_H value for heterogeneity and the relative *P*-value for the χ^2 test were both included. At the same time, the index I^2 was also calculated, considered as representative of the total variation due to heterogeneity. A forest plot was obtained for better visualization of the results, and a funnel plot was drawn to assess potential publication bias. The software used to perform this meta-analysis was Sinergy 3.2 (Biometrics Department, GlaxoSmithKline). All analyses were conducted with a 5% level of significance.

Results

Study selection

The search identified 1763 references up to January 2012. A further 160 references were retrieved from other sources and cross-checked references, giving a total 1923 studies. After duplicates were removed, 1824 references were available for screening. Of these, 254 publications

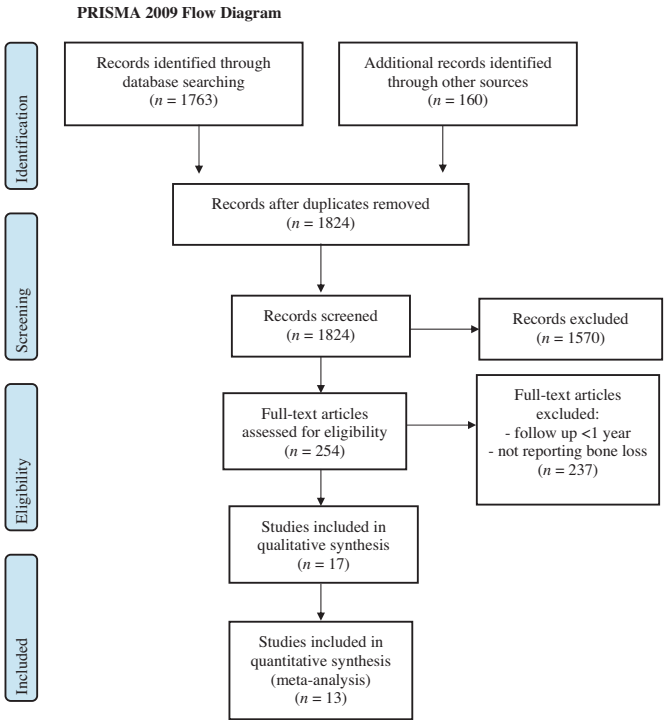


Fig. 1. Study selection process for the meta-analysis. (Based on the flow chart adapted from Ref. 12).

fulfilled the eligibility criteria; however a further 237 studies were excluded, as most of them did not report on peri-implant bone loss. After qualitative assessment of the 17 selected studies (16 cohort studies and one randomized controlled trial (RCT)), only 13 studies were included in the quantitative synthesis (meta-analysis) (Fig. 1). Agreement in study selection between the reviewers was 89.53% (kappa value = 0.46).

Study characteristics

Table 1 gives a detailed description of the studies included,[16–32] which were published from 1996 to 2011; most[16–23] reported between 2 and 5 years of follow-up (range 6 months[17] to 20 years[27]). A total of 1883 patients and 5730 implants were analyzed. Cigarette and tobacco smoking were the most prevalent exposures (identified as single factors in 11 studies). The others were osteoporosis,[18,25] IL-1 gene polymorphisms,[19,26] diabetes,[18] endocrine diseases, cardiac diseases, and arthritis,[27] and Sjögren's syndrome.[28] Radiographic bone loss was evaluated by means of intraoral apical X-rays in 11 studies,[16,19,24–32] panoramic X-rays in four studies,[20–23] and both methods were used in two studies.[17,18] Only a few studies reported soft tissue outcomes (bleeding on probing, plaque index, gingival recession, and width of keratinized tissues). Bleeding on probing was considered in one study,[25] the plaque index in three studies,[25,28,30] and the pocket probing depth in three studies.[29,30,32] No study reported data for peri-implant gingival recession or width of keratinized tissues.

