*Article*

# Bone-To-Implant Contact At 4- And 6-Week Healing Stages in Implants Having Either Machined, SLA Medium Roughness or Nanostructured Calcium-Incorporated Surface.

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**Abstract:**

**Background:** Implant surface topography is a key element in achieving osseointegration. Nanostructured surfaces have shown promising results in accelerating and improving bone healing around dental implants. The main objective of the present clinical and histological study is to compare, at 4 and 6 weeks, (w) bone-to-implant contact in implants having either machined surface (MAC), SLA medium roughness surface or a Nanostructured Calcium-Incorporated surface (XPEED®). **Methods:** 35 mini-implants with 3 different surface treatments (XPEED® (n=16) – SLA (n=13) – Machined (n=6), were placed in the posterior maxilla of 11 patients then, retrieved at either 4 or 6w in a randomized split-mouth study design. **Results:** The BIC rate measured at 4 and 6w respectively, was: 16.8 % (±5.0) and 29.0 % (±3.1) for MAC surface; 18.5 % (±2.3) and 33.7 % (±3.3) for SLA surface; 22.4 % (±1.3) and 38.6 % (±3.2) for XPEED® surface. In all types of investigated surfaces, the time factor appeared to significantly increase the BIC rate ($p < .05$). XPEED® surface showed a significantly higher values when compared to both SLA and MAC values at 4w ($p < .05$). Also, at 6w, both roughened surfaces (SLA and XPEED® ) showed significantly higher values ($p < .05$) than turned surface (MAC). **Conclusion:** Nanostructured Calcium titanate coating is able to enhance bone deposition around implants at early healing stages.

**Keywords:** Nano surfaces; Early bone formation; Implant surface; histomorphometry; osseointegration

## 1. Introduction

The first titanium dental implant placed by Brånemark in a human volunteer in 1965 had a cylindrical shape and a machined surface [1]. Since that time, the main focus of

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clinicians and researchers was to obtain a better quality of osseointegration, the functional bone formation in direct contact with the implant [2]. Owing to these improvements, the modern-day titanium implant offers much higher success rates and substantially faster function than its original predecessor [3]. After implantation, direct bone apposition onto fixture is critical for the successful loading of dental implants [4]. Surface treatment plays a major role in this biological integration [5]. Since the early phases of implantology, important alterations in the commercially available implants have been made, many of which involved different methods of surface roughening [6]. However, the "optimal" surface type is yet to be determined, quality and speed of osseointegration being the main criteria [7].To improve the favorable biologic response to titanium and decrease healing time for osseointegration, different implant surface modifications have been introduced, treatment methods have been applied to improve the surface topography and properties, such as sandblasting, acid etching, anodization, discrete calcium-phosphate crystal deposition, coatings with biologic molecules, and chemical modification [7-9]. These surface topography modifications have yielded significant results and the great majority of published articles have reported increased bone fixation and increased bone-to-implant contact for rougher implant surfaces compared to polished, milled, or turned surfaces [9-11]. Mechanical treatments of implant surface, such as media blasting (BM) and titanium plasma spraying (TPS), have been showed to increase roughness, therefore yielding higher contact surface with surrounding bone [12]. However, these techniques have shown limitations due to transmission of residue particles, such as TPS coating and non-resorbable blast media ($TiO_2$ or $Al_2O_3$) into surrounding bone and tissues, which might interfere with the osseointegration process [13]. Also, this type of surface treatment was shown to increase the risk of infection and periimplantitis [14]. Medium roughness surfaces were introduced to enhance bone healing around implants while reducing bacterial contamination and periimplantitis [15]. Therefore, sandblasting followed by Chemical surface treatment such as Acid-etching is another method for roughening titanium dental implants; it produces micro pits on titanium surfaces and has been shown to greatly enhance osseointegration [8,13,16,17]. Sandblasting with Large grit corundum followed by Acid etching with Sulfuric and Hydrochloric acid surfaces (SLA) were introduced and seemed to yield promising results with higher success rates and faster loading time [17-19]. However, while implant microtopography seemed to affect osseointegration at the cellular level, nanotopography is thought to influence cell-implant interactions at both cellular and protein level, making nano-scale implant surface characteristics an increasingly growing area of interest for biomedical engineers [20-22]. More recently, and in order to improve osseointegration and reduce healing time, Titanium implants with nanostructured calcium-incorporated surface have been introduced [21,23]. Many methods of nanometer alterations to implant surfaces have been documented such as $TiO_2$ blasting followed by hydrofluoric acid treatment [24], Ion beam assisted deposition [25] and calcium phosphate nanoparticle modification by discrete CaP crystalline deposition [26]. By incorporating Ca ions to an SLA surface (XPEED®), an animal study showed significant improvement of the overall bone-to-implant contact and removal torque after 6 weeks, in comparison to control HA-blasted titanium implants in rabbits [21]. The clinical efficiency of the nanostructured calcium-incorporated surface was also discussed by the authors in a clinical study attempting primary stability optimization by using fixtures with different thread depth depending on bone density [27]. Weekly ISQ follow-up showed little to no drop in ISQ values at 3 weeks, especially for implants placed in low density bone. The authors attributed this phenomenon to the biological effect of this surface in full expression leading to early bone deposition, particularly in cancellous bone where knife edge threads cut into the trabeculae, causing minimal osteo-compression. Also, a study monitoring pre-osteoblastic cell behavior on machined (MAC) or grit-blasted Ti surfaces with and without Ca incorporation showed that Ca incorporation may have a favorable effect on osseointegration of micro-structured Ti implants by promoting

