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Review

Osteoconductive and Osteoinductive Surface Modifications of Biomaterials for Bone Regeneration: A Concise Review

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Abstract: The main aim of bone tissue engineering is to fabricate highly biocompatible, osteoconductive and/or osteoinductive biomaterials for tissue regeneration. Bone implants should support bone growth at the implantation site via promotion of osteoblast adhesion, proliferation, and formation of bone extracellular matrix. Moreover, a very desired feature of biomaterials for clinical applications is their osteoinductivity, which means the ability of the material to induce osteogenic differentiation of mesenchymal stem cells toward bone-building cells (osteoblasts). Nevertheless, the development of completely biocompatible biomaterials with appropriate physicochemical and mechanical properties poses a great challenge for the researchers. Thus, the current trend in the engineering of biomaterials focuses on the surface modifications to improve biological properties of bone implants. This review presents the most recent findings concerning surface modifications of biomaterials to improve their osteoconductivity and osteoinductivity. The article describes two types of surface modifications: (1) Additive and (2) subtractive, indicating biological effects of the resultant surfaces in vitro and/or in vivo. The review article summarizes known additive modifications, such as plasma treatment, magnetron sputtering, and preparation of inorganic, organic, and composite coatings on the implants. It also presents some common subtractive processes applied for surface modifications of the biomaterials (i.e., acid etching, sand blasting, grit blasting, sand-blasted large-grit acid etched (SLA), anodizing, and laser methods). In summary, the article is an excellent compendium on the surface modifications and development of advanced osteoconductive and/or osteoinductive coatings on biomaterials for bone regeneration.

Keywords: coatings; metallic implants; plasma; additive modifications; subtractive modifications

1. Bone Regenerative Medicine

Common bone defects caused by trauma, pathological process, infection, and tumor resection represent a global health problem in our aging population. Repair of bone fracture is a complex process comprising sequential cellular and molecular events modulated by local and systemic factors. The important challenge for regenerative medicine is a fast restoration of large bone defects/injuries [1,2]. Consequently, bone is one of the most frequently transplanted tissues [3]. Autografts and allografts provide excellent results in the bone regeneration process, but they are characterized by a number of limitations (e.g., donor-site morbidity, the risk of infection, and disease transmission) [3,4]. Thus, the alternative solution for bone regenerative medicine are tissue-engineered products [4,5], which are biomaterials containing either patient osteoprogenitor cells/mesenchymal stem cells or cytokines/growth factors, or both cells and cytokines/growth factors [5].

Biomaterials for bone tissue engineering applications should comply with several basic structural, mechanical, and biological requirements due to their crucial role in the bone regeneration process

(Figure 1). The microstructure of developed biomaterials and their mechanical characteristics should be tailored to anatomical implantation site [6]. The three-dimensional porous structure of the bone implant, with interconnected and open porosity, accelerates the bone regeneration process by ensuring good oxygen and nutrients diffusion and waste products elimination, as well as by providing space for proliferation of the cells and newly formed blood vessels [5,7,8]. Concerning mechanical properties of the biomaterials, the implanted scaffold should possess strength and stiffness similar to surrounding bone tissue [9].

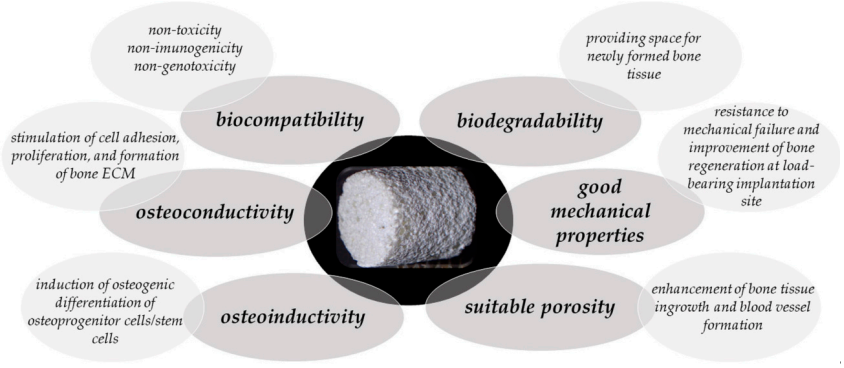

Figure 1. Scheme presenting main properties of tissue-engineered products as an alternative solution for bone regenerative medicine.

Taking into account the main requirements of the biomaterials for bone tissue engineering applications, special attention should be paid to their biological characteristics, such as biocompatibility, osteoconductivity, and osteoinductivity [6,10,11]. The biocompatibility represents the ability of the scaffold to perform appropriate host response without side effects, like cytotoxicity, mutagenesis, carcinogenesis, immunogenicity, and genotoxicity [5,12]. The osteoconductivity reflects the ability of biomaterial to stimulate cell adhesion, proliferation, and formation of the bone extracellular matrix (ECM) by the osteoblasts, supporting bone growth. Osteoinductive biomaterials are the most desired implants due to their ability to induce the osteogenic differentiation of mesenchymal stem cells toward bone-building cells (osteoblasts) [5,10,11,13]. Importantly, bone scaffolds should be preferably biodegradable to provide space for newly-formed bone tissue. Moreover, biomaterial degradation products should be nontoxic against other tissues [6]. Another very important feature of the bone scaffolds is their bioactivity, which is defined as the ability of implanted biomaterials to form bone-like apatite crystals on their surfaces, which is critical for good implant osseointegration with host tissue [10,14]. In turn, good osseointegration indicates the capacity of the implant to form a direct connection with the surrounding host bone tissue without the formation of an undesirable fibrous tissue layer [3].

Biomaterials applied in bone tissue engineering and regenerative medicine are usually categorized into polymeric, ceramic, metallic, and composite materials [15,16]. The most often used metallic biomaterials are titanium (Ti) and its alloys (e.g., Ti–6Al–4V, Ti–6Al–7Nb, Ti–6Al–2Nb–1Ta–0.8Mo, Ti–15Mo–5Zr–3Al) [17,18], stainless steel, cobalt (Co) and its alloys [15,18], magnesium (Mg) and its alloys, nickel–titanium alloy (Nitinol), tantalum (Ta) [16]. Metallic biomaterials have been commonly used as bone implants due to their corrosion resistance, fatigue strength, high ultimate tensile strength, toughness, durability, and biocompatibility [19,20]. Thus, metallic biomaterials constitute 95% of the orthopedic implants [20]. Nevertheless, metallic materials have also some limitations, such as possible release of toxic metal ions and wear debris that are produced during friction for a long time, causing acute or chronic responses after implantation [16].

Nowadays, there is a growing trend in the development of composite bone scaffolds that are composed of both organic and inorganic constituents to mimic natural bone tissue. The organic part of biomaterial provides biomaterial flexibility and improves its biocompatibility [21–23], whereas the

inorganic part provides load-bearing strength and stiffness [22]. In organic–inorganic composites, the organic matrix may be composed of natural polymers (e.g., chitosan, collagen, hyaluronic acid, fibrin, silk fibroin, alginate, amylopectin, carrageenan, agar, dextran, xanthan gum, pullulan) [15,23–26] and/or synthetic polymers (e.g., polylactic acid (PLA), polycaprolactone (PCL), poly(glycolic acid) (PGA), polyanhydride, polyphosphazene, polyether ether ketone (PEEK), polypropylene fumarate (PPF)) [27], whereas the inorganic part may be made of metal alloys [16] and ceramics, such as hydroxyapatite (HA), calcium phosphate bone cements (CPS), α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP), Bioglass (BG), glass-ceramics, as well as carbon nanotubes [15,24,27,28].

In bone tissue engineering, polymeric biomaterials are made of non-ECM components (e.g., chitosan, alginate) or/and ECM components (e.g., collagen, gelatin). Various biopolymers (naturally occurring polymers) are commonly used for biomaterial production due to their superior biological properties, such as non-toxicity and high biocompatibility. Importantly, the microstructure of biopolymeric materials allows for good gas diffusion, nutrients flow, and removal of wastes. Nevertheless, biopolymer-based implants possess weak mechanical properties and biostability, which may be improved by blending them with synthetic polymers or by using chemical and physical crosslinking treatments [23].

Currently, there are several manufacturing technologies enabling porous scaffold fabrication (e.g., 3D printing, bioprinting, electrospinning, stereolithography, fused deposition modeling, selective laser sintering, freeze-drying, gas foaming, solvent casting/particle leaching, and phase separation) [20,22,27,29]. Despite rapid development of manufacturing technologies for biomaterial fabrication, researchers are still faced with a challenge to develop completely biocompatible material with appropriate physicochemical and mechanical properties. Furthermore, one of the fundamental requirements of the bone scaffold is controlled interaction between implant surface and surrounding biological environment, without inflammation, coagulation, or infections events [30]. To improve biological properties of the biomaterials for bone regeneration, many combinations of the starting materials as well as their surface modifications are often applied. Consequently, various surface modification techniques have been developed to improve implant osteoconductivity/osteoinductivity and thus the success rate of bone regeneration (e.g., coating, gradient coating, grafting, roughening, patterning, and multilayer films) [18]. It should be noted that modification of biomaterials surface allows to create more favorable environment for cells by specific chemical or physical treatment, which improves cell adhesion, proliferation, and migration [31]. Moreover, implant surface coatings containing metallic ions, such as silver (Ag), zinc (Zn), copper (Cu), and lithium (Li), impart antibacterial property to the biomaterials, thereby reducing risk of infection at the implantation site [32]. This review article presents recent findings concerning additive and subtractive surface modifications to improve osteoconductive and osteoinductive properties of the biomaterials for bone regeneration applications (Figure 2).

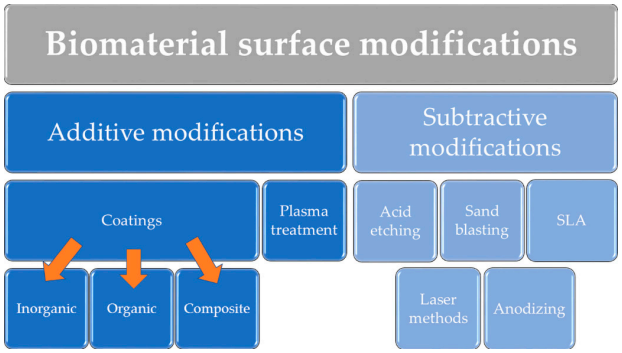

Figure 2. Scheme presenting various types of possible surface modifications of biomaterials for bone tissue engineering and regenerative medicine applications aiming to improve their osteoconductive and osteoinductive properties.

2. Surface Modifications of Biomaterials to Improve Their Osteoconductivity and Osteoinductivity

2.1. Additive Modifications of Biomaterial Surface

Additive modification of the biomaterials includes techniques that create additional structures on the implant surface. One of the most commonly used additive modification method (mainly applied for metallic biomaterials) is coating, aiming to cover the biomaterial surface by the coating material [33]. Dependent on the type of material used, the resultant coatings can be divided into organic, inorganic, and composite [33]. Coatings on the surface of the implants may be formed using various technologies, including electrophoretic deposition, sol-gel technique, enameling, physical vapor deposition (pulsed lased deposition and pulsed electron deposition), and magnetron sputtering [34]. Another method that belongs to additive modifications of biomaterial surface is plasma technology [35]. In this section, the additive modifications of biomaterial surface by using inorganic, organic, and composite coatings, plasma technology, and the magnetron sputtering method will be discussed.

2.1.1. Inorganic and Composite Coatings

Biomaterials (mainly metallic implants) coated with a layer of calcium phosphate (CaP) (e.g., hydroxyapatite (HA; $Ca_{10}(PO_4)_6(OH)_2$), TCP, or CaP glass-ceramics) are frequently developed, since formation of the CaP-based bioactive layer on the implant surface leads to the improved osseointegration between biomaterial and host tissue. Importantly, CaP-based coatings have been found to enhance the ability of biomaterial to provoke an appropriate host response, which results from their chemical similarities to natural bone HA [28,36]. Moreover, metallic implants covered with CaP-based coatings show boosted corrosion resistance and reduced metal ion release to the implantation site [19]. Additionally, CaP-based coatings promote osteoblast attachment, proliferation, and differentiation, which has been confirmed in several studies. De Oliveira et al. [37] studied biological response to HA coating on the Ti implant through gene expression analysis of major osteogenic markers (such as runt-related transcription factor 2 (Runx2), bone alkaline phosphatase (bALP), and osteopontin (OPN)) using a rat model in vivo. Gene expression analysis revealed that HA-coated implants supported new bone formation compared to control groups. Popkov et al. [38] showed that HA-coated stainless steel and titanium wires induced bone formation, and provided better bioactivity and osseointegration. Whereas Fu et al. [39] showed that silicon-doped HA (SiHA) coating on the surface of Ti was more favorable for spreading and osteogenic differentiation of mouse calvarial preosteoblasts (MC3T3-E1 cell line) than HA coating, which was evaluated by gene expression analysis for bALP, OPN, type I collagen (Col I), zinc finger structure transcription factor, and osteocalcin (OCN). Moreover, Si-doped HA coating on the surface of Ti promoted migration and angiogenesis-related gene expression in human umbilical vein endothelial cells (HUVEC cell line). In another study, Mumith et al. [40] assessed the effect of SiHA and strontium-substituted HA (SrHA) coatings on the Ti–6Al–4V implant on osseointegration in vivo using a sheep model. They proved that the implants electrochemically coated with SiHA and SrHA exhibited improved osseointegration compared to uncoated samples. While Mokkaber et al. [41] developed a silver-containing CaP coating (Ag/CaP) via electrochemical deposition on Ti substrates to increase the biocompatibility and antibacterial properties of biomaterials for bone regeneration applications. They revealed that Ag/CaP coating—where Ag ions were deposited as metallic silver nanoparticles on the CaP coating—showed not only lack of cytotoxicity against osteosarcoma derived osteoblast-like cells (Saos-2 cell line), but also bactericidal activity. Moreover, Saos-2 cells cultured on the surface of the coated samples were well spread and attached what confirmed excellent biocompatibility of applied coating. Marzban et al. [42] used nanostructured akermanite glass-ceramic ($Ca_2MgSi_2O_7$) coating to modify the surface of Ti–6Al–4V substrate. They revealed that coated biomaterial enhanced spreading and proliferation of Saos-2 cells in vitro.