Risk of bias

For the cohort studies, there were question marks for blinding in six studies, for follow-up in eight studies, and for loss-to-follow-up in five studies (see Table 2). Identification of the most important confounders received a positive mark in 13 studies. Only one study[20] was considered non-methodologically acceptable (two plusses); acceptable studies scored four,[17,18,21,28] five,[16,22,23,25,27,30,31] six,[19,24] and seven[26,29] plusses (Table 2). For the RCT,[32] all blinding-related items received a question mark, but it was considered acceptable (six plusses, Table 3).

Results for the selected studies

The meta-analysis could be performed by reviewing and combining the results of only 13 studies – those analyzing the effect of smoking on peri-implant bone loss, since this was the only common systemic risk factor. Four studies were excluded from the meta-analysis because no further information could be retrieved, even after contact with the authors. In detail: one study[24] did not contain the standard deviation of loss information for the groups; one study[29] showed unusual results for bone gain that would have generated heterogeneity; one study[25] compared peri-implant bone loss between osteoporotic and non-osteoporotic patients; one study[28] is a case series reporting bone loss in patients with Sjögren's syndrome. These studies are described in a narrative manner.

Results for studies included in the quantitative analysis (meta-analysis)

This group comprised 13 studies, with a total number of 1685 patients (478 smokers and 1207 non-smokers). A power value of 0.958 to detect a significant effect size of 0.2 (small) among groups was achieved, with a 95% confidence level. The homogeneity test confirmed that the 13 studies were heterogeneous and not suitable for calculation of a combined effect measure ($Q_H = 89.2$, χ^2 $P < 0.001$, and $I^2 = 0.86$). The result of the meta-analysis suggests that smoking has a harmful effect on bone loss (WMD > 0). Moreover, considering some of the reports,[18–20,23,30,32] this effect would be statistically significant (95% CI not containing the value 0), but this was not the case for the remaining studies. Further, the χ^2 test result for the 13 selected studies concluded that smoking increases the annual rate of bone loss by 0.164 mm/year (95% CI 0.101–0.226), this being statistically significant ($P < 0.001$, $Q_A = 26.39$) (Table 4). The forest plot depicted extremely high values for the harmful effects of smoking (Fig. 2).

Results for studies excluded from the quantitative analysis

Isidor et al.[28] studied the effect of implant-supported prostheses in eight women affected by Sjögren's syndrome. All patients reported very poor conditions with their conventional dentures. Fifty-four Brånemark implants were installed, and seven implants (in four patients) did not osseointegrate during the abutment connection period. The average radiographic bone loss in the first year was 0.7 mm, with additional loss of 0.6 mm after 4 years of treatment. Two years after prosthetic treatment, just one patient reported poor comfort with the prosthesis.

Carlsson et al.[24] observed 44 patients for 15 years; they received fixed, implant-supported prostheses in the mandible and

Table 1. Characteristics of the selected studies.

