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## PRACTICE



## RESEARCH



**Title picture:** From the case report of Önder Solakoglu, Niusha Amiri and M. Oliver Ahlers, here Figure 2: Pre-operative radiograph of tooth #37 with grade II furcation lesion and an advanced infrabony defect at the mesial aspect, p. 98–110; (Fig. 2: Ö. Solakoglu)

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Norbert Enkling

# Immediate dental implant placement, immediate restorative treatment and immediate loading: treatment options in dental practice?


## Background

Immediate treatment concepts in dental implantology are becoming increasingly popular because the reduction in treatment time is highly appreciated by patients and uncomfortable provisional restorations can be avoided. Given the correct indication, the prognoses of immediately placed implants and their prosthetic restoration are comparable to conventional, delayed treatment concepts. Thus, immediate treatment concepts should be considered as therapeutic options in routine dental practice.


## Introduction

A distinction is made between immediate, early and late treatment concepts in terms of both the surgical and prosthetic phases of implant therapy. This results in 9 different possibilities relating to the temporal sequence of treatment.

Implant therapy includes the following possibilities: immediate after tooth extraction, delayed-immediate after the healing of the mucosal wound (approximately 8–12 weeks after extraction) or late after bone healing (from 6 months after extraction). The healing of the implant can ensue non-submerged or submerged under the mucosa. If a partially edentulous dentition is restored, the implant is fitted immediately with a provisional fixed restoration in the form of a provisional crown or bridge, without static and dynamic occlusal contacts after its insertion. Immediate loading involves the direct insertion of a restoration that is in occlusion. In cases where the edentulous jaw is rehabilitated, immediate loading is thus achieved in principle. In prosthetic dentistry, a distinction is likewise made between early loading (after approximately 6 weeks/or rather 1–6 weeks after implant placement) and late loading concepts, with the latter approach ensuing after osseointegration (starting after approximately 6–8 weeks) [18, 19].

With regard to restorative treatment, fixed restorations and removable prostheses can be planned using different loading options. This emphasizes the need to specify which option is being referred to when discussing the topic of the temporal sequence in implant therapy. In a recent review, Gallucci et al. compiled implant survival rates of fixed implant-supported restorations as a function of the different, temporal treatment concepts in partially edentulous patients (Table 1). From the 9 conceivable surgical-prosthetic treatment options, the scientific data concerning 8 treatment concepts was evaluated and published. Very good implant survival rates of 96–100 % were described. No publications could be found regarding the option of delayed-immediate implant placement and immediate restoration, and therefore, this treatment option is an outlier. On the other hand, the following 4 options, which are supported by a large body of scientific data, are recommended as they show strong long-term clinical evidence:

- immediate implant placement and delayed loading (implant survival rate 96 %),
- delayed-immediate implant placement and delayed loading (implant survival rate 96.3 %),
- delayed implant placement and early loading (implant survival rate 98.3 %),
- delayed implant placement and delayed loading (implant survival rata 97.7 %).

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| Surgery/implant placement after extraction | Restorative treatment, loading after implant placement | Implant survival rate | Scientific documentation |
|---|---|---|---|
| Immediate | Immediate | 98.4 % | + |
| Immediate | Early | 98.2 % | + |
| Immediate | Late | 96 % | ++ |
| Early | Immediate | n.a. | o |
| Early | Early | 100 % | o |
| Early | Delayed | 96.3 % | ++ |
| Delayed | Immediate | 97.9 % | + |
| Delayed | Early | 98.3 % | ++ |
| Delayed | Delayed | 97.7 % | ++ |

++: scientifically and clinically validated
+: clinically documented
o: insufficient clinical documentation

**Table 1** Different time-based protocols for surgical implant insertion and prosthetic implant restoration (according to Gallucci et al. [22])

Immediate implant placement and immediate restoration (implant survival 98.4 %) as well as late implant placement and immediate restoration (implant survival 97.9 %) also show very good values, but are less documented clinically in the long term [22].

Brånemark's treatment concepts, which represent the beginning of modern dental implantology, involve delayed implant placement and implant loading times [13]. This results in treatment periods of one year and more. In a recent review, it was stated that submerged implant healing is advantageous with regard to the implant survival rate. However, initially submerged implants displayed more crestal bone loss after one year of function, on average, than implants healing openly [48]. Open healing can also be used in conjunction with a provisional restoration. This appears to be advantageous given the appropriate indication because immediate loading tends to stabilize the peri-implant bone, and approximately 0.1–0.2 mm less bone resorption occurs than in late loading [19, 43]. This suggests that, in case of doubt, submerged healing should be performed. However, in cases where the bone condition is good, the implant's primary stability is sufficient, no bone or soft tissue augmentation is needed and the patient is in good general health, open healing may be preferable.

Based on past experience, conservative treatment concepts involving late loading tend to be selected in cases of doubt [42]. Modern implant designs and surfaces exhibit osseointegration features which permit the application of faster restoration concepts with predictable success. Current data shows that immediate concepts have equivalent implant survival and success rates as conventional protocols [2, 21, 34, 39].

The extraction wound initially closes with soft tissue after tooth extraction, whereas bone healing takes about 6 months. In this time, the remodeling and resorption of the bone occurs, after which, the bone structure remains relatively constant. The maxilla shows higher bone resorption rates than the mandible [16]. In a review, Tan et al. showed that within the first 4–12 months after extraction, circa 50 % of the width of the alveolar process and about 15 % of its height resorbed; a vertical loss of 3.1–5.9 mm and a horizontal loss of 1 mm took place [46]. Based on the thickness of the vestibular alveolar lamella, varying degrees of bone atrophy can be expected because the bundle bone close to the tooth resorbs after extraction. Thus, a large change in the vestibular contour results when thin alveolar walls are present (< 1 mm). Considerable bone loss often requires vestibular augmentation, especially in esthetically relevant jaw areas, which in turn prolongs the treatment time [3, 12, 23]. Due to the resorption of the bundle bone, on average, about 1 mm of resorption occurs in the anterior maxilla in immediate implant placement [12, 49]; therefore, immediate implant placement cannot com-

**Figure 1** Initial radiological situation: fractured tooth 12

pletely prevent bone remodeling [17]. Moreover, the careful selection of the diameter and position of the implant is important in immediate implant placement. The diameter of the implant must not be chosen to be too large, and particularly for maxillary implants, a more palatal position should be selected due to the centripetal resorption pattern of the maxilla. These measures help to reduce the risk of vestibular recession with areas of exposed implant surface [5, 24, 49].

Immediate implant placement and immediate restorative treatment of the partially edentulous dentition is anticipated to result in a vestibular mucosal recession of approximately 0.5–0.9 mm on average, although more than 1 mm of recession may occur in 20 % of cases [9]. These soft tissue changes occur within the first 3 months [28]. The following variables have been identified as risk factors for increased mucosal recession [24]: smoking, absent or thin buccal alveolar walls (< 1 mm), thin gingival biotypes, limited buccal keratinized mucosa, facially-oriented implant positions, and excessive implant diameters [7, 26, 29, 37]. However, if guided bone regeneration in the form of filling the alveolar crevices with bone substitute material [3, 6, 12, 32] and/or buccal soft tissue augmentation with free connective tissue is performed at the same time as immediate implant placement, the esthetic result can be influenced favorably through the preservation of the buccal contour [23].

Immediate implant placement in conjunction with direct, immediate restoration using bridges or single provisional crowns helps support the circular soft tissues and preserve the existing optimal red-white esthetics. The peri-implant soft tissue is supported reliably in the papillae region [5, 10] and the preservation of the papillae facilitates the attainment of esthetically pleasing results. In delayed restorative therapy, the flattened proximal soft tissues must first be grown again and reconstructed into a pseudo papilla; via the step-by-step reconstruction of, or pressure on, the approximal emergence profile using provisional crowns, very

**Figure 2** Initial clinical situation: fractured tooth 12

beautiful results can be achieved in early or late restorative treatment on implants. However, this procedure is rather labor-intensive, and thus, time-consuming and financially demanding for patients [20, 51].

Immediate implant placement for single restorations is performed more frequently in the anterior region than in the posterior region. This is reflected by the number of existing scientific studies. Immediate implant placement in the posterior region is likely to result in increased bone loss, although the presence of a buccal alveolar lamella reduces the bone loss [37, 40]. In immediate implant placement, the implant's stability is usually ensured by the residual bone apical to the alveolar socket. A height of 3 mm should be available in this case. Especially for implants that are intended to support single crowns, sufficient primary stability seems to be relevant. With regard to implant geometry, tapered (conical) implants are superior to parallel-walled implants [4]. A favorable condition for immediate loading is usually considered to be an ISQ of 60 and an insertion torque of 35 Ncm [42]. However, there is disagreement in the literature as to whether primary stability values of 35 Ncm or 25 Ncm should be used for immediate loading. In a recent review, the implant survival rates did not differ between torque values of 25 Ncm or 32 Ncm [49]. In principle, higher torque seems to lead to better implant survival rates, notably, when 40 Ncm or 50 Ncm was defined as the limit [30]. Lower primary stability values have been described successfully for splinted full-arch restorations as well [31, 50]. For immediate loading, ideally, a quadrangular, primary splinting of the implants appears to be beneficial for the survival prognosis [41]. For instance, the secondary splinting of immediately loaded interforaminal implants using 1 to 2 Dalla Bona-type ball attachments averaged an implant survival rate of only 81.6 % after one year, although the majority of the implant failures occurred within the first month after loading [27]. In contrast, when a dolder bar was used for the primary splinting of 2 implants, a survival rate of 98.8 % was seen after 1–3 years [45].

When planning the immediate loading of several implants, implant splinting should be performed in the healing phase. The "All-on-Four" concept of cross-arch splinting, for example, shows very good results when 4–6 implants are splinted together in the edentulous jaw. Given that the "All-on-Four" method has been well-documented in the literature, it is has become an evidence-based and real planning option that can be discussed with patients [33, 38, 44]. The "All-on-Four" method restores the edentulous jaw with fixed restorations by using 4 implants which are placed specifically into the existing subnasal maxilla or interforaminal mandibular bone, preferably in the region of the second incisors and second premolars. Bone augmentation over the inferior alveolar nerve

**Figure 3** Prepared provisional restoration (CAD/CAM)

**Figure 4** Post-operative X-ray: immediate implant placement in region 12 (SICvantage tapered: 3,7 x 14,5 mm/ SIC invent AG, Basel, CH), Flap-less, Guided-Surgery.

or in the region of the maxillary sinuses is avoided through the distal inclination of the dorsal implants, and an adequate prosthetic support polygon is thus established. Implants that are placed obliquely do not show increased failure rates or increased bone resorption compared to vertically placed implants [15, 35]. The "All-on-Four" concept, developed as an immediate implant placement protocol by Malo in the 1990s, has the advantage that the phase of passive edentulism can be avoided.

The extent to which occlusal loading should be avoided for immediate restorations in partially edentulous dentition and the provisionals should initially be designed in non-occlusion has not been scientifically clarified so far; single-tooth implants appear to osseointegrate under occlusal load with similar success rates as in non-occlusion [11, 19, 49]. On the other hand, the splinting together of several implants appears to be beneficial because single provisional restorations show poorer implant survival rates compared to horseshoe-shaped full-arch restorations [41]. At present, non-occlusion is recommended clinically for the immediate restoration of single-tooth implants [41].

In a recent review, flap-less surgery was shown to be riskier in terms of implant survival compared to open surgery (risk factor: 1.70-fold). If immediate loading is also performed, the risk increases to 2.24-fold [12, 52]. The extent to which current digital techniques will optimize these results is currently the subject of clinical studies; in a currently ongoing study by the Implantology and Biomaterials Research Group at the University of Bonn (DRKS No. 00022273), very good intermediate results have been documented for flap-less, guided implantology in a fully digital workflow with prepared single-tooth provisionals (CAD-CAM technique), for both the indication immediate implant placement and immediate loading as well as the indication late implant placement and immediate loading (Fig. 1–6).

Immediate concepts show an optimized patient satisfaction and are preferred by patients; long treatment times represent a burden for patients because the provisional phase is usually associated with shortcomings in terms of the masticatory function, phonetics, and esthetics [1, 25]. This helps to explain why clinical experimentation with shorter, immediate treatment concepts began as early as the 1970s and why various protocols with shortened treatment times were documented. The collected data points to the fact that immediate treatment approaches have an evidence base and can be successfully applied in clinical practice nowadays, given that the indication is carefully selected [13]. In summary, from the patient's viewpoint, immediate implant placement combined with immediate restorative treatment in the visible region and immediate loading in the edentulous jaw, in the form of either immediate or late implant placement, appear to be particularly interesting.

## Clinical Recommendations

In **immediate implant placement and immediate restorative treatment**, the implant is placed in the area of the fresh extraction socket during the same appointment as tooth extraction. Immediate implant placement is not indicated in an alveolar socket that shows signs of acute inflammation. On the other hand, chronic apical periodontitis does not represent a contraindication for immediate implant placement. The scientific literature largely describes similar implant survival rates as in immediate implant placement in healthy alveolar sockets [8, 29, 37]. However, a recent review reports a 3-fold increased risk in the rate of implant failure [14]. This suggests that thorough excochleation of granulation or cystic tissue is necessary before implant placement.

Clinical studies show very good results for immediate implant placement with an implant survival and success rate of 98.4 % after 2 years (95%-CI: 97.3–99 %) and < 1 mm of bone loss. An improvement of the survival rate could be achieved by administering systemic antibiotic therapy post-operatively [28]. Immediate implant placement is possible for both fixed restorations and removable prostheses. However, the position of the implant does not usually follow the exact course of the alveolar socket. Instead, attention is needed to ensure that the implant's axis is inclined away from the alveolar socket's original course, to be offset palatally into the local bone and deepened into the basal bone; this approximates to 1 mm below the buccal bone level or 3 mm apical to the cementoenamel junction of the adjacent teeth [49]. For multi-rooted teeth, insertion into the interradicular bone or positioning into the palatal alveolar socket is also possible. When the implant is positioned, caution to achieve primary stability and to anticipate subsequent alveolar healing should be exercised. Usually, this results in a palatal offset and a subcrestal position of the implant's shoulder.

**Figure 5** Clinical situation: 1 week after immediate restoration with a provisional restoration in non-occlusion.

**Figure 6** Close-up X-ray: 1 week after immediate restoration

(Tab. 1, Fig. 1–6: N. Enkling)

The impending prosthetic restoration should also be taken into account when positioning the implant; if a screw-retained crown is planned in the anterior region, a steep implant axis should be chosen so as to allow screw access in the area of the palatal cingulum and prevent contact with the incisal edge. If, on the other hand, a steeply placed implant is to be restored with a cemented crown, a palatally over-contoured crown would be the result. An implant that is planned for cementation must have an oblique insertion direction so that the abutment required for cementation can be integrated in the contour of the crown. Good surgical and prosthetic planning is therefore essential [49]. Given sufficient primary stability, the prognosis of implant success for immediate restorative treatment is comparable to the results of restorative treatment after osseointegration has been completed [13]. The provisional restoration is usually prepared and inserted during implant surgery. The splinting together of adjacent implants is desirable during the provisional phase.

Conversely, **immediate loading** represents an implant-supported prosthesis in the edentulous jaw which is fixed, if possible, within the first day (up to the third day) after implant placement [13]. In this case, occlusal loading is unavoidable. The restoration may be either provisional or definitive. Immediate loading is possible for both fixed restorations and removable prostheses. According to current data, the restoration of the edentulous mandible using a dolder bar on two standard implants is considered a safe immediate loading concept [36, 47]. When quadrangular primary splinting is used for immediate loading, as is the case in the "All-on-Four" concept, even implants with lower primary stability (around 20–30 Ncm) can be loaded immediately in the mandible and maxilla with success [31, 50]. A combination of immediate implant placement and immediate loading is possible. However, from a prosthetic standpoint, it must be noted that a pronounced change in hard and soft tissue morphology occurs as a result of alveolar healing; this leads to a change/cavity formation in the interface between the mucosa and the prosthesis, thus requiring the adjustment of the prosthesis at a later point [13]. Provisional restorations are usually used for double immediate treatment for this reason. Exceptions to this are definitive restorations with PMMA coating; PMMA can be used as part of a relining procedure and the transition subsequently optimized.

In the "All-on-Four" concept, prosthetically, the red esthetics are made using pink gingival replacement materials (PMMA or ceramic). The transition zone between the pink gingival replacement material and the natural mucosa must be located outside of the esthetically relevant zone, which is visible during laughter. Therefore, it is often necessary to level the alveolar bone; this means that, in immediate implant placement, the crestal alveolar portions must be removed generously and the implant is placed primarily in the basal bone. The extent of bone remodeling that occurs after implant placement is not comparable to immediate implant placement in a preserved extraction socket, but is considerably less. The surgical vertical ridge reduction must be taken into account beforehand, especially when the vertical bone availability is evaluated in order to determine realistic implant lengths. This flattening of the alveolar bone and the possible smooth, basal design of the bridge pontics presents hygiene advantages; the contact surface between the mucosa and the base of the restoration is reduced and it becomes easy to clean using hygiene tools.

A risk factor for a subsequent increase in the incidence of peri-implant mucositis and peri-implantitis is the amount of keratinized mucosa at the implant [37]. Thus, the quality of the soft tissue (keratinized gingiva and biotype) must be considered before making a decision [26, 29, 37], and this emphasizes the need for appropriate patient selection; if the initial esthetic and anatomical situation is good, immediate concepts should be applied to preserve good esthetics.

## Conclusion

The expected vestibular contour changes of the alveolar process when immediate concepts are used must be functionally and esthetically accept-

able. An ideal starting point for the use of immediate concepts is thus an excess of hard and soft tissue [9]. Particularly for fixed prostheses in the esthetically relevant zone, especially maxillary anterior prostheses where a gummy smile exists, the indication for immediate therapy should be decided with caution because a vestibular soft tissue recession of 0.5–1 mm must be expected. If hard and soft tissue deficits need to be compensated for through augmentative procedures, delayed or late treatment concepts are preferable. In this respect, immediate treatments supplement, but do not replace conventional protocols. A timely and precise collaboration between surgeons and prosthodontists is required for the implementation of immediate restoration and immediate loading concepts. Ideally, this is best achieved in a team. Further clinical research would be useful in order to continue to optimize treatment protocols for immediate treatment concepts.

## Conflicts of interest

In the past, Prof. Dr. Norbert Enkling has given paid lectures at scientific conferences and lectures with workshops for implant companies such as Nobel Biocare, SIC Invent, Dentaurum Implants, 3M Espe and Condent.

### References


1. Abdunabi A, Morris M, Nader SA, Souza RF: Impact of immediately loaded implant-supported maxillary full-arch dental prostheses: a systematic review. J Appl Oral Sci 2019; 27: e20180600

2. Al-Sawai AA, Labib H: Success of immediate loading implants compared to conventionally-loaded implants: a literature review. J Investig Clin Dent 2016; 7: 217–224

3. AlKudmani H, Al Jasser R, Andreana S: Is bone graft or guided bone regeneration needed when placing immediate dental implants? A systematic review. Implant Dent 2017; 26: 936–944

4. Atieh MA, Alsabeeha N, Duncan WJ: Stability of tapered and parallel-walled dental implants: a systematic review and meta-analysis. Clin Implant Dent Relat Res 2018; 20: 634–645

5. Benic GI, Mir-Mari J, Hämmerle CH: Loading protocols for single-implant crowns: a systematic review and meta-analysis. Int J Oral Maxillofac Implants 2014; 29 (Suppl): 222–238

6. Caneva M, Botticelli D, Morelli F, Cesaretti G, Beolchini M, Lang NP: Alveolar process preservation at implants installed immediately into extraction sockets using deproteinized bovine bone mineral – an experimental study in dogs. Clin Oral Implants Res 2012; 23: 789–796

7. Caneva M, Botticelli D, Rossi F, Cardoso LC, Pantani F, Lang NP: Influence of implants with different sizes and configurations installed immediately into extraction sockets on peri-implant hard and soft tissues: an experimental study in dogs. Clin Oral Implants Res 2012; 23: 396–401

8. Chen H, Zhang G, Weigl P, Gu X: Immediate placement of dental implants into infected versus noninfected sites in the esthetic zone: a systematic review and meta-analysis. J Prosthet Dent 2018; 120: 658–667

9. Chen ST, Buser D: Esthetic outcomes following immediate and early implant placement in the anterior maxilla – a systematic review. Int J Oral Maxillofac Implants 2014; 29 (Suppl): 186–215

10. Cheng Q, Su YY, Wang X, Chen S: Clinical outcomes following immediate loading of single-tooth implants in the esthetic zone: a systematic review and meta-analysis. Int J Oral Maxillofac Implants 2020; 35: 167–177

11. Chrcanovic BR, Albrektsson T, Wennerberg A: Immediately loaded non-submerged versus delayed loaded submerged dental implants: a meta-analysis. Int J Oral Maxillofac Surg 2015; 44: 493–506

12. Clementini M, Tiravia L, De Risi V, Vittorini Orgeas G, Mannocci A, de Sanctis M: Dimensional changes after immediate implant placement with or without simultaneous regenerative procedures: a systematic review and meta-analysis. J Clin Periodontol 2015; 42: 666–677

13. De Bruyn H, Raes S, Ostman PO, Cosyn J: Immediate loading in partially and completely edentulous jaws: a review of the literature with clinical guidelines. Periodontol 2000 2014; 66: 153–187

14. de Oliveira-Neto OB, Lemos CA, Barbosa FT, de Sousa-Rodrigues CF, Camello de Lima FJ: Immediate dental implants placed into infected sites present a higher risk of failure than immediate dental implants placed into non-infected sites: systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2019; 24: e518–e528

15. Del Fabbro M, Bellini CM, Romeo D, Francetti L: Tilted implants for the rehabilitation of edentulous jaws: a systematic review. Clin Implant Dent Relat Res 2012; 14: 612–621

16. Del Fabbro M, Testori T, Kekovic V, Goker F, Tumedei M, Wang HL: A systematic review of survival rates of osseointegrated implants in fully and partially edentulous patients following immediate loading. J Clin Med 2019, 8(12), 2142; https://doi.org/10.3390/jcm8122142

17. Denardi RJ, da Silva RD, Thomé G et al.: Bone response after immediate placement of implants in the anterior maxilla: a systematic review. Oral Maxillofac Surg 2019; 23: 13–25

18. Esposito M, Grusovin MG, Coulthard P, Worthington HV: Different loading strategies of dental implants: a Cochrane systematic review of randomised controlled clinical trials. Eur J Oral Implantol 2008; 1: 259–276

19. Esposito M, Grusovin MG, Maghaireh H, Worthington HV: Interventions for replacing missing teeth: different times for loading dental implants. Cochrane Database Syst Rev 2013;2013:Cd003878.

20. Furze D, Byrne A, Alam S, Wittneben JG: Esthetic outcome of implant supported crowns with and without peri-implant conditioning using provisional fixed prosthesis: a randomized controlled clinical trial. Clin Implant Dent Relat Res 2016; 18: 1153–1162

21. Gallardo YNR, da Silva-Olivio IR, Gonzaga L, Sesma N, Martin W: A systematic review of clinical outcomes on patients rehabilitated with complete-arch fixed implant-supported prostheses according to the time of loading. J Prosthodont 2019; 28: 958–968

22. Gallucci GO, Hamilton A, Zhou W, Buser D, Chen S: Implant placement and loading protocols in partially edentulous patients: a systematic review. Clin Oral Implants Res 2018; 29 (Suppl 16): 106–134

23. Grunder U: Crestal ridge width changes when placing implants at the time of tooth extraction with and without soft tissue augmentation after a healing period of 6 months: report of 24 consecutive cases. Int J Periodontics Restorative Dent 2011; 31: 9–17

24. Hammerle CH, Araujo MG, Simion M:. Evidence-based knowledge on the biology and treatment of extraction sockets. Clin Oral Implants Res 2012; 23 (Suppl 5): 80–82

25. Huynh-Ba G, Oates TW, Williams MAH: Immediate loading vs. early/conventional loading of immediately placed implants in partially edentulous patients from the patients' perspective: a systematic review. Clin Oral Implants Res 2018; 29 (Suppl 16): 255–269

26. Kinaia BM, Ambrosio F, Lamble M, Hope K, Shah M, Neely AL: Soft tissue changes around immediately placed implants: a systematic review and meta-analyses with at least 12 months of follow-up after functional loading. J Periodontol 2017; 88: 876–886

27. Kronstrom M, Davis B, Loney R, Gerrow J, Hollender L: Satisfaction and clinical outcomes among patients with immediately loaded mandibular overdentures supported by one or two dental implants: results of a 5-year prospective randomized clinical trial. Int J Oral Maxillofac Implants 2017; 32: 128–136

28. Lang NP, Pun L, Lau KY, Li KY, Wong MC: A systematic review on survival and success rates of implants placed immediately into fresh extraction sockets after at least 1 year. Clin Oral Implants Res 2012; 23 (Suppl 5): 39–66

29. Lee J, Park D, Koo KT, Seol YJ, Lee YM: Comparison of immediate implant placement in infected and non-infected extraction sockets: a systematic review and meta-analysis. Acta Odontol Scand 2018; 76: 338–345

30. Lemos CAA, Verri FR, de Oliveira Neto OB et al.: Clinical effect of the high insertion torque on dental implants: a systematic review and meta-analysis. J Prosthet Dent 2020; 08 Sep 2020, doi: 10.1016/j.prosdent.2020.06.012

31. Malo P, Lopes A, de Araujo Nobre M, Ferro A: Immediate function dental implants inserted with less than 30 N.cm of torque in full-arch maxillary rehabilitations using the All-on-4 concept: retrospective study. Int J Oral Maxillofac Surg 2018; 47: 1079–1085

32. Matarasso S, Salvi GE, Iorio Siciliano V, Cafiero C, Blasi A, Lang NP: Dimensional ridge alterations following immediate implant placement in molar extraction sites: a six-month prospective cohort study with surgical re-entry. Clin Oral Implants Res 2009; 20: 1092–1098

33. Mericske-Stern R, Worni A: Optimal number of oral implants for fixed reconstructions: a review of the literature. Eur J Oral Implantol 2014; 7 (Suppl 2): S133–153

34. Mitsias M, Siormpas K, Pistilli V, Trullenque-Eriksson A, Esposito M: Immediate, early (6 weeks) and delayed loading (3 months) of single, partial and full fixed implant supported prostheses: 1-year post-loading data from a multicentre randomised controlled trial. Eur J Oral Implantol 2018; 11: 63–75

35. Monje A, Chan HL, Suarez F, Galindo-Moreno P, Wang HL: Marginal bone loss around tilted implants in comparison to straight implants: a meta-analysis. Int J Oral Maxillofac Implants 2012; 27: 1576–1583

36. Pardal-Peláez B, Flores-Fraile J, Pardal-Refoyo JL, Montero J: Implant loss and crestal bone loss in immediate versus delayed load in edentulous mandibles: a systematic review and meta-analysis. J Prosthet Dent 2020;

37. Parvini P, Obreja K, Becker K, Galarraga ME, Schwarz F, Ramanauskaite A: The prevalence of peri-implant disease following immediate implant placement and loading: a cross-sectional analysis after 2 to 10 years. Int J Implant Dent 2020; 6: 63

38. Penarrocha-Diago M, Penarrocha-Diago M, Zaragozi-Alonso R, Soto-Penaloza D: On Behalf Of The Ticare Consensus M. Consensus statements and clinical recommendations on treatment indications, surgical procedures, prosthetic protocols and complications following All-On-4 standard treatment. 9th Mozo-Grau Ticare Conference in Quintanilla, Spain. J Clin Exp Dent 2017; 9: e712–e715

39. Pigozzo MN, Rebelo da Costa T, Sesma N, Laganá DC: Immediate versus early loading of single dental implants: a systematic review and meta-analysis. J Prosthet Dent 2018; 120: 25–34

40. Ragucci GM, Elnayef B, Criado-Cámara E, Del Amo FS, Hernández-Alfaro F: Immediate implant placement in molar extraction sockets: a systematic review and meta-analysis. Int J Implant Dent 2020; 6: 40

41. Sanz-Sánchez I, Sanz-Martín I, Figuero E, Sanz M: Clinical efficacy of immediate implant loading protocols compared to conventional loading depending on the type of the restoration: a systematic review. Clin Oral Implants Res 2015; 26: 964–982

42. Schimmel M, Srinivasan M, Herrmann FR, Müller F: Loading protocols for implant-supported overdentures in the edentulous jaw: a systematic review and meta-analysis. Int J Oral Maxillofac Implants 2014; 29 (Suppl): 271–286

43. Sommer M, Zimmermann J, Grize L, Stübinger S: Marginal bone loss one year after implantation: a systematic review of different loading protocols. Int J Oral Maxillofac Surg 2020; 49: 121–134

44. Soto-Penaloza D, Zaragozí-Alonso R, Penarrocha-Diago M, Penarrocha-Diago M: The all-on-four treatment concept: systematic review. J Clin Exp Dent 2017; 9: e474–e488

45. Stoker GT, Wismeijer D: Immediate loading of two implants with a mandibular implant-retained overdenture: a new treatment protocol. Clin Implant Dent Relat Res 2011; 13: 255–261

46. Tan WL, Wong TL, Wong MC, Lang NP: A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans. Clin Oral Implants Res 2012; 23 (Suppl 5): 1–21

47. Thomason JM, Kelly SA, Bendkowski A, Ellis JS: Two implant retained overdentures – a review of the literature supporting the McGill and York consensus statements. J Dent 2012; 40: 22–34

48. Troiano G, Lo Russo L, Canullo L, Ciavarella D, Lo Muzio L, Laino L: Early and late implant failure of submerged versus non-submerged implant healing: a systematic review, meta-analysis and trial sequential analysis. J Clin Periodontol 2018; 45: 613–623

49. Weigl P, Strangio A: The impact of immediately placed and restored single-tooth implants on hard and soft tissues in the anterior maxilla. Eur J Oral Implantol 2016; 9 (Suppl 1): S89–106

50. Wentaschek S, Scheller H, Schmidtmann I et al.: Sensitivity and specificity of stability criteria for immediately loaded splinted maxillary implants. Clin Implant Dent Relat Res 2015; 17 (Suppl 2): e542–549

51. Wittneben JG, Gavric J, Sailer I, Buser D, Wismeijer D: Clinical and esthetic outcomes of two different prosthetic workflows for implant-supported all-ceramic single crowns-3 year results of a randomized multicenter clinical trail. Clin Oral Implants Res 2020; 31: 495–505

52. Zhuang J, Zhao D, Wu Y, Xu C: Evaluation of outcomes of dental implants inserted by flapless or flapped procedure: a meta-analysis. Implant Dent 2018; 27: 588–598

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# The use of Bone Allograft material and Enamel matrix derivates in the regenerative treatment of mandibular furcation class II defects in localised periodontitis with trauma from occlusion: a report of two cases and a narrative review of the literature

**Introduction:** Periodontitis can result in irreversible loss of connective tissue and supporting alveolar bone. Despite advances in regeneration therapy, treatment of periodontal furcation defects is still a challenge. This case report describes a combined regenerative approach in the treatment of grade II furcation defects in mandibular molars.

