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Title: The relevance of biomaterials to the prevention and treatment of osteoporosis. Opinion paper

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Abstract: Osteoporosis is a worldwide disease with a very high prevalence in humans older than 50. The main clinical consequence is bone fractures, which often lead to patient disability or even death. Currently, there are a number of commercial biomaterials used to treat osteoporotic bone fractures, but most of them have not been specifically designed for that purpose. Simultaneously, many drug- or cell-loaded biomaterials have been proposed in research laboratories, but hardly any has received approval for commercial use. In order to analyze this scenario and propose alternatives to overcome this scenario, the Spanish and European Network of Excellence for the Prevention and Treatment of Osteoporotic Fractures "Ageing" was created. This network integrates three communities, e. g. clinicians, materials scientists and industrial advisors, tackling the same problem from three different points of view. Keeping in mind the premise "living longer, living better", this commentary is the result of the thoughts, proposals and conclusions obtained after one year working in the framework of this network.

Dear editor,

Please find the detailed answers to reviewers, indicating the changes introduced in the text. We hope that this revised version will satisfy the standards of Acta Biomaterialia.

Sincerely

Maria Vallet-Regí

Reviewer #1: General comments

This is a summary of expert opinion on using biomaterials in the treatment of osteoporosis, especially fractures. The perspective taken is novel and speaks directly to factors limiting application of biomaterials clinically. Interestingly, while regulatory concerns are discussed, part of the "blame" is on the research community which has not focused on developing materials specifically for osteoporosis and osteoporotic fractures. The broad perspective on frailty and disability provided by this article will be helpful to the biomaterials community. A key concept is early return to function, which is important because it dictates design criteria for biomaterials.

Thank you for your positive comments

The discussion of regulatory requirements will be helpful to the basic scientist, but the description of why so few devices have been approved could be improved. Besides factors mentioned by the authors, key limitations often include lack of clear-cut, simple clinical endpoints for trials, and the cost-benefit analyses that companies perform to decide if there will ever be profit for a relatively small indication. With regard to fracture, a limitation is that approval for a device is often for only one type or a very limited set of fractures (i.e., very narrow range of indications).

Our intention was not to list all factors hindering innovation, but mentioning a few important ones. Nevertheless, the reviewer is perfectly correct in his/her statements. We propose the following modifications:

We added the following text (page 24) :

Since artificial joints may only prove their efficacy after 10 years, this requirement is particularly questionable and cost-intensive. Also, proving the efficacy of an implant may require multiple in vivo or clinical studies to support broad claims. For example, whereas it was possible in the past to only make one in vivo study for a "bone void filler, the authorities tend to require now more than one in vivo study.

Further, we added (page 24):

Currently, there is a trend towards the alignment of pharma and orthopedic product approvals. However, there is a major difference: whereas pharma products have generally a systemic action, orthopedic products have a local action (narrow range of indication). In other words, osteosynthesis plates or orthopedic implants are bone / joint specific, so each plate / implant requires a separate registration. The limited market size and increasingly large regulatory burdens are obviously important aspects / brakes in the decision processes occurring during product development. In fact, many R&D departments are nowadays focused on maintaining the product portfolio and reducing the costs, rather than developing new products.

Reviewer #2: This manuscript reviews possible solutions for preventing and treating osteoporosis. It integrates the communications from clinicians, materials scientists and industrial advisors. The review is very comprehensive and will serve as a good reference for researchers working in the field. There are a few grammar mistakes within the article. It would be helpful if the authors proofread the manuscript prior to finalizing it.

Here are a few examples:

Page 2, Abstract, line 10, it should be ".such as clinicians, materials scientists and .."

Page 4, 1st paragraph, line 1, it should be: ".may make it difficult for both the pre-.."

Page 4, 2nd paragraph, line 1: it should be "..most of national health systems.."

Page 4, 2nd paragraph, line 5: it should be "...the sustainability of some national health systems in the next a few years"

Page 4, 4th paragraph, line 6, it should be ".from user needs to formal clinical outcome .."

Page 5, 3rd bullet point, it should be "think about possible innovative treatments."

The authors thank your positive comments. The grammar mistakes have been removed.

Reviewer #3: General comments:

1) There are two clinical approaches in total hip replacement surgery. Hip prostheses can be fixed to bone with or without bone cements. The proportion of total hip replacements utilizing each type of fixation and the advantages and drawbacks of the approaches may be added.

Following the reviewer suggestion, discussion about using bone cements in hip prostheses is added. We have added the following text (page 10) with the corresponding references (refs 47 to 51 in the revised version):

The dilemma in the choice of fixation method of prosthesis to bone (cemented or uncemented) is solved in favor of cemented prostheses ,taking into account the mean age of our patients (more 80 years) more of 95% of arthroplasties are fixed to bone whit cement , because loss of bone mass in osteoporotic bone prevents good primary stability by press-fit of the uncemented prosthesis and less to achieve perfect bony integration of components , on the other hand the cemented prosthesis have less revision rates that uncemented for aseptic loosening and excellent clinical results. Only in younger patients (less 70 years) with good bone quality and long life expectancy can be indicated uncemented arthroplasties.

2) In section 3.1 the authors discuss the strategies used to increase the contact surface between bone and implant suggesting various approaches for implant designs related to improved osteointegration. The authors should also discuss the surface material properties of the materials related to their osseointegration. Surface roughness and wettability of the material are of crucial importance when trying to establish good bioactivity an osseointegration.

The authors agree with the reviewer about the significance of roughness and wettability on the osteointegration of bone implants. We propose to add the following text (page 14) with the corresponding references references (refs 72 to 78 in the revised version):

Another interesting topic is the role of surface roughness and wettability in implants osteointegration . This strategy has reached some degree of success especially in metallic implants for periodontal surgery. For instance, modifications of microtopography in titanium implants have demonstrated enhanced osteointegration . Prospective studies on implants with rough surfaces evidence very promising clinical results compared with those with smoother surfaces. In addition, the recent development of nanotechnology in biomaterials filed also allows the incorporation of nanofeatures onto implants surface. In this sense there are some studies that evidence the significance of nanotopography in the success of peri-implant bone formation , . Besides, the surface wettability is closely related with the surface micro/nanoroughness and also influences the osteoblast behavior. In principle, hydrophilic surfaces enhanced the osteoblast maturation , thus leading to better clinical results .

3) The concept of implant coating is not discussed in the paper which may also be of interest for the readership. This reviewer recommends the following papers for further information: Bream et

al. Acta Biomater 2013 Oct 22, Nguyen et al. Biomaterials. 2004; 25:865-76, Yang et al. Biomaterials. 2005 ;26:327-37, Surmenev et al. Acta Biomater. 2013 Nov 5.

Following the reviewer's comment, the following text (page 14) and the corresponding references (79 to 83 in the revised version) has been added to the manuscript:

The coating of the surface of metallic implants has been successfully applied for decades to improve their bone-binding properties, with the cementless hip endoprosthesis and dental implants as the best-known examples. In particular, calcium phosphate coatings have been applied by various techniques, e.g. plasma spraying, sputtering techniques and sol-gel coating. Although an increased bone-binding ability has been found, a recent review points out that long-term clinical studies lead to contradictory results. However, it may be envisioned that in osteoporotic bone, a surface modification of metallic implants, be it by calcium phosphate or by drug-releasing coatings will help to improve the clinical outcome, at least in the short-term performance when the primary stability is needed.

4) Another important issue that could be added when describing the physical properties of the materials is a comparison of the materials' pore size and distribution as they greatly affect the ingrowth of new tissue and the degradation of the implanted material.

In agreement with the reviewer's comment, the following paragraph has been added (page 16) together with the corresponding references (refs 105 to 109 in the revised version)

In this sense, the design and development of porous ceramics have attracted much attention in the last years. Not only pore size, but also pore distribution can play a fundamental role in the bone regeneration, angiogenesis and implant degradation. The incorporation of free form preparation methods such as 3D printing to the biomaterials field, allow the design of hierarchical pore structures to facilitate these processes. An interconnected macropore structure of 150- 1000 μm allows cell colonization and enhances the diffusion rates to and from the center of a scaffold, as well as angiogenesis and bone ingrowth . Small pores allow phagocytic cells to adhere and resorb the scaffolds whereas larger pores encourage the invasion of new vessels and ingrowth of bone tissue .

5) When discussing the properties of calcium silicate cements the authors may also mention injectable bone cements and carriers for local drug delivery is nicely explained in the article. The authors may also add their beneficial influence on the mechanical properties of biological materials (Liu et al. Int Journal of Nanomedicine 2010, 5: 299 -313).

The field of calcium silicate cements is not relevant for this review and such materials were not discussed in our paper. The report covers where appropriate the more relevant calcium phosphate cements. Regarding injectable calcium phosphate cements (assuming the referee refers to this group of biomaterials), the following statement has been added to the manuscript (page 12) to address the referee's comment (and 4 new relevant references (55 – 58) have been added):

Indeed there is increasing research in the field of injectable calcium phosphate cements with recent efforts focusing on incorporating different additives including inorganic bioactive elements, e.g. bioactive glass, radiopacifiers, e.g. tantalum oxide or barium sulfate, biodegradable polymers to improve the injectability and modifications to incorporate antibiotic releasing capability.

6) The usage of nanoparticles as carriers for local drug delivery is nicely explained in the article. The authors may also add their beneficial influence on the mechanical properties of biological materials (Liu et al. Int Journal of Nanomedicine 2010, 5: 299 -313).

Following the reviewers comment the following text has been added to the manuscript (page 20), together with the corresponding references (148 -151 in the revised version)

Note that in general, nanoparticles have not only been discussed as delivery agents, but that they can also be used to increase the mechanical strength after embedding into a polymeric matrix. This follows the concept of a biomimetic hierarchically structured material, mimicking bone itself.

