New Developments in Vertebroplasty Materials

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Nuevos desarrollos en materiales para vertebroplastia

Nous desenvolupaments en materials per vertebroplàstia

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SUMMARY

Increasing life expectancy is leading to an increase in age-related diseases, like osteoporosis, which often involve the breakdown of bone. One of the main problems related with such disease is the formation of vertebral compression fractures (VCF). The impact of the vertebral compression fractures that have been described is diverse, such as distortion in the spine (kyphosis), chronic back pain, reduced physical function with risk of immobility, decline of lung function, gastroesophageal reflux and change in appearance that may led to social isolation, loss of self-esteem and depression. Vertebral fracture is just the beginning of the constant deterioration of the health of the affected patients.

Until now, the treatments applied in this type of fracture are mainly three: conservative medical treatment, invasive surgical intervention, and vertebroplasty and kyphoplasty. These last two techniques, minimally invasive, have shown interesting results though there is still room for improvement, especially due to the lack of an ideal bone cement material. In this review, we will focus on the recent developments in vertebroplasty, their pros and cons and the needs for further achievements. We therefore begin with a brief description of vertebroplasty followed with a description of the biomechanical and the osteoregeneration needs that materials should fulfill to be useful in this application. Finally, we describe the recent materials developments for vertebroplasty and the different proposals for improvement.

Keywords: Vertebroplasty; bone cement; nanostructured materials

RESUMEN

El aumento de la esperanza de vida está llevando a un aumento de las enfermedades relacionadas con la edad, como la osteoporosis, que a menudo implica la descomposición de los huesos. Uno de los principales problemas relacionados con dicha enfermedad es la formación de fracturas vertebrales por compresión (FVC). El impacto de las fracturas de compresión vertebral que se han descrito es diverso, como distorsión en la columna vertebral (cifosis), dolor de espalda crónico, función física reducida con riesgo de inmovilidad, disminución de la función pulmonar, reflujo gastroesofágico y cambio en la apariencia que puede conducir al aislamiento social, la pérdida de la autoestima y la depresión. La fractura vertebral es solo el comienzo del deterioro constante de la salud de los pacientes afectados.

Hasta ahora, los tratamientos aplicados en este tipo de fracturas son principalmente tres: tratamiento médico conservador, intervención quirúrgica invasiva y vertebroplastia y cifoplastia. Estas dos últimas técnicas, mínimamente invasivas, han mostrado resultados interesantes, aunque todavía hay margen de mejora, especialmente debido a la falta de un material de cemento óseo ideal. En este review, nos enfocaremos en los desarrollos recientes en la vertebroplastia, sus pros y contras y las necesidades de nuevos logros. Por lo tanto, comenzamos con una breve descripción de la vertebroplastia seguida de una descripción de las necesidades biomecánicas y de osteorregeneración que los materiales deben cumplir para ser útiles en esta aplicación. Finalmente, describimos los desarrollos recientes de materiales para la vertebroplastia y las diferentes propuestas de mejora.

Palabras clave: Vertebroplastia; cemento óseo; materiales nanoestructurados.

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RESUM

L'augment de l'esperança de vida està donant lloc a un augment de les malalties relacionades amb l'edat, com l'osteoporosi, que sovint implica la ruptura de l'os. Un dels principals problemes relacionats amb aquesta malaltia és la formació de fractures de compressió vertebral (FCV). L'impacte de les fractures de compressió vertebral que s'han descrit és divers, com la distorsió a la columna vertebral (cífosi), el mal d'esquena crònic, la reducció de la funció física amb risc d'immobilitat, disminució de la funció pulmonar, reflux gastroesofàgic i canvi d'aparença que pot conduir a l'aïllament social, la pèrdua de l'autoestima i la depressió. La fractura vertebral és només el principi del deteriorament constant de la salut dels pacients afectats.

Fins ara, els tractaments aplicats en aquest tipus de fractura són principalment tres: tractament mèdic conservador, intervenció quirúrgica invasiva i vertebroplàstia i cifoplàstia. Aquestes dues últimes tècniques, mínimament invasives, han mostrat resultats interessants, encara que hi ha marge de millora, especialment a causa de la manca d'un material ciment ossi ideal. En aquesta review, ens centrarem en els recents desenvolupaments de la vertebroplàstia, els seus pros i contres i les necessitats de nous assoliments. Per tant, comencem amb una breu descripció de la vertebroplàstia seguida d'una descripció de les necessitats biomecàniques i d'osteoregeneració que els materials haurien de complir per ser útils en aquesta aplicació. Finalment, es descriuen els recents desenvolupaments de materials per a la vertebroplàstia i les diferents propostes de millora.