There are several other ceramic coatings, such as oxides, piezoelectric and ferroelectric ceramics, carbides, and zeolites coatings, which may also possess great potential in tissue engineering applications to accelerate bone tissue regeneration. For example, Zhang et al. [43] produced novel titanium dioxide/zinc oxide (TiO_2/ZnO) coating by micro-arc oxidation, hydrothermal treatment, and heat treatment. The resultant TiO_2/ZnO-coated Ti biomaterials enhanced cell adhesion as well as osteogenic differentiation of Saos-2 cells cultured on the surface of the coated samples. Precisely, the TiO_2/ZnO coating enhanced bALP activity and secretion of main ECM proteins (collagen, OPN, OCN) in Saos-2 cells. In turn, Schitea et al. [44] developed derivative bioactive glass-ceramics (SiO_2/P_2O_5/CaO/MgO/Na_2O) coating, which was deposited on silicon substrates by a pulsed laser deposition method at room temperature and at 300 °C substrate temperature. In vitro experiments using human skin fibroblasts (BJ cell line) showed that all prepared coatings were cytocompatible. However, the coating produced at room temperature was slightly more favorable for cell growth. In a study performed by Huang et al. [45], evaluation of the osteoconductive and osteoinductive properties of the magnetic iron/polydopamine (Fe_3O_4/PDA) coating was conducted using in vitro (human bone marrow-derived mesenchymal stem cells (BMDSCs)) and in vivo (rabbit femoral bone defects) models. The coating was fabricated by co-deposition of Fe_3O_4 nanoparticles and PDA on the surface of 3D-printed porous Ti scaffolds. It was proved that the Fe_3O_4/PDA coating supported cell attachment, proliferation, and osteogenic differentiation of BMDSCs and enhanced new bone formation in vivo. Moreover, researchers observed enhancement of the osteogenic ability of the coating with applied static magnetic field.

The piezoelectric ceramics, such as barium titanate ($BaTiO_3$) [46–48], lead-free zirconate titanate derivatives (e.g., (Ba,Ca)(Zr,Ti)O_3) [49], and lithium tantalate ($LiTaO_3$) [50], are often applied to promote bone growth, remodeling and regeneration due to their excellent biocompatibility and ability to improve osseointegration. Moreover, the piezoelectric biomaterials may generate a bioelectrical signal influenced by mechanical stress exposure, that may mimic the stress-generated potentials of natural bone. This type of biomaterials may also be subjected to electrical stimulation or ultrasound to promote bone healing [25]. Fan et al. [46] used $BaTiO_3$ to modify the surface of Ti scaffold. Applied modification supported adhesion, proliferation, and differentiation of rabbit BMDSCs in vitro and increased new bone formation in vivo by enhancing osteogenesis and osseointegration. In turn, Ehterami et al. [48] fabricated electrically polarized porous $BaTiO_3$-based scaffolds coated with gelatin and nanostructured HA. They showed that the modified scaffolds supported adhesion and proliferation of osteosarcoma derived osteoblast-like cells (MG63 cell line).

The zeolites are crystalline materials with precisely defined pore structure and high stability. Moreover, zeolites are characterized by good biocompatibility, antioxidant, antimicrobial, anti-apoptotic, and anti-inflammatory activity. Due to all above-mentioned features, zeolites seem to be an ideal coating material on metallic implants [51]. Qing et al. [52] used in situ hydrothermal crystallization method to deposit zeolite coating with Ag ions onto porous stainless steel substrate. In vitro experiments showed antibacterial effects of Ag-incorporated zeolite coating (against *Escherichia coli* and *Staphylococcus aureus* strains) and slight inhibitory effects on viability, adhesion, and proliferation of rabbit BMDSCs. In another study, Chen et al. [53] modified the surface of the Ti substrate with zeolitic imidazolate framework-8 (ZIF-8), which is a Zn-based metal-organic framework belonging to nanoporous solid crystals. The ZIF-8 films with nanoscale and microscale sizes were deposited onto Ti substrates using hydrothermal and solvothermal methods, respectively. The ZIF-8 film with nanoscale size inhibited the growth of *Staphylococcus* mutans, showed good biocompatibility, enhanced ECM mineralization, and increased expression of genes for bALP and Runx2 in MG63 cells. In contrast to nanoscale size film, the ZIF-8 film with microscale size exhibited cytotoxicity to MG63 cells.

Carbon coatings (in the form nanocrystalline or polycrystalline diamond, diamond-like carbon, amorphous carbon, carbon nanotubes, graphene) have non-cytotoxic character and are often used in the engineering of biomaterials to coat metallic biomaterials (Figure 3), providing them better biocompatibility, what has been reported by many findings [28,54–57]. For example, Zhang et al. [54]

revealed that amorphous carbon-coated β-TCP enhanced adhesion and proliferation of rat BMDSCs. Furthermore, amorphous carbon coating enhanced expressions of osteogenic markers (Runx2, OPN, Col I, and OCN) and increased bALP activity in rat BMDSCs, which confirmed the stimulative effect of the coating on the differentiation of rat BMDSCs toward osteogenic lineage. Moreover, in vivo experiments showed that amorphous carbon coating enhanced the early bone regeneration capacity. Rifai et al. [55] showed that polycrystalline diamond coating on Ti scaffold promoted attachment and proliferation of Chinese Hamster Ovarian (CHO) cells and enhanced apatite deposition. In turn, Tien et al. [56] demonstrated that ultra-nanocrystalline diamond coating on silicon microchip reduced foreign-body response and protected the biomaterial from degradation in vivo. Whereas Patel et al. [57] proved that carbon nanotube-coated PCL nanofibers improved adhesion, osteogenic differentiation (high expression of genes for bALP, Col I, OCN, bone sialoprotein (BSP)), and ECM mineralization of human BMDSCs. In vivo experiments showed that carbon nanotube coating stimulated angiogenic marker expressions, such as von Willebrand factor (vWf) and new blood vessel formation, as well as accelerated bone regeneration and increased bone mineral density. Moreover, carbon nanotube-coated PCL nanofibers reduced expression of pro-inflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) in vivo, suggesting reduction of inflammatory effect. Similarly, Mori et al. [58] used carbon nanotubes to coat a glass surface. Their studies revealed that single-walled carbon nanotubes stimulated osteogenic differentiation and mineralization of rat BMDSCs in vitro that was confirmed by high expression of osteogenic markers like bALP, Runx2, OCN, and bone morphogenetic protein-2 (BMP-2). In turn, Przekora et al. [59] demonstrated that chemically oxidized multi-walled carbon nanotubes coating onto Ti surface despite non-toxic character inhibited cell growth and proliferation of human fetal osteoblasts (hFOB 1.19 cell line). Whereas Benko et al. [60] modified the surface of the Ti substrate with multi-walled carbon nanotubes functionalized with OH groups. Applied modification supported attachment, spreading and growth of hFOB 1.19 cells in vitro. Additionally, graphene coatings on biomaterials may increase their potential for applications in the biomedical fields. For example, Li et al. [61] synthesized alginate-based scaffolds with graphene oxide coating, which were characterized by good cytocompatibility and supported proliferation and osteogenic differentiation of human adipose tissue-derived stem cells (ADSCs).

Boron nitride (BN) is another promising material that may be used as inorganic coating on the bone implants. It was proved that BN nanotubes are biocompatible and enhance attachment, growth, and osteogenic differentiation of rat BMDSCs in vitro [62]. Özmeriç et al. [63] studied the effects of cubic boron nitride (cBN) and hexagonal boron nitride (hBN) on bone fracture healing using a rat animal model. The stainless steel wires were coated by two different allotrope boron nitride using a physical vapor deposition system. In vivo experiments showed increase in bone volume:tissue volume ratio and bone surface values in group with cBN coating compared to groups with hBN and with uncoated samples. Moreover, cBN coating increased bALP levels, suggesting its superior effect on bone fracture healing compared to other groups.

In the literature, there are several findings concerning the use of composite coatings made of CaP (or its derivatives) and polymers (natural or synthetic) to modify biomaterial surface. Application of composite coating has paid special attention recently due to the possibility to mimic natural bone environment, and thereby accelerating bone regeneration. Furthermore, composite coatings—which contain at least two different constituents—have the prospect for achieving synergetic effect of two or more components of the coating. For instance, Yu et al. [64] developed Ti–6Al–4V substrates coated with HA and collagen-HA (Col/HA) composite using a biomimetic coating process. Both HA and Col/HA coatings supported the growth of MC3T3-E1 cells; however, osteoblasts cultured on the surface of biomaterial with Col/HA coating displayed a slightly higher cell proliferation rate in comparison to the HA coating. Additionally, researchers showed enhanced cell adhesion and spreading on the surface of Ti–6Al–4V coated by both HA and Col/HA composite. In another study, HA/chitosan/gentamicin coating deposited by an electrophoretic process on the surface of Ti showed non-toxic character against mouse fibroblasts (L929 cell line) and human lung fibroblasts (MRC-5 cell line), as found by

Stevanović et al. [65]. In turn, Qiaoxia et al. [66] deposited HA/tannic acid composite coating on the Ti modified with TiO_2 nanotubes. Resultant biomaterial showed good cytocompatibility as applied HA/tannic acid composite coating enhanced adhesion and proliferation of MC3T3-E1 cells. Moreover, created coating exhibited antioxidant activity. Gorgin Karaji et al. [67] developed Ti biomaterials covered by coating composed of TCP, silk, and vancomycin. The coating prepared by electrophoretic deposition method revealed antibacterial activity against *Staphylococcus aureus* strain and good osteoconductive properties, as it had the ability to increase adhesion, proliferation, and mineralization of MC3T3-E1 cells. While Harb et al. [68] prepared poly(methyl methacrylate)-silicon dioxide (PMMA/SiO_2) coatings on Ti–6Al–4V alloy by using dip-coating process. They found that the composite coating enhanced hFOB 1.19 cell proliferation compared to the PMMA coating and to the uncoated Ti–6Al–4V alloy. In turn, Zhou et al. [69] demonstrated that CaP/PLA-coated porous tantalum scaffold supported attachment and spreading of MG63 cells under in vitro conditions. Moreover, tantalum scaffold covered with CaP/PLA containing vascular endothelial growth factor (VEGF) and transforming growth factor (TGF) accelerated bone regeneration after its implantation into the rabbit subchondral bone defects. Table 1 shows a summary of the research concerning surface modifications of biomaterials using inorganic and composite coatings to improve osteoconductive and osteoinductive properties of the biomaterials for bone regeneration.

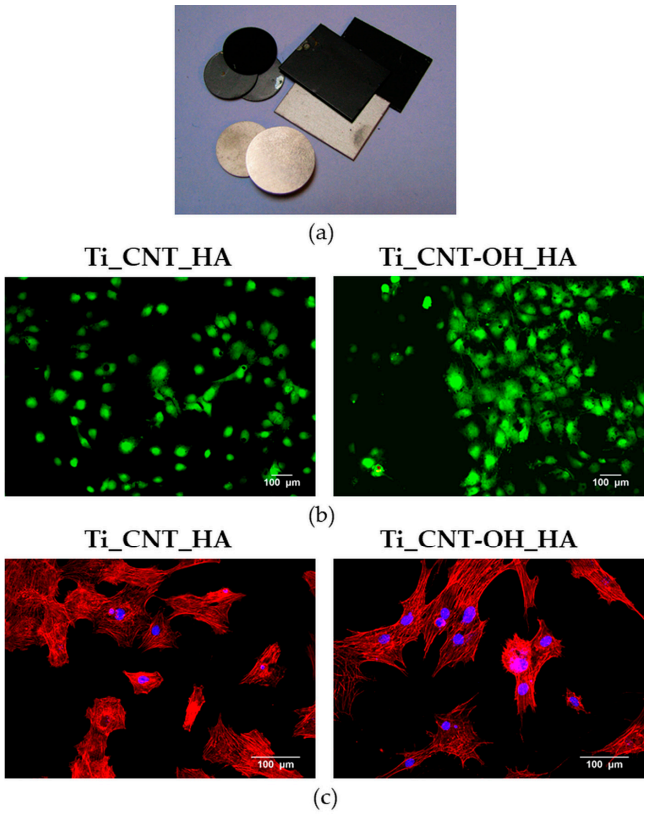

Figure 3. MC3T3-E1 preosteoblasts behavior on the titanium (Ti) samples coated by electrophoretic deposition with multi-walled carbon nanotubes and nanohydroxyapatite (sample marked as Ti_CNT_HA) and coated with multi-walled carbon nanotubes functionalized with OH groups and nanohydroxyapatite (sample marked as Ti_CNT-OH_HA): (**a**) Image presenting unmodified and modified (black) Ti samples; (**b**) confocal laser scanning microscope (CLSM) images showing viable cells on the surface of the samples after staining with the mixture of calcein-AM (viable cells—green fluorescence) and propidium iodide (dead cells—red fluorescence), magnification 100×, scale bar = 100 µm; (**c**) CLSM images showing well spread cells on the surface of the samples after staining with AlexaFluor635-Phalloidin (cytoskeleton filaments—red fluorescence) and DAPI (nuclei—blue fluorescence), magnification 200×, scale bar = 100 µm.

Table 1. Surface modifications of bone implants using inorganic and composite coatings.