**Material and Methods:** In the present case study, 2 clinical cases with advanced localised periodontitis and an occlusal trauma as a cofactor were studied over 8 and 5 years, respectively. Following initial occlusal adjustment, the periodontal defects were treated successfully with guided tissue regeneration along with allogenic cancellous bone, enamel matrix proteins and endogenous growth factors.

**Results:** The treatment was effective in the regenerative therapy of destructive periodontal disease in both patients. Significant amount of bone fill was seen in clinical and radiographic re-evaluation and clinical results were maintained in the follow-up after 8 and 5 years.

**Conclusion:** Successful regeneration of periodontal tissues can be achieved using the combination of guided tissue regeneration (GTR), Allograft bone substitute, Emdogain and plasma rich in growth factor (PRGF). The combination therapy resulted in regeneration of tooth supporting tissue with improved clinical attachment levels and healthy gingiva.

**Keywords:** guided tissue regeneration; chronic periodontitis; Enamel matrix derivates; Allograft bone substitute; plasma rich in growth factor; occlusal trauma

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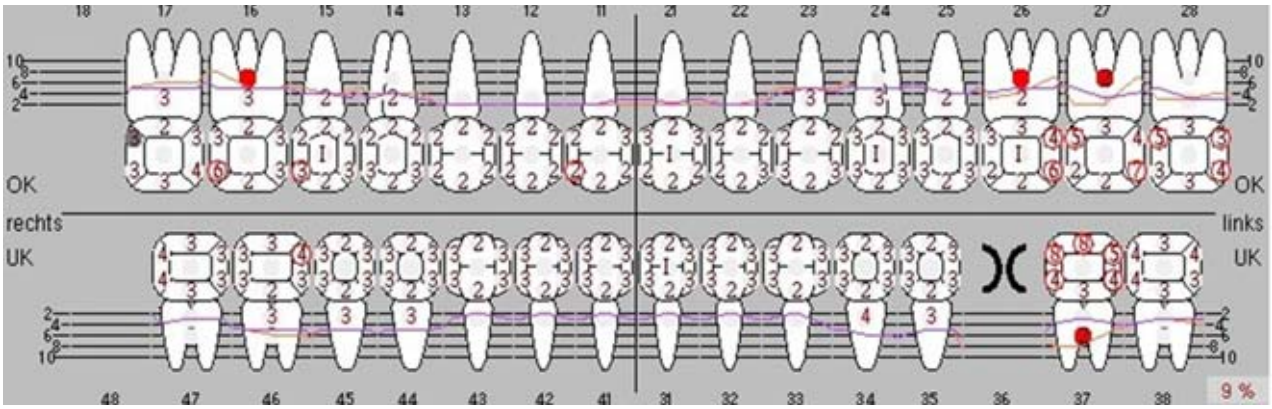



**Figure 1** Initial periodontal measurement at baseline of case #1.

## Introduction

The prevalence of periodontal diseases in Germany is estimated to be about 90 % [41]. Many of these patients are unaware that inadequate oral hygiene is a risk factor for the emergence of periodontal diseases as well as of the fact that periodontitis interacts with various systemic diseases, notably diabetes, atherosclerosis, rheumatoid arthritis and pulmonary infections [56]. In spite of this, awareness is steadily increasing, even in the group of senior citizen patients, that they can contribute substantially to the health of their own teeth and these patients are prepared to invest time and resources into their dental health [34].

The onset of periodontal inflammation is usually associated with the accumulation of biofilm and calculus. Pathogenic microbiota in the subgingival biofilm start an immune-inflammatory response that leads to pocket formation. The host responses through innate and adaptive immunity attenuates the bone resorption and breakdown of connective tissue [27]. This pathogenic process can lead to tooth loss if left untreated.

In addition to the inflammatory processes, a variety of cofactors have been described in the literature, which may favour the progression of a periodontal lesion. In addition to general medical factors, such as incorrectly adjusted diabetes mellitus, autoimmune diseases, and nicotine consumption, local factors may also adversely affect the aetiology and progression of periodontal defects [22]. These factors may be e.g. poorly adapted restorative margins, endodontic infections and occlusal trauma. Grinding and clenching of teeth due to sleep- and awake-bruxism is caused by muscle hyperactivity and can result in occlusal trauma of vulnerable teeth. Since 1965 it has been controversely discussed in the literature if occlusal trauma could act as a contributing factor in periodontal destruction, which may potentially cause degenerative changes in the periodontal ligament and the loss of supporting alveolar bone [25]. Waerhaug refused this theory suggesting that functional traumatic forces cannot act as a co-factor in the causation of angular defects [59]. After the presentation of the co-destruction theory researchers started to examine the concept of multiple risk factors that resulted in the initiation and progression of periodontal diseases. As stated in a study by Ramfjord and Ash, uncorrected occlusal discrepancies have been shown to exacerbate periodontal disease, occlusal adjustments should be performed in the initial periodontal treatment phase in order to eliminate dysfunctional overloading of symptomatic teeth [48].

**Figure 2** Pre-operative radiograph of tooth #37 with grade II furcation lesion and an advanced infrabony defect at the mesial aspect.

Periodontal Treatment Planning is a complex and multidisciplinary procedure that requires different

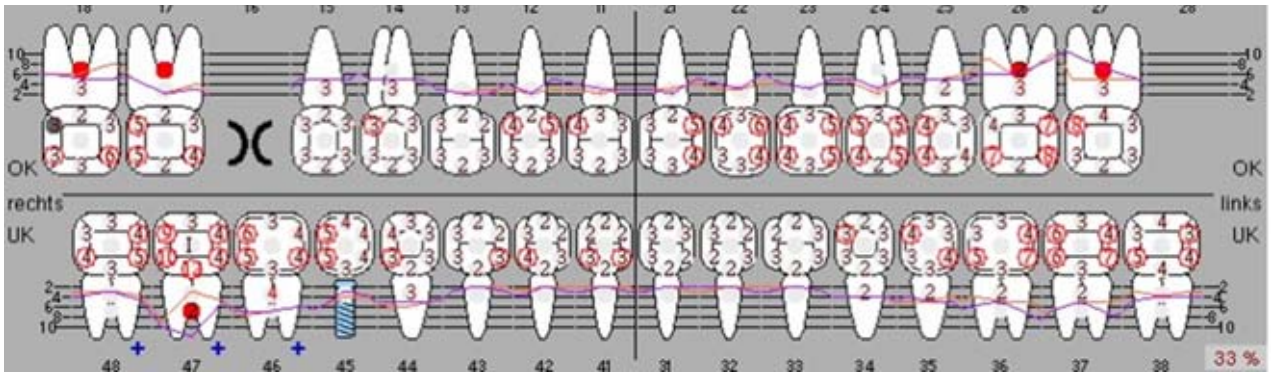



**Figure 3** Initial periodontal measurement at baseline of case #2.

**Figure 4** Pre-operative radiograph of tooth #47 with a grade II furcation involvement and an advanced infrabony defect at the distal aspect.

therapeutic steps. One of the most important steps in the treatment of periodontal diseases is the diagnosis of co-factors and their elimination early in the course of periodontal therapy. Inflammation reduction is achieved through initial periodontal therapy, including supragingival and subgingival scaling, localised or generalised deep scaling and root planning in combination with the administration of antibacterial substances. According to the new S3 guideline for subgingival instrumentation and adjunctive antibiotics it is not recommended to use adjunctive antibiotics if the patients are over the age of 56 years and present with less than 35 % of periodontal pockets with a pocket probing depth (PPD) exceeding 5 mm (S3 guideline DGZMK, AWMF no.: 083–029). During the phase of periodontal repair, the healing process leads to the formation of a long epithelial attachment. Long epithelial attachment is considered as non-functional scarring, since the periodontal tissue architecture is not restored. At the end of the initial periodontal treatment a re-evaluation indicates if further surgical procedures are necessary, or the elimination of inflammation has been achieved successfully and can be maintained through supportive periodontal therapy.

One of the most common dento-alveolar consequences of periodontitis in molar teeth is the involvement of the furcation of the infected tooth. The therapy of furcation defects has always been a challenge and different therapies have been proposed according to the anatomical situation, the degree of furcation involvement as well as other local and systemic factors [15]. In general, 2 significantly different treatment approaches should be distinguished, a resective or a regenerative approach.

In the following, the treatment objective was to achieve complete recovery of periodontal tissue through periodontal regeneration. Periodontal regeneration can be achieved by guided tissue regeneration (GTR), a periodontal surgical procedure that aims at the formation of new alveolar bone and new connective tissue attachment, functionally oriented on the newly formed cementum [3]. Regeneration of the involved furcation depends also on anatomic factors. The location of the furcation entrance has a great impact on a positive outcome of the procedure. A furcation entrance being located relatively far subgingivally due to a high root trunk increases the chances of success compared to a more coronally located furcation entrance, due to a low root trunk. Furthermore, the root divergence also plays a role. If the roots are relatively far apart, they can be cleaned more sufficiently due to a better access and therefore the prognosis for a more successful outcome of the regenerative procedure is better compared to a narrow root divergence [28]. It should also be noted that the vitality of the tooth must be evaluated ini-

tially. A non-vital tooth can be maintained through an endodontic treatment and could also be treated regeneratively, but a non-vital tooth that lacks endodontic treatment must not be treated with regenerative therapy [51].

Different techniques and materials have been described in the literature to achieve this goal [17]. In order to enhance the results of the treatment and restore periodontal new attachment with bone reconstruction, combined techniques have been advocated. The use of grafting materials with or without barrier membranes and osteopromotive agents, like enamel matrix derivates (Emdogain, Straumann AG, Basel, Switzerland), has been proposed to increase the percentage of cases with successful new attachment and periodontal reconstruction [7, 30, 42]. Emdogain is a mixture of enamel matrix derivatives (EMD) that contributes to periodontal ligament cells regeneration in a process mimicking natural root development [37]. Plasma rich in growth factors (PRGF, Biotechnology Institute [BTI], Vittoria, Spain) seems to be one of the most promising and novel methods used for tissue repair and regeneration [4]. The application of PRGF-Endoret technology provides proteins and growth factors that activate and accelerate the regeneration process. It is also capable of stimulating bone tissue regeneration by enhancing osteoblast proliferation, migration, chemotaxis, and the expression of a wide range of pivotal molecules involved in tissue regeneration [60]. Moreover, PRGF-Endoret provides a three-dimensional, biocompatible and biodegradable fibrin scaffold that retains and later releases growth factors; furthermore it also acts as a temporal nesting scaffold for the cells [6]. In this procedure the white blood cells are excluded so that pro-inflammatory activity which may act as a negative factor for tissue regeneration is also removed [43].

Although in theory this process appears straightforward, the implementation into daily practice is complicated and dependent on the respective practical skills of the periodontist. If dysfunctional cofactors are involved the professional interaction with the referring dentist or a specialist in the diagnosis and treatment of craniomanidublar dysfunction (CMD) may be helpful [24].

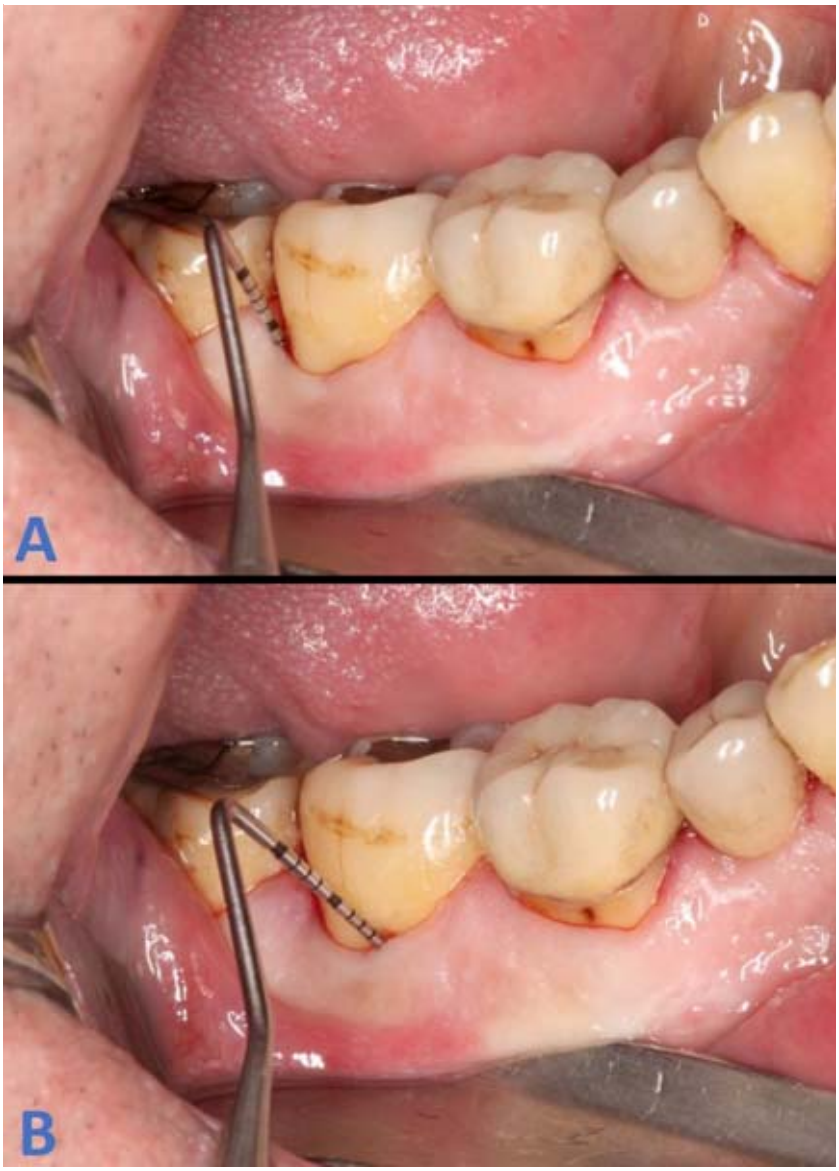



**Figure 5 A** Periodontal probing at the distal aspect of tooth #47 (case 2); **B** Periodontal probing at the mid-buccal furcation aspect of tooth #47 (case 2).

The aim of this publication is to present 2 cases of localised periodontitis with mandibular furcation lesions grade II which were treated using allograft bone, bio-resorbable pericardium membrane (Jason Membrane, Botiss Company, Berlin, Germany) and Emdogain following the concept of guided tissue regeneration. In both cases the co-factor of localized occlusal trauma had to be controlled before the initiation of regenerative periodontal therapy. The case reports are followed by a literature review including the application of regenerative procedures in periodontics.

## Case Reports

Both cases presented in this article were treated in a private practice limited to Periodontology and Implant Dentistry by the same clinician (Dr. Ö. S., FPI-Hamburg, Germany). Both patients were referred to this office for the treatment of advanced periodontal disease. They were in good general health and indicated on the medical history forms not to smoke cigarettes and not to suffer from any other diseases and not to take any

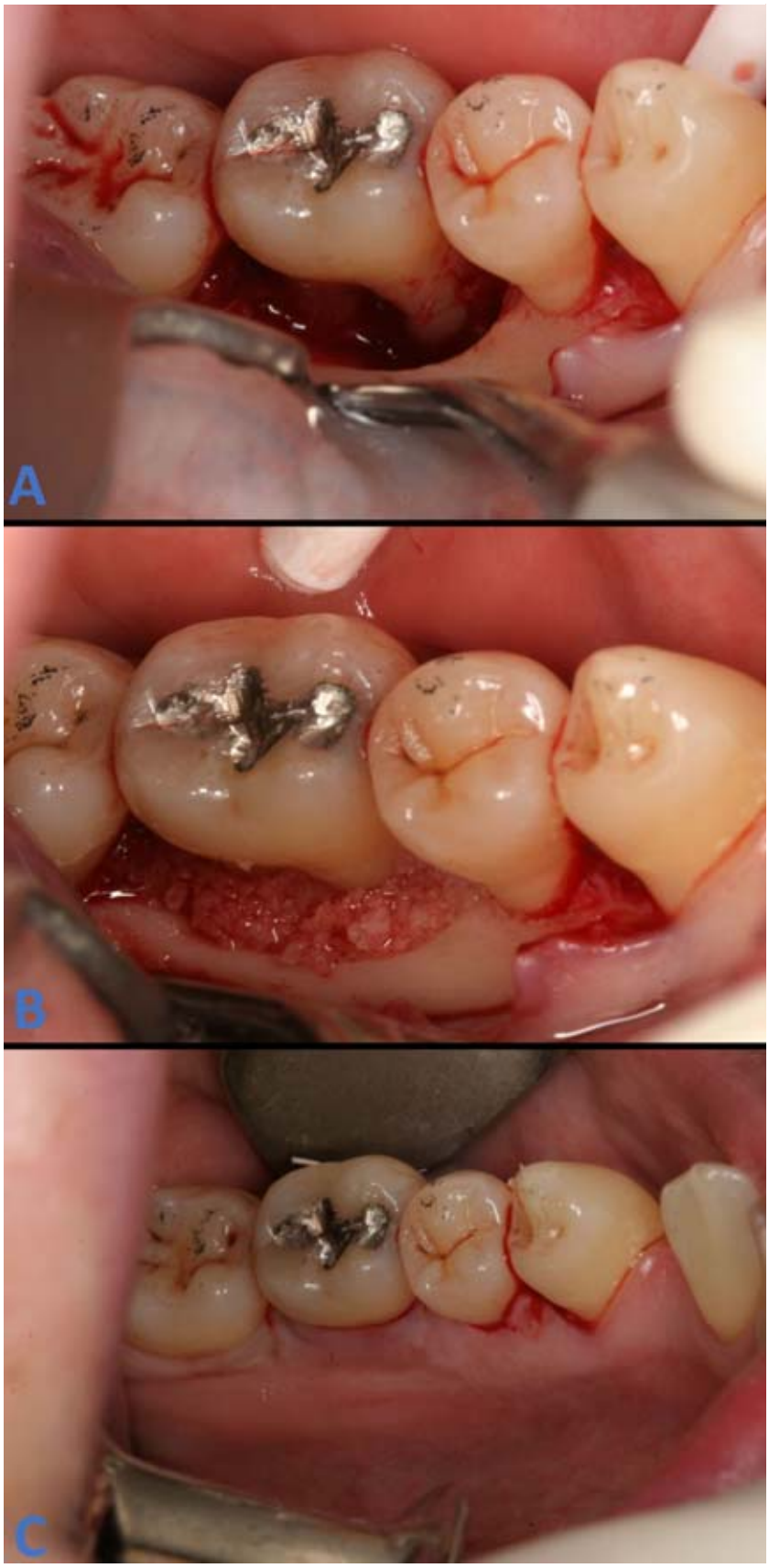



**Figure 6 A** Intraoperative view following flap reflection and removal of the granulation tissue at tooth #37 (case 1); **B** Intraoperative view following application of EMD and the bone allograft material at tooth #37 (case 1); **C** Intraoperative view following primary wound closure using a circumferential suture (case 1).

medications. According to the new classification of periodontal diseases both patients presented with a stage III disease due to their furcation grade II defects, PPD exceeding 5 mm and the potential of tooth loss. Furthermore, they presented with a fast progression rate on the molar teeth with furcation grade II involvement due to the local co-factor of occlusal trauma, which resulted in a grading of III. The individual caries risk was low for case 1 and medium for case 2. Any operative, restaurative, or endodontic dental treatment was carried out by the referring dental offices.

Informed consent was obtained from patients prior to periodontal therapy. The initial treatment consisted of professional teeth cleaning with further oral hygiene instructions and aids for interproximal cleaning. The plaque index (PI) was monitored and recorded and periodontal treatment was initiated when the PI was below 10 %, indicating an efficient oral hygiene. Systematic periodontitis treatment including deep scaling and root planning was performed following the modified concept of full-mouth-disinfection. Sixteen weeks later the clinical situation was re-evaluated, and the patients were informed about the option of subsequent regenerative periodontal therapy. Except the co-factor of occlusal trauma the teeth scheduled for treatment were vital and no caries or other limiting factors like insufficient margins were detectable.

## Case 1

A 40-year-old healthy female presented in 2010 for treatment of localized advanced periodontitis.

The general (BOP) was at 9 % and most of the bleeding was provoked around the tooth scheduled for regenerative treatment. The PI was reduced to 8 %, which indicates efficiency of plaque control performed by the patient. Nevertheless, the initial examination of tooth 37 revealed a pocket probing depth (PD) of 8 mm and bleeding on probing on all the sites, except mid-buccal (Figure 1). On the obtained periapical radiograph, the furcation involve-

ment with interradicular bone destruction is clearly visible (Fig. 2).

Diagnosis regarding occlusal trauma determined an occlusal dysfunction as a co-factor for the aetiology of this periodontal defect. Therefore, prior to periodontal treatment the referring dentist was asked to eliminate the overloading on the respective teeth from the suspected sleep bruxism habit by means of a night guard. This was followed by a final re-evaluation, which should be the basis for the later following regenerative periodontal procedure.

## Case 2

A healthy male patient, 56 years of age at the onset of treatment, was referred by a general practitioner to us in 2013 for treatment of advanced periodontal disease. The periodontal status is illustrated in Figure 3. Several advanced periodontal defects were detected throughout the patient's dentition, that were scheduled for non-surgical periodontal treatment. Suppuration was recorded at tooth #47. An advanced periodontal defect is visible on the radiograph indicating the influence of occlusal trauma as a cofactor by means of widened periodontal ligament spaces surrounding the mesial and distal roots of tooth #47 as well as at the distal root and the interradicular area of tooth #46. Additionally, a very mild vertical bony defect was visible at the distal aspect of tooth #46 as well as significant subgingival calculus. Gutta-percha points were inserted into the pocket before a periapical radiograph was taken. The distally inserted gutta-percha point shows the circumferential infrabony defect (Figure 4), the 6-point pocket depths measurements (Figure 5) indicated pocket depths of up to 12 mm and a vertical component of 6 mm (subgroup B), according to the classification of Tarnow and Fletcher [55] as well as a BOP of 33 %. Furthermore, the tooth #47 showed degree 1 mobility as well an enamel crack in occluso-gingival direction (type II) [53], which could also be interpreted as a result of occlusal trauma.

In interdisciplinary cooperation with the specialist for diagnosis and treatment of craniomandibular dysfunction (Priv.-Doz. Dr. M. O. A., CMD-Centrum Hamburg-Eppendorf), the patient received functional therapy involving occlusal adjustments aimed at the elimination of occlusal trauma as well as wearing an occlusal splint beforehand. The occlusal splint was constructed following the concept by Ramfjord using a maxillary ("Michigan") splint [49]. This maxillary occlusal stabilization splint covers all teeth, features a cuspid rise and freedom in centric in an area of 0.5–1.0 mm on the splint's occlusal plane [8]. In this bite plane, centric relation represents the therapeutic position that stabilizes the mandible in occlusal relations. Increasing the vertical dimension that is achieved by occlusal part results in relaxation of masticatory muscles.


**Figure 7 A** Intraoperative view following flap reflection and removal of the granulation tissue at tooth #47 (case 2); **B** Intraoperative view following application of EMD and the bone allograft material at tooth #47 (case 2); **C** Intraoperative view following positioning of the pericardium membrane at tooth #47 (case 2); **D** Intraoperative view showing the autogenous fibrin membrane before application at tooth #47 (case 2); **E** Intraoperative view showing the autogenous fibrin membrane positioned on top of the pericardium membrane at tooth #47 (case 2); **F** Intraoperative view following primary wound closure using a circumferential suture (case 2).

# Materials and Methods

## Materials

The surgical procedure followed the manufacturer's protocol in a step-by-step approach: Removal of the granulation tissue adhering to the infected root surface, smoothing of the root surface, application of EDTA Prefgel (Straumann AG, Basel, Switzerland) and subsequent rinsing with sterile saline was followed by the application of the EMD.

For the optimal precipitation of the enamel matrix proteins on the root surface, EMD was applied immediately after preparation with PrefGel and the root surface was free from blood and saliva.

Thirty-six ml venous blood was collected from the patients prior to surgery in 4 tubes each containing 0.5 cc concentrate of sodium citrate

3.8 % as anti-coagulant and centrifuged according to the manufacturer's specifications (Biotechnology Institute, Vitoria, Spain). After centrifugation, regularly the following layers are obtained:

- the yellowish top layer – the plasma;
- the leukocyte layer or "buffy coat" below the plasma layer, about 5 mm in thickness;
- the bottom layer, which contains the red cells.

The plasma, in turn, is divided in 2 different fractions, which are characterized by different concentration of platelets:

- a bottom fraction, "fraction-2", which covers a layer of 2 ml thickness above the leukocyte layer or "buffy coat"; this fraction contains 2 to 3 times more platelets compared with the blood;
- the superficial fraction-1 (above the fraction-2) contains a similar number of platelets as the peripheral blood. This fraction forms a gelatinous fibrin membrane after activation with 10 % calcium-chloride in a ratio of 1:2.

After it's formation the fibrin membrane was placed under the grid of the compression box and gently compressed with the lid of the box in order to obtain a standardized thickness. Puros allograft (Zimmer Dental GmbH, Munich, Germany) was first rehydrated in sterile saline solution and then immersed in the fraction-2 of the PRGF system. The tissue was first covered with a pericardium membrane and then covered with a PRGF fibrin membrane.

## Surgical protocol

Following the administration of local anaesthesia (Ultracain D-S forte 1:100.000, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany an intrasulcular incision was made and mucoperiosteal flaps were raised.

