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RESEARCH ARTICLE

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A comparative analysis of dual-axis implants placed into maxillary anterior extraction sockets versus virtual planning with uniaxial implants: A simulated cone beam computed tomography study of implant length and diameter

Seung Jun Song DMD, MS[1] | Stephanie M. Chu DMD[2,3] | Stephen J. Chu DMD, MSD, CDT[3,4] | Hanae Saito DDS, MS, CCRC[5] | Barry P. Levin DMD[3,6] | Nicholas L. Egbert DDS, MDS, FACP[3,7] | Guido O. Sarnachiaro DDS[3] | Dennis P. Tarnow DDS[3,8]

[1]Division of Prosthodontics, Columbia University College of Dental Medicine, New York, New York, USA

[2]Post-Graduate Periodontics, New York Harbor Healthcare System, US Department of Veterans Affairs, New York, New York, USA

[3]Private Practice

[4]Ashman Department of Periodontology and Implant Dentistry, Department of Prosthodontics, New York University College of Dentistry, New York, New York, USA

[5]Department of Advanced Sciences & Therapeutics, Division of Periodontics, University of Maryland School of Dentistry, Baltimore, Maryland, USA

[6]Department of Periodontology, University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania, USA

[7]General Dentistry (AEGD) Residency, College of Dental Medicine at Roseman University of Health Sciences, South Jordan, Utah, USA

[8]Division of Periodontics, Columbia University College of Dental Medicine, New York, New York, USA

Correspondence
Seung Jun Song, 630 W 168th Street PH7W-314, New York, NY 10032, USA.
Email: seungjunsongdmd@gmail.com

Abstract

Objective: The biaxial nature of the anterior maxilla poses a surgical and restorative challenge in implant dentistry. The present study sought to investigate the apical socket perforation rate (ASPR) from a simulated uniaxial implant placement and to determine the effect of implant length and diameter on ASPR when a uniaxial implant was placed compared with the orientation of the pre-existing dual-axis implant.

Material and Method: Cone beam computed tomography (CBCT) scans from the database of three private practices were searched for patients who received dual-axis implants within the esthetic zone in immediate tooth replacement therapy. A uniaxial implant was virtually placed using the pre-existing screw access channel of the dual-axis implant as a reference. The closest length and diameter were selected for the simulated implant. ASPR by the uniaxial implant was recorded. In addition, the affordable maximum length of a corresponding uniaxial implant that would avoid apical socket perforation was measured.

Result: Eighty-one patients with a total of 101 dual-axis dental implants were selected for analysis. A simulated virtual surgical planning with uniaxial implants revealed high ASPR (48.51%). When the length of the uniaxial implant was reduced to 11 and 9 mm, ASPR was decreased to 41.58% and 20.79%, respectively.

Conclusion: Dual-axis implant design effectively evades anatomical challenges in the anterior maxilla (esthetic zone). Considering the current evidence, efforts should be made to carefully consider the angular disparity between the extraction socket-alveolus complex and the future restorative emergence so that a harmonious biologic-esthetic result may be more predictably and consistently obtained.

KEYWORDS
digital dentistry, implants, periodontics/prosthodontics, radiology

1 | INTRODUCTION

The anatomy of the maxilla presents unique challenges to immediate implant placement into anterior extraction sockets. One such challenge is the proclination of the alveolar ridge that is frequently not perpendicular to the occlusal plane, complicating prosthetically driven implant placement.[1] In addition, the sagittal orientation of the tooth root axis is frequently positioned directly against the facial cortex of the alveolus.[2] Often, this bone is composed of exclusively bundle bone with a limited dimension,[3,4] therefore immediate implants are usually placed by engaging apical and palatal bone.

The three-dimensional implant position plays a significant role in the way prostheses are connected. It has been reported that there is a high incidence of perforation that would occur with a cingulum emergence of most uniaxial anterior implants.[5–7] Although there is inconclusive evidence pertaining to fenestration/dehiscence defects and long-term survival of implants,[8] one would wish to avoid possible fenestration as it has been recommended that implants be encased in 1.5 to 2 mm of bony housing.[9,10] In attempts to avoid this potentially detrimental outcome, most immediate implants are placed in a slightly facial-inclined manner, necessitating that most maxillary anterior implants be restored with cement-retained restorations.[6,7] However, this spatial position of the implant placement can lead to soft tissue recession and compromised esthetics over time as there tends to be less soft and hard tissue thickness around the implant and abutment complex.[11] Even with angulated screw-channel abutments, the restorative angle correction emerges coronal to the level of the crestal facial bone within the confines of the peri-implant soft tissues. This can be associated with unwanted pressure on the supracrestal mucosa, leading to apical migration of the free gingival margin and esthetic complications.[12]

