Contact-Zone Tissue Allocation Explains Surface-Dependent Osseointegration in Composite Bone after Maxillary Sinus Floor Elevation

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Abstract: Implant healing following maxillary sinus floor augmentation takes place in a composite bone milieu where new bone, remaining xenograft granules, mineralized bone interconnections, marrow cavities, and soft tissues compete for implant contact area space. In this research paper, we explored whether greater osseointegration found with a moderately rough ZirTi mini-implant surface results from higher peri-implant bone density in 400 μm peri-implant tissue region or from more efficient use of tissue distribution in implant contact area. The data set was taken from a clinical histomorphometry trial where lateral sinus floor elevation had been performed with bovine hydroxyapatite granules, with or without collagen membrane covering the lateral window. After 6 months of graft healing, two paired mini-implants with ZirTi and turned surfaces had been installed, extracted following 3-month period of submerged healing, and histological evaluation done. Finally, 14 pairs of specimens remained in the sample set, which comprised 6 patients in membrane group and 8 patients in no-membrane group. Implant contact parameters provided assessment of new bone, interconnecting bone network, old bone, residual bone graft, and soft tissue at implant surface, whereas 400 μm point counting assessed new bone density, total bone density, old bone density, residual bone density, and soft tissue density in peri-implant tissue. No statistically significant differences were found between ZirTi and turned implants regarding new bone density (22.9% and 21.5%, respectively) and total bone density (30.1% and 29.9%) within 400 μm from the implant surface. However, there was a difference in implant contact area: new bone contact percentage on ZirTi was 29.8% and total bone contact - 39.6%; at turned implants, corresponding percentages were 10.0% and 20.6%. Soft tissue contacts amounted to 29.7% and 52.5% at ZirTi and turned surfaces, respectively. The direct anchorage index, bone-to-soft-tissue ratio, and composite bone ratio were higher at ZirTi surfaces. Thus, surface topography had no effect on peri-implant bone density but led to favorable tissue distribution in implant contact area in favor of bone-to-soft tissue balance.

Keywords: maxillary sinus floor elevation; composite bone; osseointegration; implant surface topography; histomorphometry; bone-to-implant contact; residual graft; interpenetrating bone network; biomaterials.

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1. Introduction

Maxillary sinus floor elevation procedure belongs to one of the most reliable ways of regenerating an atrophic maxillary posterior edentulous site. However, despite its predictability, the postoperative biologic process is not limited to the development of new bone in the vertical dimension only. A newly created elevated compartment consists of a number of different components: newly created bone tissue, bone marrow, vascular channels, remaining graft material, and remodeled bone tissue associated with biomaterial. While the overall success of sinus floor augmentation has been documented using systematic reviews based on randomized controlled trials comparing lateral or transcrestal sinus augmentation procedures with implants placed at different timing intervals [1–4], it should be mentioned that there was no consensus about the composition of grafted bone, the type of membranes applied during the surgery, time periods of regeneration, and surface design of an implant. Therefore, it should be taken into account that the stability of implants implanted at a grafted site is provided not only by the presence of a certain amount of bone but by proper tissue structure within a close proximity to an implant.

Posterior maxillary region provides specific conditions for the development of the regenerative site due to a low alveolar ridge, a low number of trabeculae and lack of cortical bone in the regenerated region. The objective of maxillary sinus augmentation is to create a space between the Schneiderian membrane and underlying bone tissue, thus providing additional volume. According to the majority of protocols, the space should be filled with bone substitutes that are characterized by a relatively slow degradation rate. As a consequence, a biopsy performed at the implant bed can indicate a high percentage of mineralized tissue; however, there is always a possibility that the implant can come into contact with a residual substitute or unmineralized tissue.

Application of barrier membrane in addition to lateral approach for maxillary sinus augmentation has been discussed in several scientific papers as an effective method of providing better protection against soft tissues proliferation inside the regenerated volume. Some authors have demonstrated an increase in vital bone formation rates when barriers have been used in lateral maxillary sinus lift surgery [5–7]. Other results suggest that there is a reduction of graft displacement in case of lateral window membrane application. Histomorphometric meta-analysis of vital bone content in lateral-window approach did not show significant differences between groups with and without membranes – 32.36% and 33.07%, respectively [8]. This discrepancy might be explained by the nature of the study and biopsy locations: the latter might belong to the healing area rather than to the implantation area. To solve the problem, it is necessary to understand whether membrane placement affects a tissue structure contacting an implant inserted into the grafted bone.

The geometric design of the antrostomy and the location of the access window represent yet another level of complexity since they define the exact entry point into the sinus cavity, how the graft is enclosed, and where the augmented compartment is harvested or implanted. In randomized studies using tomographic measures, the location and height of the antrostomy have been found to modify dimensional changes following sinus elevation procedures. In parallel histologic experiments, researchers have looked into the healing characteristics of mini-implants when embedded into regions grafted differently depending on the nature of the access window [9–12]. Tomographic assessment of the degree of protection offered by collagen membrane on the antrostomy also suggests that it modifies dimensional change in the region of the window without necessarily providing any histological advantage in the grafted chamber containing the implant [13]. These data provide further support for the hypothesis of a spatially selective process underlying sinus elevation. It should be understood that the access window, the grafted chamber, and the interface contacting the implant are different components of the same surgical field; however, they represent distinct targets of measurement. When evaluating the osseointegration process of composite bone in a manuscript, the anatomical origin of the tested component needs to be considered carefully, distinguishing the healing of the window, volume of the grafted bone, local density of mineralized tissue, and contact between bone boundary and the implant.

Implant surface topography is a second variable to consider. Osseointegration of titanium, initially based upon the functional and direct contact between living bone tissue and the artificial structure, is still an essential component of its modern definition that includes signaling, surface energy, microtopography, and chemistry [14–16]. While the general trend favors rougher surfaces for early bone apposition in experimental conditions, the difference in healing rates relative to turned surfaces appears to depend on defect shape and the local environment [17–19]. Surface roughness increases available bone-implant contact area, modifies fibrin retention and protein adsorption, and promotes osteogenic cells' adherence. But rough surfaces are not universally advantageous: peri-implant disease may arise or progress more readily due to altered inflammatory response on certain rough surfaces [20–23]. A critical evaluation of the impact of surface characteristics thus requires the distinction between early osseointegration occurring in a controlled healing environment and possible biological adverse effects of the same surfaces when exposed to the inflamed oral cavity.