The relevance of biomaterials to the prevention and treatment of osteoporosis. Opinion paper

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Abstract

Osteoporosis is a worldwide disease with a very high prevalence in humans older than 50. The main clinical consequence is bone fractures, which often lead to patient disability or even death. Currently, there are a number of commercial biomaterials used to treat osteoporotic bone fractures, but most of them have not been specifically designed for that purpose. Simultaneously, many drug- or cell-loaded biomaterials have been proposed in research laboratories, but hardly any has received approval for commercial use. In order to analyze this scenario and propose alternatives to overcome this scenario, the Spanish and European Network of Excellence for the Prevention and Treatment of Osteoporotic Fractures “Ageing” was created. This network integrates three communities, e. g. clinicians, materials scientists and industrial advisors, tackling the same problem from three different points of view. Keeping in mind the premise “living longer, living better”, this commentary is the result of the thoughts, proposals and conclusions obtained after one year working in the framework of this network.

1. Introduction and put in context.

Ageing of the musculoskeletal system is a rapidly growing issue due to the demographics associated with ageing populations throughout the world. Its consequences on health are linked, among others, to osteoporosis, degenerative osteoarthritis and muscle deterioration or sarcopenia. These three elements interact to produce a picture of frailty, which often leads to bone fracture when a fall occurs, typically in people of advanced age. Fracture prevention, patient recovery, and avoidance of subsequent fractures constitute a challenge not yet resolved [1].

Bone weakening due to osteoporosis is far from finding a satisfactory solution. As a consequence of poor bone quality, surgical procedures performed to implant a device in weakened bone often lead to a clinical result that is worse than if such an intervention was performed on a young and strong bone. The risk of fracture increases exponentially with age, and the recovery process from a fracture is often slow, difficult and may lead to a disability or even to the death of the patient. Up to 25% of patients who suffer a femur fracture will die in the following year. Of those who survive, approximately half are totally or partially dependent [2]. Chronic pain, functional limitation, social

dependence, psychological disorders, reduced mental health score and social isolation converge on a serious deterioration in the quality of life.

There are treatments available today to reduce the impact of bone fragility, but there is a lack of alternatives to restore bone strength. Moreover, there are no comprehensive treatments available for the whole damaged system, i.e. able to address the three factors of musculoskeletal unit fragility: bone, cartilage, and muscle. These three factors are both cause and consequence of the osteoporotic fracture [3].

The economic aspects that surround this social and health issue are also of paramount importance [4], hence any action aimed at cost reduction should be seriously considered. It is worth mentioning that a surgical intervention for a hip prosthesis implantation has a health service cost of around €20,000, including direct, indirect and intangible costs [5]. For instance, the total current cost for hip fracture treatments with osteoporotic origin in the U.S. is 20.3 billion of U.S. dollars. This cost, far from diminishing, has experienced continuous growth throughout the 20th century and the first decade of the 21st century [6-8]. In fact, the total number of osteoporotic fractures in 1950 was 1.47 million and the projection for 2050 is around 6.3 million [9]. In the framework of the European Union, direct costs related to osteoporotic fractures in 2000 were estimated to €31.7 billions [10]. Moreover, the increase in life expectancy of an increasingly ageing population leads to predict even more serious difficulties for the future.

In the context of a socio-health problem such as osteoporosis, we may highlight three main agents involved in it:

- The patient. All publications and web sites devoted to osteoporosis show that there is currently no satisfactory solution and that it remains as one of the major challenges for public health. This claim is based on significant mortality and disability (personal costs) and its relationship with the economic costs of the management, including treatment, of the patients (social costs). The patient, as a key player in the issue, is therefore still waiting for a satisfactory solution.
- The therapeutic team. Once the fracture (whether of hip, spine, wrist, etc.) has occurred, the surgeon has only very few surgical solutions. In addition, other issues concerning general health (frailty, malnutrition, cognitive disorders, co-morbid conditions, polypharmacy, etc.) may make it difficult both the pre- and post-surgical

management of the patients. The reports issued by many of these professionals support the idea that enormous patient benefits could stem from preventive solutions.

- The National Health System. In the European Union, most of national health systems are the purchasers of the prosthetic products and the defrayers of the intervention and hospitalization costs. Undoubtedly, the gradual ageing of society entails an increased number of osteoporotic patients, and this scenario could challenge the sustainability of some national health systems in the next a few years.

Research into biomaterials has produced many variants of technologies, materials and physical forms intended to supplement or replace osteoporotic bone over the last 30 years. However, very few of these have achieved broad application in either prevention or treatment of osteoporotic bone and its lesions. For those who are not directly involved with the commercialization of biomaterials it may be surprising that so little biomaterials research output reaches the operating theatre as part of a clinical treatment. However, there are many obstacles that biomaterials and their creators must overcome to prove safety and efficacy to the level required by the regulatory bodies in each country. Even where these are overcome it is far from certain that a biomaterial will be commercially exploited. Thus, the position today is that there are more limitations than opportunities for transferring biomaterials into clinical use, particularly in the management of poor bone quality. This opinion article will discuss some of the issues that account for the paucity of biomaterials in clinical use and also suggest what more might be done to encourage more viable clinical applications.

To begin with, there are some mismatches between the aspirations of biomaterials researchers and (unmet) clinical needs. The goals of industry and academia are broadly similar to the surgeon community in wanting to improve clinical outcomes in a given clinical treatment. However, biomaterials are often developed by identifying the unmet clinical needs (note the terms used here such as “user needs” are as required in design control and quality systems for medical device design). Even where the unmet needs are properly researched, their effective translation from user needs through to formal clinical outcome studies is quite uncommon. Even rarer is that a proper post-market surveillance is undertaken to ensure that any adverse outcomes are recognized as part of a quality system.

Considering this scenario, an interdisciplinary group of experts comprising clinicians, materials scientists and industrial advisors have constituted the Spanish and European Network of Excellence for the Prevention and Treatment of Osteoporotic Fractures “Ageing” (www.agening.net). This network shares and puts together information coming from different specialties and proposes possible solutions for the treatment of ageing diseases in bone, such as:

- identify the most prevalent clinical problems and the most relevant clinical solutions,
- analyze and discuss the role of drugs, implants, biomaterials and surgical techniques in such treatments, and
- think about **possible innovative** treatments and even prevention.

This article is the result of one year of discussions and thoughts, proposals and conclusions obtained in the “Ageing” framework.

2. Osteoporosis. A clinician’s point of view.

2.1. Significance of osteoporosis to frailty and disability.

Last century a profound demographic change took place, the main consequence of which was a significant increase in the percentage of people older than 65, reaching levels of around 17%. In addition to this demographic change, a second transition occurred: the epidemiological transition, which produced a shift from the predominance of acute, single and communicable disease to a predominance of chronic, multiple and non-communicable diseases. As a consequence of these two complementary transitions the spectrum of diseases and the way of being ill has **dramatically changed**. If we finally take into account **that life expectancy will slowly continue extending** (EUROPOP forecasts support a modest increase in life expectancy around 5-7 years in the European Union countries for the next 50 years), the focus of health interventions should change from prolonging life to improve the quality of life.

The most important surrogate of this quality of life is function. As functional status deteriorates, the quality of life gets worse. During the last century, as we prolonged life expectancy we were opening the door to the increased risk of disability with age, that would not be the case with a relatively young population. With **agening**, the loss of

functional reserve capacity put people at risk of developing disability, even under low-power stressors. This is the explanation for the increase in the rates of disability that accompanied the extension of life expectancy during the last century (**Fig. 1**). But during the last 25 years, this tendency has changed in many countries. Although we do not know the causes explaining this drop in disability rates, this fact clearly shows that disability is an avoidable consequence of the ageing process and that if its main causes were known **we** could intervene in the hope of decreasing the prevalence of disability [11].

The fight against disability has several options, but probably the least attractive is to passively wait for the development of a disability. As previously stated, the main cause of disability is the loss of functional reserve capacity. But to successfully recover from disability a high level of that capacity is needed. In fact, only a small percentage (around 30%) of older people with incident disability is able to **improve functionally** during the first year [12]. This is why the main approach to improve the population functional status is the prevention of disability, instead of waiting to treat it. With this purpose in mind the concept of frailty has emerged as a relevant tool to detect people with the highest risk of developing a disability, both at short- and long-term (**Fig. 2**). Frailty is a state of increased vulnerability to stressors due to a decreased physiological reserve in multiple systems and a limited capacity to maintain homeostasis [13]. Its prevalence is around 10%, ranging from 1-3% for 65 years old people to more than 30% in people older than 80. It predicts the risk of suffering from multiple adverse outcomes, including death, hospitalization, disability and falls [14]. Detecting frailty is of clinical importance [15] as it has been shown that some therapeutic approaches, mainly based on physical exercise, are able to pull out patients from a frailty state, or at least delay frailty progression to full disability [16].

Within this framework, the approach to osteoporosis, as it is also the case for many other chronic conditions usually present in older people, should be focused on the prevention of the clinical pictures associated with frailty and disability. The most frequent of these conditions is the hip fracture. Taking into account that the most important risk factor for hip fracture is the risk of falls, the right way to manage these patients is based on a comprehensive assessment and management of falling patients. For this purpose the introduction of specialized Falls and Fracture Units is becoming the

standard approach to manage these patients, as recommended by different organizations, e.g. WHO, NICE, British Orthopaedic Association and the US Preventive Services Task Force.

In this regard, the focus in these Units is to reinforce the idea of the continuum of care and a comprehensive approach to avoid or prevent disability in these patients, taking advantage of all available opportunities. One of these opportunities stems from the advances in the biomaterials used in the surgical materials used in those patients with hip fracture. These materials should have a double aim in the prevention of frailty and disability: firstly to allow an early mobilization of the patient after surgery and secondly to provide a quick and efficient restoration of bone and, as far as possible, of the musculoskeletal unit.

2.2. Clinical aspects, prophylaxis and treatment of osteoporosis.

Osteoporosis is a common disease with a rapidly increasing incidence associated to the population ageing [17,18]. The loss of bone and deterioration in its quality [19] induce decreased bone strength with the associated increase in fracture risk [20]. The main clinical consequences of the condition, therefore, are the fractures, associated with significant morbidity [21] and mortality [22].

Several factors contribute to an increased risk of osteoporosis and fracture. These risk factors have recently been structured in a decision algorithm, the FRAX[®] tool, that allows the clinician to calculate the absolute risk of fracture in ten years for an individual patient [23]. This formula has been validated in a number of countries [24] and is available in several languages and for a large number of countries. Moreover and also partially integrated into FRAX, an important number of comorbidities **have been** identified that also influence fracture risk either by deteriorating bone or by increasing the propensity of patients to fall [25].

