

Article

Implant Stability of Biological Hydroxyapatites Used in Dentistry

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Abstract: The aim of the present study was to monitor implant stability after sinus floor elevation with two biomaterials during the first 6 months of healing by a resonance frequency analysis (RFA), and how physico-chemical properties affect the implant stability quotient (ISQ) at the placement and healing sites. Bilateral maxillary sinus augmentation was performed in 10 patients in a split-mouth design using a bobine HA (BBM) as a control and porcine HA (PBM). Six months after sinus lifting, 60 implants were placed in the posterior maxilla. The ISQ was recorded on the day of surgery from RFA at T1 (baseline), T2 (3 months), and T3 (6 months). Statistically significant differences were found in the ISQ values during the evaluation period. The ISQ (baseline) was 63.8 ± 2.97 for BBM and 62.6 ± 2.11 for PBM. The ISQ (T2) was $\sim 73.5 \pm 4.21$ and 67 ± 4.99 , respectively. The ISQ (T3) was $\sim 74.65 \pm 2.93$ and 72.9 ± 2.63 , respectively. All the used HAs provide osseointegration and statistical increases in the ISQ at baseline, T2 and T3 (follow-up), respectively. The BBM, sintered at high temperature with high crystallinity and low porosity, presented higher stability, which demonstrates that variations in the physico-chemical properties of a bone substitute material clearly influence implant stability.

Keywords: hydroxyapatite, xenografts; implant design; implant surface

1. Introduction

The edentulous ridge in the posterior maxilla often presents a limited bone volume due to both lack of alveolar bone after ridge remodeling and maxillary sinus pneumatization [1]. Adequate alveolar ridges play a crucial role when it comes to rehabilitation with implants, and some augmentation technique is necessary for patients who suffer from alveolar atrophy [2]. The most predictable and commonly used means of facilitating implant therapy in the atrophic posterior maxilla has been sinus augmentation [3]. Although alternatives, e.g., using shorter implants, are beginning to be investigated [4-6], any available scientific evidence is modest and insufficient to conclude that the success of sinus lift procedures in bone with a residual height between 4 mm and 9 mm will be better, or not, than when short implants are used [7,8]. Maxillary sinus floor grafting has become the commonest surgical intervention when increasing alveolar bone height before placing endosseous dental implants in the posterior maxilla [9].

Several factors influence maxillary sinus floor grafting results : specific surgical techniques, a simultaneous *versus* a delayed procedure, using barrier membranes over the lateral window,

implant surface characteristics, the length and width of implants, and selecting the graft material [10].

As regards the last factor/variable, researchers have not reached an agreement about the most suitable material for sinus augmentation [11]. In the clinical practice, the main purpose of bone augmentation procedures is bone formation, where implants are positioned to best support prosthetic rehabilitation. The bone tissue around dental implants must be mechanically competent after augmentation procedures [12].

Today not many controlled research works evaluate the use of different bone grafting materials for sinus augmentation. Sinus elevation, performed with a wide variety of different graft materials, has been used. However, it still remains unclear which is the most suitable bone grafting material for enhancing bone regeneration in the augmented sinus [13, 14]. Deproteinized xenografts, constituted primarily of natural apatites, which are either sintered or not, have good physical and physico-chemical properties. Deproteinization is an indispensable process followed to eliminate antigenicity in xenograft bones. Different physicochemical conditions selectively modulate the host organism's tissue response [15]. Some authors have reported the same observations in reaction to the microscopic structure in commercial products subjected to thermal deproteinization processes [16, 17]. Sintering temperature is considered an important factor that might alter the HA's characteristics [18]. However, the sintering temperature effect on the physico-chemical properties of natural HA (HA of a natural source), especially HA from bovine bone, is still not fully understood and research in this area is still wide open.

The ultra-structural interface of the graft bone tissue interface, as well as the ideal time point of placing implants, have not yet been described [19].

Typical surgical protocols are simultaneous one-stage lateral or crestal antrostomy when the residual crestal bone is greater than 3-6 mm, or a two-stage delayed procedure, which is recommended when the residual bone is less than 3-6 mm. Furthermore, the risk of implant failure is halved when the two-stage technique is used [20].

The graft consolidation gradient reflects the features of each bone substitute at sinus augmentation sites [21]. According to some studies, the physico-chemical properties of each bone material graft may influence the osseointegration process, and this influence may result in shorter healing times between implant placement and restoration. Therefore, a profound understanding of not only the different aspects of biomaterial properties, but also of their relation to and influence on bone healing has proved to be of utmost importance [22].

An undisturbed healing period of at least 3 to 6 months at surgical sites is the generally accepted protocol after implant placement. This can ensure uneventful healing and improve osseointegration between the implant and bone. The reason for this approach is based on the fact that the functional force around the bone-implant interface causes implant micromotion during wound healing, while implant micromotion may induce fibrous tissue rather than bone contact, which results in clinical failure. All these concerns about waiting periods have long since been a challenge for both patients and clinicians. Changing trends and demands have rendered the introduction of early loading techniques necessary as a result of searching for faster dental function restoration using implants [23]. Successful osseointegration is a prerequisite for functional dental implants; absence of osseointegration has been reported for implants with no primary stability [24].

Implant stability can be defined as the combination of both mechanical and biological stability. While mechanical stability appears as the result of bone tissue compression during implantation, biological stability is obtained as a result of the formation of new bone cells on the implant surface during the osseointegration process. Hence implant stability is associated with the quality and quantity of local bone [25]. Nowadays, the technique most frequently used to detect implant stability during healing times and in subsequent follow-ups is the non invasive diagnostic tool known as resonance frequency analysis (RFA) [26-27]. Continuous monitoring at various time points is important to determine the implant stability status and to estimate a long-term prognosis for successful therapy [28]. Evaluating bone density has long since been one of the most important parameters to quantify bone quality as it is thought to be a major determinant of primary stability. In

other words, primary implant stability is dependent on not only the thickness of the bone into which the implant is placed, but also on bone density. Therefore, all these factors should be taken into account when making the clinical decision to perform a one-stage or a two-stage procedure [29]. The level of bone density at the implant site could be of utmost importance as it is related with failure rates and primary stability. When it comes to evaluating primary implant stability in relation with bone density, the implant stability quotient (ISQ) and the resonance frequency analysis can be used [30]. The primary stability of a dental implant, absence of mobility at the osseous site after implant insertion, and the quality of the receptor bone site are highly correlated. Likewise, primary stability is also strictly correlated to the mechanical relationship between the implant surface and the recipient bone. This relationship can determine implant placement outcomes by avoiding micromovements on the interface [31].

Optimal outcomes in implant survival terms have been demonstrated for implants placed in the maxillary sinus filled with deproteinized bovine bone mineral, and this material can be considered a safe predictable graft material for sinus floor augmentation [32]. However, very little is known about the physico-chemical properties of used grafts and the impact on both bone density and early implant stability after they have been employed. The aim of this randomized split-mouth design was to compare the stability of dental implants placed after sinus floor elevation with two HAs during the first 6 months of healing by means of RFA, and to monitor how the physico-chemical properties affect the implant stability quotient (ISQ) at the placement and healing sites.

2. Results

2.1. Graft Implants Characterization

Figure 1 shows the xenograft materials before inserting for maxillary sinus floor elevation. The BBM (Bovine Bone Material) consists of HA particles of 500-1000 µm on average, with rounded edges and pores of 100 µm on average. The PBM (Porcine Bone Material) consists of HA and collagen particles of 600-1000 µm on average. A summary of the microstructural parameter studied in a previous paper is shown in Table 1 to provide a better understanding of the materials’ microstructure [33].

