

Results of an open prospective multicentre study with 190 patients

Application of a synthetic hydroxyapatite in dental surgery

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Many different bone replacement materials or bone substitutes are available for the filling of bone defects and for bone augmentation. The aim of this multicentre study was to evaluate the new synthetic hydroxyapatite Osbone in various indications in dental surgery.

In dentistry, and especially in oral and maxillofacial surgery, there is a very considerable demand for bone replacement materials. The fresh autologous corticocancellous or cancellous bone graft is the most potent biological actor. But before relying on it exclusively, the re-entry requirement, possible complications, relatively limited availability, logistical efforts and potential forensic consequences must be taken into account [7].

Alternatively, a variety of synthetic and biological materials is available that differ in porosity, surface structure and absorption kinetics. Hydroxyapatites, for example, have been used as bone substitutes within the entire human skeleton for several decades. The primary distinction is between hydroxyapatites synthesized from calcium and phosphate on the one hand and hydroxyapatite of allogeneic or xenogeneic origin on the other. Biological hydroxyapatites are subjected to extensive alkaline and heat treatments in order to eliminate organic components [13]. Osbone granules (curasan AG) consist of synthetically produced, pure-phase hydroxyapatite. Its phase purity makes for favourable healing characteristics, which in turn ensure stable bone augmentation. The development of Osbone is not least the result of decades of experience on the part of curasan AG in the development and production of synthetic bone substitute and reconstruction materials (especially the familiar Cerasorb).

Recent findings in the field of bone regeneration suggest that Osbone has the following properties: interconnecting, open multiporosity (approximately 80 per cent), a polygonal granular structure and high similarity to human cancellous bone (Fig. 1). The special structure promotes speedy ingrowth of newly formed bone tissue, the diffusion of blood and body

fluids, deep penetration of osteogenic cells, and replacement of the synthetic matrix with bone. The pores are organized in an interconnecting system for progressive angiogenesis and vascularization, thus ensuring that active cell nutrients are available throughout the process of osseointegration. For use in dental surgery, Osbone is available in grain sizes 0.25–1 mm and 1–2 mm. The aim of this multicentre study pursuant to §23b of the German Medical Device Act was to gain further insights into the efficacy and tolerability of Osbone for various indications in dentistry and in oral surgery.

*For study participants

Materials and methods

The prospective multicentre study was conducted in Germany by experienced oral surgeons and implantologists. A surveillance plan defining objectives and practical details was drawn up. All findings were entered into prepared documentation sheets. The study was to include 200 patients of both sexes from age 18 with the following preoperative diagnoses or

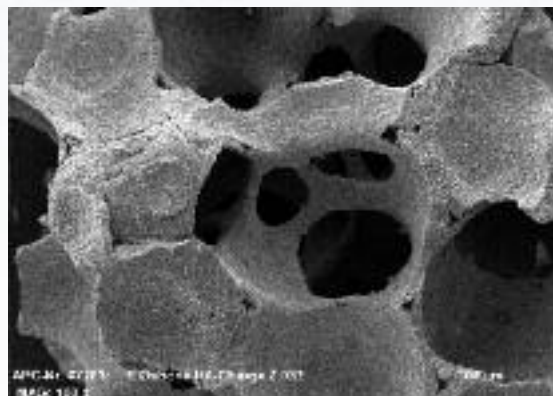


Fig. 1 SEM image, Osbone, x 100 magnification.

indications: alveolar defect, apical resection, implant bed preparation, filling of cysts, sinus floor elevation, periodontal pocket and similar indications. Exclusion criteria for treatment within the framework of this study were autoimmune diseases, diabetes mellitus with diabetic syndromes (such as eczema, periodontal disease, impaired wound healing), regular medication that may affect wound healing (such as cortisone, immunosuppressants, etc.) and nicotine abuse.

Baseline documentation included a medical history and physical examination (including radiographs if possible). All patients were duly informed and gave their consent to surgical treatment (type of intervention; amount and grain size of the Osbone granules used; additional measures such as mixing in platelet-rich plasma/PRP or platelet mediator concentrate/PMC; use of a membrane; soft-tissue closure; etc.) and the follow-up examinations performed within one to two weeks postoperatively as well as after approximately three, six, nine and twelve months – sometimes later, depending on the progress of regeneration and healing.