Author, year (Ref.)	Title	Design/setting	Follow-up time	Number of patients	Number of implants	Single or multiple prosthetic unit	Systemic factor	Peri-implant bone loss (mm)	Soft tissue outcomes
Haas et al., 1996[30]	The relationship of smoking on peri-implant tissue: a retrospective study	Retrospective Smokers with dental implants Non-smokers with dental implants BS, IMZ implants (both groups)	*S* = 22.4 months NS = 21.9 months	*S* = 107 NS = 314	*S* = 366 NS = 1000	FPD, OD (both groups)	Cigarette smoking	Mean values (peri-apical) *S* = 3.95 Max, 1.97 Mand NS = 1.64 Max, 1.32 Mand	Mean values (Max/Mand): S: PI 0.96/1.12; BI 1.75/0.70; PPD 4.32/2.31; MI 1.0/0.46 NS: PI 0.60/1.1; BI 0.85/0.89; PPD 2.78/2.37; MI 0.38/0.47
Isidor et al., 1999[28]	Outcome of treatment with implant-retained dental prostheses in patients with Sjögren syndrome	Case series BS dental implants (6 per patient) Dental arches with poor denture retention/stability	4 years	8	54	Multiple OD, complete, FSP	Sjögren's syndrome	Mean radiographic bone loss (peri-apical) < 1.0 (0–4 years)	PI (1 year): 0.4 PI (4 years): 0.3
Carlsson et al., 2000[24]	Long-term marginal peri-implant bone loss in edentulous patients	Prospective Duplicated data from Lindquist et al. (1996 and 1997)	15 years	44	273	FxMd prostheses (15	mm = bilateral cantilever)	Cigarette smoking	Mean values (peri-apical), Max/Mand *S* = 1.0/1.25 NS = 0.7/0.63
No report									
Geurs et al., 2001[20]	Retrospective radiographic analysis of sinus graft and implant placement procedures from the Academy of Osseointegration Consensus Conference on Sinus Grafts	Retrospective Sinus grafts (7 types) and implant placement Selected patients, digitized panoramic radiographs	3 years	100 (145 sinus grafts)	*S* = 55 NS = 266	No report	Tobacco smoking	Mean loss in sinus graft height on panoramic radiographs *S* = 1.75 NS = 1.36	Not possible (only radiographs were analyzed)
von Wowern and Gotfredsen, 2001[25]	Implant-supported overdentures, a prevention of bone loss in edentulous mandibles? A 5-year follow-up study	Prospective follow-up AST, two-stage implant placement Mandibular OD 11 patients (bar attachment) 11 patients (ball attachment)	5 years	22 (18 women) OP: *S* = 2, NS = 5 NOP: *S* = 6, NS = 5	44 (2 per patient)	OD	Osteoporosis Cigarette smoking	MBL (standard, peri-apical radiographs) OP = 0.47 NOP = 0.01	GI: OP = 0.29, NOP = 0.57 PI: OP = 0.07, NOP = 0.20

Feloutzis et al., 2003[19]	IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population	Retrospective Heavy smokers, moderate smokers, previous smokers, non-smokers IL-1A (+4845) and IL-1B (+3954)	5.6 years	HS = 14 MS = 14 FS = 23 NS = 39	119 IL-1-neg 56 IL-1-pos	No report	IL-1 polymorphisms Cigarette smoking	ABL: IL-1-neg = 0.45; IL-1-pos = 0.215 Peri-apical, long-cone ABL (median values): HS = 1.98; MS = ?; FS = 0.24; NS = 0.18; NS = 0.07 IL-1-pos, 0.36 IL-1-neg	Reported, but not divided by smoking groups
Gruica et al., 2004[26]	Impact of IL-1 genotype and smoking status on the prognosis of osseointegrated implants	Retrospective Smokers (light, heavy), non-smokers, former light smoker, former heavy smoker IL-1A (+4845) and IL-1B (+3954)	8 years	53 127 (64 = IL-1-pos)	292	No description	IL-1 polymorphisms Cigarette smoking	Mean change (1–8 years) (peri-apical radiographs) NS = 0.21; FLS = 0.13; FHS = −0.014; LS = 0.38; HS = 0.08	No report
Peñarrocha et al., 2004[31]	Radiologic study of marginal bone loss around 108 dental implants and its relationship to smoking, implant location, and morphology	Retrospective Single or partial tooth loss in maxilla and mandible Solid ITI dental implants (SLA)	1 year	42 (total) *S* = 16 NS = 26	*S* = 47 (total) G1: *n* = 18 G2: *n* = 18 G3: *n* = 11 NS = 61	Single and multiple prosthetic units	Cigarette smoking	Mean bone loss (peri-apical radiographs) G1: 1–10 cig/day, 0.59 G2: 11–20 cig/day, 0.91 G3: >20 cig/day, 0.89 NS = not reported	No report
Galindo-Moreno et al., 2005[22]	Influence of alcohol and tobacco habits on peri-implant marginal bone loss: a prospective study	Prospective BS, IMTEC (TPS), Calciteck (HA)	3 years	185 *S* = 63 NS = 122	514 *S* = ? NS = ?	Fixed prosthesis, OD, single crowns	Tobacco smoking	MBL (digital panoramic radiographs) *S* = 1.36 NS = 1.25	No report
Nitzan et al., 2005[21]	Impact of smoking on marginal bone loss	Retrospective Different implants used	*S* = 42.9 months NS = 48.4 months	*S* = 59 NS = 102	*S* = 271 NS = 375	No report	Cigarette smoking	MBL (panoramic radiographs) *S* = 0.15 NS = 0.047	No report
DeLuca and Zarb, 2006[27]	The effect of smoking on osseointegrated dental implants. Part II: peri-implant bone loss	Retrospective Consecutive complete or partially edentulous patients BS implants	20 years	235	767	Single, multiple, and OD	Endocrine diseases, cardiac diseases, and arthritis Cigarette smoking	Mean bone loss (peri-apical), following the first year of clinical loading S2 = 0.07 NS2 = 0.04	No report

