

Effect of Heavy Smoking on Dental Implants Placed in Male Patients Posterior Mandibles: A Prospective Clinical Study

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The objective of this study was to evaluate the implant stability and peri-implant tissue response in heavy smokers receiving dental implants due to partially edentulous posterior mandibles. Forty-five ITI Straumann dental implants were placed into the partially edentulous posterior mandibles of 16 heavy smokers and 16 nonsmokers. One implant in each patient was evaluated for implant stability after surgery and before loading, and for the modified plaque index (mPLI), modified sulcus bleeding index (mSBI), probing depth (PD), and marginal bone loss (MBL) after loading. Meanwhile, the osteogenic capability of jaw marrow samples collected from patients was evaluated via an in vitro mineralization test. For both groups, the implant stability quotient (ISQ) initially decreased from the initial ISQ achieved immediately after surgery and then increased starting from 2 weeks postsurgery. However, at 3, 4, 6, and 8 weeks postsurgery, the ISQ differed significantly between nonsmokers and heavy smokers. All implants achieved osseointegration without complications at least by the end of the 12th week postsurgery. At 6 or 12 months postloading, the MBL and PD were significantly higher in heavy smokers than in nonsmokers, whereas the mSBI and mPLI did not differ significantly between the 2 groups. The 1-year cumulative success rate of implants was 100% for both groups. Within the limitations of the present clinical study (such as small sample size and short study duration), which applied the loading at 3 months postoperation, heavy smoking did not affect the cumulative survival rate of dental implants placed at the posterior mandible in male patients, but heavy smoking did negatively affect bone healing around dental implants by decreasing the healing speed. These results implied that it might be of importance to select the right time point to apply the implant loading for heavy smokers. In addition, heavy smoking promoted the loss of marginal bone and the further development of dental pockets. Further clinical studies with larger patient populations are warranted to confirm our findings over a longer study duration.

Key Words: dental implant stability, resonance frequency analysis, heavy smoking

INTRODUCTION

Dental implants have become a safe and effective therapy for replacing missing teeth in partially edentulous patients.¹ It has been reported that the general survival rates of dental implants are higher than 90% in various clinical situations.² However, failures of dental implants still frequently occur in patients receiving dental implantation.³ Especially lower success rates have been observed in patients with certain systemic diseases or habits such as smoking.²

Recent studies have revealed that the deleterious effects of smoking tobacco progress through a series of direct and indirect systemic and local influences on bone metabolism at the bone-implant interface.¹ Nicotine down-regulates the gene expression of several key enzymes that are important in the regulation of osteoblast proliferation, differentiation, and apoptosis, thus impacting bone formation and remodeling. Moreover, exposure to nicotine also has direct effects on blood vessels via the induction of vasoconstriction and systemic

venoconstriction, thus decreasing blood perfusion. This eventually causes low oxygen and even ischemia. These malfunctions also interfere with the interactions among osteoblasts, osteocytes, osteoclasts, and vascular cells at a variety of levels, thus impairing bone formation and remodeling.⁴

Recently, limited evidence has emerged to show that smoking significantly affects the success rates of dental implants and the risk of postoperative infections as well as marginal bone loss in patients receiving dental implants.⁴⁻⁶ Some studies have confirmed that smoking negatively affects the clinical success of implant treatment and the long-term prognosis.⁷⁻¹⁰ A recent study found that heavy smokers (>20 cigarettes/d) had the highest implant failure rate. A longitudinal study involving more than 2900 implant patients found that smoking had a greater negative effect after the second surgical stage.¹¹ A Dental Implant Clinical Research Group reported that the implant failure rate after the second surgical stage was significantly higher in smokers than in nonsmokers based on their study of more than 2000 dental implant patients.¹² Moy et al examined 1140 patients with 4680 implants retrospectively for 21 years (1982–2003) and reported that the failure rate in smokers was as high as 20%.¹³ The failure rate was highest during the first year after denture restoration.

