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Five-year outcome of a retrospective cohort study comparing smokers vs. nonsmokers with full-arch mandibular implant-supported rehabilitation using the All-on-4 concept

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Abstract: The aim of this study was to compare the 5-year outcome of full-arch mandibular fixed prosthetic rehabilitation using the All-on-4 concept in smoking and nonsmoking patients. This retrospective cohort study included 200 patients (*n* = 100 smokers, *n* = 100 nonsmokers), 119 women and 81 men, with an average age of 53.7 years, rehabilitated in immediate function with 800 implants. Implant cumulative survival rate estimation (Kaplan-Meier with log-rank test) and marginal bone resorption (MBR) at 5 years (Mann-Whitney test) were compared between both groups. Multivariable analysis was used to investigate potential risk indicators for MBR ≥ 2.8 mm at 5 years. Nine patients (4.5%) were lost to follow-up. Four patients lost eight implants, specifically one nonsmoking patient (*n* = 1 implant) and three smoking patients (*n* = 7 implants), resulting in a cumulative survival rate estimation of 99.0% and 96.9% for nonsmokers and smokers, respectively (*P* = 0.296). The average (standard deviation) MBR at 5 years was 1.68 mm (0.76 mm) and 1.98 mm (1.02 mm) for nonsmokers and smokers, respectively (*P* = 0.045). Smoking (odds ratio = 2.92) was the only risk indicator significantly associated with MBR ≥ 2.8 mm in multivariable analysis. Smoking should not be an absolute contraindication for rehabilitation of the edentulous mandible through the All-on-4 concept; however, smoking habits were significantly associated with MBR ≥ 2.8 mm.

Keywords: dental implant; smoker; All-on-4; full-arch; mandible.

Introduction

Smoking has long been causally associated with several cancers, heart disease, and chronic obstructive pulmonary disease and represents the leading cause of premature death and morbidity in the Western world (U.S. Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. 2004; 1). Cigarette smoking was previously reported to have a detrimental effect on early bone tissue response around dental implants, with marginal bone loss, gaps, and fibrous tissue surrounding the implants retrieved from smokers, together with a significant decrease in bone to implant contact percentage compared to nonsmokers (2). Furthermore, smoking is considered by several publications to be a risk factor for the success of dental implants (3-7) irrespective of the loading regimen (delayed or immediate loading) (3). A 5-year pragmatic multicenter retrospective cohort study of 1,178 nonsmokers and 549 smokers investigating the influence of cigarette

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smoking on the survival of dental implants registered significantly more implant failures in smokers compared to nonsmokers when all implant failures within 5 years of loading were taken into account (5). Previous systematic reviews and meta-analysis investigating the influence of smoking on the survival outcome of dental implants concluded that the insertion of implants in smokers significantly affected the failure rate, with a statistically significant risk ratio of implant failure for smokers (risk ratio = 2.2) (6,8) and marginal bone loss with a mean difference of 0.32 mm favoring nonsmokers (6,8). The results of a long-term retrospective study demonstrated higher marginal bone loss for current and former smokers compared to nonsmokers for all time intervals evaluated: during the first year of function, between the first and fifth year of function, and from the sixth year of function until the end of follow-up (up to 14 years) (9). The literature is not consistent however. A number of publications reported no significant differences between smokers and nonsmokers in clinical parameters (10), implant failure (9-12), or implant surface (only affecting implants with machined surfaces) (13). A retrospective cohort study of 64 patients with an average follow-up of 6 years comparing the survival and marginal bone loss of single-tooth dental implants between past, current, and nonsmokers, registered no difference in implant survival between the groups (9). Another retrospective study investigating risk indicators associated with the survival rate of 940 dental implants reported that smoking did not affect the survival rate, with no significant differences between the survival curves of smokers compared to nonsmokers (11). Moreover, a retrospective study evaluating the long-term survival rate of dental implants between smokers and nonsmokers in two separate cohorts (one with exclusive use of smooth-surface implants and another with exclusive use of anodically oxidized surface implants) reported differing results: for the smooth-surface implants, smoking significantly influenced the implant failure rate (hazard ratio = 3.1), whereas smoking did not significantly influence implant survival outcomes for anodically oxidized surface implants (13).

However, several methodological issues existed in the studies described above, leading to potential bias in the estimates. These include statistical bias due to the use of the implant as the unit of analysis, resulting in potential overestimations (5), only using bivariate analysis and excluding potential confounders and/or competing risk indicators (5,7,9-11), only including significant variables in the multivariable model (3), using the relative risk in a retrospective study design (3), selection bias by excluding patients with any history of systemic disease (7), small sample sizes in one of the groups (9,10), sample erosion with less than 32% of the patients completing follow-up (13), and the inclusion of several reports with less than 5 years of follow-up in meta-analytic studies, which calls into questions the validity of 5-year or longer observations (6).