Coating Material	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Limitations	Ref.
HA	Titanium	In vivo (rat model)	Supported new bone formation in vivo	Not provided	[37]
HA and Si-doped HA	Titanium	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1 and HUVECs cell line)	Supported cell spreading and osteogenic differentiation	Not provided	[39]
Oxidized multi-walled carbon nanotubes	Titanium	In vitro (human fetal osteoblast cell line—hFOB 1.19)	Highly conductive and non-toxic character	Inhibited cell growth and proliferation	[59]
Multi-walled carbon nanotubes functionalized with OH groups	Titanium	In vitro (human fetal osteoblast cell line—hFOB 1.19)	Nanorough topography supporting cell attachment, spreading and growth	Not provided	[60]
Calcium phosphate (CaP)/Ag	Titanium	In vitro (human osteosarcoma cell line—Saos-2)	Non-toxic character, supported cell attachment and spreading	Cytotoxic character of microsized silver phosphate particles (unlike nanoparticles)	[41]
TiO_2/ZnO	Titanium	In vitro (human osteosarcoma cell line—Saos-2)	Enhanced cell adhesion and osteogenic differentiation	Not provided	[43]
Zeolitic imidazolate framework-8 film	Titanium	In vitro (human osteosarcoma cell line—MG-63)	Enhanced bALP activity, superior expression of genes for bALP, Runx2, and increased ECM mineralization	Cytotoxic character of microsized zeolitic imidazolate framework-8 film (unlike nanosized film)	[53]
HA/chitosan/gentamicin	Titanium	In vitro (mice fibroblast cell line—L929 and human lung fibroblast cell line—MRC-5)	Non-cytotoxicity	Risk of the development of antibiotic resistance	[65]
Tricalcium phosphate (TCP)/silk/vancomycin	Titanium	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1)	Enhanced cell attachment, spreading, proliferation, and ECM mineralization	Risk of the development of antibiotic resistance	[67]
HA/tannic acid	Titanium modified by TiO_2 nanotube arrays	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1)	Improved cell adhesion and proliferation	Not provided	[66]
HA	Titanium alloy Ti–6Al–4V, Stainless steel	In vivo (canine model)	Induced bone formation and proved good osseointegration in vivo	Not provided	[38]
Si-doped HA and Sr-doped HA	Titanium alloy Ti–6Al–4V	In vivo (sheep model)	Increased osseointegration	Not provided	[40]
Glass-ceramics	Titanium alloy Ti–6Al–4V	In vitro (human osteosarcoma cell line—Saos-2)	Supported cell spreading and proliferation	Disordered/random surface topography	[42]
$BaTiO_3$	Titanium alloy Ti–6Al–4V	In vitro (rabbit BMDSCs) and in vivo (rabbit model)	Supported cell adhesion, proliferation, and osteogenic differentiation in vitro; increased new bone formation in vivo	Decreased compressive strength	[46]
Fe_3O_4/polydopamine	Titanium alloy Ti–6Al–4V	In vitro (human BMDSCs) and in vivo (rabbit model)	Supported cell attachment, proliferation and osteogenic differentiation in vitro; accelerated new bone formation in vivo	Not provided	[45]
Polycrystalline diamond	Titanium alloy Ti–6Al–4V	In vitro (Chinese hamster ovarian cell line—CHO)	Enhanced cell growth in vitro	Not provided	[55]
HA and HA/collagen	Titanium alloy Ti–6Al–4V	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1)	Improved cell adhesion and proliferation	Decreased mechanical properties	[64]
poly(methyl methacrylate) (PMMA)/SiO_2	Titanium alloy Ti–6Al–4V	In vitro (human fetal osteoblast cell line—hFOB 1.19)	Enhanced cell proliferation	Decreased surface roughness	[68]

Table 1. *Cont.*

Coating Material	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Limitations	Ref.
CaP/PLA	Tantalum	In vitro (human osteosarcoma cell line—MG-63) and in vivo (rabbit model)	Supported cell attachment and spreading in vitro; accelerated new bone formation in vivo	Not provided	[69]
Gellatin/HA	$BaTiO_3$-based scaffold	In vitro (human osteosarcoma cell line—MG-63)	Supported cell adhesion and proliferation	Not provided	[48]
Zeolite/Ag	Stainless steel	In vitro (rabbit BMDSCs)	Non-cytotoxicity	Slightly decreased cell adhesion and proliferation	[52]
Boron nitride (BN)	Stainless steel wire	In vivo (rat model)	Accelerated fracture healing by increase in bone volume/tissue volume ratio and bone surface values, increased bALP levels	Decreased osteocalcin levels	[63]
Ultra-nanocrystalline diamond	Silicon microchips	In vivo (mouse model)	Reduced foreign-body response in vivo	Not provided	[56]
$SiO_2/P_2O_5/CaO/MgO/Na_2O$	Silicon	In vitro (human fibroblast cell line—BJ)	Non-cytotoxicity	Not provided	[44]
Carbon nanotubes	Glass	In vitro (rat BMDSCs)	Promoted expression of osteogenic markers and ECM mineralization	Unaffected ECM mineralization on multi-walled carbon nanotubes coating (unlike single-walled carbon nanotubes coating)	[58]
Amorphous carbon	β-TCP	In vitro (rat BMDSCs) and in vivo (rat model)	Enhanced cell adhesion, proliferation, and bALP activity; supported new bone formation in vivo	Decreased surface roughness	[54]
Carbon nanotubes	PCL nanofibers	In vitro (human BMDSCs) and in vivo (rat model)	Supported cell adhesion and bone formation in vitro; enhanced ECM synthesis and new bone formation in vivo	Slightly reduced elastic modulus	[57]
Graphene oxide coating	Alginate-based scaffold	In vitro (human ADSCs)	Supported cell adhesion, proliferation, and osteogenic differentiation	Not provided	[61]

2.1.2. Organic Coatings

Natural and synthetic polymers—including various proteins such as laminin [70,71], whey protein isolate [72], collagen [73], and BMP-2 [74]—are organic materials which may be used in the coating process of metallic and ceramic biomaterials for bone tissue engineering applications. Organic coatings are not only characterized by high cytocompatibility and biodegradability, but they may also prevent metallic implants and ceramic materials against corrosion and uncontrolled degradability, respectively [75]. Most polymers are highly biocompatible what makes them ideal modifiers for incompatible biomaterials. Moreover, some polymers due to their specific structure are enabled to mimic microstructural properties of the bone ECM [21]. Osteoconductive and osteoinductive properties of organic coatings have been confirmed in several studies (Table 2). For instance, Rabe et al. [72] coated glass biomaterial with whey protein isolate fibrils to improve its biological properties. They confirmed that coated samples not only enhanced spreading and re-organization of the cytoskeleton of BMDSCs, but also increased tissue non-specific ALP activity. In turn, Zhao et al. [73] studied the impact of polyelectrolyte multilayer coating composed of hyaluronic acid/collagen or chondroitin sulfate/collagen on response of murine embryonic fibroblasts (C3H10T1/2 cell line). Cells cultured on the chondroitin sulfate-based samples showed more elongated morphology compared to the cells cultured on the hyaluronic acid-based samples, which confirmed their better adhesion to chondroitin sulfate/collagen coating. Moreover, cells grown on chondroitin sulfate-based samples exhibited

noticeably higher ALP activity. In another study, albumin coating on Ti material contributed to increased osteoblast viability [76]. Whereas 3D-polylactic acid (PLA) scaffold coated with gelatin and mucic acid supported cell adhesion, promoted osteogenic differentiation of murine embryonic fibroblast cell line (C3H10T1/2 cell line), and ECM mineralization, as shown by Ashwin et al. [77]. Liu et al. [74] covered porous β-$Ca_3(PO_4)_2$/Mg–Zn (β-TCP/Mg–Zn) composites with dopamine/gelatin/recombinant human BMP-2 coating. The applied coating improved cell proliferation and enhanced bALP activity in BMDSCs in vitro and improved bone regeneration in vivo. Khojasteh et al. [78] developed poly(lactic-co-glycolic) acid (PLGA) coated β-TCP scaffold containing VEGF for bone tissue engineering applications. PLGA coating along with VEGF release from the scaffold increased adhesion and proliferation of canine mesenchymal stem cells (cMSCs) and canine endothelial progenitor cells (cEPCs). The coating also enhanced expression of the osteogenic markers (Col I and Runx2) in culture of cMSCs. Positive impact of PLGA coating on proliferation and osteogenic differentiation of stem cells (BMDSCs cell line) in vitro was also confirmed by the work of Wei et al. [79], where PLGA nanofibers combined with aspirin were used to coat Ti-polydopamine sample via electrospinning method. Moreover, mentioned PLGA/aspirin coating displayed anti-inflammatory action via inhibition of M1 polarization of macrophages. Interestingly, the coating also inhibited receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclast differentiation of macrophages, leading to reduced osteoclastogenesis on the coated biomaterial and improved osseointegration of PLGA/aspirin coating at the implantation site. In turn, Ding et al. [80] developed plasma-sprayed HA-coated polyethylene terephthalate (PET) ligaments with a simvastatin–chitosan coating, which significantly enhanced osteogenic differentiation of MC3T3-E1 cells by increasing the level of expression of osteogenic-related genes, including Col I, BMP-2, OC, and bALP. Developed coating had also the ability to improve osseointegration of the implant with bone tissue in vivo in a rat model.

Table 2. Surface modifications of biomaterials using organic coatings.

Coating Material	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Limitations	Ref.
Albumin	Titanium	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1)	Increased cell viability	Not provided	[76]
Whey protein isolate fibril	Glass	In vitro (human BMDSCs)	Promoted cell spreading and osteogenic differentiation	Not provided	[72]
Hyaluronic acid/collagen and chondroitin sulfate/collagen	Glass	In vitro (murine embryonic fibroblast cell line—C3H10T1/2)	Promoted cell adhesion and osteogenic differentiation	Not provided	[73]
PLGA	β-TCP	In vitro (canine mesenchymal stem cells and canine endothelial progenitor cells)	Increased cell attachment and proliferation, enhanced osteogenic differentiation	Decreased total porosity	[78]
Dopamine/gelatin/rhBMP-2	β-TCP/Mg–Zn	In vitro (rat BMDSCs) and in vivo (rabbit model)	Supported cell proliferation and osteogenic differentiation in vitro; enhanced new bone formation in vivo	Not provided	[74]
Gelatin/mucic acid	PLA	In vitro (murine embryonic fibroblast cell line—C3H10T1/2)	Supported cell adhesion, osteogenic differentiation, and ECM mineralization	Decreased mechanical properties and increased degradation degree	[77]
PLGA/aspirin	Ti-polydopamine	In vitro (rat BMDSCs) and in vivo (rat model)	Increased cell proliferation, induced osteogenic differentiation, anti-inflammatory effect in vitro; improved osseointegration in vivo	Not provided	[79]
Simvastatin/chitosan	HA-coated polyethylene terephthalate	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1) and in vivo (rat model)	Induced osteogenic differentiation in vitro; enhanced osseointegration in vivo	Not provided	[80]

2.1.3. Plasma Modifications

Plasma modifications techniques are widely established technologies generally used to coat the surface of biomaterials for various applications to improve their bioactivity, biocompatibility, and interaction with tissues. Importantly, plasma treatment may not only alter the chemistry and topography of the biomaterials, but it also may modify the surface charge [33,81]. There are two main classes of plasma—thermal and non-thermal plasmas [82]. Thermal spraying methods have been commonly applied to modify ceramic or metallic substrates [34]. Principal thermal plasma spraying techniques include: atmospheric plasma spraying, high velocity suspension flame spraying, suspension plasma spraying, solution precursors plasma spraying, flame spraying [19,34,83], and plasma electrolytic oxidation [84,85]. Plasma surface modification technologies may not only be applied for metallic implants, but also for polymeric biomaterials. To modify the surface of the polymer-based biomaterials, non-thermal plasma techniques are frequently used due to possibility of application of much lower gas temperature compared to the thermal plasmas [82] (e.g., air plasma [86] or plasma polymerization technique [87,88]). There are various plasma modification strategies of polymer-based biomaterials, including introduction of specific functional groups to the surface of biomaterials, surface graft polymerization, plasma syn-irradiation, or plasma post-irradiation grafting [82,89].

In the available literature, there are numerous studies related to the use of plasma techniques in bone tissue engineering applications. This section will present an overview of recent findings concerning surface modifications of biomaterials using plasma treatment to improve osteoconductive and osteoinductive properties of biomaterials for bone regeneration (Table 3). Xing et al. [90] applied air-plasma treatment of Ti biomaterial which was coated with strontium-doped CaP (Sr–CaP). Conducted in vitro studies showed that simultaneously applied Sr–CaP coating and air-plasma spraying enhanced adhesion, proliferation, osteogenic differentiation (high bALP activity), and ECM mineralization of rabbit BMDSCs. Similar results were obtained by Liu et al. [91], who coated Ti alloy Ti–6Al–4V with silicon-doped nanostructured HA (Si-nHA) using atmospheric plasma spraying. Additionally, they proved that Si-nHA coating enhanced angiogenic differentiation of rabbit BMDSCs, what was confirmed by the analysis of gene expression levels for hypoxia-inducible factor 1-alpha (HIF-1a) and VEGF. Moreover, applied coating on Ti alloy Ti–6Al–4V downregulated mRNA expression for RANKL, which indicated repression of osteoclastogenesis in cell culture. In vivo experiments using a rabbit model showed that the Si-nHA coating significantly promoted new bone formation and osseointegration. The atmospheric plasma spraying was also used to deposit tantalum-doped HA on the Ti substrates by Lu et al. [92]. The tantalum-doped HA coatings promoted cell adhesion, proliferation, and osteogenic differentiation of rat BMDSCs. Longo et al. [93] deposited titanium carbide coating on the surface of Ti samples by the ion plating plasma assisted (IPPA) technology and showed enhanced adhesion, spreading, and proliferation of osteoblasts cultured on the coated biomaterials under in vitro conditions. In another study, Veronesi et al. [94] coated Ti implants with a 500 nm nanostructured layer composed of 60% graphitic carbon, 25% titanium oxides and 15% titanium carbide, which was deposited by IPPA technology. In vivo experiments using a rabbit model showed that coated implant improved osseointegration at the implantation site compared to uncoated implants.

