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REVIEW

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Biomaterials with Enhanced Biological Functions for Medical Applications

Reka BALINT[1], Gertrud Alexandra PALTINEAN[1], Gheorghe TOMOAIA[2,3], Daniel OLTEAN-DAN[2], Aurora MOCANU[1], Maria TOMOAIA-COTISEL[1,3*]

[1]Babes-Bolyai University of Cluj-Napoca, Faculty of Chemistry and Chemical Engineering, Research Centre of Physical Chemistry, 11 Arany Janos Str., RO-400028, Cluj-Napoca, Romania
[2]Iuliu Hatieganu University of Medicine and Pharmacy, Department of Orthopedic Surgery, 47 General Traian Mosoiu Str., Ro-400132, Cluj-Napoca, Romania
[3]Academy of Romanian Scientists, 3 Ilfov, RO-050044, Bucharest, Romania

[*]**Corresponding author**: Maria Tomoaia-Cotisel, mcotisel@gmail.com
maria.tomoaia@ubbcluj.ro

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Abstract

Biomaterials and their use as implant coatings have been evaluated focusing on biocompatibility, biodegradability and constructive responses in terms of osseointegration, cell proliferation and cell adhesion. Biomaterials from natural (protein and polysaccharide) and synthetic (metallic, polymeric, ceramic and composite) sources have been identified. The role of biomaterials and implant coatings in the body through in vivo and in vitro experiments has been highlighted. In addition, methods for activating the surface of implants such as mechanical, chemical and physical ones are presented, as well as the classification of the deposition procedures but also of the interactions with the living system. This review addresses a topic with future challenges and perspectives in the biomedical field with the well-defined goal of maintaining and enhancing tissue elasticity, facilitating the healing of diseases suffered by patients and developing innovative materials capable of replacing or regenerating affected tissues.

Keywords*:* biomaterials, implants, nanoparticles, cell membrane, cellular behavior, regenerative medicine, tissue engineering

Introduction

Bone replacement is one of the most controversial methods of bone regeneration in orthopedic surgery. In the medical field it is necesary to develop materials as closest as possible to chemical composition and structure of natural bone that favors faster healing with minimal side effects. The bone makes up the entire skeleton of the human body and is one of the largest organs that perform the functions of movement, support, mineral intake and protection. It also has the ability to reshape and self healing [1-7] that means absorption of old or damaged

bone tissue occurs at the same interface where osteoblasts produce new bone to replace resorbed bone. However, in the critical cases when the bone pathology is severely damaged, self-healing is not enough. Thus biomaterials capable of substituting or regenerating the affected tissues have been developed [8-10].

To understand what biomaterials mean and their role, the scientific community defines them as materials created in various forms such as fillers, implants, devices, catheters, nanoparticles, tubes, plates, wires and others that are intended to treat some diseases but also to partially or totally replace tissues or organs that come into contact with the body system [11]. Their use in medicine is essential to facilitate the healing of patients following the pathologies suffered and only if they have been accepted by the living cell matrix. Not all biomaterials are suitable for certain pathology.

Classification of biomaterials according to origin

A classification of biomaterials is highlighted in Figure 1. Depending on their origin, there are two main categories, natural and synthetic [12].

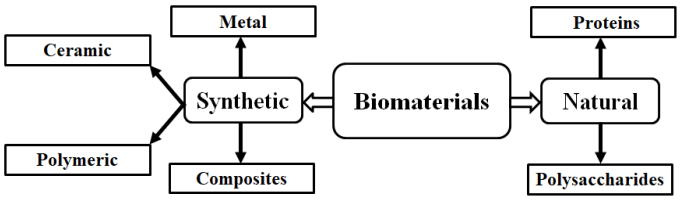

Fig. 1. Classification of biomaterials according to origin

Natural biomaterials represent a diversified class of materials with significant challenges for medicine. They are used to regenerate the affected area following accidental fractures or silent disease that over time has damaged the biological functional system. With their help, it is desired to be able to treat the ailments and to follow the evolution in time. In case of an unfavorable response, tissue replacement should be used. This procedure requires special attention in order to choose the biomaterial that best mimics the characteristics of the extracellular matrix and that helps to heal wounds faster [13,14].

Natural biomaterials contain proteins such as collagen, gelatin, elastin, keratin and polysaccharides such as alginate, starch, chitosan, cellulose, hyaluronic acid. Both proteins and polysaccharides help to maintain the quality of the body system and its proper functioning. Of all the proteins mentioned, *collagen* is one of the basic components of the body. It is present in the form of a fibrous structure of the extracellular matrix and connective tissue, located in the bones, muscle tissue, skin and tendons [15]. To date, 28 types of collagen have been identified that are composed of 46 distinct polypeptide chains, all with triple helix. Of all these, type

I, II, III and IV are the most common. Collagen can be extracted from rats, pigs, cattle and humans. It has been and is successfully used both in tissue regeneration and in cosmetic surgery [15, 16]. Its use in pharmaceuticals and regenerative medicine is due to the biocompatibility and biodegradability characteristics that give rise to favorite responses in terms of cell survival, proliferation and adhesion [17-20]. It is considered the ideal biomaterial for the multidisciplinary biomedical field; it helps the absorption of toxins and pathogens, the bone healing and the maintenance of structural integrity [21-31].

Gelatin is a protein derived from hydrolyzable collagen and is also found in the extracellular matrix. It has attracted the attention of researchers due to its biological origin similar to collagen [32]. The literature highlights its importance in biomedical applications that serve to skin, bone, eye and cardiovascular regeneration [33]. Gelatin exhibits excellent biodegradability, non-antigenicity, cost-effectiveness and high traction mode against collagen [34, 35]. However, its major disadvantage is that it dissolves as a colloidal gel at temperatures of 37^{o}C or above, and gels almost at room temperature [36].

Elastin, like collagen and gelatin, is a natural protein with the extracellular matrix as its source. Its role as a natural biomaterial in the body is to maintain tissue elasticity and ensure cell adhesion. Its crosslinking network consists of soluble precursor tropoelastine, resulting in an insoluble polymer. The elastic fiber is composed of amorphous elastin and microfibers that act as a scaffold on which elastin is deposited. They can be self-assembled in physical condition. The most important mechanical property is elasticity, due to which they are used for the replacement of skin and vascular grafts [37, 38].

Keratin is a protein rich in cysteine, insoluble in water and is the major component of the protective structures of the living being (horns, hooves, wool, feathers, hair and nails). It can be defined as a three-dimensional hierarchical structure based on amino acid chains such as nonionic polar amino acids (cysteine, serine), ionic polar amino acids (arginine, lysine), non-polar amino acids (glycine, valine). These chains differ in number and sequences of amino acids, polarity, charge and size [39- 41]. They are also excellent for cell adhesion and proliferation. Studies in the literature noted that keratin-based biomaterials have very good biocompatibility and unique chemical structure, based on which scaffolds, hydrogels, and films for biomedical applications can be prepared [41-43].

Chitosan is a ntural polysaccharide derived from chitin of animal origin (e.g. shrimp, crabs, crustaceans) and fungal [44, 45]. It is intensively studied as a biomaterial due to its biocompatibility, non-toxicity, biodegradability as well as antitumor, antimicrobial and antioxidant activities [46]. Due to the wide range of

characteristics, chitosan is used in biomedical and pharmaceutical applications in the form of scaffolds, hydrogels, films, nanoparticles, fibers and other. In vitro studies have shown cell adhesion and proliferation on chitosan scaffolds and antimicrobial activity against Gram-positive, Gram-negative bacteria, fungi and yeasts [47-50]. Chitosan-based biomaterials help regenerate different types of chains that involve seeding certain molecules on a biodegradable porous matrix, maintaining structural shape, differentiating and cellular maturation in order to heal bones [44, 51-53].

Starch is a polysaccharide produced by plants and contains amylopectin and amylose in its structure. It is explored due to its biodegradability and biocompatibility but also to adaptive factors in terms of drug transport and probiotics administration [54, 55].

Alginates are the constituent of seaweed with a wide range of natural polysaccharides and nutrients. It is used in the biomedical field in drug transport, in cell encapsulation, in tissue engineering and even in dentistry [54, 56].

Hyaluronic acid (HA) is a linear, unsulfated polyanionic polysaccharide containing a glycosaminoglycan with high molecular weight. It is composed of repeated disaccharide units of N-acetyl-D-glucosamine and D-glucuronic acid. It can be extracted from coconut combs, bovine eyes and human umbilical cord or from bacterial fermentation of group C steptococci, e.g. hemolytic streptococci [57, 58]. It is a major constituent of the extracellular matrix in connective, epithelial and neutral tissues in the body. It has important biological and physico-chemical properties such as lubrication, visco-elasticity, water retention, biocompatibility, favoring cell proliferation, morphogenesis and repair of inflamed plaques [57, 59, 60]. HA can be degraded by both intermediate reactive oxygen and hyaluronases, which are synthesized by macrophages, fibroblasts and endothelial cells [61, 62]. Purified HA has been used in cosmetics, eye drops, food additives, medical devices, pharmaceuticals, tissue engineering and cell therapy [63-66].