Results

A total of 32 dental surgeries and oral and maxillo-facial clinics throughout Germany took part in the study. The observation period was May 2010 to May 2012 (first treatment day, first patient, to last follow-up, last patient). Documentation sheets were analyzed for a total of 190 patients (107 women and 83 men aged 20 to 83 years; mean age: 53.15 years; median age: 54 years; no age given for four patients).

The most common diagnosis (75 instances) was atrophy of the alveolar ridge, followed by non-salvageable teeth (25), periodontitis (18), root canal treatment/resection (14), loss of teeth (13), cyst surgery (13) and alveolar defects (10). Further nominations included tooth loss following trauma or root fracture.

A total of 58 comorbidities were mentioned, most frequently hypertension (18 cases), hyperthyroidism (7), heart disease (6) and cardiac arrhythmia (4). The number of different drugs given concomitantly was 40, most antihypertensives (14 cases), antiplatelet drugs (8) and thyroxine (6). 31 patients smoked, under ten cigarettes/day (15) or over ten cigarettes/day (16). Augmentation was performed at 458 locations:

- 1st quadrant: 150
- 2nd quadrant: 179
- 3rd quadrant: 63
- 4th quadrant: 66

Most augmentations were performed at site 26 (44 augmentations), followed by site 16 (37). Augmentation procedures and the use of membranes followed

the usual guidelines with regard to the quality of the local bone and the size and nature of the defect.

Osbone granules 0.25–1 mm in size were used in 128 cases, while granules 1–2 mm in size were used in 71 cases. The amounts used were: 0.5 g (51 patients), 1g (107), 1.5 g (8), 2g (19), 3g (4), 4g (3), 5g (1). Osbone was mixed with autologous bone in 36 patients. Other interventions involved PRP (27 cases), TM and fibrin autologous blood (10). Cerasorb and BioOss granules were used, respectively, in two additional cases.

Antibiotics were given preoperatively (73 patients) or postoperatively (131), most commonly clindamycin (74 patients), followed by amoxicillin (50) and amoxicillin clavulanate. The duration of treatment varied between two and 14 days, most commonly three days (31 patients), five days (24) and seven days (36). 137 patients performed regular mouthwashes, mostly with chlorhexidine (95) or Meridol mouthrinse (30).

A total of 128 interventions involved the use of a membrane, of which 107 resorbable, 15 non-resorbable and six instances of titanium mesh.

Complete primary wound closure was achieved in 144 cases; a gap of less than 3 mm was found in 19 patients and of more than 3 mm in 14 cases.

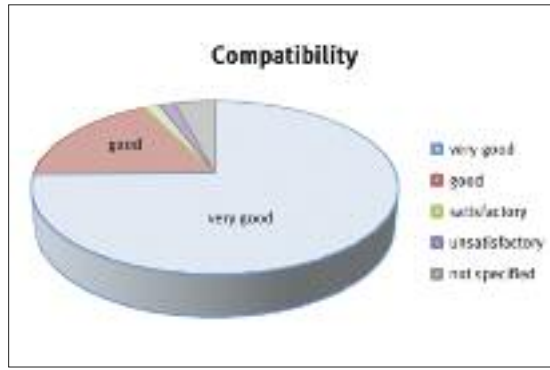
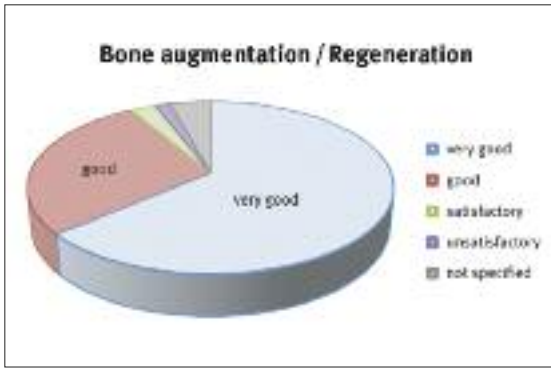
	Ideal	Good	Satisfactory	Unspecified
Soft-tissue healing	82	71	11	26
Membrane assessment (n = 128)	64	44	8	12
Patient compliance	105	77	3	5

Table 1 Results of the follow-up one to two weeks postoperatively.