In the context of composite bone, where the surface of the implant meets a heterogenous population of tissues, the distinction becomes particularly meaningful. Several experimental works on extraction socket, circumferential defects, and marginal gaps have demonstrated that the presence of bone walls and the distance that needs to be bridged for bone formation in the healing defect determine the speed and efficiency of bone deposition around an implant [24–29]. When an implant is placed in a mature alveolar ridge, several sources of osteogenic cells and bone particles contribute to the interface development. But when an implant is placed in a newly-formed grafted sinus, particulate matter left behind reduces the number of sources within the proximity of the implant and competes with new bone for surface attachment sites.

The design of this study depends on the difference between peri-implant reservoir and contact zone. Peri-implant reservoir represents the tissue composition at a distance of 400 μm from the surface. In this layer, there is new bone, interpenetrating bone network, old bone, graft, and soft tissue that can all be quantified with morphometric measures as a regional field. Contact zone consists of tissue composition at the point of actual linear contact with the implant. The hypothesis is that moderate roughness increases the level of osseointegration by enhancing the amount of available bone in the area; therefore, the field measures should show significantly increased new-bone and total-bone densities in the case of ZirTi compared to turned surfaces. On the other hand, the difference can be produced through changes in which tissue gets the chance to gain the implant boundary. In this situation, the field composition remains unchanged while the contact zone shows marked differences. These two approaches represent the same research hypothesis formulated from two different biological perspectives.

Both human and animal studies demonstrate the necessity for such a distinction in relation to sinus augmentation. Composite biopsies obtained after maxillary sinus lift contain a high level of vital bone along with some significant amounts of anorganic bovine bone or other xenogeneic particles. According to Galindo-Moreno et al., the cores obtained after maxillary sinus augmentation contain a considerable portion of anorganic bovine bone along with a large amount of vital bone and can ensure dimensional stability of the graft area; the remaining xenogeneic material cannot be regarded as purely negative [30]. Similar processes were observed in minipigs and human patients: autogenous bone and deproteinized bovine bone have been shown to remodel in different speeds, while some systematic review articles suggest that implants in the sites of sinus augmentation maintain a relatively high survival rate regardless of the chosen technique [3,4,31]. Yet, high survival rate says nothing about what exactly occupies the surface of the implant: new bone, interpenetrating mineralized tissue, or any other type of tissue present. This is precisely the gap where histomorphometry still has something to offer.

Therefore, the research question posed was whether the process of osseointegration with different surfaces in composite maxillary bone can be explained by higher regional bone density or more efficient tissue allocation at the site of direct contact. An additional question related to whether the lateral collagen membrane changes this process. The research hypothesis suggested that the surface of moderately rough ZirTi will show higher direct new-bone and total-bone contact despite being surrounded by the same tissue field as turned implants; the lateral collagen membrane will not produce a similar effect. Formulation of the hypotheses brings up a biomaterials perspective to the problem, in addition to its clinical aspect: the issue is not only about increasing the amount of bone formed around the implant but about translating available tissue field to the process of anchorage. If two titanium surfaces are surrounded by similar tissue fields yet exhibit different contact zones, this means that the surface is able to allocate tissues differently rather than stimulate their growth.

2. Materials and Methods

The clinical data was collected during a randomized trial assessing the osseointegration of mini-implants following lateral sinus floor elevation in combination with a bovine hydroxyapatite grafting material [32]. The study was conducted based on approval from the Ethical Committee of the University Corporation Rafael Nunez, Cartagena de Indias, Colombia, registration number 02-2015, and registration at ClinicalTrials.gov (NCT03899688). Study inclusion criteria consisted of an edentulous maxillary posterior region with remaining sinus-floor height no more than 4 mm requiring a fixed implant-supported restoration. The inclusion criteria also stipulated that the patients had to be adults aged 21 years or more. Subjects excluded from the study were those with systemic or local contraindications for oral surgery procedures, chemotherapy or radiotherapy, acute or chronic sinusitis, prior augmentation in the region, pregnant women, smokers consuming more than ten cigarettes daily, and users of bisphosphonates. The clinical trial was conducted as a triple-blind procedure regarding the subjects, the surgeon, and the outcome assessor with respect to the treatment being applied.

During the surgery, the bone lateral window was created by means of a sonic-air device, the sinus mucosa was lifted, and the subantral cavity filled with Cerabone granulate of 1.0–2.0 mm particle size. Cerabone is a bovine-based ceramic hydroxyapatite subjected to processing by heat above 1200 °C and exhibiting macroporosity. In some subjects, the lateral window was covered with a porcine corium collagen membrane, while in others, it remained uncovered. Thus, the membrane comparison comprised the window management intervention used in the augmentation procedure. Six months later, two titanium screw-type mini-implants with a diameter of 2.4 mm and length of 8 mm were inserted into the augmented maxilla of each eligible patient. The mini-implants had different surfaces: one mini-implant had a moderately rough ZirTi surface, and another one had a turned surface. These surfaces were randomly assigned to the distal or mesial position after osteotomy preparation to allow the comparison of the surfaces in a common regenerating environment.

The mini-implants remained submerged for three months. Afterwards, biopsies with mini-implants were harvested using the eccentric trephine technique, and definitive implants were inserted into the same location. The samples obtained were fixed in 10% buffered formalin, dehydrated in ethanol series, embedded in resin, longitudinally cut around the implant axis, stained with acid fuchsine and toluidine blue, and evaluated microscopically. Photographs of the samples obtained were taken at 200× magnification. The rater remained blind to the mini-implant allocation, and the intra-rater agreement coefficient exceeded 0.90. Five tissue categories were analyzed: new bone, interpenetrating bone network, old bone, remaining graft, and soft tissues. The interpenetrating bone network referred to the areas where new bone interpenetrated with the graft residuals, thus creating a unique histologic pattern as compared to the formation of direct contacts between the new bone and the surface [33,34].

Two measurement domains were utilized for complementation. The first was histometric contact analysis measuring the fraction of the implant surface occupied by each tissue category from the highest bone contact along the implant toward the implant apex. The second was morphometric field analysis measuring tissue density within 400 μm of the implant surface by point counting with a 50 μm lattice. The key variable in this study was new bone tissue for both the linear and regional analyses, while the rest of the tissue fractions were considered as secondary variables. The statistical comparison in the clinical trial involved checking for normality distribution followed by paired or non-parametric paired tests for surface comparison and unpaired or non-parametric tests for membrane comparison, with significance threshold set at $\alpha = 0.05$ [32]. In this interpretation, group means from the clinical sample were maintained, as well as p values, but were supplemented with three dimensionless indices aimed at explaining the contact zone dynamics.