Cleaning, removal of the granulation tissue and smoothing of the root surface, especially in the furcation area was carried out with ultrasound hand instruments, fine rotating diamond instruments and a Piezosurgery device. The situation was precisely re-evaluated intraoperatively in order to rule out a grade III furcation defect, as regenerative treatment would not have been performed in the presence of a grade III furcation lesion. The finding of grade II furcation defects confirmed the evaluation of the diagnostic X-ray. The root surface was then conditioned with PrefGel and after 2 minutes, it was rinsed with a sterile saline solution and EMD was applied. Puros allograft was firstly rehydrated with normal saline and consecutively mixed with the fraction-2 containing platelet concentrate and then placed on the defect site.

In order to achieve accelerated wound healing, the Puros allograft was used in combination with the PRGF-Endoret fibrin membrane. The graft material was compacted into the infrabony defect, compressing against the surrounding bone, layer by layer, until the furcation defect was filled. The pericardium membrane was used to cover the bone graft and then the fibrin membrane, obtained from the fraction-1 of the PRGF system was used to cover the pericardium membrane before primary closure was achieved. The surgical procedures are illustrated in Figures 6 and 7.

Wound closure was performed by tension-free primary closure using non-resorbable PTFE sutures (Goretex company, Flagstaff, Arizona, USA). After the tissues were sutured, the incision line was inspected for any open areas or particles.

## Postoperative care

The patients received postoperative instructions including rinsing with 0.2 % chlorhexidine (Glaxo Smith Kline, Brentford, UK) 3 times daily for 2 weeks as well as amoxicillin 1 g (3 times daily) for 1 week and ibuprofen 600 mg as needed [26]. They were advised to avoid brushing the area up to 2 weeks after surgery. The sutures were removed after 14 days. At follow-up appointments 2 months after the surgery the wound healing was monitored. For a period of 1 year after the regenerative treatment no subgingival debridement or probing was performed.

Supportive periodontal therapy was carried out regularly after the treatment. Patients were advised to have their routine supportive periodontal care every 3 months by their general dentist – without any subgingival intervention. Additionally, the patients were seen in the periodontal practice for annual recall appointments in order to re-evaluate the treatment outcomes.

## Results

After 12 months, 6-point pocket chart measurements demonstrated distinctive clinical improvements. Furthermore, patients were placed in an alternating 3-month recall during supportive periodontal therapy (SPT) and clinically and radiologically evaluated at 1 year, 3 years, and 5 years postoperatively. The results during 8-years of SPT in case 1 and 5 years of SPT in case 2 are presented in the following section.

### Case 1

During the follow-up period of 8 years there were no signs for inflammation detectable and the periodontal tissues appeared healthy (Figure 8). Radiographic examination 8 years after the surgery revealed almost 100 % defect fill; no furcation involvement was radiographically visible or clinically detectable (Figure 9). A significant reduction of the PPD from 8 mm initially to a maximum of 3 mm 1 year after the regenerative treatment was observed and this clinical condition remained stable without bleeding on probing throughout the subsequent follow-up period of 8 years (Figure 10). The occlusal condition was evaluated on a regular basis and the night guard was worn regularly by the patient and adjusted in order to ensure the elimination of dynamic interferences on the splint in the premolar- and molar-region while maintining equilibrated static occlusal contacts.

### Case 2

Five years after the regenerative surgery on tooth #47, probing pocket depths were recorded indicating probing depths ranging from 2 to 5 mm without any signs of gingival inflammation. In comparison, the initial PPD of 12 mm on deepest pocket before surgery and a residual

probing depth of 3 mm at the same location on the tooth 5 years after the procedure demonstrates a 9 mm gain in clinical attachment level and no furcation involvement or mobility was observed. Radiographic evaluation obtained 5 years after therapy showed an almost complete defect fill and an increased radiopacity in the furcation area, compared to the situation at baseline (Figures 11–12). Furthermore, the non-surgically treated molar teeth #26, #27 and #36, #37 presented without inflammation and increased PPD throughout the follow-up period, tooth #38 unfortunately developed an advanced periodontal pocket at the mesial aspect and will be scheduled for treatment in the near future. As described in the case 1 the occlusal situation of the teeth was evaluated annually as was the occlusion on the occlusal splint. The splint was worn by the patient every night.

**Figure 8** Clinical view of tooth #37 after 8 years postoperatively.

**Figure 9** Radiographic evaluation of tooth #37 after 8 years postoperatively.

## Discussion

### Occlusal Trauma

In the present case report, the combined regenerative therapy with GTR, allograft bone substitute and the application of EMD, a pericardium membrane, and PRGF is presented in 2 patients who suffered from severe localised periodontitis. Both patients were treated by the same periodontist and were followed up for 8 and 5 years, respectively.

The initial assessment of the general periodontal condition of the 2 patients presented in this report confirmed that at the beginning of the therapy both patients suffered from dental trauma from occlusion. The role of trauma from occlusion in periodontal diseases has been debated controversially in periodontal literature.

The evaluation of records from a private practice limited to periodontics strongly suggest an association between initial occlusal discrepancies and various clinical parameters indicative of periodontal disease [44]. In another study by the same authors, teeth with multiple types of occlusal contacts had shown significantly deeper initial probing depths and poorer prognosis compared to teeth without occlusal discrepancies [29]. The results of a study, performed on a group of 31 individuals in Japan, suggested that involuntary masseter muscle activity caused by bruxism might be related to the severity of periodontitis [35]. Statistically significant correlations were found in between the total amount of secondary occlusal trauma per patient and the severity of periodontitis and attachment loss in a study with 288 cases [10].

A cross sectional study on 2,980 subjects has shown the association of non-working side contact with deeper probing depth and more clinical attachment loss [9]. Recently, it has been demonstrated that traumatic occlusion can aggravate the symptoms of periodontitis [46]. According to Ramfjord and Ash, occlusal therapy may be required to enhance occlusal stability at any stage of periodontitis but is most often necessary in advanced periodontitis [48]. A literature review has concluded that untreated occlusal discrepancies can exacerbate periodontal disease; therefore, occlusal therapy should be an integral part of the periodontal treatment [40]. It has

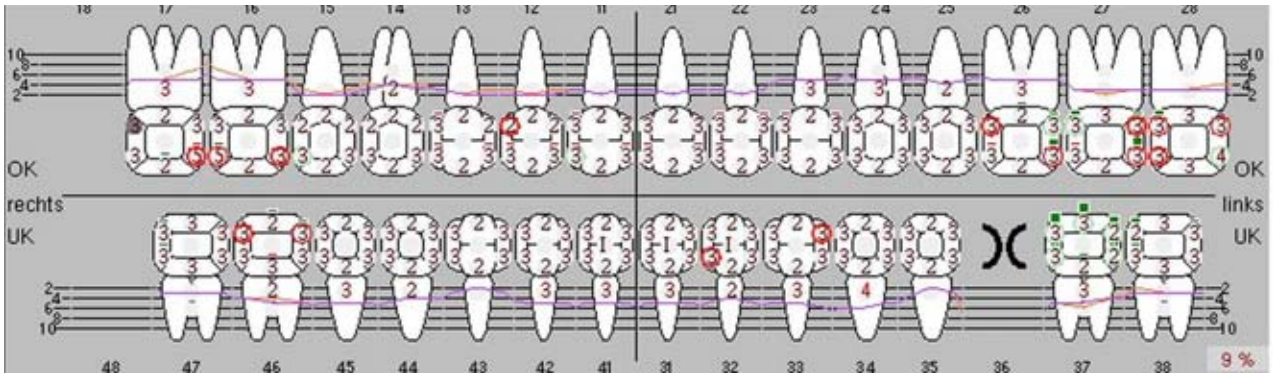



**Figure 10** Periodontal measurement at 8 years postoperatively (case 1).

also been stated that clinician's decision, whether or not to use occlusal adjustment as a component of periodontal therapy should be related to an evaluation of clinical factors involving patient comfort and function [50]. Burgett et al. evaluated the effect of occlusal adjustment combined with periodontal treatment on the level of connective tissue attachment, the depth of gingival pockets and tooth mobility [11]. The results of this study indicated a greater gain of attachment level when occlusal adjustments have been performed in the treatment of periodontitis. McGuire et al. postulated that patients are twice as likely to loose their teeth if there is increasing mobility, if they have a parafunctional habit and do not wear a bite guard [39]. The results of a 10– to 18-year follow up study in patients suffering from chronic generalized moderate to severe periodontitis revealed that patients affected with bruxism who did not wear a splint had an inferior periodontal prognosis compared to those who did wear a splint [45]. The results of a literature review performed by Sutthiboonyapan and Wang indicated that an occlusal splint appears to be a useful device to treat patients with parafunctional habit related symptoms and dentists should consider recommending occlusal splints as part of the comprehensive dental care for patients with bruxism [54]. In a recent narrative review Fan and Caton evaluated the role of occlusal trauma and excessive occlusal forces and postulated that in animal and human studies some associations between occlusal trauma and occlusal discrepancies and the progression of periodontal disease exists. Therefore, occlusal trauma seems to be a very important potential co-factor for the progression of periodontal diseases and should be identified and controlled throughout interdisciplinary therapy [18]. Furthermore, the new classification of periodontal diseases also identifies occlusal trauma as an important factor for modifying the risk of disease progression (grading) [57].

According to these expert opinions and outcomes of scientific literature patients suffering from periodontal disease should be regularly screened for bruxism. The new Bruxism-Screening-Index of the German Society of Craniomandibular Function and Disorders in the DGZMK (www.DGFDT.de) was introduced recently in order to facilitate a simplified identification of the respective patients.[1]

Furthermore, in the light of the cited literature it appears reasonable to specifically check for occlusal trauma prior to periodontal therapy as described in this paper and – if applicable – to perform occlusal therapy before the initiation of periodontal regenerative procedures.

## Guided Tissue Regeneration in advanced periodontal defects and mandibular class II furcation defects

In the present case reports we applied a combination of allograft bone substitute, EMD, a pericardium membrane, and PRGF for the regenerative therapy of advanced localized periodontal mandibular class II defects using the technique of GTR. As mentioned before, both patients were treated by the same periodontist and were followed up for 8 and 5 years, respectively.

The role of trauma from occlusion in periodontal diseases has been controversially discussed in the first part of the discussion. The following part of the discussion will discuss the rational and the evidence for the use of the before mentioned materials.

## The use of GTR combined with osseous grafts in mandibular class II furcation defects

Different therapeutic modalities have been proposed in guided tissue regeneration in order to achieve the regeneration of periodontal tissues. Among these, the use of different bone grafting materials, barrier membranes, enamel matrix derivates and growth factors has been described and investigated in the literature.

The effects of GTR combined with osseous grafts and GTR alone in the treatment of class II furcation defects was investigated in a meta-analysis of 20 randomized con-

[1] Bruxismus-Screening-Index: https://www.dgfdt.de/documents/266840/3732097/Bruxismus-Screening+DGFDT/f52a44c1−6b03−4b7b-8dd0-c301be890e08

trolled clinical trials [14]. According to this investigation, in GTR combined with osseous grafts the closure rate of the furcation, the attachment level gain and the bone fill (vertical/horizontal) were higher compared to conventional open flap debridement procedure and GTR alone [14]. The combination of resorbable membranes and bone replacement materials can improve the chances of recovery, although so far limited human clinical trials are available [51].

The use of allogeneic bone grafts with a resorbable pericardium membrane as described in the present case reports facilitated new bone formation by inhibiting connective tissue invasion as well as epithelial downgrowth [1]. There are many types of allografts available that are suitable to use in different types of defect. Puros allograft is available as particulate grafts or as a bone block. The allogeneic material offers a combination of preserved natural collagen, mineral crystals, and structural bony architecture that is percieved to be optimal. Furthermore, the material is produced through the validated Tutoplast Refinement Process [52].

This graft cleaning and preservation process includes a solvent dehydration that virtually eliminates the possibility of disease transmission and removes unwanted materials while preserving the natural collagen matrix. The Tutoplast process is well established after 40 years of experience. The manufacturer states the application in more than 5 million procedures. The matrix of puros aims to facilitate the regeneration and bone formation in greater quantities. Histological examinations in the sinus lift or the extraction sockets have shown that the material indeed is mostly converted into vital, endogenous bone within 4 to 7 months, resulting in a bone density similar to that of the original host bone. Histomorphometric evaluation of the bone has indicated between 5 % and 8 % residual content of augmentation material, which further demonstrates the resorption of this bone grafting material during healing [11, 39, 45].

**Figure 11** Radiographic evaluation of tooth #47 after 5 years postoperatively.

The high volume stability of allograft bone can significantly reduce absorption of the buccal bone lamella in extraction sockets but it is not able to prevent it [19].

## The use of enamel matrix derivates (EMD)

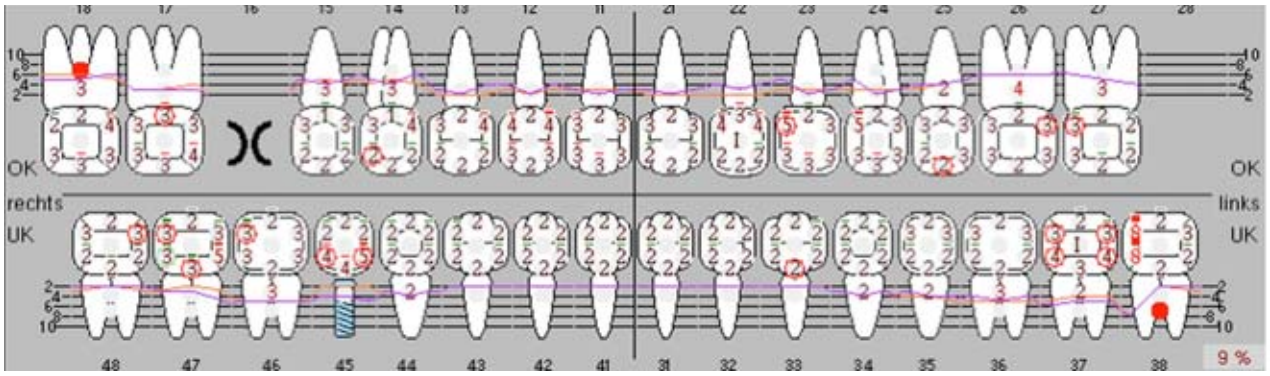
For more than 2 decades, enamel matrix derivates have been used in the treatment of intrabony defects, furcation defects, and recession defects [38, 42]. The wound-healing-promoting effect of EMD and the lowering of systemic inflammatory factors have been investigated repeatedly [23, 61]. Recently, EMD has also been suggested as an adjunct to non-surgical periodontal treatment in deep inflamed periodontal pockets of 5–9 mm depth [2]. A large number of studies indicate that EMD may have the potential to trigger regenerative responses in periodontal ligament cells [31, 37].

## The use of enamel matrix derivates (EMD) combined with GTR in the treatment of mandibular furcation grade II defects

Clinical success in using GTR without EMD or in combination with EMD also depends on cofactors such as smoking, age, oral hygiene status. In a study from Dresden it was shown in 51 patients that the use of EMD led to a significant reduction of the inflamed gingival pocket depth, as compared to the exclusive GTR treatment alone [30]. The use of EMD with GTR for the treatment of mandibular molar grade II furcation defects has shown clinical improvements. In a 24-month prospective clinical study, however, a significant reduction in proximal furcation defects was found in a test group of 12 patients [13]. Nevertheless, a complete regeneration of the defect cannot always be expected.

## The use of enamel matrix derivates (EMD) combined with osseous grafts in mandibular furcation class II defects

Outcomes of regenerative periodontal surgery using a combination of an EMD and autogenous bone has shown higher soft and hard tissue improvements compared to the treatment with EMD alone [63]. The use of bovine-derived xenograft with EMD has shown to be effective in enhancing new bone and cementum formation in the treatment of intrabony defects [62]. In another study, EMD in combination with a bone




(Fig. 1–12: Ö. Solakoglu)

**Figure 12** Periodontal measurement at 5 years postoperatively (case 2).

substitute graft has shown to improve the treatment of class II furcation defects in 41 patients, but with no significant improvement compared to bone substitute graft alone [47]. According to yet another study, EMD either alone or in combination with grafts can be effectively used to treat intra-osseous defects and the additional use of a graft seems to enhance the clinical outcomes [58].

## The use of enamel matrix derivates (EMD) combined with GTR and osseous grafts

The synergistic effects of using a resorbable membrane with an allograft bone substitute material as well as EMD were demonstrated in a case-control study performed on 30 patients with chronic periodontitis. It was shown that the combination of EMD and allograft and barrier membranes could significantly reduce the pocket depth as well as the vertical attachment level – compared to the treatment with allograft and barrier membranes alone [32].

## The use of platelet-rich-growth factors (PRGF)

Furthermore, platelet-rich-growth factors (PRGF) have been used to facilitate bone and tissue healing. It specifically stimulate angiogenesis and proliferation and migration of osteoblasts [6]. According to Döri et al., the use of PRGF enables the stimulation, the proliferation and the differentiation of periodontal ligament cells and osteoblasts [16]. Fibrin matrix releases growth factors and acts as a temporal nesting scaffold for the cells [5].

## The use of GTR and platelet-rich-growth factors (PRGF)

A higher improvement trend was seen in grade II furcation lesions that were treated with PRGF/GTR compared to GTR alone [33] and fibrin membrane has shown to have the potential of improving GTR results in the management of intrabony defects [36]. The PRGF-Endoret technology was implicated with inorganic bone substituents in lateral sinus lift procedures and it has shown to increase the healing process and help to obtain a more reliable bone regeneration and also higher quality of bone [12].

In summery, the literature indicates that the combination of the EMD with the technique of Guided Tissue regeneration and osseous grafts with the application of platelet-rich-growth factors (PRGF) may be superior to the application of individual materials and techniques and bears a synergistic effect in the regenerative treatment of furcation defects. The 2 case reports presented in this publication illustrate the practical procedures and the potential of this technique.

## Conclusion

Choosing the most suitable regenerative procedure is based on general and site specific conditions. Accurate assessment of the periodontal defect, appropriate selection of the therapeutic approach, management and long-term retention of teeth with periodontal defects, depends not only on the operator's skill and experience but also on the selection of the suitable regenerative materials and techniques. Osseous defect characteristics, the degree of furcation involvement and the tooth's endodontic status significantly influences the therapeutic success. Moreover, teeth that are treated as intensely as demonstrated in this report should be relieved from occlusal trauma in order to optimize the condition for successful regeneration.

Furthermore, the cost-benefit ratio for this treatment approach should be discussed with the patient beforehand. The scientific literature provides evidence for long-term stability of successfully periodontally regenerated teeth. This approach is much less invasive than for example the treatment option of a 3 unit bridge and has a superior long-term prognosis if good supportive periodontal care is provided. However, the treatment option with a dental implant needs also be addressed in the decision making process. The longterm prognosis of a dental implant is comparable to a periodontally regenerated tooth. The costs involved for the placement of a dental implant is at least in Germany much higher than for periodontal regeneration of a single tooth and exceeds including the prosthodontic rehabilitation at least 2.5 times the amount for regeneration. Furthermore, the treatment time and the number of surgical interventions is much higher for implant restaurations than for tooth maintenance.

In conclusion, it can be stated that the combination of allogeneic cancellous bone substitute, EMD,

PRGF, fibrin membrane and a resorbable pericardium barrier membrane promises good clinical results in the regenerative treatment of furcation degree II defects in mandibular molars. Furthermore, teeth that are treated as intensely as demonstrated in this report should be relieved from occlusal trauma in order to optimize the condition for successful regeneration.

## Conflicts of interest

The authors declare that there is no conflict of interest within the meaning of the guidelines of the International Committee of Medical Journal Editors.

### References

1. Ahn YS, Kim SG, Kim CS, Oh JS, Lim SC: Effect of guided bone regeneration with or without pericardium bioabsorbable membrane on bone formation. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 114: 126–131

2. Aimetti M, Ferrarotti F, Mariani GM, Romano F: A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: a 24-month randomized controlled clinical trial. Clin Oral Investig 2017; 21: 327–337

3. Alpiste Illueca FM, Buitrago Vera P, de Grado Cabanilles P, Fuenmayour Fernandez V, Gil Loscos FJ: Periodontal regeneration in clinical practice. Med Oral Patol Oral Cir Bucal 2006; 11: E382–392

4. Anitua E: The use of plasma-rich growth factors (PRGF) in oral surgery. Pract Proced Aesthet Dent 2001; 13: 487–493

5. Anitua E, Alkhraisat MH, Orive G: Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release 2012; 157: 29–38

6. Anitua E, Tejero R, Zalduendo MM, Orive G: Plasma rich in growth factors promotes bone tissue regeneration by stimulating proliferation, migration, and autocrine secretion in primary human osteoblasts. J Periodontol 2013; 84: 1180–1190

7. Ausenda F, Rasperini G, Acunzo R, Gorbunkova A, Pagni G: New perspectives in the use of biomaterials for periodontal regeneration. Materials (Basel) 2019; 12 (13). pii: E2197. doi: 10.3390/ma12132197

8. Badel T, Simonić-Kocijan S, Lajnert V Dulčić N, Zadravec D: Michigan splint and treatment of temporomandibular joint. Medicina Fluminesis 2013; 49; 112–120

9. Bernhardt O, Gesch D, Look JO The influence of dynamic occlusal interferences on probing depth and attachment level: results of the Study of Health in Pomerania (SHIP). J Periodontol 2006; 77: 506–516

10. Branschofsky M, Beikler T, Schäfer R, Fleming TF, Lang H: Secondary trauma from occlusion and periodontitis. Quintessence Int 2011; 42: 515–522

11. Burgett FG, Ramfjord SP, Nissle RR, Morrison EC, Charbeneau TD, Caffesse RG: A randomized trial of occlusal adjustment in the treatment of periodontitis patients. J Clin Periodontol 1992; 19: 381–387

12. Călin DL, Mitrea M, Rusu A: External sinus lift using the technology PRGF endoret: A case report. Rev Română Anat funcțională și Clin macro- și Microsc și Antropol 2017; XVI: 80–86

13. Casarin RCV, Ribeiro EP, Nociti FH et al.: Enamel matrix derivative proteins for the treatment of proximal class II furcation involvements: A prospective 24-month randomized clinical trial. J Clin Periodontol 2010; 37: 1100–1109

14. Chen TH, Tu YK, Yen CC, Lu HK: A systematic review and meta-analysis of guided tissue regeneration/osseous grafting for the treatment of Class II furcation defects. J Dent Sci 2013; 8: 209–224

15. Chowdhary Z, Mohan R: Furcation involvement: Still a dilemma. Indian J Multidiscip Dent 2017; 7: 34–40

16. Döri F, Huszár T, Nikolidakis D et al.: Effect of platelet-rich plasma on the healing of intrabony defects treated with Beta tricalcium phosphate and expanded polytetrafluoroethylene membranes. J Periodontol 2008; 79: 660–669

17. Eickholz P, Pretzl B, Holle R Kim TS: Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. III. Class II furcations after 10 years. J Periodontol 2006; 77: 88–94

18. Fan J; Caton JG: Occlusal trauma and excessive occlusal forces: Narrative review, case definitions, and diagnostic considerations. JClin Perio 2018; 45 (Suppl 20): S199–206

19. Fotek PD, Neiva RF, Wang HL: Comparison of dermal matrix and polytetrafluoroethylene membrane for socket bone augmentation: a clinical and histologic study. J Periodontol 2009; 80: 776–785

20. Froum SJ, Wallace SS, Elian N, Cho SC, Tarnow DP: Comparison of mineralized cancellous bone allograft (Puros) and anorganic bovine bone matrix (Bio-Oss) for sinus augmentation: histomorphometry at 26 to 32 weeks after grafting. Int J Periodontics Restorative Dent 2006; 26: 543–551

21. Gapski R, Neiva R, Oh T-J, Wang HL: Histologic analyses of human mineralized bone grafting material in sinus elevation procedures: a case series. Int J Periodontics Restorative Dent 2006; 26: 59–69

22. Gaudilliere DK, Culos A, Djebali K et al.: Systemic immunologic consequences of chronic periodontitis. J Dent Res 2019; 98: 985–993

23. Gennai S, Petrini M, Tonelli M, Marianelli A, Nisi M; Graziani F: PD065: Acute phase response following non-surgical periodontal therapy with enamel matrix derivative. A randomized clinical trial. J Clin Periodontol 2018. doi.org/10.1111/jcpe.66_12914

24. Gher ME: Changing concepts. The effects of occlusion on periodontitis. Dent Clin North Am 1998; 42: 285–299

25. Glickman I, Smulow JB: Effect of excessive occlusal forces upon the pathway of gingigval inflammation in humans. J Periodontol 1965; 36: 141–147

26. Goodson JM, Haffajee AD, Socransky SS et al: Control of periodontal infections: A randomized controlled trial I. The primary outcome attachment gain and pocket depth reduction at treated sites. J Clin Periodontol 2012; 39: 526–536

27. Graves D: Cytokines that promote periodontal tissue destruction. J Periodontol 2008; 79 (8 Suppl): 1585–1591

28. Hamp SE, Nyman S LJ: Periodontal treatment of multirooted teeth. Results after 5 years. J Clin Periodontol 1975; 2: 126–135

29. Harrel SK, Nunn ME: The association of occlusal contacts with the presence of increased periodontal probing depth. J Clin Periodontol 2009; 36: 1035–1042

30. Hoffmann T, Richter S, Meyle J et al: A randomized clinical multicentre trial comparing enamel matrix derivative and membrane treatment of buccal class II furcation involvement in mandibular molars. Part III: Patient factors and treatment outcome. J Clin Periodontol 2006; 33: 575–583

31. Iviglia G, Kargozar S, Baino F: Biomaterials, current strategies, and novel nano-technological approaches for periodontal regeneration. J Funct Biomater

2019; 10(1). pii: E3. doi: 10.3390/jfb10010003.

