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# EVALUATION OF DENTAL IMPLANT ANGULATION ON MARGINAL BONE LOSS IN POSTERIOR MAXILLARY AREA

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#### ABSTRACT

**Objective:** To assess the marginal bone loss in the angled implant in the posterior maxillary region. **Subjects and methods:** A total of 14 implants, 7 angled implants and 7 straight implants in posterior maxilla with surgical guide were placed. Seven patients ranged in age between 40.0 - 43.0 years with a mean age of  $41.71 \pm 1.25$  years for angulated implant group; and seven patients ranged in age between 44.0 - 45.0 years with a mean age  $44.43 \pm 0.53$  years for straight implant group. Flap less approach through surgical guide with angulation 25-30 for angled implant and straight implant without angulation. **Results:** Angulated implant showed a higher significant buccal marginal bone loss than straight implant at prosthetic and 6 months after loading. **Conclusion**: The angled implant showed a higher significant palatal marginal bone loss than the straight implant on the prosthesis and 6 months after loading. However, angulated implants can be a satisfactory alternative to vertical implants to avoid transplant procedures.

**KEYWORDS:** Posterior maxilla, angled implant, marginal bone loss.

#### **INTRODUCTION**

The definition of osseointegration is that osteoblasts and mineralized matrix touch the implant surface even when loaded. On the other hand, the failure of osseointegration of a previously stable anchored implant is the failure of the mineralized extracellular matrix that adheres directly to the artificial surface, since a mechanically competent implant/bone bond depends on an intact mineralized interface structure. Branemark et al. defined true osseointegration as direct bone-to-implant contact, which was later more functionally defined as direct bone-to-implant contact under load<sup>(1)</sup>. Implant failure is defined as a dental implant that does not meet this criterion. Early failure refers to an implant that cannot be osseointegrated prior to stage two surgery or exposure of the implant. Late failure refers to the loss of osseointegration or mechanical failure of an implant after a second stage surgery. Most research on the success of dental implants focuses on the first few years after placement <sup>(2)</sup>. In contrast to natural teeth, osseointegrated implants do not have a periodontal band to compensate for inaccuracies, but only show minimal mobility, which is caused by the elasticity of the bone tissue<sup>(3,4)</sup>.

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Angled implant placement to optimize available bone has recently been seen as an advantage. The mesiodistal inclination of the implants enabled the avoidance or bypassing of vital anatomical structures such as maxillary sinuses, neurovascular (e.g., mental) foramina and tooth roots, and the use of longer height implants. Angled abutments can be used for cemented single and multiple restorations if the long axis of the implant is about 15 to 30 ° out of parallel to the clinical long axis of the adjacent teeth. There should be enough soft tissue thickness to define margins of at least 0.5 mm subgingivally for esthetics <sup>(5,6)</sup>.

The advantages of an angled abutment include stability even with minimal bone volume: Longer implants can be used with the smallest bone volume, with the advantage that the contact between bone and implant is increased and the need for vertical bone augmentation is reduced. Great clinical results. Eliminates the need for a bone graft, which is aggressive and has unpredictable consequences could be done in patients with various systemic conditions that are contraindications to bone grafting. Angled implants allow placement that bypasses anatomical structures. It has the advantage that tilted distal implants are used instead of distal cantilever units; and reduces the length of the cantilevers without performing bone grafting or sinus lifting<sup>(5,6)</sup>.

One of the indications for tilted implants is that sufficient alveolar ridge volume is found in the anterior area, while severe bone resorption as a result of tooth loss can occur in the premolar and molar areas<sup>(4)</sup>. The presence of the maxillary sinus and a limited ridge size must also be considered when placing implants in this region<sup>(5,6)</sup>. Another alternative therapy option in the case of limited bone availability is the use of implants of reduced length. In the rear upper jaw, however, there should be a minimum ridge height of 6 to 7 mm in order to be able to safely place implants with a length of less than 8 mm. On the other hand, the use of short implants may be contraindicated due to the risk of nerve injury in the case of an extremely atrophic posterior mandible, where the alveolar nerve is often superficial <sup>(7, 8)</sup>. Dental implants must meet certain criteria that result from special functional requirements. These criteria include biocompatibility, sufficient mechanical strength, optimal integration of soft and hard tissue and the transfer of functional forces to the bone within physiological limits <sup>(9,10)</sup>.