Direct anchorage ratio was defined as a ratio of new bone anchorage to total bone contact, where total bone contact consisted of the new bone and interpenetrating mineralized tissue. It was used as an estimate of the share of unequivocally new bone anchorage, compared to graft-induced interpenetrating mineralization. Bone to soft-tissue ratio was calculated as a ratio of new bone contact to soft tissue contact and served as an index of whether the contact zone is mainly characterized by anchorage or non-mineralized tissue such as marrow and other soft tissues. Composite bone anchorage ratio was calculated as a ratio of new bone to the sum of residual graft and soft tissue contacts, thus indicating the extent to which the contact zone favours bone formation over the two main components constituting non-anchored tissue pool. All these indices were calculated using group means and could not be associated with any patient-level significance, since they are purely interpretive and explanatory indices rather than any statistical models. The fourth comparison was made by subtracting turned surface value from ZirTi for each tissue category in the direct-contact as well as 400 μm field measurements. This index served to assess the extent to which the surface modification effect was localized on the implant surface, rather than dispersed within tissue reservoir. Since it was a contrast, it was interpreted descriptively, using group means, as compared to statistical tests.

A total of twenty patients were recruited. Two instances of sinus mucosal perforation occurred during augmentation surgery in both experimental groups, both being protected by collagen membrane, but without any further complications. After 6 months one patient in the membrane group had insufficient hard tissue to secure mini-implants and was excluded from histological analysis. Another 3 months passed, and five patients were found to have non-integrated mini-implants after their retrieval, resulting in 14 patients and 28 mini-implants for analysis, of which 6 patients belonged to the membrane group, and 8 – to the no-membrane group. The number of 14 patients and 28 mini-implants is crucial for interpretation because the comparisons in the dataset involved paired comparisons of surfaces, while the effect of the membrane was assessed in a pairwise manner. Thus, the denominator was the same for both analyses.

Figure 1. Augmented sinus rendering.

Figure 2. Composite implant bed.

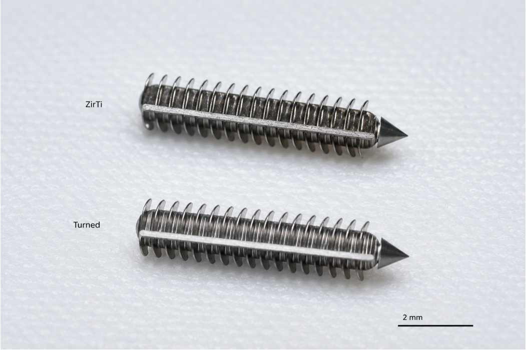

Figure 3. Paired mini-implants.

Figure 4. Retrieved sectioning context.

In an anatomical context, Figures 1 and 2 identify the implant-containing area in the augmented sinus rather than the lateral access window. Figure 3 helps understand the nature of the material comparison, namely two custom-made mini-implants installed within the same regeneration zone, while Figure 4 depicts the context of sectioning for histologic assessment of the implants.

3. Results

The final pair showed clear separation with regard to direct contact composition versus tissue density in the region under examination. It should be noted that there are some issues with regard to the denominator used in the analyses of the tissue fractions. In particular, it should be noted that the final paired samples were collected from only fourteen patients who participated in the research project. These patients included only those participants who had intact mini-implants after the augmentation phase and without the integration process occurring in the other five subjects. This does not reduce the importance of using a paired retrieval for tissue evaluation, but does make it difficult to interpret the results as a survival analysis. However, it does mean that both surface types are represented in each participant analyzed.

As could be seen from the data gathered during the analysis of tissue fractions in both groups, the biggest contrast was observed on the surface of the implants. The ZirTi surface had a larger amount of newly formed bone tissue compared to the turned surface, with 28.9% and 11.0%, respectively, in the membrane subgroup and 30.5% and 9.2%, respectively, in the no-membrane subgroup. These differences were statistically significant ($p = 0.030$ in the first case and $p = 0.008$ in the second). The average values in the pooled dataset were equal to 29.8% and 10.0%. The difference, hence, is 19.8 percentage points.

First of all, Table 1 shows that ZirTi did not outperform the turned surface via elimination of residual graft at the interface. Direct new-bone contact was still very close to 30% for ZirTi regardless of membrane coverage, whereas turned surface had 10% on average. Such stability across different window management groups may be considered an evidence of surface-dependent effect because, otherwise, it might happen due to one exceptionally favorable subgroup only. On average, the difference in new-bone contact was 17.9 percentage points under membrane coverage and 21.3 percentage points without membrane coverage.

The surface effect, thus, maintained its direction and magnitude despite dissimilarity of grafted and lateral-window conditions around ZirTi and turned implants.

Table 1. Direct contact tissue fractions.

Group	Surface	n	New bone	IBN	Total bone	Old bone	Graft	Soft tissue
Membrane	ZirTi	6	28.9	13.5	42.4	1.6	25.2	30.8
Membrane	Turned	6	11.0	16.6	27.6	1.2	27.2	43.9
No membrane	ZirTi	8	30.5	7.0	37.5	3.0	30.6	28.9
No membrane	Turned	8	9.2	6.1	15.3	2.4	23.4	58.9
Pooled	ZirTi	14	29.8	9.8	39.6	2.4	28.3	29.7
Pooled	Turned	14	10.0	10.6	20.6	1.9	25.0	52.5

Residual graft contact was quite significant at ZirTi and turned implants as well with mean values equal to 28.3% and 25.0%, respectively. Soft-tissue contact made the largest difference between surfaces in our analysis with the share reaching 29.7% for ZirTi and 52.5% for turned surfaces in the pooled comparison. Moreover, the gap became especially large in the case of no-membrane subgroup with respective shares amounting to 28.9% and 58.9% ($p = 0.016$). Thus, tissue reallocation did not take place between residual grafts and bone. Instead, soft tissue moved towards direct new bone.

Total bone contact supported this conclusion. The gap between surfaces was moderate in case of membrane subgroup while being significantly larger in case of no-membrane subgroup: 14.8 percentage points vs. 22.2 percentage points, respectively. The former number should not be attributed to higher values of direct new-bone contact but to higher fraction of interpenetrating bone network (IBN). The reason is that interpenetrating bone network could increase total bone contact without direct new bone, and this fact is crucial in order to evaluate the quality of surface effect.

Quantitatively, the sum of new bone contact and interpenetrating bone network amounted to 42.4% at ZirTi vs. 27.6% at turned surface. In the case of no-membrane subgroup, total bone contact was 37.5% vs. 15.3% with $p = 0.001$. As for the pooled samples, total bone contact was 39.6% for ZirTi and 20.6% for turned implants. Finally, pooled IBN was quite similar for ZirTi and turned implants – 9.8% vs. 10.6%. Hence, it is clear that additional bone contact at ZirTi was mainly associated with new bone rather than graft-mineralized tissue overlap.