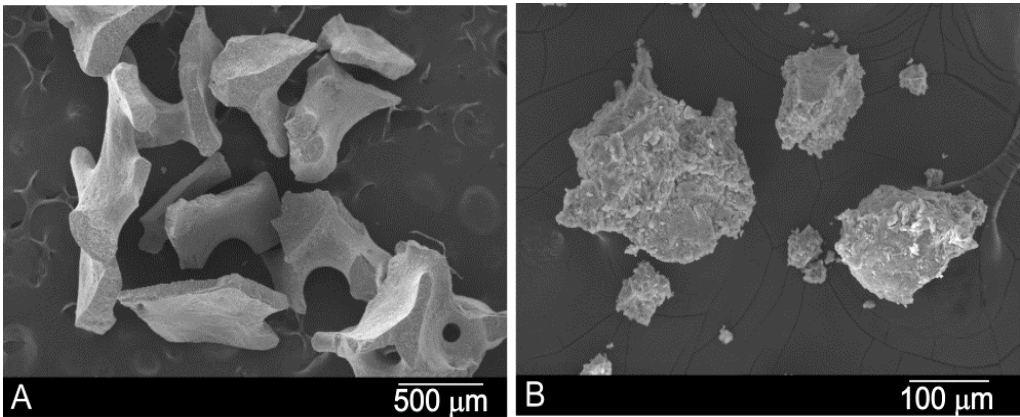


Figure 1. Scanning electron micrographs of (A) the BBM and (B) PBM xenograft materials before implantation.

Table 1. Physical properties of the two xenograft materials [33].

Phase/s		Ca/P ratio	Particle size (µm)	Crystal size (nm)	Real Density (g/cc)	Porosity (%)	Surface Area (m ² /g)
PBM	HA+Coll	2.22±0.08	600-1000	325	2.85	59.90	97.84
BBM	HA	2.31±0.09	500-1000	732	2.98	49.13	2.77

2.2 Radiological and Thermographic Results

After a 6-month follow-up period of our ten partially edentulous patients treated with xenograft materials for sinus floor augmentation, the success rate was 100%. No sinus membrane perforation or other clinical complications, such as sinusitis or pain, resulted from surgery. The increased volumes produced by the xenograft procedures were stable by the end of the healing period, as seen in Figure 2. Deproteinized bone particles of two different temperatures induced osteoconduction 6 months after implantation.

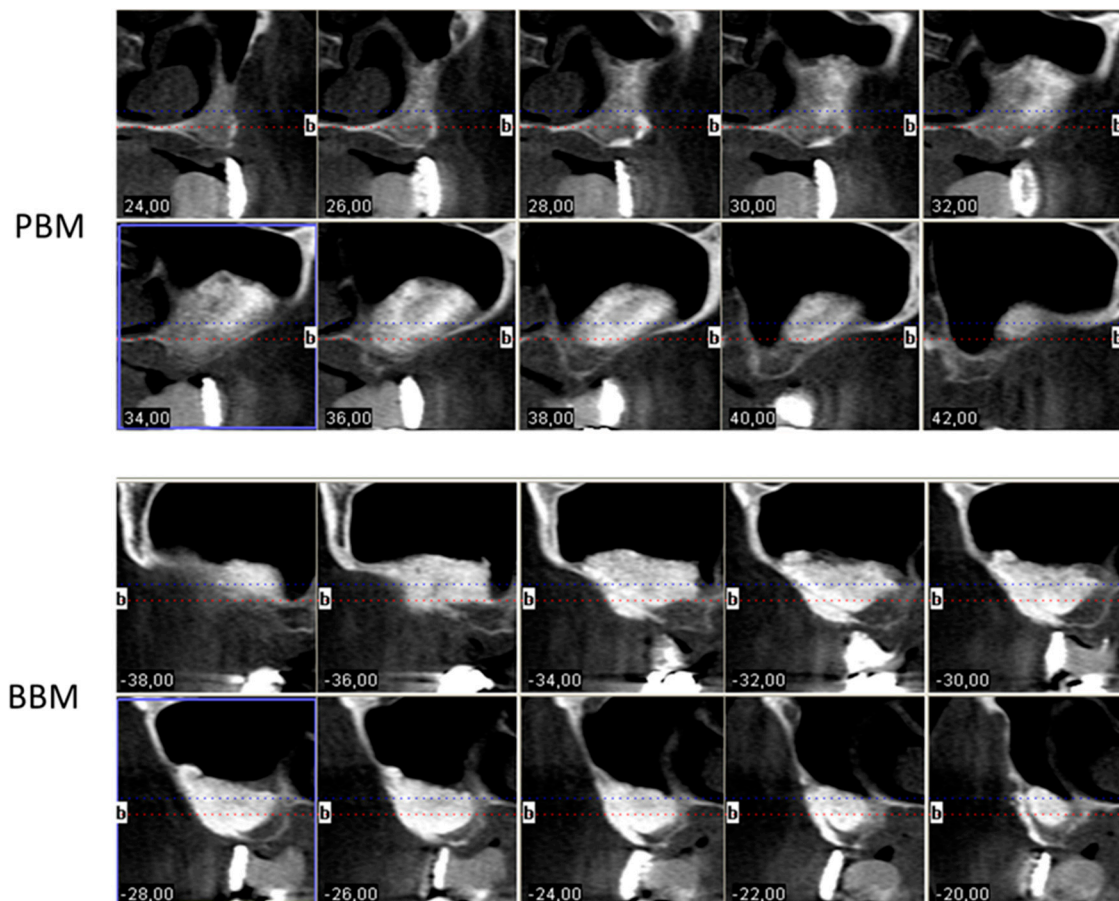


Figure 2. The i-CAT Vision postoperative image shows the increased volumes produced by the xenograft procedures 6 months after maxillary sinus elevation with a porcine hydroxyapatite (axial cuts 24–42) and a bovine hydroxyapatite (axial cuts -38–20).

Bone density at the implant site could be crucial as it has been reported to correlates with failure rates and primary stability. The bone density in the grafted area with both biomaterials was evaluated radiologically as a routine diagnostic approach. Color thermal graduation was used to observe changes in radiopacity in the intrasinus bone grafted area. At the time of implant insertion, and after a 6-month healing period, the augmentation sites treated with the PBM showed denser new bone formation, which was achieved along the inner surface of the replaced bony window than the area on the bone graft (Fig. 3 A-B). The BBM shows that denser new bone formation was achieved in the area on the bone graft compared to the original augmentation density (Fig. 3 C-D). The bone area differed in the groups after implantation and increased with time. Bone initially formed on the sinus wall and proliferated into the center of the augmented sinus cavity. Newly formed bone came consistently into close contact with particles, and no gaps were present on the bone particle interface. Particles appeared to act as a scaffold by supporting new bone formation. Scaffolding is a critical component in tissue engineering because it provides the three-dimensional clues for cell seeding, migration and growth, and also for new tissue formation.

Although the radiopacity of the augmented volume increased with time for both xenograft materials, the receiving control sites showed a higher density of radiopacity compared with the PBM. Maxillary sinus membrane preservation is important to avoid the displacement of graft materials into the sinus cavity. However, nonobserved small perforations can imply a risk if left untreated.