Paraules clau: Vertebroplàstia; ciment ossi; materials nanoestructurats.

INTRODUCTION

Osteoporosis is a systemic disorder that compromises bone strength and predisposes patients to an increased risk of fractures. It is reported in the literature that osteoporosis is the disease that produces most bone compression fractures[1]. Moreover, it is a difficult disease to diagnose in the early stages. In fact, it is even difficult to specify exactly when the fracture began, and for this reason osteoporosis is often named the "silent" disease, because vertebral fractures may also go unnoticed[2]. Recently, a study stated that less than a third of the vertebral fractures cause enough symptoms to be diagnosed and addressed immediately by a doctor (clinical vertebral fractures). Thus, two thirds of them only cause minor pain, which results in a late diagnosis (subclinical vertebral fractures). This is a key point because a fracture of this type has very severe and durable consequences over time. So, it is important to treat the vertebral compression fractures as soon as they appear, both safely and effectively, to avoid negative short- and long-term consequences for the patient[3].

The impact of the vertebral compression fractures that have been described is diverse, such as distortion in the spine (kyphosis), chronic back pain, reduced physical function with risk of immobility, decline of lung function, gastroesophageal reflux and change in appearance that may lead to which contributes to social isolation, loss of self-esteem and depressionVertebral fracture is just the beginning of the constant deterioration of the health of the affected patients[4,5].

The treatments applied in this type of fractures are mainly three: conservative medical treatment, invasive surgical intervention and vertebroplasty and kyphoplasty.

On the one hand, conservative medical treatment is based on the ingestion of drugs and includes a short period of bed rest followed by gradual mobilization with external orthoses and a hyperextension brace. These braces are usually beneficial for the first few months, until the pain is reduced. Only young patients are able to tolerate braces, because elderly patients suffer from stronger pain and tend to require more bed rest. However, immobility predisposes patients to venous thrombosis and life-threatening complications such as pulmonary embolism. It can also lead to pressure ulcers, pulmonary complications, urinary tract infections, and progressive deconditioning. In addition, it has been reported that bone mineral density decreases from 0.25% to 1.00% per week in patients who are on bed rest[6].

On the other hand, surgical intervention is advised when conservative therapy fails with those patients who suffer from hopeless back pain or a severe spinal deformity. However, twenty years ago, doctors observed that highly invasive operations succeeded in some cases but for most patients, the pain and reduced mobility persisted forever. Procedures consisted of stabilizing the vertebra by inserting screws, plates, cages, and rods. These procedures were challenging because it was difficult to achieve an adequate fixation in the osteoporotic bone[7]. Also, invasive surgical interventions are less attractive, especially in elderly patients, due to the increase of risks like allergy to anesthesia and low bone density that involves future fractures and invasiveness[8].

Vertebroplasty and kyphoplasty, minimally invasive techniques with encouraging results in the treatment, have emerged as an interesting alternative for the treatment of vertebral compression fractures (VCFs) with the potential to overcome the problems related with other described treatments. They have shown interesting results but there is still room for improvement, especially due to the lack of an ideal bone cement material. In this review, we will focus on the recent developments in vertebroplasty, their pros and cons and the needs for further achievements. We therefore begin with a brief description of vertebroplasty followed with a description of the biomechanical and the osteoregeneration needs that materials should fulfill to be useful in this application. Finally, we describe the recent materials developments for vertebroplasty and the different proposals for improvement.

Vertebroplasty

As it has been stated, vertebral compression fractures (VCFs) constitute a serious health problem in the world, not only because of their high incidence but also due to their direct and indirect negative consequences on the patient's health-related quality of life and the costs to the health care system[9].

For dealing with this type of fractures, the classical open surgery with decompression and stabilization of the fractured vertebra with different kinds of metal implants often fails because of the poor quality of osteoporotic bone. Also, because of the risk of open surgery in elderly patients, these procedures have generally been limited to cases where there is concurrent spinal instability, or neurological deficit[10].