However, sensitivity analysis suggested that smoking only has significantly effects on the survival of implants inserted in

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the maxilla.⁴ The limited reports in the literature on the survival of dental implants placed in the mandible of smokers and nonsmokers suggest that smoking does not significantly affect the survival of implants in mandible.⁴ Currently, informative studies on the influence of heavy smoking on single-tooth implants placed at the posterior mandibles of smokers are lacking. However, this information/knowledge is needed for surgeons to make informed decisions and refine treatment plans to optimize outcomes.

The objective of this study was to evaluate the postsurgery bone healing and peri-implant tissue response in heavy smokers receiving dental implants due to partially edentulous posterior mandibles. Specifically, the implant stability was monitored by measuring the implant stability quotient (ISQ) for up to 12 weeks after surgery. Loading was placed at the end of 3 months after surgery. The modified plaque index (mPLI), modified sulcus bleeding index (mSBI), probing depth (PD), and marginal bone loss (MBL) were determined at 6 and 12 months after loading.

MATERIALS AND METHODS

Patient recruitment

The present study was approved by the Ethics Committee of First Affiliated Hospital of Xi'an Jiaotong University and complied with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Humans. Written informed consent was obtained from all patients enrolled in this study after they were given oral and written information regarding the study. From February 2012 to June 2012, 16 heavy smokers and 16 nonsmokers with partially edentulous posterior mandibles were consecutively recruited into this study according to the inclusion and exclusion criteria at the Department of Oral in the First Affiliated Hospital of Xi'an Jiaotong University. These patients were assigned to 1 of 2 groups: the heavy smoker ($n = 16$) or nonsmoker ($n = 16$) group based on their smoking habits. Random selection of patients was not used due to the limited number of patients eligible for this study. The surgical treatment, data collection, and data analysis in this study complied with the principles of a double-blind study.

The inclusion criteria were: male visiting the Department of Oral at the First Affiliated Hospital of Xi'an Jiaotong University between February 2012 and June 2012 for a partially edentulous posterior mandible; age in the range of 25–65 years old; either heavy smoking or nonsmoking habit; and possessing an adequate quantity and quality of native bone to achieve primary implant stability. Heavy smokers were defined as individuals who were actively smoking 1 or more boxes of cigarettes (20 cigarettes per box) a day for 10 years (postoperatively with no intervention), whereas nonsmokers were individuals with no smoking history.

The exclusion criteria were: unwilling to give written informed consent; having chronic or acute systemic pathologies that might affect the surgical procedure, the subsequent prosthodontic treatment/retreatment, or necessary follow-ups; and having undergone a tooth extraction or surgery in the area of interest in the preceding 6 months.

All patients recruited for this present study received treatment of supragingival scaling just 1 week before surgery to ensure that they had no periodontal disease before surgery and had good oral hygiene.

Preparation of examiners/surgeons

Before the start of this study, all examiners and surgeons involved were specifically trained in the measurements and evaluations of ISQ, mPLI, mSBI, PD, and MBL for this clinical study. All measurements were performed under the supervision of the principal investigator (PI) and conducted in duplicate by 2 different people separately. Only minor differences were observed between the duplicated measurements. The surgeon and PI made clinical assessments jointly regarding bone type at implant placement.

Surgery treatment

At the time of surgery, the bone structures at the implantation sites were first classified according to the criteria of Lekholm and Zarb¹⁴ before the implant beds were prepared at these sites. The surgeon and PI made clinical assessments jointly regarding the bone type for each site according to a 4-tiered scale: high density (type I), moderate density (type II), low density (type III), and very low density (type IV).¹⁴ The bone morphology for all cases was rated as either Type II (thick compact bone surrounding highly trabecular core) or Type III (thin cortical bone surrounding highly trabecular core). In particular, 22 patients (10 heavy smokers and 12 nonsmokers) had Type II, and 10 patients (6 heavy smokers and 4 nonsmokers) had Type III.