Recently, a novel implant with an inverted body-shift design and dual-axis restorative interface was introduced to address the shortcomings of conventional uniaxial tapered implants. This implant features an apical portion consisting of a tapered design with aggressive threads to enhance primary stability and a narrower, cylindrical coronal portion with shallower threads that provides more space for grafting with biomaterials for augmentation while maintaining greater distance between adjacent natural teeth and implants. Importantly, this implant features a 12° sub-crestal prosthetic angle correction (SAC) within the implant body to allow for ideal positioning with a mitigated risk of apical socket perforation and facilitation of screw-retention of the prosthesis.[13]

Traditionally, clinicians tend to treatment plan with wider and longer implants as each increase of 1 mm in implant diameter may increase the functional surface area by 30%, depending on the implant macrogeometry.[14] Additionally, to ensure sufficient initial stability, the presence of apical bone consisting of 20%–35% of the proposed implant length has been recommended.[5–7] This increase in surface area and length may lead to enhanced stability imperative for immediate implant placement and loading protocols. Recent studies have shown that the ability to deliver a direct or straight channel screw-retained restoration without apical socket perforation occurs at a rate of only 10%–24% with uniaxial implants.[7] Furthermore this rate is dependent upon implant length and diameter; that is, the greater the implant length and diameter, the lower the incidence of screw-retention of the restoration.[7] However, no study exists on comparing dual-axis implants that have been placed into maxillary extraction sockets with virtual planning of uniaxial implants within the same cases.

Therefore, the purpose of this virtual study was twofold: (1) to determine the apical socket perforation rate (ASPR) when a uniaxial implant was simulated in position to deliver a screw-retained restoration in the anterior maxilla (maxillary second premolar to second premolar) and, (2) to determine the affordable maximum length of a corresponding uniaxial implant that would avoid apical socket perforation.

2 | MATERIALS AND METHODS

This observational cross-sectional study was compliant with strengthening the reporting of observational studies in epidemiology (STROBE). The data used for this study was extracted from the Inverta Data Registry, secure repository for the implant with an inverted body-shift design and dual-axis restorative interface (INVERTA Implants, Southern Implants). The registry was approved by the Western Institutional Review Board (study number 1252367), and registered patients provided consent in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Dual-axis implants with a 12° SAC were placed in accordance with the manufacturer's recommendation. The surgical protocol required incisal edge orientation during osteotomy preparation and implant placement (Figure 1A). Since the SAC is incorporated into the body of the implant, the ability to deliver a direct screw-retained restoration increases significantly and is much more consistent (Figure 1B).

2.1 | Patient selection

Cone beam computed tomography (CBCT) scans (Veraviewepocs 3D R100, Morita, Irvine, CA; GALILEOS Comfort^{PLUS}, Dentsply Sirona; Planmeca ProMax 3D, Planmeca) from the database of three private practices were searched for patients who received dual-axis implants (Co-Axis Implants; INVERTA Implants) within the anterior maxilla (maxillary second premolar to second premolar) in immediate tooth replacement therapy (e.g., with adequate initial torque value enabling immediate placement of provisional restoration) between November 2019 and August 2022. Exposure parameters were 90 kV, 8 mAs, 9.3 s, voxel size 125 μm; 85 kV, 28 mAs, 14 s, voxel size 125 μm; 96 kV, 29 mAs, 4.8 s, voxel size 150 μm, respectively. All included scans were of patients with direct or straight channel screw-retained restorations taken immediately after implant placement and subsequent provisionalization void of apical socket perforation. Scans were excluded if one of the following exclusion criteria applied: presence of artifacts[15] (scattering and blooming) affecting the visualization of the facial bone plate; distorted images such as double margins; a field of view that did not capture the entirety of the dental implant (Figure 2).