The clinical diagnosis of osteoporosis relies mainly in the measurement of bone mineral density by dual energy X-ray absorptiometry (DEXA) in several skeletal regions [26]. Other methods also calculate the mineral density by using ultrasound or quantified computerized tomography (QCT) scanners but their use in the general population is limited. These methods have in common the limitation of measuring only one of the determinants of bone strength, the amount of mineral or bone mass, but do not capture

the quality of the material. For this to be adequately done, laboratory testing of “ex vivo” specimens is required for measuring a broad spectrum of mechanical properties (brittleness, toughness, work to failure, etc.) [27]. Recently new techniques have been developed for the direct measurement of bone tissue strength [28, 29]. Biochemical markers of bone turnover, reflecting the rate of cell activity in the bone remodeling cycle have been also extensively developed and can predict the future fracture risk. [30] They also inform the clinician about the response to treatments [31]. Last but not least the simple detection in a routine radiograph or after a trauma permits the identification of fractures, the cornerstone of the disease and the responsible event for the morbidity and mortality associated with osteoporosis. Suffering a low-energy traumatic fracture (fragility fracture) is the ultimate demonstration of osteoporosis and constitutes per se a diagnostic marker.

Osteoporosis prevention has two phases, primary prevention and secondary prevention. Primary prevention starts during intrauterine life, childhood and adolescence, given that this determines the development of a healthy strong skeleton in the adulthood. Even though genetic factors determine to a great extent how our bones are, the promotion of physical activity, adequate nutrition and the avoidance of negative factors for the normal bone development are extremely important.

Secondary prevention starts once bone loss or bone fracture has occurred. Suffering a fracture is the most potent predictor of new fractures, in a progression of risk of a so called “fracture cascade”. Two main groups of drugs are currently available for the management of the patients with osteoporosis: anticatabolics and anabolics [32]. The anticatabolic or antiresorptive agents suppress or attenuate the activity of the bone-resorbing cells, the osteoclasts, hence stopping bone loss and increasing bone strength. On the other hand, anabolic agents are capable of inducing bone formation and, therefore, can revert in part the deterioration induced by the osteoporosis progression. The advances in this therapeutic field have been very significant over the last two decades since there are now several classes of drugs, including both chemical to biological entities, that decrease the risk of vertebral fracture and some also of non-vertebral fractures (e.g. hip). The main development in treatment has been in postmenopausal osteoporosis in women although we have also treatments for glucocorticoid-induced osteoporosis [33,34] and osteoporosis in men [35]. In spite of the substantial body of clinical evidence, the management of this disease is still largely variable across different countries [36] and a considerable part of cases does not

respond to the treatment [37,38]. Whilst antiosteoporosis drugs have their side effects [39], these bone treatments have shown other health benefits such as cancer reduction in some instances [40] and also a decrease of the overall mortality [41]. In summary, there are now some effective tools that enable detection, diagnosis and treatment of osteoporosis to combat the progression of this metabolic disease, resulting from ageing societies worldwide.

2.3. Surgical treatment of osteoporotic fractures.

Osteoporotic bone has special morphological and biological characteristics. Fracture healing depends mainly on the mechanical stability at the fracture site and the biological process of bone repair. Osteoporosis entails a decreased bone mass and an altered bone structure, leading to a lowered mechanical strength. So, osteoporotic fractures are often severely comminuted, especially in trabecular bone areas. Fracture comminution and trabecular collapse not only result in bone defects with impaired fracture stability, but also make anatomical reduction and surgical reconstruction difficult. Biologically, the mesenchymal stem cells (MSCs) of osteoporotic bone have less capacity to differentiate into osteoblasts than those of healthy bone, possibly due to impaired osteoinductive signals and/or lower expression of bone morphogenetic protein-2 (BMP-2). A decreased angiogenic capacity at the fracture site is also common in osteoporotic bone [42].

Fracture fixation planning is determined by the special mechanical conditions of osteoporotic bone. It has to be noted that even in normal everyday activity, the loads supported by bones and joints are both large and dynamic, changing in both magnitude and direction with every step the patient makes. While implant failure is potentially a risk, less rigid fixation devices such as intramedullary nails, bridge plates and tension band constructs are preferred for minimizing bone-implant interface stress and the concomitant risk of bone failure. In compromised bone, improved screw holding power is essential to prevent screw pullout and/or migration and to minimize implant loading. Moreover, comminution makes fracture reduction more difficult, requiring the use of autologous bone grafts or biomaterials to fill bone defects and to augment bone fragments. It is therefore possible by combining implants and biomaterials to achieve sufficient overall assembly stability and fracture healing. Less load-resistant materials, even with bioactive capacity, may be used in the upper limb fractures. However, spine

and lower limb fractures require the use of inert biomaterials with greater load-bearing capacity, although calcium phosphate cements may be occasionally used.

The most common osteoporotic fractures involve the spine, the hip and the distal radius. Surgical treatment of these fractures has changed in recent years. The distal radius fracture is known as “sentinel fracture” because it is the first warning sign of osteoporosis. We now know that surgical treatment of distal radial fractures, particularly by plates through palmar or dorsal approaches, does better than conservative treatment [43]. Severe comminution and bone fragment collapse are often present, requiring the use of biomaterials to fill bone defects, achieve fracture stability and promote bone union.

Spine fracture is the most frequent osteoporotic fracture. Early diagnosis and medical treatment with anabolic drugs are essential to increase bone strength and prevent the so-called “fracture cascade”. Vertebroplasty and kyphoplasty as minimal-invasive techniques show excellent results on quality of life, pain relief and functional recovery both short and long term [44]. More importantly, Edidin et al. [45] showed that the mortality of patients suffering from a vertebral bone fracture was significantly reduced when their fractures were treated by vertebroplasty or kyphoplasty.

Treatment of hip fractures varies according to their anatomical location and classification. These are divided according to anatomically defined region: Intracapsular neck, extracapsular neck, pertrochanteric, intertrochanteric and subtrochanteric. Intracapsular fractures (see figure 3) have biological problems due to the loss of blood supply to the proximal fragment. Osteosynthesis is only indicated for undisplaced Garden I and II type intracapsular fractures in patients younger than 70 years. Total or partial hip arthroplasty, depending on the patient age, is the preferred technique for the displaced grades (Garden III and IV) fractures [46]. The dilemma in the choice of fixation method of prosthesis to bone (cemented or uncemented) is solved in favor of cemented prostheses, taking into account the mean age of our patients (more 80 years) more of 95% of arthroplasties are fixed to bone with cement, because loss of bone mass in osteoporotic bone prevents good primary stability by press-fit of the uncemented prosthesis and less to achieve perfect bony integration of components, on the other hand the cemented prosthesis have less revision rates than uncemented for aseptic loosening and excellent clinical results. Only in younger patients (less 70 years) with

good bone quality and long life expectancy can be indicated uncemented arthroplasties [47-51]

The sliding hip screw, a device used in the treatment of trochanteric fractures, has been to some extent replaced over the years by intramedullary nails with a sliding cephalic screw. These are often made from titanium alloy and may feature reduced diameter and length to enable implantation by minimally invasive surgery [52]. The key determinants for good outcome are the correct placement of the cephalic screw and good anatomical fracture reduction. If a large posteromedial comminution is present, the bone defect can be augmented with a bone substitute such as a calcium phosphate cement. In cases of severe osteoporosis, bone structure of the femoral head can be strengthened by injecting PMMA cement through the cephalic screw, a technique known as augmentation, which prevents the cut-out.

The challenge for the future will be the development of bioactive biomaterials that combine load bearing, interconnected porosity and the ability to be loaded with biologic factors that promote fracture healing.

3. Osteoporosis. A materials scientist's point of view.

In an osteoporotic scenario, the paucity of bone and the decreased osteoblastic function result in an impaired response to implants compared with healthy bones. As mentioned in previous sections, this evidence is often observed by orthopedic surgeons in their daily practice of fracture reduction in osteoporotic patients. The experience of clinicians, outlined in section 2, teaches us that the primary issue with these patients is that they suffer from fractures that require some form of fixation, and the osteosynthesis elements such as plates, screws, nails, etc. are difficult to fix in low-quality bone. Besides, other scenarios different of fractures also affect the biomaterials performance in osteoporotic patients. For instance, the response of osteoporotic bone to endosseous implants, such as stems of total joint prostheses or endosseous dental implants, is also strongly impaired. In these cases, the implant failure is due to the poor biological fixation, which is consequence of an insufficient osteogenesis around the implant [53]. Despite of these evidences, there are no clinically approved biomaterials specifically tailored for application in osteoporotic bones. Certainly, there are some examples of

medical devices for osteosynthesis with special designs, but they are made of the same biomaterials than the conventional ones, such as titanium alloys, cobalt alloys or stainless steel.

Attempting to reduce osteoporotic fractures, two classes of biomaterials are mainly used: metallic implants and cements. Their function is slightly different: whereas metallic implants are used as primary fixation devices, cements are mainly used as reinforcement of the metallic hardware. However, cements are also used as stand-alone devices, for example for bone augmentation procedures (injection of the cement into osteoporotic bone) [54]. Indeed there is increasing research in the field of injectable calcium phosphate cements with recent efforts focusing on incorporating different additives including inorganic bioactive elements, e.g. bioactive glass [55], radiopacifiers, e.g. tantalum oxide or barium sulfate [56], biodegradable polymers to improve the injectability [57] and modifications to incorporate antibiotic releasing capability [58]. Another difference between metallic implants and cements is the way they are adapted for osteoporosis-related indications. As mentioned above, metallic biomaterials are the same as those used in non-osteoporotic patients, but the implant shape is modified to accommodate osteoporosis-specific requirements. Sometimes, even new implants are created. For cements, the accent is set on a change of composition to obtain specific properties such as constant viscosity or high radiopacity. In addition, bioactive and/or resorbable ceramics such as calcium phosphates or bioactive glasses can be used to fill voids, thus avoiding the harvest of autogenous bone from the iliac crest.