Histological source crops in Figure 5 and Figure 6 show the microscopic image of mineralized tissue around the implant boundary used for contact measurement. Paired pooled renderings in Figure 7 and Figure 8 provide a visual interpretation of contact fractions for ZirTi and turned implants, showing that ZirTi had wider mineralized contact zones while the turned implant had broader soft-tissue fields. Surface-specific subgroups in Figure 9, Figure 10, Figure 11, and Figure 12 illustrate the same dependence between surface effect and membrane coverage.

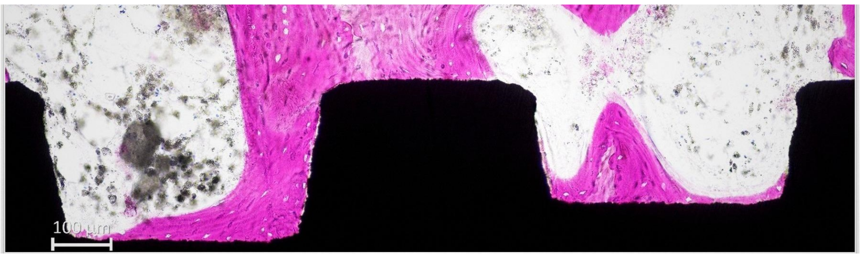

Figure 5. Direct new-bone contact.

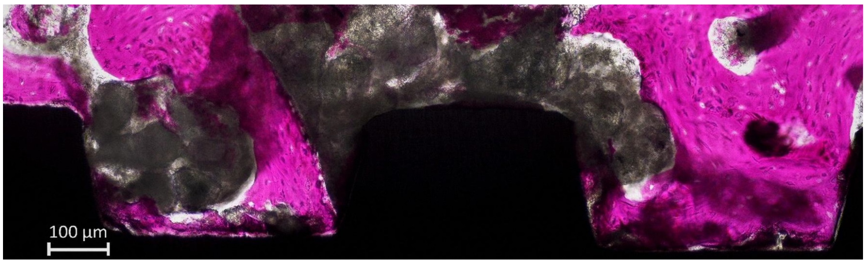

Figure 6. Graft-adjacent contact.

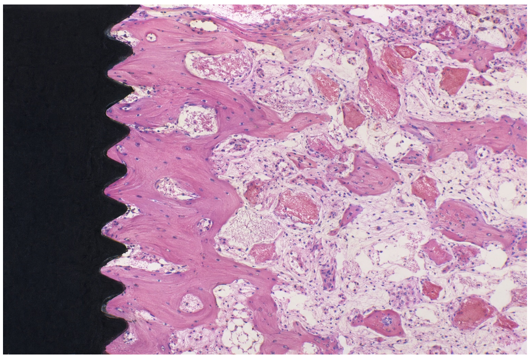

Figure 7. Pooled ZirTi contact.

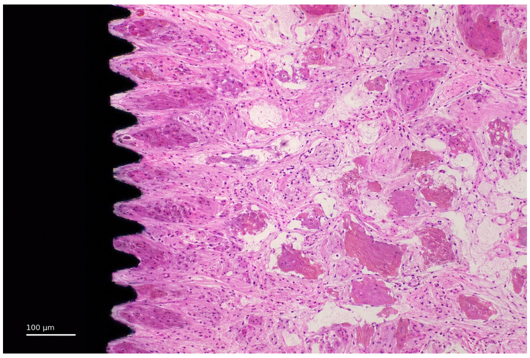

Figure 8. Pooled turned contact.

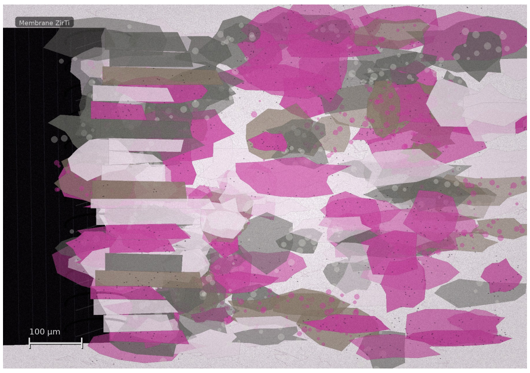

Figure 9. Membrane ZirTi contact.

Figure 10. Membrane turned contact.

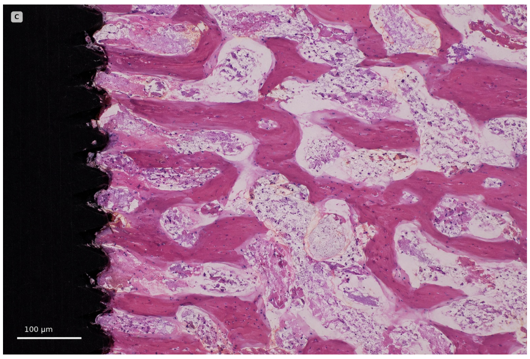

Figure 11. No-membrane ZirTi contact.

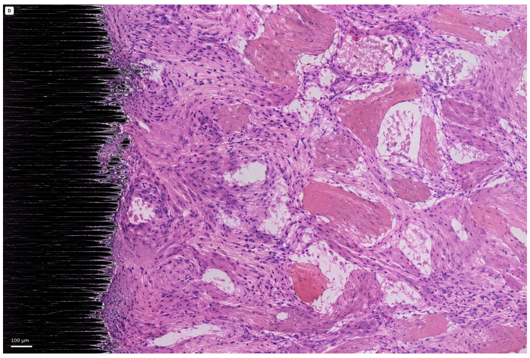

Figure 12. No-membrane turned contact.

The regional morphometry in the 400 μm vicinity of the implant surface revealed an opposite trend. The question posed in the field analysis was whether the tissue reserve zone of ZirTi implants had higher mineralization than the same reserve zone around the turned surfaces. Again, the answer to this question is negative. There are similarities in new bone density near the two types of surfaces in the membrane group, the no-membrane group, and the pooled sample. Therefore, the increased direct contact at ZirTi cannot be justified by the excess of new bone in close proximity to the implant.

In numerical terms, there is little difference in the new bone density around the mini-implants in all four subgroup combinations, from 19.9% to 23.7%. Specifically, the peri-implant new bone density in the membrane group was equal to 21.8% (ZirTi) and 19.9% (turned), while in the no-membrane group, it was 23.7% (ZirTi) and 22.6%. Pooling the data yielded 22.9% (ZirTi) and 21.5% (turned). The differences between groups are insignificant relative to the dramatic disparity in direct new bone contact. Total bone density at the distance of 400 μm is almost identical, 30.1% and 29.9% respectively.

