The role of a moderately rough and chemically modified implant surface in an early loading protocol: a literature review

Tércio Pessoa **TABOSA E SILVA**[1], Caio César Leite **MIRANDA**[1], Rodinei Luiz da Silva **BUCCO JR**[1], Ticiana Pessoa **TABOSA E SILVA**[2], Bruno Salles **SOTTO-MAIOR**[3]

Objective: *The aim of this study was to accomplish a literature review, based on currently available evidence, about the early periods of bone integration around endosseous implants with moderately rough and chemically modified surface (MRCM).* **Methods:** *The review was performed through an electronic survey via PubMed, using a combination of keywords, including: osseointegration, bone-to-implant contact, wettability, chemically modified surface and bone healing. Experimental* in vitro *studies, in animal models and in humans, covering physicochemical characteristics, biological mechanisms and initial histological events related to MRCM implant surface were considered.* **Results:** *Experimental studies report higher bone apposition and better bone anchorage to MRCM surfaces during early stages of bone healing in animal models. These experimental results were validated by prospective clinical studies, studies measuring implant stability with resonance frequency analysis, gene expression profiles and temporal histological studies in human models.* **Conclusion:** *Within the limitations of this MRCM surface study, it is suggested that high surface energy and increased wettability positively influence bone formation in the initial periods of bone repair.* **Keywords:** *Dental implants. Wettability. Osseointegration. Surface properties.*

[1]MSc in Implantodontics, São Leopoldo Mandic, Dental Research Center, Campinas, São Paulo, Brazil.
[2]MSc in Clinical Pharmacology, Universidade Federal do Ceará (UFC), Fortaleza, Ceará, Brazil.
[3]Professor, Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, Minas Gerais, Brazil.

How to cite this article: Tabosa e Silva TP, Miranda CCL, Bucco Jr RLS, Tabosa e Silva TP, Sotto-Maior BS. The role of a moderately rough and chemically modified implant surface in an early loading protocol: a literature review. Dental Press Implantol. 2015 Apr-Jun;9(2):76-88. DOI: http://dx.doi.org/10.14436/2237-650X.9.2.076-088.oar

Submitted: June 12, 2015 - **Revised and accepted:** June 20, 2015

Contact address: Tércio Pessoa Tabosa e Silva - Rua Marcos Macêdo, 1333 - CEP: 60.150-190
Pátio Dom Luís, Torre Corporate, sala 1711 - Fortaleza / CE - Brazil - E-mail: terciopessoa@yahoo.com.br

» The authors report no commercial, proprietary or financial interest in the products or companies described in this article.

» Patients displayed in this article previously approved the use of their facial and intraoral photographs.

INTRODUCTION

Since the early 1980s, different characteristics of titanium surfaces, such as morphology, roughness, surface chemistry, wettability and thickness of the oxide layer, have been extensively investigated in an attempt to improve predictability and bone apposition in properly executed dental-implant treatments.[1,2,3] Some of these characteristics, including chemical properties and surface topography, were already considered parameters of great importance in achieving osseointegration and clinical success.[4]

Roughness of implant surfaces is a factor that has shown a positive correlation with positive rates of osseointegration.[5,6,7] Implants with a moderately rough surface (Sa between 1-2 μm), compared to implants with machined surfaces (Sa < 0.5 μm), showed a significantly higher bone-to-implant contact (BIC) rate.[5-10] In a literature review[8] covering histomorphometric and biomechanical studies of removal torque, the author concluded that surface topography influences bone response at the micrometer level with assumptions that it also has some influence at the nanometer level.

