Usability and Tissue Stability of CAD/CAM Prefabricated Allogenic Bone Blocks for the Reconstruction of Severe Bone Defects in the Aesthetic Zone of the Maxilla

Thesis Booklet

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1. Introduction

Bone grafting and bone reconstruction is a surgical procedure with the goal of replacing missing or resected bone material. This can be indicated when a patient suffered severe trauma to the bone, after resection of bone material, in patients with tumors or after the loss of teeth, due to severe periodontitis for example or due to the physiological atrophy of unloaded bone. The goal of bone reconstruction is to completely restore the lost bone material which would not heal properly unassistedly for functional and aesthetic reasons. Bone augmentation uses transplanted bone and bone substitute materials to repair and restore diseased or damaged bone. This can be done almost everywhere in the body.

Especially in the fields of maxillofacial and oral surgery the bone grafting techniques and materials have been improved significantly during the past years and decades. The reason for this progress in research and development is the necessity of sufficient bone when it comes to dental implantation. Surgical procedures like osteoplastic operations, often combined with bone transplants or bone substitute materials, are used where the pristine bone of the patient has been damaged and needs to be restored, so that the bone cells inside the bone graft can seal themselves to the native bone of the patient. For bone grafting, there are several possibilities, types and techniques.

Autologous bone grafts have been considered as the gold standard to date because these materials provide in certain circumstances osteogenesis as well as neovascularisation. Nevertheless, several risks with autologous bone grafts have been described. Advantages of autologous bone grafts are histocompatibility and possess of osteogenic properties. Further, there is no risk of a possible transmission of diseases. Problematics and challenges, which are associated with autologous bone grafting can be the need for general anesthesia, the limited supply, the increased magnitude of surgery and thus, increased time for the operational procedure as well as the amount of blood loss for the patient. To date, the greatest concern with autologous bone grafting is the donor site morbidity.

While autologous bone graft materials originate from the same species and the same individual, allogenic transplants are derived from the same species but not the same individual. So, this means for humans that the patients themselves receive the bone graft from another individual. Allogenic hard tissue grafts have gained popularity

in the field of dental bone grafting, due the limited amount of donor tissue and to the possible complications, which can arise during or after harvesting. In contrast to autologous bone material, pure allogenic bone is not capable of growing new bone by itself. Allogenic bone transplants are used as framework and the osseous tissue, which proliferates into the allogenic transplant derives from the patient's natural bone, which grows around the graft.

Nevertheless, allogenic bone graft materials possess several advantages over autologous bone:

1) No risk of donor site morbidity and related complications

2) No second surgical site

3) Less patient discomfort

4) Reduced surgery time

5) Unlimited supply

6) Low antigenic potential

Allografts can be categorized into fresh-frozen bone (FFBA), freeze-dried bone (FDBA) and demineralized bone (DFDBA). Allogenic bone is available as micellized and cancellous chips, demineralized bone matrix, corticocancellous- or cortical graft materials. Furthermore, osteochondral and whole bone segments and blocks are available.

A significant benefit of allogenic bone blocks over autologous bone material is the possibility of CAD/CAM technology. The allogenic bone blocks can be designed and fitted for each patient individually. The bone blocks are patient customized and are suitable for complex alveolar ridge augmentation. But still, there is limited research and limited literature on alveolar bone grafting with patient customized allogenic bone blocks.

2. Objectives

2.1. General objective

The general objective of this thesis was to increase the knowledge about and provide evidence for the new technology of CAD/CAM allogenic bone blocks for bone grafting.
Another goal of the current study is to demonstrate the high implant survival rate, related to this new technology, as well as the success rate of the surgical procedure. We collected data with autologous bone grafts from the literature and compared them to our patient data with the novel CAD/CAM-allogenic bone block technology. We intend to show that both techniques are comparable in clinical outcomes, implant survival rates, patient morbidities and aesthetic aspects.