Minimal invasive spinal surgery techniques have evolved in the past two decades as an alternative to open surgery with decompression. Briefly, acute painful vertebral compression fractures have been targeted for treatment through percutaneous procedures termed vertebroplasty (VP) or balloon kyphoplasty (BK)[11]. Vertebroplasty is a percutaneous injection of bone cement directly into the fractured vertebral body. In this way, the vertebra is welded to prevent fracture progress and augment the weakened vertebral body. Thus, the bone cement can stabilize and restore it to as much of its normal height and functional state as possible[12-14]. Kyphoplasty is similar to vertebroplasty because it is a minimally invasive surgical procedure and uses bone cement to increase and stabilize the vertebrae. However, in kyphoplasty, an orthopedic balloon is inserted into the damaged vertebra to restore its structure before injecting the bone cement[15].

These minimally invasive percutaneous procedures entail placing large spinal needles into the fractured vertebral body through a channel made in the pedicle and injecting cement under radiologic control into a fractured vertebral body. These techniques have shown that they strengthen the bone and reduce the intense pain caused by VCFs, and for now they are a good alternative. In fact, the large number of orthopedic procedures performed each year has led to great interest in injectable cements for regeneration of bone[16].

A variety of cements have been developed for these applications, including ceramics, naturally derived substances and synthetic polymers. These materials demonstrate overall biocompatibility and appropriate mechanical properties, as well as promote tissue formation, thus providing an important step towards minimally invasive orthopedic procedures[17,18]. However, they also carry many difficulties like necrosis, injected cement leakage, inflammation, fracture of adjacent vertebrae and many others[19]. These materials will be described later in this review

Biomechanical properties: Assessment and desired properties

For the design of a material for vertebroplasty, the assessment of the product in biomedical implants and devices is necessary to measure and evaluate if the needs that demand the treatment are being covered.

Most used materials for these surgeries are biodegradable. Other general characteristic of such materials is that they can be easily injected into the vertebral body through a specific needle for spinal surgery, and then they completely set inside the vertebral body[20]. With this approach, a significant pain relief is achieved through the mechanical stabilization of the vertebra[21].

In can be said that a second operation to remove the implant is not necessary because it biodegrades over time and the charge transfer occurs in a progressive way. This is an advantage for the patient and reduces the operating cost of treating injuries. Moreover, the biodegradation is interesting from a mechanical point of view. An injured connective tissue such as in a fractured bone needs the protection of the surgical implant to allow restoration. During the healing process, the implant reduces progressively its protective function and transfers gradually more load to the tissue, stimulating a faster healing and accelerating the process of remodeling.

This two phenomena can be seen in figure 1. On the one hand, the degradation of the implant, which gradually loses its function, and on the other, the increase of the strength of the tissue during the healing process.

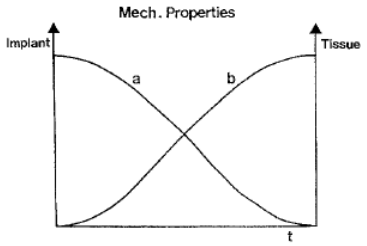

Figure 1. *Optimal degradation characteristic of an implant for tissue protection (a) and improvement of tissue strength during the healing process (b) according to*[22].

Initially, the fractured bone has no strength and the material carries the entire load. Therefore, the implant must have the highest mechanical properties at that time. As the healing process progresses, the material reduces its stiffness as part of the load is supported by the regenerated tissue. Moreover, this reduction in rigidity allows a better load transfection to the bone. When bone healing is over, the material loses its mechanical function. In this sense, it is important to underline that the most important limiting factors for the application of biodegradable implants are their mechanical properties. Additionally, the mechanical properties are also very important for bone cements in vertebroplasty because their use affects the stiffness in vertebral body and the load transfer in adjacent vertebra[23, 24].

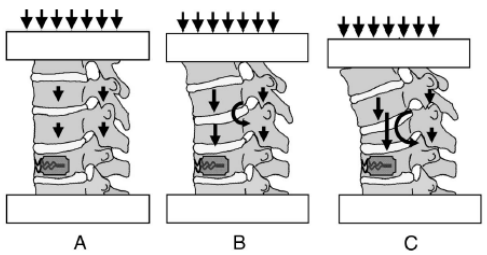

Figure 2. *Load transfer in adjacent vertebra according to*[25].