Cellulose is the most abundant polysaccharide on earth, with several thousand units of D-glucose in a polymer chain [67, 68]. It forms the structural framework of plants and is isolated in the form of microfiber. Cellulose can be enzymatically degraded, resulting in the formation of D-glucose units. We can mention some cellulose derivatives in the form of ethers, esters and acetates, for example methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose [69]. Cellulose can be used for various applications such as the development of surgical instruments, dialysis membranes, biosensors and tissue engineering [70-72].

Synthetic biomaterials are another class of materials that, as the name suggests, are made by specialists in the field in order to obtain a component as close as possible to the extracellular matrix with which it comes into contact. Interactions with the host involve biological processes that can contribute to tissue healing or can cause severe reactions. Such biomaterials are exemplified in Figure 1, metallic, ceramic, polymeric and composites.

Metallic biomaterials are intended for the manufacture of surgical implants. Due to their strength, fracture rigidity proper processing and ease of manufacture, they are successfully used in the field of orthopedics and dentistry (eg screws, plates and nails). Of course, in this field are also present the cardiovascular devices (formerly artificial heart valves) and neurovascular implants (formerly aneurysm clips) [73-75]. Always these biomaterials, before being implanted are characterized by clinical trials so as to meet the conditions necessary for a proper functioning of the biological system and which are accepted by the Food and Drug Administration (FDA) [76].

Example of metallic biomaterials

Metallic biomaterials can be made of ***stainless steel***, which was also the first metallic material used in surgery [77]. The use of 316 and 316L stainlees steels is due to the resistance to corrosive agents, biocompatibility, low cost compared to other metals and easy accessibility. The American Society for the Testing of Metals (ASTM) recommends the use of 316L stainless steel, which contains the following as components: 0.022% C, 0.79% Si, 1.6% Mn, 0.25% P, 0.002% S, 15.30% Cr, 14.09% Ni, 2.63% Mo and 0.05% Cu. In vivo experiments have shown that nickel ions are released, which leads to poor resistance and adverse reactions to the biological system. For this reason, an alternative has been found to avoid this disadvantage by introducing a new type of Co-Cr alloys [78-80].

Co-Cr alloys began to be used in dentistry in the 1930s as cast implants and later adapted for orthopedic applications.Mechanical strength and corrosion resistance is much better due to the high chromium content compared to stainless steel. However, a major disadvantage of these alloys is that they biocorrode. This means that there is an uncontrolled release of metal ions which leads to severe interactions in the body [81, 82].

Tantalum attracts the attention of researchers due to its bioactive interaction with the human body and biocompatibility. In vivo tests have shown that cell proliferation occurs due to porosity, low elasticity and corrosion resistance in body fluids allowing the stabilization of the implant even without a screw [82-84].

Pure titanium and its alloys are the most widely used metallic biomaterials at present in orthopedic and dental surgery due to the lack of side effects. The chemical property of titanium and its alloys that makes them special is the

resistance to corrosion in the biological environment but also the mechanochemical properties and low specific weight 4.5g/cm^3 recommend them for use as implants. Biocompatibility and high corrosion resistance is given by the thin layer of titanium oxide acting as a barrier between the tissue and the titanium particles of the substrate. The thin layer of titanium oxide is formed by the interaction of titanium with air [85-88].

Gold Nanoparticles (GNPs) are recently considered as biomaterials. They have enhanced the interest of researchers due to the increased potential in the fields of nanotechnology and nanoscience as well as in biomedical, bioanalytical and dental applications. Physico-chemical properties such as localized surface plasmon resonance and characterization methods like SEM, TEM and AFM electron microscopy are among the most discussed in the literature providing essential information for targeted application.

They are intensively studied and used worldwide in medical diagnostics and different therapies, in controlled administration of drugs and in biosensors [89, 90]. They are easily synthesized by chemical and biological methods and allow functionalization with various biomolecules, organic ligands and polymers with specific functions [91-96]. Drugs [97, 98], proteins [99-101, 49, 50] and amino acids [102-108] are among the most used in combination with GNPs.

The interactions between GNPs and biomolecules produce surface changes and forms conjugates or complexes with better stability. They open various opportunities in the development of new biomaterials for controlled drug release and improve the overall treatment of cancer [97, 109, 110]. As an example, GNPs were synthesized and capped with resveratrol, Resv, resulting the GNPs-Resv, which was further functionalized with drugs, like doxorubicin, Dox, leading to the GNPs-Resv-Dox complex as shown in Figure 2.

The GNPs-Resv and GNPs-Resv-Dox complexes were investigated by MTT test of cell viability in HeLa and CaSki cell lines of cervical cancer and the results showed strong anticancer activity. Finally, it was demonstrated that resveratrol and GNPs can mediate the activity of doxorubicin at its low concentrations, and thus, opening perspectives for cervical cancer treatment [97].

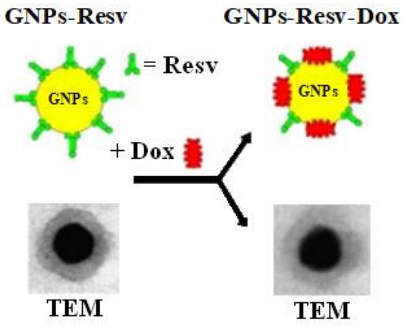

Fig. 2. The GNPs-Resv and GNPs-Resv-Dox complexes were evidenced by UV-Vis spectra and TEM images [97].

Also, it was demonstrated that anesthetics, such as tetracaine, dibucaine and procaine, strongly interact with GNPs. Their association reveals the potential for the formation of well-defined molecular surfaces but also for self-assembly that can bring benefits in the administration of drugs and their penetration into cells or in the detection of anesthetics from various biological fluids [98, 111].

As osteoinductive biomaterials, GNP has a high potential in the development of biological processes, such as applications in tissue engineering, hard tissue growth, cell surface adhesion and osteogenic differentiation in stem cells. An extremely beneficial achievement is the interaction between GNP and hydroxyapatite. Hydroxyapatite is a major biomaterial of bone and dental tissue. The binding of the two biomaterials aims to develop promising materials for tissue engineering applications. [112-116].

In the field of dentistry, GNPs are used in the treatment of gum disease, dental caries and in dental implantology as filler. They improve the mechanical qualities of the materials, which is of particular interest in making scaffolds to improve cell differentiation [117].

All these studies prove that GNP is essential as biomaterials that can be incorporated into composites and the progress will continue in the exploration of new applications from health fields.

Given the worldwide pandemic situation, the use of GNPs in coronavirus diagnosis and in colorimetric detection of Sars-Cov has been highlighted [118, 119].

Silver nanoparticles (SNPs) are the most widely used among metallic nanoparticles in the medical and pharmaceutical fields [120]. They have demonstrated their antibacterial efficacy through the mechanism of action given by the interaction at the level of the bacterial membrane, seen in Figure 3. The interaction produces distinct effects on the bacterial cell, namely, the attack of cell

walls, the generation of reactive oxygen species and oxidative stress and changes in functionality between proteins, mitochondria, ribosomes and DNA. Eventually the functional imbalance of the bacterium occurs and death is caused [121, 122].

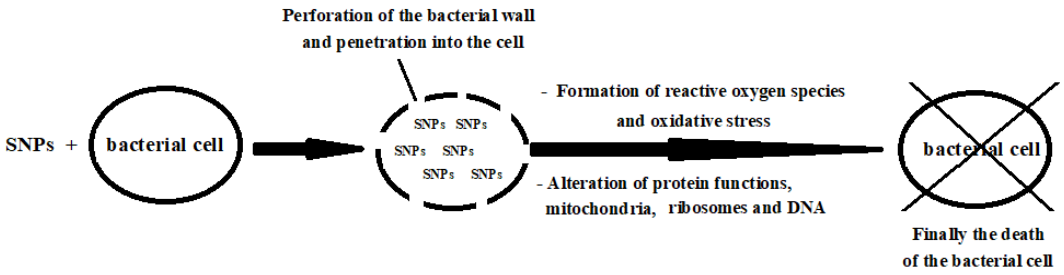

Fig. 3. Interaction of SNPs with bacterial membrane

In the fight against pathogens is very important the method of preparing nanoparticles and the use of reducing and coating agents that can influence the interactions between the drug and silver and can determine the size and shape [92, 123-126]. Silver nanoparticles can be synthetized by chemical and biological methods, the most known being reduction of silver nitrate ($AgNO_3$) with a large variety of reducing agents such as sodium citrate [123, 127, 128], sodium borohydride [129], glucose [130, 131], gallic acid, ascorbic acid and plant extract [92, 132] but also by electrochemical or photochemical methods.

The approach of functionalizing SNPs with various biomolecules (proteins, aminoacids, and antibiotics) has improved the qualities and action of silver, thus increasing the reactivity and effect on the biological processes in which it is involved. SNPs are a powerfull biocide against fungi, viruses and other microorganisms. They are able to form stable self-assemblies and have a high potential in biomedical research. The interactions with biomolecules allow the development of new biomaterials with implications in nanoscience and nanotechnology [111, 133].