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osteoblast proliferation and differentiation during the early healing phases after implantation [28]. Many clinical and radiographic evaluation methods have been developed for objective assessment of osseointegration (Resonance Frequency Analysis, Reverse Torque Analysis) [29-31]. However, one of the most objective techniques to evaluate implant surface performance is still the histomorphometric measurement and calculation of Bone-Implant contact (BIC) [32-35]. This technique has been successfully used in many studies to monitor, visualize, and assess bone apposition on implant surface [36-38]. The main objective of the present study was to compare, at 4 and 6 weeks, BIC in implants having either machined surface, SLA medium roughness surface or a Nanostructured Calcium-Incorporated surface (XPEED®). The null hypothesis (*H0*) under test considered no statistically significant differences in BIC rate for SLA, MAC and XPEED® surfaces after 4 and 6 weeks of healing time.

## 2. Results

### 2.1. *Histological*

A central section of each of the samples was analyzed and measured. However, and for a more detailed description, two specimens for each group were reported.
Samples from the same group (MAC, SLA or XPEED) at different times (4 and 6 weeks) were reported in a sequential comparison. 4-week MAC samples (Fig. 1)

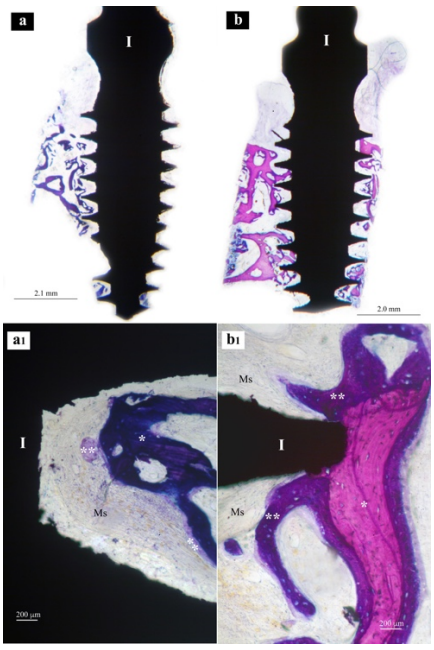


*FIG. 1 Central sections of two implants of the MAC group after 4 weeks of healing. In* ***a*** *and* ***b,*** *original magnifications (x12), the implant bodies (I) appear to be partially surrounded by bone tissue in the threaded regions. In* ***a1*** *and* ***b1****, original magnifications (x200), implant threads (I) appear to be in an early phase of osseointegration. Ms, marrow spaces; *, native bone; **, newly formed bone.*

showed bone growth mainly related to distance osteogenesis. Osteoid tissue was mainly present in contact with native bone and only in some small area in direct contact with implant surface. 6-week MAC samples (Fig. 2)

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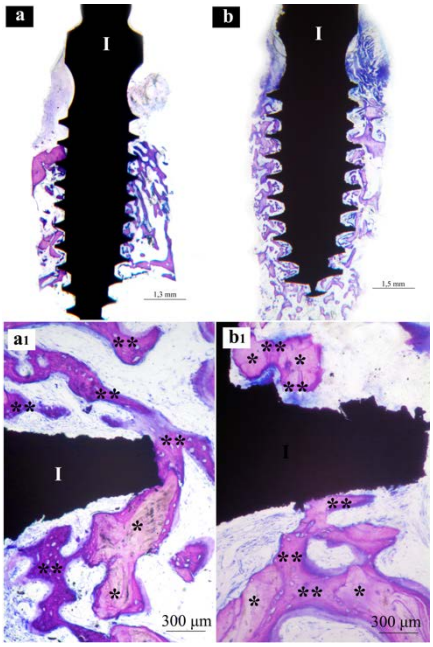


*FIG. 2 Central sections of two implants of the MAC group after 6 weeks of healing. In **a** and **b**, original magnifications (x12), the implant bodies (I) appear to be, in the threaded regions, surrounded by much more bone tissue than in FIG. 1. In **a1** and **b1**, original magnifications (x200), the implants threads (I) appear to be in a more advanced phase of osseointegration. *, native bone; **, newly formed bone.*

showed the same histological findings of Fig. 1 with a distance osteogenesis bone growth modality associated to an evident increase of newly formed bone along the implant surface. 4-week SLA samples (Fig. 3)

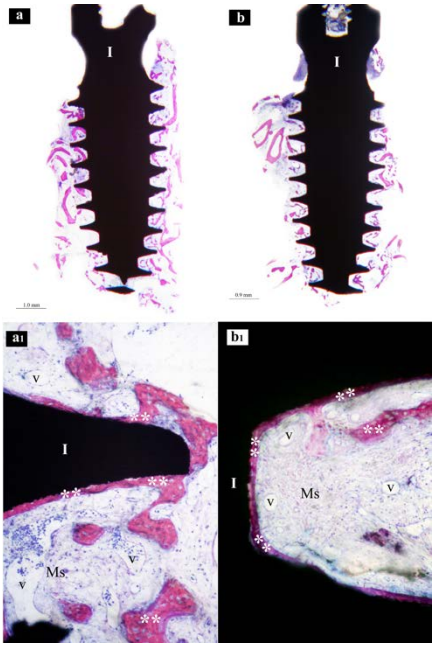


*FIG. 3 Central sections of two implants of the SLA group after 4 weeks of healing. In **a** and **b**, original magnifications (x12), the implant bodies (I), mainly in the threaded regions, appear*