32. Jaiswal R, Deo V: Valuation of the effectiveness of enamel matrix derivative, bone grafts, and membrane in the treatment of mandibular Class II furcation defects. Int J Periodontics Restor Dent 2013; 33: e58–64

33. Jenabian N, Haghanifar S, Ehsani H, Zahedi E, Haghpanah M: Guided tissue regeneration and platelet rich growth factor for the treatment of Grade II furcation defects: A randomized double-blinded clinical trial – A pilot study. Dent Res J (Isfahan); 2017; 14: 363–369

34. Jordan AR, Micheelis W: Fünfte Deutsche Mundgesundheitsstudie (DMS V) Deutscher Zahnärzteverlag, Köln 2016

35. Kato S, Ekuni D, Kawakami S, Mude HM, Morita M, Minagi S: Relationship between severity of periodontitis and masseter muscle activity during waking and sleeping hours. Arch Oral Biol 2018; 90: 13–18

36. Lei L, Yu Y, Han J et al.: Quantification of growth factors in advanced platelet-rich fibrin and concentrated growth factors and their clinical efficiency as adjunctive to the GTR procedure in periodontal intrabony defects. J Periodontol 2020; 91: 462–472

37. Lyngstadaas SP, Lundberg E, Ekdahl H, Andersson C, Gestrelius S: Autocrine growth factors in human periodontal ligament cells cultured on enamel matrix derivative. J Clin Periodontol 2001; 28: 181–188

38. Masaeli R, Zandsalimi K, Lotfi Z, Tayebi L: Using enamel matrix derivative to improve treatment efficacy in periodontal furcation defects. J Prosthodont 2018; 27: 733–736

39. McGuire MK, Nunn ME: Prognosis versus actual outcome. III. The effectiveness of clinical parameters in accurately predicting tooth survival. J Periodontol 1996; 67: 666–674

40. Meredyk K, Kostrzewa-Janicka J, Nędzi-Góra M: The effect of occlusal loading on the periodontal tissues. A literature review. Part I – Occlusion and periodontitis. Dent Med Probl 2015; 52: 215–221

41. Micheelis W: Deutsche Mundgesundheitsstudie – DMS IV – ein kurzer Überblick. Deutscher Zahnärzte Verlag, Köln 2006, S. 1–10

42. Miron RJ, Sculean A, Cochran DL et al.: Twenty years of enamel matrix derivative: the past, the present and the future. J Clin Periodontol 2016; 43: 668–683

43. Nishiyama K, Okudera T, Watanabe T et al.: Basic characteristics of plasma rich in growth factors (PRGF): blood cell components and biological effects. Clin Exp Dent Res 2016; 2: 96–103

44. Nunn ME, Harrel SK: The effect of occlusal discrepancies on periodontitis. I. Relationship of initial occlusal discrepancies to initial clinical parameters. J Periodontol 2001; 72: 485–494

45. Nunn ME, Fan J, Su X, Levine RA, Lee HF, McGuire MK: Development of prognostic indicators using classification and regression trees for survival. Periodontol 2000 2012; 58: 134–142

46. Pan W, Yang L, Li J et al.: Traumatic occlusion aggravates bone loss during periodontitis and activates Hippo-YAP pathway. J Clin Periodontol 2019: 46: 438–447

47. Queiro LA, Santamari MP, Casati MZ, et al.: Enamel matrix protein derivative and/or synthetic bone substitute for the treatment of mandibular class II buccal furcation defects. A 12-month randomized clinical trial. Clin Oral Investig 2016; 20: 1597–1606

48. Ramfjord SP, Ash MM: Significance of occlusion in the etiology and treatment of early, moderate and advanced periodontitis. J Periodontol 1981; 52: 511–517

49. Ramfjord SP, ASH MM: Reflections on the Michigan occlusal splint. J Oral Rehabil 1994; 21: 491–500

50. Sanadi DRM, Chelani DLR, Bhakkand DSR, Sheth DJK: Role of trauma from occlusion in periodontal disease – A controversy. IOSR J Dent Med Sci 2016; 15: 118–122

51. Sanz M, Jepsen K, Eickholz P, Jepsen S: Clinical concepts for regenerative therapy in furcations. Periodontol 2000 2015; 68: 308–332

52. Schoepf C: The Tutoplast® process: A review of cfficacy. Int Mag Oral Implantol 2006; 1: 10–15

53. Segarra MS, Shimada Y, Sadr A, Sumi Y, Tagami J: Three-dimensional analysis of enamel crack behavior using optical coherence tomography. J Dent Res 2017; 96: 308–314

54. Sutthiboonyapan P, Wang HL: Occlusal splints and periodontal/implant therapy. J Int Acad Periodontol 2019; 31: 45–50

55. Tarnow D, Fletcher P: Classification of the vertical component of furcation involvement. J Periodontol 1984; 55: 283–284

56. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J: Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. J Clin Periodontol 2017; 44: 456–462

57. Tonetti MS, Greenwell H; Kornman KS: Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Clin Periodontol 2018; 45 (Suppl 20): S149–161

58. Trombelli L, Farina R: Clinical outcomes with bioactive agents alone or in combination with grafting or guided tissue regeneration. J Clin Periodontol 2008; 35: 117–135

59. Waerhaug J: The angular bone defect and its relationship to trauma from occlusion and downgrowth of subgingival plaque. J Clin Periodontol. 1979; 6: 61–82

60. Wang H-L, Pappert TD, Castelli WA, chiego DJ Jr., Shyr Y, Smith Ba: The effect of platelet-derived growth factor on the cellular response of the periodontium: an autoradiographic study on dogs. J Periodontol 1994; 65: 429–436

61. Wennström JL, Lindhe J: Some effects of enamel matrix proteins on wound healing in the dento-gingival region. J Clin Periodontol 2002; 29: 9–14

62. Yamamoto S, Masuda H, Shibukawa Y, Yamada S: Combination of bovine-derived xenografts and enamel matrix derivative in the treatment of intrabony periodontal defects in dogs. Int J Periodontics Restorative Dent 2007; 27: 471–479

63. Yilmaz S, Cakar G, Yildirim B, Sculean A: Healing of two and three wall intrabony periodontal defects following treatment with an enamel matrix derivative combined with autogenous bone. J Clin Periodontol 2010; doi.org/10.1111/j.1600–051X.2010.01567.x

(Photo: Önder Solakoglu)

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# Self-monitoring to improve home-based oral hygiene in seniors

**Introduction:** In order to achieve an optimal brushing result when performing self-responsible home-based oral hygiene, patients should be able to self-monitor both their brushing process and the cleaning result. This pilot study conducted in cross-over design aimed to determine if an app or an abacus can aid patients in implementing the "CIOTIPlus" tooth brushing system and technique when performing self-responsible home-based oral hygiene.

**Methods:** Sixteen participants (8 female, 8 male; average age: 72.6 ± 4.2 years) were included in the study. The study was divided into 3 phases. In each phase, a different tool (self-developed app or "CIOTIPlus-Abacus") was used to support self-monitor home-based oral hygiene. In the baselinel examination (t0), in addition to the general anamnesis, the DMF-T/S and PSI, QHI and mAPI were recorded. The participants recorded their home-based oral hygiene for 3 weeks by noting the cleaned tooth surfaces/areas in each phase. In phase 1 (t1), the documentation was performed solely by using the app. In phase 2 (t2), the documentation ensued through the use of the app as well, but in contrast to t1, more functions were accessible on the app. In phase 3 (t3), the daily home-based oral hygiene was recorded using an abacus ("CIOTIPlus-Abacus"). The participants were also asked to fill out a questionnaire at t0, t2 and t3.

**Results:** In the basic examination (t0), the participants showed an average $QHI_{t0}$ of 2.1 ± 0.7 and an average $mAPI_{t0}$ of 3.5 ± 0.6. At t1, the subjects showed significantly lower plaque-index values (PI values) in the area of the smooth and proximal surfaces ($QHI_{t1}$ 1.6 ± 0.6; $p = 0.004$; $mAPI_{t1}$ 2.9 ± 0.7; $p = 0.003$). At time t2, compared to t0 and t1, the average PI values were again significantly lower in the area of both the smooth ($QHI_{t2}$ 0.8 ± 0.4; $p < 0.0001$) and proximal surfaces ($mAPI_{t2}$ 1.7 ± 0.5; $p < 0.0001$). Fourteen participants (7 female, 7 male) were included in phase 3. The PI values in the area of the smooth and proximal surfaces at time t3b were also significantly lower in comparison to both t0 and t1. At time t3b, the PI value in the area of the smooth surfaces did not differ significantly compared to t2 ($QHI_{t2}$–$QHI_{t3b}$; $p = 0.147$), but the PI value in the area of the proximal surfaces was significantly lower ($mAPI_{t2}$–$mAPI_{t3b}$; $p = 0.024$).

**Conclusion:** The results of this pilot study show that an app or an abacus are suitable tools for supporting patients to self-monitor their home-based oral hygiene, which could lead to significantly improved oral health.

**Keywords:** self-monitoring; self-responsible home-based oral hygiene; CIOTIPlus-App; CIOTIPlus-Abacus

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## Introduction

Caries and periodontitis are biofilm-associated diseases with multifactorial causes. In addition to regular visits to the dentist and dietary control, the efficient removal of oral biofilm plays a major role in the prevention of these diseases. The removal of biofilm is not only the responsibility of the dental professional, but primarily that of the patient who should carry out regular home-based oral hygiene [5]. Self-responsible home-based oral hygiene is thus an essential component for maintaining oral health.

The oral health awareness of the German population has increased significantly in recent years. In the Fifth German Oral Health Study (DMS V), between 70–85 % of the respondents, depending on age group, were convinced that they could contribute "very much" or "much" to maintaining or improving their oral health [17]. Patients therefore appear to be well aware that the removal of plaque/biofilm as part of self-responsible home-based oral hygiene is of great importance in the prevention of caries and periodontitis. Especially in the young senior age group (65 to 74 years), a significantly increased awareness of their own oral health was observed in DMS V [17]. However, DMS V also shows that a relatively large number of patients are still affected by caries (especially root and crown margin caries) and inflammatory periodontal diseases. Successful prevention concepts, combined with advances in the field of restorative dentistry, have made it possible to preserve natural teeth for much longer or even for the entire lifespan [19]. A clear trend towards "tooth preservation in old age" (significant reduction in tooth loss) is evident [17]. Yet, the more teeth are preserved, the more they are exposed to the risk of disease such as periodontitis or caries. The cause of increased susceptibility to root or crown margin caries in older people is multifactorial (e.g. increased proportion of exposed root surfaces or crown margins, extensive prosthetic restorations, inadequate plaque removal, reduced salivary flow [drug-induced], previous periodontal therapy) [1, 6, 15, 20].

Regarding the prevalence of periodontitis, DMS V shows that 75.4 % of younger seniors suffer from moderately severe (every second; 50.8 %) or severe periodontitis (nearly every fourth; 24.6 %) and 80.6 % of older seniors (75- to 100-year-olds) from moderately severe (every second; 50.5 %) or severe periodontitis (nearly every third; 30.1 %) [17]. However, since the disease increases with age, the demographic trend suggests that the need for treatment is likely to increase in the future.

There is now ample evidence from epidemiological, clinical and experimental studies to suggest that periodontal infections are not only influenced by systemic factors, but that they themselves can produce systemic effects [18]. Oral health, meaning the unrestricted functionality and freedom from inflammation and discomfort, is an important component of general health and of a healthy diet and is thus closely linked to quality of life [7, 24]. One can only live up to the motto "health begins in the mouth" if a well-functioning and well-maintained masticatory system is present. The effectiveness of good home-based oral hygiene, combined with regular prophylactic dental care, for preventing caries and periodontitis has been demonstrated in studies [2, 5].

In order for patients to achieve optimal self-responsible home-based oral hygiene results, they should have the opportunity to independently assess/monitor both their cleaning process and result. Many patients seem to find it difficult to regularly implement a certain system of daily dental and oral hygiene. There are various possibilities for patients to self-monitor their cleaning process or system. In the digital age, apps offer the possibility of assisting patients in performing their daily dental and oral hygiene. However, most of the "tooth brushing apps" which are currently available on the market can only be used in combination with a corresponding electric toothbrush [16]. The number of apps which can be used together with a manual toothbrush is limited and is mainly directed towards children and adolescents [16]. In a qualitative analysis of the free apps, which are currently available on the market, and which are suited for use with manual toothbrushes, 5 "tooth brushing apps" were compared; from the 5 apps, only 2 of them were suited for adults [16]. The analysis revealed that in all apps, the implementation of a clear system of tooth brushing and reminder functions promotes regular oral hygiene [16]. The authors concluded that "tooth brushing apps" also have the potential to contribute to dental hygiene education for adults, although most apps provide insuffi-

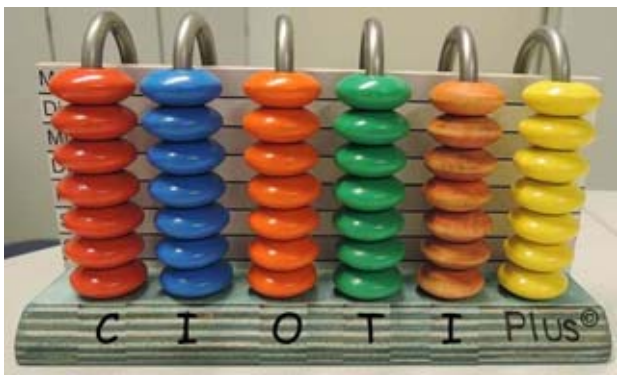



**Figure 1a** Front view of the "CIOTIPlus-Abacus"

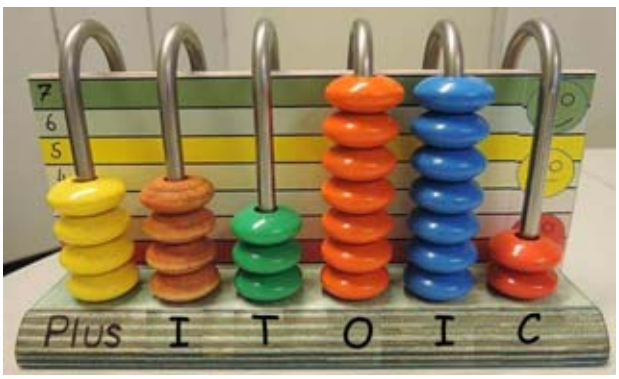
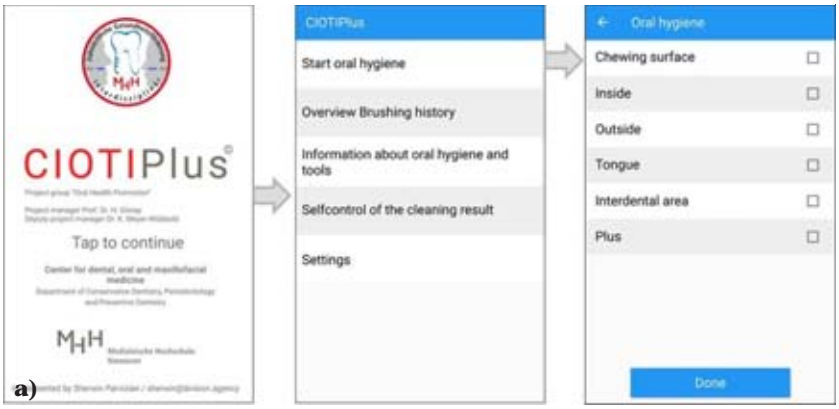
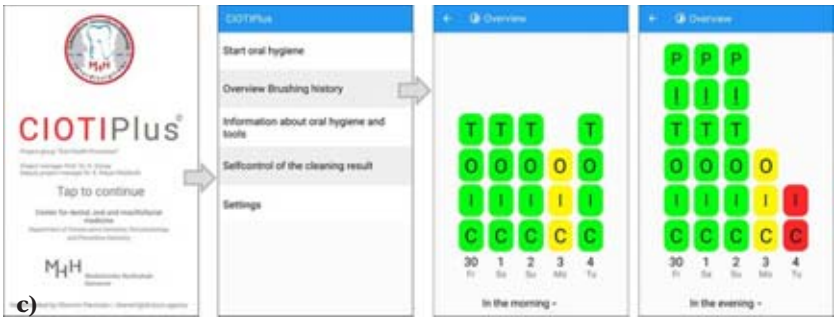



**Figure 1b** Back view of the "CIOTIPlus-Abacus"







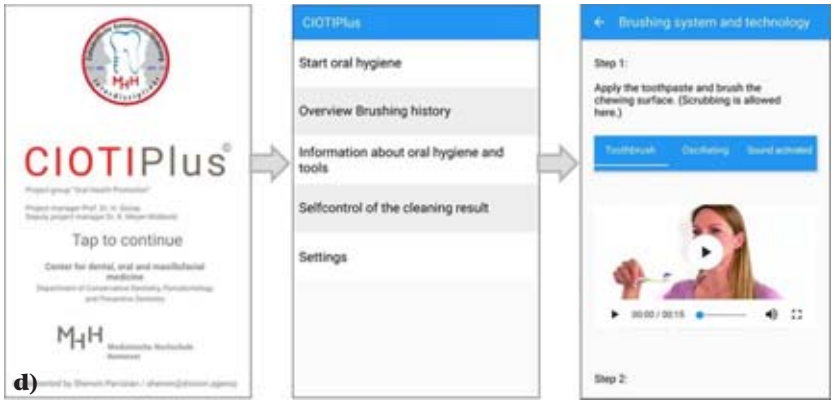




**Figure 2a** The user can mark the individual cleaned surfaces/areas by touching the boxes in the "start oral hygiene" submenu in the CIOTIPlus-App.

**Figure 2b** Confirmation in the submenu "start oral hygiene" in the CIOTIPlus-App. In this submenu, a feedback is given based on whether the system has been implemented. Depending on the number of marked areas, a different smiley appears. The "red smiley" indicates an inadequate implementation of the system. The "yellow smiley" indicates a satisfactory implementation and the "green smiley" indicates a complete implementation of the system.

**Figure 2c** A graphic in the submenu "overview brushing history" in the CIOTIPlus-App illustrates the components of the "CIOTIPlus" system performed by the user per day and time of day.

**Figure 2d** In the submenu "information about oral hygiene and tools" in the CIOTIPlus-App, the user has access to texts and videos which explain the individual steps of the "CIOTIPlus" system.

cient instructions regarding brushing techniques and others contain too many tools which distract users from the actual purpose of dental and oral hygiene [16]. It should also be considered that apps are not suitable for everyone. Many older people, especially, use newer technical devices less than younger ones.

In order to provide these patients with the possibility to self-monitor their home-based oral hygiene, our working group "oral health care promotion interdisciplinary" initially developed an "oral hygiene protocol" in which the patients could record the system they had adopted on a daily basis. Particularly in the evening, it is recommended that patients implement the "CIOTIPlus" system. When using the "CIOTIPlus" tooth brushing system, the sequence of brushing begins on the **c**hewing surfaces, continues onto the **i**nside surfaces and finishes on the **o**utside surfaces. This is then followed by the cleaning of the **t**ongue and the **i**nterdental spaces. After this procedure, in a separate step, the patients should systematically brush the already cleaned tooth surfaces and gums with an equal pea-sized amount of toothpaste for at least one minute using small circular movements (**Plus**) [10–14]. We evaluated the use of the protocols in a study and were able to show that such protocols work well for short periods of time when self-monitoring the brushing process and can thereby improve oral hygiene [10]. However, such simple protocols are often not very attractive for the patient in the long term. For this reason, we have additionally developed a type of abacus (Fig. 1a and b). With this tool, the patient has the chance to record the "CIOTIPlus" tooth brushing system and technique daily/weekly in an easy and entertaining manner. This in turn increases the motivation to use this tool for the purpose of documenting and self-monitoring. Unfortunately, however, no evaluation can be con-

ducted over a longer period of time which is why we have also developed an app (Fig. 2a–d).

As part of a pilot study in crossover design, it was evaluated if the app described above or the "CIOTIPlus-Abacus" can assist patients in implementing the "CIOTIPlus" tooth brushing system and technique during self-responsible home-based oral hygiene.

## Methods

The study participants were patients from the recall system (supportive periodontal therapy) belonging to the Department of Conservative Dentistry, Periodontology and Preventive Dentistry of the Hanover Medical School. The patients were between 67 and 79 years old.

An important exclusion and inclusion criterion for the selection of participants was their general state of health. The following diseases/conditions were defined as exclusion criteria:

- severe general diseases,
- mental or physical disabilities which do not permit cooperation,
- xerostomia,
- patients having exclusively implant-supported restorations,
- heavy smokers.

Furthermore, the participants had to have sufficient remaining teeth (at least 20 natural teeth). The patients were randomly included in the project if they presented interest upon being requested to participate in the project. Participation in the project was voluntary and could be discontinued at any time without giving reasons. The project received a positive vote from the ethics committee of the Hannover Medical School (vote no.: 8512_BO_K_2019).

### Description of the "CIOTIPlus-App"

A self-developed app was installed on a tablet PC (Lenova Tab E7 TB-7104F 7"TN Display). The tablet was not connected to the Internet. Neither the tablet PC nor the app recorded or saved any personal or patient-related data (e.g. name, age, gender, date of birth). The app included 2 phases. In phase 1, the user only could self record which tooth surfaces/areas had been brushed during home-based oral hygiene (chewing surfaces, inside surfaces, outside surfaces, tongue, interdental spaces, plus) (Fig. 2a). When the user started the program, the day and time were registered by the program. When the program ended, the time (tooth brushing time) was also recorded by the program. In phase 2, the user could access additional information regarding the "CIOTIPlus" tooth brushing system. The user now had the opportunity to retrieve information regarding the system at any time in image, text and video form (with sound) (Fig. 2d).

Also in this case, the user once again recorded the tooth surfaces or areas which were brushed as part of their home-based oral hygiene. The program automatically recorded the day, start time and duration (tooth brushing time) until the point when the user finished using the program. Furthermore, after the individual tooth surfaces/areas were recorded into the program, the program had the function of reminding the user whether or not particular tooth surfaces/areas were considered. The user then had the possibility to brush these missing tooth surfaces/areas and to record them as brushed (Fig. 2b).

### Description of the "CIOTIPlus-Abacus"

This special abacus was made of wood and metal (robust and moisture resistant) (Fig. 1a and b). It consists of 6 metal arches. Each arch possesses 7 wooden beads which represents a component of the "CIOTIPlus" system. On the abacus' base, the abbreviations corresponding to the "CIOTIPlus" system were drawn in front of the respective metal arch. The corresponding 7 wooden beads have different colors depending on the component of the "CIOTIPlus" system. The front side of the vertical board is marked with the days of the week; the back side is marked with the numbers 1 to 7 and with colored lines. Every evening after the participant has finished their oral hygiene procedure, the wooden bead corresponding to the surface/area which the participant has brushed is moved from the front side to the back side of the abacus. On the back side, the participant can check their daily hygiene routine. At the end of the week, the number of wooden beads on the back side presents the participant with an overview of the surfaces/areas that may have been neglected during home-based oral hygiene. This visual aid is intended to promote discipline.

### Study design and recorded clinical parameters

All examinations were performed by a practitioner with the help of an assistant. For all participants, the baseline examination (t0) comprised of a general anamnesis, a detailed oral examination and the recording of the periodontal screening index (PSI). The plaque was made visible with the aid of a plaque disclosing agent (Mira-2-Ton®, Hager & Werken, D-Duisburg). Afterwards, magnifying glasses (2.5x, Orascoptic, Fa. Sigma Dental) were used to determine the modified Quigley-Hein Plaque Index (QHI) according to Turesky [23] as well as a modified plaque index based on the Quigley-Hein Plaque Index (modified Proximal Plaque Index – mAPI) for the purpose of assessing the extent of plaque in the proximal areas [11]. Before the initial examination, patients were asked to fill out a questionnaire. The questions were mainly multiple-choice and included topics such as "oral hygiene" and "evaluation and assessment". After completing the questionnaire, the patients were shown the stained plaque on their teeth surfaces using a magnifying mirror and a mouth mirror. They were again asked to appraise their oral hygiene using a questionnaire. In order to create uniform starting conditions, the test persons received a professional tooth cleaning, which included cleaning and polishing of both the smooth and proximal surfaces. The "CIOTIPlus" brushing system was explained, demonstrated and practiced. In addition, all participants received an information leaflet which explained the system once again in image and text. The participants were instructed that they should practice implementing the system at least once daily during oral hygiene, es-

pecially in the evening. All patients received a tablet PC (Lenova Tab E7 TB-7104F 7"TN Display) on which the self-developed app described above was installed. With the help of the app, the patients were expected to record the systematic procedure as part of their daily home-based oral hygiene. The patients were instructed in how to use the tablet PC and the program. At this point, the user only had access to "phase 1" of the program. The participant was asked to record their daily home-based oral hygiene (noting the cleaned tooth surfaces/areas) using the app for 3 weeks.

After 3 weeks, re-examination (t1) was performed. The plaque indices (QHI and mAPI) were recorded after the plaque was made visible by staining and then the teeth (have been) cleaned. Afterwards, "phase 2" was activated on the tablet PC. The participants were asked to record their daily practice of home-based oral hygiene (noting the cleaned tooth surfaces/areas) for 3 weeks using the "CIOTIPlus-App".

After 3 weeks, a re-examination (t2) was performed. The plaque indices (QHI and mAPI) were determined after the plaque was made visible by staining and then the teeth were cleaned. Before the examination, the patients were asked to fill out a questionnaire which consisted of multiple-choice questions regarding the tooth brushing system and the "CIOTIPlus-App".

After t2, a 6-month break in the form of a "washout phase" ensued in order to avoid a possible "Hawthorne effect" in phase 3 (t3). At time t3a, a re-examination (QHI/mAPI), professional tooth cleaning and fluoridation were performed. The "CIOTIPlus" tooth brushing system (+ leaflet) and the use of the "CIOTIPlus-Abacus" (phase 3) were explained to the participants. The participants were asked to record the total number of beads per component of the "CIOTIPlus" system at the end of each week in a documentation sheet (Fig. 3). The participants were once again requested to record their home-based oral hygiene in the evening using the "CIOTI Plus-Abacus" for 3 weeks.

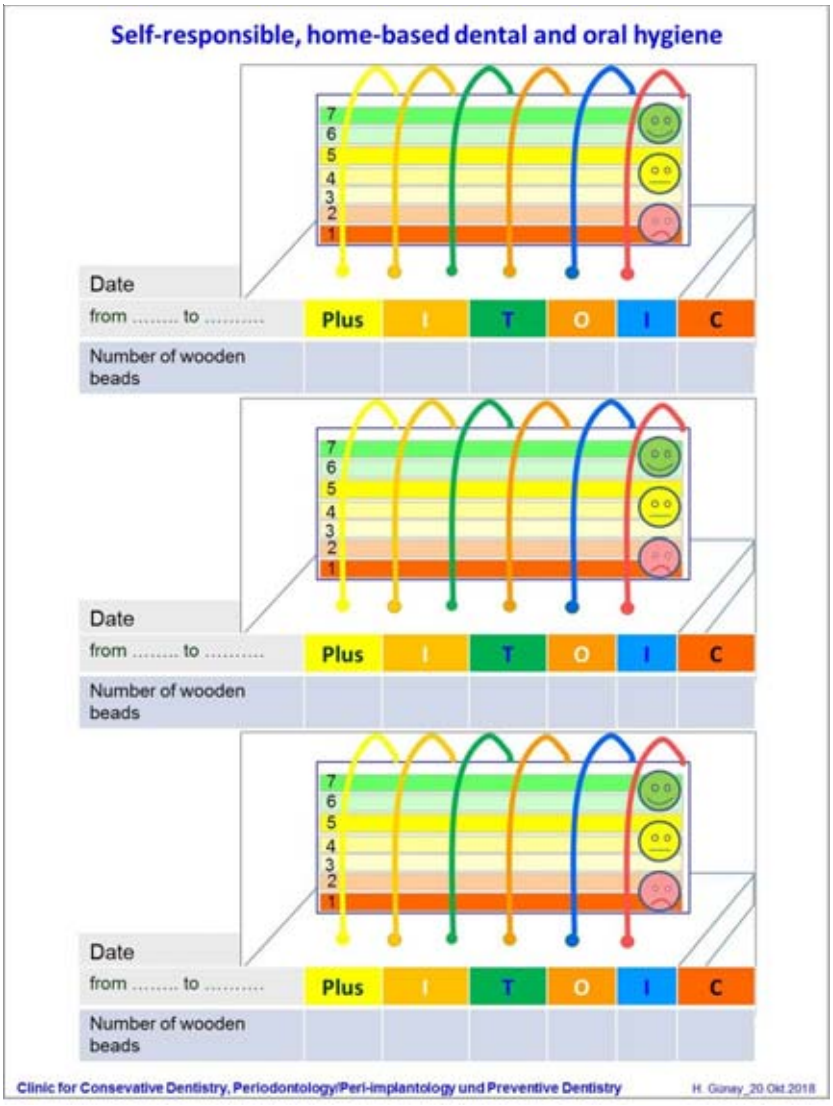



**Figure 3** Documentation sheet for phase 3

After these 3 weeks, the last examination (t3b) was performed. Analogous to t1 and t2, the plaque indices (QHI and mAPI) were recorded after plaque staining. Then, the teeth were cleaned and fluoride was applied.

Figure 4 summarizes the project's timeline (flowchart of the project).

## Data protection and statistical analysis

The evaluation performed in this project was anonymous. The participants were informed that their personal data would be kept anonymous and that it would be exclusively used for the purpose of data collection. The tablet was not connected to the Internet at any time. Neither the tablet PC nor the "CIOTIPlus-App" recorded or stored any patient-related data (e.g. name, age, gender, date of birth). A consent form was signed by each participant.

Data analysis was performed with the statistical analysis program SPSS/PC Version 25.0® for Windows (SPSS Inc., Chicago, IL, USA). All collected data was analyzed through pseudonymization. First, mean values, standard deviations and frequencies were calculated for the descriptive statistics. The collected values arising from repeated measurements within a group were analyzed for variance using the paired T-test. The statistical significance level was set at $p < 0.05$.