The exploitation of SNPs has intensified in recent years due to the invasion of pathogens in the health system and the resistance of bacteria to antibiotics. In this sense, there are experimental studies that highlight the effectiveness of SNPs functionalized with vancomycin and other antibiotics potentiating their effect on bacterial strains [124, 134].

It was investigated also the interaction of SNPs with local anestestetics, procaine, dibucaine and tetracaine, which can be exploited to evaluate the concentrations of anesthetics in various media [130, 111].

The importance of functionalization of SNPs is given by the ability to forming complexes that increase their effect, so the action of SNPs is not limited only to antimicrobial activity but also to antifungal, antiviral, antiinflamatory and

anticancer one. The most recent activity of functionalized SNPs is antimalaria. A group of researchers used drug for malaria like Artemisinin (a component extracted from the leaves and flowers of Sweet Wormwood) and its derivates Artemether and Artesunate. They use the density functional theory (DFT) and simulation of molecular dynamics suggesting based on the results obtained that SNPs with low toxicity and antiviral activity can be used as a carrier of drugs against malaria and new strains in Covid-19 [135].

The antimicrobial effect of silver ions was also studied by adsorption on ceramic disks of hydroxyapatite or by incorporation into a polymer matrix made of BIS-GMA and TEG-GMA [136, 137]. SNPs are used in the development of optimal compositions for bone tissue engineering, medical devices and metal implants. This approach is of real interest in orthopedics and dentistry in combating bacterial strains such as S. aureus, E. coli, B. Cereus, C. albicans which can cause various postoperative infections [138-140].

Currently, study on the development of new biomaterials or composite to treat the new virus are encouraged but still require time to optimize an appropriate solution [141]. Viruses are larger in size than SNPs. In other words, the small size of SNPs makes possible their antiviral effects. Experiments in this direction were performed only on animals and not humans.

The association of SNPs with various biomolecules has led to improved systems for the controlled release of drugs to the sites to be treated. Although they are in continuous development, they help to improve the innovative materials used in the biomedical field (orthopedic, cardiovascular and dental implants, wound dressings), in the field of environmental protection (surface disinfection and water purification), in the chemical, cosmetic, food industry, and other areas of interest. Here's how a nanoscale product can be useful in a wide range of applications created by human socio-industrial activities.

Ceramic biomaterials represent the class of inorganic materials of ceramic origin with biocompatible and osteoconductive properties and high compressive strength. They can be used in the preparation of scaffolds for tissue engineering and hard tissue regeneration [142].

The most common ceramic biomaterials are:

***Alumina* (Al_2O_3)** has proven to be a bioinert ceramic, with high hardness and high abrasion resistance, excellent wear and abrasion behavior. These characteristics are associated with high surface energy and surface roughness. In vivo and in vitro experiments have shown that this ceramic also has a good biocompatibility [142, 143].

Zirconia **(ZrO_2)** is a biocompatible and bioinert biomaterial used for the manufacture of hip prostheses and more recently for hip joint balls. Its osseointegration was determined by the results obtained in in vivo and in vitro tests. The acquired characteristics are more efficient than those of alumina, they are chemically stable, but in high concentrations they produce unwanted biological responses [144, 145].

Biomaterials made of ***carbon fibers*** (with a micro graphite crystal structure) or pyrolytic carbon are biocompatible and bioinert and are used for implants and biomedical devices. The literature specifies the compatibility of carbon materials with bone and soft fabrics resulting in low tensile strength which prevents their use in high load applications. They can be used in contact with sangvinic flux because they have the ability to resist coagulation at the interface between the surface of the material and the tissue [146, 147].

Calcium-based phosphates (Hydroxyapatite, HAP and β-tricalcium phosphate)

Hydroxyapatite (HAP) **- $Ca_{10}(PO_4)_6(OH)_2$** is the most widely used component for hard tissue regeneration or replacement with a Ca / P ratio of 1.67. It is the most stable calcium phosphate that closely mimics the chemical composition of natural bone and teeth. It has exceptional biocompatibility with hard tissues, skin and muscle tissues [148]. It is bioactive, non-toxic and capable of osseointegration, osteoconduction, osteoinduction and ion exchange. Having these essential characteristics, it becomes the main choice in bone reconstruction both as a filling material and as a covering material for metal implants [149]. Numerous studies have shown that hydroxyapatite induces new bone formation in vivo [150]. Its microporosity is essential in the development of bone growth and formation. Specialized research has shown that osteoinduction is very important and is caused by the concentration of bone growth factors in the circulation of biological fluids [151-154]. It is important to note that osteoinduction is mediated by host mesenchymal stem cells that differentiate into bone-forming osteoblasts [155, 156]. Biodegradation of hydroxyapatite is initiated by changes in the surrounding biofluids and by the adsorption of biomelecules. The process of chemical dissolution depends on the surface / volume ratio, fluid convection, acidity and temperature [157]. Regarding bioresorption, it is mediated by osteoclast and macrophages cells [158, 159].

Hydroxyapatite allows different isomorphic substitutions in its structure by partially or totally replacing Ca^{2+} ions with other divalent, monovalent or trivalent cations, while its PO_4^{3-} and OH-anions can also be replaced by other anions and thus different stoichiometric structures are possible and nonstoichiometric ones as well [160]. It can also improve the structure by doping with various elements such as Mg, Zn, Sr and Si, which are involved in bone development and

metabolism, regulate cell activities such as proliferation, differentiation, adhesion and migration, regulate osteoblast and osteoclast activity and for the other hand can be considered systems for the release of biological active ions [161-165].

Magnesium is involved in bone growth and remodeling through the activity of osteoblast cells [166]. It stimulates bone tissue regeneration, helps increase bone density, inhibits osteoclasts and increases osteoblast response and has anti-inflammatory and antimicrobial effects [167, 168]. Strontium reduces resorption and improves bone formation, increases osteoblast activity and decreases resorption that acts on osteoclasts [169-171]. Strontium can replace calcium in hydroxyapatite in any proportion, even up to 100%. Silicon plays an important role in biological performance by improving bioactivity, stimulates the proliferation and development of osteoblasts and mesenchymal stem cells [172-177].

β-tricalcium phosphate is used in bone regeneration. It is less stable than hydroxyapatite, but has a faster degradation rate and higher solubility [178]. β-tricalcium phosphate is used because it increases biocompatibility [179], promotes the proliferation of osteoblast and bone marrow cells, and is a suitable component in bone substitutions [180-182].

Forsterite (Mg_2SiO_4) is a ceramic intensively explored at present due to its antimicrobial activity so it can be a promising biomaterial in biomedical applications. Specialized studies have shown that forsterite may be a good choice for bone implants. They have good bioactivity and biocompatibility. It has the ability to improve cell adhesion and proliferation as well as being used in bone strengthening. Forsterite can also be used as a carrier of silver nanoparticles against pathogens and therefore used as a coating material for metal implants [138, 183-190].

Polymeric biomaterials (biopolymers) are materials that can be used in physiological environments without causing adverse reactions in the body and in obtaining prostheses in order to replace parts of the body [191]. These polymers can be natural or synthetic, their properties being similar to the replaced tissues [192].

Natural polymers are the proteins and polysaccharides described above and are intended for use in reconstructive tissue engineering such as plastic surgery, vascular surgery, maxillofacial surgery and others [193]. They have applicability in biomedicine due to their biocompatibility, bioactivities, imitate very well the native cellular environments, have unique mechanical properties and are biodegradable by an enzymatic or hydrolytic mechanism. However, they also have disadvantages, such as the risk of viral infection, antigenicity and the supply of unstable materials [194, 195]. The challenges of these natural polymeric

biomaterials in surgery involve clinical application, acceptance by the FDA and EMA of the materials used, short and long term effects, cost, risk of infection, etc. [196]. Considering these aspects, the specialized literature highlights that with the help of these procedures it is desired to decrease the mortality among the patients.

Synthetic polymers are inert and non-immunogenic biomaterials used more and more often in tissue engineering for biomedical applications [197, 198]. A classification of them is described below:

Poly alpha esters (Polylactic acid, polyglycolic acid, polycaprolactone)

Polylactic acid (PLA) is an aliphatic, thermoplastic, non-toxic, biodegradable and biocompatible polymer, derived from lactic acid. Lactic acid can be produced by fermentative or chemical synthesis. Chemical synthesis is mainly based on the hydrolysis of lactonitrile in acidic medium when an echimolecular mixture of the two optical isomers is formed, a racemic mixture of the two enantiomers D and L lactic acid [197, 199, 200]. PLA has been approved by the Food and Drug Administration (FDA) since 1970 until now [201].

