

Overview on

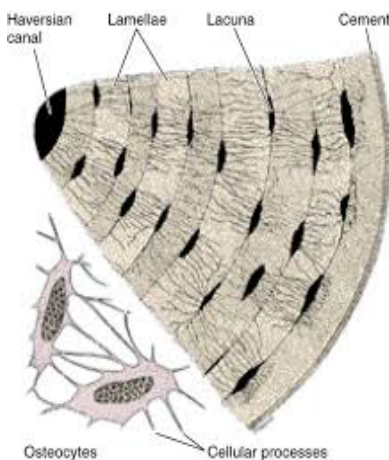
# Bone formation , Bone grafts materials , and Augma Biomaterials bone cements

## Bone modeling and remodeling | How does a bone form without augmentation?

### Bone Modeling | Initial formation of a bone

A necessary condition for a bone formation is the creation a blood clot at the area. The blood clot sets the infrastructure in which osteoblasts<sup>1</sup> (bone building cells) as well as growth factors (BMP's) will penetrate the area, causing a new blood vessels to form ("angiogenesis"). The extent of supporting bony walls increases the probability of an accelerated bone formation.

Osteoblasts secrete collagen (protein) which rapidly creates an immature bone matrix. The formed bone (osteoid) is a *woven bone* which is soft and unorganized. During the maturation process, the woven bone will transform into lamellar bone which is stronger and more solid. While the bone is formed, the bone matrix receives mainly calcium minerals in a process called *calcification*.



### Bone Remodeling |

During the life cycle of the bone, the bone is repetitively built and destroyed by the actions of osteoblasts (bone building cells) and osteoclasts (bone destroying cells). When the bone is formed, some of the osteoblasts creating the bone matrix are captured in it. These captured osteoblasts mature in their way to become *osteocytes*<sup>2</sup>

- Click [here](#) for an introduction to bone biology
- Click [here](#) to watch the bone remodeling process

### If the bone remodels, why using bone grafts?

Without bone grafts, the bone is formed on the primary blood clot functioning as a scaffold for the bone modeling process. Why, then, do we need to use bone grafts?

The answer lies within the space maintaining characteristics of the blood clot. As explained, the first stage is the formation of an immature *woven bone*, allowing the formation of a mature lamellar bone. However, since the blood clot resorbs fast and is considered as a

---

<sup>1</sup> *Stem cells* (primitive, undifferentiated cells) turn into osteoblasts (bone forming cells) which, in turn, accelerate the bone regeneration process by producing *osteoid*.

<sup>2</sup> Osteocytes - cells which are responsible for maintaining the bone's vitality.

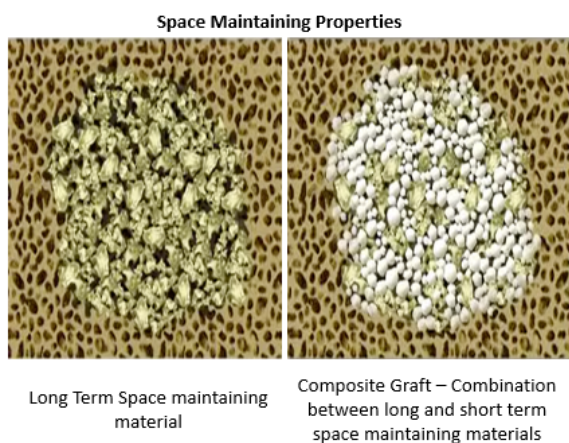
*short term space maintainer*, it is not sufficient in cases where the bone defect is large or lacks supporting bony walls.

Therefore, long term space maintaining bone substitutes create an extended scaffold enabling the bone formation and remodeling. Matching the bone substitute to the indication is crucial to achieve an optimal regeneration. If the bone graft resorbs slower than the remodeling process, it will remain instead of the vital bone. Alternatively, if the bone graft resorbs faster, it will resorb before a full regeneration is complete.