The use of immediate function for prosthetic implant-supported rehabilitation provides a number of advantages for the patient including psychological benefits and a potential cost reduction (14). Previous reports have demonstrated that the All-on-4 concept for rehabilitation of edentulous jaws is a viable treatment alternative for the fixed prosthetic rehabilitation of the complete edentulous mandible, with good long-term outcomes (15). Recent studies concerning the rehabilitation of complete edentulous mandibles using the All-on-4 concept registered a higher incidence of implant failure (15) and marginal bone loss over 2.8 mm at 5 years (16) in patients with smoking habits. Nevertheless, studies directly estimating the effect of smoking on the outcome of patients rehabilitated through immediate loading (at 5 or more years) are scarce.

The aim of this report was to compare the outcome after 5 years of implant insertion with regard to immediate function for rehabilitation of edentulous mandibles using the All-on-4 concept in smokers and nonsmokers.

Materials and Methods

This retrospective study was performed in Malo Clinic Lisbon (a private clinic in Portugal) and was approved by an independent Ethics Committee (Ethical Committee for Health, authorization no. 001/2010).

The patients were included in this study, provided the need for full-arch fixed prosthetic rehabilitation in the mandible through dental implants inserted with an immediate function protocol. Exclusion criteria were patients rehabilitated through dental implants inserted in one-stage or two-stage surgical approaches and patients that underwent bone grafting procedures at the location of the implants.

Between January 2003 and December 2006, 434 patients were rehabilitated with implant-supported fixed dental prostheses for full-arch restoration of the mandible through the All-on-4 treatment concept (Nobel Biocare, Göteborg, Sweden): 100 patients with smoking habits (any cigarette smoking) and 334 patients without smoking habits. One-hundred patients without smoking habits were randomly selected for inclusion in this study using a random sequence generator. The patients were identified through their medical records.

Sample size calculation

The detectable alternative calculation derived from the sample size was performed using a software program (power and sample size calculations, version 3.0.34, Dupont WD and Plummer WD Jr, Department of Biostatistics, Vanderbilt University, Nashville, TN, USA). Considering the study with 100 patients with smoking habits and 100 control patients (without smoking habits), a 25% probability of exposure to smoking among the controls (1), and a median follow-up of 5 years, the planned number of cases and controls provided a true odds ratio (OR) for disease between 0.33 and 2.33 in subjects exposed to smoking compared to unexposed subjects with power = 0.8 and a type I error probability of 0.05 associated with the test of the null hypothesis of OR = 1.

Treatment planning

The medical histories of all patients were reviewed. A clinical observation to plan the surgical and prosthodontic steps was performed together with radiographic exams through orthopantomography (used to evaluate bone height) and a computerized tomography scan (to evaluate the bone volume and landmark anatomical structures for the concept—the dental nerve—per protocol).

Surgical protocol

The surgical and prosthetic procedures are described in previously published papers (15,16). In brief, surgery was performed with the patient under local anesthesia using articaine clorhidrate (72 mg/1.8 mL) with epinephrine (0.018 mg/1.8 mL) 1:100,000 (Artinibsa 2%, Inibsa Laboratory, Barcelona, Spain). Prior to the surgical procedure, the patients were administered with diazepam (Valium 10 mg, Roche, Amadora, Portugal). The administration of antibiotics was performed 1 h before surgery and on a daily basis thereafter for 6 days (amoxicillin 875 mg and clavulanic acid 125 mg, Labesfal, Campo de Besteiros, Portugal). Corticosteroids were given daily in a regression mode (15 mg on the day of surgery to 5 mg on the 4th day) (prednisone 5 mg, Meticorten Schering-Plough Farma, Ltd., Agualva-Cacém, Portugal). Anti-inflammatories (ibuprofen 600 mg, Ratiopharm, Ltd., Carnaxide, Portugal) were given for 4 days postoperatively starting on the 4th day. Analgesic medication (clonixine 300 mg, Clonix, Janssen-Cilag Farmaceutica, Ltd., Barcarena, Portugal) was administered to the patients on the day of surgery and only used postoperatively when the patient experienced pain. Antacid medication (omeprazole 20 mg, AstraZeneca, Lisbon, Portugal) was administered to the patients on the day of surgery and on a daily basis thereafter for 6 days.