2.2. Special objective

Even though several case reports have shown the high success rate of CAD/CAM allogenic bone blocks for bone grafting even in complex and severe bone defects, no study with a larger number of patients has been carried out to date. The current thesis comprises a retrospective cohort study with 23 patients, receiving CAD/CAM allogenic bone blocks for alveolar bone grafting in the esthetic zone of the maxilla. The current study aims to:

1) Provide evidence for the usability of CAD/CAM allogenic bone blocks
2) Analyze the clinical outcomes in patients with severe bone defects receiving bone grafting with CAD/CAM allogenic bone blocks
3) Investigate possible complications and drawbacks of the method of bone grafting with CAD/CAM allogenic bone blocks
4) Analyze the complication rates of this new technology and compare them to the complications in autologous bone grafting in the literature
5) Analyze the advantages of the CAD/CAM allogenic bone block technology and compare them to those of autologous bone grafting from the literature
6) Introduce this new technology on a large scale
7) Introducing a new digital technology to monitor volume changes in transplants during the healing process

8) Additionally, a newly developed remote incision technique is presented. This technique is meant to avoid wound dehiscence

3. Materials and methods

3.1. Sources and collection of data

3.1.1. General study design

Based on the data analysis of digital volume-tomography, 23 patients, who had severe bone defects in the region 13-23 could be reconstructed with computer-designed allogenic bone.

Patient data was collected in our Institute of Dres. Back and Blume, private practice and clinic for maxillo-, facial- and oral surgery in Munich, Germany. The participation in the study was not associated with further surgical interventions or with high risk of morbidity. We collected the data from patients we had treated in our private practice from their digital case histories. The medical histories of the patients were, therefore, already known age, gender, substance abuse, co-morbidities and prescribed medications. Each patient was educated in detail about the surgical procedure with the CAD/CAM-technology as well as about other, alternative methods of treatment, eventually each patient in the current study gave consent and is therefore, the free will of each patient in the current study.

The following parameters were collected carrying out the current monocentric retrospective study:

1) Patients age

2) Patients gender

3) Location and geometry of the bone defect

4) Clinical diagnosis

5) Type of bone defect

6) The reason why the bone defect has occurred

7) Type of allograft and manufacturer

8) Post operative complications

9) Wound healing parameters

10) Extent of new bone growth (in ml)

11) Implant health and stability

12) Patient satisfaction

The programs coDiagnostiX (digital planning software coDiagnostiX, version 10.2.0.15659, Dental Wings Inc., Montreal, Canada) and Slicer (an open-source medical image processing software platform, 3D Slicer, www.slicer.org) were used to take the measurements of the area of the bone defect on different time points:

T1: before bone grafting

T2: 2 months after the insertion of the bone graft

T3: 6 months follow-up

Our goal was to measure the three-dimensional bone gain after bone grafting and healing. Therefore, the volume of the bone graft was measured at T1 and T2 and the difference between those values was calculated. Additionally, volumetric changes of the bone blocks during the healing process were examined and analyzed. Additionally, we analyzed the average survival time of the bone blocks as well as the implant success rate. The data was plotted and analyzed by Kaplan Meier plot.

Complications like membrane exposition, soft tissue dehiscence, bone block exposure or exposure of the osteosynthesis screws were documented and statistically analyzed and correlation with health status of the patient, gender, age, nicotine abuse or drug intake was calculated. Measurements were performed with the semi-automatic segmentation (SA) method (Slicer) and with the global thresholding segmentation (GT) method (coDiagnostiX).

Volumetric hard tissue changes were evaluated with two different radiographic methods by two independent examiners. The primary evaluation method utilized semi-automatic segmentation (SA) methods to acquire 3D virtual models of Cone-

beam computed tomography (CBCT) datasets whereas in the second evaluation method a global thresholding segmentation (GT).

3.1.2. Semi-automatic segmentation method (SA)

The open-source medical image processing software platform (3D Slicer, www.slicer.org) was used to reconstruct T1, T2 and T3 CBCT images as 3D virtual models. After performing an image segmentation of the CBCT scans, automatic voxel intensity-based registration was done. To analyze the hard tissue changes between the different timepoints, logical operators were used to subtract the aligned 3D models from one another. Then, 3D models of the new hard tissues at T2 and T3 timepoints could be created. Furthermore, we could calculate the dice similarity coefficient (DSC) to determine the spatial overlap between the created models. The DSC metric provides information on how well the implanted bone block retained its original shape.

3.1.3. Global thresholding segmentation method (GT)

In the GT method, the three-dimensional models of the CBCT scans at each time point could be automatically acquired with the coDiagnostiX software package. The CBCT scans at each timepoint were aligned, thereby, the software mathematically calculated the volumetric differences between the 3D models. We calculated the volume stability of the allogenic bone block by taking the ratio of T3/T2 in percent. This was carried out in both of the models used.