### Regeneration & Repair | 2 important terms to remember

- **Regeneration** – the body ability to rebuild a missing part completely is similar to the lizard ability to regenerate its tail. In cases of augmentation, ideal regeneration is achieved only in cases where the patient’s own bone is formed within the augmented area.
- **Repair** – when the defect area is rehabilitated by the interference of another substance such as a bone graft material (even with the combination of the patient’s bone). Obviously, only complete regeneration is considered as the ultimate rehabilitation.

Clinicians aspire to achieve bone regeneration by matching the space maintaining properties to the bone defect indications. However, due to the large diversity and complexity of bone defects, choosing the optimal bone graft is very challenging, and sometimes requires the clinician to mix between bone grafts (creating a *composite graft*) to achieve a higher rate of regeneration.



### Repair differences | caused by space maintaining properties

When a long term space maintaining bone graft is used, the bone formation is minimal because the bone forms only at the spaces between the granules of the bone substitute.

However, when a composite graft comprised of two different matrices with different resorption properties is used, it allows the short term space maintainer bone graft to resorb faster while the other long term space maintainer matrix preserves the 3 dimensional

space as well as the volume of the new formed bone during the healing process. The use of a composite graft encourages a better healing process, creates more vital bone and shortens the healing time.

In summary, bone substitutes resorb in a different pace. To achieve optimal results, clinicians pursue the best possible bone regeneration solution.

## **Bone substitutes background and Augma's products uniqueness**

As stated, complete regeneration of the bone (in terms of 3D volume maintenance, shape and bone quality) is the ideal augmentation result, for it enables clinicians to repair the defected area and rehabilitate it well.

Autogenous bone graft, which the clinician harvests from the patient's body, seems like the obvious solution. It is considered as the *Gold Standard* since it has many unique qualities needed for bone regeneration.

### **Autogenous bone graft qualities**

- Osteointegration – can heal and unite perfectly with the regenerative bone
- Osteoconduction – is used as a scaffold until the regeneration process is complete
- Osteoinduction – contains growth factors such as BMP,<sup>3</sup> which encourage primitive stem cells' selection to become osteoblasts<sup>4</sup>
- Osteogenesis – contains osteoblasts participating in the regeneration process.

Harvesting autogenous bone involves an additional surgical operation which is either internal or external to the oral cavity. The clinician can harvest the bone as a block or as granules (by grinding the bone), and implant it at the work area. In some cases, clinicians perform augmentation with bone remnants created from the implant drilling procedure.

### **Autogenous bone graft disadvantages**

Although autogenous bone graft is considered the gold standard, it also comes with significant shortcomings. First the harvesting is limited, and requires a high level of expertise and training. Second, even when the clinician is well trained, the necessary usage of a membrane to stabilize and set the bone (in a form of granules or block) in the area is costly and time consuming. Third, a surgical operation to harvest the bone increases the time needed for the whole operation and creates additional risks.

Moreover, an autogenous bone graft is not a “one-size-fits-all” solution. In large defects, or in indications where long term space maintainer is needed, an autogenous bone graft would resorb before the regeneration process is completed. In such cases, the clinician should combine the autogenous bone graft with other, long space maintaining bone graft which slowly resorbs. In other words, the clinician creates a composite graft to slow down the overall resorption.

In order to overcome the barriers of limited quantity and harvesting expertise, clinicians use many alternative/complementary bone graft materials stemming from different origins: allografts (cadaver), xenografts (animals) and alloplasts (synthetic). Unlike autogenous bone grafts, those substitutes do not require an additional surgical operation to harvest the bone, and are unlimited in quantity.

---

<sup>3</sup> Bone Morphogenetic Protein

<sup>4</sup> Bone regeneration cells

Bone substitutes also share similarities with autogenous bone grafts. They are osteoconductive, and come in the form of granules and putty, or blocks (contained in a driver or a vial). Consequently, a membrane is required to stabilize and set the material, a process which is both costly and time consuming.