Implant insertion (Brånemark System Mk III and Mk IV and NobelSpeedy, Nobel Biocare) followed standard procedures (17). The exception was the use of under-preparation, employed to guarantee a final torque of over 32 N/cm before seating the final implant. Implant length ranged from 10 to 18 mm. The two most anterior implants were inserted following the direction determined by the anatomy of the jaw. The two posterior implants were inserted (one implant on each quadrant) anterior to the mental foramina with a distal tilt between 30° and 45° relative to the occlusal plane, aiming for good implant anchorage, large inter-implant distance and short cantilevers (15,16,18).

The implants were positioned at bone level. Whenever possible, bicortical anchorage was established. Soft tissue was readapted and sutured back into position on each patient using 3-0 nonresorbable sutures (Silkam, B. Braun Surgical SA, Rubi, Spain). The choice of abutment was made based on the use of straight multiunit abutments (Nobel Biocare) for the anterior implants and 30° angulated abutments for the posterior implants. When further compensation of the angulation in the anterior implants was necessary due to jaw anatomy, 17° abutments were used. The specific choice of abutments was made with the objectives of allowing the fixed dental prosthesis to have a passive fit, maintaining the fixed dental prosthesis with an acceptable thickness, and having the prosthetic screw-access holes emerging on the occlusal or lingual aspects of the fixed dental prosthesis.

Patients were informed that the surgical area should be kept cool and under minimal pressure for the first 48 h after the surgery and advised to ingest only soft and cold foods during that period.

Immediate interim prosthetic protocol

High-density acrylic resin (PalaXpress Ultra; Heraeus Kulzer GmbH, Hanau, Germany) screw-retained fixed dental prostheses with titanium cylinders (Nobel Biocare) were manufactured at the dental laboratory and inserted on the same day (n = 200 interim prostheses). The occlusion scheme adopted in the interim prosthesis privileged anterior occlusal contacts and canine guidance during lateral movements. On the interim prostheses, the emergence positions of the screw-access holes were typically at the second premolar level for the posterior implants. The interim prostheses exhibited a minimum of 10 teeth. Figures 1-5 illustrate the surgical and immediate interim prosthetic protocols of a full-arch mandibular rehabilitation through the All-on-4 concept (Nobel Biocare).

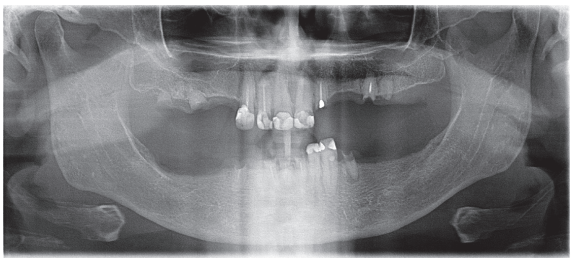

Fig. 1 Preoperative orthopantomography.

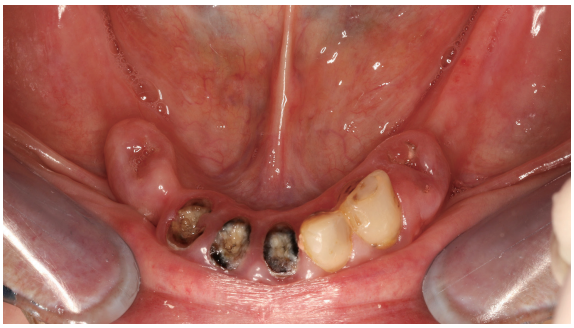

Fig. 2 Preoperative intra-oral photograph of the mandible.

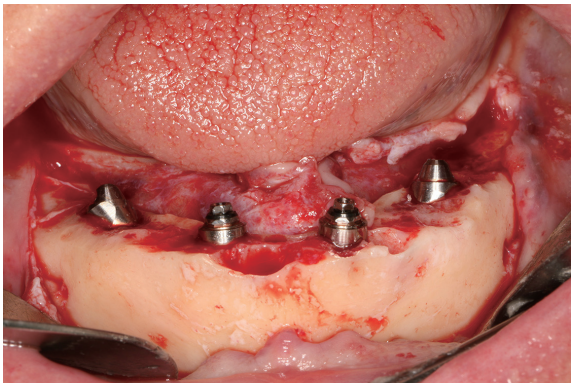

Fig. 3 Preoperative intra-oral photograph of the mandible after insertion of two anterior implants in the axial position and two posterior implants inserted distally tilted for support of a full-arch fixed prosthetic restoration through the All-on-4 concept.