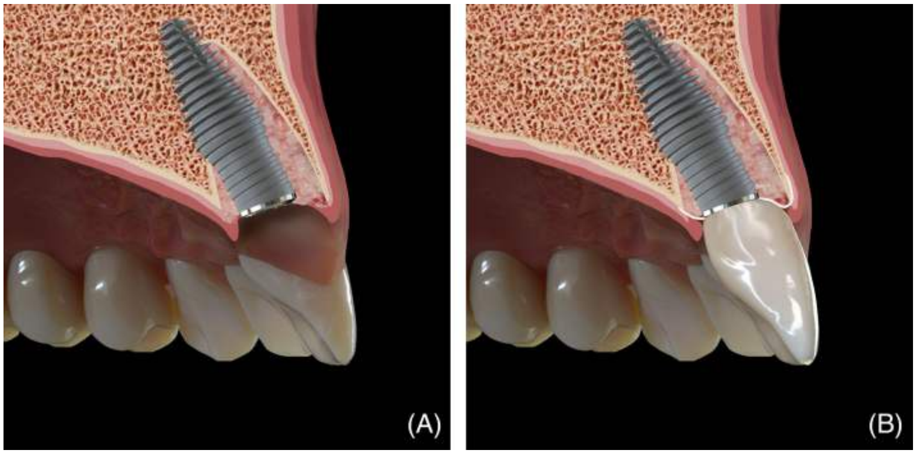

FIGURE 1 (A) The osteotomy is prepared, and implant is placed following incisal edge orientation; (B) a screw-retained restoration is readily attainable due to the SAC design feature incorporated into the body of the implant. *Source*: Reprinted from Chu et al., 2021 with permission

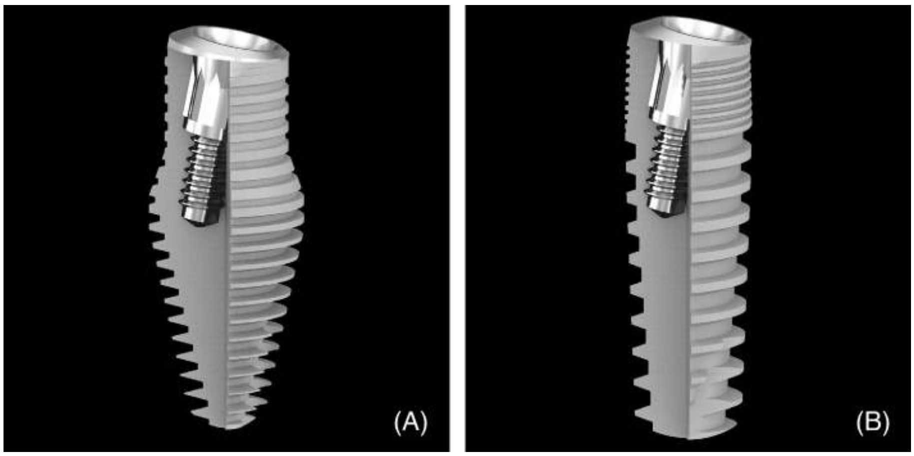

FIGURE 2 Dual-axis implants with 12° SAC. (A) INVERTA implant; (B) PROVATA implant

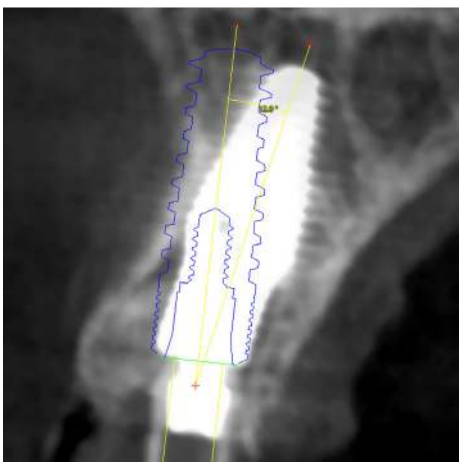

FIGURE 3 Screw access channel was utilized as a reference to align uniaxial implant to dual-axis implant

2.2 | Demographic variables

The recorded demographic variables included age, gender and tooth/implant site.

2.3 | Image analysis

CBCT data sets were saved in Digital Imaging and Communications in Medicine (DICOM) files. DICOM files were exported in multi-file, uncompressed format and were processed using a virtual surgical planning software (coDiagnostiX, Dental Wings Inc.). Data was reconstructed by using cross-sectional slices in the radial plane, perpendicular to the alveolar ridge at 1.0 mm intervals.