Due to its characteristics it has attracted attention and interest as an innovative material for a wide range of biomedical and pharmaceutical applications (eg drug delivery systems, sutures, bone fixation implants), scaffolds for soft and hard tissue repair, synthetic grafts [201, 202]. The absorption rate depends on the molecular mass, morphology and purity [199]. Surface modification strategies have been proposed such as physical, chemical, plasma and induced radiation in order to create a surface with favorable properties on biomaterial [203, 204]. PLA biodegradation is essential in biomedical applications and has been studied in both animals and humans. In vivo experiments demonstrated the degradation of PLA by hydrolysis, and the soluble oligomers formed are metabolized by cells [205, 206]. Biodegradability time makes it an attractive candidate for in vivo implants. More recently, the PLA/PEG or the PLA/HAP mixture have been used in order to improve physicochemical properties and the printing process [207, 208].

PLA-based 3D scaffolds are used in tissue engineering as an in vitro support for the adhesion and proliferation of cells that simulate the mechanical support of the extracellular matrix. In vivo they are used for organ regeneration. Patient-specific 3D scaffolds can be designed, ie to be in accordance with their anatomical data [209-211].

Polyglycolic acid (PGA) is the simplest alpha-polyester, thermoplastic, rigid and with high crystallinity which makes it insoluble in organic solvents [212-216]. PGA-based materials are used as fibers and composites that help heal tendons, ligaments, bones [217], and for resorbable implants in the form of rods, plates, fibers, and bone marrow transplants. PGA is in the attention of researchers due to

its characteristics of biodegradability, biocompatibility and non-toxicity [218, 219].

Poly-ε-caprolactone (PCL) belongs to the family of linear and semi crystalline aliphatic polyesters [220, 221]. It is used successfully in sutures and dressings, in cardiovascular tissue engineering, nerve regeneration, drug transport and bone tissue engineering [220, 222]. Polycaprolactone is a polymer approved by the Food and Drug Administration (FDA) due to its non-toxicity, biodegradability, compatibility with a wide range of polymers, good process ability, the possibility of manufacturing in different structures and shapes and low cost [223-225].

Poly (lactic-co-glycolic acid) (PLGA) is a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). The monomer ratio is useful for identifying PLGA copolymers. For example, PLGA 50:50 means a PLGA copolymer 50% of each, glycolide and lactide [226, 227]. It has been approved by the Food and Drug Administration (FDA) in the manufacturing procedures of various therapeutic devices, including tissue grafts, surgical sutures, bone scaffolds, and drug carrier systems [228]. It has excellent biocompatibility, controlled biodegradability, high degradation rate, mechanical properties, and thermal process ability and can encapsulate molecules of almost any size [229-231].

P*olyurethanes*

They are a class of segmented copolymers, composed of fine, soft and hard segments. The soft segment has as component polyester or polyester polyol while the hard segment is composed of a diisocyanate. The soft segment provides elasticity, while the hard segment contributes to strength and rigidity [232, 233]. Polyurethanes are widely used in industry (rubber, paints, foams), in biomedicine (long-term implants) and pharmaceuticals (medicines). Possessing excellent biocompatibility, in vivo experiments showed cell growth without side effects in the tissue [233, 234].

Polyethylene glycol (PEG) is a widely used synthetic polymer due to its hydrophilicity; biocompatibility and the resulting gels are approved for this purpose by the Food and Drug Administration (FDA). Polyethylene glycol can be modified with acrylate or methacrylate groups, which allow the formation of hydrogels in the presence of precursors. PEG is a biomaterial intended for engineered cell and tissue applications implant coating, biosensors and drug delivery [235, 236]. It is soluble in water and organic solvents, inhibits the formation of vacuoles and scars, reduces inflammation, protects the nerve membrane, reduces cell death and protects mitochondria [237, 238].

Composite biomaterials

Diseases in bone tissue engineering are most common in the elderly and are the cause of clinical challenges in the development of biomaterials capable of regenerating chronic bone defects and reducing mortality [239]. These biomaterials are made up of the combination of two or more chemically different materials [240]. Examples of composite biomaterials (polymer / polymer, polymer / ceramic, metal / polymer, metal / polymer / ceramic) are presented below [241].

A polymeric composite is a multiphase material in which the reinforcement fillings are integrated with a polymeric matrix, resulting in synergistic mechanical properties that can be obtained only from both components together [242-244].

Polymer / Polymer

PLGA/BSM (bladder submucosa matrix) ***scaffold.***These scaffolds have been developed to cure critical bone defects and cartilage regeneration. In vivo experiments demonstrated bone remodeling from day 30, forming thin trabeculae and also observed the adhesion of osteoblasts to produce the extracellular matrix [245]. PLGA scaffolds are hydrophobic, and this prevents cell adhesion and proliferation [246]. For this reason, a naturally derived collagen matrix from porcine was chosen such as BSM (bladder submucosa matrix). This is biocompatible and promotes cell adhesion on different strains, such as embryonic cells (EC) and primary bovine osteoblasts (bOB). BSM_PLGA scaffolds are nontoxic and hydrophilic that helps to seeding, adhesion and proliferation of cells. It also increases the process of bone formation. BSM_PLGA-based scaffolding helps to penetrate the culture medium, seeding, even distribution and increased migration due to BSM's hydrophilicity. Adhesion and proliferation of PLGA stem cells and osteoblast cells (on BSM scaffolds) were tested and showed an 80% improvement over PLGA [247].

PLA/PCL-collagen multilayer scaffold have been made to mimic the dura mater structure that serves to protect the new layer. Dura mater is a membranous connective tissue located on the outside of the meninges around the brain and spinal cord. It is responsible for storing cerebrospinal fluid, covering and supporting the dural sinuses and ensures the transport of blood from the brain to the heart. Experimental results have shown that combining the PLA-PCL with collagen prevents tissue adhesion on the inside surface and promotes cell growth on the outside surface [248].

PLGA/COL, PLA/alginate, PLA/collagen scaffolding. Several types of scaffolds have been experimented with, eg: collagen-coated PLLA, poly (L-lactic acid) sponge, collagen fibers embedded in PLA, PLA/alginate, PLGA/collagen hybrid sponge. In vivo and in vitro experiments have shown that the PLGA/Collagen sponge is more effective for chondrocyte adhesion and

proliferation than the individual PLGA sponge. The formation of articular tissue similar to cartilage has been observed which is due to the homogeneous distribution of chondrocytes [249].

Polymer / Ceramics

HAP/gelatin scaffold. HAP/gelatin scaffolds were prepared for trabecular bone tissue engineering. Analyzes of these scaffolds have shown that the compressive modulus increases with the HAP content. The morphology and structure of these scaffolds were analyzed by SEM and it was observed that the pores are interconnected and their size varies between 80 and 400 μm. The pores are large enough to accommodate the cells. Research has shown that by adding HAP the walls of the scaffolds become thicker and the porosity decreases. Thus, it can be concluded that HAP improves their mechanical properties [250-252]. Scaffolds showed good compatibility with host tissue and cell attachment, spread and proliferation were observed [252].

The researchers showed a significant increase in protein adsorption and osteoblast adhesion on the nanoceramic surface than on traditional ceramics. Increased adhesion of osteoblasts has been observed with decreasing particle size. HAP/ polymer scaffolds can serve as a better three-dimensional layer for cell attachment and migration in the process ofbone tissue engineering [253].

nHAP/PCL scaffolds with different ratios (1:2, 1:4, 1:8). HAP/PCL nano scaffolds are porous, the pores are interconnected. Two types of pores can be observed: large pores measuring 250-400 μm and small pores of about 10 μm. Histological analyzes revealed the growth and proliferation of cells on these scaffolds. The ADN content on all scaffolds gradually increased over 14 days. In the formation of new bones is important the size of the pores and the interconnectivity of the scaffolds that influence cell migration, proliferation and vascularization of tissues. Interconnectivity and porosity are important factors for bone growth leading to good osseointegration and fixation [254].

nHAP/PLLA scaffolds in different ratios and in different solvents. Specialized research has shown that nano HAP/polymer composites have a better compressive modulus. Protein adsorption on nHAP/PLLA scaffolds is much higher than on regular HAP. For scaffolds that contain more HAP than polymer, the protein adsorption is much higher than in the case of simple polymer. The use of solvents produces significant changes in the morphology of the scaffolds and the absorption of proteins. These results suggested that protein adsorption on scaffolds could be controlled by the amount of HAP, particle size and scaffold morphology. The porosity of the scaffold is determined by the solvent (dioxin), temperature gradient and HAP particles. The temperature gradient by crystallization of the solvent forms an anisotropic structure. The addition of HAP

particles to the polymer solution caused an irregular pore structure. From mixed solvents (dioxin and water) that were used, a random structure and interconnected pores resulted, and the pore size was much smaller [255].