Compared to autogenous bone grafts, bone substitutes (allograft, xenograft, alloplast) are only osteoconductive scaffold, and they lack growth factors that contribute to the bone growth process.

Bone substitutes also differ from each other. The quality and volume preservation of the created bone is determined by the resorbing quality, as well as the time it can function as a space maintaining material. In many cases, clinicians choose to create a composite graft combining autogenous bone grafts and other bone substitute material to improve the end result.

In conclusion, the disadvantages in using the current bone substitutes are apparent in aspects of **handling, cost and most importantly – the end result**. Autogenous bone graft augmentation is complicated, more risky and limited in quantity, while augmentation with other bone substitutes is deficient in aspects of full regeneration and bone quality.

#### **Augma Biomaterials – Better Handling, Better Results, reduced costs**

Augma Biomaterials is a bone substitute company focusing in the development and manufacturing of alloplasts for the dental field. Augma's products are comprised of existing natural minerals which lead to improved performance in terms of handling and end result, along with the economic benefit of reduced costs.

With years of experience and a profound understanding of augmentation procedures, Augma's R&D is focused on providing better solutions for the complexities and hardships accompanying augmentation procedures.

#### **Augma's Vision and Credo**

Rather than reproducing similar materials on the market with a "me-too-but-better" strategy, Augma's "Credo" is to renovate the concept of bone substitutes, so it could revolutionize augmentation with innovative technology. With the development of unique cements, Augma is able to achieve a breakthrough in the field of maxillofacial augmentation, without experiencing many bone substitute's trade-offs:

- **Better Handling** – a user-friendly material with easy implementation leading to faster and better augmentation procedures.
- **Improved regeneration** – improved healing, with more vital bone to the patient
- **Cost effective** – Using Augma's products, clinicians can perform most augmentation procedures without the use of a membrane

## **Why cements?**

<https://www.youtube.com/watch?v=UeKlpXL6WQ0&t=30s>

Working with cements allows clinicians to inject the bone graft material directly at the working site. At this stage, the clinician can shape the cement and watch it quickly set. The

quick stabilization of the cement dismisses the need to stabilize granules and prevent their movement, as normally happens with many bone substitute products on the market. As well, this reduces need for membrane coverage in most of the clinical cases.

There are, though, several bone substitute products with a putty texture due to their chemical compound, and therefore are shapeable and easier to handle. However, such putty-like bone substitutes are unlikely to set and stabilize at the work area, and thus require a membrane to complete the augmentation procedure.

### **Augma's development of calcium sulfate – Renovating augmentation with 120 years old material**

The search and development for Augma's ultimate bone substitute began as a start-up 15 years before Augma was founded.

The wide and frequent usage in the orthopedic field triggered Augma's developers to seek the hidden potential in cements, and adjust it to maxillofacial augmentation field. Between 1982-1993 calcium-phosphate based cements entered the orthopedic field, and gained massive popularity. In fact, in less than 35 years calcium phosphate products have replaced almost entirely the orthodox usage in orthopedic bone grafting.

Nevertheless, the different characteristics of dental augmentation procedures requirements compared to orthopedic procedures, prevented the entrance of the calcium phosphate. Knowing the benefits of cement-based materials, Augma's developers sought an answer in the academic literature. The review presented 2 possible cements for augmentation: calcium phosphate and calcium sulfate. Since calcium phosphate was already dismissed as a viable solution, Augma's developers performed a further examination of calcium sulfate in regard to whether it could fit for dental augmentation.

Here are some interesting facts about calcium sulfate: it has been used for augmentation procedures since 1892. It was widely used in many medical fields such as oncology, maxillofacial, plastics, orthopedics etc. Researchers have conducted and wrote thousands of articles and scientific material regarding this ancient material, and it is considered the oldest bone graft material<sup>5</sup>

And yet, the establishment of calcium sulfate is not correlated with its success. Why is calcium sulfate not popular among dentists performing augmentation procedures? And more importantly, how, despite its limitations, did calcium sulfate exist 120 years with countless efforts to revive it?