Subtractive methods, such as sandblasting and acid etching, are commonly used to obtain superficial roughness.[8] Sandblasting and acid etching are associated in specific situations. One example is the moderately rough (MR) SLA surface, developed by Straumann® in 1994 (Fig 1). The reason for the association of these two methods is that the blasting procedure hypothetically achieves optimal roughness for mechanical fixation whereas additional etching smoothens out some sharp peaks and may add a high frequency component to the implant surface, with potential significance for protein adhesion that seems to be qualitatively and quantitatively improved in this type of surface compared to machined or just acid-etched surfaces.[8,9] The SLA surface has been scientifically examined, and evidence has concluded that implants with this type surface can be successfully loaded after 6 and 8 weeks, with favorable survival and success rates up to 5 years of follow-up.[11-17]

In an *in vivo* study with Labrador dogs,[10] implants with moderately rough (MR) surface (Straumann® SLA, AG, Basel, Switzerland) showed, from week two onward, BIC percentages that reflected a substantially and significantly greater contact area between the newly formed bone and the MR surface compared to implants with machined surfaces. Thus, osseointegration, in regard to the rate of bone formation and magnitude, can be considered more prominent at MR than at machined surfaces. After 6 to12 weeks, differences in bone pattern and in tissue components had disappeared, but direct BIC remained superior for the MR surface.

In 2006, the new moderately rough and chemically modified (MRCM) SLActive surface (Straumann® AG, Basel, Switzerland)