# SUBJECTS AND METHODS

#### Sample size:

A total sample size of 7 will be sufficient to detect an effect size of 1.33 an actual power (1 $\beta$  error) of 0.8 using a two sided hypothesis, Significance level ( $\alpha$  error) 0.05 for data.

#### **Patient selection:**

Patients were selected from Department of Oral and Maxillofacial Surgery; Faculty of Dental Medicine; boys, Cairo Al-azhar university, seeking the treatment of immobilization. Ethical committee acceptance number was 154/153. The patients were selected with seven patients ranged in age between 40.0 - 43.0 years with a mean age of  $41.71 \pm 1.25$ years for Angulated implant group and seven patients ranged in age between 44.0 - 45.0 years with a mean age  $44.43 \pm 0.53$  years for Straight implant group. Angulated implant group had 2 males and 5 females, while Straight implant group had 3 males and 4 females. Only patients with missed teeth/ tooth in posterior maxilla were included. Patients had a total of 2 follow up postoperative and one for abutment loading.

### 1: Study group:

#### Angulated implants placement:

The Patient recieved two implants (Dentium, South Korea), Implant 17 received size (4\*10) with angle 15, Implant 27 received size (4\*8) with angle 22 (figure1al). Implant insertion steps were similar for all patients following the manufacturer instructions. The difference between the two groups was the surgical stents which determined the direction of implant insertion (straight or inclined). Ring infiltration and palatal anaesthesia was given in the surgical region using Scandonest 2% solution (mepicaine hydrochloride 36mg adrenaline 18mg).

Using punch drill through 3D printed surgical guide which was constructed from a previous treatment plan using digital software. A hole was made at the implant site to start the procedure for faster healing of the soft tissues and not being time consuming. The fixture was screwed in place using surgical wrench and a cover screw is added (figure 1c & d).

## 2: Control group:

## Straight implant placement:

The procedure was carried out same as the previous study group, the only exception was the angle by which the implant was placed and the different surgical guides. The patients were instructed bite on a pack of gauze for one hour, not to drink hot beverage and eat soft food for that day.

#### **Postoperative Evaluation:**

#### Radiographic and clinical assessment:

- 1: Cone beam CT (Promaxclassic,planmeca,Fi nland) up to 6 months postoperatively were considered.
- 2: A software (3diagnosys, 3 diemme, Italy) was employed to quantify, before implant insertion (T1) crestal point for each site in which the enrolled dental implant was positioned, and to identify, from 3 to 6 month after implant placement (T2) the dental implant apex then was used as the axis origin (figure1a).
- 3: On crosssectional images, marginal bone levels (MBLs) for the buccal and palatal regions were measured parallel to the long axis of the studied implant, and at a distance of 0.5 mm

buccally, and then palatally, whereas (MBLs) were calculated employing the same method for the mesial and distal regions using cone beam imaging.

- 4: Before any numerical computation, axial images of the original CT scans (T1and T2) were reoriented parallel to palatine vault for maxilla, this was used as the reference plane for the upper jaw.
- 5: As suggested by Tong et al <sup>(11)</sup>, to indicate tooth location in three dimensional space, labiolingual inclination and mesiodistal angulation of a dental implant were described.
- 6: After dental implant insertion, peri-implant bone levels at the marginal site for all of the four aspects were intra operatively measured; the distance between bone and the most marginal portion of the implant neck (distance named implant shoulder (IS)) were acquired by a single examiner using a surgical caliper, a positive number of (IS) indicated that the position of neck will be marginal to the bone (supracrestal), while a measured negative value of IS (subcrestal) indicated the contrary.
- 7: The measurements of residual bone width of buccal and palatal plate at the level of implant base were also recorded.

#### **Statistical analysis**

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent.The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test, Fisher's Exact correction, Student t-test, ANOVA with repeated measures.