Answering both questions required thorough analysis of academic calcium-sulfate articles. The analysis provided an important insight: Clinicians perceive it as an ambivalent material. On the one hand, calcium sulfate is encouraging complete bone regeneration, since it

---

<sup>5</sup> Excluding, of course autogenous bone graft.

resorbs at the exact pace needed for an ideal bone regeneration (similar to the “Gold Standard” - autogenous bone graft). On the other hand it had 2 major disadvantages:

1. **Absolute disadvantage: Inability to set in a presence of blood and saliva** – it takes at least 20 minutes for calcium sulfate to set in general and approximately 10X more in the presence of blood, protein and saliva. In maxillofacial augmentation the presence of blood and saliva is inevitable, and poses major difficulties for a wide adoption of calcium sulfate. Overcoming the difficulties demanded the clinician to carefully dry the work area, put layers of calcium sulfate slowly one above the other, and wait for each one to dry and set at least partially. As described, this long, non-practical procedure explains why clinicians felt reluctant to use calcium sulfate. Efforts to accelerate the setting time by cement-based companies still did not turn calcium sulfate into a desired material since it failed to react optimally in the presence of blood and saliva.
  - a. **Pre-setting creates good regeneration but unsatisfied handling** – calcium sulfate’s regenerative qualities encouraged bone substitute companies to set it before (already at the manufacturing process), grind it to granules and sell it similarly to other bone substitute materials. Indeed, this form of calcium sulfate functioned better in the presence of blood and saliva, and could completely resorb, allowing an improved bone regeneration. The tradeoff, however, was losing the cement handling characteristics. Calcium sulfate became similar to other bone substitutes materials, and as such it required stabilization and the usage of a membrane.
2. **Relative Disadvantage: Short term space maintainer** – since calcium sulfate functions as a *short term space maintainer*, it is mostly used in small, 10mm wide or less defects with a support of at least 3 bony walls. In other cases, calcium sulfate is useful only as a composite graft (combined with other, long term space maintaining material) and useless by itself in many indications of larger defects.

In Summary, despite its clear advantages, 2 major disadvantages prevented calcium sulfate from being widely used among clinicians:

1. **Absolute disadvantage** – inability to set in a presence of blood and saliva
2. **Relative disadvantage** – short term space maintaining material which resorbs fast, and is not efficient by itself in larger defects.

For years Augma's developers tried to turn calcium sulfate into the ultimate cement, by maintaining the handling advantages along with the desired ability to set in the presence of blood and saliva. Regarding the relative disadvantage, Augma’s developers seized the opportunity to create designated protocols making calcium-sulfate the ultimate bone graft material for the large diversity of indications.

Eventually, 15 years of development have led Augma’s developers to achieve a breakthrough: The creation of **Biphasic Calcium Sulfate** - A material which maintains all of calcium sulfate’s advantages, without modifying its chemical structure and without adding materials which change its qualities.

## What is Calcium Sulfate, and how is it different from existing products?

The understanding of biphasic calcium sulfate requires some basic background knowledge on calcium sulfate's chemical structure.

### Calcium Sulfate - History

The use of calcium sulfate began thousands of years ago, and is widely used in various industries. In construction, it is used as a material to build and design models. In CPG, companies use it as a beer and flour supplement. In medicine, doctors use it to set fractured bones, and in dentistry clinicians and technicians use it to create models to work with, as well as to perform augmentation procedures. Obviously, augmentation procedures with calcium sulfate compel the highest level of purity under the medical grade standards.

### Calcium Sulfate phases

Calcium sulfate has 3 phases describing the level of water connection ( $H_2O$ ) to the calcium sulfate molecules ( $CaSO_4$ ).