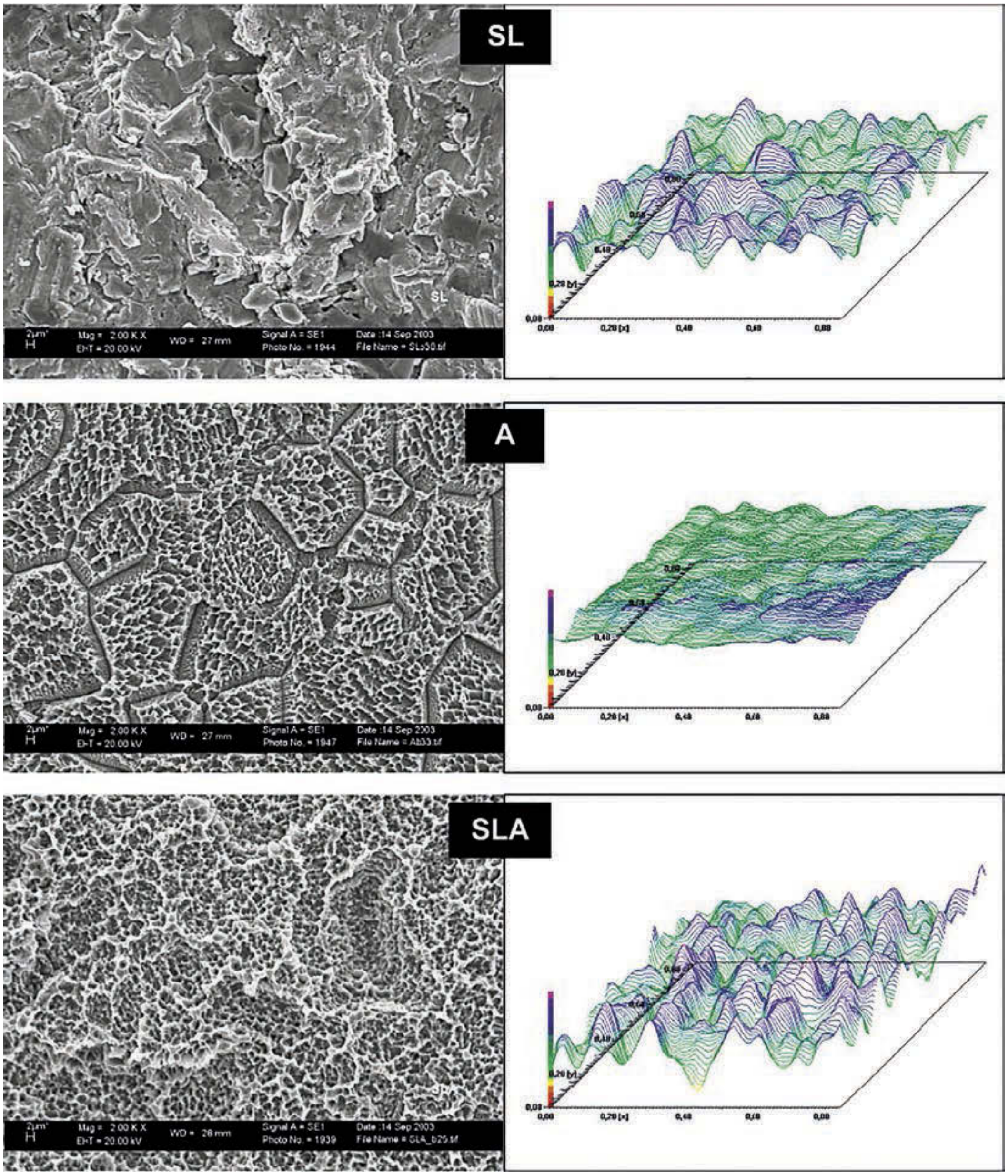

Figure 1. SEM images of sandblasted (SL), acid etched (A), and sandblasted/acid etched (SLA) surfaces. Ti modifications along with their respective profilometric contact style topographies on the right. (Source: Rupp et al,[20] 2006).

was introduced into the market with promises of accelerating the process of bone repair around endosseous implants, reducing to just three weeks the conventional implant loading protocols that commonly recommend a 12-week or longer period of undisturbed healing following implant placement. This shorter restoration period was justified by the surface hydrophilic characteristics, responsible for increased wettability,[18-21] which provides enhanced interaction between the implant surface and the biologic environment.[20, 22-25]

Therefore, the aim of the present study is to analyze and understand the early periods of bone repair around endosseous implants with MRCM surface, verifying the feasibility and predictability of an early loading protocol, based on currently available evidence.

SURFACE CHARACTERISTICS

MRCM surfaces undergo the same production subtractive methods (sandblasting and acid etching with HCl/H_2SO_4) as MR surfaces, but after these initial procedures, the hydrophilization technique is applied, in which implants are rinsed under N_2 protection and directly stored in an isotonic NaCl solution, protected again by N_2 rinsing[20] (Fig 2). This specific production technique is related to the maintenance of high free energy of TiO_2 surface, preventing adsorption of contaminants from the atmosphere, such as hydrocarbon and carbonates, thus producing a chemically clean and reactive surface.[19] This assumption is supported by XPS analyses in which reduced carbon concentration in MRCM surfaces was found (18.4 + 2.7%) in comparison to MR surfaces (37.3 + 3.4%). Furthermore, the hydrophilic property of MRCM surface is evidenced by 0° dynamic contact angle measurements with water (DCA = 0°), while the MR surface presents a DCA of 138°.[18-21]

IN VIVO STUDIES IN ANIMALS

The first study using animal models to investigate osseointegration of experimental implants with MRCM surface was

Figure 2. Implant stored in isotonic NaCl solution.

performed by Buser et al[18] in 2004.The authors evaluated bone apposition compared to conventional MR surface in the initial stages of bone repair. Histomorphometric assessment revealed that the MRCM surface had a BIC percentage statistically superior than the MR surface after two (49.30% *versus* 29.42%) and four weeks (81.91% *versus* 66.57%). After eight weeks, results were similar (78.47% *versus* 75.45%), with no statistically significant difference. It was concluded that the MRCM surface promotes greater bone apposition during the early stages of osseointegration.

In a study by Ferguson et al,[26] shear strength at the bone-implant interface was evaluated by implant removal torque testing of 162 implants placed in the jaws of 27 minipigs. Mean removal torque values for implants with MRCM surface were 1,485 Nm at two weeks, 1,709 Nm at four weeks and 1,345 Nm at eight weeks; and correspondingly, 1,231 Nm, 1,585 Nm, and 1,143 Nm for conventional implants with MR surface. It was concluded that, compared to the MR surface, the MRCM surface achieves better bone anchorage during the initial stages of osseointegration.

Two studies by Schwarz et al,[27,28] performed bilaterally in the upper and lower jaws of dogs, showed similar patterns of initial immunohistochemical reactions for angiogenesis and osteogenesis in response to the MRCM surface. A strong adhesion of blood clot to the hydrophilic surface was observed after one day of bone repair. After four days, the clot had been replaced by connective tissue with a dense network of vascular structures and bundles of collagen fibers arranged perpendicular to the implant surface. Furthermore, the first signs of osteocalcin synthesis were also observed on the fourth day. In contrast to the MRCM surface, osteocalcin synthesis near the MR surface was observed only on the seventh day. A higher percentage of BIC for the MRCM surface was observed after 7 and 14 days of bone repair. Histological and immunohistochemical results of these studies support the observation that the MRCM surface promotes greater bone apposition during the early stages of bone repair.