PLA/HAP scaffolding is obtained by mixing ceramics with natural or synthetic polymers, obtaining good results due to the properties of both components. PLA/HAP biocomposites are used for both scaffolding and drug delivery. These composites could improve bone regeneration by forming new tissue, removing certain unwanted effects from each component. Use as a scaffold for fixing bones mimics as much as possible the tensile and compressive strength properties of natural bone. These have values in the range of 50-150 MPa and 130-180 MPa respectively. Grafting the polymer can improve the mechanical strength and can establish a direct chemical bond between the polymer and the hydroxyapatite by the reactive hydroxyl groups on the surface of the HAP particle. The mechanical properties of the PLA/HAP composite are influenced by the percentage of HAP and the processing temperature. These composites are biocompatible for osteosarcoma, osteoblast and fibroblast cells, promoting increased cell adhesion and promoting the differentiation of osteoblasts by alkaline phosphatase [256-259]. Sadudeethanakul et al. made PLA/HAP (5%, 10%, 15% HAP) plates by hot modeling (140^{o}C, 150^{o}C, 160^{o}C) and hot compression (3 MPa, 5 MPa, 7 MPa) methods. The bending power was investigated by a universal testing machine (UTC). As a conclusion to this research, the optimal bending conditions were found for plates with 5% HAP, 160^{o}C, 7 Mpa [260].

3D PLA/HAP scaffolding. 3D scaffolds with PLA and 10% HAP improve osteogenic properties without changes in cell compatibility or shear strength of the composite. In the analyzed study, the PLA/HAP scaffolds showed a good accuracy compared to PLA scaffolds. The addition of HAPs in the composition has been shown to increase dimensional stability and increase mechanical properties [261]. Other research has synthesized different PLA scaffolds with different concentrations of HAP, namely 5%, 10% and 20%. The roughness of their surfaces that influences cell attachment was investigated and it was observed that HAP10% produces consistent surfaces during 3D printing. Also, through the in vivo tests performed, the authors claim that for the composite with 10% HAP the cellular attachment was favorable compared to the other compositions. However, this composition showed a decrease in tensile strength and modulus of elasticity which can be explained by the increased crystallinity [262]. Mondal et al. highlights that HAP nanoparticles improve the surface roughness of PLA scaffolds, their porosity can be controlled and it has a better quality in terms of mechanical stability and osteoconduction and osseointegration properties. The results of in vivo testing showed cell attachment and proliferation on PLA/HAP scaffolds and less on PLA scaffolds [263].

As a conclusion regarding these scaffolds, the literature shows that the introduction of HAP in the composition of PLA polymer improves the qualities of its surface and physico-chemical, mechanical and biological properties.

COL/HAP scaffolding

Major bone components, such as hydroxyapatite and collagen, are frequently used in bone reconstruction. Hydroxyapatite is an inorganic component of bone and has biocompatible, osteoconductive and bioactive properties. Collagen is the organic component of bone a fibrous protein and the main component of the extracellular matrix. Collagen type 1 is most used for the formation of new bones with characteristics of biocompatibility, biodegradability and osteoconduction which helps cell migration and proliferation. Given the individual characteristics of the two components, COL/HAP-based composites possess excellent biocompatible properties because bone is made up of calcium phosphate and collagen. By mixing the two components, bone fragility decreases due to the good properties of collagen [264, 265].

Mineralization of the collagen matrix increases the mechanical modulus of the scaffold. The introduction of HAP crystallites into collagen fibrils can limit the deformation of the collagen network, reduces its viscosity and increases elasticity. COL/HAP scaffolds were prepared using a microwave oven and by the co-precipitation method. Mineralization of the collagen matrix improved the mechanical properties of the scaffold, because HAP crystallites in collagen fibers restricted the deformation of the collagen network [266].

COL/HAP composite materials due to the fact that they mimic the structure of natural bone have become a hotly debated topic in the literature.These materials have good mechanical properties, biocompatibility and good osteoconductivity. Specialist studies have shown that these composites can lead to calcification of the bone matrix after replacement of mesenchymal stem cells. The morphological analysis of the scaffolds showed the interconnectivity of the pores and the porous structure of the layers that were perfectly integrated at the interface of the scaffold.This integration promotes cell infiltration and tissue regeneration in different layers of the scaffold. By lyophilizing the scaffolds, the pore size can be controlled. The average pore size is sufficient for the adhesion and proliferation of osteoblasts. Cell proliferation has shown that the addition of HAP improves the hydrophilicity of the scaffold, bioactivity and cell attachment. HAP/COL scaffolds have also been found to have excellent biological properties compared to pure COL scaffolding [267]. Kane et al. investigated angiogenesis and osteogenesis of scaffolds with 85% porosity and consolidated with 40% HAP; their results showed that after 8 weeks new bone formation was seen [268].

The preparation of COL/HAP scaffolds made by freezing induced the separation of the solid-liquid phase followed by the vacuum sublimation of the solvent crystallites to form their porosity.When the collagen concentration increases, the pore size decreases and they become clogged. HAP concentration is an important factor in controlling the size of scaffold pores. As the amount of HAP in the composition increases, the size of the scaffold pores decreases, the pore walls become thicker, the structure becomes irregular appearing like a honeycomb and the breaking strength increases [269].

Scaffolds from MgHAP/ COL.Synthetic or natural polymers have been combined with MgHAPs to create fibrous meshes that have lower stiffness, facilitate cell attachment and help form soft tissues. During synthesis, collagen allows structural and morphological control over HAP crystallites forming a bone-like structure. The results show that a composite has been formed with morphological and mechanical properties that allow cell adhesion and migration. Morphological investigationsshowed that MgHAP nuclei were deposited on the collagen thread, increasing their roughness compared to the mineralized collagen fibers. In the in vitro study, mesenchymal cells are differentiated when seeded on MgHAP/COL scaffolds, and host cells are osteogenic. New bone formation has been observed [270].

Preparation of metal surfaces for coatings

Each material mentioned above has advantages and disadvantages. Metallic materials release metal ions that could lead to implant removal due to side effects. Polymeric materials are easy to manufacture, are biocompatible but have poor mechanical properties. For better properties and results for tissue and implant engineering, the combination of the two metallic and polymeric materials is ideal [271].The most studied metal is **titanium**. The metal surface has an oxide layer with an important role in its biocompatibility. Another important role is to modify the surface to improve cell adhesion and osseointegration for faster healing [272]. Surface modification can be accomplished by physicochemical or biochemical methods that use organic or inorganic agents, or a combination thereof.

The following methods of activating the metal surface have been studied in the literature: mechanical (by grinding, polishing with abrasive paper and sandblasting, processing), chemical (by etching with different acids, alkaline etching or anodizing), physical by vacuum treatment, thermal treatment, laser treatment or their combination [273, 274]. In vivo experiments have shown good osseointegration in terms of activation methods compared to those in which they do not opt for this stage. Each activation method improves the qualities of the implant. The mechanical activation shown in Table 1 is necessary to create a specific surface using materials such as alumina, silica, abrasive paper or

diamond. Depending on the material chosen for processing, surfaces are formed from hard to very fine (mirror gloss). A characterization of the implants following the mechanical activation will highlight the surface roughness and the orientation of the processing direction [275-281].

Table 1. Mechanical activation surface of the implant surface [278]

Mechanical methods	***Modified layer***	***Objective***	***Ref.***
Grinding	It is made by bombarding the surface with hard particles (alumina or silica) suspended in liquid at a high speed. Hard surfaces between 200-600 μm can be made.	Creating specific surfaces begining from hard one to very fine up to the mirror oglinda	[277, 278]
Polishing	It is made with SiC, alumina or diamond paper in the presence of lubrication and at a certain speed. With this method you can get very fine surfaces up to the mirror, 0.1 μm or smaller.		[279, 280]
Machining (tensioning, milling, threading)	The surface of the implant is characterized by valleys or mountains oriented along the processing direction. Their size depends on the speed and direction of processing. With this method, surfaces between 0.3-0.6 μm can be obtained.		[278, 281]

Herrero-Climent et al. treated the metal surface both chemically and mechanically in order to observe their difference both in vivo and in vitro. Chemical activation was performed by treatment with 0.35 M HCl acid and by combining these two methods. Microscopic analysis showed that the acid-treated samples formed small craters with grooves, while the samples that used sandblasting create a heterogeneous surface, with peaks and valleys of different geometries, with several flat faces. The combination of acid and sandblasting showed a surface similar to the micro-sponge structure, which was later detailed with other analyzes. This surface was the hardest of all. Osteoblasts adhere to a surface with increased roughness, and this effect has been observed on samples that have been treated with acid and blasting, resulting in the best effect for dental implants [282]. Kim et al. used titanium in their study. The titanium samples were washed and dried in acetone mechanically polished to give a $Ra \leq 0.06$ μm, after which they were treated with HF acid [283]. Albrektsson et al. reported that sandblasted and acid-treated titanium helps bone growth faster than plasma-sprayed titanium [284].

Implanted materials must have a physical and biological compatibility with the bone for which chemical activation was used [273].

Chemical activation of the implant surface is important to achieve because it has the role of improving osseointegration and osteoinduction. Table 2 mentions the acids most used in chemical activation, working parameters (volumetric concentrations, temperature between 30-180ºC, time - where 30 sec is the optimal, ultrasonic cleaning) and results obtained. These steps were completed by successive washing of samples in ultrapure water, alcohol or acetone [285-289].