Subsequently, implantation surgery was performed by multiple clinicians consistently with standard surgical protocols^{15,16} under the supervision of the PI. A total of 45 Straumann dental implants (RN, 4.8 mm × 10 mm; Straumann Company, Basel, Switzerland) were placed in the 32 patients. After surgery, patients received prescriptions for a postoperative antibiotic regimen consisting of amoxicillin (500 mg) or clindamycin (150 mg) 3 times per day for 7 days and chlorhexidine gluconate (0.12%) mouth rinse twice a day for 2 weeks. During the whole observation period, all patients brushed their teeth effectively. After the 3-month healing period, denture restorations were placed for all implants.

Stability evaluation

The literature suggested that most failures occur during the second surgery phase and the first year of functional loading. Therefore, we evaluated the implant stability using a noninvasive and objective method resonance frequency analysis (RFA) during the period of 12 weeks after the surgery and before loading, and continued to monitor the peri-implant tissue responses in the first year after loading. In particular, implant stability was determined via RFA immediately after implant insertion and at 1, 2, 3, 4, 6, 8, and 12 weeks after surgery by the same clinician using an Osstell Mentor (Integration Diagnostics AB, Goteborg, Sweden). The use and calibration of this Osstell Mentor were performed according to the manufacturer's instruction. Briefly, the transducer was directly attached to the implant perpendicular to the alveolar crest using a

screwdriver at ~10 Ncm according to the manufacturer's instructions. Implant stability was measured in duplicate for 1 implant per patient. Moreover, for any individual implant at each observation time point, the ISQ was the average of measurements performed in 2 different directions, the mesial and the buccal.

Postloading evaluation

After loading, the periodontal and marginal bone changes were monitored for 1 implant per patient at 6 and 12 months postloading. Briefly, standardized clinical dental radiography (1.65 μ Sv a piece) was performed to check the marginal bone levels for determining the MBL. In particular, the marginal bone level, which was the distance between the implant shoulder and the first visible bone-implant contact, was determined by examining the standardized dental X-ray images. For any implant, the MBL at the time of 1 follow-up visit (either 6 or 12 months postloading) was calculated by subtracting its marginal bone level found right after implant placement (abutment placement) from its marginal bone level found at this visit. To compensate for distortion on the standardized dental X ray, the measured distance was adjusted with respect to the known total length of the implant. All radiographs were analyzed by 2 examiners who did not know any clinical parameters or patients' smoking habits. Images were transferred to a computer and digitized at 100% of their real size at a resolution of 600 dpi using a BenQ5560B scanner (BenQ Corp, Xi'an, China). Digital image analysis software (Digimizer, Xi'an, China) was used to measure the distance between any 2 points. Internal calibration was performed on 3 interthread distances totaling 3.75 mm in length for each implant. The average of the 2 examiners' results was used as the final MBL value.

In addition, the 6 aspects around 1 individual implant per patient were scored for mPLI with 0 for no plaque detected, 1 for plaque recognizable by running a probe across the smooth marginal surface of the implant, 2 for plaque visible to the naked eye, and 3 for an abundance of soft matter.^{17,18} The final mPLI for each implant was the average of the 6 scores for that particular implant.

The 6 aspects of each implant were also assessed for mSBI with 0 indicating no bleeding when a periodontal probe was passed along the sulcus adjacent to the implant, 1 indicating visible isolated bleeding spots, 2 for blood forming a red line in the sulcus, and 3 for heavy or profuse bleeding from the sulcus.¹⁹ The final mSBI for each implant was the average of the 6 scores for that particular implant.

Probing depth (PD)²⁰ was assessed at 6 aspects of each implant in millimeters. The average of the 6 measured values was used as the PD for that implant.

In vitro mineralization test

During the surgery to place the implants, jaw marrow samples were obtained from 3 patients randomly selected in each group. This sampling did not affect the implant placement in the corresponding period.