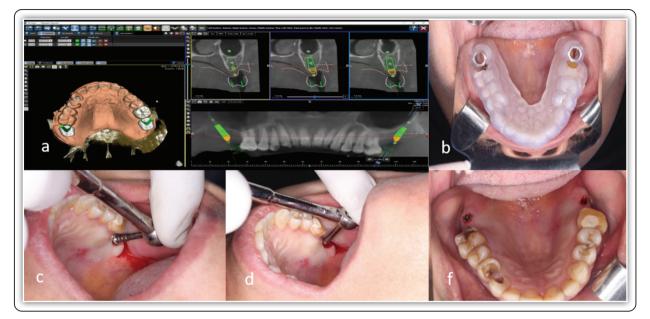


FIG (1) a), Planning implant placement, b), Hard methaacrylate surgical guide in place, c & d) Screwing the implant using torque ratchet, and e) Surgical site after finishing the procedure.

# RESULTS

In the present study, Angulated implant showed a higher significant marginal bone loss than Straight implant at prosthetic and 6 months after loading as see in table 1.

	Angulated implant (n = 7)	Straight implant (n = 7)	t	р
Buccal of marginal bone level				
Immediate	$1.23 \pm 0.21$	$1.26 \pm 0.05$	0.343	0.742
Prosthetic	$2.04\pm0.20$	$1.47 \pm 0.05$	7.385*	< 0.001*
6 months after loading	$2.31 \pm 0.11$	$1.56 \pm 0.05$	$16.760^{*}$	< 0.001*
Increase from immediate to				
Prosthetic	$0.81 \pm 0.04$	$0.21 \pm 0.04$	29.698*	< 0.001*
6 months after loading	$1.09\pm0.11$	$0.30 \pm 0.0$	19.445*	< 0.001*
Palatal of marginal bone level				
Immediate	$0.71 \pm 0.11$	$0.96 \pm 0.05$	5.376*	< 0.001*
Prosthetic	$1.46\pm0.05$	$1.07\pm0.05$	$14.100^{*}$	< 0.001*
6 months after loading	$1.76\pm0.05$	$1.19 \pm 0.04$	23.094*	< 0.001*
Change from Immediate to				
Prosthetic	$0.74\pm0.05$	$0.11 \pm 0.04$	25.403*	< 0.001*
6 months after loading	$1.04 \pm 0.05$	$0.23 \pm 0.05$	29.767*	< 0.001*

TABLE (1): Comparison between the two studied groups according to buccal and Palatal marginal bone level

*t:* Student *t*-test p: p value for comparing between the studied groups \*: Statistically significant at  $p \le 0.05$ 

#### DISCUSSION

This study focused on evaluating bone resorption receiving angulated implants. Axial implant placement has been recognized worldwide as a successful treatment for prosthetic rehabilitation. When considering various criteria for the success of an implant prosthesis such as osseointegration, crestal bone loss around the implant neck, longevity or survival of the restoration, etc. along with complications related to implants; Most studies have shown an excellent success rate averaging over 95% over a period of time (1-10 years). Generally recognized criteria for assessing the success of the implant were used by Albrektsson et al. <sup>(12)</sup>,Misch et al. <sup>(13)</sup> suggested.

Based on the above criteria, a number of studies have been reported in which a success rate in the order of 78 to 100% with an observation period of more than 15 years has been reported (14-16). If the upper jaw is atrophied, it is not possible to place an implant without performing invasive procedures such as bone augmentation or sinus lift or both. Various types of complications may arise during and after the sinus augmentation procedure, such as: B. perforation of the Schneiderian membrane, nosebleeds, postoperative pain and swelling, although no important negative effect on the success rate of implants has been described (17). However, the patient may be under psychological stress and additional stress from additional surgery and increased costs if there is not enough bone available to perform the sinus lift and the implant placement at the same appointment (18).

Although bone grafting is viable these days, it depends on many factors such as the type of bone graft used (autogenous, alloplastic, or xenograft), the host's response, the patient's age, various complications related to the grafting process, the infection, and above all of the time that is spent while the graft material matures and is absorbed by the bone. With all of these things in mind, an angled implant placement that avoids both invasive procedures such as sinus lift and bone augmentation procedures is a viable treatment option <sup>(19)</sup>.