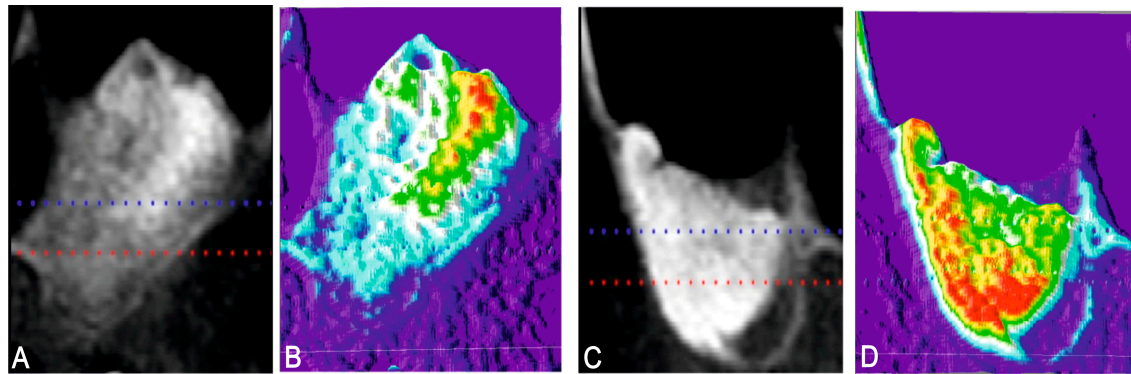


Figure 3. X-Ray of the implant site 6 months after xenograft materials implantation and the corresponding color bone density (A, B) the PBM material and (C, D) the BPM material.

2.3. ISQ Results

Primary implant stability in relation with bone density can also be evaluated by the implant stability quotient (ISQ). Detailed distributions for the implants and ISQ values over the investigated time periods are depicted in Table 2. Three implants were not osseointegrated at the end of the study, which left 57 implants for controls (a 95% success rate). Dropouts were not observed during the evaluation period.

Table 2. Demographic data.

Number of patients (total)	10					
Number of implants (total)	60					
Osseointegrated (%)	57 (95)					
Non osseointegrated	3 (5)					
Vestibule-Lingual (ISQ values)	T1		T2		T3	
	PBM	BBM	PBM	BBM	PBM	BBM
Mean	62.4	63.4	66.9	73.9	72.6	73.8
SD	2.92	2.88	2.67	4.11	7.67	2.99
Median	62.5	63.2	66.6	70.6	73.7	74
Mesio-Distal (ISQ values)	T1		T2		T3	
	PBM	BBM	PBM	BBM	PBM	BBM
Mean	62.8	64.2	67.1	75.2	74.2	74.2
SD	3.23	3.18	2.33	4.29	7.59	3.01
Median	62.5	64.8	69.1	72.4	75.8	75.5

ISQ: Implant stability quotient; T1: baseline; T2: at 3 months; T3: at 6 months.

The means and standards deviation of the ISQ values.

The ISQ (Baseline) averaged values were 63.8 ± 2.97 for a sintered BBM and 62.6 ± 2.11 for a non sintered PBM, and differences were statistically significant. The ISQ (Stage 2) average values were 73.5 ± 4.21 for the BBM and 67 ± 4.99 for the PBM, and differences were statistically significant. The

ISQ (Stage 3) average values were 74.65 ± 2.93 for the BBM and 72.9 ± 2.63 for the PBM, and differences were statistically significant. The detailed distributions for the groups are depicted in Figure 4. The analysis of variance demonstrated a statistically significant difference ($p < 0.0001$).

In the Vestibule-Lingual direction, the mean and standard deviation ISQ values measured at Baseline, Stage 2, and Stage 3 were 63.4 ± 2.88 , 73.9 ± 4.11 and 73.8 ± 2.99 , respectively for the BBM, and were respectively 62.4 ± 2.92 , 66.9 ± 2.67 and 72.6 ± 7.67 for the measured PBM ISQ values.

In the Mesio-Distal direction, the mean and standard deviation ISQ values measured at Baseline, Stage 2, and Stage 3 were 64.2 ± 3.18 , 75.2 ± 4.29 and 74.2 ± 3.01 , respectively for the BBM, and were respectively 62.8 ± 3.23 , 67.1 ± 2.33 and 74.2 ± 7.59 for the measured PBM ISQ values.

The multivariate regression analysis (R^2 adjusted = 0.58, multiple correlation coefficient = 0.78) demonstrated significant influences on the ISQ values in relation to age ($p = 0.0120$; $r = -0.13$), gender ($p < 0.0001$; $r = -0.48$), group ($p = 0.0017$; $r = 0.16$), position ($p = 0.0002$; $r = 0.19$) and time ($p < 0.0001$; $r = 0.69$).

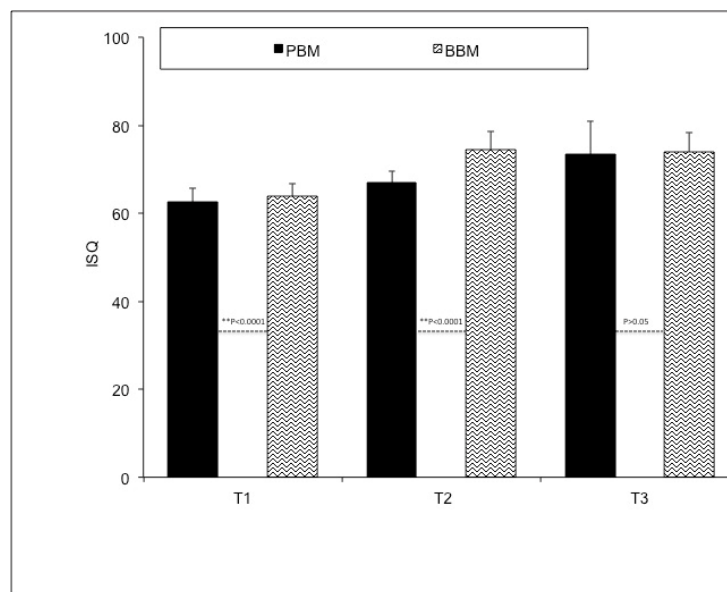


Figure 4. Implant stability quotient for both xenograft materials

3. Discussion

This clinical study describes a comparison of the RFA of implants placed and delayed with maxillary sinus grafting with two biomaterials deproteinized at different temperatures during three distinct time periods. Sixty implants were fitted in 10 patients. Three implants were lost throughout the study time period, and the survival rate of dental implants in the present study was 95%. The results also showed a positive correlation between the used biomaterial and the ISQ values. The results of a systematic review of the survival of implants in bone grafts, Aghaloo and Moy, found that the survival of implants by the maxillary sinus grafting technique was 95.6% [2]. Presently, no agreement about the advantages of using grafting material in maxillary sinus elevation techniques with dental implant insertions has been reached because the question whether these techniques and materials may determine implant survival, compared to pristine bone, remains unsolved [34, 35]. To find the answer to this question, long-term stability up to 20.2 years was retrospectively examined after the placement of implants at both augmented and non augmented sites. The results of this retrospective study determined that the implants inserted into an augmented site had a similar implant survival to those inserted into non augmented sites [36]. Based on evidence, it can be stated that the implants inserted into augmented bone offer a similar implant survival to those placed in native bone [37]. In our study the implicated grafting material might not compromise implant survival.