Virtual surgical planning was subsequently performed by one prosthodontist (SS). Patient coordination was adjusted to better align the point-of-view to the long axis of the existing dual-axis implant. A simulated uniaxial implant (Deep Conical Tapered Implants) was aligned to the existing dual-axis implant (Co-Axis Implants, Southern Implants; INVERTA Implants, Southern Implants) utilizing the screw access channel as a reference line (Figure 3). The crest module of the simulated implant was aligned with the existing dual-axis implant. For the initial simulation, simulated implants were of a similar length and diameter in accordance with the dual-axis implant placed as the implant was chosen by clinicians to obtain primary stability from the bone apical to and palatal aspect of the pre-extraction tooth (Figure 4). For example, if the dual-axis implant was at its narrowest diameter

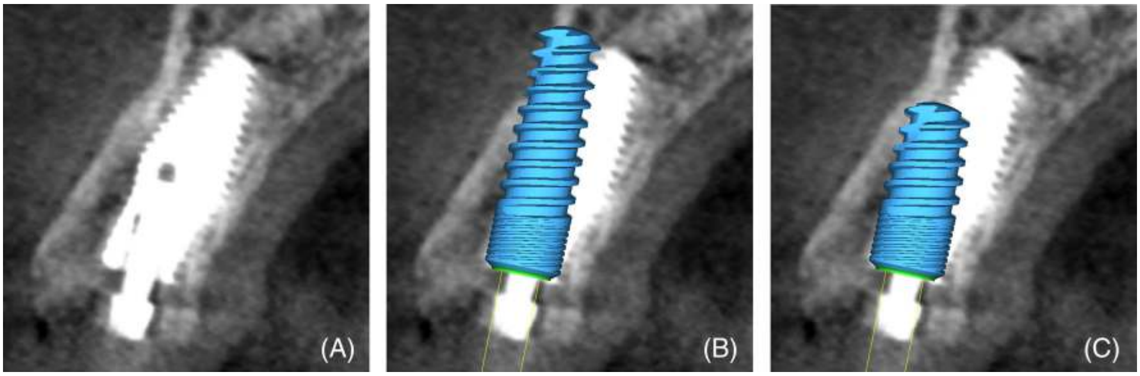

FIGURE 4 (A) Cross sectional view of post-operative CBCT of dual-axis implant (3.5/4.5 × 13 mm) placement; (B) simulated placement of 4.0 × 13 mm which exhibits apical socket perforation; (C) simulated placement of 4.0 × 9 mm which is within the confines of alveolus

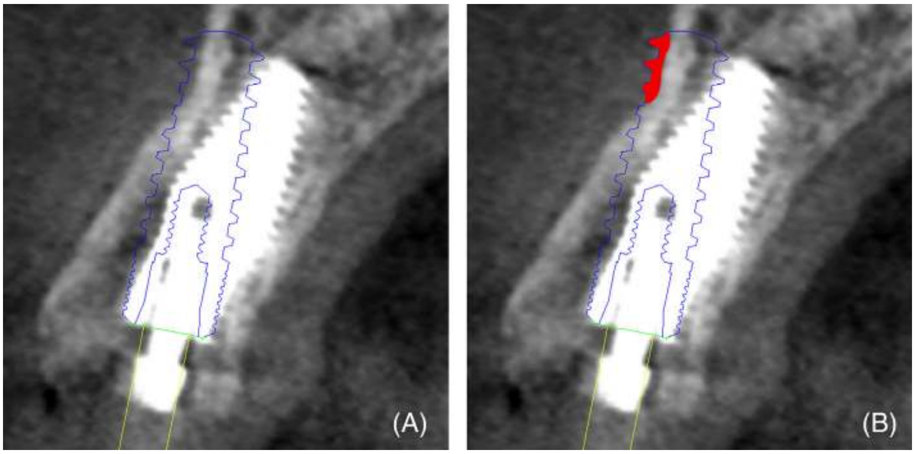

FIGURE 5 (A) Uniaxial implant aligned to dual-axis implant; (B) apical socket perforation annotated in red with a graphics editor program. *Source*: Adobe Photoshop 2022, Adobe Inc., San Jose, CA