Table 2 Chemical activation of the implant surface

Type of acid	***Concentration***	***Temp ºC***	***Time***	***Cleaning methods***	***Characteristics***	***Ref.***
HF HNO_3	9% V/V hydrofluoric acid, 12% V/V nitric acid	30	15 – 600 sec	Ultrasonic cleaner	Surface roughness: on Grade 2 samples was in the interval of 0.3-0.6 μm and On nano titanium discs 0.2-0.4 μm.	[285]
H_3PO_4	0.5%, 1% și 2%	180	2h	With 1200 grit SiC abrasive paper and successively cleaned in acetone, alcohol and deionized water (processed surface)	H_3PO_4 (0.5% w/w) nonhomogeneous surface morphology - micro-raw surface using high concentrations of H_3PO_4 (2% w/w). 0.5% H_3PO_4 Ra = 0.32 μm 1% H_3PO_4 Ra = 0.98 μm 2% H_3PO_4 Ra = 1.17 μm	[286]
H_3PO_4	(5%, 10%, and 20%; v/v)	90	30 min	using 800 and 1200 grit SiC paper, ultrasonically cleaned with deionized water, rinsed with acetone, 70% ethanol and deionized water	Control Ra = 0.01907 μm and Rq 0.02474 μm 5% H_3PO_4 Ra = 0.01659 μm and Rq 0.02192 μm 10% H_3PO_4 Ra = 0.02566 μm and Rq 0.03485 μm 20% H_3PO_4 Ra = 0.01901 μm and Rq 0.02514 μm	[287]

Polyphosphoric acid orthophosphoric acid	0.1; 1, and 10% wt 10% wt	37	24 h	first time by successive ultrasonic rinsing in trichlorethylene and ethanol (10 min every)	The maximum surface roughness (Rt) of the treated Ti surface also increased significantly ($p < 0.0001$) due to the dose dependence of polyphosphoric acid -the roughness of the surface Ti treated with 10% by weight polyphosphoric acid and 10% by weight orthophosphoric acid showed a significantly harder surface than that of untreated Ti (control)	[288]

Chemical activation of the titanium surface can be achieved with various acids H_2SO_4, HNO_3, HCl, H_3PO_4 and Kroll's reagent (mixture of 100 ml water, 1-3 ml HF, 2-6 ml HNO_3). The process of chemical activation with acids requires increased attention because the system heats up and releases heat, according to the data in table 2 to engrave the surface of the implant. In this etching with acid were used concentrations of acids starting from 0.5% to 20% in volumetric ratio. Time and temperature are also important factors that help to obtain a surface that is as biologically active as possible so as to allow osseointegration and the formation of new bone. Surface cleaning can be performed at high temperatures with or without ultrasound. From the results of the experiments it was concluded that etching with HCl has the optimal time of 30 seconds which allows a better integration of the metal bone [285-288] and to maintain a desired temperature for example 30ºC, acetone can be used, which has the role of cooling the system.

Engraving / chemical activation dissolves the oxide on the metal surface. An aqueous mixture of 10-30% nitric acid 1-3% hydrofluoric acid is important because it decreases the formation of free hydrogen upon reaction with titanium. Acid etching produces a roughness of the metal surface between 1-10 μm.

Other methods of surface activation are electroplating, anodizing shown in Table 3.

Table 3 Activation of the implant by anodizing

Implant activation	*Cleaning methods*	*Characteristics*	*Ref*
Chemical anodizing	anodized in a cell with two electrodes, in 1mol / l H_3PO_4 solution at a constant potential difference between 3 and 30 V for 60 min	Phosphoric acid was selected as anodizing electrolyte in order to promote incorporation of P to the oxide film	[289]
Anodizing	Half of the samples were subsequently subjected to the anodizing process in an anodizing bath heated at 20°C of 1.0 M phosphoric acid under a current density of 5 $mAcm^{-2}$ due to the stabilized current of 80 V	The sample surfaces were grit-blasted with 180 μm aluminum oxide at 0.25 MPa producing Ra values ranging from 1.5 to 2.5 μm and acid-etched in a 5N HNO_3 and 5N HF solution at room temperature (20°C) for 20 min.	[290]

It has been shown that treatment with sulfuric acid produces a rougher surface than treatment with H_3PO_4, HCl and HNO_3 this can be used for biological applications. Titanium samples were treated with 48% H_2SO_4 at various times intervals. The longer the engraving time, the rougher the surface of the implant will be. Treating surface with strong acids such as HCl, H_2SO_4 and HNO_3 produces micro-pits on the titanium surface ranging from 0.5 to 2 μm and improves the osseointegration of the surface. It has been shown that double acid treatment promotes faster osseointegration and osteoinduction, ie bone growth directly on the implant. Due to the fact that titanium is very reactive with fluoride ions, soluble TiF_4 is formed, and this promotes osseointegration of the implant [291]. Phosphoric acid treatment influences the attachment and proliferation of cells by changing the morphology, roughness and texture of the implant surface. In this sense, coatings were made with different materials for a better osseointegration [292, 293].

Polymer/Ceramics coatings on metals

Ti/chitosan/HAP. The ideal coatings are those materials that have characteristics similar to those of natural bone. Titanium is mirror polished and used as a support. The natural polymer, ie chitosan in coatings, acts as a bio binder (bioadhesive) for HAPs particles [294]. In this sense, HAP/CHI coatings have been developed to obtain favorable osteoblastic responses. By creating these coatings, a porous surface has been created, which is beneficial for the long-term release of antibiotics. In vitro results have shown that the chitosan-laden scaffold exhibits antimicrobial activity and increases the adhesion and proliferation of osteoblastic cells at low concentrations [295].

Ti/COL/HAP. COL/HAP scaffolds are important for rapid osseointegration. The titanium support coated with COL/HAP was tested in vivo and a new tissue was observed around the implant compared to those coated with HAP only. New bone height was higher in COL/HAP scaffolds [296].The COL/HAP nano composite deposited on titanium support was made by the spin coating method. By this method, a thin layer was made without HAP aggregates, having a good hydrophilicity, favoring cell attachment and proliferation. As the amount of HAP increases, the activity of alkaline phosphatase has improved. In vitro experiments have shown that alkaline phosphatase performs better on coated titanium than bare titanium. The composite becomes harder and cracked as the HAP content increases. The polymer is used as a bio adhesive for HAP particles and for adhesion of the composite to the substrate. In vitro tests showed that cells cultured on polished titanium had an elongated shape and were flattened on titanium coated with COL. Cell proliferation is higher on HAP/COL composite (10% and 20%) than on pure titanium. Small cell proliferation was observed in the composite with 30% more HAP than 10% HAP, and this can be explained by the fact that a harder and more hydrophobic surface was formed [297].

Ti/PDLLA/HAP.The scaffolds made have the role of improving osteoconductivity. It was observed that PDLLA/HAP is stable in terms of fixation and a significant amount of new bone was formed on the implant compared to PDLLA (poly D, L-lactic acid). The development of biomaterials that are as close as possible to the composition and structure of the body's biological tissues have managed to increase the lifespan of suffering patients. However, it should be borne in mind that over time, no matter how much we want to improve the quality of materials and have favorable responses, the influence of the biological environment and the mechanisms of interaction are still a factor contributing to the alteration of implants regardless of their nature [298].

Classification of deposition/coating methods

Coating, materials are available in a wide variety of applicability in different fields. The deposition method, the deposited material, the substrate, the thickness and the density are qualities that improve the behavior of the substrate, but thermal stability, biocompatibility and corrosion must also be taken into account. The correct selection of material and substrate is essential to achieve successful coating. The deposition materials have different mechanisms of action and must be researched to discover the beneficial effects and side effects. Some examples of deposit methods are described below [299].

Thermal spray coating

This method uses the chemical combustion as the heat source to melt the sprayed materials at high speed on the surface of the substrate to form a protective

layer. They can be used to cover different materials. In this case we can mention two coating methods, such as plasma spray coating - a process that can be performed both in vacuum and in atmospheric conditions. The materials to be deposited are introduced into the hot plasma stream that melts the material and the molten droplets are deposited on the substrate. It is a technique with which, uniform layers can be deposited and has corrosion protection. The disadvantage of this method is the use of hot flow which can lead to the decomposition of the material. The experiments showed that the use of this method leads to a value of the thickness of the deposited layer in the range of 30-300 μm [299-301]. High Velocity Oxygen Fuel (HVOF) - means that a gaseous or liquid mixture suffers continuous combustion in a chamber to supply high pressure gas steam. The combustion products in the chamber are removed through a nozzle to create high-speed spraying, the gas stream and the powder particles are directed to the covered surface. The powder is partially melted and deposited on the substrate in the form of drops. The advantages of this method are corrosion protection and good biocompatibility. On the other hand high temperature can decompose the materials which are not desirable and the particle size depends on the diameter of the nozzle. The layer thickness using this method is in the range of 30-300 μm [302, 303].

Precipitation method

It is based on the phenomenon of heterogeneous nucleation. The supersaturation of the solution, the concentration of the reagents, the temperature, and the presence or absence of mixtures in the precipitation mechanisms must be taken into account.