Besides the osteoporotic fractures reduction, biomaterials science also faces the quest of the impaired osteointegration of permanent endosseous implants. The osteointegration in these cases is seriously affected, mainly due to the decreased osteoblast activity. An osteoporotic environment strongly affects the primary (short-term) stability of the implant, because the quality of the host bone is significantly decreased. Moreover, biological stability (early and long-term) is also impaired, as it requires deposition of newly formed bone in intimate contact with the implant [59]. Since this process involves the balanced action of osteogenic and bone resorbing cells, osteoporosis often has a poor prognosis and delayed healing and osteointegration with endosseous implants. However, similarly to devices for fracture fixation purposes, the research

efforts do not **comprise** the preparation of new metal alloys specifically intended to fabricate endosseous implants for osteoporotic patients [60].

On the contrary, research on bioceramics (even playing a minor role compared with metals in the treatment of osteoporosis) envisions this scenario in a different way and often deals with the specific case of osteoporotic bone. In this sense, calcium phosphates bioceramics [61, 62] and SiO₂ based mesoporous materials have been widely proposed as potential local antiosteoporotic drugs delivery systems [63], when used for void fillers in fracture fixation, bone grafting or augmentation.

Combinations of biomaterials with cellular therapy and local drug delivery are of enormous interest because of the great opportunities that they offer to this problem [64-66]. However, the technical and biological problems of the cells or materials to be used are important. These include (1) the limited cell viability; (2) the transient mechanical properties of the materials once implanted until they are substituted by regenerated bone; and (3) the biological integration at the specific bone site where they are implanted. To solve these problems, *in vitro* and *in vivo* tests should be performed in experimental conditions that mimic as much as possible the most prevalent situations associated with bone pathologies: estrogens depletion, diabetes mellitus, ageing, and treatment with glucocorticoids. To progress in this area, standard procedures to collect, manipulate and store mesenchymal osteoprogenitors (such as the bone marrow) should be defined. Thereafter, it would be possible to start considering the fabrication of a medical device following criteria accepted by **n**ational and **i**nternational regulatory **a**gencies for on-demand administration.

3.1. Metallic implants

Since osteoporotic bone is much more fragile than healthy bone, metallic implants used to treat osteoporotic bone fractures have to be designed differently. One strategy consists in increasing the contact surface area between bone and implant. This can be done by increasing the diameter of osteosynthesis screws [67]. Another approach is to use locked osteosynthesis plates [68]. In the latter case, plate loosening is only possible if all screws get loose simultaneously. This is in large contrast with unlocked plates whose fixation onto the bone relies on the compressive action of screws. A third approach consists in designing completely new implants, for example expandable spacers for vertebral height restoration (e.g. “VBS” (DePuy Synthes), “Spinejack

Vexim” (Vexim), “Kiva” (Benvenue Medical)) or cannulated screws (e.g. “Matrix Spine System” (Depuy Synthes)) to permit cement injection through the screw [69]. The cement injection through the screws (**figures 4 and 5**) gets an increase in the resistance of the fractured vertebral body and avoids the pull-out of screws in osteoporotic spine [70,71].

Another interesting topic is the role of surface roughness and wettability in implants osteointegration [72]. This strategy has reached some degree of success especially in metallic implants for periodontal surgery. For instance, modifications of microtopography in titanium implants have demonstrated enhanced osteointegration [73]. Prospective studies on implants with rough surfaces evidence very promising clinical results compared with those with smoother surfaces [74]. In addition, the recent development of nanotechnology in biomaterials field also allows the incorporation of nanofeatures onto implants surface. In this sense there are some studies that evidence the significance of nanotopography in the success of peri-implant bone formation [75,76]. Besides, the surface wettability is closely related with the surface micro/nanoroughness and also influences the osteoblast behavior. In principle, hydrophilic surfaces enhanced the osteoblast maturation [77], thus leading to better clinical results [78].

The coating of the surface of metallic implants has been successfully applied for decades to improve their bone-binding properties, with the cementless hip endoprosthesis and dental implants as the best-known examples. In particular, calcium phosphate coatings have been applied by various techniques, e.g. plasma spraying, sputtering techniques and sol-gel coating [79-82]. Although an increased bone-binding ability has been found, a recent review points out that long-term clinical studies lead to contradictory results [83]. However, it may be envisioned that in osteoporotic bone, a surface modification of metallic implants, be it by calcium phosphate or by drug-releasing coatings will help to improve the clinical outcome, at least in the short-term performance when the primary stability is needed.

3.2. Cements

Polymethylmethacrylate (PMMA) cement is the material of choice for the reinforcement of metallic implant fixation or osteoporotic bone due to its high

mechanical properties and low cost. However, PMMA cement has very important drawbacks such as monomer toxicity [84], risk of bone necrosis due to a highly exothermic setting reaction [85], absence of biodegradation that may lead to fatigue failure [86], or too high material stiffness that may increase the fracture risk of vertebra adjacent to PMMA-reinforced vertebra [87]. As a result, various cements have been proposed to replace PMMA cement, but their success remains very limited due to toxicity, regulatory, price, or mechanical issues. For example, a few years ago the company “Orthovita” proposed a few years ago a dual paste cement called “Cortoss”. This cement is inspired from the composition of dental cement i.e. it consists of a matrix of Bis-GMA (2,2-bis [4-(2-hydroxymethacryloxypropyl)phenyl] propane), Bis-EMA (2,2-bis [4-(2-methacryloxyethoxy)] phenyl propane), and TEGDMA (triethylene glycol dimethacrylate) and is reinforced with bioactive glass particles [88]. “Cortoss” presents better handling, higher mechanical properties, and lower toxicity than PMMA cements. Unfortunately, it has a limited success, possibly due to price issues (higher production costs than PMMA cements). More recently, a silicone cement called “VK100” was proposed by the company “BonWRX”. This dual paste cement contains dimethyl methylvinyl siloxanes (87 %), barium sulfate powder (14 %), and a platinum catalyst (15 ppm as metal) in the first component, and dimethyl methylvinyl siloxanes (78 %), barium sulfate powder (15 %), and a methylhydrogensiloxane cross-linker (7 %) in the second component. Unfortunately, preliminary results for bone augmentation applications (“elastoplasty”) are very poor with more than 60% leakage (cement flowing outside the targeted location, e.g. into the spinal canal) and pulmonary embolism [89]. The too slow setting reaction was also mentioned.

Considering the poor biological properties of polymer cements, quite a few ceramic cements have been proposed for bone augmentation procedures. Interesting candidates have been calcium phosphate cements (CPCs), but the results have been rather disappointing [90-93]. One main issue is the CPCs poor mechanical (shear stress) properties. Thus, CPCs can at most be used in load-sharing sites. Also, several deaths have been reported after the use of “Norian XR” CPC [94,95], suggesting some biocompatibility issues of CPCs in spinal applications. Higher mechanical properties were achieved with a calcium aluminate cement (“Xeraspine” from “Doxa AB”), but the results were not very good either [96]. The last ceramic cement that should be mentioned here is Plaster of Paris (= calcium sulfate hemihydrate). This material readily

dissolves in vivo due to its comparatively high solubility (i.e. without the help of osteoclasts), but nevertheless has been proposed for bone augmentation [97,98] and bone void filling applications, for example for the filling of the “Kiva” device. Besides bone augmentation, ceramic cements have also been used for screw augmentation [99-102]. Some results are very promising [103,104], but more data are needed to assess the long-term success of this approach.

3.3. Bioceramics for bone tissue regeneration

Altogether, calcium phosphate ceramics and related compounds, i.e. calcium phosphate cements, bioglasses and calcium sulfate cements, represent the most important class of biomaterials for bone regeneration. Different types of calcium phosphate ceramics, glass-ceramics and glasses are currently being used and further developed for bone reconstruction and repair. In the present section the most prominent inorganic systems and, where appropriate, their composites in combination with polymers are described highlighting effects of ion release to induce osteogenesis and angiogenesis both functions required for effective bone tissue regeneration. In this sense, the design and development of porous ceramics have attracted much attention in the last years. Not only pore size, but also pore distribution can play a fundamental role in the bone regeneration, angiogenesis and implant degradation [105]. The incorporation of free form preparation methods such as 3D printing to the biomaterials field, allow the design of hierarchical pore structures to facilitate these processes [106]. An interconnected macropore structure of 150- 1000 μm allows cell colonization and enhances the diffusion rates to and from the center of a scaffold, as well as angiogenesis and bone ingrowth [107,108]. Small pores allow phagocytic cells to adhere and resorb the scaffolds whereas larger pores encourage the invasion of new vessels and ingrowth of bone tissue [109].

3.3.1. Calcium phosphates

Calcium phosphate constitutes the inorganic mineral phase in mammalian bone and teeth. Therefore it is well known to the body and biocompatible by all current standards [110-112]. The calcium phosphate mineral in bone consists of nanocrystalline platelets of biological apatite, which chemically is a hydroxyapatite with ionic substitutions,

mainly carbonate [113]. A number of synthetic calcium phosphate ceramics are on the market as bone substitution material, with hydroxyapatite, $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ (HAP), and β -tricalcium phosphate, $\beta\text{-Ca}_3(\text{PO}_4)_2$ (β -TCP) and combinations of them ("biphasic calcium phosphate"; BCP) being the most prominent ones. They are available in different morphologies (typically as solid or porous blocks or as granules with different particle size) and with different origin (fully synthetic or derived from biological sources like animal bone or chemically transformed calcareous algae) [114]. In general, they are well accepted by the body, but as ceramics they are brittle by nature and therefore not able to withstand the mechanical challenge in a larger defect. With time, newly formed bone grows onto and into calcium phosphate ceramics and finally leads to a stable osteointegration [115]. The resorption of calcium phosphate ceramics typically involves acidic dissolution by osteoclasts [116,117].