Dehiscences were observed in 17 patients.

Time/ Evaluation	F1/3 months Day 7 – 202, M = 92	F2/6 months Day 23 – 279, M = 179	F3/9 months Day 86 – 530, M = 280	F4/12 months Day 230 – 659, M = 379
Radiograph	103	95	60	50
Osbone visible	66	43	22	14
Reddening	14	5	5	2
Swelling	7	2	2	–
Infection	4	1	2	–

Table 2 Overall treatment (n = 190, absolute values).



Figs. 2a and b Overall assessment of efficacy and tolerability.

The following complications were reported at the various follow-up examinations:

- 3-month follow-up, one patient each: Sinusitis on the contralateral side; titanium mesh exposure (requiring the removal of the mesh and granules); purulent infection with granule loss; required removal of membrane fragments
- 6-month follow-up, one patient each: Unexplained contralateral swelling; fistulae at the surgical site; re-augmentation of the bone necessary; unexplained urticaria
- 9-month follow-up: Fistula at the surgical site
- 12-month follow-up: Pressure pain at the surgical site

The final overall assessment of the clinical outcome of the defect filling or augmentation as well as compatibility is shown in Figures 2a and b.

In 117 patients, the implant was placed on the day of defect filling and augmentation; in 37 patients, it was placed between 14 and 304 days post-augmentation (mean: 159.3 days; median: 161 days); no data were available for 36 patients. The total number of implants placed was 3794.

Site / Q-I	Number of implants	Site / Q-II	Number of implants	Site / Q-III	Number of implants	Site / Q-IV	Number of implants
11	12	21	23	31	4	41	7
12	22	22	19	32	5	42	1
13	14	23	16	33	9	43	7
14	19	24	23	34	8	44	7
15	25	25	24	35	9	45	10
16	35	26	39	36	12	46	13
17	8	27	13	37	6	47	6
18	1	28	1	38	1	48	1

Table 3 Number of implants per site.

At the time of implant placement, the available bone at the insertion site was assessed as follows:

Ideal	Good	Limited suitability	Unsuitable	Unspecified
36	68	47	2	37

Gingival conditions were identified as follows:

Ideal	Good	Bad	Unspecified
65	89	5	31

In 61 documentation forms, primary implant stability at the time of placement was reported at 20 Ncm; more than 20 Ncm was achieved in 93 cases; no data are available for 36 cases.

Discussion

The use of bone replacement and regeneration materials is part of the daily practice in oral and maxillo-facial surgery. Different materials can be employed, depending on the indication. In the presence of severe atrophy, vertical and horizontal, a bone block graft will usually be inevitable. In the presence of moderate horizontal atrophy, reconstruction with a bone substitute may be considered, provided that the implant can be firmly anchored in the remaining bone. The materials used today, such as hydroxyapatite (HA) or beta-tricalcium phosphate (β -TCP), are available as granules, and are not suitable for stabilizing implants in severe atrophy cases. Smaller bone defects, however, can often be augmented with bone substitutes simultaneously with implantation [10]. The usefulness of β -TCP for this purpose is limited, as it may resorb prematurely in vestibular augmentation sites. HA is the better choice, as this material has slower absorption kinetics and degrades only slightly and over an extended period of time.

Earlier bone substitutes made of hydroxyapatite, which is the less soluble phase of the calcium phosphate system, exhibited lower porosity and larger



Fig. 3a 46-year-old patient, loss of tooth 21, no augmentation alio loco.



Fig. 3b Following implant placement.



Fig. 3c After augmentation with Osbone granules, size 0.25–1 mm, and coverage with a resorbable membrane.



Fig. 3d Closure with a collagen membrane.



Fig. 3e The suture is impervious to saliva.



Fig. 3f Radiographic control after eight weeks. Good osseointegration of the implant.

areas with dense ceramics. In the past, this would result in significantly denser and stronger areas in the augmentation region, which could lead to complications when an implant bed was prepared by drilling. Therefore, high porosity and a trabecular structure were required to minimize the amount of extraneous material per bone defect. Because of its porosity of 80 per cent, corresponding to that of human cancellous bone, Osbone is highly stable and vascularizes rapidly.