Table 3. Surface modifications of biomaterials using coating materials and plasma.

Coating Material and Plasma Technique	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Ref.
Air-plasma spraying treatment and strontium-doped CaP coating	Titanium	In vitro (rabbit BMDSCs)	Enhanced cell adhesion, proliferation, osteogenic differentiation and ECM mineralization	[90]

Table 3. *Cont.*

Coating Material and Plasma Technique	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Ref.
Ion-assisted plasma polymerization treatment and BMP-2 coating	Titanium	In vitro (human BMDSCs and mouse macrophage reporter cell line—RAW Blue) and in vivo (rat model)	Promoted spreading, proliferation, and osteogenic differentiation of stem cells in vitro, supported adhesion and viability of macrophages without promoting NF-κB activation in vitro. Promoted new bone formation in vivo	[105]
Tantalum-doped HA coating deposited by atmospheric plasma spraying	Titanium	In vitro (rat BMDSCs)	Enhanced cell adhesion, spreading, proliferation, osteogenic differentiation, and ECM mineralization	[92]
Titanium carbide coating deposited by ion plating plasma assisted	Titanium	In vitro (human osteosarcoma cell line—Saos-2 and human primary osteoblasts)	Enhanced cell adhesion, spreading, and proliferation	[93]
Coating composed of 60% graphitic carbon, 25% titanium oxides and 15% titanium carbide deposited by ion plating plasma assisted	Titanium	In vivo (rabbit model)	Improved osseointegration	[94]
Zinc ions containing coating deposited by plasma electrolytic oxidation	Titanium	In vivo (rabbit model)	Enhanced osseointegration and new bone formation	[96]
Magnesium-doped titanium dioxide coating deposited by plasma electrolytic oxidation	Titanium	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1) and in vivo (rabbit model)	Promoted cell adhesion, proliferation, and osteogenic differentiation in vitro; enhanced osseointegration in vivo	[97]
Silicon-doped HA coating deposited by atmospheric plasma spraying	Titanium alloy Ti–6Al–4V	In vitro (rabbit BMDSCs) and in vivo (rabbit model)	Improved cell proliferation, osteogenic and angiogenic differentiation, hindered osteoclastogenesis in vitro; promoted new bone formation and osseointegration in vivo	[91]
Zinc-doped HA coating deposited by liquid precursor plasma spraying	Titanium alloy Ti–6Al–4V	In vitro (rat BMDSCs and mouse osteoclast-like cell precursor cell—RAW 264.7 cell line)	Moderately promoted osteogenic differentiation of BMDSCs and hindered osteoclastic activity at early stages	[101]
ZnO-, SiO_2-, Ag_2O-doped HA coating deposited by inductively coupled radio-frequency plasma spraying system	Titanium alloy Ti–6Al–4V	In vivo (rat model)	Enhanced new bone formation, osseointegration, and bone mineralization	[103]
MgO-, Ag_2O-doped HA coating deposited by plasma spray process	Titanium alloy Ti–6Al–4V	In vitro (primary human osteoblasts)	Slightly positive effect on cell proliferation and osteogenic differentiation	[104]
Diamond-like carbon and diamond-like carbon with silver nanoparticles coatings deposited by plasma-enhanced chemical vapor deposition	Titanium alloy Ti–6Al–4V	In vivo (rabbit model)	Enhanced osseointegration	[106]
Hydrogenated black TiO_2 coating deposited by inductively coupled radio-frequency plasma spraying system	Titanium alloy Ti–6Al–4V	In vitro (rat BMDSCs)	Improved cell adhesion, proliferation, and differentiation	[102]

Table 3. *Cont.*

Coating Material and Plasma Technique	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Ref.
Calcium and phosphorus ions containing coating deposited by plasma electrolytic oxidation	Titanium alloy Ti–6Al–4V	In vivo (rat model)	Enhanced osseointegration and new bone formation	[95]
Calcium ions containing coating deposited by plasma electrolytic oxidation	Titanium alloy Ti–13Nb–13Zr alloy	In vitro (human BMDSCs)	Enhanced cell adhesion, proliferation, and osteogenic differentiation	[100]
Bilayer coating containing HA nanorods and MgO with HA/$Mg(OH)_2$ deposited by plasma electrolytic oxidation	Magnesium	In vitro (rabbit BMDSCs) and in vivo (rabbit model)	Enhanced ECM mineralization in vitro; promoted osseointegration in vivo	[98]
Calcium, phosphorus, and silicon or fluorine ions containing coating deposited by plasma electrolytic oxidation	Magnesium 0.8 wt.% calcium alloy	In vitro (mouse calvarial preosteoblast cell line—MC3T3-E1)	Supported cell growth, collagen secretion, and ECM mineralization	[99]
Nano fibrous titania coating deposited by high intensity laser-induced reverse transfer	Glass	In vitro (human BMDSCs)	Promoted cell spreading, proliferation, differentiation, and ECM mineralization	[109]
Silicon nitride coating deposited by inductively coupled plasma-enhanced chemical vapor deposition	PEEK	In vitro (rat BMDSCs)	Promoted cell spreading, proliferation, and osteogenic differentiation	[107]
Titanium coating deposited by plasma spray process	PEEK	In vitro (human fetal osteoblast cells—hFOB 1.19)	Promoted cell proliferation and ECM mineralization	[108]

Polo et al. [95] proved enhanced osseointegration by facilitating better bond strength and acceleration of new bone formation in vivo by means of plasma electrolytic oxidation (PEO) coating containing Ca^{2+} and P^{5+} on the Ti implant surface. Similar results were found by He et al. [96], who deposited Zn-containing coating on the Ti implant surface through the PEO method. In another study, osteogenic activity and antibacterial ability on Ti surfaces modified with magnesium-doped titanium dioxide (Mg–TiO_2) coating deposited also by PEO method were confirmed by the work of Zhao et al. [97]. They showed that the Mg–TiO_2 coating significantly enhanced adhesion, proliferation, and differentiation of osteoblasts (MC3T3-E1 cell line), as well as had the ability to inhibit the growth of *Staphylococcus aureus* in vitro. In vivo experiments demonstrated that the Mg–TiO_2 coating could improve osseointegration through the extracellular signal-regulated kinases/c-Fos (ERK/c-Fos) signaling pathway. In turn, Li et al. [98] showed enhanced ECM mineralization of rabbit BMDSCs in vitro and improved osseointegration in vivo (rabbit model) in response to a bilayer-structured coating, comprising HA nanorods and MgO with HA/$Mg(OH)_2$ deposited by PEO and hydrothermal treatment on magnesium substrate. Moreover, they proved the immunomodulatory character of bilayer-structured coating, since it had the ability to significantly decrease expression of genes for pro-inflammatory cytokines, like TNF-α and IL-1β, and increase expression of gene for anti-inflammatory cytokine – IL-10. Whereas, Santos-Coquillat et al. [99] deposited calcium, phosphorus, and silicon or fluorine on magnesium alloy using PEO to improve osteoblast growth, collagen secretion, and ECM mineralization. In turn, Michalska et al. [100] modified the surface of the Ti–13Nb–13Zr alloy by electropolishing and PEO technique. They proved that the PEO coatings (containing calcium ions) on the Ti–13Nb–13Zr alloy significantly improved the cytocompatibility of biomaterial by promoting adhesion, proliferation, and osteogenic differentiation of human BMDSCs.

Meng et al. [101] deposited zinc-substituted HA coating on the Ti–6Al–4V alloy substrates by liquid precursor plasma spraying technique. The zinc-substituted HA coating showed moderate effect on the promotion of osteogenic differentiation of BMDSCs and the ability to hinder osteoclastic activity of osteoclast-like cell precursor cells (RAW 264.7 cell line) at early stages of co-culture condition.

However, at later stages osteoclastic activity of RAW 264.7 cells was promoted. In another study, hydrogenated black TiO_2 coating deposited on the Ti–6Al–4V alloy substrates by inductively coupled radio-frequency plasma spraying had the ability to improve adhesion, proliferation, and osteogenic differentiation (high bALP activity and the expression of bone-related genes, including Runx2, OC, OPN, and BSP) of rat BMDSCs, as confirmed by the work of Zhang et al. [102]. Similarly, Vu et al. [103] used inductively coupled radio-frequency plasma spraying for the deposition of ZnO-, SiO_2-, and Ag_2O-doped HA coating (ZnSiAg-HA) on the Ti implants for orthopedic and dental applications. They demonstrated, using a rat model, that developed ZnSiAg-HA coating had the ability to enhance bone formation, bone mineralization, and osseointegration, suggesting that applied surface modification of the implants may result in faster bone regeneration. Moreover, silver ions released from the coating provided antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* in vitro. Nevertheless, plasma-sprayed MgO-, Ag_2O-doped HA coating on the Ti substrate (which was also prepared by laser engineered net shaping) did not enhance osteoblast proliferation and osteogenic differentiation compared to pure HA-doped coating [104], but still exhibited antibacterial effect against *Escherichia coli* and *Staphylococcus aureus* bacterial strains. In another study, Ti implant was treated with ion-assisted plasma polymerization (IAPP), and subsequently coated with BMP-2 [105]. Obtained multifaceted biomimetic surface was characterized by high cytocompatibility and non-immunogenicity, promoted spreading, proliferation, and differentiation (high bALP activity) of BMDSCs, and supported adhesion and viability of macrophages (RAW Blue cell line) without supporting undesirable NF-κB activation in vitro. In vivo experiments using a rat model showed accelerated new bone formation. In another study, diamond-like carbon and diamond-like carbon with silver nanoparticles coatings were deposited by plasma-enhanced chemical vapor deposition onto the surface of Ti–6Al–4V alloy, slightly enhancing osseointegration in vivo [106].

Xu et al. [107] used inductively coupled plasma-enhanced chemical vapor deposition to coat PEEK surface with silicon nitride. In vitro experiments showed that applied silicon nitride coating significantly improved adhesion, proliferation, and osteogenic differentiation of rat BMDSCs. Moreover, high level of expression for osteogenic-related genes (including Runx2, bALP, OPN, OC) was observed in rat BMDSCs cultured on the modified surface of PEEK compared to uncoated one. Hickey et al. [108] also modified the surface of PEEK by deposition of Ti coating using plasma spray process. They demonstrated that Ti-PEEK surface had the ability to stimulate cellular proliferation and ECM mineralization in hFOB 1.19 osteoblasts.

2.1.4. Magnetron Sputtering Modifications

Among various methods for additive modifications of biomaterial surface, a magnetron sputtering deserves special attention as it enables deposition of many types of coating (ceramics and metals) onto substrate materials under vacuum condition [110,111]. For example, Hwang et al. [112] fabricated tantalum-coated polylactic acid membranes using the magnetron sputtering technique. In vitro experiments exhibited that coated membranes promoted attachment, proliferation, and differentiation of MC3T3-E1 cells, whereas in vivo studies using a rabbit model showed that tantalum-coated polylactic acid membranes had better osteoconductivity than the uncoated ones. Whereas Yang et al. [113] deposited tantalum nanofilms onto Ti substrate via magnetron sputtering and showed excellent biocompatibility and antibacterial activity in vivo of applied coatings. In turn, Milan et al. [114] deposited Cu/a-C:H thin coating onto Ti alloys via magnetron sputtering and they showed that applied coating improved antibacterial activity as well as stimulated angiogenesis and osteogenic differentiation of human BMDSCs in vitro. Similarly, Tolde et al. [115] applied magnetron sputtering techniques to cover Ti alloys and stainless steel with niobium titanium (TiNb) coating. Resultant materials were subsequently applied as a substrate for deposition of $BaTiO_3$ film characterized by better biocompatibility in comparison with pure TiNb.

2.2. Subtractive Modifications of Biomaterial Surface

Several subtractive modifications of biomaterial surface, such as acid etching, sand blasting, grit blasting, anodizing, as well as hydrothermal and laser methods have been developed (Figure 4) [116]. Subtractive methods are usually applied to achieve porous and rough surface of the bone implants. Topography of the biomaterial surface plays a critical role in the first stages of osseointegration and thereby precludes from implant failure. It is well known that meso-/microporosity and roughness of the biomaterial surface exert positive impact on cellular response, including better cell adhesion, proliferation, and differentiation [22,117,118]. Moreover, macroporous (pore size > 50 μm) structure enhances osseointegration and bone ingrowth, whereas microporosity (pore size < 2 μm) increases surface area which contributes to higher protein adsorption capacity of the biomaterial. Adsorbed to the implant proteins participate in the adhesion of osteoblasts and osteoprogenitor cells and are considered as a major factor providing appropriate interaction between cells and biomaterial [5,119]. Microporosity has also impact on biomaterial bioactivity since it increases ion exchange, supporting formation of the apatite-like layer on the implant surface [7,8,117].