Electrophoretic deposition **(EPD)** - means that particles are suspended in a liquid and migrate under the influence of an electric field with direct current (electrophoresis). The deposition takes place on a conductive substrate of opposite charge It is the first technique used to deposit calcium phosphate on a metal substrate. The advantage of this method is low costs, easy deposition and uniform thickness. The problem with this technique is that the coating produces cracks which are not desirable. The thickness of the film is in the range of 0.1-2 mm [303, 304].

Sol-gel coating - is the preparation of the soil by dissolving calcium phosphate in ethanol or distilled water. The mixture is heated until the water evaporates and the viscosity increases, this transformation of the liquid solution into a gel phase is called sol-gel. The substrate is immersed in sol-gel at a constant and controlled speed. Soil is a two-phase suspension of colloidal particles in a liquid, while gels are considered composites because they consist of a skeleton or solid network that include liquid phase or excess solvent. Low costs, multi-layer coatings and

uniformity can improve existing layers by sealing porous structures or cracks. Due to these advantages, this method of covering biomedical devices is also the most frequently used. The thickness of the deposition layer can have values <1 μm [305, 306].

Dip coating - This is done by immersing a substrate in a suspension at a constant speed. It is a simple method, easy to apply; low cost and allows the realization of multilayers. The thickness of such a deposited layer is in the range 2 μm-0.5 mm [307-309].

Spin coating - involves the application of a uniform thin film on flat substrates. This means that a drop of resin is deposited in the center of the substrate and this substrate is rotated with centrifugal force at high speed to disperse the drop so as to form a thin film on the surface. Is a method in which the spin speed is the most important factor in the coating. The speed of the substrate (rpm) affects the degree of radial (centrifugal) force applied to the liquid resin, as well as the characteristic speed and turbulence of the air immediately above it. The advantage of this method is low production costs and easy application but cracks can occur in layers. Layers with a thickness between 2 μm-0.5 mm can be made [310].

Hydrothermal deposition - performs hydrothermal treatment at high temperatures over a long period of time. Complex shapes can be made but require very high temperature. Layers with a thickness between 0.2-2 μm can be made [311].

Micro-arc deposition - It is achieved by electrochemical oxidation of the metal surface by applying high voltage with spark treatment on aqueous electrolytic baths. Layers can be made with a thickness between 3-30 μm [312, 313].

Vapor deposition techniques which may be physical or chemical

Laser pulse deposition - It is a physical deposition technique, in which the high power laser provides a source of energy for melting and vaporizing materials. It makes both porous and dense layers but involves high temperatures and high realization costs. The layer thickness is between 0.05-5 μm [314, 315].

Magnetron sputtering - It is a physical deposition technique in which the thickness of the film can be 0.5-3 μm. Uniform coatings with a very thin layer are obtained [316].

Classification of biomaterials according to the interaction with the body

Regarding the interaction of synthetic biomaterials with the biological system, in Figure 4 is highlighted their classification [317, 318]. A biomaterial can be bioinert, ie it must not cause allergic reactions with the host tissue or with the organs with which it comes into contact within the physiological system.

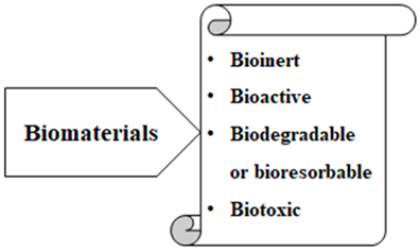

Fig. 4. Classification of biomaterials according to the interaction with the host tissue

Bioactive means that it binds directly to living tissue after implantation and forms a soft tissue that leads to faster regeneration or healing [319].

Biodegradable or **bioresorbable**, ie the biomaterial decomposes when it interacts with the biological fluid, and is then gradually resorbed in the body by metabolic processes forming a new bone [319, 320].

Biotoxic – that is, it rejects living tissue near the implant [321, 322].

The literature highlights the importance of scientific studies in terms of identifying biomaterials that help bone regeneration. A biomaterial can be optimized according to the needs of the application or can be associated with other biomaterials in order to obtain synergistic effects [323]. In 1986, the European Society for Biomaterials drew up a series of definitions for the concept of biomaterial, one of which was "non-viable materials used in a medical device intended to interact with biological systems". In the case of reconstructions or substitutions of living organs and tissues, biomaterials used in medicine must meet certain characteristics in order not to be rejected by the body highlighted in Figure 5 [324]. These can be organic or polymeric materials capable of functioning normally from a physiological and biological point of view [325, 326].

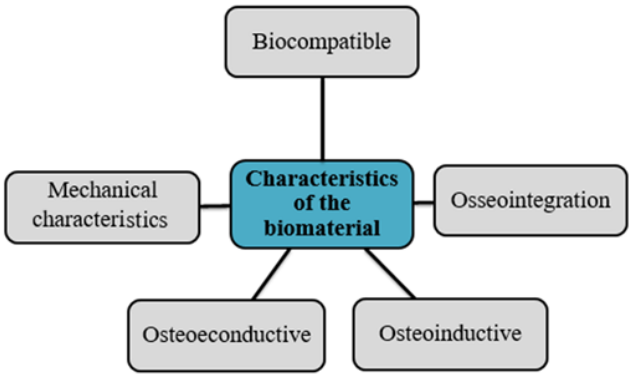

Fig. 5. Main characteristics of biomaterial

In order for a biomaterial not to be rejected by the body, it must be:

Biocompatible. This means that the biomaterial used, be it an implant or filler, and has the ability to give a positive response to the purpose for which it is used. It does not cause inflammation and side effects, it adapts to biological and structural requirements, adapting to the place where it is implanted. In order for these requirements to be met, biocompatibility is determined using in vivo and in vitro tests, which involve interaction with the body system [317, 326].

Osteointegrated which means the bone grows directly on the surface of the implant. It should be mentioned that the modification of the implant surface leads to the improvement of the osseointegration process, the healing time being a short.Surface modification is an important feature of the osseointegration process because it can increase the growth and attachment of osteoblasts. The more rough the modified surface, the more compact and stable the surface composition is, which leads to the facilitation of the process of osseointegration and adjustment of cellular activity [327-329].

Osteoinductive. The biomaterial used has the ability to induce the formation of new bone, without the presence of osteogenic factors which provides support for cell growth [76].

Osteoconductive. The biomaterial can be used as a substrate or scaffold to guide the formation of new bone [330].

Mechanical properties of biomaterials influence the interactions with the cells, determining cell behavior and the final repair or regeneration effects of the treated tissue in the clinical field [331-334]. The most important off all, are the modulus of elasticity, hardness, tensile strength, elongation and other.

Nanoparticles interaction with biological membranes and living system

This review provides useful information on the development of innovative nanomaterials, made of nanoparticles, capable of interacting with the living system and producing positive responses in terms of integration. The importance of the use of nanostructured biomaterials in biomedical and pharmaceutical applications is of increasing interest in terms of their safety, biocompatibility and toxicity [335]. A part of the nanoscience of materials that is less known but that is gaining ground in the safe and efficient design of medicine is the interaction with the biological environment [336, 337] to support and enhance a biological function. There is evidence in the literature that nanoparticles not only interact with living cells, particularly with the cell membrane, but they can even mediate molecular processes to regulate cellular functions [338]. It should be specified that the interaction of nanomaterials with the cell membrane depends on the size, morphology and shape of the nanoparticles, which have different reactions with

different cells at the time of cell absorption. Ligands and bioactive molecules self-assembled on the NPs surface will determine the direction to a specific cell [339]. The nanoscale interactions of cells and biomaterial nanoparticles, NPs, are essential to be exploring to explain the cellular behaviors. There is a need for 2D technologies that can control the nanoscale presentation of multiple bioactive molecules and better understand the cellular biology. Among these techniques, self-assembled supramolecular structures at fluid interfaces, known as Langmuir-Blodgett techniques, LBT, can be highly useful for membrane model and for the investigation of the passage of NPs through cellular plasma membrane leading to interesting biological answers for cell therapy and tissue engineering. The cellular plasma membrane is made up of phospholipid bilayers [340-351] that describe favorable physical characteristics such as membrane fluidity. It is particularly important to understand the mechanism by which nanoparticles of biomaterials interact with the cell plasma membrane or its models, by using various self-assemblies of biomolecules at various interfaces. The various self-assemblies can be described by Langmuir-Blodgett models, LBM, of various molecules at air-water [352-365] and oil-water [366-372] interfaces, specifically fatty acids [363, 364, 373-377], lecithins [357, 359, 378], galactolipids and carotenoids supramolecular structures [378-392]. Antioxidants, proteins and anesthetics that are able to form oriented nanostructures in various fluid environments are also studied [393-402]. The scheme of the cell plasma membrane is illustrated in Figure 6.