For ideal regeneration of large bone defects, the current literature suggests a minimum pore size of 200–400 µm in order to achieve adequate neovas-

cularization and osteoconduction with formation of mineralized tissue within the scaffold [11]. For the penetration of individual bone cells, a lower threshold of 80 µm has been postulated. An important aspect is the degree of interconnectivity of the pores within a given particle bone replacement material. The new bone substitute Osbone fulfils these condi-

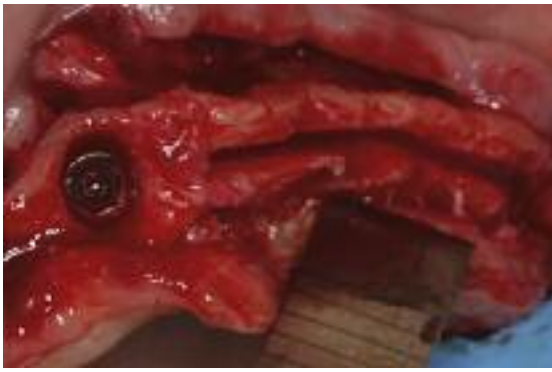


Fig. 4a Bone splitting.



Fig. 4b Implant insertion following bone splitting.



Fig. 4c Immediate loading with temporary posts and simultaneous augmentation with Osbone granules, size 0.25–1 mm.



Fig. 4d Coverage with a collagen membrane.

Images 4a to d: Dr. H. Lerner, Baden-Baden, Germany

tions [11], because Osbone was developed under the proviso to mimic cancellous bone as closely as possible to provide the most suitable structure for osseointegration. Micro-CT images show that the average pore diameter is 500 μm , with “beam” widths of 150 μm on average. This inorganic, purely synthetic material differs from bone graft materials of biological origin in that it is produced with precisely defined physico-chemical and crystal-chemical properties, exhibits consistent across-batch quality and therefore facilitates a more predictable biological response.

In cell culture studies with SaOS-2 cells, clearly adherent cells with a long-segmental morphology could be observed on the Osbone granules as early as one day after colonization. A steady increase in osteoblasts was seen on further cultivation. The number of cells detected on day 28 of the culture was three to five times that on the first day [15].

In an in-vitro study, Bernard and co-workers investigated the colonization behaviour of three bone substitute materials (Cerasorb M, Osbone and BioOss) with SaOS-2 cells for four weeks. Osbone granules had very good results for the following parameters: osteoblast attachment, proliferation and osteogenic differentiation. In contrast, only a low osteoblast

attachment was found on BioOss granules at the earlier time points [2]. This is not surprising, since different sintering and production parameters of hydroxyapatite-based ceramic materials can affect physical properties such as solubility and probably also biological behaviour [18]. The in-vitro study concludes that the new hydroxyapatite product, Osbone, supports the adhesion, proliferation and osteogenic differentiation of SaOS-2 osteoblasts. The morphology and number of the cells and the expression of markers characteristic of bone growth such as alkaline phosphatase, osteonectin and osteopontin are comparable to those of the established β -TCP ceramic, Cerasorb M [2].

In a comparative study of different bone substitutes with different porosity and absorption kinetics, Osbone was studied over 18 months in sheep bones. During the entire course of the study, the material exhibited excellent osteoconductivity and biocompatibility in critical-size defects. The Osbone granules showed excellent bone-to-particle contact and very good bone integration and particle degradation; the ceramic particles were not completely resorbed after 18 months, but that is exactly what they were designed for, as they were developed for indications where increased mechanical stability is required. Nor



Fig. 5a Fractured ceramic implant at site 12.



Fig. 5b Immediate implant placement, maintenance of alveolar ridge height with healing post, vertical augmentation with a poly lactide membrane (SonicWeld, KLS Martin, Jacksonville, Florida, USA).



Fig. 5c Augmentation with Osborne granules, size 0.25–1 mm, and autologous bone.



Fig. 5d Collagen membrane, cut to size, above the augmented area.



Fig. 5e The suture is impervious to saliva.



Fig. 5f Provisional restoration in place (Maryland bridge).

Images 5a to f: Dr. H. Lerner, Baden-Baden, Germany

were there any inflammatory or local or systemic toxic reactions at any time during the tests [12].