Table 1 (*Continued*)

Author, year (Ref.)	Title	Design/setting	Follow-up time	Number of patients	Number of implants	Single or multiple prosthetic unit	Systemic factor	Peri-implant bone loss (mm)	Soft tissue outcomes
Norton, 2006[16]	Multiple single-tooth implant restorations in the posterior jaws: maintenance of marginal bone levels with reference to the implant–abutment microgap	Retrospective Missing posterior teeth, some cases with sinus grafts AST dental implants	3 years	*S* = 7 NS = 47	173 *S* = ? NS = ?	Multiple, freestanding prostheses	Smoking	Mean bone loss (peri-apical) *S* = 0.77 (0.1–1.6) NS = 0.63 (0–2.7)	Purulent exudate (1 implant) Apical infection (2 implants)
Herzberg et al., 2006[17]	Implant marginal bone loss in maxillary sinus grafts	Retrospective Patients with the need of a dental implant and maxillary sinus grafts cpTi and HA-coated dental implants	6–56.5 months (mean 21.7 months)	60	*S* = 56 NS = 104	No report	Cigarette smoking	Mean bone loss (panoramic or intraoral) *S* = 0.24/year NS = 0.09/year	Two patients with swelling and sinus membrane perforations
Sanna et al., 2007[23]	Immediately-loaded CAD–CAM manufactured fixed complete dentures using flapless implant placement procedures: a cohort study of consecutive patients	Prospective At least 1 completely edentulous arch BS (TiUnite) immediately loaded dental implants	5 years (mean 2.2 years)	*S* = 13 NS = 17	212	Multiple Complete, fixed supported prostheses	Cigarette smoking	Mean bone loss after 4 years (digital panoramic radiographs) *S* = 2.6 (25 implants) NS = 1.3 (22 implants)	No report
Tandlich et al., 2007[18]	Removable prostheses may enhance marginal bone loss around dental implants: a long-term retrospective analysis	Retrospective BioCom, rough-surface dental implant	≥30 months	*S* = 17 NS = 65	265	Single (*n* = 63); multiple (*n* = 52); OD (ball) (*n* = 22)	Osteoporosis Diabetes Cigarette smoking	BLRate (panoramic or peri-apical): *S* = 0.065 NS = 0.05	No report

Sánchez-Pérez et al., 2007[29]	Tobacco as a risk factor for survival of dental implants	Retrospective Consecutive patients Screw-taped, sandblasted, acid-etched dental implants (Bis)	5 years	*S* = 40 NS = 26	*S* = 95 NS = 70	No report	Cigarette smoking	Retroalveolar radiographs, parallel technique MBL1: *S* = 2.7; NS = 2.78 MBL2: *S* = 2.41; NS = 3.13	PPD *S* = 3.0 NS = 2.5
Stoker et al., 2012[32]	Long-term outcomes of three types of implant-supported mandibular overdentures in smokers	Randomized controlled clinical trial 36 patients (2IBA group) 37 patients (2ISB group) 37 patients (4ITB group) One-stage ITI/ Bonefit dental implants	8.3 years	110 baseline 103 for analysis after follow-up	256	OD	Smoking	Mean bone loss (long-cone) S: 2IBA = 1.53; 2ISB = 1.17; 4ITB = 2.46 NS: 2IBA = 0.7; 2ISB = 0.83; 4ITB = 1.24	PPD (overall) 2IBA: 3.1 2ISB: 3.5 4ITB: 3.6