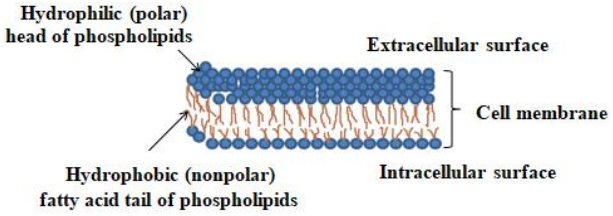

Fig. 6. Representative scheme of the cell membrane

The adsorption of NPs on the cell membrane and its crossing through the plasma membrane involve electrostatic charges and wan der Waals forces. The researchers conducted extensive studies on the interaction of nanoparticles with the cell membrane and highlighted two of the most common mechanisms: endocytosis seen in Figure 7 and direct penetration seen in Figure 8 [403]. Depending on the mechanism of NPs penetration into the cell membrane and the nature of the nanoparticles, the purpose for which they were created can be elucidated.

Endocytosis was discovered in 1963 by Christian de Duve. It is an intrinsic cellular function that allows the ingestion of large particles and the absorbtion of

liquids and macromolecules. The specialized studies show that the process is eficient in the administration of drugs. The materials are captured from the cell surface and wraps by a small region of plasma membrane forming a vesicle that contains ingested matarials [403-405]. Endocytosis is subdivided into phagocytosis, pinocytosis and receptor mediated endocytosis.

Phagocytosis also known as cell eating, Figure 7a, is the mechanism by which the cell ingests particles larger than 0.5 μm and a small portion of the cell membrane deforms and envelops NP, thus forming a phage. The phagocytosis also can eliminate the microbial phatogens and apoptotic cells. Phagocytosis implies Np-binding receptors [403, 406, 407]. This means that receptors initiate signaling pathways to recognize the target particle and lead to membrane expanding to cover it.

Pinocytosis known as cell drinking, Figure 7b, captures the fluids, solutes from extracellular fluid. It is a process in which a small portion of the inside of the membrane opens to the outside, and then detaches to form a large intracellular vesicle (0.5-5 μm) which containing materials. This vesicle inside contains protein receptors with which it can recognize the molecules to be closed [407-409]. A disadvantage of endocytosis is that sometimes NP cannot be released from the phage and cannot reach the target cell.

Receptor mediated endocytosis, Figure 7c, is a form of endocytosis that absorbs specific macromolecules. These macromolecules bind to specific receptors of the cell surface and form clathrine coated pits. Chlatrine is a protein used in a formed of coated vesicle. The pits bud and develop small vesicles that contain bound macromolecules [407].

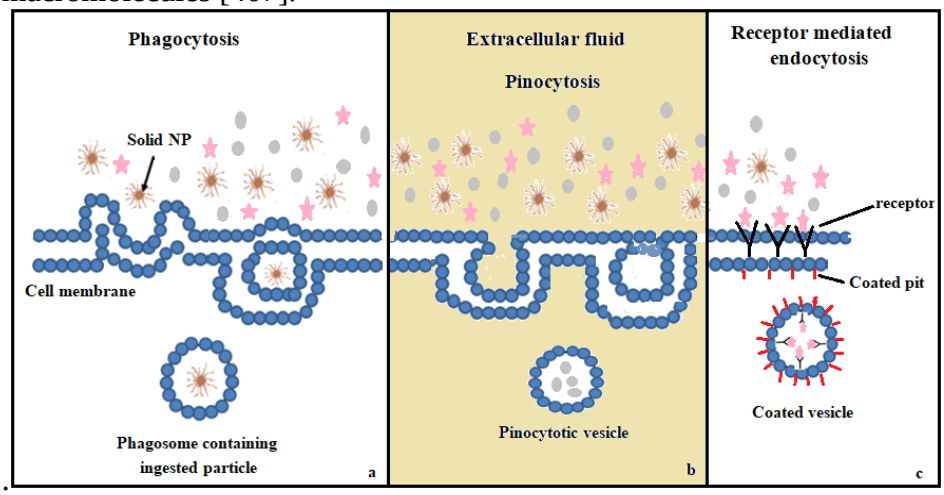

Fig. 7. The endocytosis pathways a) phagocytosis, b) pinocytosis and c) receptor mediated endocytosis

The direct penetration, Figure 8, is the way in which NP is delivered directly to the target cell without forming vesicles [403]. This process allows an easier release of the drug [410, 411]. While these studies are important for medicine, it has been scientifically proven that antimicrobial loading is also important in the activity of NPs. The mechanism is based on the electrostatic attraction between the cell membrane of positively charged microorganisms and negatively charged NPs [412]. Negatively charged nanoparticles accumulate better in tumor tissues, and positively charged ones can be most easily taken up by cells [413-415].

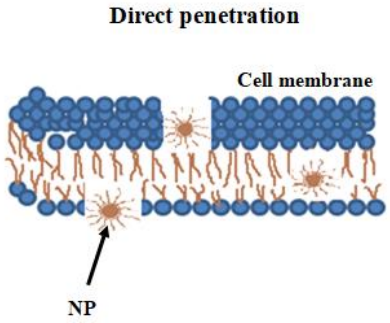

Fig. 8. Direct penetration

Future studies on the interaction of innovative nanostructured materials with the human biological system may bring benefits in terms of pathogen reduction. Although the interaction of NPs with the cell membrane depends very much on the nature and chemical composition, structure, morphology and other characteristics, it is essential to understand the mechanism of the activities carried out. In this way, the potential cytotoxicity can be evaluated, it contributes to the acquisition of knowledge about cancer cells, the targeted transport of drugs and last but not least, a better design of innovative materials for biomedical applications can be obtained [413-415].

The cell adhesion and proliferation is evidenced by biomaterials scaffolds used in vitro by the interaction of biomaterials with the living system [161, 259]. Thus, our research team managed by preparing innovative materials (HAP, substituted HAP) to perform cell viability tests (MTT) and in vitro biocompatibility tests with fluorescein diacetate and Alamar blue [161]. The obtained results showed that the prepared materials can be used successfully in orthopedic surgery and in the regeneration of osteoporotic bones.

This review is an extensive research of the literature that demonstrates the close link between materials science and regenerative medicine. Involvement in such research has an educational and practical purpose in forming elites. Such research with medical applications is appreciated among surgeons. In vivo

experiments have shown very good results [259] and also facilitate decision-making regarding the treatment or replacement of diseases.

Infections of the oral cavity are initiated by pathogens in the form of biofilm on the surface of the teeth causing the destruction of tooth enamel and supporting tissues. The severity of the diseases (e.g. periodontal disease) caused by these infections can range from a simple inflammation of the gums to tooth loss if left untreated in time [416-418]. The progression of diseases of the oral cavity is due to excessive consumption of unhealthy foods (sugars), oral hygiene, and poor quality of teeth. Regarding healing, there are attempts to use certain micronutrients to treat inflammatory lesions, while in the case of enamel denaturation there are treatments for remineralization of hard tissues with hydroxyapatite embedded in toothpaste [416-418]. Tissue regeneration is a revolutionary method in all medical fields that have led to intense research in obtaining synthetic biomaterials as close as possible to the composition of the tissues to be cured [416-418].

The development of biomaterials, usually defined as materials for medical and biological applications, recently reached a superior degree of complexity and their effectiveness has increased significantly. Biomaterials made today through biologically inspired design incorporate biologically active components derived from nature. In the future, biomaterials with enhanced biological functions will have a greater role in medicine and medical devices.

Conclusions

Materials science has made great advances in the development of biomaterials usable in regenerative medicine. The research in this review highlighted the variety of biomaterials in terms of source and interaction with the biological system. Their potential in effective application in bone regeneration and partial replacement of a part of an affected tissue has been discussed.

The review describes coatings on implants with concrete examples of biomaterials deposited on the metallic implant surface and used in regenerative medicine. The perspectives of these coated implants are outlined as the physico-chemical and biological experiments *in vivo* and *in vitro* clarifying the aspects that determine their activities and applicability.

This review has demonstrated the usefulness of biomaterials and coated implants for clinical applications in any trauma. Any challenges in medicine can be overcome if innovative materials are designed for improved applications for which they were made and interact beneficially with the biological systems of the living being.

Abbreviation list

HA - hyaluronic acid

FDA - Food and Drug Administration

ASTM - The American Society for the Testing of Metals

Al_2O_3 - alumina

ZrO_2 - zirconia

HAP – Hydroxyapatite

EMA - European Medicines Agency

PLA - polylactic acid

PEG - polyethylene glycol

PGA - polyglycolic acid

PLLA – poly L lactic acid

PLGA – poly lactic-co-glycolic acid

BSM - bladder submucosal matrix

EC - embryonic cells

bOC - bovine osteoblasts

nHAP – nano hydroxyapatite

PCL – poly-ε-caprolactone

COL – collagen

MgHAP – hydroxyapatite with magnesium

HCl – hydrochloric acid

HNO_3 - nitric acid

H_3PO_4 - phosphoric acid

Ti - titanium

Ra – average surface roughness

TiF_4 - titanium tetrafluoride

CHI – chitosan

PDLLA - Poly-D, L-lactic acid

HVOF - High Velocity Oxygen Fuel

EPD - Electrophoretic deposition

GNPs – gold nanoparticles

SNPs – silver nanoparticles

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