These two factors may lead to an adjacent vertebral failure (AVF) which is a frequently observed post-surgery complication of percutaneous vertebroplasty. Clinical studies showed that 12% to 24% of patients suffered subsequent fractures post vertebroplasty within 1 year. Also, 41% to 67% of the subsequent fractures occurred in the adjacent vertebra of the treated (augmented) vertebra. The fracture rate of adjacent vertebra is 3 times higher than in the non-adjacent vertebra[25].

Therefore, it is essential to consider the mechanical properties of vertebral trabecular bone (elastic modulus), where the injected cement is inserted (which varies from 109 to 327 MPa in the area)[26]. This would be the target elastic modulus of any bone cement intended to be used in verterbroplasty.

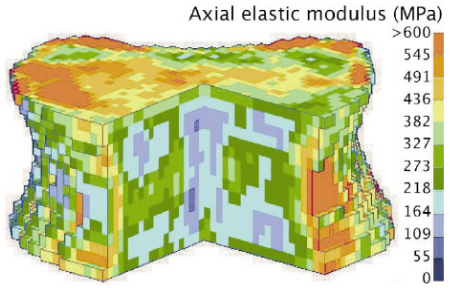

Figure 3. *Distribution of axial elastic modulus within a lumbar (L1) vertebral body according to*[27].

Another problem associated with the mechanical properties of the implant is injectability. Bone cement must be injectable because it is an essential property in minimally invasive clinical applications as described below.

However, bone cements may show different problems when they are injected. For instance, most of the materials already described in the paper suffer a phenomenon named liquid-phase migration. This effect, produced due to the poor stability of the injectable formulation, leads to an excess of liquid (mainly water) in the injected cement. The phenomenos is clearly related with the pressure needed for the injection. Even though the forces required for injecting the material are very reasonable and the cement can be manually applied by doctors, a filter-pressing phenomenon can occur leading to a dramatical increase of the injection force needed, which complicates manual injection. To solve this problem, an increase in the ratio liquid/particles has been proposed in the final formulations. However, this approach has shown a dcrease of the mechanical properties of the final cement due to the formation of highly porous cements, mechanically weak[28-29]. Another feature related with the filter-pressing problem is time dependence. Although high injection speed reduces the liquid migration and improves the cement homogeneity, the reduction of observation time during the minimally invasive medical intervention, increases the patient risk[28].

Two other solutions have been proposed to overcome the filter-pressing problem: to increase the viscosity of the liquid mixture and to reduce the permeability of the particles. With these solutions, the capability of the liquid mixture to pass through particles is reduced, so the filter-pressing problem. Nevertheless, 100% injectability is not reached. This implies that filter-pressing occurs, as stated, even at very small forces[29].

Other factors influencing the filter-pressing problem are the syringe gauge (the smaller, the less filter pressing), and the use of a cannula (cannula increases filter-pressing).

Another important characteristic that materials used in vertebroplasty must have is easiness-of-handling. This property is key for any biomaterial intended for clinical use. Cements should be easily prepared at the operating theatre to facilitate surgery[18]. Therefore, viscous properties must be balanced between two needs: the need of the material to remain at the site of injection to prevent leakage of bone cement and the need of the surgeon to easily manipulate its placement to fill successfully the gap created by the fracture[30]. It is necessary to complete the last need before the hardening process begins, while avoiding the risk of extravasation[24]. Obviously, the working (which includes mixing and injection) and setting times should be compatible with the surgical procedure, to ensure a slot in which the cement is still injectable and a rapid hardening when the cement is in situ. In this sense, it is worth to indicate that vertebral cement must be completely set at the end of the surgical procedure, to allow the immediate mobilization of the patient after the treatment. Also, if the setting reaction involves a temperature change, the increase or decrease should be as small as possible to reduce damage to the surrounding tissues[31-32].

Finally, biocompatibility is also an obvious imperative characteristic of any new material and it should be delivered with an appropriate host response in its specific application. This means that the material must not provoke an unresolved inflammatory response or show extreme immunogenicity or cytotoxicity. These characteristics must be accomplished for the intact material, for the degradation products and for any of its unreacted components[33-36].