The regional field values presented in Table 2 thus serve as the core negative control within this analysis. Specifically, the percentage of graft was in fact higher in the surrounding tissue field of ZirTi than in turned implants in each case: 46.2% versus 36.6% when membrane was present and 39.1% versus 28.9% without membranes. Assuming that residual graft was blocking direct bone-to-surface contact, then these numbers would predict less contact at ZirTi; yet, precisely the reverse was found. Thus, this evidence makes it likely that ZirTi's positive effect is due not to a cleaner or greater presence of bone in the local region but rather to its successful negotiation of bone contact despite having more graft material.

Table 2. Peri-implant field tissue fractions.

Group	Surface	*n*	New bone	IBN	Total bone	Old bone	Graft	Soft tissue
Membrane	ZirTi	6	21.8	7.4	29.2	0.1	46.2	24.5
Membrane	Turned	6	19.9	11.4	31.3	3.2	36.6	28.9
No membrane	ZirTi	8	23.7	7.1	30.7	4.9	39.1	25.4
No membrane	Turned	8	22.6	6.3	28.9	3.2	28.9	39.0
Pooled	ZirTi	14	22.9	7.2	30.1	2.8	42.1	25.0
Pooled	Turned	14	21.5	8.5	29.9	3.2	32.2	34.7

In other words, if a more robustly roughened surface was generating its relative success through increased availability of bone tissue within the 400 μm tissue neighborhood, then a significant separation in either new bone or total bone should be expected from the pooled morphometric data set. However, the surrounding field around ZirTi showed significantly greater amounts of residual graft than turned implants (42.1% versus 32.2%), yet less soft tissue content (25.0% versus 34.7%). It appears that the tissue neighborhoods were not identical in all categories, but the values clearly do not point to an explanation based on a high degree of regional bone density enhancement. Instead, the rougher surface generated greater direct bone contact despite similar surrounding mineralized reservoirs.

This difference becomes apparent from analyzing the histologic field information provided in Figure 13, Figure 14, Figure 15, and Figure 16. In addition, the rendering of the fields from pooled cases in Figure 17 and Figure 18 illustrates that while surrounding bone reservoirs remained the same, the contact behavior differed. These two findings back up the core analysis that ZirTi had more effect on the tissue at the border than on the total amount of adjacent bone.

The derived indices made the same point more sharply in the form of transforming percentage occupancy into terms of contact function. A surface that is highly associated with bone contact but relatively low with direct anchorage fraction might be heavily reliant on graft-derived mineralized surfaces. A surface that shows high ratio of bone to soft tissue represents a more favorable biological environment in that not only does new bone exist but it succeeds in competition against soft tissue in the quest for surface occupancy. The composite bone ratio can be considered to be extending this concept by measuring direct new bone in relationship to a combination of compartments least likely to contribute to osseointegration length.

The derived indices made the same point. For the membrane group, the direct anchorage fraction was 0.68 for ZirTi and 0.40 for turned implants. In the no-membrane group, the anchorage fractions were 0.81 and 0.60, respectively. The direct anchorage fractions in pooled comparisons were 0.75 for ZirTi and 0.49 for turned implants. So, the majority (3/4) of the mineralized contact for the pooled ZirTi group was in the form of direct new bone, whereas only a little more than half of pooled mineralized contact for the turned surface was of the same kind. Bone-to-soft tissue ratio showed even bigger difference. Pooled bone-to-soft-tissue ratios were 1.00 for ZirTi, thus indicating equal amount of new-bone and soft tissue contacts, and only 0.19 for the turned surface. The composite bone ratio was 0.68 for ZirTi and 0.27 for turned implants based on pooled studies.

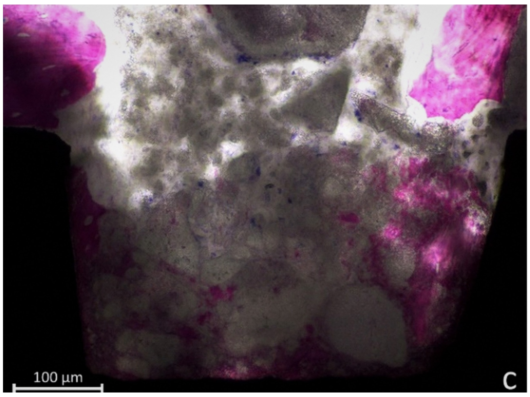

Figure 13. Particle-dominant field.

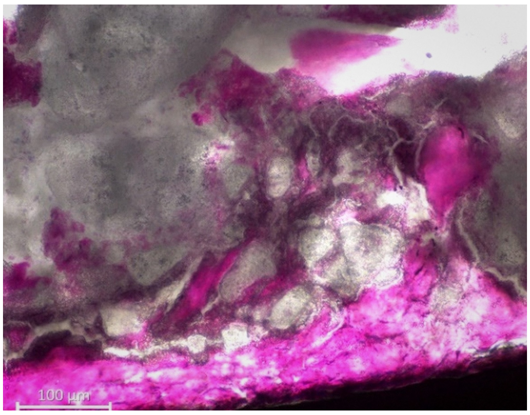

Figure 14. Lower contact region.

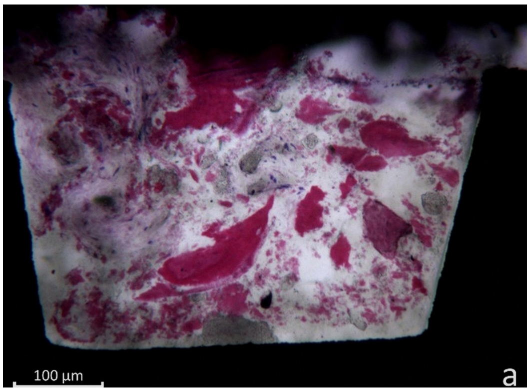

Figure 15. Residual particle field.

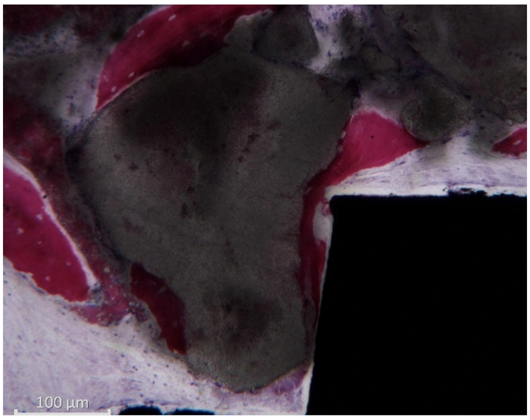

Figure 16. Residual graft interface.