A study by Bornstein et al,[29] performed with dogs' mandibles, demonstrates significantly more bone apposition for the MRCM surface than the standard MR surface after two weeks of bone repair (Fig 3). This difference was no longer evident after four weeks. It was suggested that this increased bone apposition may allow further reduction of the healing period following implant placement for patients undergoing early loading protocols.

In comparison to implants with MR surface, implants with MRCM surface also demonstrated a greater potential for bone repair of dehiscence type and circumferential defects.[30,31,32]

HUMAN STUDIES

A clinical study conducted by Oats et al[33] assessed stability of implants with a MRCM surface and compared their outcomes to those of control implants with a standard MR surface, using resonance frequency analyses (RFA) exams. The implant stability quotient (ISQ) was assessed on a weekly basis over the first six weeks following implant placement. Implants with MRCM surface showed a higher stability quotient during the early stages of bone repair. A shift in implant stability from decreasing stability to increasing stability occurred after two weeks for the MRCM implants and after four weeks for the control implants. A clinical study by Bornstein et al[34] assessed the ISQ of implants with MRCM surface at the time of placement and after 3, 4, 7, 12 and 26 weeks. All implants were installed in the posterior region of the mandible. Of the 56 implants, 54 were functionally loaded after a healing period of three weeks. Two implants were considered "spinners" (rotated slightly during healing cap removal) at day 21 and left unloaded for an extended period. None of the implants failed to integrate and the ISQ values increased steadily throughout the follow-up period, exhibiting a mean of 74.33 at implant placement, and a mean of 83.82 after 26 weeks.

Prospective clinical studies by Bornstein et al[35] and Morton et al[36] assessed the success rate of implants with MRCM surface. They showed, respectively, that 96.4% and 95.6% of implants were suitable to be functionally loaded after 21 days of bone repair. In both studies, implants that rotated slightly during healing cap removal were considered to be "spinners" after the initial healing phase and were not loaded according to the early loading protocol. In the study by Bornstein et al,[35] all 56 implants, including the two "spinners", successfully integrated, presenting favorable clinical and radiographic conditions resulting in a 3-year survival and success rate of 100% (Figs 4, 5). In the study by Morton et al,[36] the overall success rate after a 2-year follow-up was 97.7%.

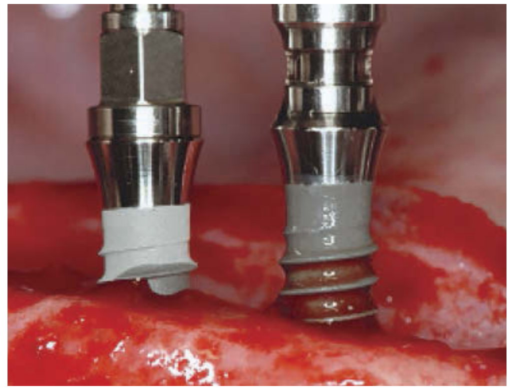

Figure 3. Dental implants with MR (left) and MRCM (right) surfaces placed in a dog's mandible. The hydrophilic characteristics of the MRCM surface are demonstrated by the ascending blood in the threads. (Source: Bornstein et al,[29] 2008).