For clinicians, one of the most important parameters to measure the scope of mechanical loading capability is implant stability. The baseline information that it provides serves as a tool to

evaluate clinical outcomes and time courses [28]. Several attempts have been made to find innovative techniques that allow implant stability to be measured [27]. An RFA, which is a non invasive technique that presents high reproducibility results, has been proposed [23, 38, 39]. This technique has become one of the most widely used techniques to measure implant stability immediately, which makes determining the probable loading protocol and assessing the long-term survival of implants possible—[25]. The comparison of the type of bone graft and initial implant stability was performed herein. The results of this study showed that the implants placed and delayed (2-stage) with the maxillary sinus lift with different biomaterials presented distinct ISQs, with statistically significant differences.

From a clinical point of view, it would appear relevant to know the significance of RFA measurements and the relationship between their values and implant osseointegration success or failure. A previous study has observed that implants retrieved after 6 months show a strict correlation between the RFA values and the percentage of bone implant contact (BIC) [40]. The aim of the present study was to determine whether the same correlation existed at earlier time points, specifically in implants inserted after 3 or 6 months. A statistically significant correlation was detected between the RFA values and healing time. During the bone-healing period, the implants' ISQ value varied with time. In the surgical phase (baseline), the average ISQs for all the implants were 63.8 ± 2.97 for a sintered BBM, and 62.6 ± 2.11 for a non sintered (PBM), with statistically significant differences. The ISQ (Stage 2) average values were 73.5 ± 4.21 for the BBM and 67 ± 4.99 for the PBM, where differences were statistically significant. The ISQ (Stage 3) average values were 74.65 ± 2.93 for the BBM and 72.9 ± 2.63 for the PBM, with statistically significant differences.

The present study examined the same implants 3 and 6 months after their installation for the implants inserted by a two-step procedure. The RFA values after 3 months showed that the grafted sites provided good implant stability and, on average, the BBM were better than the PBM group sites. This difference was still present after 6 months and was also statistically significant. The importance of bony quality in relation to implant stability has been previously highlighted. Given the relative lack of bone, there is some concern about the initial stability of the implants placed in grafted bone. An RFA enables the stability under load to be qualitatively measured, and has been advocated as a means of assessing implant stability at the time of placement and in later phases when providing restorations [41].

This is the first study to compare ISQs with density values after sinus lift procedures 6 months after healing and primary stability. The primary initial stability (IS) is a crucial factor to establish osseointegration [42–44], and might be subject to the influence of the following factors: bone quality, surgery technique and implant macrodesign [44].

The above studies have demonstrated a strong correlation between implant displacement and bone properties, and have concluded that better bone quality leads to better implant stability. Al-Khalidi has also proven that implants with a high degree of density placed in bone have higher initial stability values than those placed in soft bone [45], according to the results of insertion torque (IT), ISQs and removal torque values (RTV) [46]. However, ISQs can improve through changes in the implant macrodesign [47]. Moreover when using a different drilling protocol in soft bone, Sennerby et al. confirmed that when comparing tapered implants with parallel implants, the former showed a higher primary stability than the latter [48].

A previous study on the same pool of implants used in our study (tapered implants) demonstrated that grafted bone can offer good primary stability to implants and that, during the surgical procedure, only a few mechanical characteristics of implants (length and diameter) were able to influence ISQ values [49]. Degidi et al have suggested that the length and width of implants can influence primary stability because of the increased bone-implant contact surface area [50]. In the present study, the macrodesign, and the length and diameter of the implant were not used as evaluation factors as all the used implants were 4 mm in diameter and 11.5 mm in length, with tapered internal hexagon implants, and are consistent with these studies, which report no statistically significant differences in ISQ due to ISQ length or diameter [51, 52]. From the clinical point of view, implants that have been placed in soft or grafted bone show better mechanical stability values when they have a narrow diameter and a tapered macrodesign [53, 54]. In fact nearly every implant company offers tapered-design implants for alveolar ridges with deficient bone quality and quantity.

This should be taken into account for alveolar ridges with deficiencies in bone quality and quantity, which is the reason why almost every company in the sector has introduced tapered-design implants.

In our study we used a small particle size of two different deproteinized bone grafts. Jensen et al evaluated the influence of the particle size of DBBM on bone formation and implant stability when used for sinus floor elevation in a mini-pig model. In the initial healing phase, small particle size DBBM showed marginally higher osteoconductive capacity than large particle size DBBM. However, no differences were observed in the amount and speed of bone formation, BIC or implant stability between the two test groups. However at the baseline and at 6 and 12 weeks, the BIC values were comparable, or even higher, than in our study in humans. Primary implant stability is dependent on not only the thickness of the bone into which the implant is placed, but also on bone density, thread configuration and implant shape, and the presence of an implant neck. Therefore, all these factors should be taken into account when making the clinical decision to perform a one-stage or a two-stage procedure [55].

As evidenced in the review of Browaeys et al. on using biomaterials in sinus augmentation, within the limitation of the animal studies examined, and based only on histological examinations, the biomaterial used in grafting procedure does not influence the initial osseointegration of dental implants [56].

The correlation between the RFA values and good bone quality reported herein seemed to confirm the different importances of the factors that determine RFA values upon implant insertion and if it is able to maintain this stability after 3 or 6 months. In fact good quality bone probably reacts better to implant insertion, and implant stability after bone remodeling could be greater.

Long-term stability has also been reported by Hallman et al.. In their study 108 dental implants were placed 6 months after sinus floor augmentation with a mixture of autogenous and deproteinized bovine bone. After 3 years of loading, implant stability was recorded using an Osstell instrument. The mean reported RFA values were 67.4 ± 14.5 for residual bone and 65.6 ± 13.8 for the augmented sites. Unfortunately, no more data are currently available about the importance of bone quality in determining long-term RFA values, so more studies have to be conducted [57].

Healing times of 6–9 months before implant placement are usually recommended for sinus elevation in combination with grafting material [58], and an additional 3–6-month period of

implant healing time is needed. However, extended integration periods and multiple surgeries pose a challenge for patient acceptance [59].

Our results also indicate that regardless of the substitute material, the implants inserted into a grafted sinus can be predictably loaded as the implants inserted into a grafted area. Previous studies have concluded that the prognosis of implants inserted into augmented sinuses and the fixed restoration supported by these implants do not appear to be influenced by factors such as graft material, restoration type, residual bone height and time of implant placement. Within the limits of this review, the prognosis of implants and fixed restorations did not seem to be influenced by the restoration type, graft material, residual bone height and time of implant placement. However, the conclusions of this review are based on studies that provide a low level of evidence. Therefore, careful interpretations are required. Multicenter randomized controlled clinical trials with sufficient statistical power that concentrate on a few factors are needed to draw sound conclusions [11].

The differences between the two HAs, in porosity, crystallinity, density, surface area and composition terms, may determine different behaviors of this material, and might affect early implant stability in this clinical situation. The HA of a bovine origin sintered with high crystallinity, low porosity, high density and larger granule size presents better stability, which demonstrates that variations in the physico-chemical properties of a bone substitute material clearly influence implant stability. A profound knowledge of the graft material characteristics is of utmost importance when assessing their clinical outcomes. The physico-chemical properties of bone substitute materials can influence osseointegration and shorten healing times from implant placement to restoration. Understanding not only biomaterial properties, but also their relation and influence on bone healing, seems crucial.