Bone tolerates the forces more favorably when they are directed vertically. Forces on axial implants are directed vertically along the longitudinal axis of an implant and should be more favorable because they distribute the stress more evenly across the implant <sup>(20)</sup>. This explains the high survival or success rate of axially placed implants with minimal crestal bone loss of 0-0.2 mm / year <sup>(21-23)</sup>. However, the scenario is different for angled implants. The angled implants direct the forces at an angle and are therefore associated with higher forces acting on the implant bone interface during axial loading, which should logically induce bone resorption by disrupting the bone implant interface <sup>(24)</sup>.

In the present study, the baseline characteristics of the participants such as age and gender distribution had no influence on the outcome of the study, as the baseline characteristics were evenly distributed among the groups and did not show any statistically significant results. In the present study, the angled implant showed a higher significant marginal bone loss than the straight implant on the prosthesis and 6 months after loading. In agreement with our results, Bruschi et al. (25) determined the possible influence of the implant inclination on the periimplant marginal bone loss after 18 to 24 months of functional loading. Compared to axial implants, tilted implants showed a significant statistical difference for peri-implant buccal bone loss, but no further differences were observed for peri-implant bone loss or for implant survival and success rate. Fixed partial or full rehabilitation with tilted or axial implants, or with tilted and axial implants, could be a reliable technique with benefits for patients and operators.

Bone resorption in edentulous patients and the resulting anatomical limitations such as exposing the alveolar nerve in the lower jaw or widening the lower paranasal sinuses in the upper jaw prompt doctors to develop surgical techniques that are an alternative to bone grafting or other bone augmentation procedures. Tilted implants can be used instead of straight ones to avoid anatomical structures, reduce patient discomfort and financial costs, and shorten the overall treatment time. In the upper jaw, tilted implants can be placed mesial or distal to the maxillary sinus; in the lower jaw, they can be inserted into intra-foraminal regions. The reason for using tilted implants is that the vertical forces exerted during function are intended to cause greater bone resorption than horizontal forces that act around tilted implants. The angulation of distal implants enables the occlusal forces to be divided into vertical and horizontal vector components, which effectively reduces the load distribution in the surrounding bone tissue (26-29). In addition, by placing tilt implants in a reduced volume of bone, longer implants can be used that take up a greater amount of residual bone, thereby increasing implant stability (30).

One study, however, has shown excellent results with an immediately loaded fixed full denture <sup>(31)</sup>. It has also been shown that tilting posterior implants improves prosthetic support <sup>(32)</sup>. Various studies on the success rate of angled implants have shown the same or less crestal bone loss than axial implants<sup>(33,34)</sup>.

Vertical forces exerted during chewing and deglutition are believed to cause more bone destruction than horizontal forces exerted around an angled implant. In addition, the stress values are directly proportional to the angulation of the implant. Deflection and stress concentration generally increase with increasing size or increasing load angle. When vertical loads are exerted on vertical and angled implants, there is only apical migration with vertical implants, but with angled implants there is significant deflection, combined with a certain apical migration <sup>(35)</sup>. The duration of the force exerted has a greater influence on bone resorption and deformation than the force <sup>(36)</sup>. In contrast, Hopp et al. <sup>(37)</sup> the comparison of the marginal bone loss and the implant success after a 5-year follow-up examination between axial and tilted implants that were used for the rehabilitation of the upper jaw in the full arch. Within the limits of this study and taking into account a follow-up period of 5 years, it can be concluded that tilted implants behave similarly in terms of marginal bone loss and implant success compared to axial implants in full arch rehabilitation of the maxilla. To check this result, longer-term results (from 10 years) are required.

## CONCLUSION

In conclusion, the angled implant showed a higher significant marginal bone loss than the straight implant at the prosthesis and 6 months after loading, but angled implants can be a satisfactory alternative to vertical implants to avoid transplant procedures.