2IBA, two implants with ball attachments; 2ISB, two implants with bar attachment; 4ITB, four implants with triple bar; ABL, absolute bone loss; AST, Astra-Tech; BI, bleeding index; BLRate, bone loss rate in millimetres per month; BS, Brånemark System; CAD–CAM, computer-aided design/machining; cpTi, commercially pure titanium; FHS, former heavy smoker; FLS, former light smoker; FPD, fixed partial denture; FS, former smokers; FSP, fixed supported prosthesis; FxMd, fixed mandibular prosthesis; GI, gingival index; HA, hydroxyapatite-coated surface; HS, heavy smokers; IL-1, interleukin-1; IMZ, intra-mobile cylinder; ITI, International Team for Implantology; LS, light smoker; Max, maxilla; Mand, mandible; MBL, marginal bone loss; MBL1, marginal bone loss at functional loading; MBL2, marginal bone loss at most recent follow-up; MI, mucosal index; MS, moderate smokers; NS, non-smoker; NOP, non-osteoporotic group; OD, overdenture; OP, osteoporotic group; PI, plaque index; PPD, pocket probing depth (mm); S, smoker; SLA, sandblasted and large-etched; TPS, titanium plasma-spray.

maxilla. Only 1% (3/273) of implants were lost in the mandible and 7% (5/75) in the maxilla. The mean peri-implant bone loss around all implants was less than 1 mm over a 10-year period after implant placement. In this study,[24] smokers lost more bone than non-smokers, but the effect was significant only for the mandibular arch.

Sánchez-Pérez et al.[29] performed a retrospective analysis of 165 dental implants. Sixteen implants failed (9.7%). The success rates for smokers and non-smokers were 84.2% and 98.6%, respectively. The risk of implant failure was 31% higher in those smoking more than 20 cigarettes/day.von Wowern and Gotfredsen[25] analyzed the changes in mineral bone content in 22 long-term edentulous mandibles (18 women and four men) with implant-supported overdentures compared to a physiological situation, and the influence of osteoporosis on peri-implant bone height as well. The authors found that mandibular osteoporosis prior to implant treatment may be a risk factor for bone loss around implants.

Discussion

This systematic review tried to determine whether systemic patient-related risk factors (systemic disease, genetic traits, chronic drug or alcohol consumption, and smoking status) could influence peri-implant bone loss at least 1 year after prosthetic loading. This could help the clinician to provide a more specific response to patient desires and lower the level of anxiety in those exposed to such risk factors, with direct implications for dental implant treatment. In the past, these have been systematically reviewed only in terms of an adverse implant outcome (survival and failure rates). Moreover, five recent systematic reviews[2,6,33–35] have evaluated cigarette smoking as a risk factor for an adverse implant outcome. Four of the five reviews[2,6,34,35] found smoking to be significant.

Since the classical inclusion of radiographic bone level changes within the criteria for dental implant success dates back more than 25 years,[36] a large, robust body of evidence could be expected. However, only 13 studies were included in the quantitative synthesis (meta-analysis): 12 of these were observational studies, while only one was an RCT,[32] and there was also considerable heterogeneity among them. The result for the 13 selected studies showed smoking to increase the rate of bone loss by 0.164 mm per year, this being statistically significant. For some

Table 2. Results of quality assessment-cohort studies.[a]