Osteoconductivity and bone apposition

Another point that must be taken into account when a material is designed for VCF treatment is the capability to induce bone regeneration. Although bone is a tissue with a great capacity to regenerate bone defects generated by a fracture, when the fracture is caused by several traumas like bone cancer or osteoporosis, it is then difficult to regenerate it or heal it spontaneously.

In this sense, regeneration would be faster if biomaterials used in vertebroplasty were able to regulate and direct cell behavior and function[37-38]. Among all the studies carried out to study the osteoconductivity of bone cements, only a few of them have shown efficacy in vivo[39].

It is important to mention that blood-biomaterial interactions take place just after the implantation

of the biomaterial, with the formation of the provisional matrix in the bone and the development of granulation tissue and a fibrous capsule. These interactions can lead to inflammation and foreign body reaction[40]. Moreover, during this process several proteins are generated, which modulates the healing process and the foreign body reaction[41].

One of the cellular responses to the implantation of biomaterials is chronic inflammation. This type of inflammation is recognized by the presence of mononuclear cells such as lymphocytes and plasma cells. This inflammation is usually confined to the implant zone[40].

Another type of chronic inflammation is detected by the presence of monocytes, macrophages and/or foreign body giant cells (FBGC), which are present at the tissue-biomaterial interface. This type of inflammation is identified by the formation of new granulation tissue which is recognized by macrophages. Often, the granulation tissue is separated from the biomaterial by cellular components of the foreign body reaction, resulting in several layers of monocytes, macrophages or FBGC. FBGC are much more effective reacting against the implant than individual macrophages and therefore the material degrades much more efficiently[41].

After surgery, the number of macrophages normally peaks in about a week; however, they may persist at the site of the injury for months. Their presence is critical for tissue repair and regeneration. Also, the inflammatory response can be significantly enhanced by the foreign body reaction induced. Device interactions with other tissues lead to protein deposition in the biomaterial forming a provisional matrix which affects subsequent interactions. The chemistry and topography of the implant surface may be primarily responsible for the intensity of the reactions caused by the infiltration of immune cells[42]. In addition, the cell-derived matrix can contain biological impurities or allogeneic signals resulting in an increased inflammation at the implant site[43].

Another point that needs to be considered is the process that occurs in bone remodeling. This process is carried out by two types of cells: osteoblasts and osteoclasts. Osteoblasts are responsible for synthesizing the calcified bone matrix by deposition and are in charge of the maintenance, growing and reparation of the bone. In addition, they form a cellular layer at sites of bone formation. Osteoclasts are responsible for the degradation and absorption of the bone. Both osteoblasts and osteoclasts are involved in the natural remodeling of the bone[44-45]. In this bone repair process, where there is a lot of damaged tissue that needs to be regenerated, enhancing bone degradation and absorption (osteoclasts) is not desired. Therefore, the injected product in the vertebra should specially enhance the activity of osteoblasts.

A final goal is to enhance the activity of osteoblasts to differentiate them until they become osteocytes on the bone surface. When they are surrounded by extracellular matrix materials, they become osteocytes. These cells are unable to divide and they have the ability to segregate or resorb bone matrix that surrounds them. In fact, these cells are like trapped in their own secretion substance. In spite of the distance between osteocytes because of the extracellular matrix, they remain in contact through small channels, which are along the bone. Osteocytes communication is important to control the amount of formed and deteriorated bone[46].

Osteoblastic differentiation from human bone marrow stromal cells (hBMSC) is also an important step of bone formation and regeneration. The maturation of hBMSCs into osteoblasts is essential in bone growth, fracture healing and the osseointegration of bone-anchored implants, as well as the general bone turnover process, governed by the interactions between osteocytes, osteoblasts and osteoclasts.

The differentiation process towards osteoblasts is regulated by a number of key factors and signaling pathways. Some of the factors involved are commonly used as markers[47]. These markers are very important to evaluate if the bone cement can regenerate the fractured vertebrae.

One of the most important markers is the effector protein alkaline phosphatase (ALP), which is responsible for the mineralization of the extracellular matrix (ECM). In fact, the use of ALP enzyme activity assays is the most common to follow the mineralization process because if a bone cement regenerates the fractured bone, then it is also able to differentiate the hBMSCs until they mineralize[47].