The human alveolar bone marrow-derived mesenchymal stem cells (hABMMSCs) obtained were cultured separately in α -minimal essential medium (α -MEM) culture medium containing

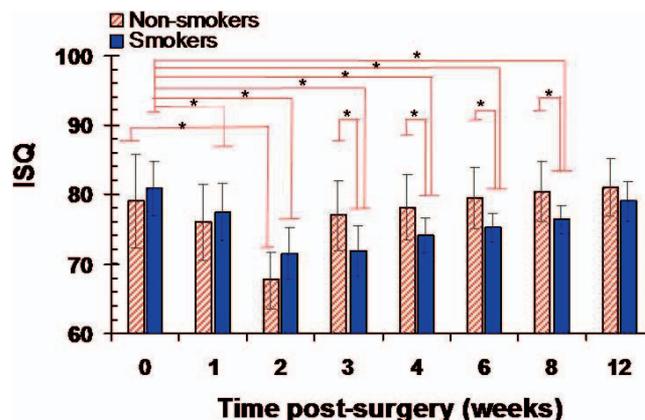


FIGURE 1. The change in ISQ over time during the initial 12 weeks postsurgery and before loading in the groups of smokers and nonsmokers. Paired *t* test was used for statistical analysis. **P* < .05.

10% fetal bovine serum at 37°C and in 5% CO₂. Cells were subcultured upon reaching a confluence of about 80%. The third passage cells were seeded separately in 6-well plates at 1 × 10³ cells/well. Once they reached 60% confluence, the culture media were replaced with osteogenic solution (α -MEM supplemented with 0.1 μ M dexamethasone, 10 mM β -glycerophosphate, 50 mg/L vitamin C, 10% fetal bovine serum). The osteogenic solutions in the wells were replaced with fresh osteogenic solutions every 3 days to induce mineralization. Three weeks after the switch of culture medium to osteogenic solution, the cells were washed twice with PBS after the removal of osteogenic solution and then treated with 4% paraformaldehyde for 30 minutes. The wells were photographed after staining with 1% alizarin red staining. Leica Q-Win image analysis software was used to analyze the obtained images.

Statistical analysis

The statistical unit for all outcomes was the implant. All numerical data were managed using commercial statistical software SPSS (version 17.0), and final numerical results are reported as mean \pm standard deviation (SD) values determined from the means of individuals in the groups. A paired *t* test was used to determine if there was any statistically significant difference between 2 data points. A *P* value less than .05 indicated a statistically significant difference between analyzed data.

RESULTS

To investigate if heavy smoking has any effects on the bone healing and peri-implant tissue response dental implants placed in male patients due to partially edentulous posterior mandibles, we monitored the ISQ change over a period of 12 weeks after operation and before loading, and the mPLI, mSBI, PD, and MBL at 6 and 12 months after loading.

Figure 1 shows the changes in ISQ values determined via RFA over the 12 weeks postsurgery for both heavy smokers and

nonsmokers. Immediately after the placement of implants, there was no statistically significant difference in the ISQ between the nonsmoker and heavy smoker groups ($P > .05$). During the initial 2 weeks after implant placement, the ISQ continuously decreased as compared with the corresponding initial ISQ immediately after surgery for both groups. At 2 weeks postsurgery, the nonsmokers had a more significant decrease in the mean ISQ from its initial ISQ as compared with the heavy smokers ($P < .05$). At 3 weeks postsurgery, the ISQ for the nonsmokers had significantly increased from that at 2 weeks, whereas the ISQ for the heavy smokers showed almost no change from that at the 2 weeks postsurgery. The nonsmokers then had a slow, steady increase in the ISQ, and at 6 weeks postsurgery, the ISQ had reached the initial ISQ achieved immediately after surgery for this group. However, the ISQ of the heavy smokers steadily increased through the period from 3 weeks postsurgery to 12 weeks postsurgery. At any time point of 3, 4, 6, and 8 weeks postsurgery, the ISQ for the group of heavy smokers was significantly lower than that for the group of nonsmokers. However, at 12 weeks postsurgery, the difference in the ISQ between the 2 groups was no longer statistically significant. Statistically, at 12 weeks postsurgery, the ISQ for the group of smokers reached the initial ISQ achieved immediately after surgery for this group. In addition, during the whole healing period before loading, no complications or implant failures were observed in all 32 patients.