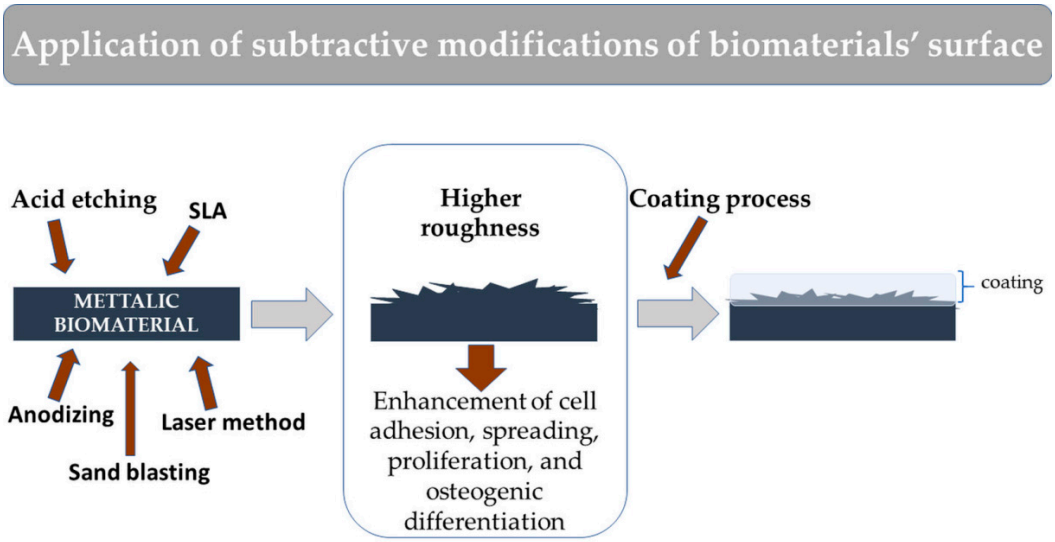

Figure 4. Scheme presenting application of subtractive modifications of biomaterial surface.

Texture modification techniques, such as subtractive methods, allow to modify or change surface characteristics to increase the biocompatibility of biomaterials for bone tissue engineering and regenerative medicine applications. For instance, acid etching method allows to obtain irregular and complex surface of Ti implants using strong acid solutions such as sulfuric acid (H_2SO_4), hydrochloric acid (HCl), hydrofluoric acid (HF), nitric acid (HNO_3), and any combination of mentioned acid solutions [120]. Etching increases roughness and wettability of the implant [121] but exerts negative effect on its mechanical properties [120]. Surface modification technique combining acid-etching and sand blasting is defined as sand-blasted, large-grit, acid etched (SLA), which indicates application of an acid onto the blasted surface [120,122]. SLA allows to obtain macro-roughness and micro-pits, increasing surface area and roughness of the implant, and thereby improving osseointegration [122]. The increase in the surface roughness of the implants may also be achieved by grit blasting treatment which uses hard ceramic particles (such as Al_2O_3, TiO_2, SiO_2, CaP) and compressed air. The size of achieved roughness depends on the size of ceramic particles used for the subtractive modification. The ceramic particles should be stable and biocompatible since residual blasting material particles might be very hard to remove from the sample surface [120,123]. Another processing method of metallic implants is anodizing. Anodization technology is defined as anodic oxidation of metals (e.g., Ti and Ti alloys) via an electrochemical method which allows formation of a uniform oxide layer with desire thickness on the metal implants. Moreover, anodizing allows formation of the

nanopores and nanotubes to change topographic features of the implant. The changes in the texture of the implant may be controlled by application of various oxidation voltage, oxidation duration, type of electrolyte solution (e.g., H_2SO_4, HNO_3, hydrofluoric acid (HF)), and electrolyte solution concentration [120,124]. Laser treatment of the implants is an innovative surface modification method which allows modification of the surfaces at a nano-, micro-, and macro-size scale using a stationary laser beam. Major advantages of the laser treatment include possibility to modify both chemistry and surface topography and no necessity to use any acid and metal sand which significantly reduces risk of contamination of the modified surface compared to other techniques [125,126].

Multiple subtractive modifications of biomaterial surface have been studied so far (Table 4). For example, Zhang et al. [127] modified three-dimensional printed Ti alloy (Ti6Al4V) via SLA technique and showed that applied surface modification enhanced cell adhesion, proliferation, and osteogenic differentiation (high level of bALP activity and ECM mineralization) of rat BMDSCs in vitro as well as increased osseointegration in vivo in a rat animal model. Similar results were obtained by He et al. [128] who modified Ti samples by SLA and micro-arc oxidation. In turn, Zhan et al. [129] modified pure Ti and Ti–24Nb–4Zr–8Sn (Ti2448) alloy using SLA and anodizing and studied their influence on cellular response. Anodizing treatment increased hydrophilicity of pure Ti and Ti2448 alloy as well as promoted ECM mineralization in human BMDSCs. In another study, De Tullio et al. [125] demonstrated using a sheep model that SLA- or laser-treated Ti substrates supported osseointegration in vivo. In turn, Kunrath et al. [130] applied acid etching and anodizing methods to alter physicochemical properties of Ti substrate in order to improve biocompatibility of the material. They showed that simultaneous application of double acid etching (hydrochloric acid and sulfuric acid) and anodizing treatment of the Ti surface provided the best support for osteoblast adhesion. Nevertheless, the highest roughness was obtained for samples treated with only double acid etching, which unfortunately significantly increased bacterial proliferation in vitro. Yu et al. [131] applied picosecond laser ablation to modify Ti substrate and demonstrated that the resultant surface of Ti with micro-groves promoted cell adhesion.

Table 4. Subtractive surface modifications of biomaterials.

Subtractive Modification Method	Type of Biomaterial	Experimental Model	Impact of Surface Coating on Biological Properties of Biomaterial	Limitations	Ref.
Acid etching and anodizing	Titanium	In vitro (rat ADSCs)	Promoted cell adhesion	Not provided	[130]
SLA or laser-treatment	Titanium	In vivo (sheep model)	Increased osseointegration	Not provided	[125]
SLA and micro-arc oxidation	Titanium	In vitro (rat BMDSCs) and in vivo (dog model)	Enhanced cell adhesion, proliferation, and osteogenic differentiation in vitro; promoted osseointegration in vivo	Not provided	[128]
SLA or anodizing	Titanium and titanium alloy Ti–24Nb–4Zr–8Sn	In vitro (human BMDSCs)	Only anodizing increased ECM mineralization	SLA and anodizing decreased cell proliferation	[129]
SLA	Titanium alloy Ti–6Al–4V	In vitro (rat BMDSCs) and in vivo (rat model)	Enhanced cell adhesion, proliferation, and osteogenic differentiation in vitro; increased osseointegration in vivo	Not provided	[127]
Picosecond laser	Titanium alloy Ti–6Al–4V	In vitro (rat BMDSCs)	Supported cell adhesion	Not provided	[131]

The subtractive modifications of biomaterial surface may also be applied to prepare the surface before the coating process (Figure 4) [132–139]. By increasing the roughness of the surface, better adhesive bond between the coating and the surface of modified material may be achieved [140]. For example, Wu et al. [132] modified the surface of Ti using sand blasting, acid etching and ultraviolet

(UV) radiation or using anodizing and UV radiation and then applied cell-derived ECM coating to obtain biomimetic implants. In vitro experiments showed that sample modified by anodizing, UV radiation and covered with ECM coating exhibited better osteoconductivity and osteoinductivity than sample treated with sand blasting, acid etching, UV radiation, and ECM coating. In turn, Li et al. [136] deposited graphene oxide coating onto SLA-treated Ti substrates and showed that SLA/graphene oxide-modified materials supported adhesion, proliferation, and osteogenic differentiation of rat BMDSCs in vitro, as well as provided excellent osseointegration in vivo in a rat animal model.

3. Concluding Remarks

Over the years, a great number of novel biomaterials have been developed for bone tissue engineering and regenerative medicine applications. Unfortunately, many of them showed a lack of cytocompatibility. The current trend in engineering of biomaterials is to produce biomimetic biomaterials (comprising organic and inorganic components) that would have the ability to mimic a natural bone environment, accelerating regeneration process. Nevertheless, the development of bone scaffold with both high biocompatibility and desired mechanical properties is regarded as a huge challenge for the researchers. Thus, surface modifications of biomaterial with desired mechanical properties in order to improve its biocompatibility appears to be a promising approach to obtain an ideal bone implant. The presented review has shown the recent findings in the field of engineering of biomaterials regarding surface modifications of metallic implants or composite biomaterials to improve their biological properties. It is well known that osteoconductive and osteoinductive properties of bone implants play a crucial role in enhancing osseointegration with host tissues. Surface modifications of the biomaterials aiming to improve their biocompatibility may be divided into two groups: additive and subtractive. Additive modification methods, which lead to the formation of additional structures on the surfaces, are very good approach for metallic biomaterials (such as Ti or stainless steel), since organic or composite coatings may create surface-mimicking natural bone, whereas metallic biomaterials provide good mechanical strength. The subtractive modifications primarily focus on increasing surface roughness of the biomaterials to support cell attachment, spreading, proliferation, and osteogenic differentiation. Nevertheless, it is well known, that high surface roughness may exert a detrimental impact on the fatigue life of the biomaterials [141]. Moreover, the coating thickness and created micro-crack during coating formation may reduce fatigue resistance of the resultant implant [19]. Therefore, when developing new coatings on the biomaterials for clinical applications, special attention should be paid to potential stress concentrations/stress raisers that may occur at the implantations site, causing failure or collapse of the bone implant.

Literature overview revealed that both types of surface modifications (additive and subtractive) lead to significant improvement of cellular response to the biomaterial compared to unmodified samples. Furthermore, available literature presents a great variety of modifications techniques. Since each biomaterial is characterized by different chemistry, microstructure, and mechanical properties, it is impossible to select one universal modification method that would ensure successful enhancement of osteoconductivity/osteoinductivity of the bone implant. Nevertheless, it is clearly observed that primary choice in the case of bioceramics biomaterials is organic (biopolymer) coating (additive technique). Whereas metallic implants are primarily subjected to either subtractive methods or plasma modifications (additive techniques) or inorganic coating procedures (additive technique). It is worth noting that some subtractive modifications (e.g., acid etching) may decrease the mechanical strength of the resultant biomaterial. Thus, it is important to take into consideration the end application of the implant (load-bearing site or non-load-bearing site) during selection of surface modification technique.

Although there are a number of surface modification techniques described in the literature, many methods are costly and very complex, limiting transfer of these technologies into the clinical market. Moreover, improvement of biological properties of the biomaterials is often related with reduced mechanical strength and fatigue resistance of the resultant bone implant, especially when subtractive modifications are used. There is also relatively small number of reports in the available

literature presenting modifications of the biomaterials leading to the formation of osteoinductive surfaces, which are the most desirable in clinical applications. Therefore, nowadays, the greatest challenge for the researchers is to develop surface modification method that would be not only relatively simple and cost-effective, but also would allow to achieve osteoinductive surface on the bone implant without worsening its mechanical strength.

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References

1. Arvidson, K.; Abdallah, B.M.; Applegate, L.A.; Baldini, N.; Cenni, E.; Gomez-Barrena, E.; Granchi, D.; Kassem, M.; Konttinen, Y.T.; Mustafa, K.; et al. Bone regeneration and stem cells. *J. Cell. Mol. Med.* **2011**, *15*, 718–746. [CrossRef]
2. Zivic, F.; Affatato, S.; Trajanovic, M.; Schnabelrauch, M.; Grujovic, N.; Choy, K.L. *Biomaterials in Clinical Practice. Advances in Clinical Research and Medical Devices*; Springer International Publishing: Cham, Switzerland, 2018; ISBN 978-3-319-68025-5.
3. Oryan, A.; Alidadi, S.; Moshiri, A.; Maffulli, N. Bone regenerative medicine: Classic options, novel strategies and future directions. *J. Orthop. Surg. Res.* **2014**, *9*, 1–27. [CrossRef] [PubMed]
4. Rose, F.R.A.J.; Oreffo, R.O.C. Bone tissue engineering: Hope vs hype. *Biochem. Biophys. Res. Commun.* **2002**, *292*, 1–7. [CrossRef] [PubMed]
5. Przekora, A. The summary of the most important cell-biomaterial interactions that need to be considered during in vitro biocompatibility testing of bone scaffolds for tissue engineering applications. *Mater. Sci. Eng. C* **2019**, *97*, 1036–1051. [CrossRef] [PubMed]
6. Dolcimascolo, A.; Calabrese, G.; Conoci, S.; Parenti, R. Innovative biomaterials for tissue engineering. In *Biomaterial-Supported Tissue Reconstruction or Regeneration*; Barbeck, M., Jung, O., Smeets, R., Koržinskas, T., Eds.; IntechOpen: London, UK, 2019; pp. 1–18.
7. Karageorgiou, V.; Kaplan, D. Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials* **2005**, *26*, 5474–5491. [CrossRef] [PubMed]
8. Mour, M.; Das, D.; Winkler, T.; Hoenig, E.; Mielke, G.; Morlock, M.M.; Schilling, A.F. Advances in porous biomaterials for dental and orthopaedic applications. *Materials* **2010**, *3*, 2947–2974. [CrossRef]
9. Prasadh, S.; Wong, R.C.W. Unraveling the mechanical strength of biomaterials used as a bone scaffold in oral and maxillofacial defects. *Oral Sci. Int.* **2018**, *15*, 48–55. [CrossRef]
10. Tang, Z.; Li, X.; Tan, Y.; Fan, H.; Zhang, X. The material and biological characteristics of osteoinductive calcium phosphate ceramics. *Regen. Biomater.* **2018**, *5*, 43–59. [CrossRef]
11. Fillingham, Y.; Jacobs, J. Bone grafts and their substitutes. *Bone Jt. J.* **2016**, *98*, 6–9. [CrossRef]
12. Morais, J.M.; Papadimitrakopoulos, F.; Burgess, D.J. Biomaterials/tissue interactions: Possible solutions to overcome foreign body response. *Am. Assoc. Pharm. Sci.* **2010**, *12*, 188–196. [CrossRef]
13. Stevens, M.M. Biomaterials for bone tissue engineering. *Mater. Today* **2008**, *11*, 18–25. [CrossRef]
14. Kazimierczak, P.; Benko, A.; Palka, K.; Canal, C.; Kolodynska, D.; Przekora, A. Novel synthesis method combining a foaming agent with freeze-drying to obtain hybrid highly macroporous bone scaffolds. *J. Mater. Sci. Technol.* **2020**, *43*, 52–63. [CrossRef]
15. Xie, Y.; Hu, C.; Feng, Y.; Li, D.; Ai, T.; Huang, Y.; Chen, X.; Huang, L.; Tan, J. Osteoimmunomodulatory effects of biomaterial modification strategies on macrophage polarization and bone regeneration. *Regen. Biomater.* **2020**, *7*, 233–245. [CrossRef] [PubMed]
16. Alvarez, K.; Nakajima, H. Metallic scaffolds for bone regeneration. *Materials* **2009**, *2*, 790–832. [CrossRef]
17. Hanawa, T. Titanium-tissue interface reaction and its control with surface treatment. *Front. Bioeng. Biotechnol.* **2019**, *7*, 170. [CrossRef]