4. Materials and Methods

4.1. Commercial xenograft materials

The commercial graft materials used in this study were two different types of bone deproteinized hydroxyapatite materials of different origins employed in dentistry: deproteinized porcine bone mineral hydroxyapatite (PBM), called OsteoBiol® (OsteoBiol, TecnoSS Dental SRL, Torino, Italia); deproteinized bovine hydroxyapatite (BBM), called Endobon® (RegenerOss™, BIOMET3i, Palm Beach, FL, USA). The physico-chemical and morphological characterizations of both xenograft materials are found in a previous study [33].

4.2. Implant procedure

4.2.1. Patient selection and protocol

Ten partially edentulous patients (five females and five males), whose ages ranged from 37 to 60 years, attended the Department of Oral and Maxillofacial Surgery. Patients who demanded fixed restorative appliances in the posterior maxilla were selected for maxillary sinus augmentation because sufficient bone tissue was lacking to place endosseous dental implants. The protocol for harvesting bone samples was approved by the University Ethics Committee and informed consent was obtained from all the patients (UCAM-Ethics Committee, approval ID: 6637). The study was designed following the Declaration of Helsinki guidelines for experimentation on human subjects. Any possible complications that could arise from surgical therapy were treated following standard dental management protocols.

4.2.2. Inclusion and exclusion criteria

Atrophy of the lateral-posterior maxilla and residual crestal bone height was classified according to Cawood et al.'s subsummizing classes I–VI. All the patients underwent CBCT before surgery as a routine diagnostic approach to carefully evaluate the available bone at the intended surgical site and for planning the grafting procedure.

The inclusion criteria were as follows: maxillary partial bilateral edentulism that involves premolar-molar areas. The cases with a crestal bone height between 7 mm and 0 mm, and with high postero-lateral atrophy (Cawood V–VI), are most likely to undergo a two-stage lateral antrostomy.

The exclusion criteria were: patients who suffer from an uncontrolled systemic disease or a condition known to alter bone metabolism (i.e., osteoporosis, diabetes mellitus, etc.); subjects who were taking/had taken medications known to modify bone metabolism; e.g., bisphosphonates, corticosteroids, etc.; women who were pregnant or trying to get pregnant at the time of screening; patients who presented existing sinus conditions, sepsis, a history of cancer and/or radiation to the oral cavity; complications derived from any of these conditions that affect the sinus area.

4.2.3. Surgical procedure. First phase

The study was performed in two surgical phases. In the first phase all the patients took 875/125 mg of amoxicillin/ clavulanic acid every 8 h starting 1 day before surgery. A 300-mg dose of Clindamycin every 8 h was prescribed to penicillin-allergic patients. This medication was maintained for 7 days. All the surgical procedures were performed under local anesthesia (Ultracain, Aventis Inc., Frankfurt, Germany). The basic surgical procedure was represented in all the patients by maxillary sinus floor elevation via a lateral approach, as described by Boyne and James (Fig. 5).



Figure 5. A lateral window is prepared and the schneiderian membrane is elevated.

After membrane elevation, a bioabsorbable collagen barrier membrane was placed under the sinus membrane and adapted to come into contact with peripheral bony walls (Evolution Fine® OsteoBiol®, TecnoSS Dental S.R.L., Torino, Italy). Sinuses were allocated to the non sintered HAs (PBM) or to the sintered HAs (BBM) group via a standard randomization protocol (<http://www.randomization.com>). On one side, sinus cavities were grafted with the PBM (OsteoBiol® mp3, TecnoSS Dental S.R.L., Torino, Italy). After grafting, an absorbable collagen membrane (Evolution Fine® OsteoBiol®, TecnoSS Dental S.R.L., Torino, Italy) was placed over the window to minimize soft tissue invasion. On the other side, sinus cavities were grafted with the BBM (Endobon®, RegenerOss™, BIOMET3i, Palm Beach Gardens, FL, USA). The grafting materials were mixed with venous blood from the defect area and were carefully packed in the created volume following mucous membrane elevation. After bone grafting, a short-term absorbable collagen membrane (Evolution Fine® OsteoBiol®, TecnoSS Dental S.R.L., Torino, Italy) was placed over the window. Primary closure was achieved in both cases by suturing with 3–0 silk

suture (Laboratory Aragón, Barcelona, Spain). Sutures were removed 2 weeks after surgery. During the postoperative period, patients were clinically and radiologically followed up at monthly intervals (Fig. 6).



Figure 6. (A) A short-term absorbable collagen membrane. (B) Grafting materials mixed with venous blood.

4.2.4 Radiographic Thermal Imaging Analysis

During the post-operative period, patients were clinically and radiologically followed up at monthly intervals. All the patients underwent CBCT 6 months after surgery as a routine diagnostic approach using an I-CAT® (Imaging Sciences International, Hatfield, USA) Cone Beam 3D and were analyzed using the I-Cat vision software. The obtained images were processed by the Image J software, developed by the National Institute of Health (NIH) of the USA; a 3D plug-in with a thermal LUT and a grid size of 128x128, smoothing of 6.0, and a perspective of 0.2 on a 1:1 scale. Color thermal graduation was used to observe the changes in radiopacity in the grafted area (intrasinus bone graft). The scale was graduated with values from 0 to 240, where 0-20 were the values assigned to air, 20 to 100 were the values assigned to water and soft tissues, 100 to 140 were the values assigned to lower density bone, and 140 to 220 were the values assigned to higher density bone (Fig. 7).

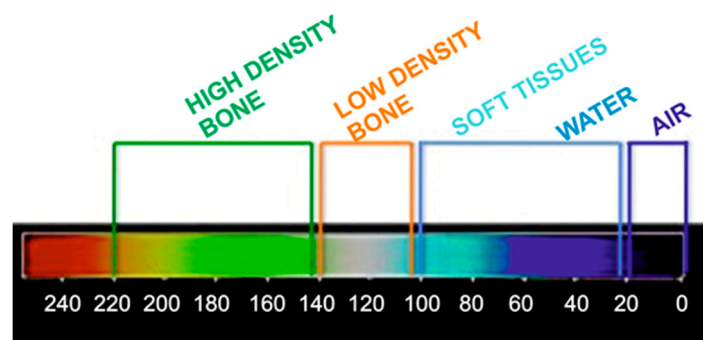


Figure 7. Color-graduated density scale for thermal imaging interpretations.

4.2.5. Surgical procedure. Second phase. Implant Insertion

The second surgical phase was performed after the healing period. Functional implants were placed on each side. Each side received three implants (3i T3® Implante Certain® Cónico (BIOMET 3i® Palm Beach Gardens, Florida) placed 6 months after augmentation. All the patients took 875 mg/125 mg units of amoxicillin/ clavulanic acid every 8 h starting 1 day before surgery. A dose of 300 mg of Clindamycin every 8 h was prescribed to penicillin-allergic patients. This medication was maintained for 7 days. All the surgical procedures were performed under local anesthesia (Ultracain, Aventis Inc., Frankfurt, Germany) in an outpatient setting by the same surgeon, who was familiar with the implant system. For the procedure, a full thickness mucoperiosteal flap was elevated on the sides. The osteotomy using a conical drill, with copious irrigation using saline solution, was done on the crest of the bone. Then osteotomies for fitting implants were produced using the initial drill to determine the depth and direction of the site. Afterward implants were positioned in the local, predetermined at the crestal bone level. Sixty conical implants with an

internal hexagon connection were applied, which were all 11.5 mm long with a 4.0 mm diameter. Implants were selected according to the prior evaluation of each case. All the implants were fitted using surgical guides, and wounds were sutured in a tension-free state. Antibiotics and analgesics were given for 1 week. All the patients took 875/125 mg of amoxicillin/clavulanic acid every 8 h starting 1 day before surgery, and 300 mg of Clindamycin every 8 h were prescribed to penicillin-allergic patients. This medication was maintained for 7 days. Patients were asked to rinse with 0.12% chlorhexidine 3 times daily for 2 postoperative weeks. Sutures were removed 2 weeks after surgery. All the implants were prepared with a healing abutment until rehabilitation commenced.