Figure 2 shows the evaluation results at 6 and 12 months postloading for both nonsmokers and heavy smokers. The nonsmokers had a significantly lower MBL as compared with the heavy smokers (Figure 2a, $P < .05$ for both time points). No significant differences were observed in the mSBI and mPLI between the 2 groups at either 6 or 12 months after loading (Figure 2b and c, $P > .05$). The nonsmokers had significantly less PD as compared with the heavy smoker (Figure 2d, $P < .05$ for both time points) at 6 and 12 months postloading. Moreover, there were slight, although not statistically significant, increases in both the MBL and PD observed from 6 months postloading to 12 months postloading for the heavy smoker group.

We further studied the capability of jaw marrow samples collected to form new bone via in vitro mineralization tests. Figure 3 shows the results of in vitro mineralization tests with the jaw marrow retrieved from both groups. Red-brown mineralized nodules were observed in the 3 samples from the nonsmoker group (Figure 3a1 through a3) and the 3 samples from the heavy smoker group (Figure 3b1 through b3). However, the red-brown mineralized nodules for both groups were quite different in term of sizes and density. The heavy smoker group had small, dispersed nodules with low density, whereas the nonsmoker group had large and centrally arranged nodules with a high density (Figure 3a1 through a3). For the nonsmokers, the resulting alizarin red staining covered $32.06\% \pm 2.43\%$ of the whole image area, which was a significantly larger area than the $9.22\% \pm 1.43\%$ covered for the heavy smoker group (Figure 3c).

DISCUSSION

Successful osseointegration is a key requirement for long-term survival of dental implants. Osseointegration is a process in which

dental implants and bone join together by forming a rigid, clinically asymptomatic fixation that is maintained during functional loading.²¹ Implant stability includes primary stability and biological stability. Primary stability is the mechanical fitting via mechanical insertion of the implant fixture device in the base bone, whereas biological stability is generated by bone remodeling at the implant–bone interface and plays a key role in the survival of implants. Currently, the ISQ determined from RFA is an objective worldwide standard for measuring implant stability.^{22–26} The changes in ISQ during the course of bone healing before loading reflect the change at the implant–bone interface.

In the present study, we chose 1 uniform implant (RN, diameter 4.8 mm; length 10 mm), enrolled male patients only, performed conventional implant surgery, and placed the implants at a uniform depth (a cantilever was used to measure the distance between the smooth implant surface and rough bone surface) in order to avoid bias due to the limitations of RFA.

In this study, we observed that the mean ISQ values in both groups decreased during the initial 2 weeks after surgery (Figure 1). This is consistent with multiple longitudinal studies reported in the literature, which also showed a decline in the ISQ during the first few weeks postoperatively.^{27–29} This decrease in ISQ was due to bone resorption at the bone–implant interface. After the lowest ISQ was reached around 2 weeks after surgery, both groups showed an increase in the ISQ, which was due to the gradually enhanced biological stability. This indicated that osteointegration had started at the bone–implant interface. Although at 12 weeks after surgery, the ISQ values for both groups reached the respective initial implant stabilities achieved immediately after surgery, the ISQ values for the nonsmoker group were significantly higher than those for the heavy smoker group at 3, 4, 6, and 8 weeks after surgery. This indicated that heavy smoking negatively affected the process of osteointegration. The trough span for the nonsmoker group was relatively shorter, lasting for only 1 week, whereas that for the heavy smoker group lasted for approximately 10 weeks.

We obtained samples from both groups in order to elucidate the mechanism underlying the prolonged trough time for heavy smokers. In vitro mineralization results showed that the representative samples from the nonsmokers exhibited a significantly better ability to form calcified nodules and mineralization than those from heavy smokers (Figure 3). These might contribute the aforementioned phenomenon, since a reduced capability to mineralize would slow the osseointegration.