18. Qiu, Z.Y.; Chen, C.; Wang, X.M.; Lee, I.S. Advances in the surface modification techniques of bone-related implants for last 10 years. *Regen. Biomater.* **2014**, *1*, 67–79. [CrossRef]
19. Dehghanghadikolaei, A.; Fotovvati, B. Coating techniques for functional enhancement of metal implants for bone replacement: A review. *Materials* **2019**, *12*, 1795. [CrossRef]
20. Yadav, D.; Garg, R.K.; Ahlawat, A.; Chhabra, D. 3D printable biomaterials for orthopedic implants: Solution for sustainable and circular economy. *Resour. Policy* **2020**, *68*, 101767. [CrossRef]
21. Diekjürgen, D.; Grainger, D.W. Polysaccharide matrices used in 3D in vitro cell culture systems. *Biomaterials* **2017**, *141*, 96–115. [CrossRef]
22. Sachot, N.; Engel, E.; Castano, O. Hybrid organic-inorganic scaffolding biomaterials for regenerative therapies. *Curr. Org. Chem.* **2014**, *18*, 2299–2314. [CrossRef]
23. Ullah, S.; Chen, X. Fabrication, applications and challenges of natural biomaterials in tissue engineering. *Appl. Mater. Today* **2020**, *20*, 100656. [CrossRef]
24. Przekora, A.; Palka, K.; Ginalska, G. Chitosan/β-1,3-glucan/calcium phosphate ceramics composites—Novel cell scaffolds for bone tissue engineering application. *J. Biotechnol.* **2014**, *182*, 46–53. [CrossRef] [PubMed]
25. Przekora, A. Current trends in fabrication of biomaterials for bone and cartilage regeneration: Materials modifications and biophysical stimulations. *Int. J. Mol. Sci.* **2019**, *20*, 435. [CrossRef] [PubMed]
26. Mano, J.F.; Silva, G.A.; Azevedo, H.S.; Malafaya, P.B.; Sousa, R.A.; Silva, S.S.; Boesel, L.F.; Oliveira, J.M.; Santos, T.C.; Marques, A.P.; et al. Natural origin biodegradable systems in tissue engineering and regenerative medicine: Present status and some moving trends. *J. R. Soc. Interface* **2007**, *4*, 999–1030. [CrossRef]
27. Roseti, L.; Parisi, V.; Petretta, M.; Cavallo, C.; Desando, G.; Bartolotti, I.; Grigolo, B. Scaffolds for bone tissue engineering: State of the art and new perspectives. *Mater. Sci. Eng. C* **2017**, *78*, 1246–1262. [CrossRef]
28. Nouri, A.; Wen, C. Introduction to surface coating and midification for metallic biomaterials. In *Surface Coating and Modification of Metallic Biomaterials*; Wen, C., Ed.; Woodhead Publishing: Cambridge, UK, 2015; pp. 3–60. ISBN 9781782423164.
29. Turnbull, G.; Clarke, J.; Picard, F.; Riches, P.; Jia, L.; Han, F.; Li, B.; Shu, W. 3D bioactive composite scaffolds for bone tissue engineering. *Bioact. Mater.* **2018**, *3*, 278–314. [CrossRef] [PubMed]
30. Pagel, M.; Beck-Sickinger, A.G. Multifunctional biomaterial coatings: Synthetic challenges and biological activity. *Biol. Chem.* **2017**, *398*, 3–22. [CrossRef]
31. Bose, S.; Robertson, S.F.; Bandyopadhyay, A. Surface modification of biomaterials and biomedical devices using additive manufacturing. *Acta Biomater.* **2018**, *66*, 143–169. [CrossRef]
32. Arjunan, A.; Robinson, J.; Al Ani, E.; Heaselgrave, W.; Baroutaji, A.; Wang, C. Mechanical performance of additively manufactured pure silver antibacterial bone scaffolds. *J. Mech. Behav. Biomed. Mater.* **2020**, *112*, 104090. [CrossRef]
33. Oshida, Y.; Guven, Y. Biocompatible coatings for metallic biomaterials. In *Surface Coating and Modification of Metallic Biomaterials*; Wen, C., Ed.; Woodhead Publishing: Cambridge, UK, 2015; pp. 287–343. ISBN 978-1-78242-303-4.
34. Sergi, R.; Bellucci, D.; Cannillo, V. A comprehensive review of bioactive glass coatings: State of the art, challenges and future perspectives. *Coatings* **2020**, *10*, 757. [CrossRef]
35. Ahn, T.-K.; Lee, D.H.; Kim, T.; chol Jang, G.; Choi, S.; Oh, J.B.; Ye, G.; Lee, S. Modification of titanium implant and titanium dioxide for bone tissue engineering. In *Novel Biomaterials for Regenerative Medicine*; Chun, H., Park, K., Kim, C., Khang, G., Eds.; Springer: Singapore, 2018; pp. 355–368. ISBN 9789811309465.
36. Surmenev, R.A.; Surmeneva, M.A.; Ivanova, A.A. Significance of calcium phosphate coatings for the enhancement of new bone osteogenesis—A review. *Acta Biomater.* **2014**, *10*, 557–579. [CrossRef] [PubMed]
37. de Oliveira, P.G.F.P.; de Melo Soares, M.S.; Silveira e Souza, A.M.M.; Taba, M.; Palioto, D.B.; Messora, M.R.; Ghiraldini, B.; Nunes, F.A.D.S.; de Souza, S.L.S. Influence of nano-hydroxyapatite coating implants on gene expression of osteogenic markers and micro-CT parameters. An in vivo study in diabetic rats. *J. Biomed. Mater. Res. Part A* **2020**. [CrossRef] [PubMed]
38. Popkov, A.V.; Gorbach, E.N.; Kononovich, N.A.; Popkov, D.A.; Tverdokhlebov, S.I.; Shesterikov, E.V. Bioactivity and osteointegration of hydroxyapatite-coated stainless steel and titanium wires used for intramedullary osteosynthesis. *Strat. Trauma Limb Reconstr.* **2017**, *12*, 107–113. [CrossRef] [PubMed]
39. Fu, X.; Liu, P.; Zhao, D.; Yuan, B.; Xiao, Z.; Zhou, Y.; Yang, X.; Zhu, X.; Tu, C.; Zhang, X. Effects of nanotopography regulation and silicon doping on angiogenic and osteogenic activities of hydroxyapatite coating on titanium implant. *Int. J. Nanomed.* **2020**, *15*, 4171–4189. [CrossRef] [PubMed]

40. Mumith, A.; Cheong, V.S.; Fromme, P.; Coathup, M.J.; Blunn, G.W. The effect of strontium and silicon substituted hydroxyapatite electrochemical coatings on bone ingrowth and osseointegration of selective laser sintered porous metal implants. *PLoS ONE* **2020**, *15*, e0227232. [CrossRef] [PubMed]
41. Mokabber, T.; Cao, H.T.; Norouzi, N.; Van Rijn, P.; Pei, Y.T. Antimicrobial electrodeposited silver-containing calcium phosphate coatings. *ACS Appl. Mater. Interfaces* **2020**, *12*, 5531–5541. [CrossRef]
42. Marzban, K.; Rabiee, S.M.; Zabihi, E.; Bagherifard, S. Nanostructured akermanite glass-ceramic coating on Ti6Al4V for orthopedic applications. *J. Appl. Biomater. Funct. Mater.* **2019**, *17*, 1–8. [CrossRef]
43. Zhang, R.; Xu, N.; Liu, X.; Yang, X.; Yan, H.; Ma, J.; Feng, Q.; Shen, Z. Micro/nanostructured TiO_2/ZnO coating enhances osteogenic activity of SaOS-2 cells. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 2838–2845. [CrossRef]
44. Schitea, R.I.; Nitu, A.; Ciobota, A.A.; Munteanu, A.L.; David, I.M.; Miu, D.; Raileanu, M.; Bacalum, M.; Busuioc, C. Pulsed laser deposition derived bioactive glass-ceramic coatings for enhancing the biocompatibility of scaffolding materials. *Materials* **2020**, *13*, 2615. [CrossRef]
45. Huang, Z.; He, Y.; Chang, X.; Liu, J.; Yu, L.; Wu, Y.; Li, Y.; Tian, J.; Kang, L.; Wu, D.; et al. A magnetic iron oxide/polydopamine coating can improve osteogenesis of 3D-printed porous titanium scaffolds with a static magnetic field by upregulating the TGF β -Smads pathway. *Adv. Healthc. Mater.* **2020**, *9*, 1–13. [CrossRef]
46. Fan, B.; Guo, Z.; Li, X.; Li, S.; Gao, P.; Xiao, X.; Wu, J.; Shen, C.; Jiao, Y.; Hou, W. Electroactive barium titanate coated titanium scaffold improves osteogenesis and osseointegration with low-intensity pulsed ultrasound for large segmental bone defects. *Bioact. Mater.* **2020**, *5*, 1087–1101. [CrossRef] [PubMed]
47. Zhang, Y.; Chen, L.; Zeng, J.; Zhou, K.; Zhang, D. Aligned porous barium titanate/hydroxyapatite composites with high piezoelectric coefficients for bone tissue engineering. *Mater. Sci. Eng. C* **2014**, *39*, 143–149. [CrossRef] [PubMed]
48. Ehterami, A.; Kazemi, M.; Nazari, B.; Saraeian, P.; Azami, M. Fabrication and characterization of highly porous barium titanate based scaffold coated by Gel/HA nanocomposite with high piezoelectric coefficient for bone tissue engineering applications. *J. Mech. Behav. Biomed. Mater.* **2018**, *79*, 195–202. [CrossRef]
49. Scarisoreanu, N.D.; Craciun, F.; Ion, V.; Birjega, R.; Bercea, A.; Dinca, V.; Dinescu, M.; Sima, L.E.; Icriverzi, M.; Roseanu, A.; et al. Lead-free piezoelectric (Ba,Ca)(Zr,Ti)O_3 thin films for biocompatible and flexible devices. *ACS Appl. Mater. Interfaces* **2017**, *9*, 266–278. [CrossRef] [PubMed]
50. Zlotnik, S.; Maltez-Da Costa, M.; Barroca, N.; Hortigüela, M.J.; Singh, M.K.; Fernandes, M.H.V.; Vilarinho, P.M. Functionalized-ferroelectric-coating-driven enhanced biomineralization and protein-conformation on metallic implants. *J. Mater. Chem. B* **2019**, *7*, 2177–2189. [CrossRef]
51. Bacakova, L.; Vandrovcova, M.; Kopova, I.; Jirka, I. Applications of zeolites in biotechnology and medicine-a review. *Biomater. Sci.* **2018**, *6*, 974–989. [CrossRef]
52. Qing, Y.; Li, K.; Li, D.; Qin, Y. Antibacterial effects of silver incorporated zeolite coatings on 3D printed porous stainless steels. *Mater. Sci. Eng. C* **2020**, *108*, 110430. [CrossRef]
53. Chen, J.; Zhang, X.; Huang, C.; Cai, H.; Hu, S.; Wan, Q.; Pei, X.; Wang, J. Osteogenic activity and antibacterial effect of porous titanium modified with metal-organic framework films. *J. Biomed. Mater. Res. Part A* **2017**, *105*, 834–846. [CrossRef]
54. Zhang, X.; Li, H.; Liu, J.; Wang, H.; Sun, W.; Lin, K.; Wang, X.; Shen, S.G. Amorphous carbon modification on implant surface: A general strategy to enhance osteogenic differentiation for diverse biomaterials via FAK/ERK1/2 signaling pathways. *J. Mater. Chem. B* **2019**, *7*, 2518–2533. [CrossRef]
55. Rifai, A.; Tran, N.; Lau, D.W.; Elbourne, A.; Zhan, H.; Stacey, A.D.; Mayes, E.L.H.; Sarker, A.; Ivanova, E.P.; Crawford, R.J.; et al. Polycrystalline diamond coating of additively manufactured titanium for biomedical applications. *ACS Appl. Mater. Interfaces* **2018**, *10*, 8474–8484. [CrossRef]
56. Tien, H.W.; Lee, C.Y.; Lin, I.N.; Chen, Y.C. Long term: In vivo functional stability and encapsulation reliability of using ultra-nanocrystalline diamond as an insulating coating layer for implantable microchips. *J. Mater. Chem. B* **2017**, *5*, 3706–3717. [CrossRef] [PubMed]
57. Patel, K.D.; Kim, T.H.; Mandakhbayar, N.; Singh, R.K.; Jang, J.H.; Lee, J.H.; Kim, H.W. Coating biopolymer nanofibers with carbon nanotubes accelerates tissue healing and bone regeneration through orchestrated cell- and tissue-regulatory responses. *Acta Biomater.* **2020**, *108*, 97–110. [CrossRef] [PubMed]
58. Mori, H.; Ogura, Y.; Enomoto, K.; Hara, M.; Maurstad, G.; Stokke, B.T.; Kitamura, S. Dense carbon-nanotube coating scaffolds stimulate osteogenic differentiation of mesenchymal stem cells. *PLoS ONE* **2020**, *15*, e0225589. [CrossRef] [PubMed]