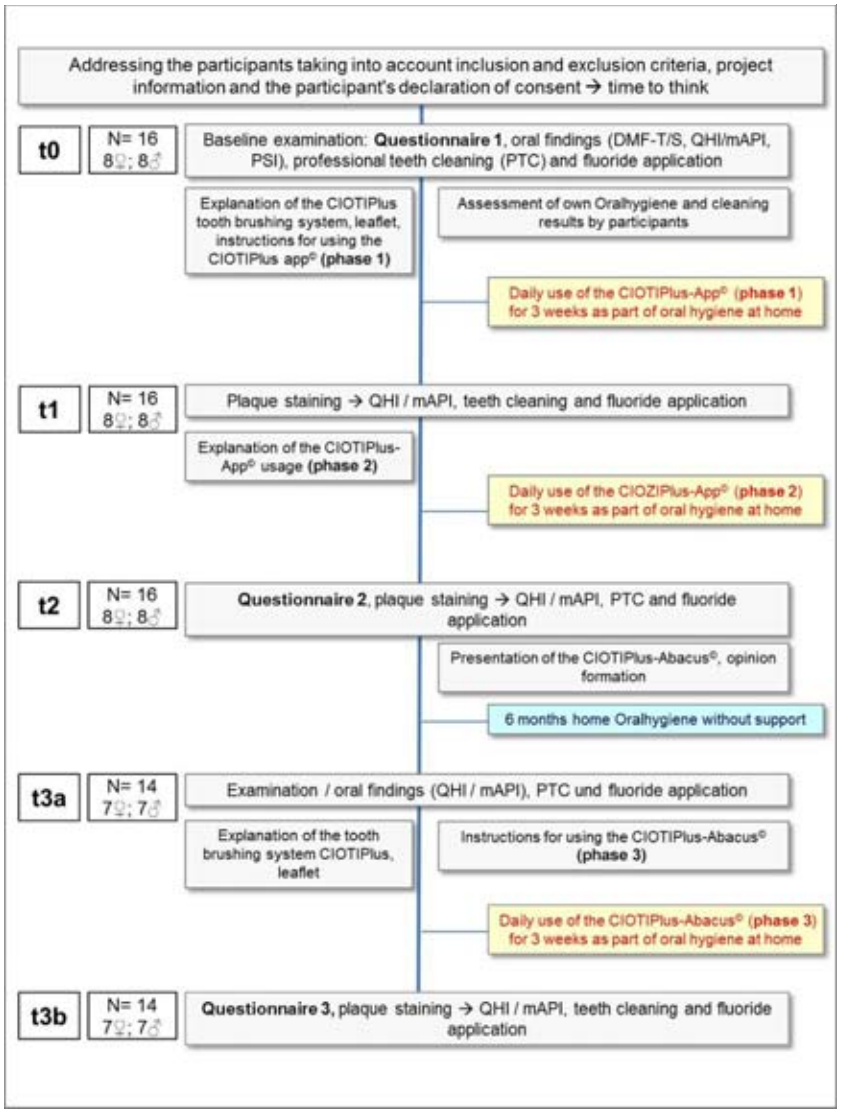



**Figure 4** Flowchart of the project

## Results

### Clinical parameters

The study included 16 participants (8 female, 8 male) with an average age of 72.6 ± 4.2 years. In the basic examination (t0), the subjects showed an average $QHI_{t0}$ of 2.1 ± 0.7 and an average $mAPI_{t0}$ of 3.5 ± 0.6. In the second examination (t1), the participants showed significantly lower average plaque index values in the area of the smooth ($QHI_{t1}$ 1.6 ± 0.6; p = 0.004) and proximal surfaces ($mAPI_{t1}$ 2.9 ± 0.7; p = 0.003) when compared to t0. In the third examination, compared to t0, significantly lower average plaque index values were once again detected on both the smooth ($QHI_{t2}$ 0.8 ± 0.4; p < 0.0001) and proximal surfaces ($mAPI_{t2}$ 1.7 ± 0.5; p < 0.0001). The plaque index values for the smooth and proximal surfaces at time t2 were also significantly lower compared to time t1 ($QHI_{t1}$–$QHI_{t2}$; p < 0.001; $mAPI_{t1}$–$mAPI_{t2}$; p = 0.033) (Fig. 5).

In phase 3, 14 participants (7 female, 7 male) remained to be included. At time t3a, the participants showed an average $QHI_{t3a}$ of 1.9 ± 0.5 and an average $mAPI_{t3a}$ of 2.9 ± 0.7, while at time t3b, they had an average $QHI_{t3b}$ of 0.7 ± 0.4 and an average $mAPI_{t3b}$ of 1.4 ± 0.6. The plaque index values on the smooth and proximal surfaces at time t3b were also significantly lower than at times t0 ($QHI_{t0}$–$QHI_{t3b}$; p < 0.001; $mAPI_{t0}$–$mAPI_{t3b}$; p < 0.001) and t1 ($QHI_{t1}$–$QHI_{t3b}$; p < 0.001; $mAPI_{t1}$–$mAPI_{t3b}$; p < 0.001). At time t3b the plaque index value in the area of the smooth surfaces did not differ significantly compared to time t2 ($QHI_{t2}$–$QHI_{t3b}$; p = 0.147), but the plaque index value in the area of the proximal surfaces was significantly lower $mAPI_{t2}$–$mAPI_{t3b}$; p = 0.024) (Fig. 5).

### Use of the "CIOTIPlus-App" and documentation of the CIOTIPlus-System

The patients were instructed at the beginning of phase 1 to use the "CIOTIPlus" tooth brushing system at least once daily when performing oral hygiene, especially in the evening. For this reason, only the use of the app/documentation of the system in the evening was considered in the following section when analyzing the results.

On average, the "CIOTIPlus-App" was used by the participants in the evening on 24.9 ± 3.3 days in phase 1 and on 18.3 ± 2.5 days in phase 2.

Using the app, the participants recorded which part of the system (chewing surface, inside surface, outside surface, tongue, interdental spaces and plus) was performed in which order. A percentage evaluation was conducted based on app's usage. The frequency of the parts of the system documented by the participant was evaluated. Also, how often the recommended system was completely implemented and if it was performed in the correct sequence was recorded. It was determined that in phase 2, compared to phase 1, the participants documented the proportions of the system "tongue" (p = 0.037) and "plus" (p = 0.016) significantly more often. In phase 2, according to the documentation provided by the participants, all parts of the system (p = 0.003) were implemented in the specified order (p = 0.016) significantly more frequently than in phase 1.

### Use of the "CIOTIPlus-Abacus" and documentation of the CIOTIPlus-System

At the beginning of phase 3, the patients were instructed to apply the "CIOTIPlus" tooth brushing system at least once daily during oral hygiene,

especially in the evening. At the end of a week, the participants were instructed to read the number of beads per component of the system from the "CIOTIPlus-Abacus" and record it in a documentation sheet (Fig. 3). The documentation sheets were completely filled out by all of the participants in phase 3, thus suggesting that the "CIOTIPlus-Abacus" was indeed used by all of the participants during the entire 3 weeks.

Based on the documentation sheets, the frequency as a percentage was calculated for each of the components of the system which was implemented by the participants. When comparing phase 3 to phase 1, all of the components of the system were implemented more frequently by the participants, although this was not statistically significant. Similarly, all components of the system except for the "tongue" were recorded more frequently in phase 3 than in phase 2. This was, however, again not statistically significant.

### Analysis of the questionnaires

All participants (100 %) stated that they had already performed their daily home-based oral hygiene according to a certain system before the project. All of them (100 %) would also like to continue to use the "CIOTIPlus" system in the future. The greater majority of those surveyed consider this system to be suitable for everyday use (93.8 %) and perceive to have a "better mouth feeling" (87.5 %) after brushing according to this system. All participants (100 %) think that a control mechanism for the systematic procedure is better for the brushing result.

About two thirds of the respondents (68.8 %) stated that the "CIOTIPlus-App" was helpful for assisting them in checking their dental and oral hygiene on their own. The majority of participants would continue to use the "CIOTIPlus-App" in the future (87.6 %) and all of them would recommend the app either generally (81.3 %) or for specific groups of people/special cases (18.8 %).

With respect to the "CIOTIPlus-Abacus", all participants (100 %) stated that it helped them to check their dental and oral hygiene on their own. More than half of the participants (57.1 %) would continue to use the "CIOTIPlus-Abacus" to assist them in their daily oral hygiene. A large proportion of the respondents (85.7 %) would recommend the abacus for self-responsible home-based oral hygiene.

The majority of the respondents (78.6 %) stated that the "CIOTIPlus-Abacus" was easier to use than the "CIOTIPlus-App" as a tool for checking home-based oral hygiene. Additionally, 64.3 % would also recommend the abacus than the app.

### Self-control of the cleaning result

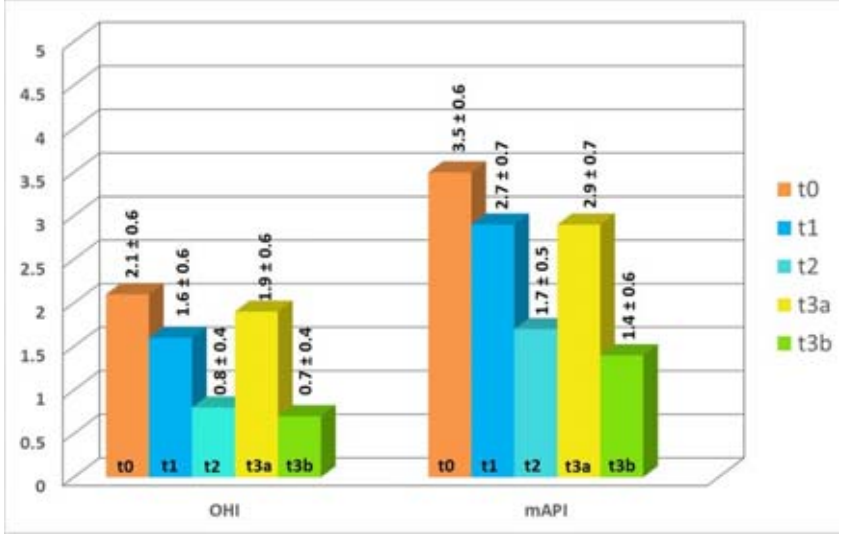
In the basic examination (t0), it was found that patients who without visualization their plaque tended to assess their oral hygiene as being considerably much better than after visualizing it. Before the plaque was stained, 6.3 % of patients rated their oral hygiene as being "good" and 93.8 % "very good". After the stained plaque and demonstration was revealed to them, the patients were very surprised and revised their assessment; 56.3 % of them rated their oral hygiene as "good", 25 % as "moderate" and 18.8 % as "poor". The differences between the assessments before and after the demonstration of stained plaque-affected areas were statistically significant ($p = 0.007$). The patients' ability to self-assessment plaque after the demonstration reflects well the objective findings of the plaque indices.

## Discussion

In the digital age, apps for the self-management and self-monitoring of chronic diseases (e.g. diabetes mellitus) have been successfully used for several years [8]. Similar to other areas of general medicine, dental prevention concepts can only be successful if compliance, self-responsibility and self-monitoring on the patient's behalf are ensured.

All participants claimed that the abacus helped them to self-monitor their home-based dental and oral hygiene. Only about two thirds of the respondents stated that the "CIOTIPlus-App" had supported them to self-monitor their dental and oral hygiene at home. When interpreting these results, it should be taken into account that apps are not suitable for everyone. Many older people use new technical devices less than younger ones. The reasons for this are manifold. Firstly, many older people have less contact with new technologies because they did not grow up with them and often lack an understanding of how modern technology works [22]. On the other hand, physical challenges that occur with old age, such as visual or hearing impairments, limitations in fine motor skills and cognitive limitations can also represent an obstacle [22]. In a survey, 41 % of over 1000 people over the age of 65 stated that they had difficulty operating modern technical equipment [21]. Also, in the present study, more than two thirds of those questioned stated that they found it easier to use an abacus than an app. An abacus appears to be a suitable tool for getting used to a tooth brushing system. The abacus is permanently present and it motivates or reminds, the patient to implement the system in daily dental and oral hygiene. This approach follows the "KISS principle", which stands for "keep it simple and stupid". This means that the easier something is to understand and use, the more likely it is that the user or patient will actually use it. The results of the present study support this assumption. The documentation forms for the "CIOTIPlus-Abacus" were completed filled out by all participants. Therefore, it is reasonable to conclude that the abacus was also used by all participants during the entire period of investigation. In contrast, the evaluation of the app showed that it was not used on a daily basis by the participants.

At time t1, the participants used a technical device and they recorded the performed components of the system using the "CIOTIPlus-App". However, this was only a pure documentation procedure which can be compared to oral hygiene protocols. This documentation alone already led to improved home-based dental and oral hygiene, which was reflected in the significantly lower




(Fig. 1–5: H. Günay, K. Meyer-Wübbold)

**Figure 5** QHI and mAPI of the participants at times t0, t1, t2, t3a and t3b

plaque index values in the area of the smooth and proximal surfaces at time t1 compared to t0. At time t2, the participants not only recorded the components of the system using the app, but they also had the opportunity to access information regarding the "CIOTIPlus" tooth brushing system and technique in image, text and video form (with sound) at any time via the app. Besides this, the user received feedback after performing oral hygiene regarding whether tooth surfaces or areas had not been taken into account. The participants then had the opportunity to clean these missing tooth surfaces or areas and record this afterwards. The significantly lower plaque index values in the area of the smooth and proximal surfaces at time t2 compared to t0 and t1 suggests that this additional information is helpful for patients to self-monitor and pursue an adequate home-based dental and oral hygiene.

Between phases 2 and 3, a longer period (6 months) without further intervention was deliberately chosen in order to avoid a possible "Hawthorne effect" in phase 3. Due to phases 1 and 2, the participants could have already been experienced in implementing the system, which in turn could have distorted the results in phase 3. In order to rule out a "Hawthorne effect", the plaque index values in the area of the smooth and proximal surfaces were again recorded at the beginning of phase 3 (t3a) and before using the "CIOTIPlus-Abacus". The values determined at time t3a clearly show that no "Hawthorne effect" occurred because the values did not differ significantly from those determined at time t0.

At time t3, the participants used a special abacus. The "CIOTIPlus-Abacus", unlike an app, is present at all times at the place for oral hygiene and should serve as a simple visual reminder and monitoring mechanism. Like at time t1, there was only a recording of the implemented components of the system using the "CIOTIPlus-Abacus". However, the significantly lower plaque index values in the area of the smooth and proximal surfaces at time t3b compared to t1 concludes that, with regard to the implementation of an adequate home-based dental and oral hygiene, the recording using an abacus appears to be more helpful than just the documentation alone using an app, which is simply based on following oral hygiene protocols. The documentation occurs in a playful way when using an abacus, while also simultaneously stimulating the motor and sensor systems. This seems to motivate and also discipline the participants more than the mere documentation via the app or oral hygiene protocols.

For the documentation using an app, the participants had to use a technical device which can only be used everywhere to a limited extent. Such technical devices are sensitive to moisture and are exposed to the risk of unintentional destruction, especially in damp rooms such as bathrooms, where daily dental and oral hygiene is usually performed. This danger does not exist with an abacus. Moreover, the documentation using an app is somewhat more demanding and takes more time than the documentation using an abacus. The technical device had to be started beforehand and also loaded in the meantime. The user was supposed to enter the individual components of the system manually in the sequence performed and could also access information or continue dental and oral hygiene after eventually receiving instructions. However, the app gave the user the opportunity to precisely view the system they had applied on a daily basis; this was possible retrospectively over a longer time consider as well. The "CIOTIPlus-App" thus provided precise information about which components of the system were implemented in which order and when. This control mechanism does not exist when using an abacus. However, these advantages are unlikely to have played a major role for the participants in the present study, at least not for the short 3-week interval of use of the two self-monitoring tools. This is reflected both in the clinically collected plaque index values and in the results of the questionnaire.

In the basic examination, it was found that many patients find it difficult to objectively assess their own cleaning results. A pure visual check, even with magnifying aids and optimal lighting conditions, or a "tongue-feel test" to identify any plaque that may still be present, is not sufficient and cannot reveal hidden "problem" or "weak points" (e.g. interdental spaces, the inner surfaces of the teeth and the areas around the gum line). We therefore recommend that patients use plaque staining agents (e.g. staining [chewing] tablets, rinsing solutions which stain plaque) to visualize plaque at

least once a week during their home-based dental and oral hygiene. Plaque staining agents, which can make a distinction between "new" and "old" plaque are also useful. Patients should visualize the plaque both before starting and after finishing home-based oral hygiene. The first staining serves as a guide for performing oral hygiene by allowing patients to concentrate directly on the "problem" or "weak points". The second staining is then used to check the brushing result. A second staining after tooth brushing is highly recommended; studies have shown that the plaque staining agent, through the brushing process and the ingredients in the toothpaste (e.g. surfactants), is partially washed out or fades, thus making the remaining plaque no longer visible to the patient [10]. A visualization of plaque helps patients to assess their own oral hygiene. In this study, it was found that patients without visualize plaque assessed their own oral hygiene as being much better than those after visualizing it. Before demonstration of the stained plaque, 6.3 % of patients rated their oral hygiene as "very good" and 93.8 % as "good". After the demonstration of the stained plaque, patients were very surprised and reconsidered their assessment. Thereafter, 56.3 % of those surveyed rated their oral hygiene as "good", 25 % as "moderate" and 18.8 % as "poor". The differences between the Assessments before and after revealing the stained plaque-affected areas were statistically significant ($p = 0.007$) [12]. The patients' self-assessment after having been shown the plaque is in accordance with the objective findings of the plaque indices. However, before recommending the self-monitoring of the cleaning result, it is necessary to provide the patient with demonstrations and explanations on how the "staining agents" are used and which spatial requirements or auxiliary tools (e.g. mouth mirror, magnifying mirror or telescopic mirror with light source) are necessary for this purpose. When patients visualize plaque as part of the self-monitoring of the brushing results, they have the opportunity to recognize their own problems and weaknesses and thus to continuously improve their brushing system and technique!

Without further intervention, the success in terms of patient compliance is likely to be short-term [3, 4]. The results of the present study support this assumption. The plaque index values collected from the participants at time t3a differed only marginally from those at time t0. Based on the previous interventions, it would have been expected that the participants at time t3a were already appropriately sensitized, which should have led to an improvement/optimization of the home-based dental and oral hygiene, and thus, to significantly lower plaque index values at time t3a compared to t0. However, between phase 2 (t2) and phase 3 (t3a), there was a 6-month period with no further intervention. In the context of self-responsible home-based oral hygiene, a permanent visual reminder with respect to the hygiene measures and system to be implemented can potentially motivate patients; for example, the continuous presence of the "CIOTIPlus-Abacus" or a small poster in the bathroom/oral hygiene area can serve this purpose. Future long-term studies should show whether there may be a need for apps for the self-monitoring of home-based dental and oral hygiene which have more functions (e.g. "live transmission" of the cleaned surfaces from the toothbrush via Bluetooth to the mobile device) in order to increase the number of long-term users. In this manner, this may improve the self-management of dental and oral health.

## Conclusions

When interpreting the results, it should be taken into account that the present study is a pilot study which provides pioneering insights and considerations regarding the self-management of home-based dental and oral hygiene. Overall, it can be concluded that an app or abacus are suitable tools for assisting patients to self-monitor their home-based oral hygiene, which can significantly improve oral hygiene. However, due to the fact that an app is not suitable for every elderly patient, it is advisable that an individualized decision is made together with the patient as to which self-monitoring option (app, protocols, abacus) is appropriate for them and to what extent it is desired. With an app, it is possible to assess the results daily, weekly or monthly, and even retrospectively, over much longer timespans. Moreover, the protocols can also be evaluated retrospectively over time. With the abacus, there is only the possibility of a daily or weekly assessment of the results. The present study could show that the integration of a self-monitoring system (e.g. an app or an abacus) into an oral prevention concept is promising. In all oral prevention concepts, self-responsibility for oral health plays a central role for a sustainable/lasting (behavioral) change.

## Conflicts of Interest

The authors declare that there is no conflict of interest within the meaning of the guidelines of the International Committee of Medical Journal Editors.

### References

1. Adriaens PA, Adriaens LM: Effects of nonsurgical periodontal therapy on hard and soft tissues. Periodontol 2000 2004; 36: 121–145

2. Axelsson P, Nystrom B, Lindhe J: The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. J Clin Periodontol 2004; 31: 749–757

3. Baab D, Weinstein P: Oral hygiene instruction using a self inspection plaque index. Community Dent Oral Epidemiol 1983; 11: 174–179

4. Baab D, Weinstein P: Longitudinal evaluation of a self inspection plaque index in periodontal recall patients. J Clin Periodontol 1986; 13: 313

5. Bastendorf KL, Laurisch L: Langzeiterfolge der systematischen Kariesprophylaxe. Dtsch Zahnärztl Z 2009; 64: 548–557

6. Bizhang M, Zimmer S: Oralprophylaxe für ältere Menschen. Wissen kompakt 2012; 6: 39–52

7. Brauckhoff G, Kocher T, Holtfreter B et al.: Mundgesundheit – Gesundheitsberichterstattung des Bundes Heft 47. Herausgeber: Robert Koch-Institut, Berlin 2009

8. Brzan PP, Rotman E, Pajnkihar M, Klanjsek P: Mobile applications for control and self management of diabetes: a systematic review. J Med Syst 2016; 40: 210

9. Dörfer CE, Staehle HJ: Strategien der häuslichen Plaquekontrolle. Zahnmed up2date 2010; 3: 231–256

10. Günay H, Brückner M, Böhm K, Beyer A, Tiede M, Meyer-Wübbold K: Effekt des doppelten Putzens auf die Wurzelkaries-Inzidenz und den parodontalen Zustand bei Senioren. Dtsch Zahnärztl Z 2018; 73: 86–93

11. Günay H, Meyer-Wübbold K: Effekt des zweimaligen Zähneputzens auf die dentale Plaqueentfernung bei jungen Senioren. Dtsch Zahnärztl Z 2018; 73: 153–163

12. Günay H, Meyer-Wübbold K: Does "CIOTIPlus" only mean "brushing twice"? Dtsch Zahnärztl Z Int 2019; 1: 4–11

13. Günay H, Meyer-Wübbold K: Effectiveness of the "CIOTIPlus"-system on cleaning of approximal surfaces. Dtsch Zahnärztl Z Int 2019; 1: 76–87

14. Günay H, Meyer-Wübbold K: Hanoverian prevention concept to improve (self-responsible) home-based oral hygiene. Dtsch Zahnärztl Z Int 2020; 2: 65–72

15. Kiss CM, Besimo C, Ulrich A, Kressig RW: Ernährung und orale Gesundheit im Alter. Aktuel Ernahrungsmed 2016; 41: 27–35

16. Klass L, Kauffmann F, Klass L: Zahnputz-Apps im Check: Eine qualitative Analyse. Prophylaxe Journal 2018; 2:16–20

17. IDZ, Institut der Deutschen Zahnärzte (Hrsg): Fünfte Deutsche Mundgesundheitsstudie (DMS V). Deutscher Zahnärzte Verlag DÄV, Köln 2016

18. Jepsen S, Kebschull M. Deschner J: Wechselwirkungen zwischen Parodontitis und systemischen Erkrankungen. Bundesgesundheitsbl 2011; 54: 1089–1096

19. Müller F, Nitschke I: Mundgesundheit, Zahnstatus und Ernährung im Alter. Z Gerontol Geriat 2005; 38: 334–341

20. Schmidlin PR: Risiken und Nebenwirkungen der Parodontitis-Therapie – Restaurative Möglichkeiten zur Verbesserung ästhetischer Defizite im Fokus. Schweiz Monatsschr Zahnmed 2012; 122: 427–432

21. Seifert A, Schelling HR (2015): Digitale Senioren. Nutzung von Informations- und Kommunikationstechnologien (IKT) durch Menschen ab 65 Jahren in der Schweiz im Jahr 2015. Zürich: Pro Senectute Schweiz. Online verfügbar unter: www.zfg.uzh.ch/de/projekt/ikt-alter-2014.html.

22. Seifert A, Schelling HR: Altersbedingte Einschränkungen – ältere Menschen in der digitalen Gesellschaft. Schweizer Accessibility-Studie 2016; 17–19

23. Turesky S, Gilmore ND, Glickman I: Reduced plaque formation by the chloromethyl analogue of vitamine C. J Periodontol 1970; 41: 41–43

24. Wiedemann B: Mundgesundheit im Alter. E&M – Ernährung und Medizin 2011; 26: 12–16

(Photos: Hannover Medical School)

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# Periodontitis as potential risk factor for Alzheimer's disease

**Introduction:** Neuroinflammation is a hallmark of Alzheimer's disease (AD). Multiple infectious agents have been demonstrated in the brain and proposed to be involved in AD, but robust evidence of causation has not yet been established. It was hypothesized that periodontitis (PD) and infection with *Porphyromonas gingivalis* may be linked to onset and progression of AD. Although inflammation is present in both diseases, the exact mechanisms and interactions between periodontitis and AD are poorly understood.

**Method:** In this narrative review, we highlight recent progress in exploring potential associations of PD with AD and its surrogates (amyloid plaques) and clinical sequelae (i.e. dementia), respectively.

**Discussion and Result:** Recent evidence suggests that periodontitis interacts with AD to increase the severity of clinical dementia and to accelerate its manifestations. These results indicate that periodontitis may be an emerging risk factor for AD and that the risk may be mediated directly by *Porphyromonas gingivalis* and its secreted neurotoxic gingipains. The recent development of an oral gingipain inhibitor, which is currently tested in a randomized controlled trial, offers the unique opportunity to verify the infectious hypothesis of AD. If successful, this research can be expected to result in a significant improvement of prevention and treatment of PD and AD.

**Keywords:** periodontitis; Alzheimer's disease; Porphyromonas gingivalis; gingipain; neuroinflammation; dementia; oral prophylaxis; therapy

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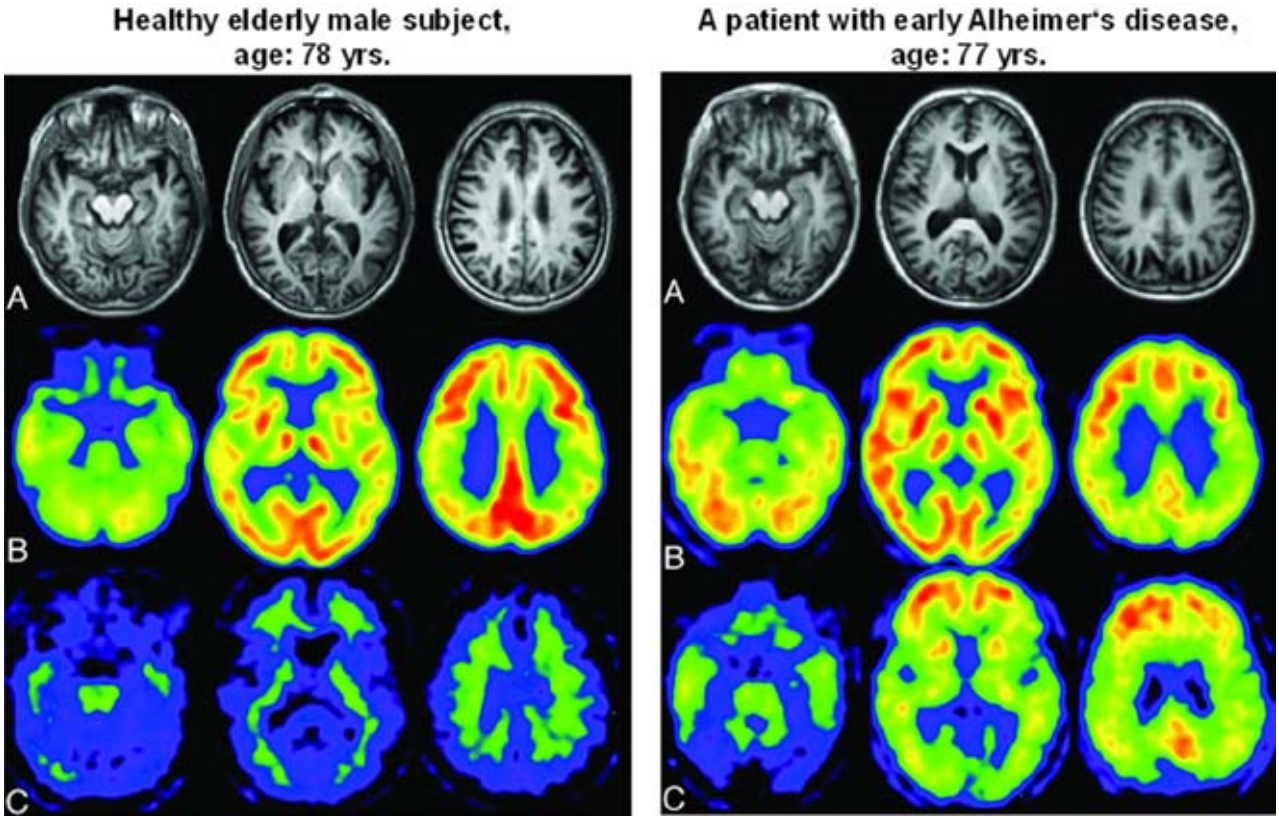



(Fig. 1: Ishii, 2014 [17], reprinted with permission from the American Journal of Neuroradiology, AJNR)

**Figure 1** Diagnosis of Alzheimer's disease by non-invasive imaging. **Left:** Healthy elderly male subject, age: 78 years, Mini-Mental State Examination score: 30. **(A)** Note the slightly enlarged right inferior horn of the lateral ventricle on the T1-weighted MR image. **(B)** Note that the regional glucose metabolism is not reduced on the FDG-PET images. Note that glucose metabolism in the posterior cingulate is much larger than that in other regions. **(C)** PiB-PET reveals nonspecific accumulation in the white matter but no PiB accumulation in the gray matter. The amyloid deposit is negative. **Right:** Patient with early Alzheimer's disease, age: 77 years, Mini-Mental State Examination score: 25. **(A)** Note the slight atrophy of the right hippocampus. **(B)** FDG-PET reveals diminished glucose metabolism in the bilateral parietotemporal association cortices and posterior cingulate gyri and precuneus. **(C)** PiB accumulation is seen in the cerebral cortices except for the occipital and medial temporal regions. High PiB accumulation is present in the medial parietal and frontal regions, indicative of positive amyloid deposit [17].
FDG = [18F]-fluorodeoxyglucose; PET = positron emission tomography; PiB = Pittsburgh Compound.