4.3. Measuring implant stability

After dental implant insertion, the resonance frequency evaluation was made using the Ostell™ Mentor (Integration Diagnostics AB, Göteborg, Sweden) to measure the implant's primary stability. A Smartpeg™ (Integration Diagnostics AB, Göteborg, Sweden) was placed in each implant and was tightened to approximately 4-5 Ncm. The transducer probe was aimed at the small magnet at the top of the Smartpeg and at a distance of 2-3 mm, and was held stable during pulsing until the instrument beeped and displayed the ISQ value (Fig. 8). The RF value is represented by a quantitative parameter called ISQ. The ISQ range went from 1 to 100. An increased ISQ indicates increased stability, whereas low values indicate reduced implant stability. The ISQ values were measured during the surgical procedure (T1-baseline), at 3 months (T2) after surgery and at 6 months (T3) after surgery. Measurements were taken twice in the bucco-lingual direction and twice in the mesio-distal direction. The mean of the two measurements in each direction was regarded as the representative ISQ for that direction. The higher values were recorded for the bucco-lingual (B-L) direction and the mesio-distal (M-D) direction. The ISQ values were separately evaluated. Each implant was also evaluated during all visits for mobility, pain and signs of infection.

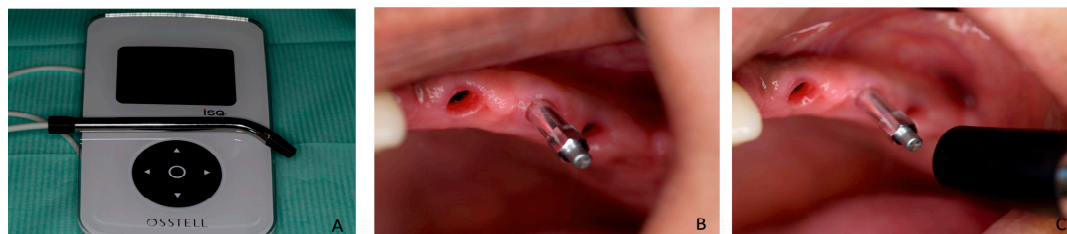


Figure 8: (A) Implant-bone contact rigidity was measured by RFA (Ostell™ Mentor, Integration Diagnostic AB, Sweden). RFA measurements were obtained before the healing cape was screwed into implant fixtures. (B) A Smartpeg (Smartpeg™, Integration Diagnostic AB, type 4 regular neck) was attached manually to the fixture with the help of a mount, and a torque of 4-5 Ncm was applied. (C) All the measurements were taken out by the same researcher. Measurements were taken at the time of implant placement and (baseline) at Stage 2 and at Stage 3. In all cases, an ISQ was calculated as the average of four measurements per implant (twice in the bucco-lingual direction and twice in the mesio-distal direction).

4.4 Statistical evaluation

All the data were recorded, reviewed and inputted into a computing system. Analyses were performed using specific software (MedCalc, Belgium). The influence of age, gender (Male, Female), group (BBM, PBM), ISQ measurement direction (BL, MD) and the evaluation time period, (T1) baseline, (T2) 3 months, (T3) 6 months, on the ISQ values was evaluated by an analysis of

variance (ANOVA) and multiple regression at the 5% significance level (backward method) with the help of appropriate software (MedCalc, v15.8. Belgium).

5. Conclusions

The differences between the two HAs found in porosity, crystallinity, density, surface area and composition terms may determine the different behaviors of this material and might affect early implant stability in this clinical situation. The HA of a bovine origin (BBM) sintered with high crystallinity and low porosity presents better stability, which demonstrates that variations in the physico-chemical properties of a bone substitute material clearly influence implant stability. Detailed information about the graft material's characteristics is crucial to evaluate its clinical outcomes. The influence of the physico-chemical properties of bone graft materials on osseointegration has led to shorter healing times from implant placement to restoration. A sound understanding of various aspects of biomaterial properties, and their relation to and influence on bone healing, is of utmost importance.

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References

1. Sharan, A.; Madjar, D. Maxillary sinus pneumatization following extractions: a radiographic study. *Int J Oral Maxillofac Implants*. **2008**, *23*, 48–56.
2. Aghaloo, T.L.; Moy, P.K. (2007) Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? *Int J Oral Maxillofac Implants*. **2007**, *22*, 49–70.
3. Corbella, S.; Taschieri, S.; Del Fabbro, M. Long-term outcomes for the treatment of atrophic posterior maxilla: a systematic review of literature. *Clin Implant Dent Relat Res*. **2015**, *17*, 120–132. doi: 10.1111/cid.12077
4. Felice, P.; Soardi, E.; Pellegrino, G.; Pistilli, R.; Marchetti, C., Gessaroli, M., Esposito, M. Treatment of the atrophic edentulous maxilla: short implants versus bone augmentation for placing longer implants. Five-month post-loading results of a pilot randomised controlled trial. *Eur J Oral Implantol*. **2011**, *4*, 191–202. doi: 10.1111/j.1600-0501.2010.01966.x.
5. Esposito, M.; Barausse, C.; Pistilli, R.; Sammartino, G.; Grandi, G.; Felice, P. Short implants versus bone augmentation for placing longer implants in atrophic maxillae: One-year post-loading results of a pilot randomised controlled trial. *Eur J Oral Implantol*. **2015**, *8*, 257–268.
6. Nedir, R.; Nurdin, N.; Abi- Najm, S.; El Hage, M.; Bischof, M. Short implants placed with or without grafting into atrophic sinuses: the 5-year results of a prospective randomized