Definitive prosthetic protocol

Typically, 6 months after surgery, the screw-retained definitive fixed dental prostheses were delivered to the patients. According to the patient's preference, the definitive prostheses were: metal ceramic implant-supported fixed dental prostheses with a titanium framework and all-ceramic crowns (Procera titanium framework, Procera crowns, Nobel Rondo ceramics, Nobel Biocare), or metal-acrylic resin implant-supported fixed dental prostheses with a titanium framework (Procera titanium framework; Nobel Biocare) and acrylic resin prosthetic teeth (Heraeus Kulzer GmbH). The occlusion scheme preferred for the definitive prosthesis was one that mimicked natural dentition.

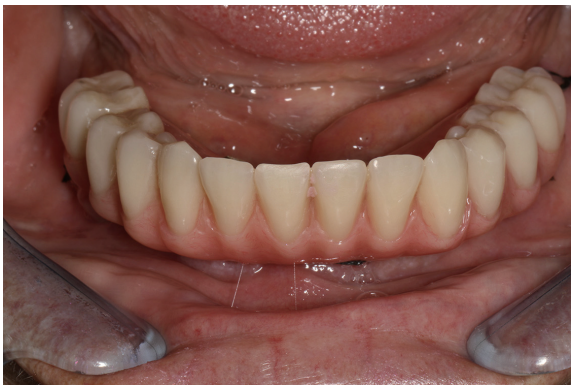

Fig. 4 Full-arch fixed dental prosthesis connected to the four implants on the day of surgery achieving immediate function.

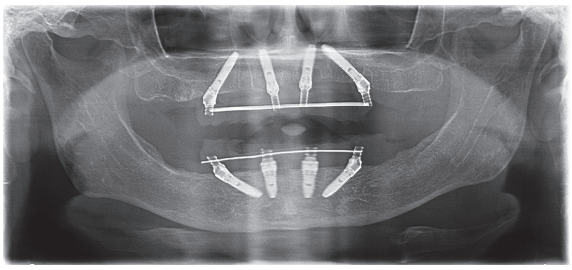

Fig. 5 Postoperative orthopantomography after rehabilitation of the mandible through the All-on-4 concept.

Postoperative care and follow-up

The patients were instructed to maintain a soft food diet for the first 4 months postsurgery. Ten days after surgery, the sutures were removed, and hygiene and implant stability (clinical mobility and suppuration by finger pressure) were evaluated. The occlusion was rechecked following the initial protocol, and the procedure was repeated after 2 and 4 months. Usually, at approximately 4 months, the interim prostheses were again removed, jet-cleaned (using Air-Flow Powder, EMS, Nyon, Switzerland), and disinfected (using 0.2% chlorhexidine; Elugel, Pierre Fabre Dermo-Cosmetique, Lisboa, Portugal), and the implants were checked for anchorage (clinical mobility), suppuration, and pain. The patients were evaluated at 6 months postsurgery, 1 year postsurgery, and every 6 months thereafter.

Outcome measures

The primary outcome measure was implant survival evaluated based on function and using the patient as the unit of analysis (first implant failure in a patient was considered a censoring event irrespective of the remaining three implants maintaining function). The implant survival was evaluated based on function and determined by fulfillment of the following criteria (16): implant fulfilled its purported

Table 1 Sample characteristics distribution in both study groups

	Total patients (%)	Nonsmoking patients (%)	Smoking patients (%)
Number of patients	200 (100%)	100 (100%)	100 (100%)
Average age in years (standard deviation)	53.7 (9.2)	54.1 (8.5)	53.2 (9.9)
Gender			
Female	119 (59.5%)	63 (63%)	56 (56%)
Male	81 (40.5%)	37 (37%)	44 (44%)
Systemic status			
Healthy patients	151 (75%)	73 (73%)	77 (77%)
Patients with systemic conditions	49 (24.5%)	26 (26%)	23 (23%)
Patients with implant failures	4 (2%)	1 (1%)	3 (3%)
Healthy patients	3 (1.5%)	1 (1%)	2 (2%)
Patients with systemic conditions	1 (0.5%)	0 (0%)	1 (1%)

function as support for reconstruction; clinical stability, no signs of persistent infection that could jeopardize the outcome of the rehabilitation; no radiolucent areas around the implants; demonstrated good esthetic outcome for the rehabilitation; and patient reported function with no discomfort. All implants that were removed were classified as failures.