3.1.4 Linear measurements

The implant positions at T3 CBCT scans were marked by radiopaque radiographic markers. At the future implantation sites absolute horizontal- and vertical linear dimensions were marked at each timepoint in 3D slicer.

The datasets of the CBCT scans were reoriented so that the coronal plane became parallel. Furthermore, the reorientation resulted in the axial plane becoming perpendicular to the long axis of the edentulous ridge. As depicted in the figure below, a vertical linear dimension of the alveolar ridge was measured. This was done from the midcrestal point along the long axis of the alveolar ridge to the base of the nasal cavity. The horizontal lines were measured 2 mm apical to the alveolar

crest at the same aspect perpendicular to the long axis of the alveolar ridge. This was done between the palatal and the buccal cortical plate.

3.2. Patient demographics

We carried out a monocentric study at the Institute of Dres. Back and Blume, private practice and clinic for maxillo-, facial- and oral surgery in Munich, Germany. In this retrospective study we analyzed the clinical and radiological data of 23 patients, who had received bone grafting in the maxilla. Goal of the current study was the evaluation whether alveolar bone defects can be treated with a cancellous customized allogeneic bone block (maxgraft bone builder®, Botiss GmbH, Zossen, Germany). We only included patients who had severe bone defects in the esthetic zone in the region 13-23, which could be reconstructed with computer-designed allogenic bone blocks. Hereby, the patients were divided into two groups: Group A and group B. In group A 13 patients with single tooth gap were included. Group B consisted of 10 patients with a multiple tooth gap.

The inclusion criteria were:

- Age over 18 years
- Severe three-dimensional bone defect of the upper jaw in the esthetic zone
- Medical indication for bone grafting
- Treated by only one surgeon medical indication of an implant
- Signed the letter of consent
- No serious previous illness (e.g. cancer)
- The patient is currently not undergoing radiation therapy
- The patient is not taking bisphosphonates

The exclusion criteria for the current study were:

- Age under 18 years old

- Medication with bisphosphonates
- Tumor disease
- The patient is currently undergoing radiation therapy
- Serious health problems (e.g. bleeding disorder, malignant tumor)

All patient data were recorded personally and pseudo-anonymized before data analysis. Every patient data received a three-digit code. In order to participate in the current study, patients had to give their consent after a detailed patient education about the risks and benefits.

The patients in the current study were treated with a customized CAD/CAM allogeneic bone block between 2017 and 2020.

The study was approved by the local ethical committee (Ethical Committee Ludwig-Maximilians-University Munich, Germany; Approval Number: 18-898). A signed informed consent was acquired from all the patients.

3.3. CAD/CAM customization

For the manufacturing of the CAD/CAM allogenic bone blocks the design tool software coDiagnostiX was used. Integration of surgical and prosthetic workflows through real-time case sharing between coDiagnostiX and Dental Wings (DWOS) CAD/CAM was possible.

We obtained tomographic data from the jaws of our patients, which are essential to plan and manufacture a CAD/CAM produced allogenic bone block. Based on the tomographic data, digital models of the bone defects were simulated, which served as template for the design of the customized allogenic bone blocks. The measurements of the designed bone blocks were then programmed into a computerized bone mill, which was used to produce a rectangular, spongious bone block, according to the previously computer-designed model.

For the current study, we used the maxgraft® bonebuilder (Botiss Biomaterials GmbH, Berlin, Deutschland; number of approvals: PEI.H.11672.01.1). The product consists of human spongiosa bone, which had been approved by the Paul Ehrlich Institute in Germany, earlier. The bone blocks were covered with a resorbable collagen membrane from porcine pericardium (Jason® membrane, Botiss Biomaterials, Germany) and fixated to the jaw ridge with titanium osteosynthesis-screws (Medartis AG, Basel, Switzerland).

3.4. Surgical procedure

3.4.1. General procedures

Following the surgical protocol of Choukroun for the preparation of platelet rich fibrin blood was taken from the patients in order to gain platelet-rich fibrin (PRF) matrices. The patients received injections of 600 mg Clindamycin for antibiotic prophylaxis. The surgical procedure was done in general anesthesia. The incision was performed with a newly developed „semi-pillar" technique. Therefore, we did not perform the incision over the alveolar ridge, but 20 mm horizontally in the flexible mucosa. This was accompanied by a lateral relief incision. A mucoperiosteal flap was elevated from the maxillary bone. This left the mucosa still covering the defect intact. Then, we perforated the cortical layer with the help of a diamond burr. This was done to improve the integration of the bone graft.