TABLE 1 Specification of simulated implants

	Initial simulation	Shortened length simulation
3.5/4.5 × 11.5	4.0 × 11.0	4.0 × 9.0
3.5/4.5 × 13	4.0 × 13.0	4.0 × 11.0, 4.0 × 9.0
3.5/4.5 × 15	4.0 × 15.0	4.0 × 13.0, 4.0 × 11.0, 4.0 × 9.0
4.0/5.0 × 10	5.0 × 11.0	5.0 × 9.0
4.0/5.0 × 11.5	5.0 × 11.0	5.0 × 9.0
4.0/5.0 × 13	5.0 × 13.0	5.0 × 11.0, 5.0 × 9.0
4.0/5.0 × 15	5.0 × 15.0	5.0 × 13.0, 5.0 × 11.0, 5.0 × 9.0

Note: Initial simulation was done with similar dimension implants. In the case of apical socket perforation, shortened length implants were simulated to identify the longest affordable implant length which can avoid perforation.

measuring 3.5 mm and at its widest diameter measuring 4.5 and 13 mm in length, the simulation was performed using a uniaxial implant with the diameter of 4 mm and length of 13 mm. ASPR by the uniaxial implant was recorded (Figure 5). In the cases with apical socket perforation, reduced implant lengths were simulated to identify the longest length of the uniaxial implant attainable while avoiding perforation. Implant length and diameter for initial and shortened length simulation are presented in Table 1.

2.4 | Data analysis

A Cohen intra-examiner agreement rate was calculated to test the accuracy of the examiner during radiographic assessment. The measurement started when the examiner reached > 90% agreement in a representative sample of 30 patients. Descriptive statistics were used to delineate the recorded data. Frequencies and percentages were used to summarize the incidence rate of observed ASPR.

3 | RESULTS

A total of 108 patients and 132 implants were screened. After the inclusion and exclusion criteria were applied, 81 patients (71.35% were female, age ranging from 22 to 91 year old with an average of 55.45 year old) with a total of 101 dual-axis dental implants (INVERTA, Southern Implants; PROVATA Implants, Southern Implants) placed within the esthetic zone (maxillary second premolar to second premolar) were selected for analysis. The reasons for the

TABLE 2 Overall distribution of length and diameter of dual-axis implants

	Central incisor	Lateral incisor	Canine teeth	Premolars	Total
3.5/4.5 × 11.5	3	2	0	2	7 (6.93%)
3.5/4.5 × 13	28	18	6	4	56 (55.45%)
3.5/4.5 × 15	7	0	5	0	12 (11.88%)
4.0/5.0 × 10	1	0	0	0	1 (0.99%)
4.0/5.0 × 11.5	3	0	0	4	7 (6.93%)
4.0/5.0 × 13	9	0	2	1	12 (11.88%)
4.0/5.0 × 15	4	0	0	2	6 (5.94%)
Total	55 (54.45%)	20 (19.8%)	13 (12.87%)	13 (12.87%)	101 (100%)

TABLE 3 Overall simulated incidence of apical socket perforation by implant length and diameter

	Central incisor	Lateral incisor	Canine teeth	Premolars	Total
3.5/4.5 × 11.5	3 (2)	2 (0)	0	2 (2)	7 (4)
3.5/4.5 × 13	28 (14)	18 (11)	6 (3)	4 (0)	56 (28)
3.5/4.5 × 15	7 (4)	0	5 (2)	0	12 (6)
4.0/5.0 × 10	1 (0)	0	0	0	1 (0)
4.0/5.0 × 11.5	3 (1)	0	0	4 (0)	7 (1)
4.0/5.0 × 13	9 (7)	0	2 (2)	1 (0)	12 (9)
4.0/5.0 × 15	4 (1)	0	0	2 (0)	6 (1)
Total	55 (29)	20 (11)	13 (7)	13 (2)	101 (49)

Note: Similar dimension (length and diameter) implant was used. The number of perforations is denoted in parentheses.

TABLE 4 Overall simulated incidence of apical socket perforation by implant length and diameter when shortened length (11 mm) uniaxial implant was used

	Central incisor	Lateral incisor	Canine teeth	Premolars	Total
3.5/4.5 × 11.5	3 (2)	2 (0)	0	2 (2)	7 (4)
3.5/4.5 × 13	28 (11)	18 (10)	6 (1)	4 (0)	56 (22)
3.5/4.5 × 15	7 (4)	0	5 (2)	0	12 (6)
4.0/5.0 × 10	1 (0)	0	0	0	1 (0)
4.0/5.0 × 11.5	3 (1)	0	0	4 (0)	7 (1)
4.0/5.0 × 13	9 (6)	0	2 (2)	1 (0)	12 (8)
4.0/5.0 × 15	4 (1)	0	0	2 (0)	6 (1)
Total	55 (25)	20 (10)	13 (5)	13 (2)	101 (42)

Note: The number of perforations is denoted in parentheses.

exclusion were difficulty in delineating facial bone plate and cone cut noted in the CBCT scans. A Cohen intra-examiner agreement rate of 95% was reached for the examiner before the initiation of the study. Among the 101 implants, 54.45% were placed in central incisor, 19.8% in lateral incisor, 12.87% in canine teeth, and 12.87% in premolar (first and second) position (Table 2).