#### REFERENCES

- Branemark P, Adell R, Breine U, Hansson B, Lindstrom J, Ohlsson. Intra-osseous anchorage of dental prostheses. I.Experimentalstudies. Scand J PlastReconstrSurg, 3:81-100, 1969.
- Weyant R, Burt B. An assessment of survival rates and with in patient clustering of failures for endosseous Oral Implants.J Dent Res, Vol. 72 Issue 1, p2, Jan, 1993.
- Chuang S, Tian L, Wei L, Dodson T. Kaplan-Meier analysis of dental implant survival: a strategy for estimating survival with clustered observations. J Dent Res, 80: 2016-20, 2001.
- VanSteenberghe D, Sullivan D, Listrom R, et al. A retrospective multicenter evaluation of the survival rate of osseointegrated fixtures supporting fixed partial prostheses in the treatment of partial edentulism. J Prosthet Dent, 1980.
- Brånemark P, Adell R, Albrektsson T, Lekholm U, Lindström J, Rockler B. An experimental and clinical study of osseointegratedimplants penetrating the nasal cavity and maxillary sinus. J Oral Rehabil, 43:497–505, 1979.
- 6. Tatum H et al. Maxillary and sinus implants reconstructions. Dent Clin North Am, 30:207–229, 1986.

- DasNeves F, Fones D, Bernardes S, do Prado C, FernandesNeto A. Short implants – an analysis of longitudinal studies. Int J Oral MaxImpl, 21:86–93, 2006.
- 8. Renouard F, Nisand D. Impact of implant length and diameter on survival rates. Clin Oral Implan Res, 2006.
- Cehreli M, Akca K. and Iplikcioglu H. Force transmission of one and two- piece Morse-taper oral implants: a nonlinear finite element analysis, Clin Oral Impl. Res, 15 (4); 481-92, 2004.
- Raghavendra S., Wood M. C., Taylor T. D. Early wound healing around endosseous implants: a review of the literature. Int J Oral Max Impl, 20(3):425-31, 2005.
- Hongsheng Tong 1, Donald Kwon, Jianlu Shi, Nicole Sakai, Reyes Enciso, Glenn T Sameshima. Mesiodistal angulation and faciolingual inclination of each whole tooth in 3-dimensional space in patients with near-normal occlusion. Am J Orthod Dentofacial Orthop, 2012 May;141(5):604-17. doi: 10.1016/j.ajodo.2011.12.018.
- Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. The International Journal of Oral & Maxillofacial Implants. 1986;1(1):11–25.
- 13. Misch CE, Morton L Perel, Hom-Lay Wang, Gilberto Sammartino, Pablo Galindo-Moreno, Paolo Trisi, Marius Steigmann, Alberto Rebaudi, Ady Palti, Michael A Pikos, D Schwartz-Arad, Joseph Choukroun, Jose-Luis Gutierrez-Perez, Gaetano Marenzi, Dimosthenis K Valavanis. Implant success, survival, and failure: the International Congress of Oral Implantologists (ICOI) pisa consensus conference. Implant Dentistry. 2008;17(1):5-15.
- Albrektsson T, E Dahl, L Enbom, S Engevall, B Engquist, A R Eriksson, G Feldmann, N Freiberg, P O Glantz, O Kjellman. Osseointegrated oral implants. A Swedish multicenter study of 8139 consecutively inserted Nobelpharma implants. J Periodontol. 1988;59:287-96.
- Engquist B, Bergendal T, Kallus T, Linden U. A retrospective multicenter evaluation of osseointegrated implants supporting overdentures. Intern J Oral Maxillofac Implants. 1998;3: 129-34.
- Jemt T, Lekholm U, Adell R.Osseointegrated implants in the treatment of partially edentulous patients: A preliminary study on 876 consecutively placed fixtures. Int J Oral Maxillofac Implants. 1989;4:211-17.
- 17. Taschieri S, Fabbro MD, Tsesis I, Corbella S. Maxillary Sinus in relation to Modern Oral and Maxillofacial Surgery. International Journal of Dentistry. 2012:1-2.