3.3.2. Bioactive glasses.

Among all bioceramics, glasses have a special position due to their ability to rapidly release different ions, but also to strongly bind to bone through the formation of an apatite-like phase in the bone-implant interface ("bioactivity"). Depending on their chemical composition, bioactive glasses can be resorbed and their degradation byproducts can stimulate the osteogenic pathways in mesenchymal stem cells present at the fracture location. Indeed, the tailored effect of dissolution products from bioactive glasses on cellular responses, e.g. to upregulate the expression of genes controlling osteogenesis and to enhance vascular endothelial growth factor (VEGF) secretion in vitro to induce vascularization, are attractive qualities of bioactive glasses (and their composites) in the context of bone regeneration strategies [118]. For instance, the effect of silicate ions was recently investigated in relation to proliferation, osteogenic differentiation and cell signaling pathways of bone marrow stromal cells [119]. It has also been shown that cells where the calcium sensing receptor (CaSR) is present, such as mesenchymal stem cells and endothelial cells, respond to specific calcium concentrations in the environment by migrating, proliferating, and differentiating, expressing alkaline phosphatase and collagen 1 and mineralizing, and forming tubules respectively [120]. Therefore, it is hypothesized that any biomaterial with the

appropriate calcium-releasing capacity would be a good candidate for bone regeneration where angiogenesis is necessary.

Typical silicate-based compositions such as “45S5” (wt. %: 45 SiO₂, 24.5 Na₂O, 24.5 CaO, 6 P₂O₅) are characterized by a high surface bioactivity enabling strong bonding to bone tissue [121,122] leading also to stimulating effects on osteogenesis [123] and angiogenesis [124]. Starting with the classic “45S5 Bioglass®” composition [121], a great number of silicate systems incorporating specific ions into the silicate network is continuously developed. The typical ions that are under investigation are magnesium, strontium, silver, iron, copper, boron, potassium, lithium, cobalt, fluoride and zinc [125]. At variance, absorbable calcium phosphate glasses are able to solubilize completely with degradation times ranging from days to years, depending on their chemical composition. The vitreous network of [PO₄] tetrahedra is easily hydrolyzed. The chemical stability of these glasses can only be modified by including different metallic oxides, such as Al₂O₃, ZnO, Fe₂O₃, and TiO₂, into the three dimensional vitreous network. TiO₂ has proved to be very efficient, given its four valences that link to four phosphate tetrahedral [126]. The capacity of calcium phosphate glasses to promote cell adhesion [127] and to induce vessels formation at the site of implantation [128] can be interpreted in terms of ion release.

Being of high relevance in the context of osteoporosis-combating materials, the effect of specific ions on bone-resorbing osteoclast cells must be considered. For example, some researchers investigated the addition of strontium ions into silicate glasses as an effective approach to develop improved bioactive glasses [129], considering the positive results achieved with strontium ranelate (SrR) applied as a drug to treat and prevent osteoporosis especially in post-menopausal women. Dedicated in vivo studies to assess potential bone healing enhancement in osteoporotic bone by grafting with bioactive glasses are still scarce [130], indicating a need for future research to realistically consider bioactive glasses as osteoporosis combating substances. It is also important to note that specific morphologies of silicate bioactive glasses (and silica), e.g. with a mesoporous structure [131] are attractive systems which enable the incorporation of a drug delivery function to enhance the intrinsic bioactive character of the inorganic silicate carrier.

3.4. Associations of biomaterials with biological entities: gene and cellular therapies.

3.4.1. Perspectives of gene therapies for bone regeneration purposes.

As there is clearly a need for rapid bone regeneration after a fracture in osteoporotic bone, people have wondered since decades how bone growth can be stimulated by adding osteogenic compounds to biomaterials. This has led systems with a local drug delivery, e.g. of bone morphogenetic proteins (BMPs) [132-134] or of angiogenic proteins like VEGF [135,136], e.g. from polymers or ceramics. The release typically consists of a burst in the first days or weeks. The preparation and incorporation of proteins into biomaterials are usually costly. Another approach is a local gene therapy, provided by suitable biomaterials in direct bone contact. Gene therapy involves the delivery of DNA which can induce the production of the encoded protein after uptake by cells (so-called "transfection"). To accomplish this goal, suitable carriers are needed as nucleic acids alone cannot penetrate the cell wall. Furthermore, they are subject to rapid biodegradation by nucleases in the body.

Two types of carriers for nucleic acids are currently discussed: Viruses and nanoparticles. They can be taken up by cells, together with their cargo of DNA. Viral transporter systems have the advantage of a very high transfection efficiency, but concerns remain about possible side-effects [137-139]. Nanoparticles can be organic (like liposomes or polymeric nanoparticles) or inorganic in nature [140, 141]. Their efficiency is typically lower than that of viruses, but they have the advantage that they can be more easily controlled due to their non-biological nature.

The advantage of such a local gene delivery is the comparatively easy way to produce DNA in mg-scale and the long-lasting action. In principle, all kinds of cells around such a DNA-releasing implant can take up nanoparticles and start to produce DNA. Thereby, proteins like BMPs or VEGF can be produced and delivered *in vivo* to induce bone growth and vascularization [142-146]. It was recently shown that it is possible to induce the production of BMP-7 and VEGF-A from a paste of DNA-functionalized calcium phosphate nanoparticles. Thereby, osteoconductivity (by calcium phosphate) and osteoinduction (by production of the proteins around the implantation site) were combined [147]. **Figure 6** shows an SEM-image of DNA-carrying calcium phosphate

nanoparticles. Note that in general, nanoparticles have not only been discussed as delivery agents, but that they can also be used to increase the mechanical strength after embedding into a polymeric matrix (see, e.g., ref [148]). This follows the concept of a biomimetic hierarchically structured material, mimicking bone itself [149-151].

Another option within the framework of gene therapy is the silencing of selected genes by administration of small-interfering RNA (siRNA). As such, the production of proteins which, e.g., inhibit bone growth or vascularization, can be down-regulated. This is called gene silencing, another highly promising method within the framework of gene therapy [152]. Again, suitable carriers like nanoparticles are necessary [153-155]. They have been successfully tested, e.g. to down-regulate inflammatory genes [156] or osteopontin and osteocalcin in osteoblasts [157]. A transfection by nanoparticles is always temporary, i.e. after a few weeks or months (depending on the release kinetics from the scaffold), it ceases, ideally after completed bone healing. This adds to the confidence after application in a bone defect.

If osteoporotic bone shall be subjected to gene therapy to improve its strength, it would probably involve a local delivery of a nanoparticle-based system which carries suitable DNA. It is conceivable that this might work as a prevention of later fracture.

3.4.2. Perspectives in the use of cell therapy in the reconstruction of osteoporotic bone.

Recent developments of biomaterials largely reviewed in this paper converge on the needs of biological enhancement of biomaterials fostering osteoinduction and osteogenesis to support and augment bone healing after osteoporotic fractures. Indeed, the reconstruction of osteoporotic bone yields significant difficulties with the solutions available today. The osteoporotic bone, currently defined by its decreased quality (not quantity) leading to a mechanically incompetent biological material [158] manifests itself by the so-called osteoporosis-related fractures. Immediate consequences are bone collapse in metaphyseal compression fractures with bone defects and joint malfunction, comminution and delayed union or non-union after diaphyseal low energy fractures with thin cortices, or periprosthetic complex fractures on sclerotic bone surrounding implants. These problematic fractures seldom heal, restricting patient mobility and eventually leading to bed-ridden patients or even death. Therefore, therapeutic targets

can be defined, where advances in biomaterials are strongly needed. Basically, it has become clear that a biological problem is underlying this brittle, non-resistant bone. Frequently underestimated, biological insufficiency leads to significant bone healing problems.

While some osteoinductive effect is observed with various biomaterials, osteogenesis is required to obtain satisfactory bone repair and directly relies on osteoprogenitors and derived osseous cell lines [159]. Yet the number of osteoprogenitors available in the surroundings of a fracture is unclear and unpredictable. Furthermore, the number of available progenitors seriously decreases with age, and estimates of stromal cells in the bone marrow drop to one eighth from young adulthood to old age. Consequently, elderly patients with osteoporosis who are more prone to fractures are associated with limited biological capabilities to heal bone. In that context, it is interesting to use a cell-based therapy. However, despite significant advances in this field, efforts are hampered by various constraints: (i) the large number of in vivo and in vitro studies that are required in a pre-clinical stage, (ii) the safety and efficacy issues, and finally (iii) the regulatory and legal constraints.

Three main cellular therapy strategies have been developed and translated into bone regenerative clinical solutions [160]. Mesenchymal stem cells (MSCs) from fresh, concentrated autologous bone marrow have been widely used to enhance bone healing at non-unions [161], usually in adults at an early age. Only a slight improvement of biological regenerative potential can be expected when 1000-1400 MSCs are obtained per 2 mL bone marrow aspirate in young patients with an aim of injecting more than 55000 MSCs per injury. This autologous treatment allows for augmentation of surgical treatment without the consideration of introducing a cell-based medication into the patient, avoiding significant legal barriers when the whole process occurs during surgery.

To further increase the biological regenerative potential, an expansion of bone marrow MSCs from the patient may lead to millions of MSCs within a few weeks. Although this manipulation transforms the cell product into an Advanced Therapy Medicinal Product (ATMP) that requires fabrication in certified GMP facilities (under Good Manufacturing Practices), proposals are being developed currently through clinical trials. A major barrier to the use of this solution today with elderly and osteoporotic patients is the limited amount of stromal cells in the bone marrow progenitor pool.

Other sources of MSCs face similar problems in elderly patients and the osteogenic line proliferation and differentiation may be further limited. Allogeneic expanded cells would be an ideal solution but safety and efficacy remains unproven and significant problems do not hold a clear solution.

A third strategy under development involves MSC expansion on biomaterials. If an appropriate combination of biomaterial, cell dosage and stimulating molecules was found, structural and biological potential would facilitate an adequate bone substitute through tissue engineering closer to real bone. Only a few publications address clinical cases treated with this strategy [162], and in the autologous design, it is far from application in osteoporotic patients.

Major issues remain to be solved before these advancements can be solidly applied into clinical trials in elderly patients with osteoporotic fractures or complications. Many questions are unclear about the adherence and osteogenic differentiation of osteoprogenitors on many biomaterials. Furthermore, it remains unproven whether osteoprogenitors expanded on biomaterials maintain the adherence and thus the location; or else, if the functional capabilities of these cells are kept after surgical implantation, in particular the osteogenic potential.

However, even if serious barriers should be overcome, research lines are in place and the confirmed needs in these particular targets will probably transform in the coming years the way we understand the clinical potential of bone tissue engineering based on advanced biomaterials and cell therapy solutions.