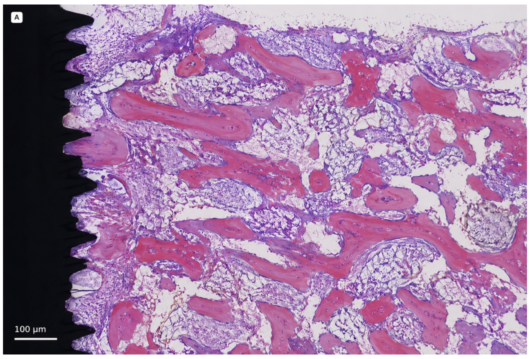

Figure 17. Pooled ZirTi field.

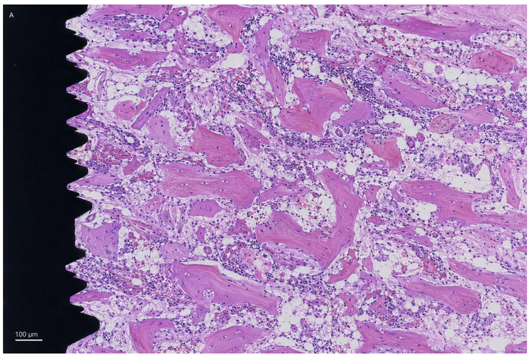

Figure 18. Pooled turned field.

Percentage efficiencies of the efficiency indices presented in Table 3 were transformed into functional interface measures. Unlike the turned surface, ZirTi had not only a higher percentage of mineralized contact, but also a higher percentage that was without doubt direct new bone, and the latter proportion was equal to or higher than the soft tissue contact at the interface. As far as turned implant is concerned, it was characterized by fewer instances of mineralized contact, and soft tissue contact predominated over it. This comparison explains why the subgroup of implants without a membrane covering did not violate the general rule. In this case, as well as in others, ZirTi could preserve advantageous ratio of mineralized to soft tissue contact, whereas the turned surface could not.

Table 3. Contact-efficiency indices.

Group	Surface	DAF	BSTR	CBR
Membrane	ZirTi	0.68	0.94	0.76
Membrane	Turned	0.40	0.25	0.39
No membrane	ZirTi	0.81	1.06	0.63
No membrane	Turned	0.60	0.16	0.19
Pooled	ZirTi	0.75	1.00	0.68
Pooled	Turned	0.49	0.19	0.27

Comparison of surfaces as ZirTi values minus those of turned could help to distinguish between contact zone and adjacent field. The value subtraction method should be used here because percentages within multiple tissues are difficult to compare simultaneously. By taking away values of the turned surface from those of ZirTi in the percentages of each tissue category, one could see what type of contrasts (increase in the same direction in both domains) was achieved. If the mechanism involved stimulation of osteogenesis in the regions around contact, both direct contact and regional field would show positive contrasts for the ZirTi surface. On the other hand, selective contact would cause positive contrasts of contact zone but weak or negative contrasts of field.

In the overall sample, differences in direct contact proportions between the two surfaces reached 19.8 percentage points of direct contact with new bone, and 1.4 percentage points in new bone density in the 400 μm field. For total bone tissue, the difference amounted to 19.0 percentage points of direct contact but only 0.2 percentage points in field. Concerning soft tissue, the differences favored the turned surface, which had 22.8 percentage points more soft tissue contact than ZirTi at the interface, and 9.7 percentage points more soft tissue in the field. While the direction of the soft tissue difference was consistent across different areas, its size was much greater at the contact line.

4. Discussion

The key result of this research is that moderate surface roughness enhances osseointegration by altering contact-zone tissue organization and allocation and not by increasing regional peri-implant bone density. It relies on analysis of the relationship between two independent measures, which are usually analyzed independently from each other. On one hand, there is bone-to-implant contact (or direct new bone contact), indicating how much the implant received. On the other hand, there is morphometric density, which shows which tissues are available in the region. While both measures matched for some of the categories, they differed greatly when it came to direct new bone contact and soft tissue. The former is precisely what makes this paper an interesting scientific contribution.

The direct contact measure indicates a statistically supported advantage for ZirTi surfaces in terms of new bone formation. However, the results of morphometry show almost equal density of new bone and total bone around both types of surfaces within 400 μm radius. This provides the biological answer needed. The surrounding tissue reservoir was not responsible for the differences observed. The key distinction was the ability of each surface to stabilize the mineralized tissue at its boundary in light of residual grafted and soft tissue.

It aligns with the understanding of the biological mechanisms underpinning early implant integration and the osseointegration as a form of wound healing. Implant insertion causes a controlled trauma, which needs stabilization first in order for bone tissue to develop in proximity. Clotting, inflammation resolution, angiogenesis, provisional matrix remodeling, osteoblast recruitment – all of these processes happen in a small spatial window adjacent to the surface. In fact, the rough surface can influence the process without increasing the density of the neighboring bone tissue by better clot stabilization, greater microtopography protection for cells, and favorable microgeometry for osteogenic growth [16,17,19].

Bone apposition at titanium implants does not happen through a uniform radial bone formation in response to an inert substrate. Bone growth takes place after stabilization of the wound, formation of the provisional matrix, invasion of the vascularization, migration of osteogenic cells, and subsequent bone remodeling at selected interfaces [14–16]. The titanium surface serves as a site-specific template for fibrin accumulation and cell attachment, which becomes more significant in the presence of competitive non-bone tissue compartments. Cortical and trabecular sources might compensate for unfavorable geometry in a pristine ridge healing process. In the case of delayed sinus grafting, graft remnants might disrupt bone sources resulting in areas where the titanium boundary is in contact with the graft or bone marrow-like soft tissue rather than viable bone.

The current results clarify the meaning of the presence of residual xenograft. Residual xenograft tissue is not necessarily a failure in sinus augmentation procedure because it might provide support of graft volume and an osteoconductive substrate [6,30,31]. However, there is a problem in this case if the limited contact area necessary for osseointegration is occupied with particles of the graft along with associated soft tissue. According to the current study, the amount of graft contacting the titanium surface is equal between ZirTi and turned implants. In contrast, much more soft tissue contacts the turned implants as compared to ZirTi implants. It means that a turned implant had no possibility to recruit new bone adjacent to it effectively enough to eliminate the presence of the soft tissue within the contact area. While ZirTi surfaces did not eliminate the composite nature of the regenerating region, they influenced on the way this composite region appeared on the interface.

It is important to emphasize that the distinction between direct new bone formation and interpenetrating bone network must be drawn because this information is used in further interpretation of the results. The term interpenetrating bone network describes a mineralized tissue associated with remnants of the graft. It might be included in the mechanical analysis. Nevertheless, it does not refer to the phenomenon described as new-bone contact with the titanium surface. While the amount of pooled IBN was nearly equal for ZirTi and turned implants, the situation changes dramatically concerning direct new-bone contact. Therefore, the benefit of a turned implant could not be explained by a higher presence of graft particles. The difference concerns direct new bone formation exclusively. Such an approach might be helpful for future research since composite bone-graft includes several categories which become indistinguishable if mineralized tissues are considered to be bone only.