Secondary outcome measures were MBR evaluated after 5 years of function using the patients as the unit of analysis. A conventional radiographic holder (super-bite; Hawe Neos, Bioggio, Switzerland) was used, and its position was manually adjusted to the estimated orthognatic position of the film. An outcome assessor examined all implant radiographs. Each periapical radiograph was scanned at 300 dpi with a scanner (HP Scanjet 4890, HP Portugal, Paço de Arcos, Portugal), and the MBR was assessed with image analysis software (Image J version 1.40 g for Windows, National Institutes of Health, Bethesda, MD, USA). The reference point for the reading was the implant platform (the horizontal interface between the implant and the abutment), and the marginal bone level was assessed and defined as the most apical contact between bone and implant. The difference in marginal bone level between the 5-year and baseline assessments was defined as the MBR. The measurements were performed on the mesial and distal sites, and average values were calculated. The radiographs were calibrated using the implant platform diameter and were accepted or rejected for evaluation based on the clarity of the implant threads; a clear thread guaranteed both sharpness and an orthogonal direction of the radiographic beam toward the implant axis. The biological complications assessed were peri-implant pathology, suppuration, and fistulae formation.

Statistical analysis

Descriptive statistics were applied to characterize the sample with regard to demographic variables, the incidence of biological complications, and the systemic status of the patients in both groups. Implant survival (using the patient as the unit of analysis and considering the first incidence of implant failure) was computed using the Kaplan-Meier product limit estimator with comparison of survival curves between groups through the log-rank test. Marginal bone loss was compared between the two groups using the Mann-Whitney test after testing the variable for normality through the Kolmogorov-Smirnov test.

Considering the outcome variable "MBR $\geq$ 2.8 mm", the present study used a logistic regression model for estimation of the ORs and corresponding 95% confidence intervals of potential explanatory variables. A cutoff value of 2.8 mm at 5 years was assumed. This value was justified based on an initial bone remodeling of up to 2.0 mm in the first year for implants in immediate function (14), as well as an annual average marginal bone loss < 0.2 mm thereafter (19). The present study used univariate analyses to identify the covariates associated with MBR $\geq$ 2.8 mm, namely age, gender, systemic status, history of periodontitis, biological complications, and smoking status. The covariates significantly associated with the outcome in univariate analysis ($P < 0.20$) were entered in a multivariate logistic regression model. The level of significance was 0.05. Statistics were computed using the Statistical Package for Social Science (IMB SPSS, version 17.0, Armonk, NY, USA).

Results

The study included 200 patients (119 women and 81 men) with an age range of 23-80 years (average = 53.7 years). The patients were followed for 5 years. The patients were separated into groups according to their smoking status: smokers (n = 100 patients) and nonsmokers (n = 100 patients). There were 49 patients with systemic conditions (smokers: 23 patients with 92 implants; nonsmokers: 26

Table 2 Dental implants with external implant-abutment connection distribution according to the type of implant, diameter, and length

Type of implants	Number of implants (implants failed)	
Mk III Narrow platform diameter: 10 mm of length	4	
Mk III Narrow platform diameter: 11.5 mm of length	3	
Mk III Narrow platform diameter: 13 mm of length	11	
Mk III Regular platform diameter: 15 mm of length	264 (2)	
Total number of Mk III implants		282 (2)
Mk IV Narrow platform diameter: 15 mm of length	4	
Mk IV Regular platform diameter: 10 mm of length	2	
Mk IV Regular platform diameter: 11.5 mm of length	3	
Mk IV Regular platform diameter: 13 mm of length	6	
Mk IV Regular platform diameter: 15 mm of length	206	
Total number of Mk IV implants		221 (0)
NobelSpeedy Narrow platform diameter: 13 mm of length	5	
NobelSpeedy Narrow platform diameter: 15 mm of length	11	
NobelSpeedy Regular platform diameter: 13 mm of length	29 (4)	
NobelSpeedy Regular platform diameter: 15 mm of length	234 (2)	
NobelSpeedy Regular platform diameter: 18 mm of length	18	
Total number of NobelSpeedy implants		297 (6)
Total number of implants		800 (8)

Table 3 Cumulative implant survival estimation at 5 years after rehabilitation of the mandible using the All-on-4 concept with the patient as the unit of analysis (Kaplan-Meier product limit estimator)

Time (months)	Status*	Cumulative proportion surviving		Cumulative events (*n*)	Patients at risk (*n*)
		Estimate	Standard error		
Nonsmokers					
12	0			0	99
43	1	0.990	0.010	1	98
60	0			1	98
Smokers					
6	1	0.990	0.010	1	99
12	0			1	97
15	1	0.980	0.014	2	96
24	0			2	93
30	0			2	92
33	1	0.969	0.018	3	91
48	0			3	89
60	0			3	89

*Failure was defined as the first implant failure in a patient irrespective of the remaining three implants maintaining function. 0 = nonfailure, 1 = failure

patients with 104 implants; Table 1).