To conclude, biomaterials used for osteoporosis-related clinical indications are fairly traditional, including metals, polymers, and ceramics. Their design (shape, composition) is generally adapted to better accommodate osteoporosis-related requirements. Part of the gap between clinical biomaterials and academic research can be explained by increasingly stringent safety regulations, as well as cost pressures. This will be discussed in more details in the next sections.

4. Biomaterials and osteoporosis. The industrial's point of view.

The previous sections have shown that there is a great need to improve the treatment of osteoporotic patients before and after the occurrence of a bone fracture. Various routes for therapeutic progress have been highlighted, including tissue engineering, drug-loaded bone graft substitutes, and gene therapy. Despite these needs and efforts, little

progress is seen clinically. In fact, the launch of BMP-loaded products a decade ago was the last important innovation. This impression is confirmed by the evolution of pre-market approvals (PMA) issued by the FDA (Fig 7). A PMA is compulsory for any device that does not have its equivalent on the market. In other words, the most innovative products have to go through a PMA review process. Over the last 10 years, the number of PMAs accepted by the FDA has decreased dramatically. Specifically, 23 PMAs were accepted from 2003 to 2007. This number dropped to 8 from 2008 to 2012. Simultaneously, there was a 50% increase of the 510k notifications, which are issued for products equivalent to other products already FDA approved. These two trends mean that companies in the US are shifting their efforts from innovations to incremental improvements of existing technologies. This situation in Europe is similar.

Many aspects have contributed to this decrease in the number of innovations. The most obvious one is related to the laws regulating medical devices. Over the past decades, the European authorities have strengthened their directives, not only by asking more data per product, but also by transferring certain products into higher product classes. This is the case for joint prostheses that were class II products until March 2010, and which are now class III products. Also, new ISO standards are continuously approved, which means that more tests have to be done to apply for a CE marking. It is clear that ISO standards are not compulsory, but it is often easier to perform the study than to explain why it was not performed. This is particularly disturbing for tests that have been shown to present important weaknesses, such as ISO 10993-5 (Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity), or the so-called “bioactivity test” (ISO 23317; Implants for surgery -- In vitro evaluation for apatite-forming ability of implant materials). In both cases, false positives and false negatives can be found (for ISO 23317, see references [163] and [164]). The trend towards stricter regulations is not expected to stop soon. In fact, much stricter directives have been proposed following the recall of PIP breast implants and DePuy metal-on-metal hip prosthesis. These directives are currently awaiting approval.

In 1985, the European parliament decided to harmonize the laws regulating medical devices within Europe to facilitate the transfer of goods. Directives were defined and implemented. Even though CE marked products can access the European market, other hurdles are still in place. For example, the French authorities ask companies to register their products prior to any reimbursement. In the US, the government decided a few

years ago to stop reimbursing vertebral bone augmentation procedures following the publication of two articles demonstrating an absence of significant effect between the treatment group and a “placebo” group [165, 166]. The fact that numerous publications have shown the limitations of these two studies has not changed the situation. In fact, medical device companies are increasingly asked to show the effectiveness of their product before reimbursement is issued. Since artificial joints may only prove their efficacy after 10 years, this requirement is particularly questionable and cost-intensive. Also, proving the efficacy of an implant may require multiple in vivo or clinical studies to support broad claims. For example, whereas it was possible in the past to only make one in vivo study for a “bone void filler, the authorities tend to require now more than one in vivo study. This is often very costly and may take years. Once a product is accepted for reimbursement, governments may decide on the product value. According to the French “Liste des Produits et Prestations” (LPP), a resorbable interference screw for ligament fixation is worth 234.16 Euros.

Currently, there is a trend towards the alignment of pharma and orthopedic product approvals. However, there is a major difference: whereas pharma products have generally a systemic action, orthopedic products have a local action (narrow range of indication). In other words, osteosynthesis plates or orthopedic implants are bone / joint specific, so each plate / implant requires a separate registration. The limited market size and increasingly large regulatory burdens are obviously important aspects / brakes in the decision processes occurring during product development. In fact, many R&D departments are nowadays focused on maintaining the product portfolio and reducing the costs, rather than developing new products.

Nowadays, governments are facing a dilemma: if they tighten the rules to obtain the CE mark of a new medical product, they restrict innovation, hence reducing chances to see new therapies; if they do not tighten the rules after the recent medical device scandals (PIP breast implants, DePuy metal-on-metal prosthesis), their electors might punish them at the next elections or even sue them as seen with the contaminated blood scandal. Currently, the former strategy is pursued worldwide, detrimentally to all clinical needs and research efforts. [167]

5. Conclusions

Osteoporosis is a disease that has become a worldwide challenge and comprises clinical, social and economic issues. This is mainly due to the increase of life expectancy, so the society, the health systems and industry should be aware of this problem, as an ageing population will be more prone to osteoporosis.

The main clinical consequences of osteoporosis are the fractures. The success of biomaterials for fracture fixation in osteoporotic patients, or simply for bone augmentation treatments, is impaired by the poor quality of bone and the decreased osteoblastic activity. In this sense, although there are a number of biomaterials to treat problems with bone in the market, they are not necessarily appropriate to address osteoporotic bone. Unsuccessful implantation can result in overpassing the line between frailty and disability in osteoporotic patients.

Clinicians, biomaterials scientists and industrial advisors are making important efforts to improve current implants and their applications, as well as provide new alternatives. Compounds able to stimulate the bone regeneration such as calcium phosphates (both ceramics and cements), calcium sulfates or bioglasses are being widely considered, especially associated with local drug and/or gene delivery as well as with cell therapy.

However, all these efforts only will be fruitful if these new biomaterials are successfully developed and commercialized. Currently, the level of commercial innovation remains well below expectations and the situation is only expected to worsen due to more stringent certification requirements and higher cost pressures. Thus, those that will play a major role in the prevention and treatment of osteoporotic conditions will most likely feature **the following points:**

- A well-developed definition of unmet needs
- It will most likely be indication-specific
- It will enable quantifiable clinical benefits to be proven in level of evidence 1 clinical studies
- It will be reimbursable
- A collaborative petition to agencies such as FDA could be helpful

Consequently, more research is necessary, driven by the clinical demand, to solve this problem. The fact that the current situation is difficult to manage should not prevent us

to seek new solutions. For this purpose, a close cooperation between fundamental research, industrial research, clinical research and regulatory bodies is required for the future. This will not be available for free (i.e. without money), but will pay off in the long run for everybody

In addition, the presence of new patients with new characteristics and new needs, mainly (but not exclusively) older people with frailty, should change not only the way to provide their management and treatment, but also the aims of the care and the way to assess the technological improvements. Regarding this last issue it should concern both the changes on how to organize the delivery of the care provided to these patients, the characteristics of the devices and its outcomes as well. This new model to assess the efficacy and effectiveness of the new technologies in the new patients should prompt a change in the rules of the regulatory agencies in order to adapt their procedures to the current needs of both the patients, the health systems and the industry, thus contributing to the well-being of the patients, the sustainability of the health systems and the competitiveness of the industry.

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Figure captions

Figure 1. Three trajectories of aging, with a differential risk for disability.

Figure 2. The path from robustness towards frailty and disability: factors, biomarkers and modulators.

Figure 3. Displaced intracapsular fracture (left) and trochanteric fracture (right).

Figure 4. Osteoporotic vertebral fractures in T12 y L4 . Vertebroplasty in T12 and reduction and fixation with cannulated screws and cement in L4.

Figure 5. Osteoporotic vertebral fractures treatment .Fixation with cannulated screws and cement

Figure 6. DNA-loaded calcium phosphate nanorods which are able to induce the formation of BMP and VEGF.

Figure 7. FDA pre-market approvals (PMAs) and pre-market notifications (510k) over the past 10 years. Sources:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> and

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

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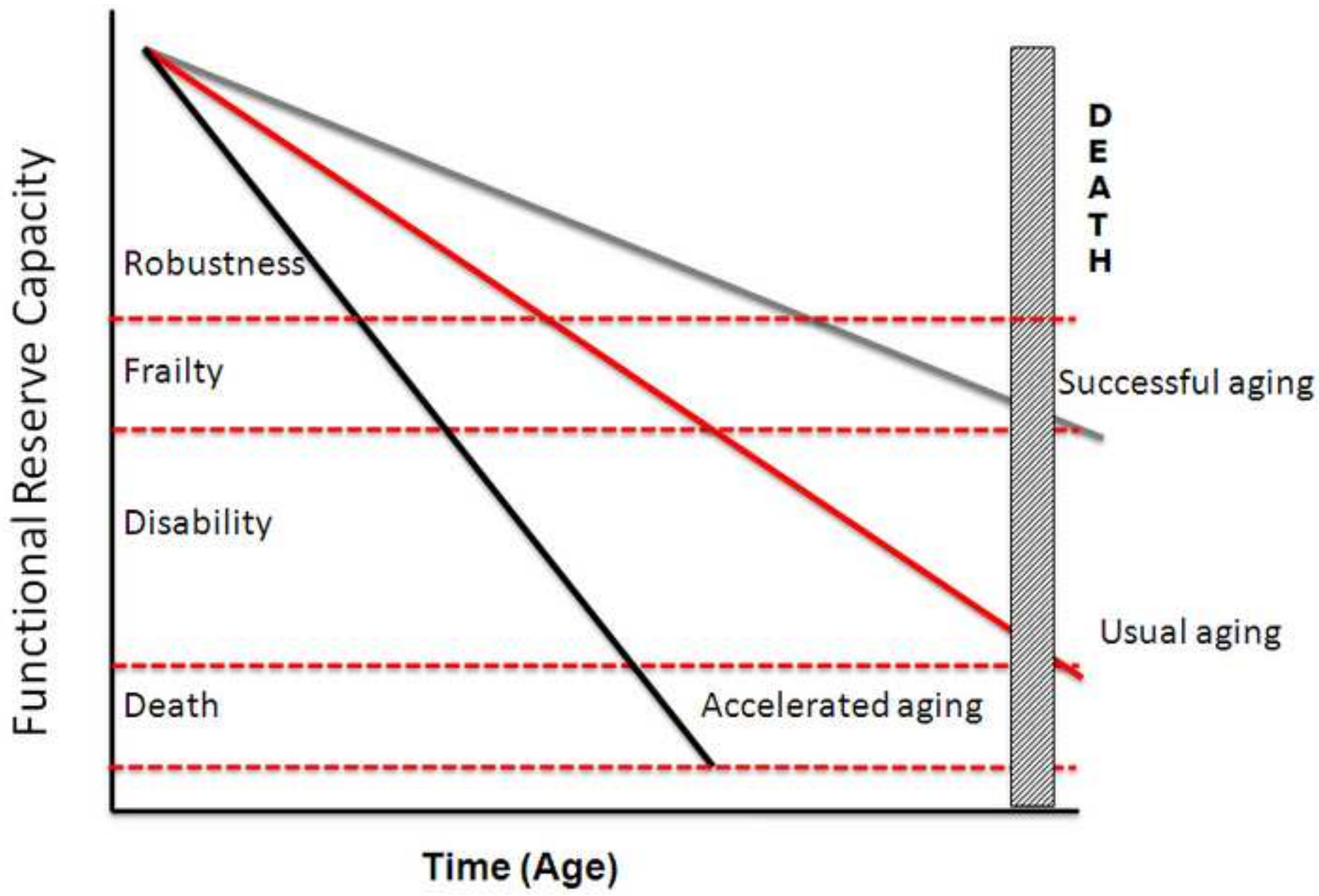