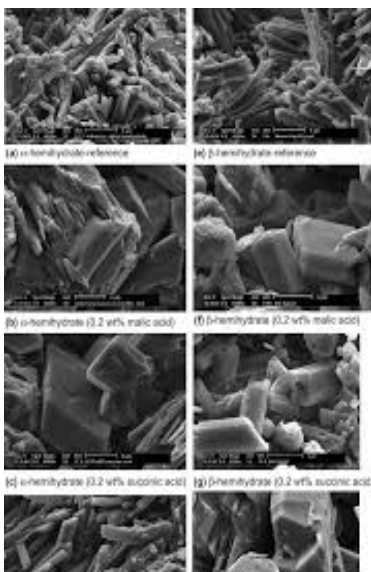
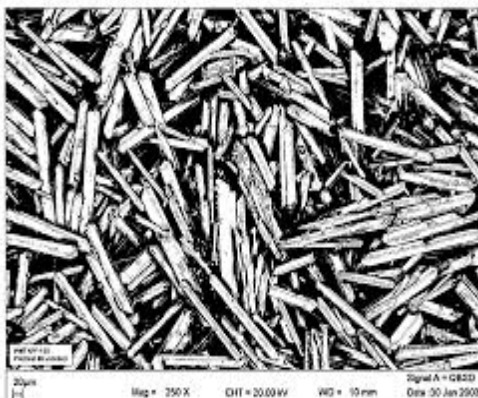


Figure 1

- Calcium Sulfate Dehydrate (CSD) -  $CaSO_4 \cdot 2H_2O$
- Calcium Sulfate Hemihydrate (CSH) -  $CaSO_4 \cdot \frac{1}{2}H_2O$
- Calcium Sulfate Anhydride (CSA) -  $CaSO_4$  Anhydride

There are 2 types of Calcium Sulfate Hemihydrate, which are defined by the crystal structures created during their setting:

- Alpha-hemihydrate – a stiff material with cube-like crystal structure
- Beta-hemihydrate – A softer material compared to alpha-hemihydrate with a needle-like crystal structure



Structure of  $\beta$ -hemihydrate

## Calcium Sulfate Production

Calcium sulfate is produced by deep mineral mining or by synthetic processing. Naturally, calcium sulfate comes in the form of **Calcium Sulfate Dehydrate ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ )**. It is relatively soft due to its pre-crystallized condition.

CSD transforms into a **Calcium Sulfate Hemihydrate ( $\text{CaSO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ )** after few hours in the oven in  $150^\circ\text{C}$ . in a process called calcination. The process of heating is causing  **$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$**  to lose water molecules from the calcium sulfate dehydrate molecules in a ratio of 1.5:1.

CSH is the familiar “plaster of Paris”. By mixing CSH with water, the material can be shaped and poured, and set in 20 minutes. Mixing the powder with water creates a crystallization reaction, so that CSH material is set by the creation of many crystals and turn into CSD.

The water process bonds each calcium sulfate molecules with 2 water molecules, but unlike the soft, unstable CSD, the mixed material is solid and stabilized. This process of crystallization setting provokes an exothermic reaction.

(*Exothermic reaction* is the professional term describing the simultaneous process of crystallized reaction while adding water to CSH, a process causing a reaction of heat emission)

If, during the calcination process the CSD is heated by more than  $180^\circ\text{C}$ , the water molecules will disappear, and CSD will turn into *Anhydride calcium sulfate* ( **$\text{CaSO}_4$  Anhydride**).

CSA is not in use to perform augmentation procedures.

### CSH Vs. CSD – great handling (moldability) vs. The preset particles with controlled degradation

The given calcium sulfate background points out CSH and CSD characteristics:

On the one hand, CSH functions well as a cement. It is shapeable, adheres to the defect area and can be stabilized. And yet, the setting of CSH presumes a dry oral cavity environment. By using CSH as a bone graft material, the clinician should face major difficulties in setting the material due to the presence of blood and saliva, making CSH difficult to control and unstable material.