Exudate serum was utilized to rehydrate the sterile allogenic CAD/CAM bone block, otherwise no further modifications were needed. The allogenic bone block was fixated with a single titanium osteosynthesis screw of 1.5 mm diameter and 7-9 mm length (Medartis AG, Basel, Switzerland). The allogenic bone block was first covered with a resorbable collagen membrane which had been manufactured from native pericardium (Jason® membrane, botiss biomaterials GmbH, Zossen, Germany). We applied a PRF membrane to support the healing of the surrounding soft tissue. The flap was then sutured with a single button pulley suture, in order to get a tenson free suture (Vicryl Rapid®, Ethicon, Raritan, New Jersey, USA).

The patients received closed-mashed monitoring after surgery. The surgical suture was removed 14 days post-operation. After a healing period of six months, the implant was set, this time only under local anesthetic. Through a jaw ridge incision, a mucoperiosteal flap was elevated minimal-invasively and the osteosynthesis

material was removed. Then the implant was inserted. According to the recommendation of an antibiotic prophylaxis with a penicillin for the insertion of dental implants the implant insertion was done under a one-shot antibiosis with 1000 mg Amoxicilline. The suture was removed 7 days post-operation. After a healing period of 3 months, healing screws were inserted.

3.4.2. Flap elevation

The flap preparation on the buccal aspect was carried out according to the semi-pillar incision design.

First, we made a horizontal incision on the buccal aspect within the mobile mucosa. The incision was made 2 cm apically from the midcrestal line. Afterwards, we carried out a single vertical releasing incision at the distal aspect of the surgical area. Then, a unilateral full-thickness mucoperiosteal flap was elevated on the buccal aspect and the keratinized mucosa on the crestal remained intact, the palatal aspects remained attached to the bone.

3.4.3. Fixation of the allogenic bone block

The cortical layer at the augmented site was perforated with a diamond bur. This was done prior to bone block position and to induce bleeding for an enhanced vascularization of the bone graft. Then, the allogenic bone block was inserted. No further adjustments were needed. The bone block was fixated by titanium osteosynthesis screws (Medartis AG, Basel, Switzerland).

To add an additional barrier function, we covered the area with a long-term resorbable porcine pericardium membrane (Jason® membrane, Botiss Biomaterials GmbH, Zossen, Germany). Tension free wound closure achieved by using single interrupted sutures utilizing 4.0 and 5.0 resorbable suturing materials (Vicryl Rapid®, Ethicon, Raritan, New Jersey, USA). Sutures could be removed after two weeks.

After a 6-month healing period guided implant placement was planned. Hard tissue augmentation was not necessary. We carried out the direct evaluation of the reconstructed alveolar ridge, removal of the block fixation screws and dental implant placement during a re-entry procedure.

3.5. Data analysis

To analyze the overall changes of the hard tissue, we used descriptive statistics. The data of 23 patients could be included in the current study. The overall changes of the hard tissue were expressed as mean standard deviation. The statistical differences were calculated with non-parametric statistical tests. The statistical differences between each time point T1-T3 for each variable was calculated by Wilcoxon matched pairs signed rank test. The differences between the variables of the groups were calculated by Mann-Whitney-U-Test. Furthermore, we used non-parametric statistical tests in order to evaluate the correlations and differences between the datasets which had been acquired by distinct evaluation methods. The statistical differences were calculated by Wilcoxon matched pairs signed rank test, correlation between the datasets was analyzed by Spearman rank order correlation. We performed all statistical calculations with the software SPSS (IBM, Armonk, USA).

4. Results

4.1. Patients and methods

In our study 23 patients, meeting our inclusion criteria were included. The patients had received bone grafting with CAD/CAM allogenic bone blocks. 14 of the 23 patients were male and 9 female. The mean age of our patients was 45,48 ± 12,52 years. 10 patients presented with multiple tooth gaps and 13 patients had only a single tooth gap. 6 patients presented with two tooth gaps, 2 patients had three tooth gaps and another two patients presented four tooth gaps. No complications would be observed, neither during surgery, nor post-operative. We could not observe any wound dehiscence nor wound infections. After a healing period of six months, all patients could be undertaken to three-dimensional radiographic diagnostics (CBCT-scans). All patients met the criteria for implant insertion. According to the horizontal, vertical, and combination- (HVC) ridge deficiency classification 27 defects could be characterized as horizontal-large, 6 were identified as combination-large, 6 defects could be classified as combination-medium, and one defect was defined as horizontal-medium.