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*to be partially surrounded by mineralized bone. In **a1,** original magnifications (x200), the implants threads (I) appear to be surrounded by newly formed bone (**), while in the marrow spaces (Ms) several vessels (v) in section are visible, In **b1**, original magnifications (x200), the implants (I) in the inter-threads space newly formed bone (**) appear to be formed in contact with the implant surface, while in the marrow spaces (Ms) several vessels (v) are visible.*

showed bone growth with contact osteogenesis modality. The newly formed bone was mainly present in direct contact with implant surface. In almost all the samples, many vessels were noted in the tissues facing the implant interthread areas. 6-week SLA samples (Fig. 4)

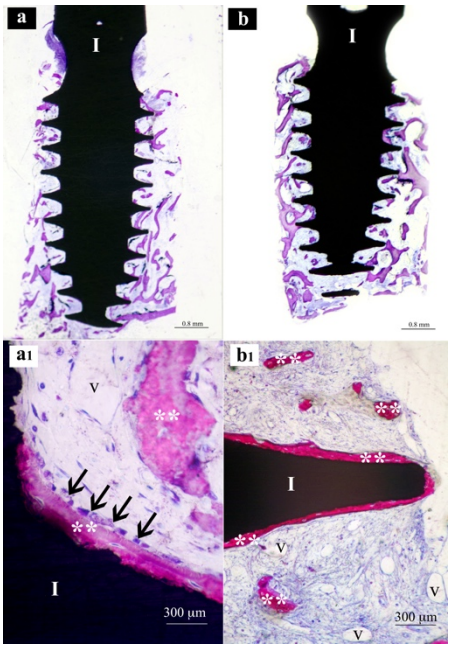


*FIG. 4 Central sections of two implants of the SLA group after 6 weeks of healing. In **a** and **b,** original magnifications (x12), the implant bodies (I) appear to be, in the threaded regions, surrounded by much more bone tissue than in FIG. 3. In **a1** and **b1**, original magnifications (x200), the implants threads (I) appear to be in a more advanced phase of osseointegration. *, native bone; **, newly formed bone.*

showed a histological image resembling that of Fig. 3 with diffuse contact osteogenesis along implant surface and an increased amount of newly formed bone. 4-week XPEED samples (Fig. 5)

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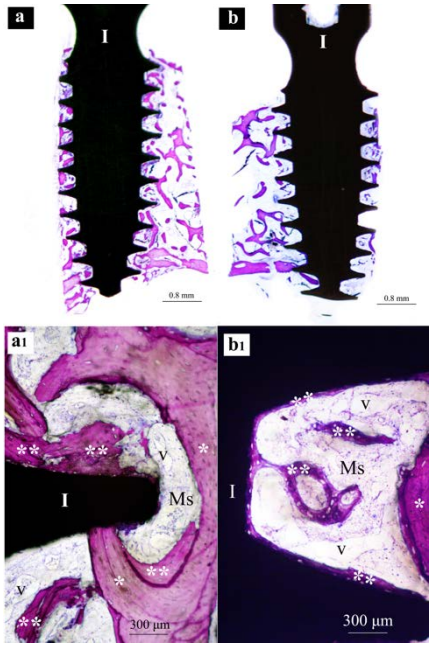


*FIG. 5 Central sections of two implants of the XPEED group after 4 weeks of healing. In **a** and **b,** original magnifications (x12), the implant bodies (I), along the entire threaded regions, appear to be surrounded by mineralized bone. In **a1,** original magnifications (x200), the implants threads (I) appear to be in contact with both newly formed bone (**) and native bone trabeculae (*), while in the marrow spaces (Ms) enlarged vessels (v) are present near the implant surface, In **b1**, original magnifications (x200), the implants (I) in the inter-threads space a thin layer of newly formed bone (**) appear to be in contact with the implant surface forming struts of bone toward area of native bone (*). In the marrow spaces (Ms) several enlarged vessels (v) are visible.*

showed an advanced degree of osseointegration, most of the implant surfaces were covered by a layer of newly formed bone. In many implant interthread spaces, thin bone trabeculae in formation were visible, starting from the newly formed bone in direct contact of the implant surface. In the marrow spaces, many vessels were also present. 6-week XPEED samples (Fig. 6)

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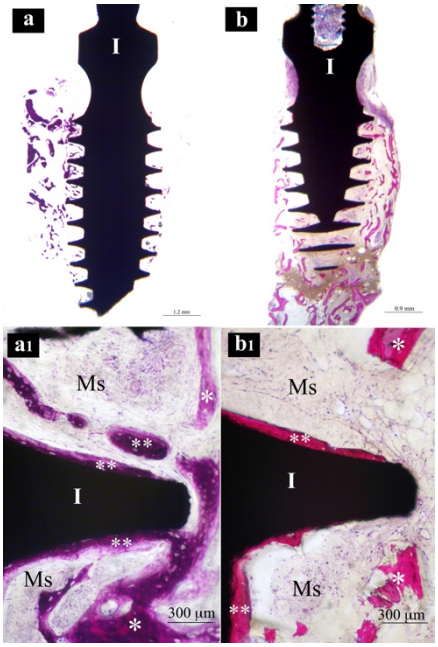


*FIG. 6 Central sections of two implants of the XPEED group after 6 weeks of healing. In **a** and **b,** original magnifications (x12), the implant bodies (I), along the entire threaded regions, appear to be surrounded by an increase amount of mineralized bone comparing to FIG. 5. In **a1,** original magnifications (x200), the implants threads (I) appear to be in contact with a layer of newly formed bone (**) covered by a rim of osteoblasts in active secretion (black arrows) near enlarged vessels (v). In **b1**, original magnifications (x2000, the implants thread (I) appear to be completely harvested by thin layer of newly formed bone (**). Several vessels (v) are visible.*

presented a histological aspect resembling that of Fig. 5 with diffuse contact osteogenesis along the implant surface and an increased amount of newly formed bone.