- controlled study. *Clin Oral Implants Res.* **2016** Jun 13. doi: 10.1111/clr.12893. [Epub ahead of print] DOI: 10.1111/clr.12893
7. Khouly, I.; Veitz-Keenan, A. Insufficient evidence for sinus lifts over short implants for dental implant rehabilitation. *Evid Based Dent.* **2015**, *16*, 21-22. doi: 10.1038/sj.ebd.6401081.
 8. Fan, T.; Li, Y.; Deng, W.W.; Wu, T.; Zhang, W. Short Implants (5 to 8 mm) Versus Longer Implants (>8 mm) with Sinus Lifting in Atrophic Posterior Maxilla: A Meta-Analysis of RCTs. *Clin Implant Dent Relat Res.* **2017**, *19*, 207-215. doi: 10.1111/cid.12432
 9. Kolerman, R.; Samorodnitzky, G.R.; Barnea, E.; Tal, H. Histomorphometric analysis of newly formed bone after bilateral maxillary sinus augmentation using two different osteoconductive materials and internal collagen membrane. *Int J Periodontics Restorative Dent.* **2012**, *32*, 21-28.
 10. Wallace, S.S.; Froum, S.J. Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review. *Ann. Periodontol.* **2003**, *8*, 328-43. doi: 10.1902/annals.2003.8.1.328
 11. Tuna, T.; Yorgidis, M.; Strub, J.R. (2012) Prognosis of implants and fixed restorations after lateral sinus elevation: a literature review. *J Oral Rehabil.* **2012**, *39*, 226-38. doi: 10.1111/j.1365-2842.2011.02259.x
 12. Traini, T.; Piattelli, A.; Caputi, S.; Degidi, M.; Mangano, C.; Scarano, A.; Perrotti, V.; Iezzi, G. Regeneration of Human Bone Using Different Bone Substitute Biomaterials. *Clin Implant Dent Relat Res.* **2015**, *17*, 150-62. doi: 10.1111/cid.12089
 13. Baqain, Z.H.; Moqbel, W.Y.; Sawair, F.A. Early dental implant failure: risk factors. *Br J Oral Maxillofac Surg.* **2012**, *50*, 239-243. doi: 10.1016/j.bjoms.2011.04.074
 14. Zinser, M.J.; Randelzhofer, P.; Kuiper, L.; Zöller, J.E.; De Lange, G.L. The predictors of implant failure after maxillary sinus floor augmentation and reconstruction: a retrospective study of 1045 consecutive implants. *Oral Surg Oral Med Oral Pathol Oral Radiol.* **2013**, *115*, 571-582. doi: 10.1016/j.oooo.2012.06.015
 15. Herliansyah, M.K.; Hamdia, M.; de-Ektessabic, A.I.; Wildanb, M.W., J.A. Toque, J.Á. The influence of sintering temperature on the properties of compacted bovine. *Mater Sci Eng C Mater Biol Appl.* **2009**, *29*, 1674-1680. <https://doi.org/10.1016/j.msec.2009.01.007>
 16. Conz, M.B.; Granjeiro, J.M.; Soares, G.A. Physicochemical characterization of six commercial hydroxyapatites for medical-dental applications as bone graft. *J Appl Oral Sci* **2005**, *13*, 136-140. <http://dx.doi.org/10.1590/S1678-77572005000200008>.
 17. Barakat, N.A.; Khalil, K.A.; Faheem, A. Sheikh; A.M. Omran; Babita Gaiher; Soeb M. Khild; Hak Yong Kim Physicochemical characterizations of hydroxyapatite extracted from bovine bones by three different methods: *Extraction of biologically desirable Hap. Mater. Sci. Eng. C Mater. Biol. Appl.* **2008**, *28*, 1381-1387. DOI: 10.1016/j.msec.2008.03.003
 18. Azran, Y.M.; Idris, B.; Rusnah, M.; Rohaida, C.H. HAp physical investigation the effect of sintering temperature. *Med J Malaysia.* **2004**, *59*, 79-80.
 19. Danesh-Sani, S.A.; Engebretson, S.P.; Janal, M.N. 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.* **2016**. doi: 10.1111/jre.12402. [Epub ahead of print] doi: 10.1111/jre.12402
 20. Felice, P.; Pistilli, R.; Piattelli, M.; Soardi, E.; Pellegrino, G.; Corvino, V.; Esposito, M. 1-stage versus 2-stage lateral maxillary sinus lift procedures: 4-month post-loading results of a

- multicenter randomised controlled trial. *Eur J Oral Implantol.* **2013**, *6*, 153-165. DOI: 10.1016/j.dental.2013.08.019
21. Busenlechner D, Huber CD, Vasak C, Dobsak A, Gruber R, Watzek G. Sinus augmentation analysis revised: the gradient of graft consolidation. *Clin Oral Implants Res.* **2009**, *20*, 1078-1083. doi: 10.1111/j.1600-0501.2009.01733.x
 22. Xu, H.; Shimizu, Y.; Asai, S.; Ooya, K. Experimental sinus grafting with the use of deproteinized bone particles of different sizes. *Clin Oral Implant Res* **2003**, *14*, 548–555. DOI: 10.1034/j.1600-0501.2003.00933.x
 23. Gupta, R.K.; Padmanabhan, T.V. An evaluation of the resonance frequency analysis device: examiner reliability and repeatability of readings. *J Oral Implantol.* **2013**, *39*, 704-707. DOI:10.1563/AAID-JOI-D-11-00099
 24. Lioubavina-Hack, N.; Lang, N.P.; Karring, T. Significance of primary stability for osseointegration of dental implants. *Clin Oral Implants Res.* **2006**, *17*, 244-250. DOI: 10.1111/j.1600-0501.2005.01201.x
 25. Sennerby, L.; Meredith, N. Implant stability measurements using resonance frequency analysis: biological and biomechanical aspects and clinical implications. *Periodontol 2000.* **2008**, *47*, 51-66. DOI:10.1111/j.1600-0757.2008.00267.x
 26. Swami, V.; Vijayaraghavan, V.; Swami, V. Current trends to measure implant stability. *J Indian Prosthodont Soc.* **2016**, *16*, 124-130. DOI: 10.4103/0972-4052.176539
 27. Cehreli, M.C.; Karasoy, D.; Akca, K.; Eckert, S.E. Meta-analysis of methods used to assess implant stability. *Int J Oral Maxillofac Implants* **2009**, *24*, 1015-1032.
 28. Atsumi, M.; Park, S.H.; Wang, H.L. Methods used to assess implant stability: current status. *Int J Oral Maxillofac Implants.* **2007**, *22*, 743-754. DOI: 10.4103/0972-4052.176539.
 29. Lundgren, S.; Cricchio, G.; Hallman, M.; Jungner, M.; Rasmusson, L.; Sennerby L. Sinus floor elevation procedures to enable implant placement and integration: techniques, biological aspects and clinical outcomes. *Periodontol 2000.* **2017**, *73*, 103-120. doi: 10.1111/prd.12165
 30. Iezzi, G.; Scarano, A.; Di Stefano, D.; Arosio, P.; Doi, K.; Ricci, L.; Piattelli, A.; Perrotti, V. Correlation between the bone density recorded by a computerized implant motor and by a histomorphometric analysis: a preliminary in vitro study on bovine ribs. *Clin Implant Dent Relat Res.* **2015**, *17*, 35-44. doi: 10.1111/cid.12121
 31. Marquezan, M.; Osório, A.; Sant'Anna, E.; Souza, M.M.; Maia, L. Does bone mineral density influence the primary stability of dental implants? A systematic review. *Clin Oral Implants Res.* **2012**, *23*, 767-774. doi: 10.1111/j.1600-0501.2011.02228.x
 32. Ferreira, C.E.; Novaes, A.B.; Haraszthy, V.I.; Bittencourt, M.; Martinelli, C.B.; Luczyszyn, S.M. A clinical study of 406 sinus augmentations with 100% anorganic bovine bone. *J Periodontol.* **2009**, *80*, 1920-1927. doi: 10.1902/jop.2009.090263
 33. Ramírez Fernández, M.P.; Gehrke, S.A.; Perrez Albacete Martinez, C.; Calvo Guirado, J.L., De Aza, P.N. SEM-EDX Study of the degradation process of two xenograft materials used in sinus lift procedures. *Materials* **2017**; *10*; 542 DOI: 10.3390/ma100050542.
 34. Nasr, S.; Slot, D.E.; Bahaa, S.; Dörfer, C.E.; Fawzy El-Sayed, K.M. Dental implants combined with sinus augmentation: What is the merit of bone grafting? A systematic review. *J Craniomaxillofac Surg.* **2016**, *44*, 1607-1617. doi: 10.1016/j.jcms.2016.06.022