Overall, the most used length of the implants was 13 mm (67.33%) and the average insertion torque value (ITV) was 54.05 N/cm (range 30–90 N/cm). Incidence of apical socket perforation noted in the initial simulation is presented in Table 3.

Initial simulation with similar dimension implants revealed overall ASPR of 48.51%. Central incisor, lateral incisor and canine teeth exhibited similar ASPR of 52.72%, 55% and 53.84%, respectively. Premolars showed a reduced ASPR of 15.38%. 33.33% of 10 and 11.5 mm, 54.41% of 13 mm, and 38.89% of 15 mm implants were shown to perforate with a simulated uniaxial implant. When a shortened length implant was used for simulation, no difference was noted with 13 mm implants. Similarly, only a marginal difference was observed with 11 mm implants. However, the overall ASPR was reduced to 20.79% with 9 mm implants. Results from a shortened length simulation with 11 and 9 mm implants are presented in Tables 4 and 5.

4 | DISCUSSION

The three-dimensional positioning of immediate implants in fresh extraction sockets is of particular concern as patients' esthetic demands grow. The average width of the facial bone plate in the anterior maxilla has been shown to be <1 mm thick, with an average of

TABLE 5 Overall simulated incidence of apical socket perforation by implant diameter and length when shortened length (9 mm) uniaxial implant was used

	Central incisor	Lateral incisor	Canine teeth	Premolars	Total
3.5/4.5 × 11.5	3 (2)	2 (0)	0	2 (2)	7 (4)
3.5/4.5 × 13	28 (5)	18 (5)	6 (1)	4 (0)	56 (11)
3.5/4.5 × 15	7 (0)	0	5 (1)	0	12 (1)
4.0/5.0 × 10	1 (0)	0	0	0	1 (0)
4.0/5.0 × 11.5	3 (0)	0	0	4 (0)	7 (0)
4.0/5.0 × 13	9 (4)	0	2 (1)	1 (0)	12 (5)
4.0/5.0 × 15	4 (0)	0	0	2 (0)	6 (0)
Total	55 (11)	20 (5)	13 (3)	13 (2)	101 (21)

Note: The number of perforations is denoted in parentheses.

0.5 mm at the most crestal aspect.[16] Any insult to this already thin and highly avascular bony wall can result in loss of primary stability, unpredictable resorption patterns, and potential esthetic sequelae.

Furthermore, thin hard tissue phenotypes have also been correlated with correspondingly thin soft tissue phenotypes[17] posing further risk for esthetic complications. Frequently, such esthetic complications around implants result from surgical and prosthetic errors in three-dimensional positioning within the confines of a limited alveolar housing and potentially over-contoured restorations necessitated by facially angulated placement that is required by the available volume of bone to engage with a uniaxial implant. Pre-surgical three-dimensional treatment planning is of utmost importance as the relationship of the anterior maxillary teeth within the alveolar housing poses unique anatomical challenges to the surgeon attempting prosthetically driven immediate implant placement.

4.1 | Interpretation of data and comparison with similar investigations

The present study reports an overall ASPR of 48.51% when utilizing a similar dimension uniaxial implant for virtual surgical planning. One study reported overall ASPR of 81.7% in a similar virtual investigation.[5] Comparable results have been reported by another study in which only 14% of 1600 simulated cases were eligible for immediate implant placement with direct or straight screw-channel screw-retained prostheses. The considerable discrepancy between the present study result may be due to the virtual implant selection, as those authors chose an implant 4- to 5-mm longer than the root length of the natural tooth whereas we have selected similar and shorter length implants in reference to the existing dual-axis implant for comparison. Another attributing factor may be the inclusion of premolar teeth, which revealed a lower ASPR (15.38%). One other virtual investigation reported 35 out of 144 cases (24%) were ideal for an immediate tooth replacement therapy with a screw-channel ideal for a screw-retained prosthesis.[6] Additionally, in 103 of the remaining 109 cases an abutment with corrected angle (within 25° and mean value of 12.7°) enabled a screw-retained prosthesis.[6] In the present study 49 out of 101 cases (48.51%) could be corrected by a dual-axis implant with 12° SAC.