## Introduction

In Germany, approximately 1.2 million mostly elderly people suffer from dementia (GDB 2016 Dementia Collaborators, 2019). The number of people living with dementia has increased significantly in the last 3 decades due to ageing. Despite of some evidence of minor decreases in the age-specific incidence rates [48], further increases in the number of people affected by dementia may be expected due to the prevailing demographic trends. Limited starting points for prevention and the absence of an effective treatment suggest that the dementia-related burden on patients, caregivers, and the health-care system will likely continue to rise.

Dementia is a neurodegenerative disease in which neurons are gradually lost. The most common forms are Alzheimer's disease (AD) and vascular dementia, which together account for approximately 85 % of all cases [14]. While AD is caused by protein deposits called amyloid plaques or senile plaques in the brain (Fig. 1), vascular dementia is due to a circulatory disorder resulting in a diminished cerebral oxygen supply. Well established risk factors for vascular dementia are hypertension, heart disease, diabetes, high cholesterol levels (hyperlipidemia), obesity, physical inactivity, and smoking [12]. Age and the ε4 allele of apolipoprotein E are major established risk factors for the frequent multifactorial forms of AD [12]. In addition, rarer familial forms exist, which are primarily due to high-penetrance mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Together, these mutations explain only 5–10 % of the occurrence of early-onset AD (reviewed by [45].

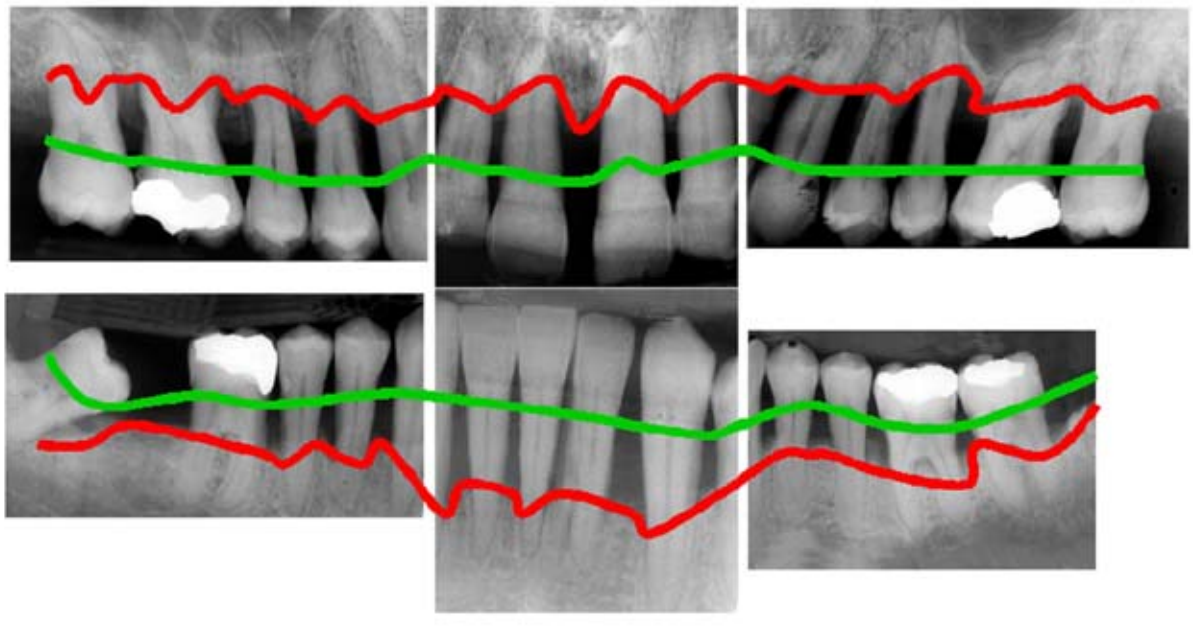
Previous research supports that chronic inflammatory processes play a pivotal role in AD dementia [24, 43, 49]; but the events that trigger inflammation in the first place are still unclear. One repeatedly postulated possibility is that AD associated inflammation may result from an infectious etiology [31]. Multiple infectious agents, including Cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), *Helicobacter pylori, Chlamydophila pneumoniae, Borrelia burgdorferi,* and *Porphyromonas gingivalis* have been demonstrated in the brain and proposed to be involved in AD, but robust evi-

dence of causation has not yet been established [28, 37]. Extracellular amyloid-β (Aβ) deposits, which accumulate in the gray matter of the brain, are a hallmark of the AD. It could be demonstrated Aβ belongs to an evolutionarily conserved family of proteins, collectively known as antimicrobial peptides (AMPs) [19, 39]. AMPs act as a first-line of defense against a large range of pathogens including bacteria, mycobacteria, viruses, fungi, and protozoans [47]. Mice lacking the amyloid precursor protein (APP) show an attenuated survival rate after bacterial infection and it is assumed that oligomerization and fibrillization is required for Aβ's antimicrobial activity [25]. The recent finding that Aβ has antimicrobial activity has motivated the scientific community to verify a possible infectious cause of AD [25, 39, 40]. It was hypothesized that periodontitis (PD) and infection with *Porphyromonas gingivalis* may be linked to onset and progression of AD. Although inflammation is present in both diseases, the exact mechanisms and interactions between PD and AD are poorly understood. The impact of inflammation on vascular dementia and its association with PD was discussed comprehensively in a recent review by Aarabi et al. [1]. Thus, this narrative review aims at presenting and evaluating recent progress in exploring potential associations of infections with *Porphyromonas gingivalis* with AD and its clinical sequelae, i.e. dementia and mild cognitive impairment (MCI). In AD, PD was shown to be associated with increased dementia severity and more pronounced cognitive decline, thus indicating a link to an increased systemic pro-inflammatory state [15]. An example of a case of severe generalized PD is shown in Figure 2.

## Methodology

The search strategy for this review was developed in view of our aim to find and present recent evidence supporting an infectious etiology of AD and the potential contribution of *Porphyromonas gingivalis* to AD and its clinical sequelae, i.e. dementia and mild cognitive impairment (MCI). The literature search was restricted to PubMed, PMC (NCBI) and Web of Science SCI with the following search terms: 1) Oral medicine: oral infection, periodontitis, gingivitis, bleeding on probing, gum disease, tooth-loss, endodontic lesion OR infection, apical OR periapical abscess, *Porphyromonas gingivalis, Porphyromonas endodentalis, Streptococcus mutans*, GroEL, lipopolysaccharide. 2) Neurology: Alzheimer's disease, dementia, cognitive decline, brain, amyloid plaques or senile plaques, magnetic resonance imaging OR tomography, CT OR computer tomography. 3) Inflammation: autoimmunity, C-reactive protein OR CRP, interleukin, periodontitis, oral infection, systemic inflammation, acute phase, endothelial AND function OR dysfunction. Other: epidemiology.

Search terms of each subject area were combined logically and resulted in 230 hits, which were recorded and screened by GA and US manually and categorized *a priori* relevant or interesting. Excluded were non-peer-reviewed studies and studies with insufficient sample sizes to yield at least a statistical power of 80 % to detect the claimed effects. Also studies that were prone to the possibility of reverse causation (typically case-control studies comparing the frequency of periodontitis in healthy subjects and dementia patients) were excluded (18 publications). Animal studies that had no direct relationship to human AD (21 publications),



(Fig. 2: T. Beikler)

**Figure 2** Example of severe periodontitis with the typical presentation of loss of alveolar bone. The x-ray shows teeth exhibiting generalized severe bone loss of 30–80 %. The red line marks the actually existing bone level. The green line shows where the original bone level was before the patient developed periodontitis. Periodontitis is an inflammatory disease and *Porphyromonas gingivalis* as well as a number of other mostly Gram-negative anaerobe bacteria play a key role in its pathogenesis.

and studies that concerned with dementia rather than with AD (146 publications) were also excluded. This prescreening procedure resulted in 45 proposed references (98.3 % agreement between both authors, Cohen's kappa: 0.95), which were stored in an Endnote web database that was accessible to all authors, who decided consensually which publication should be referenced based on the article's content (41 publications) and 8 additional references resulting from manual searches were added during peer-reviewing. This procedure resulted in the 49 references cited in this review.

## Association between chronic oral infections and dementias

Chronic oral infections such as PD may be able to modulate the risk of AD dementia. In the Third National Health and Nutrition Examination Survey (NHANES-III), a large representative cross sectional observational study among 2,355 participants ≥ 60 years of age, PD was associated with cognitive decline, which is considered to be a precursor of dementia [30]. However, the type of dementia was not assessed and brain MRI was not available for the study. A reduced number of teeth – a frequent cause of a past PD – increased the risk of higher prevalence and incidence of dementia of all causes in the Nun Study [27, 41]. The Nun Study is a longitudinal survey on aging and AD of nearly 700 nuns from across the United States. Its strength relates to the fact that AD diagnosis was performed *post mortem* to ensure a high sensitivity and specificity of the AD diagnosis. In addition, the dental records were complemented with results from cognitive tests longitudinally over a long period of time.

Data from the U.S. Department of Veterans Affairs Dental Longitudinal Study (VA-DLS) of almost 600 men aged 28 to 70 at entry who had been followed for up to 32 years showed that the risk of cognitive decline increased with the number of lost teeth and that also PD and caries lesions were associated with cognitive decline [21]. Gatz et al. evaluated data from the Swedish Twin Registry to identify potentially modifiable risk factors for AD. The most consistent risk factor for AD was tooth loss before the age of 35. Low educational status also associated with the risk for dementia and lack of physical exercise associated with the risk for non-Alzheimer's dementia [9]. However, tooth loss is a poor outcome measure because tooth loss may have an adverse influence on diet. Thus, a poor diet and not the periodontal inflammation *per se* may have been the causal factor underlying the observed association in these studies.

The hypothesis that PD may be associated with Aβ deposits in the brain was also investigated by positron emission tomography imaging, which enabled non-invasive imaging of these deposits [20]. The study included 38 healthy elderly men and women. After adjusting for confounders, clinical attachment loss of ≥ 3 mm was associated with elevated Aβ in affected brain regions ($p = 0.002$) [20]. There are a number of additional studies that supported an association between dementia and periodontal disease or tooth loss (reviewed by [44]). Although these studies had limitations, such as small sample sizes, lack of rigorous criteria to diagnose PD and differentiate between different types of dementia, and the possibility of reverse causation, the evidence for an association between PD and dementia or AD nevertheless appears to be rather solid, thus raising questions about possible mechanisms underlying these findings.

## How periodontal pathogenic bacteria cross blood-brain barriers

Key pathogens involved in the pathogenesis of PD are, amongst others, *Porphyromonas gingivalis* and *Treponema denticola* [23], which colonize deep periodontal pockets. Serum IgG antibody levels to *Porphyromonas gingivalis* were shown to be associated with an increased incidence of AD and AD progression [30, 41], suggesting an involvement of *Porphyromonas gingivalis* in AD.

In general, the blood-brain barrier protects the brain against exposure to bacteria and other toxic agents. However, there are 2 main routes *via* which bacteria may cross an impaired blood-brain barrier and enter the brain: first, by bacteremia and second, by migrating along the trigeminal nerve (mouth brain axis) [34, 43]. Pro-inflammatory cytokines that are triggered by *Porphyromonas gingivalis* and other periodontal pathogens are secreted from the infected sites at the periodontium, enter the blood stream and reach the brain via the circulation and weaken the blood-brain barrier by inducing a proinflammatory state favoring cerebral small vessel disease (CSVD). Moreover, *Porphyromonas gingivalis* can infect endothelial cells and stimulate the expression of endothelial adhesion molecules, which may promote monocyte/macrophage adhesion and infiltration into the endothelial layer of the blood-brain barrier [46]. Thus, infections with *Porphyromonas gingivalis* may contribute to the destruction of the blood-brain barrier via inflammation during CSVD. Imaging markers of CSVD were found to be associated with cognitive decline in elderly people affected by AD [7, 8]. The subgingival biofilm is composed mostly of lipopolysaccharide (LPS)-producing Gram-negative bacteria [38], some of which can trigger inflammatory responses in the brain [2], damage the blood-brain barrier in animal models of AD [18], and stimulate the production of Aβ peptides by neurons [26]. *Porphyromonas gingivalis* has the ability to impair the blood-brain barrier by gingipain-mediated degradation of the junctional adhesion molecule (JAM1), a tight junction–associated protein that regulates the epithelial barrier function [42]. Gingipains cleave JAM1 specifically at residues K134 and R234, resulting in permeability of the epithelium to LPS, and proteoglycan (PGN). Knockdown of JAM1 in cultured cells increased the permeability to LPS, PGN, and gingipains [42]. Thus, bacterial toxins may be able to penetrate the brain *via* the damaged blood-brain barrier. Moreover, oral bacteria may access

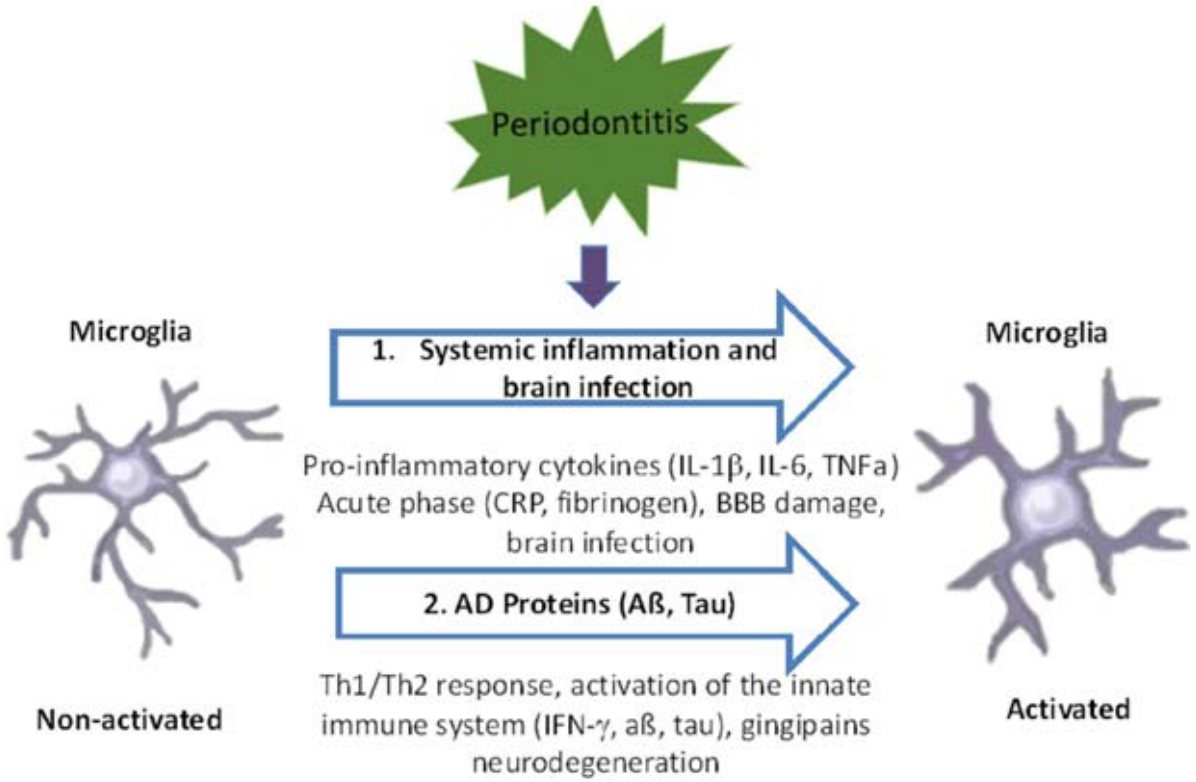
the brain via infection of monocytes followed by brain recruitment [5, 11] or direct infection of endothelial cells, which protect the blood-brain barrier [36].

Passage through the trigeminal nerve is supported by the observation that higher levels of periodontal pathogen *Treponema* could be detected in the brain and the trigeminal nerve of AD patients than in unaffected controls [34]. The trigeminal nerve innervates the oral cavity and connects it with the central nervous system. Compared to periodontally healthy subjects, patients with PD have a higher risk for trigeminal neuralgia, which is characterized by recurrent paroxysmal pain within the distribution of the trigeminal nerve [22].

The most likely mechanism employed by *Porphyromonas gingivalis* and the gingipains for passage through the nerve is axonal transport using the axonal transport machinery. It could be demonstrated, for instance, that the rabies virus enters the central nervous system by retrograde axoplasmic flow [29], the tetanus neurotoxin is retrogradely transported towards the soma in signaling endosomes after uptake at the neuromuscular junction [3] and the HSVs are transported inside the nerve in transport vesicles along with APP [4, 35]. However, whether *Porphyromonas gingivalis* and the gingipains reach the CNS via axonal transport and whether they are also co-transported with APP is currently unclear.

## Detection of Porphyromonas gingivalis and gingipains in the brain

Experimental disruption of the trigeminal nerve led to age-dependent loss of cholinergic neurons in learning and memory-related brain regions and impaired learning in a mouse model of AD (SAMP8 mice) [13], suggesting that the integrity of the trigeminal nerve, which may be impaired by oral infections, is crucial for these brain functions. Oral infection of ApoE knockout mice with *Porphyromonas gingivalis* led to sustained brain infections and activation of the complement pathway [32]. In transgenic mice over-expressing a mutated form of the human APP, oral infection with *Porphyromonas gingivalis* impaired the cognitive function and increased the buildup of AD-like deposits together with alveolar bone loss compared to non-infected mice [16]. *Porphyromonas gingivalis*, the key stone bacterium of PD, was recently detected in the brains of AD patients for the first time *post mortem* [6] and *Porphyromonas gingivalis* gingipains and LPS have also been detected in human AD brains [6, 33]. One of the first brain regions to be damaged in AD is the hippocampus. The study by Dominy et al. could demonstrate




(Fig. 3: Teixeira, 2017, [43])

**Figure 3** Periodontitis, Porphyromonas gingivalis, gingipains, and Alzheimer's disease. Periodontitis is a bacteria-induced chronic inflammation of the tooth supporting structures. Porphyromonas gingivalis is a key pathogen involved in the pathogenesis of periodontitis. The periodontal inflammation triggers bacteremia of P. gingivalis, a systemic inflammation, and a pro-inflammatory acute phase reaction, which lead to blood-brain barrier (BBB) damage. P. gingivalis has the ability to infect the brain via the damaged BBB or other means, such as the trigeminal nerve. The brain infection, which is also linked to gingipain-mediated neurodegeneration, triggers a Th1/Th2 inflammatory response and activation of the brain's innate immune system (interferon-γ (IFN-γ) leading to accumulation of fibrillar amyloid β (Aβ), and tau. Figure adopted from figure 1 in reference [43].

gingipain RgpB in neurons of the dentate gyrus and CA3, CA2, and CA1 of the hippocampus [6]. In addition, RgpB co-localized primarily with neurons and astrocytes as well as with tau tangles, and intra-neuronal Aβ, but not with microglia, which was consistent with the proposed roles of *Porphyromonas gingivalis* in the pathogenesis of AD.

## Implications for treatment of Alzheimer's disease

To date, several classes of gingipain inhibitors have been described. These include inhibitors from natural sources, synthetic compounds, antibiotics, antiseptics, antibodies, and bacteria. Most known synthetic compounds are potent gingipain inhibitors but have undesirable side effects because they also inhibit a wide range of host proteases. Natural inhibitors include cranberry and rice extracts, which inhibit gingipain activity and prevent the growth and biofilm formation of periodontal pathogens. Meanwhile a small molecule gingipain inhibitor, COR388, has been developed, which was safe and well-tolerated in 2 Phase 1 trials. COR388 is currently tested in a larger phase 2/3 clinical trial (the GingipAIN Inhibitor for Treatment of Alzheimer's Disease trial, GAIN, ClinicalTrials.gov ID: NCT03823404) to evaluate whether this oral drug is safe and can slow or halt the progression of AD by blocking the neurotoxic activity of gingipains. The GAIN trial follows a randomized controlled design and is looking to enroll more than 500 participants with mild to moderate AD at more than 90 clinical trial centers in the United States and Europe.

## Final considerations

The results reviewed here clearly support the notion that inflammation plays an important role in PD and AD. Figure 3 shows some of the basic mechanisms and the sequence of events that may be involved in the neurodegeneration induced by PD. The hypothesis that PD and *Porphyromonas gingivalis* are causally related to AD and its progression is highly attractive. On the other hand, gingipains were found also in healthy people and some people with AD did not have increased levels compared to these controls. People with AD reduce their oral hygiene and they tend to get leaky blood-brain barriers, which may increase their susceptibility to infections in their brains. Thus, it cannot be excluded that the brain infection is merely a by-product instead of a cause of the disease. The data from the mouse models may not be of much relevance for the situation in humans because *Porphyromonas gingivalis* is a pathogen that infects humans and has evolved alongside the human immune system. Nevertheless, animal models are essential to generate new hypotheses, which can be tested, preferentially in randomized clinical trials, to see whether a new intervention benefits people suffering from AD. Since it is highly unlikely that a single type of bacteria is the only cause of a disease as complex as AD, we need a better understanding of the potential role of the whole oral microbiota as a cause of the disease, *i.e.* microbiome studies of human brains *post mortem*. Also important are state-of-the-art brain magnetic resonance imaging studies to demonstrate a potential impact of the oral microbiota on preclinical surrogate markers of AD, such as global brain volume, atrophy of subcortical structures, like the hippocampus, cerebral white matter disintegration, and graph-theoretical measures of topology of large-scale structural brain networks.

Since PD is preventable and treatable, subjects with PD should be informed and treated in order to lower the microbial challenge and to prevent the systemic inflammatory burden, thereby promoting a higher quality of life. The recent development of an oral gingipain inhibitor, which is currently tested in a randomized controlled trial, for the first time offers the opportunity to verify the infectious hypothesis of AD. If successful, this research can be expected to result in a significant improvement of prevention and treatment of PD and PD-related AD.

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## Conflicts of interest

GA, CW, CM, TB, GH, and US declare no potential conflicts of interest, GT declares that he has received consulting fees from Acandis and Stryker, grants from Bayer, and lecture fees from Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb/ Pfizer, Daiichi Sankyo, Portola, and Stryker.

### References

1. Aarabi G, Thomalla G, Heydecke G, Seedorf U: Chronic oral infection: an emerging risk factor of cerebral small vessel disease? Oral Dis 2019; 25: 710–719

2. Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS: Association between periodontitis and Alzheimer's disease. N Am J Med Sci 2015; 7: 241–246

3. Bercsenyi K, Schmieg N, Bryson JB et al.: Tetanus toxin entry. Nidogens are therapeutic targets for the prevention of tetanus. Science 2014; 346: 1118–1123

4. Cheng SB, Ferland P, Webster P, Bearer EL: Herpes simplex virus dances with amyloid precursor protein while exiting the cell. PLoS One 2011; 6: e17966. doi.org/10.1371/journal.pone.0017966

5. Coureuil M, Lécuyer H, Bourdoulous S, Nassif X: A journey into the brain: Insight into how bacterial pathogens cross blood-brain barriers. Nat Rev Microbiol 2017; 15: 149–159

6. Dominy SS, Lynch C, Ermini F et al.: Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 2019; 5(1): eaau3333. doi:10.1126/sciadv.aau3333

7. Ferri CP, Prince M, Brayne C, Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366: 2112–2117

8. Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB: Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: A longitudinal study. Lancet 2000; 356: 628–634

9. Gatz M, Mortimer JA, Fratiglioni L et al.: Potentially modifiable risk factors for dementia in identical twins. Alzheimers Dement 2006; 2: 110–117

10. GDB 2016 Dementia Collaborators: Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol 2019; 18: 88–106

11. Giacona MB, Papapanou PN, Lamster IB et al.: Porphyromonas gingivalis induces its uptake by human macrophages and promotes foam cell formation in vitro. FEMS Microbiol Lett 2004; 241: 95–101

12. Gorelick PB: Risk factors for vascular dementia and Alzheimer disease. Stroke 2004; 35 (Suppl 1): 2620–2622

13. He Y, Zhu J, Huang F, Qin L, Fan W, He H: Age-dependent loss of cholinergic neurons in learning and memory-related brain regions and impaired learning in SAMP8 mice with trigeminal nerve damage. Neural Regen Res 2014; 9: 1985–1994

14. Hofman A, Ott A, Breteler MM et al.: Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997; 349: 151–154

15. Ide M, Harris M, Stevens A et al.: Periodontitis and cognitive decline in Alzheimer's disease. PLoS One 2016; 11: e0151081. doi.org/10.1371/journal.pone.0151081

16. Ishida N, Ishihara Y, Ishida K et al.: Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. NPJ Aging Mech Dis 2017; 3: 15-x. doi:10.1038/s41514–017–0015-x

17. Ishii K: PET approaches for diagnosis of dementia. AJNR Am J Neuroradiol 2014; 35: 2030–2038

18. Jaeger LB, Dohgu S, Sultana R et al.: Lipopolysaccharide alters the blood-brain barrier transport of amyloid beta protein: a mechanism for inflammation in the progression of Alzheimer's disease. Brain Behav Immun 2009; 23: 507–517

19. Kagan BL, Jang H, Capone R et al.: Antimicrobial properties of amyloid peptides. Mol Pharm 2012; 9: 708–717

20. Kamer AR, Pirraglia E, Tsui W et al.: Periodontal disease associates with higher brain amyloid load in normal elderly. Neurobiol Aging 2015; 36: 627–633

21. Kaye EK, Valencia A, Baba N, Spiro A, Dietrich T, Garcia RI: Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc 2010; 58: 713–718

22. Keller JJ, Sheu JJ, Lin HC: Chronic periodontitis and the subsequent risk of trigeminal neuralgia: A 5-year follow-up study. J Clin Periodontol 2012; 39: 1017–1023

23. Kinane DF, Berglundh T: Pathogenesis of periodontitis. In: Lindhe J, Lang NP, Karring T (Eds.): Clinical Periodontology and Implant Dentistry, 5th ed., Vol. 1, Blackwell Munksgaard, Oxford 2008, pp. 405419

24. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT: Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y) 2018; 4: 575–590

25. Kumar DK, Choi SH, Washicosky KJ et al.: Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med 2016; 8: 340ra372. doi: 10.1126/scitranslmed.aaf1059

26. Lee JW, Lee YK, Yuk DY et al.: Neuroinflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J Neuroinflammation 2008; 5: 37. doi:10.1186/1742–2094–5–37

27. Lee YT, Lee HC, Hu CJ et al.: Periodontitis as a modifiable risk factor for dementia: a nationwide population-based cohort study. J Am Geriatr Soc 2017; 65: 301–305