35. Rammelsberg, P.; Schmitter, M.; Gabbert, O.; Lorenzo-Bermejo, J.; Eiffler, C.; Schwarz, S. Influence of bone augmentation procedures on the short-term prognosis of simultaneously placed implants. *Clin Oral Implants Res.* **2012**, *23*, 1232-1237. doi: 10.1111/j.1600-0501.2011.02295.x
36. Knöfler, W.; Barth, T.; Graul, R.; Krampe, D. Retrospective analysis of 10,000 implants from insertion up to 20 years-analysis of implantations using augmentative procedures. *Int J Implant Dent.* **2016**, *2*, 25. DOI: 10.1186/s40729-016-0061-3
37. Jensen, S.S.; 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*, 218-236.
38. Herrero-Climent, M.; Albertini, M.; Rios-Santos, J.V.; Lázaro-Calvo, P.; Fernández-Palacín, A.; Bullon, P. Resonance frequency analysis-reliability in third generation instruments: Osstell mentor®. *Med Oral Patol Oral Cir Bucal.* **2012**, *17*, 801-806. doi:10.4317/medoral.17861
39. Herrero-Climent, M.; Santos-García, R.; Jaramillo-Santos, R.; Romero-Ruiz, M.M.; Fernández-Palacín, A.; Lázaro-Calvo, P.; Bullón, P.; Ríos-Santos, J.V. Assessment of Osstell ISQ's reliability for implant stability measurement: a cross-sectional clinical study. *Med Oral Patol Oral Cir Bucal.* **2013**, *18*, 877-882. doi:10.4317/medoral.19120
40. Degidi, M.; Perrotti, V.; Piattelli, A.; Iezzi, G. Mineralized bone-implant contact and implant stability quotient in 16 human implants retrieved after early healing periods: a histologic and histomorphometric evaluation. *Int J Oral Maxillofac Implants.* **2010**, *25*, 45-48.
41. Al-Khaldi, N.; Sleeman, D.; Allen, F. Stability of dental implants in grafted bone in the anterior maxilla: longitudinal study. *Br J Oral Maxillofac Surg.* **2011**, *49*, 319-323. doi: 10.1016/j.bjoms.2010.05.009
42. Friberg, B.; Ekestubbe, A.; Sennerby, L. Clinical outcome of Brånemark System implants of various diameters: a retrospective study. *Int J Oral Maxillofac Implants.* **2002**, *17*, 671-677.
43. Esposito, M.; Grusovin, M.G.; Maghaireh, H.; Worthington HV. Interventions for replacing missing teeth: different times for loading dental implants. *Cochrane Database Syst Rev.* **2013**, *28*, 3, CD003878. doi: 10.1002/14651858.CD003878.pub5.
44. Javed, F.; Romanos, G.E. Role of implant diameter on long-term survival of dental implants placed in posterior maxilla: a systematic review. *Clin Oral Investig.* **2015**, *19*, 1-10. doi: 10.1007/s00784-014-1333-z
45. Schiuma, D.; Plecko, M.; Kloub, M.; Rothstock, S.; Windolf, M.; Gueorguiev, B. Influence of peri-implant bone quality on implant stability. *Med Eng Phys.* **2013**, *35*, 82-87. doi: 10.1016/j.medengphy.2012.04.001
46. Anil, S.; Aldosari, A. Impact of bone quality and implant type on the primary stability: an experimental study using bovine bone. *J Oral Implantol.* **2015**, *41*, 144-148. doi: 10.1563/AAID-JOI-D-11-00156
47. Romanos, G.E.; Delgado-Ruiz, R.A.; Sacks, D.; Calvo-Guirado, J.L. Influence of the implant diameter and bone quality on the primary stability of porous tantalum trabecular metal dental implants: an in vitro biomechanical study. *Clin Oral Implants Res.* **2016**, *1-7* doi: 10.1111/clr.12792
48. Sennerby, L.; Pagliani, L.; Petersson, A.; Verrocchi, D.; Volpe, S.; Andersson, P. Two different implant designs and impact of related drilling protocols on primary stability in different bone

- densities: an in vitro comparison study. *Int J Oral Maxillofac Implants*. **2015**, *30*, 564-568. doi: 10.11607/jomi.3903.
49. Gehrke, S.A.; da Silva, U.T.; Del Fabbro, M. Does Implant Design Affect Implant Primary Stability? A Resonance Frequency Analysis-Based Randomized Split-Mouth Clinical Trial. *J Oral Implantol*. **2015**, *41*, 281-286. doi: 10.1563/aaid-joi-D-13-00294
 50. Degidi, M.; Piattelli, A.; Iezzi, G.; Carinci, F. Do longer implants improve clinical outcome in immediate loading? *Int J Oral Maxillofac Surg*. **2007**, *36*, 1172-1176. DOI:10.1016/j.ijom.2007.05.014
 51. Balleri, P.; Cozzolino, A.; Ghelli, L.; Momicchioli, G.; Varriale, A. Stability measurements of osseointegrated implants using Osstell in partially edentulous jaws after 1 year of loading: a pilot study. *Clin Implant Dent Relat Res*. **2002**, *4*, 128-132. DOI: 10.1111/j.1708-8208.2002.tb00162.x
 52. Ostman, P.O.; Hellman, M.; Wendelhag, I.; Sennerby, L. Resonance frequency analysis measurements of implants at placement surgery. *Int J Prosthodont*. **2006**, *19*, 77-83.
 53. O'Sullivan, D.; Sennerby, L.; Meredith, N. Measurements comparing the initial stability of five designs of dental implants: a human cadaver study. *Clin Implant Dent Relat Res*. **2000**, *2*, 85-92. DOI: 10.1111/j.1708-8208.2000.tb00110.x
 54. Romanos, G.E.; Ciornei, G.; Jucan, A.; Malmstrom, H.; Gupta, B. In vitro assessment of primary stability of Straumann® implant designs. *Clin Implant Dent Relat Res*. **2014**, *16*, 89-95. doi: 10.1111/j.1708-8208.2012.00464.x
 55. Jensen, S.S.; Aaboe, M.; Janner, S.F.; Saulacic, N.; Bornstein, M.M.; Bosshardt, D.D.; Buser, D. Influence of particle size of deproteinized bovine bone mineral on new bone formation and implant stability after simultaneous sinus floor elevation: a histomorphometric study in minipigs. *Clin Implant Dent Relat Res*. **2015**, *17*, 274-85. doi: 10.1111/cid.12101
 56. Browaeys, H.; Bouvry, P.; De Bruyn, H. A literature review on biomaterials in sinus augmentation procedures. *Clin Implant Dent Relat Res*. **2007**, *9*, 166-177. doi: 10.1111/j.1708-8208.2007.00050.x
 57. Degidi, M.; Daprile, G.; Piattelli, A. RFA values of implants placed in sinus grafted and nongrafted sites after 6 and 12 months. *Clin Implant Dent Relat Res*. **2009**, *11*, 178-182. doi: 10.1111/j.1708-8208.2008.00113.x.
 58. Jensen, O.T.; Sennerby, L. Histologic analysis of clinically retrieved titanium microimplants placed in conjunction with maxillary sinus floor augmentation. *Int J Oral Maxillofac Implants*. **1998**, *13*, 513-521.
 59. Lai, H.C.; Zhang, Z.Y.; Wang, F.; Zhuang, L.F.; Liu, X. Resonance frequency analysis of stability on ITI implants with osteotome sinus floor elevation technique without grafting: a 5-month prospective study. *Clin Oral Implants Res*. **2008**, *19*, 469-475. doi: 10.1111/j.1600-0501.2007.01501.x.