59. Przekora, A.; Benko, A.; Nocun, M.; Wyrwa, J.; Blazewicz, M.; Ginalska, G. Titanium coated with functionalized carbon nanotubes—A promising novel material for biomedical application as an implantable orthopaedic electronic device. *Mater. Sci. Eng. C* **2014**, *45*, 287–296. [CrossRef] [PubMed]
60. Benko, A.; Przekora, A.; Wesełucha-Birczyńska, A.; Nocuń, M.; Ginalska, G.; Błażewicz, M. Fabrication of multi-walled carbon nanotube layers with selected properties via electrophoretic deposition: Physicochemical and biological characterization. *Appl. Phys. A Mater. Sci. Process.* **2016**, *122*, 447. [CrossRef]
61. Li, J.; Liu, X.; Crook, J.M.; Wallace, G.G. 3D printing of cytocompatible graphene/alginate scaffolds for mimetic tissue constructs. *Front. Bioeng. Biotechnol.* **2020**, *8*, 1–11. [CrossRef]
62. Li, X.; Wang, X.; Jiang, X.; Yamaguchi, M.; Ito, A.; Bando, Y.; Golberg, D. Boron nitride nanotube-enhanced osteogenic differentiation of mesenchymal stem cells. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2016**, *104*, 323–329. [CrossRef]
63. Özmeriç, A.; Tanoğlu, O.; Ocak, M.; Çelik, H.H.; Fırat, A.; Kaymaz, F.F.; Koca, G.; Şenes, M.; Alemdaroğlu, K.B.; İltar, S.; et al. Intramedullary implants coated with cubic boron nitride enhance bone fracture healing in a rat model. *J. Trace Elem. Med. Biol.* **2020**, *62*, 126599. [CrossRef]
64. Yu, L.; Silva Santisteban, T.; Liu, Q.; Hu, C.; Bi, J.; Wei, M. Effect of three-dimensional porosity gradients of biomimetic coatings on their bonding strength and cell behavior. *J. Biomed. Mater. Res. Part A* **2020**. [CrossRef]
65. Stevanović, M.; Djošić, M.; Janković, A.; Nešović, K.; Kojić, V.; Stojanović, J.; Grujić, S.; Matić Bujagić, I.; Rhee, K.Y.; Mišković-Stanković, V. Assessing the bioactivity of gentamicin-preloaded hydroxyapatite/chitosan composite coating on titanium substrate. *ACS Omega* **2020**, *5*, 15433–15445. [CrossRef]
66. Lin, Q.; Zhou, Y.; Yin, M.; Cheng, Y.; Wei, Y.; Hu, Y.; Lian, X.; Chen, W.; Huang, D. Hydroxyapatite/tannic acid composite coating formation based on Ti modified by TiO_2 nanotubes. *Colloids Surf. B Biointerfaces* **2020**, *196*, 111304.[CrossRef]
67. Gorgin Karaji, Z.; Jahanmard, F.; Mirzaei, A.; van der Wal, B.; Amin Yavari, S. Multifunctional silk coating on additively manufactured porous titanium to prevent implant-associated infection and stimulate bone regeneration. *Biomed. Mater.* **2020**. [CrossRef] [PubMed]
68. Harb, S.V.; Uvida, M.C.; Trentin, A.; Oliveira Lobo, A.; Webster, T.J.; Pulcinelli, S.H.; Santilli, C.V.; Hammer, P. PMMA-silica nanocomposite coating: Effective corrosion protection and biocompatibility for a Ti6Al4V alloy. *Mater. Sci. Eng. C* **2020**, *110*, 110713. [CrossRef] [PubMed]
69. Zhou, R.; Xu, W.; Chen, F.; Qi, C.; Lu, B.Q.; Zhang, H.; Wu, J.; Qian, Q.R.; Zhu, Y.J. Amorphous calcium phosphate nanospheres/polylactide composite coated tantalum scaffold: Facile preparation, fast biomineralization and subchondral bone defect repair application. *Colloids Surf. B Biointerfaces* **2014**, *123*, 236–245. [CrossRef] [PubMed]
70. Bougas, K.; Stenport, V.F.; Tengvall, P.; Currie, F. Laminin coating promotes calcium phosphate precipitation on titanium discs in vitro. *J. Oral Maxillofac. Res.* **2011**, *2*, 1–10. [CrossRef]
71. Bougas, K.; Jimbo, R.; Xue, Y.; Mustafa, K.; Wennerberg, A. Novel implant coating agent promotes gene expression of osteogenic markers in rats during early osseointegration. *Int. J. Biomater.* **2012**, *2012*, 579274. [CrossRef]
72. Rabe, R.; Hempel, U.; Martocq, L.; Keppler, J.K.; Aveyard, J.; Douglas, T.E.L. Dairy-inspired coatings for bone implants from whey protein isolate-derived self-assembled fibrils. *Int. J. Mol. Sci.* **2020**, *21*, 5544. [CrossRef]
73. Zhao, M.; Anouz, R.; Groth, T. Effect of microenvironment on adhesion and differentiation of murine C3H10T1/2 cells cultured on multilayers containing collagen I and glycosaminoglycans. *J. Tissue Eng.* **2020**, *11*, 1–16. [CrossRef] [PubMed]
74. Liu, C.; Wang, J.; Gao, C.; Wang, Z.; Zhou, X.; Tang, M.; Yu, K.; Deng, Y. Enhanced osteoinductivity and corrosion resistance of dopamine/gelatin/rhBMP-2–coated β-TCP/Mg-Zn orthopedic implants: An in vitro and in vivo study. *PLoS ONE* **2020**, *15*, e0228247. [CrossRef]
75. Abdal-Hay, A.; Dewidar, M.; Lim, J.K. Biocorrosion behavior and cell viability of adhesive polymer coated magnesium based alloys for medical implants. *Appl. Surf. Sci.* **2012**, *261*, 536–546. [CrossRef]
76. Albano, C.S.; Moreira Gomes, A.; da Silva Feltran, G.; da Costa Fernandes, C.J.; Trino, L.D.; Zambuzzi, W.F.; Lisboa-Filho, P.N. Biofunctionalization of titanium surfaces with alendronate and albumin modulates osteoblast performance. *Heliyon* **2020**, *6*, e04455. [CrossRef] [PubMed]

77. Ashwin, B.; Abinaya, B.; Prasith, T.P.; Chandran, S.V.; Yadav, L.R.; Vairamani, M.; Patil, S.; Selvamurugan, N. 3D-poly (lactic acid) scaffolds coated with gelatin and mucic acid for bone tissue engineering. *Int. J. Biol. Macromol.* **2020**, *162*, 523–532. [CrossRef] [PubMed]
78. Khojasteh, A.; Fahimipour, F.; Eslaminejad, M.B.; Jafarian, M.; Jahangir, S.; Bastami, F.; Tahriri, M.; Karkhaneh, A.; Tayebi, L. Development of PLGA-coated β-TCP scaffolds containing VEGF for bone tissue engineering. *Mater. Sci. Eng. C* **2016**, *69*, 780–788. [CrossRef] [PubMed]
79. Wei, Y.; Liu, Z.; Zhu, X.; Jiang, L.; Shi, W.; Wang, Y.; Xu, N.; Gang, F.; Wang, X.; Zhao, L.; et al. Dual directions to address the problem of aseptic loosening via electrospun PLGA @ aspirin nanofiber coatings on titanium. *Biomaterials* **2020**, *257*, 120237. [CrossRef]
80. Ding, X.; Wang, S.; Jin, W.; Liu, X.; Chen, J.; Chen, S. Encapsulation of a nanoporous simvastatin-chitosan composite to enhance osteointegration of hydroxyapatite-coated polyethylene terephthalate ligaments. *Int. J. Nanomed.* **2019**, *14*, 4881–4893. [CrossRef]
81. Coelho, P.G.; Giro, G.; Teixeira, H.S.; Marin, C.; Witek, L.; Thompson, V.P.; Tovar, N.; Silva, N.R.F.A. Argon-based atmospheric pressure plasma enhances early bone response to rough titanium surfaces. *J. Biomed. Mater. Res. Part A* **2012**, *100*, 1901–1906. [CrossRef]
82. Jacobs, T.; Morent, R.; De Geyter, N.; Dubruel, P.; Leys, C. Plasma surface modification of biomedical polymers: Influence on cell-material interaction. *Plasma Chem. Plasma Process.* **2012**, *32*, 1039–1073. [CrossRef]
83. Gadow, R.; Killinger, A.; Rauch, J. Introduction to high-velocity suspension flame spraying (HVSFS). *J. Therm. Spray Technol.* **2008**, *17*, 655–661. [CrossRef]
84. Sobolev, A.; Valkov, A.; Kossenko, A.; Wolicki, I.; Zinigrad, M.; Borodianskiy, K. Bioactive coating on Ti alloy with high osseointegration and antibacterial Ag nanoparticles. *ACS Appl. Mater. Interfaces* **2019**, *11*, 39534–39544. [CrossRef]
85. Santos-Coquillat, A.; Martínez-Campos, E.; Vargas-Alfredo, N.; Arrabal, R.; Rodríguez-Hernández, J.; Matykina, E. Hierarchical functionalized polymeric-ceramic coatings on Mg–Ca alloys for biodegradable implant applications. *Macromol. Biosci.* **2019**, *19*, 1–9. [CrossRef]
86. Ong, J.; Zhao, J.; Levy, G.K.; Macdonald, J.; Justin, A.W.; Markaki, A.E. Functionalisation of a heat-derived and bio-inert albumin hydrogel with extracellular matrix by air plasma treatment. *Sci. Rep.* **2020**, *10*, 12429. [CrossRef] [PubMed]
87. Chen, Z.; Visalakshan, R.M.; Guo, J.; Wei, F.; Zhang, L.; Chen, L.; Lin, Z.; Vasilev, K.; Xiao, Y. Plasma deposited poly-oxazoline nanotextured surfaces dictate osteoimmunomodulation towards ameliorative osteogenesis. *Acta Biomater.* **2019**, *96*, 568–581. [CrossRef] [PubMed]
88. Mas-Vinyals, A.; Gilabert-Porres, J.; Figueras-Esteve, L.; Borrós, S. Improving linking interface between collagen-based hydrogels and bone-like substrates. *Colloids Surf. B Biointerfaces* **2019**, *181*, 864–871. [CrossRef] [PubMed]
89. Yoshida, S.; Hagiwara, K.; Hasebe, T.; Hotta, A. Surface modification of polymers by plasma treatments for the enhancement of biocompatibility and controlled drug release. *Surf. Coat. Technol.* **2013**, *233*, 99–107. [CrossRef]
90. Xing, H.; Li, R.; Wei, Y.; Ying, B.; Li, D.; Qin, Y. Improved osteogenesis of selective-laser-melted titanium alloy by coating strontium-doped phosphate with high-efficiency air-plasma treatment. *Front. Bioeng. Biotechnol.* **2020**, *8*, 367. [CrossRef]
91. Liu, L.; Wang, X.; Zhou, Y.; Cai, M.; Lin, K.; Fang, B.; Xia, L. The synergistic promotion of osseointegration by nanostructure design and silicon substitution of hydroxyapatite coatings in a diabetic model. *J. Mater. Chem. B* **2020**, *8*, 2754–2767. [CrossRef]
92. Lu, R.J.; Wang, X.; He, H.X.; Ling-Ling, E.; Li, Y.; Zhang, G.L.; Li, C.J.; Ning, C.Y.; Liu, H.C. Tantalum-incorporated hydroxyapatite coating on titanium implants: Its mechanical and in vitro osteogenic properties. *J. Mater. Sci. Mater. Med.* **2019**, *30*, 111. [CrossRef]
93. Longo, G.; Ioannidu, C.A.; D'Abusco, A.S.; Superti, F.; Misiano, C.; Zanoni, R.; Politi, L.; Mazzola, L.; Iosi, F.; Mura, F.; et al. Improving osteoblast response in vitro by a nanostructured thin film with titanium carbide and titanium oxides clustered around graphitic carbon. *PLoS ONE* **2016**, *11*, e0152566. [CrossRef]
94. Veronesi, F.; Giavaresi, G.; Fini, M.; Longo, G.; Ioannidu, C.A.; Scotto d'Abusco, A.; Superti, F.; Panzini, G.; Misiano, C.; Palattella, A.; et al. Osseointegration is improved by coating titanium implants with a nanostructured thin film with titanium carbide and titanium oxides clustered around graphitic carbon. *Mater. Sci. Eng. C* **2017**, *70*, 264–271. [CrossRef]