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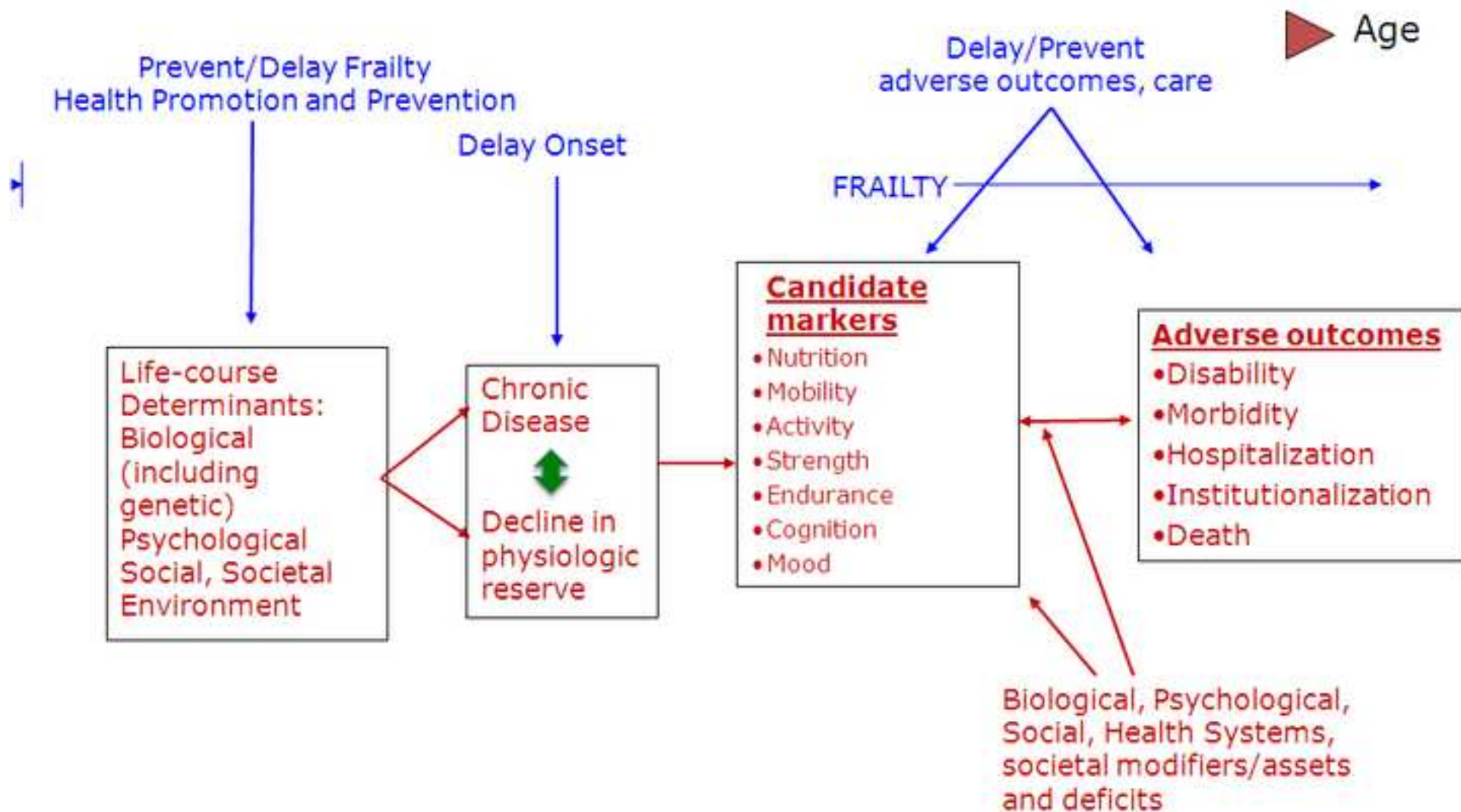


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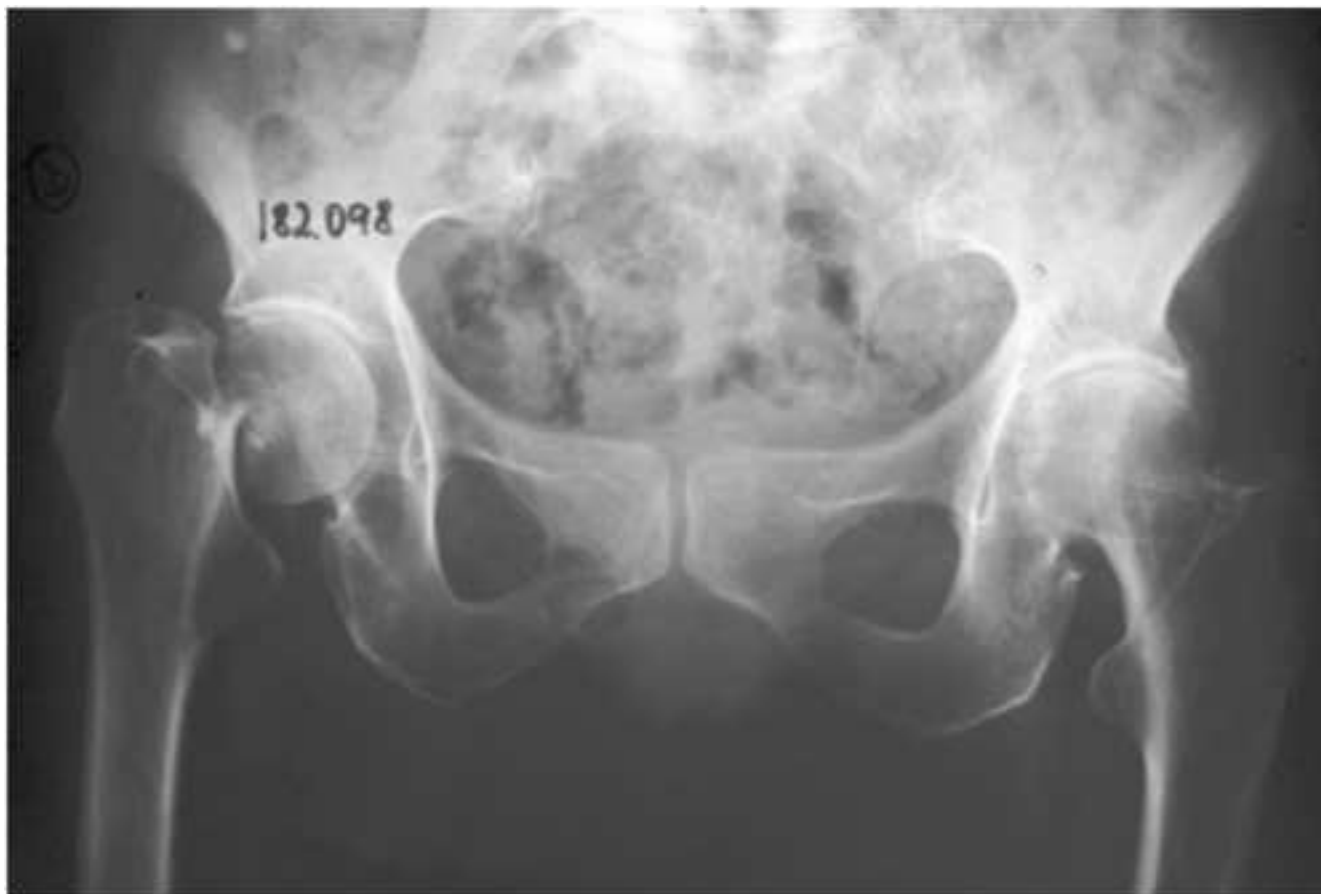