- Bortoluzzi MC, Manfro R, Fabris V, Cecconello R, Derech ED. Comparative study of immediately inserted dental implants in sinus lift: 24 months of follow-up. Ann Maxillofac Surg. 2014;4(1):30-33.
- Lim TJ, Anna C, Tassos I, Adi N, Colin WB. Intentional Angulation of an Implant to Avoid a Pneumatized Maxillary Sinus: A Case Report. Journal of the Canadian Dental Association. 2004;70(3):164.
- Rangert B, Jemt T, Jorneus L. Forces and moments on Branemark implants. Int J Oral Maxillofac Implants. 1989;4(3):241-47.
- Kline R, John E Hoar, George H Beck, Ray Hazen, Randolph R Resnik, Erwin A Crawford. A prospective multicenter clinical investigation of a bone qualitybased dental implant system. Implant Dent. 2002;11:224-34.
- Cox JF, Zarb GA. The longitudinal clinical efficacy of osseointegrated implants: A 3-year report. Int J Oral Maxillofac Implants. 1987;2:91-100.
- Lekholm U, Adell R, Lindhe J, P I Brånemark, B Eriksson, B Rockler, A M Lindvall, T Yoneyama. Marginal tissue reactions at osseointegrated titanium fixtures. II. A crosssection retrospective study. Int J Oral Maxillofac Surg. 1986;15:53-61.
- Cehreli MC, Iplikcioglu H, Bilir OG. The influence of the location of load transfer on strains around implants supporting four unit cement-retained fixed prostheses: in vitro evaluation of axial versus off-set loading. J Oral Rehabil. 2002;29(4):394–400.
- 25. Bruschi E, Manicone PF, De Angelis P, Papetti L, Pastorino R, D'Addona A. Comparison of Marginal Bone Loss Around Axial and Tilted Implants: A Retrospective CBCT Analysis of Up to 24 Months. Int J Periodontics Restorative Dent. 2019 Sep/Oct;39(5):675-684. doi: 10.11607/ prd.4110. PMID: 31449578.
- Canay S, Hersek N, Akpinar I, Aşik Z. Comparison of stress distribution around vertical and angled implants with finite-element analysis. Quintessence Int. 1996;27:591-8.
- Watanabe F, Hata Y, Komatsu S, Ramos TC, Fukuda H. Finite element analysis of the influence of implant inclination, loading position, and load direction on stress distribution. Odontology. 2003;91:31-6.
- Lan TH, Pan CY, Lee HE, Huang HL, Wang CH. Bone stress analysis of various angulations of mesiodistal implants with splinted crowns in the posterior mandible: a three-dimensional finite element study. Int J Oral Maxillofac Implants. 2010;25:763-70.

- De Vico G, Bonino M, Spinelli D, Schiavetti R, Sannino G, Pozzi A, Ottria L. Rationale for tilted implants: FEA considerations and clinical reports. Oral Implantol 2011;4:23-33.
- Asawa N, Bulbule N, Kakade D, Shah R. Angulated implants: an alternative to bone augmentation and sinus lift procedure: systematic review. ClinDiagn Res. 2015;9:ZE10-3.
- Agliardi E, Clerico M, Ciancio P, Massironi D. Immediate loading of full-arch fixed prostheses supported by axial and tilted implants for the treatment of edentulous atrophic mandibles. Quintessence international. 2010;41(4): 285-93.
- Krekmanov L, Kahn M, Rangert B, Lindstorm H. Tilting of Posterior Mandibular and Maxillary Implants for Improved Prosthesis Support. International Journal of Oral and Maxillofacial Implants. 2000;15(3):405-14.
- Rosen A, Gynther G. Implant Treatment Without Bone Grafting in Edentulous Severely Resorbed Maxillas: A

Long-Term Follow-Up Study. Journal of Oral and Maxillofacial Surgery.2007;65(5):1010-16.

- Calandriello R, Tomatis M. Simplified treatment of the atrophic posterior maxilla via immediate/early function and tilted implants: A prospective 1-year clinical study. Clinical Implant Dentistry and Related Research. 2005; 7(1):S1-12.
- Canay S, Hersek N, Akpinar I, Asik Z. Comparison of stress distribution around vertical and angled implants with fínite-element analysis. Quintessence Int. 1996;27:591-98.
- Brosh T, Pilo R, Sudai D. The influence of abutment angulation on strains and stresses along the implant/bone interface: Comparison between two experimental techniques. J Prosthet Dent. 1998;79:328-34.
- 37. Hopp M, de AraújoNobre M, Maló P. Comparison of marginal bone loss and implant success between axial and tilted implants in maxillary All-on-4 treatment concept rehabilitations after 5 years of follow-up. Clin Implant Dent Relat Res. 2017 Oct;19(5):849-859. doi: 10.1111/ cid.12526. Epub 2017 Aug 1. PMID: 28766312.