4.2 | Anatomy of the maxillary anterior teeth

Variations in tooth morphology dictate the three-dimensional position of the tooth.[18] The maxillary anterior teeth particular have a disparity between the crown and root angulations, with the two having a biaxial relationship ranging up to 25° (Figure 6A).[18,19] Immediate implant therapy for a tooth with an increased crown-root angle can thus pose a potential restorative conundrum. It would naturally follow that a replacement implant should mimic the biaxial relationship of the crown and root, offered by a dual-axis implant with SAC.

4.3 | Anatomy of the maxillary anterior alveolus in relation to the tooth positioning

The maxillary anterior alveolus is a nonuniform structure that frequently undulates in a corono-apical direction. The exact curvature of the facial alveolar housing apical to the root apex of the maxillary anterior teeth has been measured via CBCT studies.[20] Specifically this curvature constricts toward the caudal direction, resulting in a facial undercut of about 1 mm for maxillary anterior teeth, often complicating the negotiation of immediate implant placement as the implant may encroach on a very thin avascular shell of bone.[21]

Other radiographic studies analyzing the root position in relation to the available bone for osteotomy preparation in immediate implant therapy have shown that most maxillary anterior teeth (about 80%) are retroclined and positioned directly up against the facial bone plate, with a triangle of palatal bone available for implant placement.[2,22] Yet due to the more common location of maximum bone palatal to the root, uniaxial implant positioning in a fresh extraction socket frequently occurs along a more acute angle in relation to the future restoration's cingulum emergence. In addition, an interesting report[23] has shown that in the maxillary anterior region, the average angle of divergence between the long axis of the tooth and the long axis of its associated alveolar bone ranges between 10 to 20°,[23,24] with a subset of canine teeth and lateral incisors displaying up to 30° of divergence,[23] confirming the findings of previous studies (Figure 6B).[2,22]

That is to say, more often than not, during immediate tooth replacement therapy in the maxillary anterior zone, angulations of 10 to 30° may result between a uniaxial implant's emergence and the

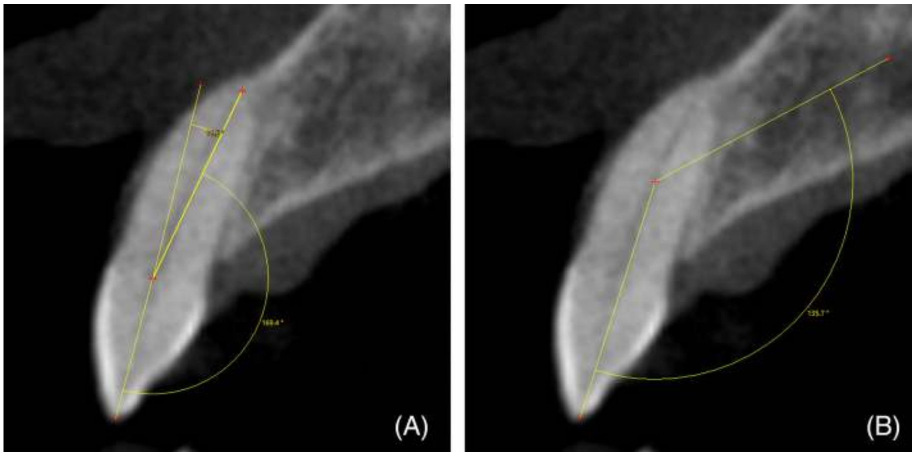

FIGURE 6 (A) Crown to root angle disparity measured to be 11.6° in a maxillary lateral incisor; (B) tooth to alveolus angle disparity to be ∼45°

ideal cingulum access emergence, which is in line with the high frequency of ASPR noted in this three-dimensional simulation study.

In a simulation to provide an alternatively shorter implant that would potentially avoid the incidence of apical socket perforation, 9 mm was found to be the maximum implant length allowable (Table 5). Theoretically, this is sensible as there would be a shorter implant length that could possibly not interfere with the facial bone plate. However, in practice such an option is not feasible due to the anatomy of the roots and dimensions of the resultant extraction socket.