The implant fixture survival rate was 100% for both the nonsmoker and heavy smoker groups at the end of 3 months postoperation. We also successfully added restorations on all 45 implant fixtures, achieving a cumulative 1-year implant survival rate of 100% at the end of 1 year postloading. Our results indicated that at the end of 3 months postoperation, the biological stability of implants might have reached the stationary phase for both groups, because the ISQ values for both reached the initial ISQ achieved right after surgery and had stabilized by 12 weeks after surgery (Figure 1). In contrast to the high implant failure rates within 1 year post-loading for heavy smokers reported by other researchers, our cumulative implant survival rate of 100% at the end of 1 year postloading might be attributed to the fact that the loading was applied

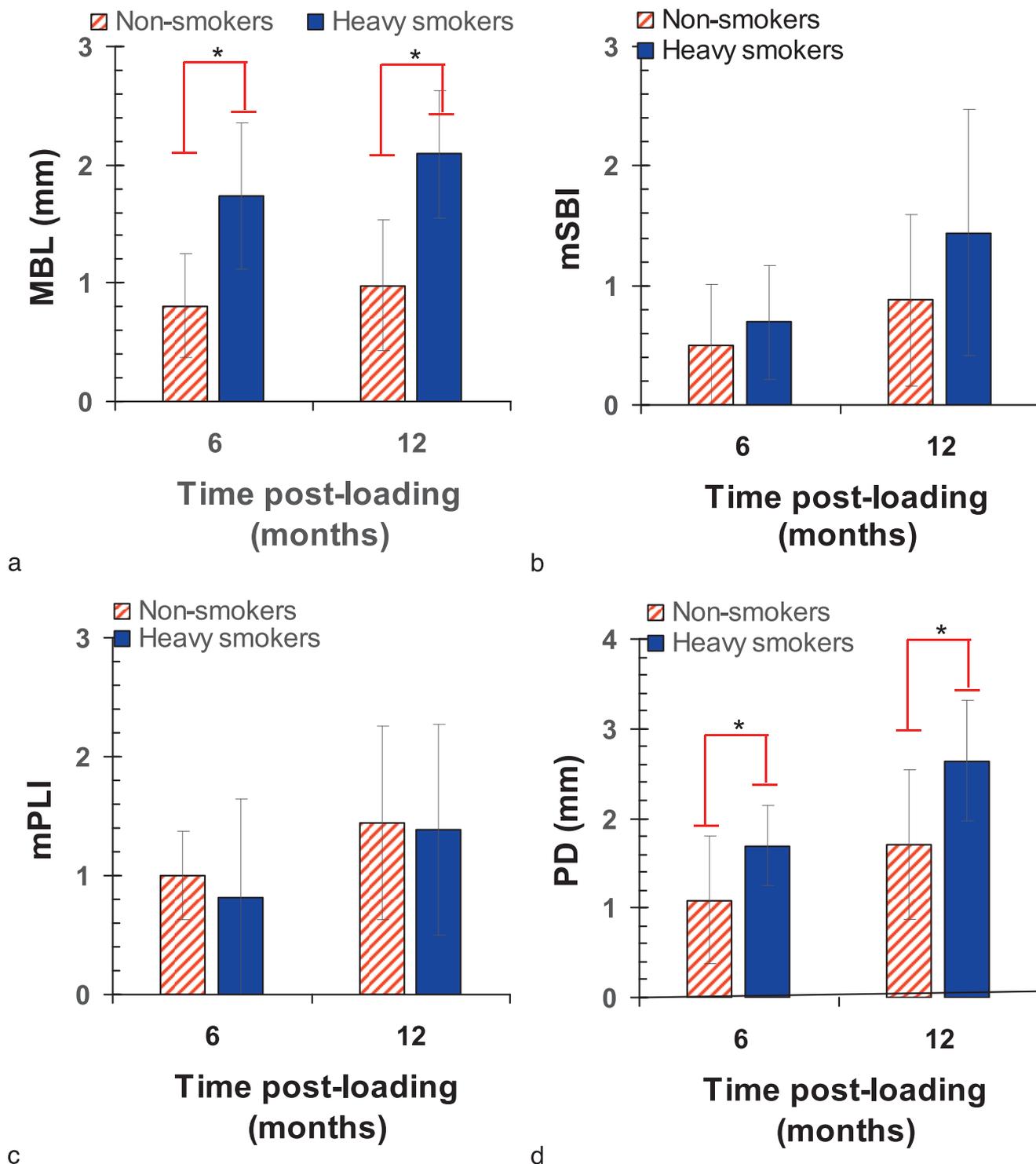


FIGURE 2. Periodontal responses for 32 implants in the groups of smokers and nonsmokers at 6 and 12 months postloading: (a) marginal bone loss; (b) modified sulcus bleeding index; (c) modified plaque index; (d) probing depth. Paired *t* test was used for statistical analysis. **P* < .05.

after the biological stability of implants had reached the stationary phase (Figure 1).

After loading, we monitored the responses of peri-implant tissues at 6 and 12 months postloading. Although there were no statistically significant differences between the 2 groups in the modified plaque index and modified bleeding index at 6 and 12

months postloading, the MBL and PD in heavy smokers were statistically significantly higher than those in nonsmokers at either 6 or 12 months after loading (*P* < .05, Figure 2). In addition, both the MBL and PD were increased at 12 months post-loading as compared with those at 6 months after loading. However, no statistically significant difference was found in the MBL between 6