The comparison of interface microphotographs presented in Figure 19 and Figure 20 clarifies the necessity to interpret the IBN category separately from the direct bone contact. Mineralized continuity appears around remnants of the xenograft particles, but its biological interpretation differs from continuous mineralized bone along the titanium boundary.

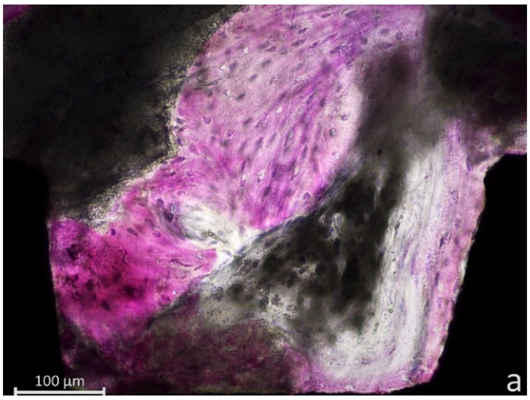

Figure 19. Interpenetrating bone region.

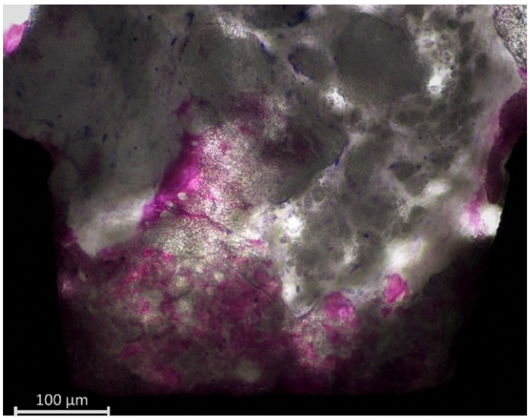

Figure 20. Graft-rich interface.

The old bone residues of the coronal region are illustrated in Figure 21 and Figure 22. These few observations confirm that the biological comparison was not due to continuous presence of the original bone but rather between direct new bone incorporation and soft tissue incorporation into the regenerative compound space.

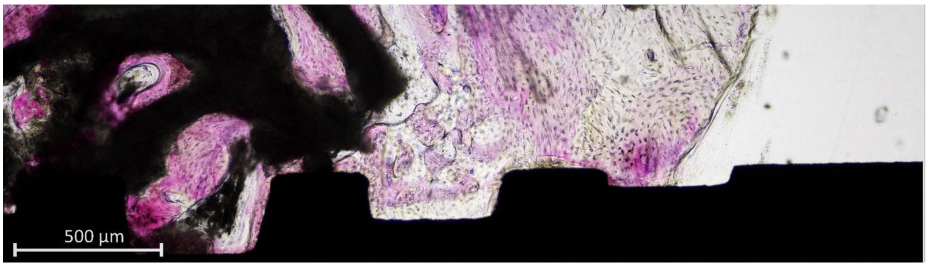

Figure 21. Coronal old-bone remnant.

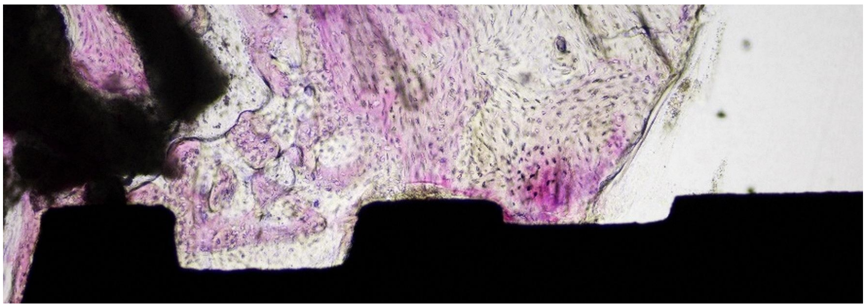

Figure 22. Old-bone contact close-up.

However, in this case, the membrane coverage of the access window did not create the equivalent effect at the surface of the implant itself. This agrees with the results of the histomorphometric meta-analysis, suggesting the similar vital bone fraction at the surface after the lateral augmentation procedure regardless of membrane application [8]. Thus, previously observed positive correlation between membrane presence and direct bone contact cannot be extended to implants since this correlation concerns the lateral window itself, which is implanted 6 months later, not into it [5,6]. At this stage, the decisive factor is not whether the access window was covered with the membrane or not but whether the surface of the implant can convert an established tissue field into direct bone contact.

The most valuable subgroup in this respect was represented by the no-membrane condition. ZirTi managed to maintain 30.5% direct bone contact in the absence of membrane coverage, whereas the turned surface had only 9.2% bone contact. Total bone contact fraction in ZirTi group equaled 37.5%, compared to 15.3% in the turned surface group.

The ratio of bone contact to soft tissue in ZirTi was 1.06, in contrast to 0.16 in the turned surface group. Thus, the turned surface still had a high potential for maintaining favorable tissue contact allocation despite the lack of lateral window membrane coverage. The turned surface, on the other hand, was highly sensitive to soft tissue occupation under this circumstance. However, the conclusion here is not that membranes are clinically irrelevant in any sinus-lift situation. Instead, the current histological analysis shows that the absence of a membrane did not help the turned surface make up for its lower contact efficiency.

The discrepancy between contact fraction and total field density provides an explanation for the potential discrepancy between clinical/radiographic assessment and histological examination of implant interfaces. Radiographs and tomographic images are necessary tools in surgery, but their voxel size and density signals do not allow to distinguish between direct bone contact, unabsorbed grafted material, bone interpenetration in graft residues, and marrow-like soft tissue at the titanium surface. Moreover, a histological core biopsy that does not include the implant surface may provide overestimated information on tissue functional readiness in cases when interface composition is overlooked and only the regional bone fraction is reported. Thus, the mini-implant retrieval method provides information unobtainable using common clinical tools.

The discrepancy between contact fraction and total field density provides an explanation for the potential discrepancy between clinical/radiographic assessment and histological examination of implant interfaces. CBCT and core biopsy can provide reliable data about bone augmentation, the mineralized tissue volume, and other necessary parameters. Yet, they cannot determine what tissues actually occupy the titanium surface. A grafted sinus can be successfully consolidated on a radiograph and have the regional bone fraction consistent with successful implant placement, whereas histologically the presence of soft tissue or grafted material occupying the titanium surface remains possible. Indeed, the current data show this scenario clearly. Total pooled bone density at 400 μm was nearly equal for both surfaces, and total bone contact differed by 19 percentage points. The clinical message is that implant placement into composite bone should not be judged only by the average amount of mineralized tissue around the osteotomy.