Item	Description	Author, year (Ref.)								
		Haas et al., 1996[30]	Isidor et al., 1999[28]	Carlsson et al., 2000[24]	Geurs et al., 2001[20]	von Wowern and Gotfredsen, 2001[25]	Feloutzis et al., 2003[19]	Gruica et al., 2004[26]	Peñarrocha et al., 2004[31]	Galindo-Moreno et al., 2005[22]
1	Are the characteristics of the comparative study clearly described?	+	+	–	–	+	+	+	+	+
2	Can selection bias be excluded sufficiently?	+	–	+	–	–	+	+	–	+
3	Is the intervention clearly described? Are all parameters treated according to the same intervention?	+	+	+	–	+	–	–	+	?
4	Are the outcomes clearly described? Are the methods used to assess the outcome adequate?	+	–	+	–	+	+	+	+	+
5	Is blinding used to assess the outcome? If not, does this have any effect on the evaluation of the results?	?	–	?	+	–	+	+	–	?
6	Is the duration of the follow-up sufficient?	?	+	+	?	+	+	+	+	?
7	Can selective loss-to-follow-up be excluded sufficiently?	?	+	+	–	+	?	+	+	+
8	Are the most important confounders or prognostic factors identified?	+	–	+	+	?	+	+	?	+

Item	Description	Author, year (Ref.)						
		Nitzan et al., 2005[21]	DeLuca and Zarb, 2006[27]	Norton, 2006[16]	Herzberg et al., 2006[17]	Sanna et al., 2007[23]	Tandlich et al., 2007[18]	Sánchez-Pérez et al., 2007[29]
1	Are the characteristics of the comparative study clearly described?	–	–	+	+	+	+	+
2	Can selection bias be excluded sufficiently?	+	–	+	+	+	–	+
3	Is the intervention clearly described? Are all parameters treated according to the same intervention?	?	+	–	–	+	+	+
4	Are the outcomes clearly described? Are the methods used to assess the outcome adequate?	–	+	+	?	–	?	+
5	Is blinding used to assess the outcome? If not, does this have any effect on the evaluation of the results?	+	?	?	?	+	+	+
6	Is the duration of the follow-up sufficient?	?	+	?	?	?	?	+
7	Can selective loss-to-follow-up be excluded sufficiently?	+	+	+	+	?	?	?
8	Are the most important confounders or prognostic factors identified?	+	+	+	+	+	+	+

[a] Four or more plusses = methodologically acceptable.

Table 3. Results of quality assessment-randomized controlled trial.[a]

Item	Description	Author, year (Ref.) Stoker et al., 2012[32]
1	Was the intervention assignment randomized?	+
2	The person who included the patients should not be informed about the randomization order. Was that the case?	+
3	Were the patients blinded for treatment?	?
4	Were the practitioners blinded for treatment?	?
5	Were the evaluators blinded for treatment?	?
6	Were the groups comparable at the beginning of the trial? If not, were the analyses corrected for this?	+
7	Are there relatively enough patients available for complete follow-up? If not, can selective loss-to-follow-up be excluded sufficiently?	+
8	Are the included patients analyzed in the group in which they were randomized?	+
9	Are the groups, besides the intervention, treated likewise?	+

[a] Four or more plusses = methodologically acceptable.

studies[18,20,23,30,32] the effect would be statistically significant (95% CI does not contain the value 0), but this was not the case for the remaining studies. This can be explained in part by the particular features of the design and methodology used in the studies. For example, Feloutzis et al.[19] reported bone loss in smokers as 1.98 against 0.20 for non-smokers. This extreme difference may be due to the fact that the smokers group consisted only of patients highly dependent on smoking, excluding moderate smokers because of the lack of data on bone loss. Also, the populations included in the above-mentioned studies are very specific and different from those recruited in the rest of the studies (it may be the case that some patients were suffering from a pathology for which the progression of loss is more sensitive to the smoking factor). In addition, it is important to highlight that different numbers of cigarettes/day, or time intervals to the quitting/interruption of smoking were considered in the selected studies to classify the smokers (light, moderate, and heavy) and non-smokers. Patient self-report rather than serum nicotine levels were recorded in most situations.