A total of 800 anodically oxidized surface implants (Brånemark System; NobelSpeedy, Nobel Biocare) were inserted: 282 MkIII implants (nonsmokers: n = 174 implants; smokers: n = 108 implants), 221 MkIV implants (nonsmokers: n = 125 implants; smokers: n = 96 implants) and 297 NobelSpeedy implants (nonsmokers: n = 101 implants; smokers: n = 196 implants; Table 2).

Nine patients (4.5%) were lost to follow-up: one patient from the nonsmokers group and seven patients from the smokers group became unreachable and one patient from the smokers group was deceased due to reasons unrelated to the implant treatment. In total, eight implants failed in four patients (n = 1 healthy patient in the nonsmokers group; n = 2 healthy patients in the smokers group; and n = 1 patient with systemic conditions in the smokers group; Table 1), giving an overall implant survival estimation of 98.0% after 5 years, with a cumulative implant survival estimation of 99.0% for nonsmokers and 96.9% for smokers (P = 0.296; Table 3, Fig. 6). The nonsmoking patient lost one implant (axial implant) after 43 months of follow-up due to peri-implant pathology. The fixed dental prosthesis was supported by the remaining three implants, and a new implant was inserted after 7 months with no further complications registered. One patient (smoker) lost all

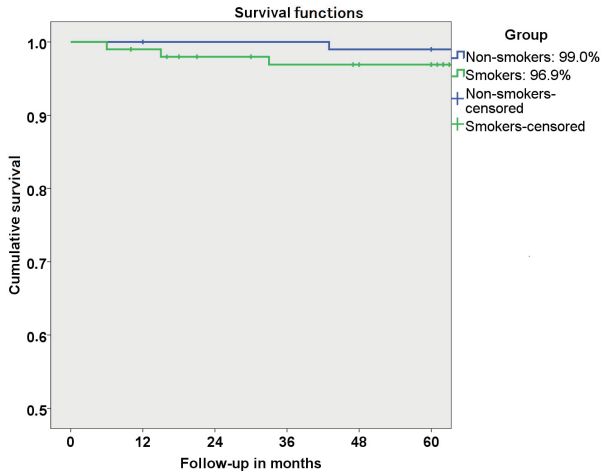

Fig. 6 Implant cumulative survival estimation (Kaplan-Meier) for nonsmokers and smokers using the patient as the unit of analysis (first implant failure regarded as a censoring event irrespective of the remaining implants maintaining function).

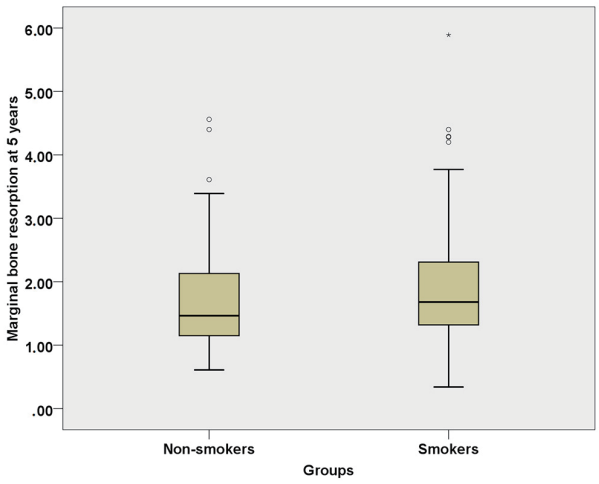

Fig. 7 Box-plot illustrating the distribution of marginal bone loss in millimeters at 5 years in both groups. The black horizontal line represents the median (50% of cases), while the lower and upper edges of the box represent the 25th and 75th percentiles, respectively.

four implants (two implants after 15 months and two implants after 41 months) and the respective fixed dental prosthesis due to loss of implant integration. Three new implants were inserted, and the definitive fixed dental prosthesis was supported by the new implants. A second patient (smoker) lost two implants (two axial implants) after 6 months due to loss of integration. The fixed dental prosthesis remained functional, supported by the two remaining implants and two new implants were inserted and loaded after 8 months with no further complications. A third patient (smoker) lost one implant (axial) after 33 months: the implant presented progressive marginal bone