On the other hand, CSD in the form of previously set granules (at the manufacturing process) are less affected by the presence of blood and saliva, but from the handling point of

view it lacks relative advantages compared to other bone grafts requiring the use of a membrane, and prevention of the granules movements in the working zone .

## **Biphasic Calcium Sulfate provides a solid solution**

Biphasic calcium sulfate comprised of a granulated powder in a unique controlled particle size distribution containing both CSD and CSH within its structure.

The combination of the 2 phases is a process of almost entire crystallization, in a stage when there are still CSH particles enabling a preservation of the cement properties.

The biphasic calcium sulfate development is an ideal solution. It can be moldable and stabilized, and can be set instantly despite the presence of blood and saliva.

Since its discovery, biphasic calcium sulfate is the only effective cement material suitable for dental augmentation procedures.

## **Augma's products –3Dbond™ & Bond Apatite®/("BondBone®") ("4matrix™")**

### **3DBond™/Bond Bone®**

In 2011, Augma launched BondBone as its first commercial product and distributed it under a private label for MIS implants Technologies, one of the leading implant companies worldwide. BondBone is sold with a unique driver and is marketed directly as well by Augma logo's under another brand name – 3DBond

3DBond contains pure biphasic calcium sulfate. To activate the product, clinicians need to mix it with saline (a physiological solution). It is commonly used by itself in specific indications, or as a composite graft with other materials.

- **3DBond by itself** - since calcium sulfate is considered a short term space maintainer the use of 3DBone is limited to small defects with supporting bony walls. 3DBond is the ultimate solution for socket grafting procedures, such as socket preservation (an augmentation procedure meant to reduce bone loss due to tooth extraction) and is indicated for incisors, canine, and premolars teeth, as well as molars where the central wall (septum) between the alveolar cavities of the extracted teeth still exists.

Hands-on video 3DBond used by itself

<https://www.youtube.com/watch?v=WZuftw62emE>

- **3DBond as a composite graft** – can be used also in larger defects, when a longer space maintaining is required and a slower resorbing material is needed. Such cases 3DBond should be combined with any long term space maintainer bone graft. It enables better handling, and better end results since the composite graft has cement properties,

allowing convenient handling and setting properties of the bone graft. Moreover, a composite graft combining 3DBond enables a complete degradation of the biphasic calcium sulfate matrix and is simultaneously replaced by the patient's own bone. While the 3 dimensional volume is kept by the slow degradable material mixed within the composite graft so it encourages the creation of angiogenesis<sup>6</sup> and a more vital bone formation at the defect area.

Hands-on video 3DBond used in a mixture of a composite graft

<https://www.youtube.com/watch?v=sd9Jt9lQOfM>

## Bond Apatite®

**Bond Apatite®** (manufacture under private label for MIS company in its brand name 4Matrix™) is a composite graft comprised of biphasic calcium sulfate and hydroxyapatite granules. The combination between the fast resorbed biphasic calcium sulfate, and the slowly resorbed Hydroxyapatite enables the clinician to use Bond Apatite in many indications. Bond Apatite is simple to use and very easy to handle. It saves clinicians time and allows them to avoid or overcome complexities in the preparation of a composite graft. In addition, Augma invented a unique and revolutionary patented all-in-one driver containing the saline and the powder, so that clinicians can avoid human errors and activate the material in one press.

Bond Apatite reduces the stages needed for augmentation procedures down to less than a minute for graft placement and stabilization manipulation. A clinician using Bond Apatite after preparing the augmentation area, simply needs to inject Bond Apatite into the defect site, press the material with a dry gauze for 3 seconds and the material will immediately set, and soft tissue closure can be proceeded directly above the graft. 3 months is the average time until regeneration is completed.

A video is worth a thousand words :

<https://www.youtube.com/watch?v=59ZGSnQNnvg>

---

<sup>6</sup> Angiogenesis - physiological process through which new blood vessels formation form from pre-existing vessels