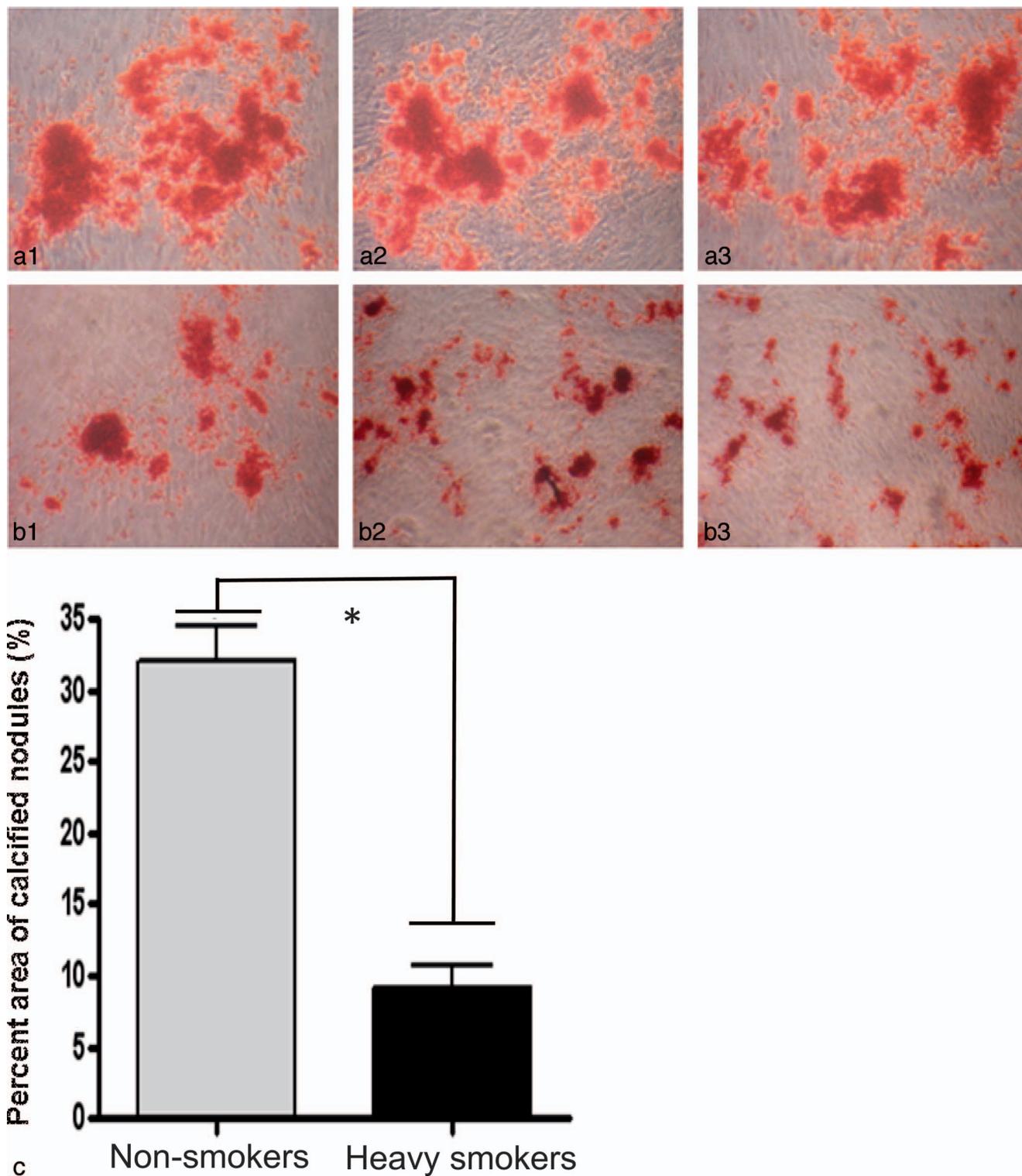


FIGURE 3. In vitro mineralization by jaw marrow samples: representative images (magnification $\times 100$) of red-brown mineralized nodules for the groups of nonsmokers (a1, a2, a3) and smokers (b1, b2, b3). (c) Percent area of red-brown mineralized nodules. Paired t test was used for statistical analysis. $*P < .05$.

and 12 months after loading in either the heavy smoker or nonsmoker fixture group ($P > .05$, Figure 2). However, in the heavy smoker group, there was a significant difference in the PD ($P < .05$, Figure 2), suggesting that as the loading time increases, the MBL

and PD increase in heavy smokers. This study also found that the mSBI in the heavy smoker group was significantly higher at 12 months compared to that at 6 months after loading ($P < .05$). This suggested that after a short time loading, the heavy smokers had a

greater chance of developing inflammation in the surrounding soft tissue. This inflammation could have an unfavorable influence on implant prognosis. These results were consistent with those of previous reports.^{30–32} Haas et al found that smokers had a greater risk of developing peri-implantitis.³⁰ Lindquist et al found that the marginal bone loss in smokers with poor oral hygiene was nearly 3 times higher than that in nonsmokers.^{31,32} They also confirmed that smokers had a significantly higher bleeding index, peri-implant PD, more frequent peri-implant inflammation, and greater mesial and distal bone loss radiographically. However, our results differed in some ways from those reported by Kumar et al, who showed that smoking had no significant impact on osseointegration and MBL in 461 patients with 1183 implants.³³ This contradiction might be attributed to the different implants used and some other unknown factors.

Within the limitations of present clinical study (such as the small sample size and short study duration), which applied the loading at 3 months postoperation, heavy smoking did not affect the cumulative survival rate of dental implants placed at the posterior mandible in male patients, but heavy smoking did negatively affect bone healing around dental implants by decreasing the healing speed. These results imply that it might be of importance to select the right time point to apply the implant loading for heavy smokers. In addition, heavy smoking promoted the loss of marginal bone and the further development of dental pockets. Further clinical studies with larger patient populations are warranted to confirm our findings over longer study duration.

ABBREVIATIONS

ISQ: implant stability quotient
 MBL: marginal bone loss
 mPLI: modified plaque index
 mSBI: modified sulcus bleeding index
 PD: probing depth
 α -MEM: α -minimal essential medium

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