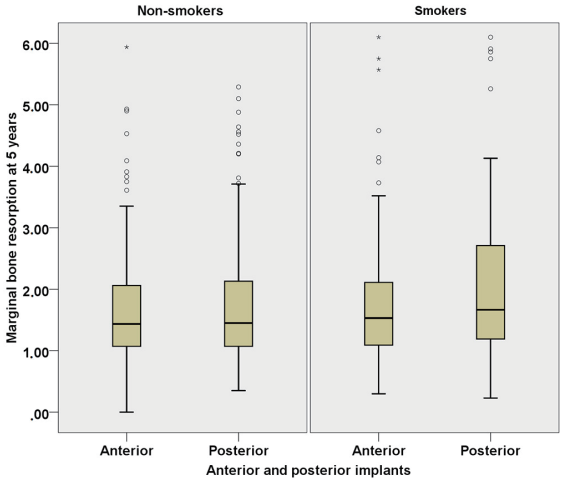

Fig. 8 Box-plot illustrating the distribution of marginal bone loss in millimeters at 5 years in both groups according to implant location: anterior implants (axial implants) and posterior implants (tilted implants). The black horizontal line represents the median (50% of cases), while the lower and upper edges of the box represent the 25th and 75th percentiles, respectively.

loss, peri-implant pockets over 6 mm, and suppuration at the 11th month of follow-up and was removed. The fixed dental prosthesis was supported by the remaining three implants, and a new implant was inserted after 1 year with no further complications registered.

The average (standard deviation) MBR after 5 years of follow-up was 1.68 mm (0.76 mm) and 1.98 mm (1.02 mm) for the nonsmokers and smokers, respectively (Fig. 7). The difference between both groups was significant ($P = 0.045$). The average (standard deviation) MBR after 5 years of follow-up for anterior and posterior implants was 1.66 mm (0.94 mm) and 1.71 mm (0.78 mm) for nonsmokers and 1.85 mm (1.28 mm) and 2.11 mm (1.37 mm) for smokers, respectively (Fig. 8).

Biological complications were registered in 11 nonsmoking patients and 13 smoking patients (total of 24 patients). During the first year of follow-up, six patients ($n = 4$ patients with four implants who were smokers and $n = 2$ nonsmokers with three implants) experienced implant infections (with increased probing pocket depths > 4 mm and suppuration), which were all resolved through nonsurgical therapy (consisting of implant scaling and administration of antibiotics), with the exception of one implant (in a patient who was a smoker) that maintained its status until removal after 33 months of follow-up. The remaining 18 patients ($n = 9$ patients with 11 implants who were smokers and $n = 9$ nonsmokers with seven implants) presented peri-implant pathology (with increased probing pocket depths > 4 mm, concurrent MBR and loss of attachment level), all

Table 4 Multivariate analysis of variables associated with marginal bone resorption ≥2.8 mm at 5 years

Factor	OR (95% CI)	*P*	OR¥ (95% CI)	*P*
Gender		0.351		
Female	1.0			
Male	1.59 (0.60, 4.24)			
Age, years	1.02 (0.97, 1.08)	0.440		
History of periodontitis		0.308		
Absence	1.0			
Presence	1.96 (0.54, 7.09)			
Biological complications		0.055		
Absence	1.0			
Presence	3.08 (0.98, 9.70)		2.92 (0.91, 9.43)	0.073
Systemic condition		0.332		
Absence	1.0			
Presence	0.53 (0.15, 1.92)			
Smoking status		0.036		
Nonsmoker	1.0			
Smoker	3.02 (1.08, 8.47)		2.92 (1.03, 8.29)	0.044

The final model included smoking status and biological complications as explanatory variables.
CI, confidence interval. ¥OR from logistic regression analysis with smoking and presence of biological complications included if significant ($P < 0.20$) in the unadjusted model

occurring after the first year of follow-up. In the smokers group, the situations were resolved in three patients with four implants through nonsurgical therapy and were not resolved in six patients with seven implants (despite surgical intervention for implant disinfection, removal of granulomatosis tissue, and suture) with the implants maintaining a stable functional status. In the nonsmoker group, the situations were resolved in five patients through nonsurgical therapy and were unresolved in two patients (through surgical interventions) with implants maintaining a stable functional status. Two patients remained under evaluation at the end of the study follow-up.

Regarding the risk indicators for MBR ≥ 2.8 mm, the variables included in the multivariate model were selected because of statistical significance ($P < 0.20$) in the unadjusted univariate analyses (Table 4), which identified the following variables as possibly associated with MBR ≥ 2.8 mm: smoking status ($P \leq 0.036$) and presence of biological complications ($P \leq 0.055$). In the multivariable logistic regression model, smoking (OR = 2.92) remained significantly associated with MBR ≥ 2.8 mm after adjusting for biological complications.