*2.1.1. Histomorphometry*

The data collected in this study were evaluated for normal distribution using both the normality test ($p$ = 0.528) and the test of equal variances ($p$ = 0. 123), demonstrating a normal distribution of the values (Table 1).

**Table 1- Summary of the statistical results for two-way ANOVA**

| | | | | | |
|---|---|---|---|---|---|
| ***Normality Test:*** | | *Passed* | *(p = 0,528)* | | |
| ***Equal Variance Test:*** | | *Passed* | *(p = 0,123)* | | |
| ***Source of Variation*** | **DF** | **SS** | **MS** | **F** | ***p*** |
| *SURFACES* | 2 | 290,982 | 145,491 | 17,956 | <0,001 |
| *TIME* | 1 | 1528,390 | 1528,390 | 188,626 | <0,001 |
| *SURFACES x TIME* | 2 | 17,050 | 8,525 | 1,052 | 0,362 |
| *Residual* | 29 | 234,980 | 8,103 | | |
| *Total* | 34 | 2481,227 | 72,977 | | |
| *Power of performed test with alpha = 0,0500:* | | *for SURFACES : 1,000* | | | |
| *Power of performed test with alpha = 0,0500:* | | *for TIME : 1,000* | | | |

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The two-way ANOVA test (Tables 1 and 2)

**Table 2 - Summary of Least square means for groups that are adjusted for means of other factors in the model**

| *Least square means for SURFACES* | | |
|---|---|---|
| ***Group*** | **Mean** | **SEM** |
| *SLA* | 26,131 | 0,811 |
| *XPEED®* | 30,514 | 0,717 |
| *MACHINED* | 22,933 | 1,162 |
| ***Least square means for TIME*** | | |
| ***Group*** | **Mean** | **SEM** |
| *4W* | 19,254 | 0,716 |
| *6W* | 33,798 | 0,780 |
| ***Least square means for SURFACES x TIME*** | | |
| ***Group*** | **Mean** | **SEM** |
| *SLA x 4W* | 18,562 | 1,006 |
| *SLA x 6W* | 33,700 | 1,273 |
| *XPEED® x 4W* | 22,400 | 0,949 |
| *XPEED® x 6W* | 38,629 | 1,076 |
| *MAC x 4W* | 16,800 | 1,643 |
| *MAC x 6W* | 29,067 | 1,643 |

showed a greater difference in the mean values among the investigated types of surfaces than would be expected by chance, after allowing for effects of differences in time, there was a statistically significant difference ($p < 0.001$) among the groups. The difference in the mean values among the different levels of time was greater than would be expected by chance after allowing for effects of differences in surfaces, the difference was statistically significant ($p < 0.001$). The effect of different types of surfaces does not depend on what level of time was present. There was not a statistically significant interaction between surfaces and time. ($p = 0,362$). For the implants with MAC surface, the Pairwise Multiple Comparison Procedures using the Holm-Sidak method (Table 3)

**Table 3 summary of all Pairwise Multiple Comparison Procedures (Holm-Sidak method): Overall significance level = 0,05**

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| *Comparison* | Diff of Means | t | Unadjusted P | Critical Level | Significant? |
|---|---|---|---|---|---|
| *Comparisons for factor:* ***SURFACES*** | | | | | |
| *XPEED® vs. MAC* | 7,581 | 5,551 | 0,00000549 | 0,017 | Yes |
| *XPEED® vs. SLA* | 4,383 | 4,047 | 0,000352 | 0,025 | Yes |
| *SLA vs. MAC* | 3,198 | 2,256 | 0,0318 | 0,050 | Yes |
| *Comparisons for factor:* ***TIME*** | | | | | |
| *6W vs. 4W* | 14,544 | 13,734 | 3,191E-014 | 0,050 | Yes |
| *Comparisons for factor:* ***TIME within SLA*** | | | | | |
| *6W vs. 4W* | 15,138 | 9,328 | 0,000 | 0,050 | Yes |
| *Comparisons for factor:* ***TIME within XPEED®*** | | | | | |
| *6W vs. 4W* | 16,229 | 11,313 | 0,000 | 0,050 | Yes |
| *Comparisons for factor:* ***TIME within MAC*** | | | | | |
| *6W vs. 4W* | 12,267 | 5,278 | 0,000 | 0,050 | Yes |
| *Comparisons for factor:* ***SURFACES within 4W*** | | | | | |
| *XPEED® vs. MAC* | 5,600 | 2,951 | 0,006 | 0,017 | Yes |
| *XPEED® vs. SLA* | 3,837 | 2,774 | 0,010 | 0,025 | Yes |
| *SLA vs. MAC* | 1,763 | 0,915 | 0,368 | 0,050 | No |
| *Comparisons for factor:* ***SURFACES within 6W*** | | | | | |
| *XPEED® vs. MAC* | 9,562 | 4,868 | 0,000 | 0,017 | Yes |
| *XPEED® vs. SLA* | 4,929 | 2,957 | 0,006 | 0,025 | Yes |
| *SLA vs. MAC* | 4,633 | 2,229 | 0,034 | 0,050 | Yes |