28. Mawanda F, Wallace R: Can infections cause Alzheimer's disease? Epidemiol Rev 2013; 35: 161–180

29. Mitrabhakdi E, Shuangshoti S, Wannakrairot P et al.: Difference in neuropathogenetic mechanisms in human furious and paralytic rabies. J Neurol Sci 2005; 238: 3–10

30. Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB: Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. J Neurol Neurosurg Psychiatry 2009; 80: 1206–1211

31. Panza F, Lozupone M, Solfrizzi V, Watling M, Imbimbo BP: Time to test antibacterial therapy in Alzheimer's disease. Brain 2019; 142: 2905–2929

32. Poole S, Singhrao SK, Chukkapalli S et al.: Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE-/- mice brains. J Alzheimers Dis 2015; 43: 67–80

33. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S: Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis 2013; 36: 665–677

34. Riviere GR, Riviere KH, Smith KS: Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol 2002; 17: 113–118

35. Satpute-Krishnan P, DeGiorgis JA, Bearer EL:Fast anterograde transport of herpes simplex virus: Role for the amyloid precursor protein of alzheimer's disease. Aging Cell 2003; 2: 305–318

36. Sheets SM, Potempa J, Travis J, Casiano CA, Fletcher HM: Gingipains from Porphyromonas gingivalis W83 induce cell adhesion molecule cleavage and apoptosis in endothelial cells. Infect Immun 2005; 73: 1543–1552

37. Sochocka M, Zwolińska K, Leszek J: The infectious etiology of Alzheimer's disease. Curr Neuropharmacol 2017; 15: 996–1009

38. Socransky SS, Smith C, Haffajee AD: Subgingival microbial profiles in refractory periodontal disease. J Clin Periodontol 2002; 29: 260–268

39. Soscia SJ, Kirby JE, Washicosky KJ et al.: The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One 2010; 5: e9505. doi.org/10.1371/journal.pone.0009505

40. Spitzer P, Condic M, Herrmann M et al.: Amyloidogenic amyloid-β-peptide variants induce microbial agglutination and exert antimicrobial activity. Sci Rep 2016; 6: 32228. doi:10.1038/srep32228

41. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ: Tooth loss, dementia and neuropathology in the Nun study. J Am Dent Assoc 2007; 138: 1314–1322; quiz 1381–1312

42. Takeuchi H, Sasaki N, Yamaga S, Kuboniwa M, Matsusaki M, Amano A: Porphyromonas gingivalis induces penetration of lipopolysaccharide and peptidoglycan through the gingival epithelium via degradation of junctional adhesion molecule 1. PLoS Pathog 2019; 15: e1008124. doi:10.1371/journal.ppat.1008124

43. Teixeira FB, Saito MT, Matheus FC et al.: Periodontitis and Alzheimer's disease: a possible comorbidity between oral chronic inflammatory condition and neuroinflammation. Front Aging Neurosci 2017; 9: 327

44. Tonsekar PP, Jiang SS, Yue G: Periodontal disease, tooth loss and dementia: is there a link? A systematic review. Gerodontology 2017; 34: 151–163

45. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K: The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet Med 2016; 18: 421–430

46. Walter C, Zahlten J, Schmeck B et al.: Porphyromonas gingivalis strain-dependent activation of human endothelial cells. Infect Immun 2004; 72: 5910–5918

47. Wiesner J, Vilcinskas A: Antimicrobial peptides: The ancient arm of the human immune system. Virulence 2010; 1: 440–464

48. Wu YT, Beiser AS, Breteler MMB et al.: The changing prevalence and incidence of dementia over time – current evidence. Nat Rev Neurol 2017; 13: 327–339

49. Wyss-Coray T, Rogers J: Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harb Perspect Med 2012; 2: a006346. doi:10.1101/cshperspect.a006346

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# The S2k-LL – Indications for the use of bone substitute materials in implant dentistry (083–009): the scientific quintessence

**Summary:** The replacement of missing teeth after unavoidable tooth loss is a core competence in dentistry. In addition to the obvious rehabilitation of the masticatory function and esthetics, there are increasingly more medical considerations that might warrant the replacement of missing teeth.
However, the prospective implant site is often compromised by defects of the alveolar process which are triggered by tooth loss or which develop after extraction. The preservation and, if necessary, the regeneration of the alveolar process thus play a major role in daily clinical practice. Various biomaterials are available to the dental practitioner besides autologous bone grafts. The following questions were addressed in the guideline "Implantological indications for the use of bone substitute materials" of the DGI and DGZMK:
1. which are the indications for bone augmentation, 2. which materials are available, 3. which techniques are recommended?
The key scientific statements of the guideline are summarized below. The literature references are therefore adapted to this format. The complete details and background are found in the guideline.

**Keywords:** tooth loss; bone augmentation; jaw atrophy; bone grafts; bone substitutes

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| Type of defect | Single-tooth gap | Extended edentulous space, free-end gap | Edentulous jaw |
|---|---|---|---|
| 1/4 | Dehiscence defect, self-limiting | Multiple dehiscence defects, self-limiting | Multiple dehiscence defects, self-limiting |
| 2/4 | Horizontal defect, not self-limiting, augmentation required outside the "skeletal envelope" | Horizontal defect, not self-limiting, augmentation required outside the "skeletal envelope" | Sharp-edged alveolar ridge |
| 3/4 | Combined defect with horizontal and vertical bone deficits | Combined defect with horizontal and vertical bone deficits | Sharp-edged alveolar ridge with vertical bone deficit (Class IV according to Cawood) |
| 4/4 | Continuous defect | Pure vertical defect | Complete alveolar ridge atrophy (class V and VI according to Cawood) |

**Table 1** ITI classification of alveolar ridge defects according to Terheyden (Cordaro L 2014; Terheyden 2010).

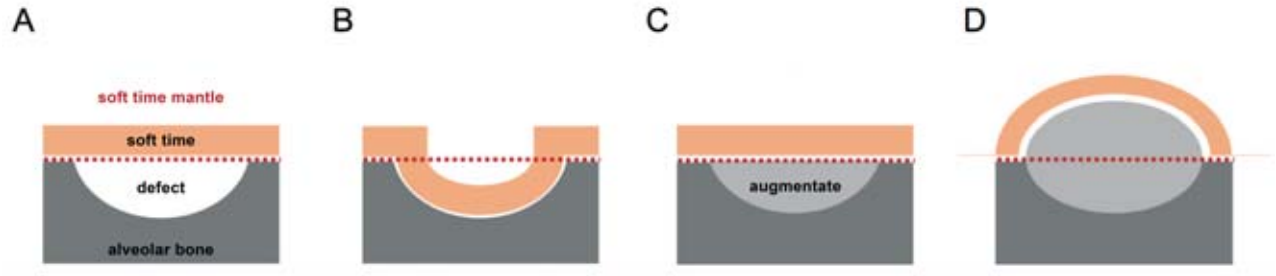



**Figure 1** Schematic representation of the bone shape, the soft tissue coat and an augmentation inside and outside of the soft tissue coat. The representation applies to horizontal, vertical and combined alveolar ridge defects. The soft tissue coat (red line) describes the natural dimension of the alveolar ridge **(A)**. If such a defect is not augmented, the soft tissue prolapses and the bone shape is altered **(B)**. A distinction is made between augmentations inside **(C)** and outside **(D)** the soft tissue coat.

## 1. Biological basis

### 1.1 Defect biology

For reliable and lasting implant placement, the alveolar process must have sufficient dimensions. Among other factors, natural resorption, periodontitis and defects resulting from tooth extraction can be causes of hard and soft tissue defects of the alveolar process. Osteoblast activity is at its highest in the apical region during the first 4 weeks after tooth extraction, after which, it shifts toward the crestal region. In this context, resorption processes also take place [1].

It is important to note that bone resorption also results in soft tissue reduction. In this regard, the soft tissue coat plays an important role in the regeneration of existing bone defects. Although there is widespread clinical acknowledgement of this problem, the evidence on this topic remains scarce. A special emphasis pertaining to this topic was applied within the framework of this guideline.

The osseous regeneration of alveolar process defects is even more difficult if an intrusion of soft tissue has occurred. This effect can be counteracted by performing ridge preservation (filling the empty alveolar socket with a suitable material). The ITI classification [2, 3] exemplifies this clinical understanding (Table 1, Figure 1).

The biological regeneration potential consequently depends directly on the quantity of the delimiting bone and the surrounding soft tissue. Defect geometries which have extensive osseous delimitation have higher regeneration potential [2, 3].

**Quintessence from the guideline**

The following classification concerning the regeneration potential of a clinical situation can be derived:

- procedures reconstructing defects of the alveolar ridge and sinus lifting: high biological regeneration capacity,
- lateral augmentation: medium biological regeneration capacity,
- combined lateral and vertical augmentation: low biological regeneration capacity.

### 1.2 The medical history of the patient

The literature search revealed a paucity of data addressing the question of the extent to which pre-existing medical conditions can affect augmentation success.

There are indications for an increased complication rate and a lower

| Type of material | Origin | Company | Product | Resorbable | Area of application |
|---|---|---|---|---|---|
| Allogeneic | Human bone matrix | Argon Dental | OsteoGraft® DBM | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® CortiFlex® | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® Femur Span | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® Cortical Granula | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® Spongiosa Granula | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® J & CGrafts | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoGraft® Osillium & Spongiosa Grafts | X | IM/PA/SA/GA/DS/AT |
| | | Straumann (botiss) | Human-Spongiosa CHB Knochenring | X | IM/GA/DS |
| | | | Human-Spongiosa CHB Granulat spongiös | X | IM/PA/SA/GA/DS/AT |
| | | | Human-Spongiosa CHB Block | X | IM/GA/DS |
| | | | maxgraft® cortico | X | IM/GA/DS |
| | | | maxgraft® bonering | X | IM/GA/DS |
| | | | maxgraft® Granulat spongiös | X | IM/PA/SA/GA/DS/AT |
| | | | maxgraft® Granulat cortico-spongiös | X | IM/PA/SA/GA/DS/AT |
| | | | maxgraft® Block | X | IM/GA/DS |
| | | | maxgraft® bonebuilder | X | IM/GA/DS |
| | | Zimmer Biomet | Puros® Allograft Block | X | IM/GA/DS |
| | | | Puros® Allograft Patienten individueller Block | X | IM/GA/DS |
| | | | Puros® Allograft Spongiosa Partikel | X | IM/PA/SA/GA/DS/AT |
| Xenogeneic | Equine | American Dental Systems | OsteoBiol® SP-Block (Bone Splitting/Spread.) | X | GA |
| | | Mectron | BIO-GEN® Spongy | | IM/PA/SA/GA/DS/AT |
| | | | BIO-GEN® Cortical | | IM/PA/SA/GA/DS/AT |
| | | | BIO-GEN® Mix | | IM/PA/SA/GA/DS/AT |
| | | | BIO-GEN® Putty | | AT |
| | Porcine | American Dental Systems | OsteoBiol® Gen-Os | X | IM/PA/SA/GA/DS |
| | | | OsteoBiol® Apatos (Mix) | | IM/PA/SA/GA/DS/AT |
| | | | OsteoBiol® mp3 | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoBiol® GTO® | X | IM/PA/SA/GA/DS/AT |
| | | | OsteoBiol® Putty | X | IM/PA/GA |
| | | | OsteoBiol® SP-Block (Bone Splitting/Spread.) | X | GA |
| | | | OsteoBiol® Bone Lamina Soft (Barrier) | X | IM/GA/DS |
| | | CAMLOG | MinerOss® XP | X | IM/PA/SA/GA/DS/AT |
| | | Champions-Implants | Matri™ Bone | X | IM/PA/SA/GA/DS/AT |
| | | | CollaWin! | X | IM/PA/SA/GA/DS/AT |
| | | Curasan (Vertrieb: mds) | CERASORB® Foam | X | IM/SA/GA/DS/AT |
| | | Dentsply Sirona | Symbios® Xenograft-Granulat | X | IM/PA/SA/GA/DS/AT |
| | | Geistlich Biomaterials | Geistlich Bio-Oss® COLLAGEN | X | IM/PA/SA/GA/DS/AT |
| | | Hess Medizintechnik | Geistlich Bio-Oss® COLLAGEN | X | IM/PA/SA/GA/DS/AT |
| | | REGEDENT | The Graft | | IM/PA/SA/GA/DS/AT |
| | | | OSSIX® VOLUMAX | X | IM/GA/DS |
| | | | OSSIX® Bone | X | IM/PA/SA/GA/DS/AT |
| | | Straumann (botiss) | collacone® max | X | IM/AT |
| | | Thommen Medical | The Graft | | IM/PA/SA/GA/DS/AT |
| | | | OSSIX® Bone | | IM/PA/SA/GA/DS/AT |
| | Bovine | BEGO Implant Systems | BEGO OSS | | IM/PA/SA/GA/DS/AT |
| | | BioHorizons (CAMLOG Dtl.) | MinerOss®-X | X | IM/PA/SA/GA/DS/AT |
| | | Bioimplon | Hypro-Oss® | X | IM/PA/SA/GA/DS/AT |
| | | CAMLOG | MinerOss® X | X | IM/PA/SA/GA/DS/AT |
| | | | MinerOss® X Collagen | X | IM/PA/SA/GA/DS/AT |
| | | Dentegris Deutschland | CompactBone B | X | IM/PA/SA/GA/DS/AT |
| | | Geistlich Biomaterials | Geistlich Bio-Oss® Spongiosa Granulat | X | IM/PA/SA/GA/DS/AT |
| | | | Geistlich Bio-Oss® Spongiosa Block | X | IM/SA/GA/DS |
| | | | Geistlich Bio-Oss® COLLAGEN | X | IM/PA/SA/GA/DS/AT |
| | | | Geistlich Bio-OssPen® Granulat | X | IM/PA/SA/GA/DS/AT |
| | | Henry Schein | NuOss® Granulat | X | IM/PA/SA/GA/DS/AT |

**Table 2** Overview of the marketed augmentation materials in dentistry and oral and maxillofacial surgery. Status: April 2019. From: Yearbook of Implantology 2019, OEMUS MEDIA AG, Leipzig. Area of application: implantology (IM), periodontology (PA), sinus floor augmentation (SA), general augmentation (GA), defect surgery (DS), alveolar treatment (AT).

| Type of material | Origin | Company | Product | Resorbable | Area of application |
|---|---|---|---|---|---|
| | | Hess Medizintechnik | Geistlich Bio-Oss® Spongiosa Granulat | X | IM/PA/SA/GA/DS/AT |
| | | | Geistlich Bio-Oss® Spongiosa Block | X | IM/SA/GA/DS |
| | | | Geistlich Bio-Oss® COLLAGEN | X | IM/PA/SA/GA/DS/AT |
| | | | Geistlich Bio-OssPen® Granulat | X | IM/PA/SA/GA/DS/AT |
| | | Nobel Biocare | creos xenogain | X | IM/PA/SA/GA/DS/AT |
| | | OT medical | BioVin® Bovine Bone | X | IM/PA/SA/GA/DS/AT |
| | | Septodont | R.T.R. Kegel | X | IM/PA/SA/GA/DS/AT |
| | | Straumann (botiss) | cerabone® | | IM/PA/SA/GA/DS/AT |
| | | Zimmer Biomet | Endobon® Xenograft Granulat | | IM/PA/SA/GA/DS/AT |
| | | | CopiOs® Xenograft Spongiosa Partikel | X | IM/PA/SA/GA/DS/AT |
| | plant-based | Dentsply Sirona | Frios® Algipore® | X | IM/PA/SA/GA/DS/AT |
| | | | Symbios® Biphasisches KAM | X | IM/PA/SA/GA/DS/AT |
| | | Gebr. Martin/KLS Martin | Martrix | X | IM/PA/SA/GA/DS/AT |
| | | SIC invent | SIC nature graft | X | IM/PA/SA/GA/DS/AT |
| Synthetic | HA/Collagen/Glycosaminoglycans | ACTEON Germany | BIOSTITE | X | IM/PA/SA/GA/DS |
| | Sodium hyaluronate | Argon Dental | OsteoGel® Hyaluron | X | IM/PA/SA/GA/DS/AT |
| | BCP | BEGO Implant Systems | BEGO OSS S | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | Bicon | SynthoGraft™ | X | IM/PA/SA/GA/DS/AT |
| | BCP | Champions-Implants | Matri™ Bone | X | IM/PA/SA/GA/DS/AT |
| | Kollagen | | CollaWin! | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | curasan (Vertrieb: mds) | CERASORB® Classic | X | IM/SA/GA/DS/AT |
| | β-TCP | | CERASORB® M | X | IM/SA/GA/DS/AT |
| | β-TCP | | CERASORB® Perio | X | PA |
| | β-TCP | | CERASORB® Plus | X | IM/SA/GA/DS/AT |
| | β-TCP | | CERASORB® Paste | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | | CERASORB® Foam | X | IM/SA/GA/DS/AT |
| | β-TCP | | CERASORB® Formteile | X | DC |
| | HA | | Osbone® | | IM/PA/SA/GA/DS/AT |
| | Calcium sulfate/β-TCP | Demedi-Dent | ethOss | X | IM/PA/SA/GA/DS/AT |
| | BCP | Dentegris Deutschland | CompactBone S | X | IM/PA/SA/GA/DS/AT |
| | Collagen | Dentium/iCT Europe | OSTEON™ | | IM/PA/SA/GA/DS/AT |
| | Collagen | | OSTEON™ Sinus & Lifting | | IM/PA/SA/GA/DS/AT |
| | Collagen | | OSTEON II™ | | IM/PA/SA/GA/DS/AT |
| | Collagen | | OSTEON II™ Sinus & Lifting | | IM/PA/SA/GA/DS/AT |
| | BCP | Dr. Ihde Dental | Nanos® | X | IM/PA/SA/GA/DS/AT |
| | $HA/SiO_2$ | Hager & Meisinger | NanoBone® \| granulate | X | IM/PA/SA/GA/DS/AT |
| | $HA/SiO_2$ | | NanoBone® \| block | X | IM/GA/DS |
| | $HA/SiO_2$ | | NanoBone® \| QD | X | IM/PA/SA/GA/DS/AT |
| | BCP | Henry Schein | BONITmatrix® | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | K.S.I. Bauer-Schraube | calc-i-oss™ | X | IM/PA/SA/GA/DS/AT |
| | BCP | | easy-graft® | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | LASAK | PORESORB-TCP | X | IM/PA/SA/GA/DS/AT |
| | HA | | OssaBase® -HA | X | IM/PA/SA/GA/DS/AT |
| | HA/BCS | MIS Implants Technologies | 4MATRIX | X | IM/PA/SA/GA/DS/AT |
| | BCP | | 4-Bone™ | X | IM/PA/SA/GA/DS/AT |
| | BCS | | BONDBONE® | X | IM/PA/SA/GA/DS/AT |
| | BCP | OT medical | OToss Synthetic Bone | X | IM/PA/SA/GA/DS/AT |
| | BCP | | OToss Synthetic Bone Inject | X | IM/PA/SA/GA/DS/AT |
| | BCS | REGEDENT | 3D Bond | X | IM/PA/GA/DS/AT |
| | HA/BCS | | Bond Apatite | X | IM/PA/GA/DS/AT |
| | BCP | | OSOPIA | X | IM/PA/SA/GA/DS |
| | Collagen | | OSSIX® Bone | X | IM/PA/SA/GA/DS/AT |
| | BCP | Shared Implantology | SinossGraft | X | IM/PA/SA/GA/DS |
| | BCP | (Novadento) | SinossGraft Resorb | X | IM/PA/SA/GA/DS |
| | BCP | | SinossGraft Inject | X | IM/PA/SA/GA/DS |
| | β-TCP | Septodont | R.T.R. Granulat | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | | R.T.R. Spritze | X | IM/PA/SA/GA/DS/AT |
| | BCP | Straumann | Straumann® BoneCeramic | X | IM/PA/SA/GA/DS/AT |

**Continuation Table 2** Overview of the marketed augmentation materials in dentistry and oral and maxillofacial surgery. Status: April 2019. From: Yearbook of Implantology 2019, OEMUS MEDIA AG, Leipzig. Area of application: implantology (IM), periodontology (PA), sinus floor augmentation (SA), general augmentation (GA), defect surgery (DS), alveolar treatment (AT).

| Type of material | Origin | Company | Product | Resorbable | Area of application |
|---|---|---|---|---|---|
| | BCP | Straumann (botiss) | maxresorb® | X | IM/PA/SA/GA/DS/AT |
| | BCP | | maxresorb® inject | X | IM/PA/SA/GA/DS/AT |
| | BCP/ Collagen | | collacone® max | X | IM/AT |
| | β-TCP | Sunstar Deutschland | calc-i-oss™CLASSIC | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | | easy-graft® CLASSIC | X | IM/PA/SA/GA/DS/AT |
| | BCP | | easy-graft® CRYSTAL | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | TAG Dental Systems | Sybone | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | Thommen Medical | Ceros® TCP Granulat | X | IM/PA/SA/GA/DS/AT |
| | β-TCP | | Ceros® TCP Putty | X | IM/PA/SA/GA/DS/AT |
| | BCS | | 3D Bond | X | IM/PA/GA/DS/AT |
| | HA/BCS | | Bond Apatite | X | IM/PA/GA/DS/AT |
| | PLA/PGA | Zantomed | FISIOGRAFT Granulat | X | IM/PA/SA/GA/DS/AT |
| | PLA/PGA | | FISIOGRAFT Gel | X | IM/PA/SA/GA/DS/AT |
| | PLA/PGA | | FISIOGRAFT Schwamm | X | IM/PA/SA/GA/DS/AT |
| | HA | | FISIOGRAFT BONE Granular | X | IM/PA/SA/GA/DS/AT |
| | HA | Zimmer Biomet | IngeniOs HA | | IM/PA/SA/GA/DS/AT |
| | β-TCP/ Silicon | | IngeniOs β-TCP bioaktiv | X | IM/PA/SA/GA/DS/AT |
| | Calciumphosphosilicate | | Nova Bone | X | IM/PA/SA/GA/DS/AT |
| Autogen | Autologous vital | BTI | PRGF® Endoret® | X | IM/PA/SA/GA/DS/AT |
| | osteogenic cells | Champions-Implants | Smart Grinder | X | IM/SA/GA/DS/AT |
| | | Schlumbohm | Autologer Knochen (KF T3) | X | IM/PA/SA/GA/DS |

**Continuation Table 2** Overview of the marketed augmentation materials in dentistry and oral and maxillofacial surgery. Status: April 2019. From: Yearbook of Implantology 2019, OEMUS MEDIA AG, Leipzig. Area of application: implantology (IM), periodontology (PA), sinus floor

rate of new bone formation in smokers, anamnestic periodontitis and poorly controlled diabetes [4–6]. Low vitamin D levels [7] and the use of PDE-5 inhibitors [8] might also play a negative role.

More consistent data exists on factors influencing implant success. Clinically, this data can be generalized to augmentations under certain circumstances. Studies associating osteoporosis, antiresorptive therapy, head and neck irradiation, selective serotonin reuptake inhibitors (SSRIs) and proton pump inhibitors (PPIs) with higher implant failure and complication rates exist [9–16].

### Quintessence from the guideline

Strong contraindications against the use of bone substitute materials cannot be found in the literature. Patients with general diseases might be at a higher risk for complications or failures. In particular, the following factors should be determined in the medical history:

- smoking, periodontal disease, diabetes, bisphosphonates, osteoporosis, radiation, vitamin D levels as well as the intake of PDE-5 inhibitors (sildenafil), selective serotonin reuptake inhibitors (SSRI) and proton pump inhibitors (PPI).

## 1.3 The different biomaterials

In general, implants placed in the augmented area – regardless of the augmentation material – do not have a poorer long-term prognosis than implants placed in local pristine bone [17–25] (Table 2).

The status of autologous bone grafts as the "biological gold standard" can be found in some sources in the literature [26–28]. However, harvesting morbidity, resorption phenomena and the required volume also play a role when selecting the material [29–31]. Consequently, bone substitute materials that are artificial in nature (alloplastic/synthetic), from a foreign species (xenogeneic) or from human sources (allogeneic) come into focus; they present the main advantages of reduced perioperative morbidity and higher quantitative availability.

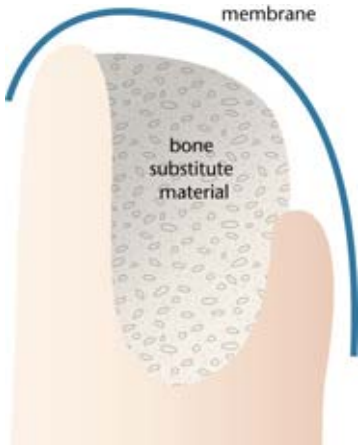
### 1.3.1 Allografts

These bone substitute materials are obtained from human donors. As a result of the multitude of existing preparation processes, consistent scientific statements, for example, regarding the success and complication rates, are difficult to make, and the availability of data for certain materials in clinical situations is limited [32]. Fragments of cells and DNA could be detected in various allografts [33–37], although their clinical significance is controversial [38–40].

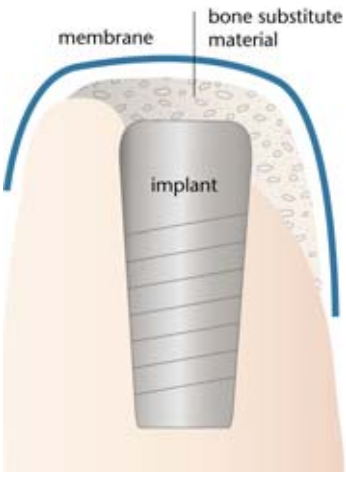
### 1.3.2 Xenografts

Bone substitute materials in this group can be obtained, for example, from cattle (bovine), pigs (porcine), horses (equine), but also from corals. Also, in this group, not every preparation has an equally good collection of data. Especially for some bovine products, there is a good collection of data with long observation periods [41–44]. These materials can be used to protect against resorption due to their very low resorption [41, 45, 46].


**Drawing 1** Ridge preservation with preserved alveolar walls, use of particulate bone substitute material without a membrane.




**Drawing 2** Ridge preservation in partially missing alveolar walls, use of particulate bone substitute with a resorbable collagen membrane.




**Drawing 3** Dehiscence defect at the implant, regeneration with particulate bone substitute material using a resorbable collagen membrane.

### 1.3.3 Synthetic/alloplastic bone substitute materials

Since these materials are produced using purely artificial methods, they do not pose any problems in terms of immunological or infectious responses. Examples include hydroxyapatites, silicon-containing bioglasses, calcium phosphates and microporous composites. In direct comparison with xenografts, synthetic bone substitute materials appear to be equivalent at best for some indications, but otherwise inferior [47–50]. However, these materials can be used successfully for selected clinical indications [22].

### Quintessence from the guideline

The available biomaterials have different properties, advantages and disadvantages. As a result, there is no one "gold standard". Moreover, it is advisable to check whether sufficient data is available for the material in question.

## 2. Regeneration of defects with high biological capacity

This group covers the treatment of defects whose regenerative capacity is classified as high according to 1.1. Characteristic to these clinical situations is that good osseous delimitations exist and that the soft tissue coat has not yet entered into the defect area.

### 2.1 Ridge preservation

The goal of ridge preservation procedures is to attenuate post-extraction resorption and preserve as much alveolar ridge and soft tissue volume as possible. The literature shows good prospects of success for a wide variety of protocols [51–55] (Drawing 1).

In a direct comparison, bovine xenogeneic material was superior [56] or equivalent [57] to allografts for this indication, although within the allograft material group, the demineralized freeze dried bone allograft (DFDBA) preparations appeared to be superior to other allogeneic preparations [32, 58]. There is also data describing the successful use of synthetic material [59] and platelet rich fibrin (A-PRF) [60] for alveolar ridge preservation.

### 2.2 The use of membranes/ guided bone regeneration (GBR) techniques for ridge preservation

Fundamental features of membranes used in GBR include the stabilization of a defect's shape, providing cell occlusivity and a barrier function [61]. When defects are present in the alveolar wall, the use of a membrane improves the result [53, 62–65] (Drawing 2). In comparing various types of membranes, resorbable collagen membranes show the most favorable ratio of success to complications [22].