Through a descriptive and qualitative histological analysis, Lang et al[37] conducted the first study evaluating the sequence of events during early osseointegration in human volunteers. A total of 49 implants, with an outer diameter of 2.8 mm and a height of 4.0 mm, and either a MR or MRCM surface were fully installed into

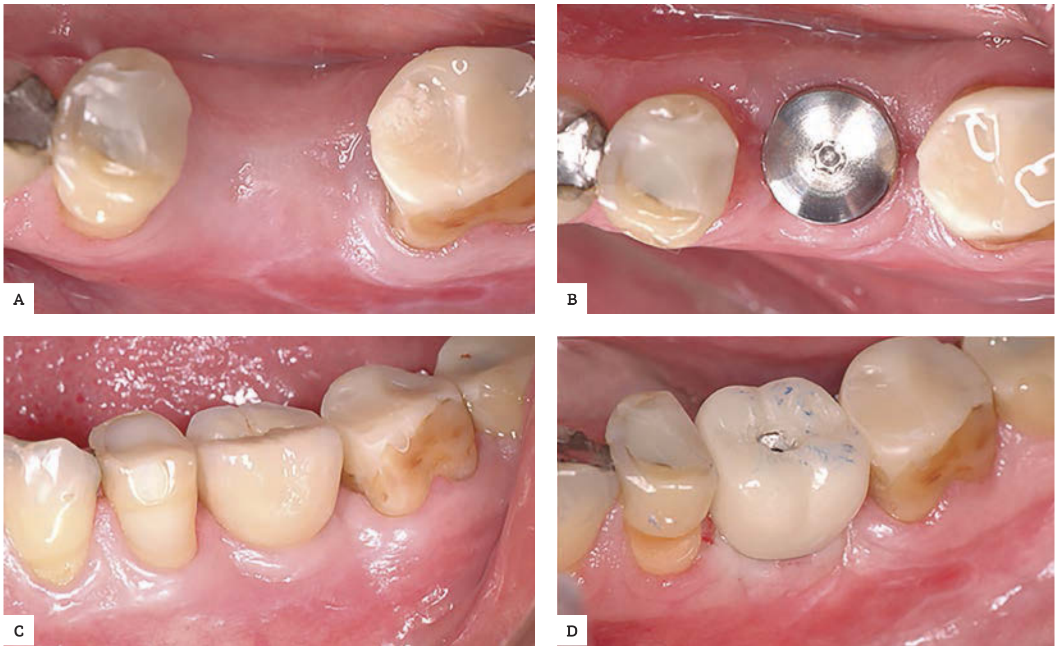

Figure 4. A) Single-tooth gap in mandibular left first molar region of a 63-year-old patient. **B**) After an uneventful healing period of three weeks, soft tissues show no signs of inflammation. **C**) A screw-retained provisional restoration on a titanium abutment was positioned and torqued to 20 Ncm, and occlusal contacts were adapted. **D**) Clinical condition of the final restoration after three years of follow-up demonstrates satisfying white and pink esthetics. (Source: Bornstein et al,[35] 2010).

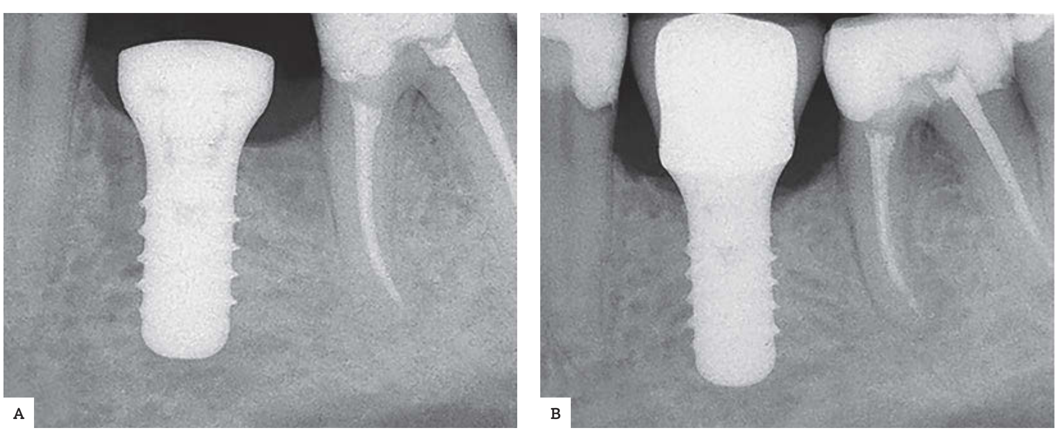

Figure 5. A) Immediate postoperative radiograph of the same patient as in Figure 4. **B**) Follow-up radiograph after three years in function reveals no signs of peri-implant radiolucency. (Source: Bornstein et al,[35] 2010).