showed, a BIC rate (±SD) of 16.8 (±5.0) after 4 weeks of healing (Fig. 1), while the BIC rate on the same group of implants increased to 29.0 (±3.1) in the 6-week specimens (Fig. 2). The group of implants with SLA surface showed a BIC rate of 18.5 (±2.3) at 4 weeks (Fig. 3) and an increase to 33.7 (±3.3) at 6 weeks (Fig.4). The test group with XPEED® surface presented rates of 22.4(±1.3) and 38.6 (±3.2) at weeks 4 (Fig. 5) and 6 (Fig. 6) respectively. For all types of investigated surfaces, the time factor appeared to increase BIC rate from 19.2 % at 4 weeks to 33.7 % at 6 weeks. Also, surface type seemed to influence BIC rate with 22.9 % for the MAC surface, 26.1% for SLA and 30.5 % for XPEED®.

### *3. Discussion*

Surface microtopography plays a major role in the speed and quality of osseointegration, therefore influencing the clinical behavior of dental implants [7]. This will mainly affect loading protocols but will also alter implant success rate, especially in soft bone [26].

The focus of the current study was to evaluate a nanostructured calcium-incorporated implant surface and histologically compare its performance to that of SLA and MAC surface implants with an identical geometry, placed in similar conditions in human subjects, then retrieved with a trephine drill at either 4 or 6 weeks. All retrieved implants were placed in the posterior edentulous maxilla. Many studies showed the reduced bone quality in that region [39-41,68] that may result in reduced primary stability and delayed osseointegration [42], making implant rehabilitation more delicate and less reliable. It was shown that implant failure can be significantly increased when placed in the posterior soft

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bone, and that placing implants in soft bone may affect the results, therefore affecting future loading protocols [43]. Comparing implants with different surfaces and otherwise identical in this type of bone may provide a more objective assessment of the behavior of different surfaces under such clinical conditions.

In this study, implants were retrieved at either 4 or 6 weeks. The rationale behind this decision was to be able to assess surface behavior at these 2 early healing phases. Understanding implant osseointegration at these time points may help ensure safer and more objective decisions-making vis-à-vis early loading protocols. While the first implants with machined surfaces were placed and loaded at 4- to 6-month intervals [1], more recent studies on modern implant surfaces show very high success rates at a fraction of that time [44-46]. If the 6-week loading time point is considered the modern-day standard for implants with adequate surfaces [16,47], a 4-week loading protocol is still exclusive to implants presenting special surface topographies.

Numerous studies showed the advantage of SLActive surface vs SLA and the possibility of loading protocol decisions at either 4 or 6 weeks [44,48,49]. Other studies showed how surface affected ISQ values at different time points. Oates et al., in a study monitoring early ISQ variations for SLActive (test) and SLA (control) surface implants, showed a shorter period of mean ISQ drop for the tested implants (lowest at 2 weeks) compared to control (lowest at 4 weeks) ($p$ <0.0001), highlighting the enhanced osseointegration for the chemically modified surface [50].

In a previous study by the same authors monitoring ISQ at early healing phases for Xpeed® surface, results showed a virtual absence of ISQ decrease in implants inserted in soft bone, which was attributed not only to implant geometry but also to the surface effect leading to early bone deposition [26].

To understand bone healing around implants and the effect of implant surface, the present study compared BIC on implants with the same geometry retrieved at either 4 or 6 weeks. Available long-term osseointegration studies in humans are commonly restricted to a small number of cases at a time and are mostly retrospective since they are usually performed on implants retrieved for reasons such as connection fracture [51,52] or at the end of an orthodontic treatment [53]. There is a significant disparity of inclusion/exclusion criteria.

In a histologic and histomorphometric evaluation of two types of retrieved human titanium implants, a solid-screw titanium plasma-sprayed (TPS) implant removed 5 years after implantation due to implant/crown connection fracture and a sandblasted acid-etched titanium implant (SLA) removed after being used as anchorage for orthodontic treatment, the measured percentage of bone-implant contact around the SLA implant (76.6 ± 11.1) was significantly higher ($p$ < .05) than that around the TPS implant (46.0 ± 5.5) [53].

In another publication, three functionally loaded, well-integrated nanotextured dental implants, were retrieved from the maxilla of a patient after 47 months of loading due to mechanical (not biological) failure. The results showed remodeled Haversian bone with BIC over 80% [54]. Also, in a case report on 3 dental implants with a sandblasted and acid-etched surface, retrieved after 45 months of function, BIC rates of 80.3% were reported [55]. Other authors conducted a study on 17 osseointegrated human dental implants with different surface types retrieved after a loading period of 4 to 20 years, found BIC values ranging from 32% to 83% [52]. Albrektsson et al.[56], in a histological analysis of more than 700 osseointegrated implants of various types, retrieved 6 months to 20 years after placement, observed BIC of > 50% for maxillary implants compared to > 75% for mandibular implants.

All the aforementioned publications have measured and compared BIC values for implants between from 6 months to 20 years after placement. Additionally, implants were mostly retrieved for mechanical failure and many variables pertaining to geometry, surface and placement conditions/sites are present. It is therefore difficult to draw objective and relevant conclusions from these studies.