4.2. Volumetric hard tissue changes

In the current study, we could find a volumetric hard tissue gain in average of 0.75 cm^3 ± 0.57 cm^3 measured with the semi-automatic segmentation method (SA), with

a median value of 0.49 cm^3. After 6 months we detected an average hard tissue gain of 0.52 cm^3 ± 0.42 cm^3 with a median value of 0.37 cm^3 and 0.29 cm^3 ± 0.12 cm^3. Between the timepoints T2 and T3 we could detect a statistically significant amount of hard tissue resorption (p<0.05). The average volume stability of the bone block determined by the T3/T2 ratio was 67.83% ± 18.72% on average with a median value of 72.46% measured with the SA method.

With the global thresholding method at T2 we could find an average of 0.69 cm^3 ± 0.56 cm^3 hard tissue gain, with a median value of 0.46 cm^3. At timepoint T3 we could measure an average hard tissue gain of 0.53 cm^3 ± 0.46 cm^3 with a median value of 0.37 cm^3. Hereby, we could detect statistically significant amount of volumetric hard tissue resorption between T2 and T3 timepoints (p<0.05). Using the GT- method resulted in an average volume stability of the allogenic bone blocks of 75.50 % ± 13.68 %, with a median value of 72.46%.

Comparing the resulting data of the two segmentation methods at T2, a statistically significant difference could be detected with the Wilcoxon matched pairs signed rank test (p = 0.009), although high level of correlation could be detected between the two metrics at (Spearman correlation coefficient: 0.95). On the other hand regarding the volumetric hard tissue gain at T3 (p = 0.89) there was no statistically significant difference between the semi-automatic- and the global thresholding segmentation method. High levels of correlation were also found between the two datasets regarding this metric (Spearman correlation coefficient: 0.91).

4.3. Linear hard tissue measurements

In the current study we performed linear measurements at 40 future implantation sites. At T1 the baseline vertical alveolar ridge dimensions at the planed implant position resulted in an average of 15.45 mm ± 3.32 mm and 3.30 mm ± 1.04 mm in the horizontal dimension. At T2 the average linear vertical dimension at future implantation sites averaged at 17.60 mm ± 2.82, horizontal ridge dimensions were measured at an average of 7.85 mm ± 1.14 mm. At T3 vertical- and horizontal ridge dimensions averaged at 16.97 mm ± 2.86 mm and 6.43 mm ± 1.27 mm respectively. Statistically significant differences were recorded between all the metrics. Resulting in a statistically significant vertical- and horizontal linear gain between T1 and both

follow-up timepoints (T2 and T3). Simultaneously a statistically significant linear hard tissue loss could be detected between T2 and T3.

4.4. Effect of surgical size on clinical outcomes

We compared the results of alveolar ridge augmentation at single- and multi-tooth gaps. Hereby, we calculated the differences in linear hard tissue dimensions at T2 and T3 and the differences in DSC values and volumetric stability (T2/T3 ratio). It can be seen that one of the linear measurements at any timepoint showed statistically significant differences (p>0.05). We found slightly higher DSC values and graft stability at larger augmentations sites, in group B compared to group A, however, the differences were statistically not significant (p>0.05).

4.5. Implant stability

All of our 23 patients were eligible for implant insertion after a six month healing period. No further augmentation was necessary. Altogether, 39 implantations were carried out.

The primary stability of the implants (Ncm) was in average 34.26, with a standard deviation of 11.42. The implants were all carried out in the regions 13-22. We used different implant types. Mostly we used 18 ITI implants, Nobel Active was used on 8 implant sites, Camlog on 7 sites, Conelog on 3 sites. On 2 implant sites Xive was utilized and on 1 site Astra. Implant stability ranged from 15 to 50 Ncm. Among the 39 implants we could not observe any complication, all implants could be successfully inserted. After a healing period of 3 months, we examined the implants and a final CBTC-scan was taken. We could not observe any pathological tissue- or bone changes. No wound infections had occurred. No patient had suffered any complications.