bone in the retro-molar area of 28 healthy volunteers with no mandibular third molars present. All solid screw-shaped implants were fabricated in the same way as the commercially available Straumann® SLA and SLActive implants for human use (Institute Straumann AG, Basel, Switzerland). After healing periods of 7, 14, 28 and 42 days, the samples were retrieved with an explantation trephine bur with an inner diameter of 4.9 mm and a length of 5.2 mm (Figs 6, 7). Histological data showed no differences for any parameters assessed for either MR or the MRCM surfaces in the 7-day specimens. A BIC of approximately 6% was registered at this time and the majority of the space between the bony bed and the implant surface was filled with soft tissue constituting a primitive matrix. The 14-day specimens were diagnosed with an increased BIC from 6% to 12.2% and 14.8% on the MR and the MRCM surfaces, respectively. At the observation period of 28 days, statistically significant differences were found. While the BIC on the MR surface was 32.4%, it reached 48.3% on the MRCM surface. After 42 days of bone repair, the BIC had again increased and reached 62% for both surfaces. The authors concluded that bone resorptive and appositional events were similar for both surfaces; however, the degree of osseointegration after four weeks was superior for the MRCM surface compared to the MR surface.

Ivanovsky et al[38] evaluated the gene expression profile associated with early healing events during osseointegration of implants with MRCM surface in a human model. Implants installed in the posterior region of the mandible of volunteers were retrieved with an explantation trephine bur after 4, 7 and 14 days of bone repair. The tissue surrounding the implant was carefully harvested, total RNA was extracted and microarray analysis was carried out. In the 4-day samples, it was observed that genes associated with the regulation of key cytokines, namely TNF-α, IL-6 and IL-2, were over-expressed, as were genes associated with proliferation and/or activation of cells from the immunoinflammatory system, particularly lymphocytes and macrophages. In the 14-day samples, the gene expression analysis diagnosed a highly statistically significant overexpression of genes associated with skeletal development and ossification, as was the case with neurogenesis- and angiogenesis-associated genes. This study contributes to our understanding of the fundamental cellular and molecular mechanisms associated with bone repair, and also provides potential targets for strategies aimed at enhancing osseointegration.

In an *in vitro* study by Hamlet et al[39] the MRCM surface compared to the standard MR surface showed a gene expression profile with significant downregulation of the key pro-inflammatory cytokines TNF-α, IL-1α, IL-1β, and the chemokine Ccl-2. The authors concluded that the downregulation of the expression of pro-inflammatory cytokine genes in the early periods of osseointegration may modulate