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To the authors' knowledge, few publications have described histomorphometric BIC results for retrieved implants in humans, in a split-mouth, posterior maxilla study design, comparing two or more implant surfaces, using fixtures with identical geometries retrieved at early healing phases.

A similar split-mouth human study on mini-implants retrieved at early healing stages was performed by Lang et al. [57]. However, the fixtures were placed in the mandibular third molar region, and the purpose was to compare regular SLA with modified SLA surfaces.

Three different surfaces were tested in the present study: MAC, SLA and XPEED®. MAC surfaces have shown limited performance at early healing phases and elevated failure rates in soft bone [58,59] this surface is considered in the present work as a negative control. SLA surface have shown enhanced results over machined and seem to yield promising results with higher success rates and faster loading time even in soft bone [17,18,60]. SLA was used as positive control. Recently, an animal study showed that by incorporating Ca ions at a nanoscale to SLA surface (XPEED) resulted in higher BIC at early stages of healing [7,25]. This surface, considered test, was compared to both SLA and MAC surfaces in the present study in order to histologically explore the advantage of Ca incorporation at early healing stages.

When comparing BIC difference between week 4 and 6, all implant surfaces showed a significant higher BIC at 6 weeks.

These results are coherent with the dynamics of bone healing around implant surfaces, since this phase is marked by woven bone formation and maturation, which is then gradually remodeled and replaced by lamellar bone [61]. Osseointegration is the consequence of a cascade of molecular and cellular events that occur after preparation of an implant bed and placement of a dental implant. It leads to the apposition of newly formed bone directly onto the implant surface. The pattern of bone formation and osseointegration seems to be similar to that observed in bone fracture healing [62]. Furthermore, the behavior of cells of osteogenic lineage is affected by microtopography and nanotopography of an implant surface [63].

In the aforementioned mandibular split-mouth study, implants were retrieved at either 7, 14, 28 or 42 days after implantation. When comparing their 4- and 6-week BIC values to our own, their numbers were higher [57]. This can be attributed to the fact that implants placed in mostly cortical mandibular bone will most probably have higher BIC rates than those inserted into posterior maxillary sites.

The comparison between the different types of surfaces after 4 weeks of healing showed a BIC average difference of 5.6% between XPEED® and MAC. The result showed that the XPEED surface was significantly more osseointegrated than the MAC surface ($p < .05$). Analyzing the effect of Ca incorporation by the comparison of SLA vs XPEED, there was also a significant increase in osseointegration of 3.9% ($p < .05$). The same comparison between the different surfaces at 6 weeks of healing showed that average BIC difference between XPEED® and MAC increased by 9.6% ($p < .05$). Also, after 6 weeks of healing, the XPEED® group showed a significant increase in osseointegration of 4.9% ($p < .05$).

Many studies have experimented on nanostructured implant surfaces and reached similar conclusions, with results showing that this kind of surface treatment enhances osteoblast adhesion, and therefore function, leading to better treatment outcomes [20].

However, when comparing the BIC rate of SLA versus MAC surfaces at 4 weeks, the difference in mean BIC between SLA and MAC (1.7%) appeared to be not statistically significant different ($p > .05$) so, the null hypothesis was confirmed. These findings may not be in line with most of the available literature comparing these two types of surface, since implants with SLA treatment became increasingly accepted as one of the most effective types of implant surface [46,64-66] and MAC surfaces are considered obsolete. In fact, many studies have shown that SLA results in a high degree of bone-to-implant contact

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and high removal torque values, as well as high osteoblasts differentiation, highlighting its osteoconductive properties, leading to enhanced bone formation and the possibility of reduced clinical healing times [18]. That being said, these values may still be relevant since the aforementioned BIC values are those of 4-week biopsies retrieved from human posterior maxillae. Most publications comparing BIC for these two surfaces are either animal studies [66,67], or follow different retrieval sites, like the study by Lang et al. [57], where BIC values are higher than the present ones, but biopsies were all retrieved from posterior mandibles where bone density is significantly greater and is very likely to yield better results.

Overall, when considering the amount of osseointegration over time, BIC rate increase was in average (± SEM) of 14.5% (0.7). When the results are split into 4- and 6-week categories and for each implant surface, MAC showed a mean increase (± SEM) of 12.2% (1.6); SLA 15.2% (1.1) and XPEED® 16.2 % (0.9). All differences were statistically significant ($p$<.05). Otherwise, the interaction between surfaces and time appeared to be not statistically significant ($p$ = 0.36). It is our opinion that this finding was mainly due to the short time interval considered in the present study and the subsequent intragroup variability of mineralization of the newly formed bone. This topic will be best addressed in a future paper on the same group of specimens which were treated with bone labeling technique to determine the mineral apposition rate on label (MARL).

From these results, it can be extrapolated that Ca incorporation may indeed enhance surface performance at early healing stages (both 4 and 6 weeks of healing) compared to SLA and MAC.

This was discussed in a Scanning Electron Microscope evaluation of the bone/implant interface of an immediately loaded implant with XPEED® surface, retrieved 1 month after function due to a traumatic injury [68]; the authors found that the implant was entirely surrounded by trabecular bone anchored to the metal surface, which is in line with our results.

Another publication also reached similar conclusions in an animal study on Ca-incorporated implants retrieved from rabbit tibiae and stated that the use of nanostructured, Ca- coated surfaces may have synergic effects on osseointegration of blasted Ti implants due to their surface properties and biological activity [19].