4.6. Histological Findings

We furthermore, carried out a histological analysis of a framework of allogenic cancellous bone. Hereby, we could observe trabeculae of varying thickness from lamellar bone with empty osteocyte cavities. We also saw attached peritrabecular direct ossification of varying width from woven bone with occasional (crestal) inital remodeling in lamellar bone. Crestal transverse trabecula of newly formed bone, covered by tight connective tissue (propria) with loose infiltrates and allogenic bone

fragments could be observed. Furthermore, we could find fragmented multi–layered squamous epithelium, partly adherent to bone fragments.

We found as preliminary diagnosis an advanced osteogenesis on the allogenic block. Also signs of remodelling could be detected. We further observed in our analysis crestal mucosal remnants and a slight inflammatory reaction crestal. Overall, our histological analysis showed active remodeling and osseointegration in progress. The osseointegration of the allogenic bone block took place in all dimensions. A histomorphometric analysis showed newly formed bone tissue within the specimen at an average of 41,5 % of residual augementation material of 29,2 % as well as soft tissue of 29,3 %.

4.7. One-year follow-up examination

4.7.1. Patient satisfaction

Twelve patients showed up for a follow-up examination at least one year post-implantation. The patients were examined clinically and radiologically. In total, 22 implants could be examined. We carried out a survey among the patients who were present for follow-up examinations. The patients had to rate, how satisfied they were with their new implants and the procedure. Thereby, on a scale from 1 to 10 they rated their personal satisfaction, while 1 stood for "unsatisfactory" and 10 "very satisfied". We found an average rating of 10, with a standard deviation of 1. The ratings ranged from 8 to 10. Our results, thus, show a very high patient satisfaction.

4.7.2. Clinical findings

The 12 patients with 22 implants were undertaken a clinical and radiological examination.

After a time period of one year (days between surgery and examination: 1175 ± 531) we could find a primary stability of the implant of 31,59 Ncm ± 10,01, while implant stabilities ranged from minimum 20 Ncm to maximum 50 Ncm. None of the patients reported pain, dull knocking sounds of the implants, infection or loosening of the implant. Average plaque index was 35,61 ± 42,51 %. In 15 of the 22 implants, we found an average gingiva index of 68,2 %. Recession on the implant side was low: We detected in average 0,1 ± 0,3 mm.

4.7.3. Radiographical findings

The 12 patients with 22 implants underwent a radiological examination as well.

Radiographical data were analyzed by the program CLINIVIEW (Version 4.2.2) and VixWinPro (Version 1.5f). Analogue pictures from the implant sites were digitalized, using a digital camera (Canon Eos 7D). Then, the height of the marginal bone level mesial and distal of the implant were measured. In order to analyze three dimensional scans, we used the program iCATVision and eXam Vision (Version 19.3.13). To assure comparability of the pictures, we reconstructed two-dimensional pictures, according to orthopantomogram. We measured the heights of the marginal bone level from the tip of the implant mesial and distal, along the dental arch. We calculated the difference between the marginal bone level on the postoperative scans and the one year follow-up scans. We could find a loss of bone of 0,5 ± 0,5 mm and 0,4 ± 0,4 mm respectively. The maximum bone loss, we detected was 1,6 mm.

5. Discussion

Due to the limitations in autologous bone grafting, customized CAD/CAM allogenic bone grafting had become an acceptable alternative for several indications.

In previous studies with CAD/CAM customized allogenic bone blocks, we could detect a low rate of complications and a significantly reduced surgical time compared to iliac crest autologous bone grafting with a significant lowered risk of infection. The studies have shown as well that customized allogenic bone blocks bear many advantages: They have been shown to be suitable for the precise fit and augmentation of complex bone defects. CAD/CAM technology enables the reduction of the space between the residual bone and the allogenic bone graft to a minimum. The physical contact between the customized CAD/CAM allogenic bone block and the residual bone can be achieved and enhanced which leads to an early revascularization.

The objective of our current study was to use customized CAD/CAM allogenic bone blocks in patients with severe defects in the maxillary bone of the aesthetic zone. In the current study, 23 patients were included. The bone defects were in the

upper anterior region, thus, in the aesthetic zone, which posed the double challenge of 1) functionally and 2) aesthetically restore the defective bone, so that tooth implants could be successfully inserted. Our patients had either single- or multiple tooth gaps.