They also align with the outcomes of experiments involving isolated and circumferential defects. Botticelli et al. found that rough surfaces provided better bone formation compared to turned surfaces in self-contained defect models, while research involving extraction sockets and peri-implant gaps highlighted the significance of bone walls and bridging distances [18,26,29]. Although in this study the defect did not consist of a gap but was a delayed composite graft, the basic principle holds: bone needs to reach the implant. In conditions where tissue sources are cut off or soft tissue takes precedence before bone formation can take place, the role of the surface topography becomes more prominent.

There is another consideration that must be made in relation to the interpretation of the results obtained. While a good early contact zone performance can be expected with the surface structure of ZirTi, this finding does not mean that the surface will perform better in the case of the development of peri-implant diseases. Reviews that were conducted have found inconsistent data concerning the relationship between the surface structure of implants and the risk of developing peri-implantitis, and many other factors may play their roles in that respect [20–23]. These include the patient-related factors, their history of periodontal disease, oral hygiene, prosthetic design, and other aspects of care. This study provides information only on early osseointegration in grafted bone in a submerged environment.

The third point that needs to be considered is that of the influence of the biomaterial and the healing period on the results. A slowly resorbable filler can help preserve space, but this also allows for retaining the particulate structure which will influence the way tissues will form in the region of the future osteotomy site. In this manner, a shorter healing period may leave more residual graft tissue, while a longer one will provide more bone formation, albeit potentially not equivalent to bone that is already fully formed. The optimal interval should therefore be understood not only in terms of the attainment of radiographic opacity and adequate bone mass. This is because the goal should be obtaining an adequate tissue bed for contact.

Finally, there is the consideration of the effect of the biomaterial type on the outcome. Bovine HA granules that were used in this experiment are known to be volume-stable and slowly resorbable, and these properties are attractive in terms of sinus elevation. At the same time, they allow for particles of the filler being present close to the site of osteotomy 9 months after the initial procedure. Different materials, alternative particle sizes, collagen-coated variants, autogenous mixtures, or no filling approaches at all can create different conditions in terms of volume and the interface [3,35–38]. This should therefore be studied further.

The use of 14 pairs of biopsy specimens allows obtaining valuable information about the structure of the human histological samples. However, it does not allow estimating sub-group modeling or prediction based on patients' individual data. The calculated indices should be considered explanatory parameters rather than separate statistical end-points since they were computed using group mean values instead of patient-level data. The loss of non-integrated mini-implants before final retrieval is yet another reason why histological denominator is limited. While this problem affects most of the human retrieval studies due to technical and ethical reasons, it remains significant. Histology Provides Information About One Time Point. As mentioned earlier, the mini-implants in this study were harvested three months after their placement into a grafted area which had been healing during six months. The contact zone of the mini-implant after three months might differ significantly from contact zones of healing wounds during the first weeks or months or from contact zones formed after loading and remodeling processes. In particular, a turned surface might increase bone contact with a mini-implant throughout the whole period while a rough surface might change its characteristics after loading and remodeling. Long-term human retrievals are virtually impossible, but an animal model can be used to study the changes in this case.

These limitations have certain implications for the value of the performed study, but they do not diminish it to the large extent. First, it allows distinguishing between two explanations which usually become confused. Second, it helps developing a terminology which will be useful for writing papers on implant healing in regenerated bone in the future. The terms such as osseointegration, bone density, and graft consolidation might suggest that they all indicate the same thing. However, the current data prove that they may refer to two different phenomena. Similar bone density around two types of surfaces in peri-implant tissue can be observed simultaneously with different contact zones. Residual grafting contact is also possible with different amounts of soft tissues' contact.

Despite these limitations, the performed analysis has considerable practical value in several ways. First, it allows separating two possible explanations of roughness-based effect on implant success rates. They include more dense bone formation near rough surfaces and higher ability of these surfaces to create direct bone contact when bone tissue is close enough. The current data provide an evidence base for the second explanation in composite maxillary bone. ZirTi and turned mini-implants showed equal new-bone and total bone densities within the range of 400 μm while having considerably different contact zones' composition. This is a materially specific and clinically relevant result because it identifies implant surface topography as a determinant of tissue selection at the interface.

Future research should consider contact zone indicators prospectively beyond using only bone-implant contact or regional bone density measurements. Although the direct anchorage fraction, the bone-soft tissue ratio, and the composite bone ratio are relatively simplistic measures, they represent different biological qualities of interface interactions. Calculations of these values on a patient level can be subjected to hypothesis testing and correlation with implant stability, as well as with micro-CT or radiographic density measurements. It might be particularly important in the field of sinus augmentation since in many cases, the clinical criterion of success, implant survival, is very high, and the differences in histological quality cannot be detected based solely on survival rates.

However, interface-specific criteria may help identify the difference associated with healing time, early loading safety, and/or performance in compromised bone environments.

In terms of translating the findings to clinical practice, the conclusion of this literature review is not that every grafted sinus requires a particular type of surface or a particular healing period. Rather, it suggests considering the quality of the contact zone when selecting implants for posterior maxilla. A sinus with sufficient height and good radiographic bone consolidation might have a micro-environment where residual particles and soft tissues would compete for bonding with new bone. In such an environment, a certain type of implant surface may have a bigger biological benefit than expected solely based on the mineralization of surrounding bone. Moreover, a better understanding of interface biology will facilitate future reporting of study results. Namely, it is important to report the proportion of direct contact between the implant and new bone, differentiate residual particles from inter-penetrated mineralized surfaces, and correlate interface results with anatomic locations of biopsies. Otherwise, the mechanisms underlying sinus graft maturation may not be revealed correctly.

5. Conclusion

A hypothesis to be confirmed by this study is if the enhanced osseointegration of ZirTi surface with medium roughness in the composite maxilla can be attributed either to higher peri-implant bone density or to selective allocation of mineralized tissues at the contact point between an implant and adjacent bone tissue. This question has been resolved positively for contact-point allocation, since new- and total-bone densities were very similar in ZirTi and turned mini-implants. On the implant surface itself, the ZirTi surface had nearly three times as much direct contact with new bone, nearly double the total bone contact area, and significantly lower levels of soft tissue occupation compared to the turned surface. Coverage by collagen membrane of the lateral window was insufficient to replicate the effects of surface topography on the outcome. This moderate-roughness surface therefore appears to have functioned as a selective interfacial design feature, creating a contact region that is different in kind from its source material by increasing mineralization while decreasing soft tissue content rather than merely creating more bone. Selection of the implant surface in sinus-augmented posterior maxillary bone harboring persistent graft particles is an approach to enhancing tissue allocation in the contact zone.

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