Also, these observations were corroborated with clinical results from our previous study, where implants with the same type of surface placed in type 4 bone showed no decrease in ISQ values at 3- and 4-week measurements, supporting the histological evidence of this type of surface's enhanced efficiency in soft bone scenarios [26].

This would also explain the non-significant difference in values for MAC and SLA, because a 4-week interval is apparently too early for surfaces without Ca incorporation to have elevated BIC, even for SLA.

Relatively to the time factor (Fig. 7),

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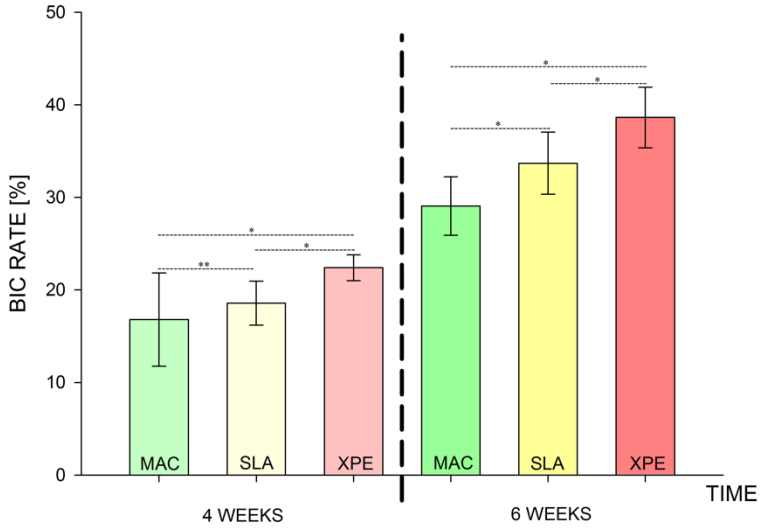


*Fig. 7 graph reporting the BIC rate weighted for time. ( * statistically significant (p < .05); **not statistically significant (p > .05).*

all implants showed a statistically significant difference between 4 and 6 weeks regardless of surface type.

After 6 weeks, comparisons showed that the time factor and surface type were always significant, particularly for XPEED® surfaces which yielded 4-week BIC levels comparable to those of the MAC surface at 6 weeks. XPEED® surfaces showed accelerated osseointegration by reaching high BIC levels within the first 4 weeks.

When compared to MAC implants, both XPEED® and SLA surfaces seemed to achieve higher BIC at 4 and 6 weeks. These findings match those of many other studies and were expected. However, XPEED® surface also had significantly higher rate of bone apposition compared to SLA at both intervals at 4 weeks (XPEED®:22.4% – SLA:18.5%) and 6 weeks (XPEED®: 38.6 %– SLA: 33.7%).

Mangano et al. [68], in the same study discussed previously, on one nanostructured calcium-incorporated surface implant retrieved 1 month after placement following an immediate function protocol, found that fixture surface was mostly covered by newly formed bone tissue, filling the spaces between threads and even growing beyond them at certain points.

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## *4. Materials and Methods*

### *4.1. Study design*

This was a split-mouth randomized case/double-control histological human study. Patients with bilateral edentulous posterior maxilla and requiring implant therapy for fixed prosthetic rehabilitation were eligible for entering this study, provided that they fulfilled the following inclusion criteria:

- Height of the residual bone crest in the programmed implant site ≥ 9 mm and thick ness ≥ 7mm.
- Availability, in each sector, of sufficient mesio-distal space allowing placement of 2 standard-sized implants and at least 2 mini-implants (3.5x8.5mm) for retrieval.
- Healed bone crest (≥ 3 months elapsed after extraction or tooth loss).
- Age > 18 years.
- Ability to examine and fully understand the study protocol.

The following exclusion criteria were adopted:

- Myocardial infarction within the past 6 months.
- Poorly controlled diabetes (HBA1c > 7.5%).
- Coagulation disorders.
- Radiotherapy to the head/neck area within the past two years.
- Present or past treatment with intravenous bisphosphonates.
- Immunocompromised patients.
- Psychological or psychiatric problems.
- Alcohol or drug abuse.
- Poor oral hygiene and motivation (full mouth plaque score > 30% and/or full mouth bleeding score > 20%).
- Uncontrolled periodontal disease.

All procedures were performed in accordance with the recommendations of the Declaration of Helsinki for investigations with human subjects, as revised in Fortaleza [38]. All patients were thoroughly informed about the procedures and signed an informed consent form. The study was approved by the Ethics Committee at the Saint Joseph University of Beirut, Lebanon (USJ-2018-56). Preoperative evaluation included clinical examination of the edentulous ridges and natural dentition, as well as a cone beam computed tomography (CBCT) of the relevant sector. Patients underwent a prosthodontic evaluation for treatment planning and all surgeries were performed by the same experienced surgeon (C.M.) at the Oral Surgery Department, Faculty of Dental Medicine, Saint Joseph University (Beirut, Lebanon) between February 2019 and July 2021.

### *4.2. Surgical Procedure*

Patients were asked to rinse with chlorhexidine digluconate solution (0.2%) for 1 min approximately 10 min before surgery. Under local anesthesia, a crestal incision and full-thickness flap elevation were performed, followed by standard implant preparation and placement of 2 regular implants per sector (AnyRidge, MegaGen, Gyeongbuk, South Korea). Then, each sector underwent drilling procedures with a 2.5 mm diameter final drill for the placement of 2 additional 3.5x8.5 mm mini-implants placed either between the 2 regular implants and/or distally to the most distal implant.