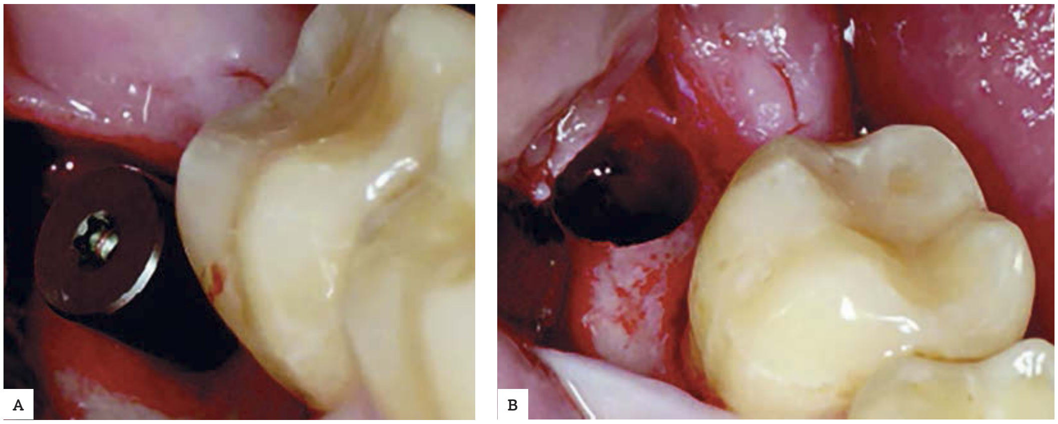

Figure 6. A) Guiding cylinder mounted on the implant. Diameter: 4.8 mm. The trephine bur is guided during explantation and produce a tissue collar of approximately 1 mm around the implant. **B**) Explantation wound following removal of the implant. A wound with a diameter of approximately 5 mm and a depth of approximately 5 mm is filled with blood clot and healed after suturing the flap over the site. (Source: Lang et al,[37] 2011).

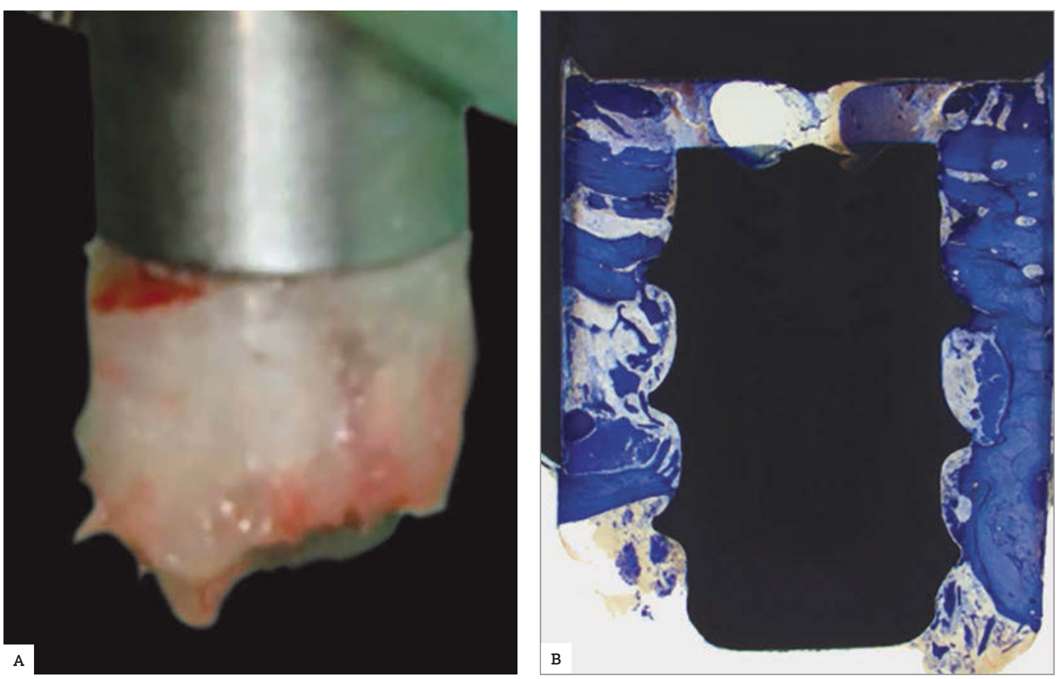

Figure 7. A) Trephine bur with intact tissue collar and screw-shaped implants after explantation. **B**) Processed histologic preparation of the entire specimen (trephine) including the implant illustrating the possibility of analyzing a collar of tissue of approximately 1 mm. (Source: Lang et al,[37] 2011).

inflammatory response and facilitate enhanced bone repair in the initial stages of osseointegration.

Another study[40] conducted with methods similar to the study by Ivanovsky et al[38] aimed to compare the gene expression profile of osseointegration associated with MR and a MRCM surfaces after 4, 7 and 14 days in human volunteers. Relevant differences started to be evident on the seventh day. In this observation period, osteogenesis- and angiogenesis-associated gene expression was upregulated on the MRCM surface. Osteogenesis and angiogenesis appeared to be regulated by BMP (bone morphogenetic protein) and VEGF (vascular endothelial growth factor) signaling, respectively. In terms of osteogenesis, BMP signaling appears to play a prominent role, with BMP4 and BMP2K both being upregulated in response to MRCM surface at day seven, with BMP subsequently upregulated at day 14 on the MR surface. This appears to be a delayed compensatory response. By day 14, VEGF signaling remained upregulated on the MRCM surface. The authors concluded that, when compared with MR, MRCM surface exerts a pro-osteogenic and pro-angiogenic influence on gene expression at day seven following implant placement, which may be responsible for the superior osseointegrative properties of this surface.