In clinical application, the vestibular simultaneous augmentation with hydroxyapatite has proven useful in grade I and II jaw atrophy, since the material is not as quickly absorbed in the buccal area as for example beta-tricalcium phosphate. For larger defects of the alveolar process, however, a bone graft is still often considered, as the sole use of hydroxyapatite granules does not necessarily achieve primary stability in dental implants [10]. However, there has been

new research showing that graft resorption of 52.4 per cent must be expected half a year postoperatively after sinus floor elevation using autologous pelvic bone [3], an absorption rate not expected with hydroxyapatite. Looking at materials that are biological in origin, it would appear that another advantage of purely synthetic bone substitutes such as Osbone is that patients need not be informed of any potential risks and complications related to bone harvesting, tissue rejection, allergization, or residual infection, as would be the case if bovine materials were used [14].



Fig. 6a External sinus floor elevation according to Tatum, preparation of the mucosa of the maxillary sinus.



Fig. 6b Mixture of Osbone granules and autologous blood.



Fig. 6c Complete filling of the defect after introducing Osbone granules.

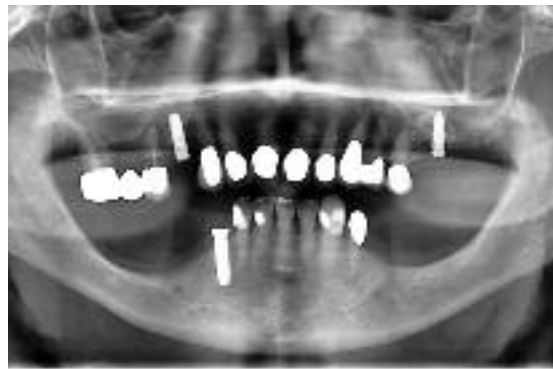


Fig. 6d Radiograph six months postoperatively, prior to re-entry and delivery. Good osseointegration of the implants, residual granules at site 26.

Images 6a to d: Dr. K. Pehrsson, Herne, Germany

This study showed excellent biocompatibility and osseointegration for Osbone. The use of additional autologous bone material was restricted to only 19 per cent of cases. The most frequent procedure was a sinus floor elevation. The postoperative administration of antibiotics in 69 per cent of cases corresponds to common practice. The very high level of patient compliance (96 per cent very good or good) certainly also contributed to the good healing results. The postoperative complications reported on the various follow-up occasions are not unusual and should not be regarded as product-specific. In three cases, a

loss of Osbone granules was described, but never any loss of a dental implant, confirming the stability of the healed ceramic material. But like other currently available osteoconductive materials based on hydroxyapatite and beta-tricalcium phosphate, Osbone has no osteoinductive activity. Although modifications have been made to bone substitutes in recent years that have given them bioactive surfaces to accelerate osseous integration and to expand the range of possible indications [17], they still do not come close to exhibiting the potency of autologous cancellous bone. Numerous attempts have therefore been made

Participants in this Osbone study

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to render the ceramic materials “more biological” as an alternative to use of autologous bone material. Autologous platelet-rich plasma (PRP) has been propagated as cost-effective and well tolerated. Clinical reports on their use in dental surgery have been published, for example, by *Anitua* [1], *Hoch* [5], *Intini* [9] and *Yilmaz* [19]. In the present study, too, PRP was used in 14 per cent of the cases. The use of RPR has special advantages in the early postoperative phase; it accelerates mucosal healing and reduces pain, minimizing the use of analgesics. One perceived benefit of faster wound closure is the reduced risk of infection of the wound or the augmentation material, increasing outcome predictability and improving the prognosis of the implants [8]. Another promising method could be the use of a platelet mediator concentrate (PMC; ATR, curasan). Recent clinical reports have described their use in the treatment of soft-tissue defects such as diabetic foot ulcers or in the treatment of problematic wounds or tendon injuries [16]. In the present study, PMC was used only on three patients; however, systematic studies in the realm of dental surgery are under preparation.

In summary it can be said that the new bone substitute, Osbone, is particularly well-suited for use in indications where increased mechanical stability is required, as it offers ideal structures for osseointegration accompanied by slow resorption kinetics and excellent biocompatibility. ■

Visit the web to find the list of references (www.teamwork-media.de). Follow the link “Literaturverzeichnis” in the left sidebar.

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