Mini-implants had either the XPEED® (MegaGen, Gyeongbuk, South Korea) tested surface (S1) or the control SLA surface. Each sector received at least one form each group; the first implant placed was chosen randomly, and whichever group it belonged to, the

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second was chosen from the other. For the contralateral site, implant positions by surface were inverted in order to reduce bias due to implant positioning and corresponding bone density. Soft tissues were approximated and sutured over it for a submerged healing protocol. Periapical radiographs were then performed following paralleling long cone technique.

Patients were prescribed analgesics and antibiotic coverage (amoxicillin 2 g/daily or in case of allergy clindamycin 600 mg/daily) for 7 days, as well as oral rinses of 0.12% chlorhexidine gluconate for 15 days following implant placement.

Patients were first recalled at 4 weeks for second stage surgery on one sector (chosen randomly), and before transgingival healing abutments were placed on the standard implants, mini-implants were retrieved using a trephine drill of 5.5 mm of internal diameter.

At 6 weeks, 2nd stage surgery was performed for contra lateral side and, mini-implants were retrieved. All standard implants were prosthetically restored 1 month following second stage surgery. Patients were then enrolled in a maintenance program and recalled every 4 months for periodontal and oral hygiene follow-up.

### *4.3. Histological processing*

To maintain the correct osmolarity at 278 mOsm/L, the retrieved biopsies were carefully rinsed with a cold 5% glucose solution to remove blood residues. They were then placed in a container with a 10% phosphate buffered formalin solution at pH 7.2 and sealed. The specimens remained in the formalin solution for two weeks.

After the fixation process was completed, specimens were placed under constant agitation in ascending concentrations of ethanol solutions as follows: 70 % ethanol for one week; 80 % ethanol for one week; 90 % ethanol for one week and 100 % ethanol for one week. After dehydration, the specimens were pre-infiltrated for 21 days in a 50% resin/alcohol solution (LR White, London Resin Co. Ltd., Aldermaston, United Kingdom), with three changes, followed by a week of infiltration in a 100% resin with two changes.

After 8 hours of heat curing at 62°C, the specimens were re-included in a light-curing hard resin (Technovit 7200 VLC, Kulzer, Wehrheim, Germany). After polymerization, undecalcified cut sections of 50 µm were prepared and ground down to about 30 µm using the TT System (TMA2, Grottammare, Italy). The sections for Bone-Implant contact measurements were stained with Azure II / methylene blue and fuchsine acid, the investigation was carried out by means of a bright field light microscope (BX 51, Olympus America, Inc.,Melville, NY, USA) connected to a high-resolution digital camera (FinePix S2 Pro, Fuji Photo Film Co. Ltd, Minato-Ku, Japan).

A histometric software package with image capturing capabilities (Image-Pro Plus 6.0, Media Cybernetics Inc, Bethesda, MD, USA) was used. To ensure accuracy, the software was calibrated for each experimental image using the 'Calibration Wizard', a feature that reports the number of pixels between two selected points of a micrometre scale. The linear remapping of pixel numbers in microns was used to calibrate the distance. All measurements were performed by the same experienced operator (T.T.).

### *4.4. Statistical analysis*

The statistical analyses were performed using IBM SPSS Statistics (IBM Corp, Armonk, NY, USA). Mean and standard deviation (SD) of Bone-Implant contact rate for different implant surfaces (SLA, MAC and XPEED®) after 4 and 6 weeks of healing were obtained. For each variable, variance normality and equality were assessed. The differences in mean values among the groups were analysed. Two-way ANOVA followed by a post hoc Holm-Sidak test were applied for multiple comparisons. The threshold value to detect statistically significant differences was set at $p < 0.05$.

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### *5. Conclusions*

Despite the scarcity of studies analyzing BIC values at such early stages, and overcoming the limitations of the present study, some conclusions can be drawn:

- Nanostructured Calcium titanate coated implant surfaces (XPEED®) has shown higher BIC values at 4- and 6-week intervals.
- When compared to SLA and MAC surfaces, XPEED® appeared to promote bone formation around implant very early on after placement, even in soft trabecular bone of the posterior maxilla.
- Both SLA and XPEED® surfaces showed bone formation with direct contact osteogenesis.

More studies with a higher number of specimens are necessary in order to establish the timeline of the bone healing, early after implant placement.

## 6. Patents

Not applicable

**Supplementary Materials:** Not applicable

**Author Contributions:** Conceptualization, K.-B. P., H.-W. A. and C.M.; methodology, C.M., A.M., PL.; software, T.T.; validation, K.-B. P., H.-W. A., T.T. and C.M. formal analysis, K.-B. P., H.-W. A., T.T. and C.M.; investigation, C.M., A.M., P.L.; resources, C.M.; data curation, A.M. and P.L. writing—original draft preparation, A.M., C.M. and P.L.; writing—review and editing, T.T., C.M.; visualization, K.-B. P., H.-W. A., T.T., P.L.; supervision, C.M. T.T.; project administration, C.M.; funding acquisition, C.M., T.T. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee at the Saint Joseph University of Beirut, Lebanon (USJ-2018-56), April 24, 2018.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Moreover, written informed consent has been obtained from the patients to publish this paper.

**Data Availability Statement:** Not applicable

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

**Appendix A** Not applicable

**Appendix B** Not applicable

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