Discussion

The results registered in this study demonstrated a successful outcome at 5 years for full-arch mandibular fixed prosthetic rehabilitation through the All-on-4 concept in both nonsmoking and smoking patients. The overall cumulative implant survival estimated in this study is comparable with that in previous studies on the rehabilitation of edentulous mandibles using the same approach, with cumulative implant survival rates between 95.3% (15) and 96.2% (16).

Despite the higher implant failure rate registered in this study for smokers compared with nonsmokers, the difference between the survival curves for both groups was not significant. Few studies investigated the influence of smoking habits on the outcome (with 5 or more years of follow-up) in patients rehabilitated through immediate loading. Inconsistent results were derived from the available literature concerning the effect of smoking habits on the survival outcome of dental implant restorations. A previous meta-analytic study registered an overall twofold increase in the risk of implant failure for smokers, suggesting (due to limited evidence) that smoking could have the potential to negatively affect healing and the outcome of implant treatment, while proposing updated periodic reviews of the available clinical research (6). Another recent systematic review and meta-analysis investigated the success of dental implants in smokers and nonsmokers, and despite the increased chance of implant failure registered in smokers (OR = 1.96), a subgroup analysis including the follow-up length failed to correlate a significant implant failure rate with increased follow-up length (12). This implies that factors other than smoking habits may impact the successful long-term outcome of implant-supported rehabilitation. A previous retrospective study investigated the effect of smoking habits in two separate cohorts of patients with exclusively smooth-surface implants or anodically oxidized implants (13) and registered a significant

increase in implant failure (hazard ratio for smoking = 3.1) in the smooth-surface implant cohort, but no significant influence in the anodically oxidized surface implant cohort (13).

Despite limitations in the methodology and sample size, other retrospective studies (9,11) reported no influence of smoking habits on the survival outcome for dental implants. These studies consisted of a retrospective cohort study of 64 patients with a 6-year average follow-up (9) and another retrospective study with 940 dental implants (11). These inconsistent results together with the specific results obtained for anodically oxidized surface implants demonstrate the necessity of further research. The results of the present study (using exclusively anodically oxidized surface implants in the sample) are consistent with the previous study by Balshe et al. (13), with smoking exerting no significant impact on implant survival.

In contrast, the impact of smoking on marginal bone loss generates more consensus when the available literature is evaluated. A recent meta-analysis registered a negative effect of smoking habits (6), together with mean differences between 0.32 (6) and 0.49 mm (12), favoring nonsmokers in marginal bone loss. Nevertheless, qualitative reserves concerning the inclusion of several studies with >5 years of follow-up (6) potentially call into question the validity of 5-year observations. Our study registered not only a statistical significance for the 0.30-mm difference between smokers and nonsmokers on the average marginal bone loss at 5 years but also a significant effect on marginal bone loss exceeding 2.8 mm at 5 years, with a nearly threefold increase for smokers when adjusted for the presence of biological complications. This particular result may imply a potential negative effect on longer follow-ups given the significant association between marginal bone level and the incidence of peri-implant pathology (20,21), with a consequent increase in the probability of implant failure. A series of previous studies investigated the risk factors of peri-implant pathology in a sample of 1,275 patients, deriving a risk model and corresponding risk score for predicting the incidence of peri-implant pathology. Among other variables, the bone level located on the implants' medium third was associated with a 14-fold increase in the likelihood of peri-implant pathology (20,21), amounting to a potential reduction in 30% of the cases of peri-implant pathology if the exposure to this variable was prevented according to the attributable fraction calculations (21). The clinical implications of the findings in the present study indicate the necessity to inform patients who are smokers prior to surgery about the higher probability of MBR in the long-term outcome of their rehabilitation.

Study limitations include the study being performed in a single center and the retrospective design. Study strengths include the large sample, long-term follow-up, low percentage of patients lost to follow-up (i.e., strong internal validity), and the use of multivariable analysis. Future research should include more studies on the long-term outcome for patients rehabilitated with immediate loading and a comparison of these groups (nonsmokers versus smokers) in different populations using a prospective study design.

The high overall survival rate of 98.0% after 5 years of follow-up and the nonsignificant difference in the survival curves between smokers and nonsmokers indicate that smoking should not be an absolute contraindication for rehabilitation of edentulous mandibles through the All-on-4 concept. Smoking habits were significantly associated with MBR $\geq$ 2.8 mm after 5 years of follow-up when controlled for the presence of biological complications.

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Conflict of interest

Paulo Maló is currently a consultant for Nobel Biocare. Other authors have no conflict of interest to declare.

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