These findings are in agreement with *in vitro*[41,42] and *in vivo*[28] studies reporting a positive angiogenic response to the MRCM surface.

DISCUSSION

It has been observed that specific properties of biomedical device surfaces, such as topography, chemistry, load, and wettability, can have an impact on protein adsorption and hence the initial regulation of cell adhesion.[22,23,24] In titanium dental implants, for example, these surface properties have been studied and improved in recent years, aiming to increase rehabilitation predictability and improve osseointegration.[2,3]

Although there are *in vitro* animal and human studies reporting that modifications on MRCM implant surface induce a fast, secure and predictable response in bone apposition, it is not sufficiently clear whether this effect is caused due to roughness, surface chemistry or changes in both properties.[43-46] While some studies indicate that modifications introduced in MRCM surface production have no structural impact and do not promote differences in topography,[18,19,39,47] some studies[45,48] yielded different results regarding roughness parameters (Sa and Sdr) for MR and MRCM surfaces. Nanometric differences between the new surface and its predecessor were also reported.[45]

When the topography of an implant surface is changed, its surface is also chemically modified. These two properties are inseparable and play important roles in bone response to the implant surface.[43,46] In addition, it is assumed that the increased wettability of the titanium implant surface is advantageous during the initial period of bone apposition.[19,27,28,30,31,43] Osteoblasts grown on the hydrophilic MRCM surface exhibited a more differentiated phenotype characterized by increased alkaline phosphatase activity and osteocalcin, generating an osteogenic microenvironment through higher production of PGE2 and TGF-beta1.[19]

It is important to remember that the development of bone-implant interface does not depend on factors related to the characteristics of the implant and its surface, only. Mechanical loads, surgical protocol and variables inherent to the patient, such as bone quantity and quality, are factors that should also be taken in consideration.[43,49]

Compared to previous experiments with animals, the rate of bone apposition was significantly slower in human models.[37] In the study by Abrahamsson et al,[10] performed with the jaws of Labrador dogs, the percentage of BIC for the MR surface at week four following implant placement was 65%. A similar result of 62% was achieved in human models with an observation period of six weeks.[37] The study by Buser et al,[18] performed in minipigs, presented a BIC percentage of 49.30% at week two following implant placement for MRCM surfaces. A similar result of 48.3% was achieved after four weeks of bone repair in human models.[37]

Thus, although the sequence of initial biological events related to bone healing in humans corresponds to that observed in animal models, the extrapolation of animal data on osseointegration to human clinical situation has to be interpreted with care, because the rate of osseointegration was substantially slower in humans.[37]

The different times for loading dental implants have been somewhat confusing in the past; however, in accordance with recently published reports, the early loading protocol is adopted when prosthesis is connected to the dental implants between 1 and 8 weeks following implant placement.[50,51]

Prospective clinical studies with up to three years of follow-up[35,36] demonstrated favorable results for implants with a MRCM surface when loaded after 21 days of bone repair using an early loading protocol under well-defined clinical conditions without bone defects. Thus, implants with a MRCM surface loaded after three weeks of bone repair achieved a similar outcome to that reported for implants with a standard MR surface using an early loading protocol after 6 to 8 weeks.

CONCLUSION

Within the limitations of this MRCM surface study, it is suggested that high surface energy and increased wettability positively influence bone formation in the initial periods of bone repair. Based on medium-term results, early loading in full occlusion of titanium implants with a MRCM surface after three weeks of healing seems to be a valuable treatment option for the clinician, and one that can be recommended under clearly defined clinical conditions for standard sites without bone defects. Nevertheless, further clinical studies involving larger sample sizes and longer follow-ups, also including anterior locations, are required to validate this treatment concept for implants in healed sites.

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