The main organic component of ECM is collagen type I. There are also two non-collagenous bone ECM proteins, osteopontin (OPN) and osteocalcin (OCN). They are commonly used as early and late markers of osteogenic differentiation, respectively. On the one hand, OPN is implicated in bone formation and remodeling. On the other, OCN is expressed at later stages of osteoblast differentiation, indicating a mature osteoblast phenotype[48]. Therefore, osteopontin and osteocalcin are two adequate differentiation markers to evaluate the ability of the cement to promote bone differentiation.

In the process of bone remodeling, transcriptional factors play an essential role too[49]. Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) family that play crucial roles in osteogenesis. BMPs play an essential role in the commitment and differentiation of osteoblastic lineage cells. BMP-2, a prototype of BMPs, promotes osteoblast maturation by increasing the expression of the transcription factor Runx2 and the expression of osteoblast marker genes [49-50]. Therefore, BMP-2 can be an adequate positive control respect to the studied bone cement to observe the increase in maturation of the stem cells hBMSCs.

To get a more general idea of the complete mechanism of coupling between bone resorption and formation, and the transcriptional factors involved a scheme is displayed in figure 4:

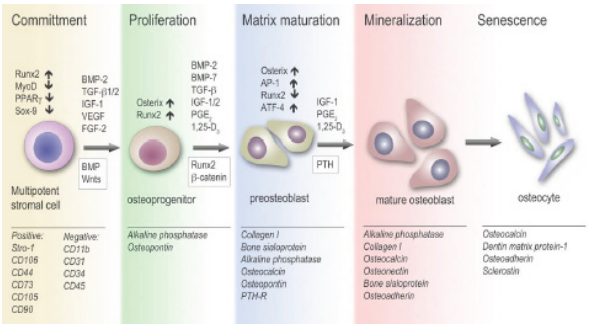

Figure 4. *Transcriptional factors involved in osteoblasts differentiation and corresponding cell markers expressed at different stages. (Up arrow is activation, down arrow is inhibition) according to*[51].

Growth factors (GFs) are expressed during different phases of tissue healing and are key elements in promoting tissue regeneration. In fact, GFs loaded orthopedic devices have been reported to enhance osteoblastic activity and implant integration. Therefore, it is important to consider adding them in the bone cement to promote bone healing.

Obtaining specific growth factors can be very expensive. An easier and inexpensive alternative to have growth factors in physiologic proportions to stimulate the regenerative process is through platelet-rich plasma (PRP)[52].

Platelet-rich plasma (PRP) is a new approach to tissue regeneration and is becoming a valuable complement to promote healing in many procedures in dental and oral surgery, especially in aging patients. PRP derives from the centrifugation of the patient's own blood and it contains growth factors that influence wound healing, thereby playing an important role in tissue repairing mechanisms. The use of PRP in surgical practice have beneficial outcomes, reducing bleeding and enhancing soft tissue healing and bone regeneration. Studies conducted on humans have yielded promising results regarding the application of PRP to many dental and oral surgical procedures (i.e. tooth extractions, periodontal surgery, and implant surgery)[53].

The use of PRP together with bone graft significantly improves the quality of bone healing. However, the use of PRP without a bone substitute does not provide adequate repair tissue because PRP needs a mechanical support to be distributed. Thus, it is much less beneficial when used alone[54].

Materials for Vertebroplasty : Bone Cements

There are three types of injectable biomaterials in vertebroplasty: calcium sulfates and calcium phosphates cements, acrylic bone cements and multimaterial cements[55].

Calcium sulfates cements (CSCs) and Calcium Phosphate Cements (CPCs)

Ceramic materials were the first materials used to repair bone tissue because of its biocompatibility and bioactivity[56]. They have a chemical similarity to the mineral phase of bony tissue, especially in calcium phosphates[57].

$CaSO_4$, also known as "plaster of Paris", has a long clinical history for use as a bone graft substitute in various skeletal sites, the use having been first proposed by Dreesmann in 1892 and developed by Peltier in 1961. However, in the original form, the recrystallization of plaster of Paris after it is mixed with water is random, and the crystalline structure contains many defects. More recently, surgical-grade CSCs have been developed, with the powder constituent being calcium sulfate hemihydrate. When mixed with a diluent, the powder is converted to calcium sulfate dihydrate, producing a paste or putty with a solid or partially solid structure; that is:

$$CaSO_4 \cdot 0.5H_2O + 1.5\ H_2O \rightarrow CaSO_4 \cdot 2H_2O$$

When used as an injectable bone cement (IBC), surgical-grade CSC inhibits fibrous tissue ingrowth, creates a slightly acidic environment that encourages angiogenesis and osteogenesis and, as the cement dissolves, bone forms, thereby allowing the void occupied by the cement to be replaced by new bone. Depending on the volume and location, surgical-grade CSC filler resorb in vivo mainly by dissolution, generally within about 2 months. One widely used commercially available brand is MIIG X3. It is a calcium sulfate hemihydrate which, when mixed with water, forms a paste that hardens in about 5 minutes. Its ultimate compressive strength (UCS) and diametral tensile strength (DTS), determined after curing in ambient laboratory air for 24 h, are 96.4 +- 5.9 and 16.0 +- 0.2 MPa, respectively [60].

Although calcium sulfate cements have been used as substitutes for bone defects since 1892, in the 1990s calcium sulfate was gradually replaced by calcium phosphate (CPCs), mainly hydroxyapatite. The reasons for this change were two-fold: the quick reabsorption of calcium sulfate that does not allow the complete restoration of the bone and its low resistance to the load that the vertebral body has to bear[58,28].

There are many different ways of categorizing CPCs, one being the rate of resorption. In this category, CPCs may be devided into two types: apatite and brushite. Depending on the initial composition, apatite cements form different forms of apatite as the end-product; for example, calcium-deficient hydroxyapatite and carbonoapatite. Apatite cements degrade more rapidly than hydroxyapatite (although their degradation rate is still regarded as being slow and some formulations (such as tetracalcium phosphate-based ones) experience an increase in strength with time in vivo and are biocompatible (although inflammatory reactions have been reported in cases when the cement does not set). Brushite cements are more degradable than apatite cements, resorb very quickly and suffer a rapid decrease in strength in vivo (although the mechanical properties of the healing bone increase as bone ingrowth occurs), and are biocompatible (although inflammatory reactions have been reported in some cases).

A CPC hardens through a slow exothermic reaction (thus preventing the attainment of high curing temperatures), during which the cement does not shrink. The main drawback of a CPC is its lack of macropo-

rosity, which means that fast bone ingrowth does not take place and the cement degrades layer by layer from the outside to the inside. Two commercially available brands are Norian SRS and BoneSource™. Norian SRS, an apatitic mineral medium-viscosity cement, is sold as a reactant pack containing the powder mixture and the mixing liquid (Na_2HPO_4 solution). In vivo, the Norian SRS paste sets to form dahllite (carbonated calcium phosphate apatite) via an isotherm crystallization reaction.

Dahllite is similar to the mineral phase of bone in terms of crystallinity and chemical composition. Histological analysis has indicated that, over time, dahllite is subjected to creeping substitution and remodeling in a manner that is similar to that observed in human bone; that is, via osteoclastic resorption. In vitro, BoneSource™ is fully converted to HA via crystallization within 24 h. The cement has a microporous structure (volumetric porosity of about 5–10%), sets in about 7 min, and reaches a mean UCS of about 26 MPa within 24 h. One experimental CPC formulation is a brushite cement composed of -TCP, MCPM, and $Na_2H_2P_2O_7$, with the last-mentioned constituent being added to control the cement's setting time[60].

However, calcium phosphates have an additional noteworthy difficulty. They require a setting time too long to be applied in VP and KP, and it is impossible to inject them directly[28].

Finally, it can be said that, although calcium sulfate and phosphate cements carry some difficulties, both are bioactive materials also capable of stimulating bone regeneration. Hence, they are good candidates so far[58].

Due to the difficulties presented by the ceramic materials, polymers have been selected as an alternative material for VP because they allow more material design possibilities.

*Acrylic Bone Cements (ABCs)**

Most bone cements used in VP are acrylic cements based on polymethylmethacrylate (PMMA).

To date, two categories of formulations of ABCs have been used in VP and KP. The first comprises the same commercially available brands that are used in cemented arthroplasties (the most frequently used being Surgical Simplex P) to which an additional amount of radiopacifier is added by the surgeon. Typically, $BaSO_4$ (to bring the loading to 20–30 wt/wt % of the cement powder) is added. The second comprises commercially available brands that are specifically formulated with a high radiopacifier concentration, two examples of which are Osteopal V28 and KyphX-HV-R™. [59].