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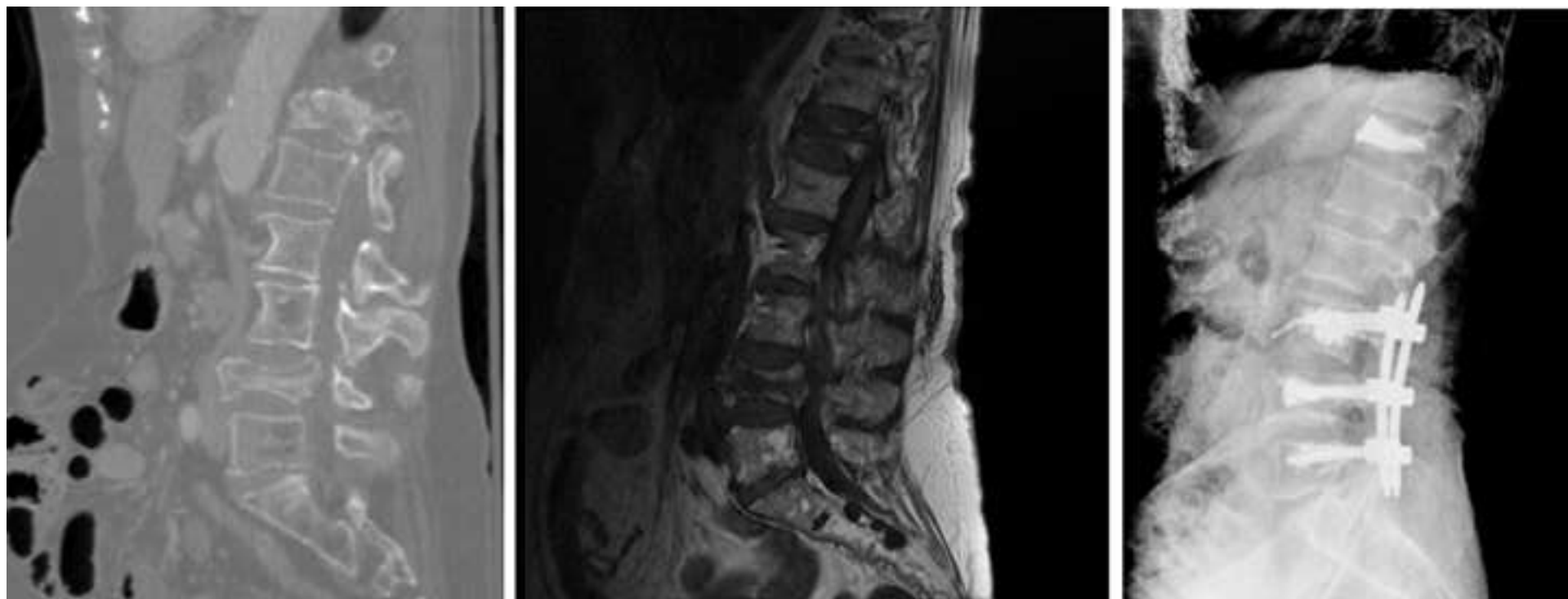


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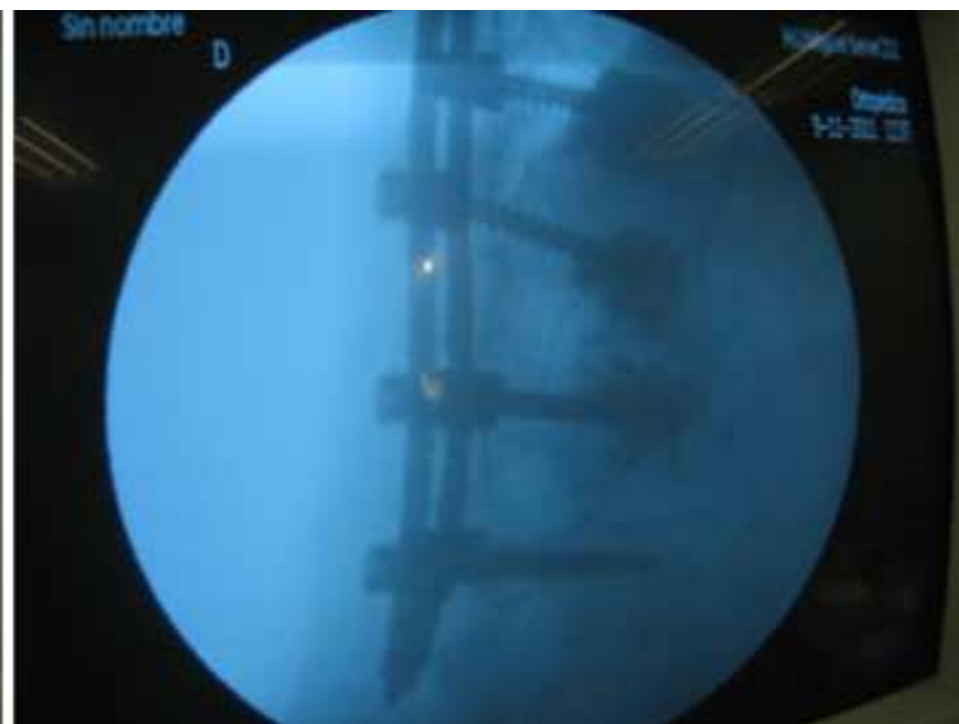
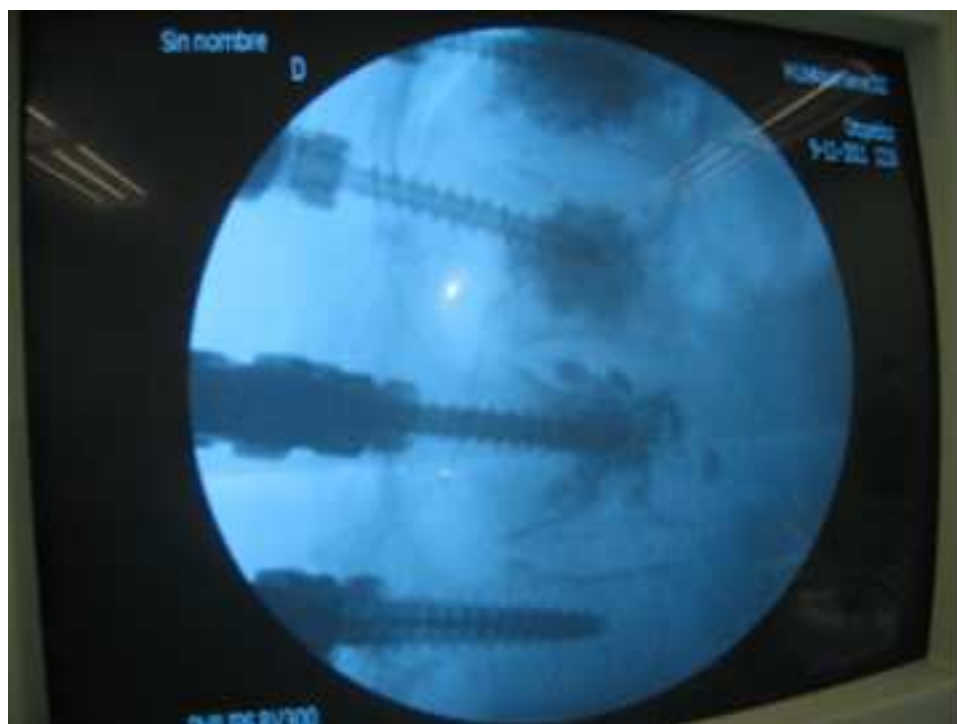


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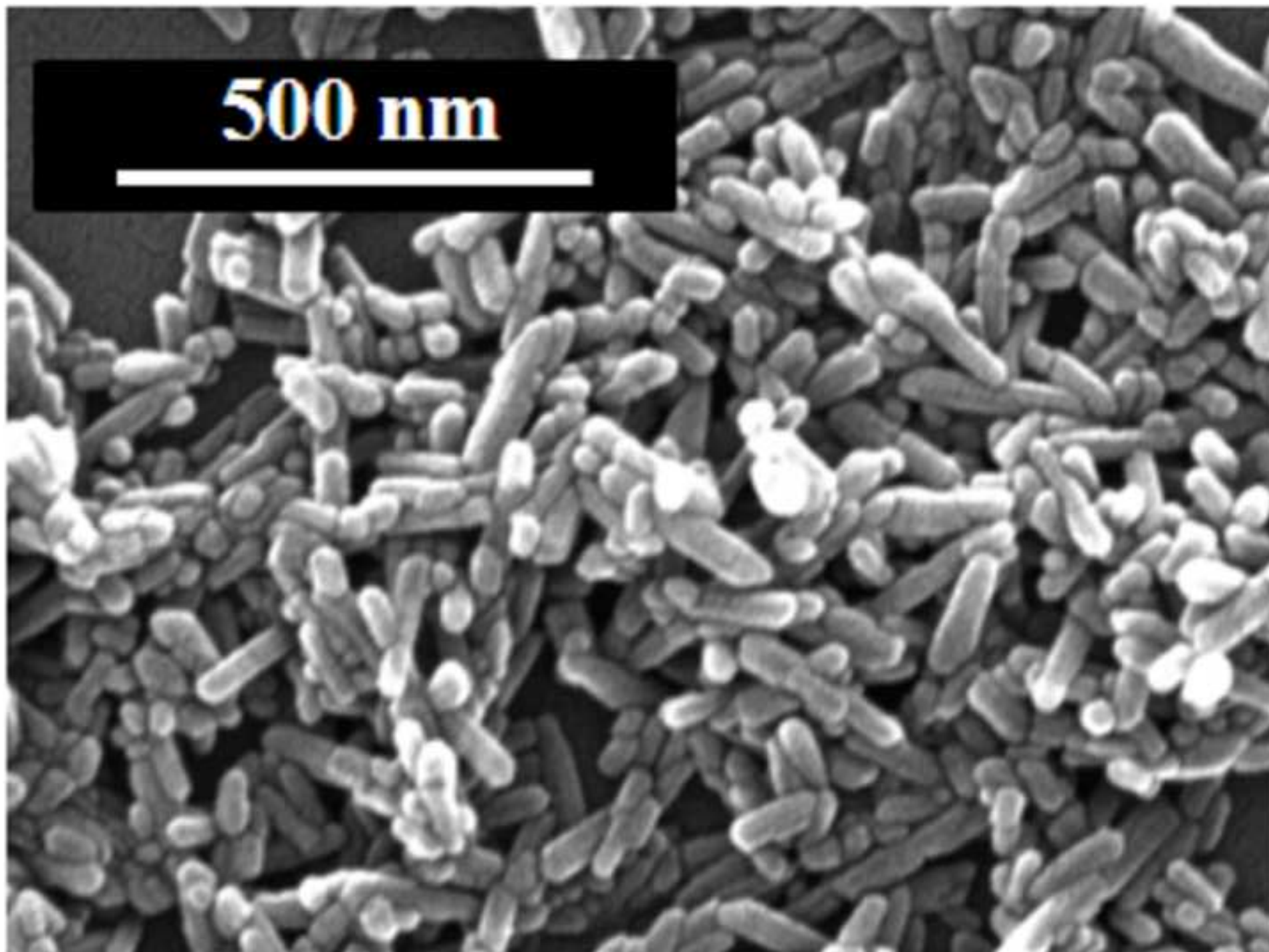


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