Besides the bone blocks, we used a new incision technique in order to minimize the risk of wound infection, wound dehiscence and thus, reduce recipient site morbidity.

In the "semi-pillar" technique we do not perform the incision over the alveolar ridge. Instead, the incision is made 20 mm horizontally in the flexible mucosa. A relief incision was additionally made laterally. The mucoperiosteal flap could then be elevated from the maxillary bone. With this new flap design the incision can be relocated into the vestibulum. The keratinized mucosa and the alveolar ridge could be still left intact and wound closure occurred tension-free. This incision technique was accompanied by low complication rates and no wound infections.

After a time period of six months we had observed optimal integration of the allogenic bone blocks and the reentry showed the formation of new, vital bone. All 23 patients met the criteria to be eligible for implantation after a healing period of six months.

In the current study, the alveolar ridge defects were categorized into two groups, according to the size of the surgical area. Patient group A had single tooth defects, while group B had multiple teeth missing. We performed volumetric and radiographic assessments with two distinct methods, as described in chapter 3. We observed that the two evaluation methods showed high correlation, there was no statistically significant difference for any of the measures. The GT method resulted in higher percentages of volume stability. This can be due to the fact that in the GT method the algorithm automatically labels voxels that fall in the threshold range. Furthermore, anatomical features cannot be recognized by the GT method. Nor can be artifacts on the CBCT scans. In contrast, with the SA method the input data for region growing and watershed segmentation algorithms are generated manually. Nevertheless, we found both methods to be feasible for the volumetric evaluation of hard tissue changes. We could validate new average volume gain at T2 of 0.75 cm^3 / 0,69 cm^3 (SA/GT) which reduced to 0.52 cm^3 / 0.37 cm^3 (SA/GT) at T3. The detected average resorption rate measured with the SA-method was with 32%

slightly higher than the average resorption rate of 25% measured with GT method. These resorption rates are similar to previously reported data on cancellous allogeneic bone blocks with approximately 29%.

Like wise to the volumetric data, a linear vertical and horizontal hard-tissue gain between T1/ T2 (vertical: 2,15mm, horizontal: 4,55mm) and a significant resorption between T2/T3 was detected (vertical: 0,63mm, horizontal: 1,42mm) in the current investigation. The implanted customized CAD/CAM allogenic bone blocks in our study presented similar or less dimensional loss than did those documented in literature showing a high-volume stability.

However, we could not find statistically significant differences in volumetric- and linear hard tissue alteration, volumetric graft stability and DSC values between alveolar ridge defects in patients with single- and multiple tooth gaps. Although we found a lower volumetric- and linear hard tissue resorption in larger surgical areas, the difference to smaller surgical areas, was not statistically significant. The size of the surgical area therefore seems to have no influence on the clinical outcomes.

In the current study, we investigated a framework of allogenic cancellous bone histologically and trabeculae of varying thickness from lamellar bone with empty osteocyte cavities. Furthermore, we observed direct ossification of varying widths. This included woven bone with initial remodeling into lamellar bone. Trabecula of newly formed bone, covered by tight connective tissue and allogenic bone fragments could be observed. Thus, our histological results confirm our radiological findings and further support the clinical data. Guided bone regeneration with CAD/CAM allogenic bone blocks seem to lead to effective formation of new bone tissue and bone regeneration. Further, our histological findings support the findings of previous studies, which showed that cancellous CAD/CAM manufactured allogenic bone blocks can be reliably used for reconstruction of severely atrophied bone and complex bone defects.

Clinical examination of the patients after a follow-up period of one year showed no complications. We detected high success rate of the implants, while the patients did not suffer any serious complications. We found good gingival indices, no infections, no pus, low plaque indices and a low rate of implant recession, furthermore we detected high implant stability. This has been shown by our research group on customized CAD/CAM allogenic bone blocks before.

Patient satisfaction was high in the current study. On a scale from 1 to 10, where 1 stands for totally “unsatisfactory” and 10 for “very satisfied”, the average rating of our patients was 10 (standard deviation 1). This shows very high patient satisfaction after a CAD/CAM customized allogenic bone grafting, following implantation in the aesthetic zone as well.

Neither in the current, nor in our previous studies, wound infections, post-operative complications or implant loss could be observed. Guided bone regeneration with customized allogenic bone blocks presented to be a safe and effective method, shown in the current study, as well as in our previous research.