Another important issue to consider is the role of confounding variables (the presence of other systemic or local risk factors) in the studied population. In a prospective study[22] included in this meta-analysis (185 patients, 514 implants, 3 years of follow-up), confounding variables and interactions were controlled by the use of multivariate linear regression analysis, and a link was established between peri-implant bone loss and the habits of tobacco smoking and alcohol consumption. In two retrospective studies[26,31] considering heavy smoking to be >20 cigarettes/day, significantly greater bone loss was found,[31] with a synergistic effect characterized by the identification of a positive IL-1 genotype (Gruica et al.[26]; 64 patients, 8 years follow-up; odds ratio = 2.32; $P = 0.0079$). The longest retrospective study[27] (20 years of follow-up) confirmed by linear regression model that a smoking history (>25 cigarettes/day) was a predisposing factor for a slightly higher risk of late implant failure. On the other hand, this association was seen only in the maxillary arch (Nitzan et al.[21]; 161 patients, 3.8 years of follow-up). Although smokers demonstrated a mean bone loss of more than twice that of non-smokers (4.5 years of follow-up; logistic regression analysis, $P < 0.011$), this result was not affected by the number of cigarettes/day.[17] Finally, one study demonstrated no difference in bone loss regardless of smoking status after 3 years, but the lack of statistical significance may be attributed to disparities in the sample sizes.[16]

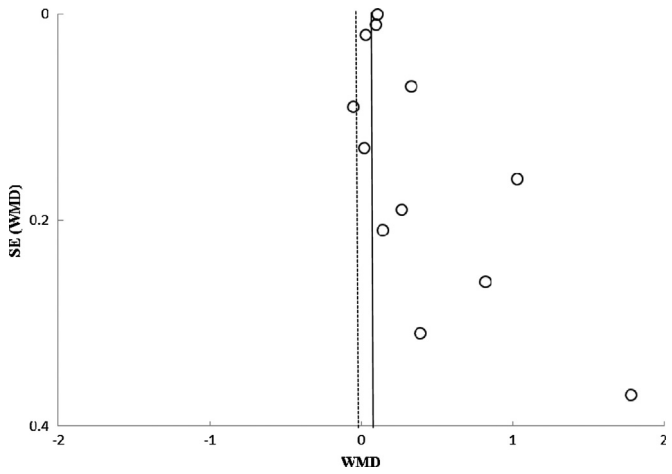


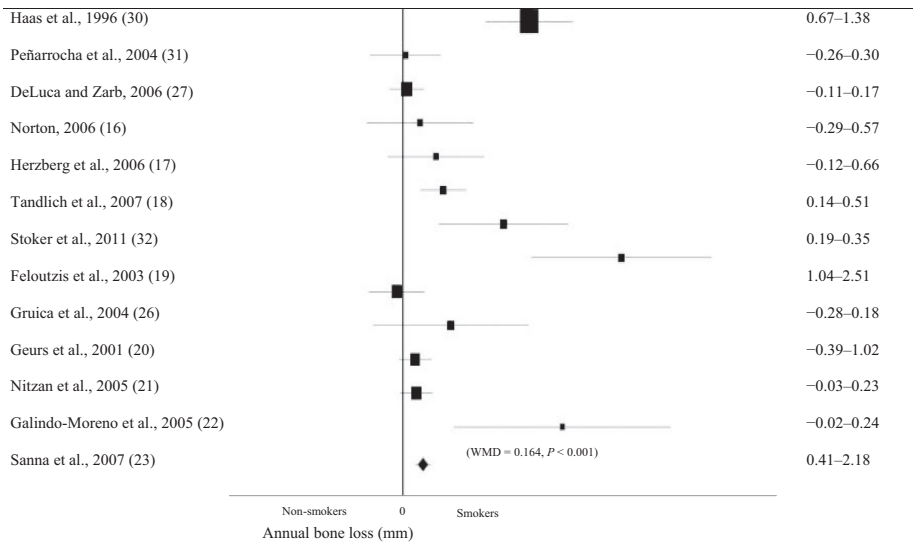
Fig. 2. Funnel plot. The vertical dashed line represents the weighted mean difference (WMD) of the zero line of no effect. The vertical solid line represents the pooled estimate (WMD = 0.164 mm).