They exhibit high compressive strength, high mechanical strength and they cure fast which lets only a short handling time. However, they also cause infection, necrosis, injected cement leakage, inflammation and fracture of adjacent vertebrae. Moreover, these polymeric materials are not biodegradable and exhibit a strengthening factor unnecessarily high which causes fractures to the adjacent vertebrae[60].

Multimaterial cements

Due to all the problems involved in the use of single materials, different multimaterial cements have been recently proposed trying to combine the advantages of different materials (e.g. Cortoss™ Cerament™ from Bone Support AB; KyphOsFS™ and ActivOs™ from Medtronic).

Cortoss™, is a low viscosity cement that is a good example of the enhanced features of these combined cements. Some features of Cortoss™ include: (1) the use of a non-volatile liquid monomer, that after mixing (2), it has a consistency of toothpaste and stays that way until it polymerizes quickly, in a matter of seconds; (3) a low polymerization exotherm, of about 63°C; (4) a modulus that is close to that of cancellous bone; (5) good bioactivity; and (6) allows the development of a cement–bone interface that strengthens over time, with bone apposition occurring at that interface without any fibrous interposition[59].

Other new multimaterials are silica-based bioactive glasses of complex compositions. In fact, bioactive glasses possess unique properties if compared to ceramic materials such as HAp and b-TCP, as their composition can be tuned to obtain materials with tailored reactivity in the human body, ranging from a slightly bioactive behaviour to a complete bioresorbability.

A complex composition also offers the unquestionable advantage of releasing ions known for their beneficial role on bone matrix mineralisation (i.e. calcium and magnesium) and/or the achievement of a proper control of local pH during ion leaching (i.e. phosphate ions), thereby avoiding cell damage due to pH variation. Furthermore, it has recently been discovered that the dissolution products from bioactive glasses exert a genetic control over the osteoblast cycle, and more specifically silicon has been found to be the ion that contributes most to the mineralisation of bone and to gene activation[63]. In addition, glasses do not melt at a constant temperature but soften as the temperature increases, which is an advantage from the conformational point of view. Different methods can be used to prepare a scaffold, and of these, the sponge impregnation technique was chosen for the present work. Polymeric sponges possess an open, trabecular structure that can be used as a template for a ceramic replica through impregnation of the sponge with a slurry of ceramic powders and a subsequent thermal treatment. This procedure to soften glasses can be successfully used to attain a good sintering of the ceramic particles while maintaining a sufficient viscosity and thus avoiding the risk of collapsing of the trabecular structure during the thermal treatment.

Moreover, scaffold's final properties will depend primarily on the nature of the biomaterial and on the processing parameters; other interesting properties can be attained through the preparation of hybrid materials obtained by loading the scaffolds with collagen, cells or more generally biomolecules. Osteogenic cells obtained from the host through a biopsy can be multiplied in vitro and seeded onto the scaffolds before implantation.

In addition to osteogenic cells production, glass– ceramic scaffolds can be also used as delivery vehicles of growth factors such as bone morphogenetic proteins (BMPs) that transform the host precursor cells into bone matrix producing cells. In fact, BMPs cannot be successfully used by themselves since they quickly diffuse and disperse from the injection site due to their low molecular weight[63].

Although a lot of effort has been devoted in the development of bone cement compositions, a complete satisfactory solution is still pending. For instance, leakage sometimes occurs with these multimaterial cements and it is difficult to treat fractures caused by cancer because they are very unstable[62].

CONCLUSIONS

As it can be seen, a lot of effort has been devoted in the development of bone cement compositions However, a complete satisfactory solution is still pending. A more suitable material is needed and more work has to be done in order to find an optimal solution. The material has to be injectable within a short working timeframe, it has to maintain an appropriate viscosity during the injection and it has to fill the fracture while it has to avoid cement extravasations into the surrounding tissues. After completing the injection, the cement should have a reduced setting time, in order to end the operation as soon as possible to avoid infections. In addition, it should have the strength and stiffness to hold up the loads that support a healthy vertebral body and then augment and stabilize it. Also, it should be osteoconductive and osteoinductive. In other words, it should be able to stimulate in-vivo bone regeneration and establish a strong bond with the surrounding bone, with controlled resorbability to restore the functional state of it.

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