The current study showed that CAD/CAM customized allogenic bone blocks may be a suitable alternative to autologous bone grafting, even in the aesthetic zone. The implants have successfully integrated. Furthermore, we could show high volume stability, low complication rate, short surgical time and high patient satisfaction.

Nevertheless, the current study has some limitations. We could include 23 patients in our study, which represents a small number of patients with CAD/CAM customized bone blocks. Most of the literature so far, are only case studies with an even smaller number of patients. Further research with large numbers of patients is required to confirm our findings. Nevertheless, our current study shows promising results with customized CAD/CAM allogenic bone blocks. CAD/CAM customized bone blocks could represent a feasible alternative to autologous bone grafts, especially in the aesthetic zones. Another limitation of the current study is that there was no long-term follow-up. We carried out a one year follow-up of the patients, while only 12 patients showed up for follow-up examinations.

To date, there are no randomized, controlled trials available comparing allogenic CAD/CAM bone blocks with autologous bone grafts from the iliac crest. Thus, further studies still remain to be carried out to confirm our results.

6. Conclusion

Even though there is plenty of literature about the successful implantation of allogenic bone materials for the reconstruction of bone defects, randomized controlled studies with a large number of patients, examining the customized allogenic CAD/CAM bone blocks are still rare, to date. The current study with 23

patients who presented with severe bone defects in the aesthetic zone in the upper jaw showed, that customized allogenic CAD/CAM bone blocks may be suitable as a reliable bone graft in those patients. We found a very small complication rate with the customized CAD/CAM bone blocks. Volume stability was comparable to autologous bone blocks. The avoidance of donor morbidity makes the customized allogenic CAD/CAM bone blocks to a serious alternative to autologous bone grafts. We found in our study that none of our 23 patients needed a re-augmentation. This demonstrates the safety and reliability of customized allogenic CAD/CAM bone blocks. The current study provided evidence for the reliability and safety of this method.

The utilization of the volumetric measuring methods utilizing Slicer and coDiagnostiX showed to be practicable and reliable to measure volume changes of hard tissue. Especially the coherence of our results demonstrated the reliability and practicability of those methods for digital volumetric measurements. To validate the results of our current study, further studies are needed, especially in other intraoral areas like the mandibula or the posterior maxilla.

7. Bibliography of the candidate's publications

7.1. Publications related to the thesis

1. Blume O, Hoffmann L, Donkiewicz P, Wenisch S, Back M, Franke J, Schnettler R, Barbeck M. 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 Oct 21;10(10):1213.

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3. Blume O, Donkiewicz P, Palkovics D, Götz W, Windisch P. Volumetric Changes of a Customized Allogeneic Bone Block Measured by Two Image Matching Tools: Introduction of a Novel Assessment Technique for Graft Resorption. Acta Stomatol Croat. 2021 Dec;55(4):406-417.

4. Blume O, Back M, Born T, Donkiewicz P. Reconstruction of a Unilateral Alveolar Cleft Using a Customized Allogenic Bone Block and Subsequent Dental Implant Placement in an Adult Patient. J Oral Maxillofac Surg. 2019 Oct;77(10): 2127.e1-2127.e11.
5. Blume O, Back M, Martin K, Windisch P. A customized allogenic bone block for alveolar reconstruction quantitated by a 3D matching technique: A case report. Clin Case Rep. 2021 Aug; 9:e04771
6. Blume O, Back M, Dinya E, Palkovics D, Windisch P. Efficacy and volume stability of a customized allogenic bone block for the reconstruction of advanced alveolar ridge deficiencies at the anterior maxillary region: A retrospective radiographic evaluation. Clin Oral Investig. 2023 Apr 14. doi: 10.1007/s00784-023-05015-0. Epub ahead of print. PMID: 37055540.

7.2. Publications not related to the thesis

1. Blume O, Schnödt EM, Back M, Wildenhof J, Probst F, Otto S. Long-Term Efficacy of Variable-Thread Tapered Implants - A Retrospective, Clinical and Radiological Evaluation Medicina 2020 Oct; 56, 564.

2. Blume O, Wildenhof J, Otto S, Probst F. Influence of clinical parameters on the primary stability of a tapered dental implant – A Retrospective analysis. J Oral Maxillofac Implants 2021 Jul; 36(4):762-770.