The average length of succedaneous maxillary central and lateral incisor roots, when measured from the CEJ to the root apex, is about 13 mm and that of maxillary canines is about 17 mm.[25] The most coronal portion of the root in reality lies 3- to 4-mm supracrestal due to supracrestal attachment dimension.[26] Immediate implants are usually placed at the level of the mid-facial osseous crest, 3- to 4-mm subgingival, accounting for this very same supracrestal attachment.[27] In immediate tooth replacement therapy, the placement of a fixture relies upon enough native bone beyond the socket apex available for mechanical engagement, usually advocated as 3- to 4-mm.[6,7]

Taking these aforementioned elements into consideration, the necessary length of an appropriate implant with enough primary stability would be at least the length of the root, which is in line with the fact that the majority (67%) of dual-axis implants placed in this study were 13 mm in length, corresponding exactly with the average length of the maxillary incisors. It would thus follow that a 9 mm length implant, despite having a less frequent ASPR, does not suffice in order to engage enough native bone apical to the socket periphery and at an appropriate level relative to the mid-facial osseous crest for biologic-esthetic harmony. Thus, the clinician is left with employing a longer implant, which may be associated with aforementioned sequelae.

Summating all these incongruities in the dimension, positioning, and angulation of the tooth-alveolus complex, one can see that there is very limited amount of viable alveolar bone available for implant engagement with resultant sufficient primary stability required for immediate placement of provisional restoration while respecting the biologic confines of the extraction socket-alveolus complex and most importantly, in a prosthetically appropriate position. Notably, none of the included implants in this simulation study perforated as detected via CBCT scan and the mean ITV for all implants was 54 N/cm, well above standards accepted for immediate loading protocols.[28]

This highlights the utility of a dual-axis design as the clinician can then more directly follow the path of available bone.[29] This offers many advantages: mitigating the risk of apical socket perforation and need for additional grafting; engaging more bone for increased primary stability; higher frequency of the ability to deliver screw-retained retorations[30–32] and avoidance of potential biologic complications from cement[33] or over-contoured restorations that may place unwanted pressure on gingival tissues[34]; increased buccal gap distance resulting in optimization of thick buccal plate for functional and esthetic longer-term stability.[10] It has been shown in a recent prospective study that the average Pink Esthetic Score (PES)[35] of these dual-axis body-shift implants with SAC, when placed immediately into flapless extraction sockets in combination with dual-zone socket management and immediate provisionalization, is 12.79.[32] Notably, a retrospective study compared the PES of conventional tapered uniaxial implants versus body-shift dual-axis implants, with both groups of implants immediately placed via a flapless extraction protocol and dual-zone socket management with immediate provisionalization. The average PES recorded for the tapered group was 10.33, versus 13.29 for the body-shift dual-axis group.[31]

4.4 | Limitations of present study

Although virtual evaluation based on radiographic datasets could be considered a limitation, a previous publication reported that there is minimum underestimation or overestimation when virtual measurements were compared with direct measurements.[36] However, the findings of the present study should be interpreted with caution as clinical application will not be as exacting as virtual simulation. Another limitation of the study is the heterogeneity (multiple clinicians, multiple CBCT devices) of the datasets evaluated.

5 | CONCLUSION

A simulated virtual surgical planning with uniaxial implants in sites which previously had dual-axis implants placed with screw-retained prostheses revealed a high ASPR (48.51%). When the length of the uniaxial implant was reduced to 11 and 9 mm, the ASPR was decreased to 41.58% and 20.79%, respectively. A dual-axis implant design effectively evades anatomical challenges in the anterior maxilla (esthetic zone). Considering the current evidence, efforts should be made to carefully consider the angular disparity between the extraction socket-alveolus complex and the future restorative emergence so that a harmonious biologic-esthetic result may be more predictably and consistently obtained.

DISCLOSURE

Stephanie M. Chu, Stephen J. Chu, Hanae Saito, Barry P. Levin, Nicholas L. Egbert, Guido O. Sarnachiaro, Dennis P. Tarnow are consultants for Southern Implants. The authors report that no corporate financial support was received for this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Seung Jun Song https://orcid.org/0000-0002-6808-0225
Stephen J. Chu https://orcid.org/0000-0002-9588-3744
Hanae Saito https://orcid.org/0000-0002-2677-1343

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