Another source of confounding is related to the method of assessment of peri-implant bone loss. As bone remodelling is a dynamic process, dental radiographs are a simple clinical tool that can provide an estimate of changes over time. As well as the number of X-ray sources/parameters of the different manufacturers, different imaging techniques (intraoral peri-apical and panoramic), analogue/digital devices, and measurement tools (magnifying lens and software) were used, and this may account for a potential bias. Just one study[31] provided the reading error among radiographic modalities. Of course, stratification on the above-cited parameters would limit the number of studies for meta-analysis.

These 13 studies involved different implant shapes and collar configurations. Therefore, it appears logical to assume a variation in reference points to score bone loss (first thread and implant abutment junction). One study[20] provided no detail of the implant shape/surface, and another study[21] made no distinction between the implant types used. To obtain adequate documentation in clinical trials,

Table 4. Forest plot for first meta-analysis.[a]

Authors, year (Ref.)	95% CI
Haas et al., 1996[30]	0.67–1.38
Peñarrocha et al., 2004[31]	−0.26 to 0.30
DeLuca and Zarb, 2006[27]	−0.11 to 0.17
Norton, 2006[16]	−0.29 to 0.57
Herzberg et al., 2006[17]	−0.12 to 0.66
Tandlich et al., 2007[18]	0.14–0.51
Stoker et al., 2011[32]	0.19–0.35
Feloutzis et al., 2003[19]	1.04–2.51
Gruica et al., 2004[26]	−0.28 to 0.18
Geurs et al., 2001[20]	−0.39 to 1.02
Nitzan et al., 2005[21]	−0.03 to 0.23
Galindo-Moreno et al., 2005[22]	−0.02 to 0.24
Sanna et al., 2007[23]	0.41–2.18



95% CI, 95% confidence interval; WMD, weighted mean differences.
[a]WMD, random-effects model; *x*-axis is annual bone loss in mm.

radiographic evaluation of the bone–implant interface at baseline and at 1-, 3-, and 5-year time intervals (every 5 years in the case of bone stability) has been recommended.[37] Also, new guidelines on patient safety have recently been published.[38]

Regarding the type of prosthetic unit, three out of six retrospective studies[16,27,31] provided details on splinted and unsplinted prosthetic units, but one prospective study[22] concluded that no association exists between the restoration type and marginal bone loss. Over the years, different occlusal philosophies have been proposed for implant-supported prostheses, but their clinical significance remains elusive.[39] The reasons for the lack of RCTs to verify the association between occlusal parameters and peri-implant bone loss are obvious, and close patient follow-up appears the most practical way to prevent mechanical complications.

In this systematic review, data on peri-implant soft tissue outcomes were frequently not present. Even though poor oral hygiene and a history of periodontitis cannot be excluded as risk factors for peri-implant bone disease,[40] aesthetics must also be included as a current goal of implant therapy, along with long-term function and the capability to maintain good oral hygiene at home (even in the posterior areas of the oral cavity). In the absence of data regarding peri-implant gingival recession or the width of keratinized tissues, it is very important to address (in cases of implant survival) how much bone is lost over time radiographically.

In conclusion, within the limits of this study, it is possible to conclude that: (1) the level of evidence for oral implant therapy in patients with systemic conditions is very low. Generally, only case reports or case series exist reporting, at the least, the implant survival rate as an outcome. (2) Smokers presented a higher level of peri-implant bone loss (0.164 mm/year) than non-smokers. (3) The design of future studies should be improved to provide more robust data for clinical application.

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Competing interests

None declared.

Ethical approval

Not required.

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.ijom.2013.11.012.

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