### 2.3 Dehiscence defects at implants

Osseous deficits that occur when implants are placed are referred to as dehiscences and these are usually regenerated with a combination of biomaterials and membranes nowadays [22, 66–68], in which, autologous, allogeneic and xenogeneic materials, especially, demonstrate the best defect regeneration [22]. The best results for peri-implant augmentation performed simultaneously with implant placement can be achieved with the simultaneous use of a resorbable collagen membrane [22, 69] (Drawing 3).

Regeneration rates of up to 90 % are achievable, although it is clear that regenerated areas have a much better long-term prognosis than non-regenerated areas [22, 70].

### 2.4 Sinus lifting

Using a variety of techniques, sinus floor elevation aims to elevate Schneider's membrane in order to permit augmentation in the created space. There are many studies with a high level of evidence showing that it is irrelevant for the survival rate of the subsequently placed implants, whether they are placed in autologous bone, or in areas regenerated with bone substitute materials, and that their success rates are comparable. These results seem to be independent of the used bone substitute material or technique [71–77] (Drawing 4).

### Quintessence from the guideline

Defects with intact bone walls can be regenerated with any biomaterial.

The largest amount of data is found for xenogeneic and allogeneic materials. In cases where a bone wall is lost, a membrane should be inserted to act as a barrier. Overall, clinical cases falling into this category have a relatively high success rate.

## 3. Regeneration of defects with low biological capacity

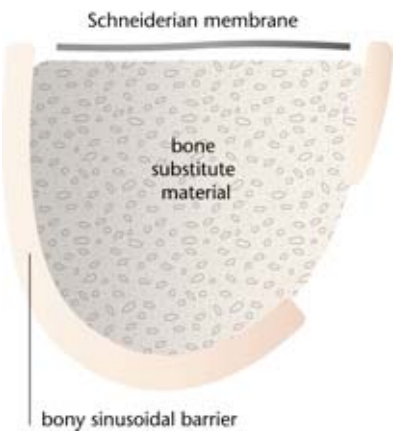
Defects whose regenerative capacity is classified as low according to 1.1 require significantly more technical and surgical effort than the situations analyzed so far. Lateral, vertical and, especially, combined lateral and vertical defects of the alveolar ridge fall into this group.

### 3.1 Regeneration with particulate bone substitute material (GBR techniques)

As long as the segment to be regenerated does not exceed 3 mm (laterally and/or vertically), particulate bone substitute material in combination with a barrier membrane can be used, analogous to the techniques presented in 2.2 and 2.3 [22] (Drawings 5 and 6).

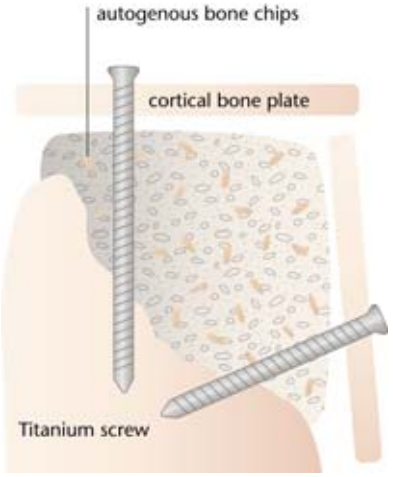
If larger defects should be regenerated with the aid of particulate bone substitute materials, specific guided bone regeneration (GBR) techniques such as titanium-reinforced membranes, individualized titanium grids, or shell techniques are required; the bone substitute material appears to play a subordinate role compared to the barrier form [22, 78–81]. In particular, the use of the dimensionally stable barriers must be emphasized, as this is the only way to achieve similarly high levels of regeneration that would otherwise be possible solely with the aid of autologous bone blocks. In this context, CAD/CAM-produced titanium grids are of particular interest, as they reduce the intraoperative effort by virtue of their preoperative preparation, and they can be customized to accurately match the existing clinical situation [82–86].

The risk of wound healing disturbances with consecutive dehiscence and the risk of implant/graft loss can only be reduced by customized soft tissue management [83, 86].

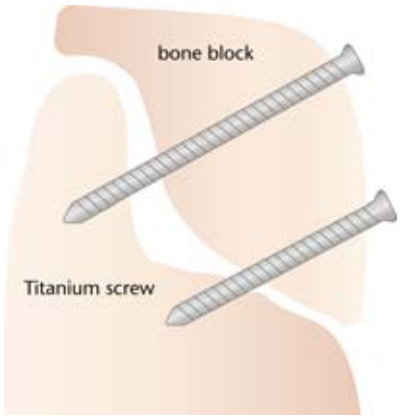



**Drawing 4** Sinus lift with particulate bone substitute material.


**Drawing 5** Lateral and vertical augmentation with a titanium mesh (then with additional resorbable collagen membrane "blue line") or as titanium-reinforced membrane. Fixation using screws or pins if necessary.




**Drawing 6** Lateral and vertical augmentation using a cortical shell technique, filling with autologous bone chips or particulate bone substitute materials.




**Drawing 7** Lateral and vertical augmentation with a bone block fixed using screws.

(Fig. 1, Drawings 1–7, Tab. 1 and 2: M. Tröltzsch)

Resorbable collagen membranes and PRF can improve dehiscence rates over titanium grids [85].

### 3.2 Regeneration with autologous blocks and blocks from bone substitute material

Numerous extraoral and intraoral donor sites are available for bone block harvesting to the experienced surgeon, though it is noteworthy to mention that evident differences with regard to the regenerative capacity from various harvesting sites exist. With intraoral blocks, defects up to 5 mm can be regenerated [22, 87, 88] (Drawing 7). For larger segments, bone from extraoral regions is recommended [22]; the iliac crest is frequently referred to as the "gold standard" based on the large amount of grafted osteoblasts [89, 90]. However, some limitations of autologous blocks need to be considered such as long-term resorption, as well as, the possible limited quantity of the volume that can be harvested and re-

moval morbidity of the graft [91–97]. As a result, the use of non-autologous blocks as an alternative is being investigated and the successful application of xenogeneic and allogeneic blocks have been described in the literature [31, 98–101]. However, direct comparisons between xenogeneic [22, 102] and allogeneic block grafts [22, 87, 103–106] have shown that autologous bone blocks are inferior in terms of regeneration outcomes and complication rates. Moreover, organic materials and DNA residues have also been detected in allogeneic and xenogeneic blocks [33–37, 89, 107, 108] and their effects are controversially discussed [34–36, 104, 105].

Overall, the available data for xenogeneic and allogeneic bone blocks is highly heterogeneous, partially controversial, and generally inadequate. The consistency of data for alloplastic blocks must be classified as even poorer.

### Quintessence from the guideline

Defects up to 3 mm can be regenerated with particulate material in combination with a resorbable collagen membrane. Larger defects require either specialized GBR techniques or the preferable use of autologous blocks. Soft tissue management is of particular importance.

## 4. Conclusion

There is no "one" biomaterial that can be termed the gold standard. All available materials have advantages and disadvantages, which the practitioner must evaluate according to the indication. The treating physician and dental practitioner are responsible for selecting the appropriate material, which should be supported by sufficient data for the given case.

The preservation and regeneration of the alveolar ridge can be performed predictably using suitable materials. Ridge preservation is a well-documented standard technique which is suitable for reducing or even preventing subsequent major defects.

The regeneration of large defects with less surrounding bone is technically more demanding and difficult than the augmentation of small defects with more extensive surrounding bone. For defect segments of up to 3 mm (lateral and/or vertical), particulate bone substitute material in combination with resorbable membranes is sufficient for regeneration; on the other hand, for larger segments, specialized GBR techniques with stable barriers or preferably autologous bone blocks is required.

## Conflicts of interest

The conflicts of interest can be found in the detailed version of the guideline "Implantological indications for the use of bone substitute materials" at www.online-dzz.de.

The full text of the guideline "Implantological indications for the use of bone substitute materials" can be freely downloaded from the DGZMK (www.dgzmk.de) and AWMF (www.awmf.org) websites.

### References

1. Nahles S et al.: Bone physiology in human grafted and non-grafted extraction sockets – an immunohistochemical study. Clin Oral Implants Res 2013; 24: 812–819

2. Terheyden H: Knochenaugmentationen in der Implantologie. Dtsch Zahnärztl Z 2010; 65: 320–330

3. Cordaro L Terheyden H: ITI Treatment Guide. Alveolarkammaugmentationen bei Implantatpatienten: Ein zweizeitiges Konzept, ed. Terheyden H, Cordaro L: Vol. 7. Quintessenz, Berlin 2014

4. Sakkas A et al.: Risk factors for postoperative complications after procedures for autologous bone augmentation from different donor sites. J Craniomaxillofac Surg 2018; 46: 312–322

5. Zhang S et al.: Type 2 diabetes affects postextraction socket healing and influences first-stage implant surgery: a study based on clinical and animal evidence. Clin Implant Dent Relat Res 2019

6. Knabe C et al.: Effect of beta-tricalcium phosphate particles with varying porosity on osteogenesis after sinus floor augmentation in humans. Biomaterials 2008; 29: 2249–2258

7. Fretwurst T et al.: Vitamin D deficiency in early implant failure: two case reports. Int J Implant Dent 2016; 2: 24

8. Orchard E et al.: Sildenafil transiently delays early alveolar healing of tooth extraction sockets. Clin Surg 2017; 2: 1458

9. Farzad P, Andersson L, Nyberg J: Dental implant treatment in diabetic patients. Implant Dent 2002; 11: 262–267

10. Heitz-Mayfield LJ: Peri-implant diseases: diagnosis and risk indicators. J Clin Periodontol 2008; 35 (8 Suppl): 292–304

11. Gomez-de Diego R et al.: Indications and contraindications of dental implants in medically compromised patients: update. Med Oral Patol Oral Cir Bucal 2014; 19: e483–9

12. Grötz CWBA-N.S.H.R. M.U.K.A.: Zahnimplantate bei medikamentöser Behandlung mit Knochen Antiresorptiva (inkl. Bisphosphonate) Langversion 1.0, 2016. AWMF Registernummer: 083–026, 2016

13. Kandasamy B et al.: Long-term retrospective study based on implant success rate in patients with risk factor: 15-year follow-up. J Contemp Dent Pract 2018; 19: 90–93

14. Schimmel M et al.: Effect of advanced age and/or systemic medical conditions on dental implant survival: a systematic review and meta-analysis. Clin Oral Implants Res 2018; 29 (Suppl 16): 311–330

15. Carr AB et al.: Relationship between Selective Serotonin Reuptake Inhibitors and Risk of Dental Implant Failure. J Prosthodont 2019; 28: 252–257

16. Wu X et al.: Proton pump inhibitors and the risk of osseointegrated dental implant failure: a cohort study. Clin Implant Dent Relat Res 2017; 19: 222–232

17. Jensen SS, Terheyden H: Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials. Int J Oral Maxillofac Implants 2009; 24 (Suppl): 218–236

18. Barone A et al.: A randomized clinical trial to evaluate and compare implants placed in augmented versus non-augmented extraction sockets: 3-year results. J Periodontol 2012; 83: 836–846

19. Aloy-Prosper A et al.: The outcome of intraoral onlay block bone grafts on alveolar ridge augmentations: a systematic review. Med Oral Patol Oral Cir Bucal 2015; 20: e251–8

20. Motamedian SR, Khojaste M, Khojasteh A: Success rate of implants placed in autogenous bone blocks versus allogenic bone blocks: a systematic literature review. Ann Maxillofac Surg 2016; 6: 78–90

21. Tran DT et al.: Survival of dental implants placed in grafted and nongrafted bone: a retrospective study in a university setting. Int J Oral Maxillofac Implants 2016; 31: 310–317

22. Troeltzsch M et al.: Clinical efficacy of grafting materials in alveolar ridge augmentation: a systematic review. J Craniomaxillofac Surg 2016; 44: 1618–1629

23. Urban IA et al.: Long-term evaluation of peri-implant bone level after reconstruction of severely atrophic edentulous maxilla via vertical and horizontal guided bone regeneration in combination with sinus augmentation: a case series with 1 to 15 years of loading. Clin Implant Dent Relat Res 2017; 19: 46–55

24. Marconcini S et al.: Clinical outcomes of implants placed in ridge-preserved versus nonpreserved sites: a 4-year randomized clinical trial. Clin Implant Dent Relat Res 2018; 20: 906–914

25. Salvi GE, Monje A, Tomasi C: Long-term biological complications of dental implants placed either in pristine or in augmented sites: a systematic review and meta-analysis. Clin Oral Implants Res 2018; 29 (Suppl 16): 294–310

26. Bauer TW, Muschler GF: Bone graft materials. An overview of the basic science. Clin Orthop Relat Res 2000; 371: 10–27

27. Fretwurst T et al.: Long-term retrospective evaluation of the peri-implant bone level in onlay grafted patients with iliac bone from the anterior superior iliac crest. J Craniomaxillofac Surg 2015; 43(6): 956–960

28. Sakkas A et al.: Autogenous bone grafts in oral implantology – is it still a "gold standard"? A consecutive review of 279 patients with 456 clinical procedures. Int J Implant Dent 2017; 3(1): 23

29. Chiapasco M, Zaniboni M, Rimondini L: Autogenous onlay bone grafts vs. alveolar distraction osteogenesis for the correction of vertically deficient edentulous ridges: a 2–4-year prospective study on humans. Clin Oral Implants Res 2007; 18(4): 432–440

30. Felice P et al.: Vertical ridge augmentation of the atrophic posterior mandible with interpositional block grafts: bone from the iliac crest versus bovine anorganic bone. Eur J Oral Implantol 2008; 1: 183–198

31. Dahlin C, Johansson A: Iliac crest autogenous bone graft versus alloplastic graft and guided bone regeneration in the reconstruction of atrophic maxillae: a 5-year retrospective study on cost-effectiveness and clinical outcome. Clin Implant Dent Relat Res 2011; 13: 305–310

32. Wood RA, Mealey BL: Histologic comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft. J Periodontol 2012; 83: 329–336

33. Fretwurst T et al.: Comparison of four different allogeneic bone grafts for alveolar ridge reconstruction: a preliminary histologic and biochemical analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 118: 424–431

34. Ghanaati S et al.: Potential lack of "standardized" processing techniques for production of allogeneic and xenogeneic bone blocks for application in humans. Acta Biomater 2014; 10: 3557–3562

35. Fretwurst T et al.: Detection of major histocompatibility complex molecules in processed allogeneic bone blocks for use in alveolar ridge reconstruction. Oral Surg Oral Med Oral Pathol Oral Radiol 2018

36. Lorenz J et al.: Allogeneic bone block for challenging augmentation – a clinical, histological, and histomorphometrical investigation of tissue reaction and new bone formation. Clin Oral Investig 2018; 22: 3159–3169

37. Li G et al.: Current updates on bone grafting biomaterials and recombinant human growth factors implanted biotherapy for spinal fusion: a review of human clinical studies. Curr Drug Deliv 2019; 16: 94–110

38. Solakoglu O et al.: Characterization of circulating DNA in plasma of patients after allogeneic bone grafting. Clin Oral Investig 2019; 23: 4243–4253

39. Solakoglu O et al.: Histological and immunohistochemical comparison of two different allogeneic bone grafting materials for alveolar ridge reconstruction: a prospective randomized trial in humans. Clin Implant Dent Relat Res 2019; 21: 1002–1016

40. Stopa Z et al.: Evaluation of the safety and clinical efficacy of allogeneic bone grafts in the reconstruction of the maxilla and mandible. Transplant Proc 2018; 50: 2199–2201

41. Klein MO et al.: Long-term bony integration and resorption kinetics of a xenogeneic bone substitute after sinus floor augmentation: histomorphometric analyses of human biopsy specimens. Int J Periodontics Restorative Dent 2013; 33: e101–10

42. Majzoub J et al.: The influence of different grafting materials on alveolar ridge preservation: a systematic review. J Oral Maxillofac Res 2019; 10: e6

43. Mendoza-Azpur G et al.: Horizontal ridge augmentation with guided bone regeneration using particulate xenogenic bone substitutes with or without autogenous block grafts: a randomized controlled trial. Clin Implant Dent Relat Res 2019; 21: 521–530

44. Thoma DS et al.: Efficacy of lateral bone augmentation performed simultaneously with dental implant placement: a systematic review and meta-analysis. J Clin Periodontol 2019; 46 (Suppl 21): 257–276

45. Mordenfeld A et al.: Histological and histomorphometrical analyses of biopsies harvested 11 years after maxillary sinus floor augmentation with deproteinized bovine and autogenous bone. Clin Oral Implants Res 2010; 21: 961–970

46. Naenni N et al.: Efficacy of lateral bone augmentation prior to implant placement: a systematic review and meta-analysis. J Clin Periodontol 2019; 46 (Suppl 21): 287–306

47. Dau M et al.: Bone formation in mono cortical mandibular critical size defects after augmentation with two synthetic nanostructured and one xenogenous hydroxyapatite bone substitute – in vivo animal study. Clin Oral Implants Res 2016; 27: 597–603

48. Hung CC et al.: Bone formation following sinus grafting with an alloplastic biphasic calcium phosphate in Lanyu Taiwanese mini-pigs. J Periodontol 2019

49. Lorenz J et al.: Volumetric analysis of bone substitute material performance within the human sinus cavity of former head and neck cancer patients: a prospective, randomized clinical trial. Ann Maxillofac Surg 2016; 6: 175–181

50. Sanz M, Vignoletti F: Key aspects on the use of bone substitutes for bone regeneration of edentulous ridges. Dent Mater 2015; 31: 640–647

51. Barone A et al.: A prospective, randomized, controlled, multicenter evaluation of extraction socket preservation comparing two bovine xenografts: clinical and histologic outcomes. Int J Periodontics Restorative Dent 2013; 33: 795–802

52. Avila-Ortiz G et al.: Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis. J Dent Res 2014; 93: 950–958

53. Avila-Ortiz G et al.: Effectiveness of three different alveolar ridge preservation techniques: a pilot randomized controlled trial. Int J Periodontics Restorative Dent 2014; 34: 509–521

54. Bonanini M et al.: Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis. Biomed Res Int 2014; 93: 950–958

55. Willenbacher M et al.: The effects of alveolar ridge preservation: a meta-analysis. Clin Implant Dent Relat Res 2016; 18: 1248–1268

56. Scheyer ET et al.: A randomized, controlled, multicentre clinical trial of post-extraction alveolar ridge preservation. J Clin Periodontol 2016; 43: 1188–1199

57. Sadeghi R et al.: A randomized controlled evaluation of alveolar ridge preservation following tooth extraction using

deproteinized bovine bone mineral and demineralized freeze-dried bone allograft. Dent Res J (Isfahan) 2016; 13: 151–159

58. Whetman J, Mealey BL: Effect of healing time on new bone formation after tooth extraction and ridge preservation with demineralized freeze-dried bone allograft: a randomized controlled clinical trial. J Periodontol 2016; 87: 1022–1029

59. Ioannou AL et al.: Evaluation of the bone regeneration potential of bioactive glass in implant site development surgeries: a systematic review of the literature. Clin Oral Investig 2015; 19: 181–191

60. Schliephake H et al.: Drugs and diseases: summary and consensus statements of group 1. The 5(th) EAO Consensus Conference 2018. Clin Oral Implants Res 2018; 29 (Suppl 18): 93–99

61. Elgali I et al.: Guided bone regeneration: materials and biological mechanisms revisited. Eur J Oral Sci 2017; 125: 315–337

62. Barone A et al.: Xenograft versus extraction alone for ridge preservation after tooth removal: a clinical and histomorphometric study. J Periodontol 2008; 79: 1370–1377

63. Brkovic BM et al.: Beta-tricalcium phosphate/type I collagen cones with or without a barrier membrane in human extraction socket healing: clinical, histologic, histomorphometric, and immunohistochemical evaluation. Clin Oral Investig 2012; 16: 581–590

64. Fischer KR et al.: Dimensional evaluation of different ridge preservation techniques with a bovine xenograft: a randomized controlled clinical trial. Int J Periodontics Restorative Dent 2018; 38: 549–556

65. Jung RE et al.: Combined use of xenogeneic bone substitute material covered with a native bilayer collagen membrane for alveolar ridge preservation: a randomized controlled clinical trial. Clin Oral Implants Res 2018; 29: 522–529

66. Hassan KS: Autogenous bone graft combined with polylactic polyglycolic acid polymer for treatment of dehiscence around immediate dental implants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 108: e19–25

67. Jung RE et al.: Cone beam computed tomography evaluation of regenerated buccal bone 5 years after simultaneous implant placement and guided bone regeneration procedures – a randomized, controlled clinical trial. Clin Oral Implants Res 2015; 26: 28–34

68. Llambes F, Silvestre FJ, Caffesse R: Vertical guided bone regeneration with bioabsorbable barriers. J Periodontol 2007; 78: 2036–2042

69. Le BT, Borzabadi-Farahani A: Simultaneous implant placement and bone grafting with particulate mineralized allograft in sites with buccal wall defects, a three-year follow-up and review of literature. J Craniomaxillofac Surg 2014; 42: 552–559

70. Jung RE et al.: A randomized controlled clinical trial comparing small buccal dehiscence defects around dental implants treated with guided bone regeneration or left for spontaneous healing. Clin Oral Implants Res 2017; 28: 348–354

71. Al-Nawas B, Schiegnitz E: Augmentation procedures using bone substitute materials or autogenous bone – a systematic review and meta-analysis. Eur J Oral Implantol 2014; 7 (Suppl 2): S219–34

72. Danesh-Sani SA, Engebretson SP, Janal MN: Histomorphometric results of different grafting materials and effect of healing time on bone maturation after sinus floor augmentation: a systematic review and meta-analysis. J Periodontal Res 2017; 52: 301–312

73. Starch-Jensen T et al.: A systematic review and meta-analysis of long-term studies (five or more years) assessing maxillary sinus floor augmentation. Int J Oral Maxillofac Surg 2018; 47: 103–116

74. Starch-Jensen T et al.: Maxillary sinus floor augmentation with synthetic bone substitutes compared with other grafting materials: a systematic review and meta-analysis. Implant Dent 2018; 27: 363–374

75. Jensen T et al.: Maxillary sinus floor augmentation with Bio-Oss or Bio-Oss mixed with autogenous bone as graft: a systematic review. Clin Oral Implants Res 2012; 23: 263–273

76. Jensen T et al.: Bone-to-implant contact after maxillary sinus floor augmentation with Bio-Oss and autogenous bone in different ratios in mini pigs. Clin Oral Implants Res 2013; 24: 635–644

77. Esposito M, Felice P, Worthington HV: Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. Cochrane Database Syst Rev 2014: Cd008397

78. Rocchietta I et al.: Vertical bone augmentation with an autogenous block or particles in combination with guided bone regeneration: a clinical and histological preliminary study in humans. Clin Implant Dent Relat Res 2016; 18: 19–29

79. Seiler M et al.: Customized lattice structure in reconstruction of three-dimensional alveolar defects. Int J Comput Dent 2018; 21: 261–267

80. Seiler M et al.: Customized titanium lattice structure in three-dimensional alveolar defect: an initial case letter. J Oral Implantol 2018; 44: 219–224

81. Urban IA et al.: Effectiveness of vertical ridge augmentation interventions. A systematic review and meta-analysis. J Clin Periodontol, 2019; 46 (Suppl 21): 319–339

82. Ciocca L et al.: Direct metal laser sintering (DMLS) of a customized titanium mesh for prosthetically guided bone regeneration of atrophic maxillary arches. Med Biol Eng Comput 2011; 49: 1347–1352

83. Ciocca L et al.: Prosthetically CAD-CAM-guided bone augmentation of atrophic jaws using customized titanium mesh: preliminary results of an open prospective study. J Oral Implantol 2018; 44: 131–137

84. Hartmann A et al.: Evaluation of risk parameters in bone regeneration using a customized titanium mesh: results of a clinical study. Implant Dent 2019; 28: 543–550

85. Lorenz J et al.: Individualized titanium mesh combined with platelet-rich fibrin and deproteinized bovine bone: a new approach for challenging augmentation. J Oral Implantol 2018; 44: 345–351

86. Sagheb K et al.: Clinical outcome of alveolar ridge augmentation with individualized CAD-CAM-produced titanium mesh. Int J Implant Dent 2017; 3: 36

87. Khojasteh A et al.: Localized bone augmentation with cortical bone blocks tented over different particulate bone substitutes: a retrospective study. Int J Oral Maxillofac Implants 2012; 27: 1481–1493

88. Khojasteh A, Morad G, Behnia H: Clinical importance of recipient site characteristics for vertical ridge augmentation: a systematic review of literature and proposal of a classification. J Oral Implantol 2012

89. Wein M et al.: Pilot investigation of the molecular discrimination of human osteoblasts from different bone entities. J Craniomaxillofac Surg 2015; 43: 1487–1493

90. Wein M et al.: Differential osteopontin expression in human osteoblasts derived from iliac crest and alveolar bone and its role in early stages of angiogenesis. J Bone Miner Metab 2019; 37: 105–117

91. Maestre-Ferrin L, Boronat-Lopez A, Penarrocha-Diago M: Augmentation procedures for deficient edentulous ridges, using onlay autologous grafts: an update. Med Oral Patol Oral Cir Bucal 2009; 14: e402–7

92. Mertens C et al.: Early bone resorption after vertical bone augmentation – a comparison of calvarial and iliac grafts. Clin Oral Implants Res 2013; 24: 820–825

93. Smolka W: Calvarial grafts for alveolar ridge reconstruction prior to dental implant placement: an update. Oral Maxillofac Surg 2014; 18: 381–385

94. Nkenke E, Neukam FW: Autogenous bone harvesting and grafting in advanced jaw resorption: morbidity, resorption and implant survival. Eur J Oral Implantol 2014; 7 (Suppl 2): S203–17

95. Barone A et al.: Morbidity associated with iliac crest harvesting in the treatment of maxillary and mandibular atrophies: a 10-year analysis. J Oral Maxillofac Surg 2011; 69: 2298–2304

96. Kuik K et al.: Donor site morbidity of anterior iliac crest and calvarium bone grafts: a comparative case-control study. J Craniomaxillofac Surg 2016; 44: 364–368

97. Putters TF et al.: Morbidity of anterior iliac crest and calvarial bone donor graft sites: a 1-year randomized controlled trial. Int J Oral Maxillofac Surg 2018; 47: 1474–1480

98. Bonanini M et al.: Vertical ridge augmentation using xenogenous bone blocks: a comparison between the flap and tunneling procedures. Biomed Res Int 2014; 72: 1660–1670

99. Pereira E et al.: Horizontal resorption of fresh-frozen corticocancellous bone blocks in the reconstruction of the atrophic maxilla at 5 months. Clin Implant Dent Relat Res 2014

100. Blume O et al.: Treatment of severely resorbed maxilla due to peri-implantitis by guided bone regeneration using a customized allogenic bone block: a case report. Materials (Basel) 2017; 10: 1213

101. Kloss FR, Offermanns V, Kloss-Brandstatter A: CEComparison of allogeneic and autogenous bone grafts for augmentation of alveolar ridge defects – a 12-month retrospective radiographic evaluation. Clin Oral Implants Res 2018

102. Pistilli R et al.: Blocks of autogenous bone versus xenografts for the rehabilitation of atrophic jaws with dental implants: preliminary data from a pilot randomised controlled trial. Eur J Oral Implantol 2014; 7: 153–171

103. Chiapasco M et al.: Fresh frozen versus autogenous iliac bone for the rehabilitation of the extremely atrophic maxilla with onlay grafts and endosseous implants: preliminary results of a prospective comparative study. Clin Implant Dent Relat Res 2013

104. Lumetti S et al.: Fresh-frozen bone blocks for horizontal ridge augmentation in the upper maxilla: 6-month outcomes of a randomized controlled trial. Clin Implant Dent Relat Res 2014; 16(1): 116–123

105. Lumetti S, Galli C: Correlation between density and resorption of fresh-frozen and autogenous bone grafts 2014; 2014: 508328

106. Leong DJ et al.: Comparison between sandwich bone augmentation and allogenic block graft for vertical ridge augmentation in the posterior mandible. J Periodontal Implant Sci 2015; 24: 4–12

107. Kubosch EJ et al.: Clinical trial and in-vitro study comparing the efficacy of treating bony lesions with allografts versus synthetic or highly-processed xenogeneic bone grafts. BMC Musculoskelet Disord 2016; 17: 77

108. Coutinho LF et al.: Presence of cells in fresh-frozen allogeneic bone grafts from different tissue banks. Braz Dent J 2017; 28: 152–157

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