95. Polo, T.O.B.; da Silva, W.P.; Momesso, G.A.C.; Lima-Neto, T.J.; Barbosa, S.; Cordeiro, J.M.; Hassumi, J.S.; da Cruz, N.C.; Okamoto, R.; Barão, V.A.R.; et al. Plasma electrolytic oxidation as a feasible surface treatment for biomedical applications: An in vivo study. *Sci. Rep.* **2020**, *10*, 10000. [CrossRef]
96. He, J.; Feng, W.; Zhao, B.-H.; Zhang, W.; Lin, Z. In vivo effect of titanium implants with porous zinc-containing coatings prepared by plasma electrolytic oxidation method on osseointegration in rabbits. *Int. J. Oral Maxillofac. Implant.* **2018**, *33*, 298–310. [CrossRef] [PubMed]
97. Zhao, Q.; Yi, L.; Jiang, L.; Ma, Y.; Lin, H.; Dong, J. Osteogenic activity and antibacterial ability on titanium surfaces modified with magnesium-doped titanium dioxide coating. *Nanomedicine* **2019**, *14*, 1109–1133. [CrossRef] [PubMed]
98. Li, B.; Gao, P.; Zhang, H.; Guo, Z.; Zheng, Y.; Han, Y. Osteoimmunomodulation, osseointegration, and in vivo mechanical integrity of pure Mg coated with HA nanorod/pore-sealed MgO bilayer. *Biomater. Sci.* **2018**, *6*, 3202–3218. [CrossRef] [PubMed]
99. Santos-Coquillat, A.; Esteban-Lucia, M.; Martinez-Campos, E.; Mohedano, M.; Arrabal, R.; Blawert, C.; Zheludkevich, M.L.; Matykina, E. PEO coatings design for Mg–Ca alloy for cardiovascular stent and bone regeneration applications. *Mater. Sci. Eng. C* **2019**, *105*, 110026. [CrossRef]
100. Michalska, J.; Sowa, M.; Piotrowska, M.; Widziołek, M.; Tylko, G.; Dercz, G.; Socha, R.P.; Osyczka, A.M.; Simka, W. Incorporation of Ca ions into anodic oxide coatings on the Ti–13Nb–13Zr alloy by plasma electrolytic oxidation. *Mater. Sci. Eng. C* **2019**, *104*, 109957. [CrossRef]
101. Meng, G.; Wu, X.; Yao, R.; He, J.; Yao, W.; Wu, F. Effect of zinc substitution in hydroxyapatite coating on osteoblast and osteoclast differentiation under osteoblast/osteoclast co-culture. *Regen. Biomater.* **2019**, *6*, 349–359. [CrossRef]
102. Zhang, W.; Gu, J.; Li, K.; Zhao, J.; Ma, H.; Wu, C.; Zhang, C.; Xie, Y.; Yang, F.; Zheng, X. A hydrogenated black TiO_2 coating with excellent effects for photothermal therapy of bone tumor and bone regeneration. *Mater. Sci. Eng. C* **2019**, *102*, 458–470. [CrossRef]
103. Vu, A.A.; Robertson, S.F.; Ke, D.; Bandyopadhyay, A.; Bose, S. Mechanical and biological properties of ZnO, SiO_2, and Ag_2O doped plasma sprayed hydroxyapatite coating for orthopaedic and dental applications. *Acta Biomater.* **2019**, *92*, 325–335. [CrossRef]
104. Ke, D.; Vu, A.A.; Bandyopadhyay, A.; Bose, S. Compositionally graded doped hydroxyapatite coating on titanium using laser and plasma spray deposition for bone implants. *Acta Biomater.* **2019**, *84*, 414–423. [CrossRef]
105. Croes, M.; Akhavan, B.; Sharifahmadian, O.; Fan, H.; Mertens, R.; Tan, R.P.; Chunara, A.; Fadzil, A.A.; Wise, S.G.; Kruyt, M.C.; et al. A multifaceted biomimetic interface to improve the longevity of orthopedic implants. *Acta Biomater.* **2020**, *110*, 266–279. [CrossRef]
106. Ankha, M.d.V.E.A.; Silva, A.d.M.; Do Prado, R.F.; Camalionte, M.P.; De Vasconcellos, L.M.R.; Radi, P.A.; Sobrinho, A.S.D.S.; Vieira, L.; Carvalho, Y.R. Effect of DLC films with and without silver nanoparticles deposited on titanium alloy. *Braz. Dent. J.* **2019**, *30*, 607–616. [CrossRef] [PubMed]
107. Xu, Z.; Wu, H.; Wang, F.; Kaewmanee, R.; Pan, Y.; Wang, D.; Qu, P.; Wang, Z.; Hu, G.; Zhao, J.; et al. A hierarchical nanostructural coating of amorphous silicon nitride on polyetheretherketone with antibacterial activity and promoting responses of rBMSCs for orthopedic applications. *J. Mater. Chem. B* **2019**, *7*, 6035–6047. [CrossRef] [PubMed]
108. Hickey, D.J.; Lorman, B.; Fedder, I.L. Improved response of osteoprogenitor cells to titanium plasma-sprayed PEEK surfaces. *Colloids Surf. B Biointerfaces* **2019**, *175*, 509–516. [CrossRef] [PubMed]
109. Beigi, M.H.; Safaie, N.; Nasr-Esfahani, M.H.; Kiani, A. 3D titania nanofiber-like webs induced by plasma ionization: A new direction for bioreactivity and osteoinductivity enhancement of biomaterials. *Sci. Rep.* **2019**, *9*, 1–17. [CrossRef] [PubMed]
110. Shi, J.Z.; Chen, C.Z.; Yu, H.J.; Zhang, S.J. Application of magnetron sputtering for producing bioactive ceramic coatings on implant materials. *Bull. Mater. Sci.* **2008**, *31*, 877–884. [CrossRef]
111. Juhasz, J.A.; Best, S.M. Surface modification of biomaterials by calcium phosphate deposition. In *Surface Modification of Biomaterials: Methods Analysis and Applications*; Williams, R., Ed.; Woodhead Publishing Series in Biomaterials: Liverpool, UK, 2011; pp. 143–169. ISBN 9781845696405.
112. Hwang, C.; Park, S.; Kang, I.G.; Kim, H.E.; Han, C.M. Tantalum-coated polylactic acid fibrous membranes for guided bone regeneration. *Mater. Sci. Eng. C* **2020**, *115*, 111112. [CrossRef] [PubMed]

113. Yang, C.; Li, J.; Zhu, C.; Zhang, Q.; Yu, J.; Wang, J.; Wang, Q.; Tang, J.; Zhou, H.; Shen, H. Advanced antibacterial activity of biocompatible tantalum nanofilm via enhanced local innate immunity. *Acta Biomater.* **2019**, *89*, 403–418. [CrossRef]
114. Milan, P.B.; Khamseh, S.; Zarrintaj, P.; Ramezanzadeh, B.; Badawi, M.; Morisset, S.; Vahabi, H.; Saeb, M.R.; Mozafari, M. Copper-enriched diamond-like carbon coatings promote regeneration at the bone–implant interface. *Heliyon* **2020**, *6*, e03798. [CrossRef]
115. Tolde, Z.; Starý, V.; Cvrček, L.; Vandrovcová, M.; Remsa, J.; Daniš, S.; Krčil, J.; Bačáková, L.; Špatenka, P. Growth of a TiNb adhesion interlayer for bioactive coatings. *Mater. Sci. Eng. C* **2017**, *80*, 652–658. [CrossRef]
116. Mistry, S.; Roy, S.; Jyoti Maitra, N.; Roy, R.; Datta, S.; Chanda, A.; Sarkar, S. Safety and efficacy of additive and subtractive surface modification of Ti6Al4V endosseous implant in goat bone. *J. Mech. Behav. Biomed. Mater.* **2016**, *57*, 69–87. [CrossRef]
117. Hannink, G.; Arts, J.J.C. Bioresorbability, porosity and mechanical strength of bone substitutes: What is optimal for bone regeneration? *Injury* **2011**, *42*, S22–S25. [CrossRef] [PubMed]
118. Annabi, N.; Nichol, J.W.; Zhong, X.; Ji, C.; Koshy, S.; Khademhosseini, A.; Dehghani, F. Controlling the porosity and microarchitecture of hydrogels for tissue engineering. *Tissue Eng. Part B Rev.* **2010**, *16*, 371–383. [CrossRef] [PubMed]
119. Chang, H.-I.; Wang, Y. Cell responses to surface and architecture of tissue engineering scaffolds. In *Regenerative Medicine and Tissue Engineering—Cells and Biomaterials*; Eberli, D., Ed.; InTechOpen: Zagreb, Croatia, 2011; pp. 569–588. ISBN 978-953-307-663-8.
120. Wang, Q.; Zhou, P.; Liu, S.; Attarilar, S.; Ma, R.L.W.; Zhong, Y.; Wang, L. Multi-scale surface treatments of titanium implants for rapid osseointegration: A review. *Nanomaterials* **2020**, *10*, 1244. [CrossRef]
121. Zahran, R.; Rosales Leal, J.I.; Rodríguez Valverde, M.A.; Cabrerizo Vílchez, M.A. Effect of hydrofluoric acid etching time on titanium topography, chemistry, wettability, and cell adhesion. *PLoS ONE* **2016**, *11*, e0165296. [CrossRef] [PubMed]
122. Jemat, A.; Ghazali, M.J.; Razali, M.; Otsuka, Y. Surface modifications and their effects on titanium dental implants. *Biomed. Res. Int.* **2015**, *2015*, 791725. [CrossRef] [PubMed]
123. Shemtov-Yona, K.; Rittel, D.; Dorogoy, A. Mechanical assessment of grit blasting surface treatments of dental implants. *J. Mech. Behav. Biomed. Mater.* **2014**, *39*, 375–390.[CrossRef]
124. Minagar, S.; Berndt, C.C.; Wang, J.; Ivanova, E.; Wen, C. A review of the application of anodization for the fabrication of nanotubes on metal implant surfaces. *Acta Biomater.* **2012**, *8*, 2875–2888. [CrossRef]
125. De Tullio, I.; Berardini, M.; Di Iorio, D.; Perfetti, F.; Perfetti, G. Comparative evaluation among laser-treated, machined, and sandblasted/acid-etched implant surfaces: An in vivo histologic analysis on sheep. *Int. J. Implant Dent.* **2020**, *6*, 4–11. [CrossRef]
126. Riveiro, A.; Maçon, A.L.B.; del Val, J.; Comesaña, R.; Pou, J. Laser surface texturing of polymers for biomedical applications. *Front. Phys.* **2018**, *6*, 16. [CrossRef]
127. Zhang, J.; Liu, J.; Wang, C.; Chen, F.; Wang, X.; Lin, K. A comparative study of the osteogenic performance between the hierarchical micro/submicro-textured 3D-printed Ti6Al4V surface and the SLA surface. *Bioact. Mater.* **2020**, *5*, 9–16. [CrossRef]
128. He, W.; Yin, X.; Xie, L.; Liu, Z.; Li, J.; Zou, S.; Chen, J. Enhancing osseointegration of titanium implants through large-grit sandblasting combined with micro-arc oxidation surface modification. *J. Mater. Sci. Mater. Med.* **2019**, *30*, 73. [CrossRef] [PubMed]
129. Zhan, X.; Li, S.; Cui, Y.; Tao, A.; Wang, C.; Li, H.; Zhang, L.; Yu, H.; Jiang, J.; Li, C. Comparison of the osteoblastic activity of low elastic modulus Ti-24Nb-4Zr-8Sn alloy and pure titanium modified by physical and chemical methods. *Mater. Sci. Eng. C* **2020**, *113*, 111018. [CrossRef] [PubMed]
130. Kunrath, M.; dos Santos, R.; de Oliveira, S.; Hubler, R.; Sesterheim, P.; Teixeira, E. Osteoblastic cell behavior and early bacterial adhesion on macro-, micro-, and nanostructured titanium surfaces for biomedical implant applications. *Int. J. Oral Maxillofac. Implants* **2020**, *35*, 773–781. [CrossRef] [PubMed]
131. Yu, Z.; Yang, G.; Zhang, W.; Hu, J. Investigating the effect of picosecond laser texturing on microstructure and biofunctionalization of titanium alloy. *J. Mater. Process. Technol.* **2018**, *255*, 129–136. [CrossRef]
132. Wu, Y.; Tang, H.; Liu, L.; He, Q.; Zhao, L.; Huang, Z.; Yang, J.; Cao, C.; Chen, J.; Wang, A. Biomimetic titanium implant coated with extracellular matrix enhances and accelerates osteogenesis. *Nanomedicine* **2020**, *15*, 1779–1793. [CrossRef]

133. Keceli, H.G.; Bayram, C.; Celik, E.; Ercan, N.; Demirbilek, M.; Nohutcu, R.M. Dual delivery of platelet-derived growth factor and bone morphogenetic factor-6 on titanium surface to enhance the early period of implant osseointegration. *J. Periodontal Res.* **2020**, *55*, 694–704. [CrossRef] [PubMed]
134. Scarano, A.; Carinci, F.; Orsini, T.; Valbonetti, L.; Qorri, E.; Bignozzi, C.A.; Lorusso, F. Titanium implants coated with a bifunctional molecule with antimicrobic activity: A rabbit study. *Materials (Basel)* **2020**, *13*, 3613. [CrossRef]
135. Feletto, L.; Bengazi, F.; Urbizo Velez, J.J.; Ferri, M.; Favero, R.; Botticelli, D. Bone healing at collagenated bicortically installed implants: An experimental study in rabbits. *Oral Maxillofac. Surg.* **2020**. [CrossRef]
136. Li, Q.; Wang, Z. Involvement of FAK/P38 signaling pathways in mediating the enhanced osteogenesis induced by nano-graphene oxide modification on titanium implant surface. *Int. J. Nanomed.* **2020**, *15*, 4659–4676. [CrossRef]
137. Choi, J.Y.; Kim, S.; Jo, S.B.; Kang, H.K.; Jung, S.Y.; Kim, S.W.; Min, B.M.; Yeo, I.S.L. A laminin-211-derived bioactive peptide promotes the osseointegration of a sandblasted, large-grit, acid-etched titanium implant. *J. Biomed. Mater. Res. Part A* **2020**, *108*, 1214–1222. [CrossRef]
138. Ko, K.A.; Kim, S.; Choi, S.H.; Lee, J.S. Randomized controlled clinical trial on calcium phosphate coated and conventional SLA surface implants: 1-year study on survival rate and marginal bone level. *Clin. Implant Dent. Relat. Res.* **2019**, *21*, 995–1001. [CrossRef] [PubMed]
139. Scarano, A.; Lorusso, F.; Orsini, T.; Morra, M.; Iviglia, G.; Valbonetti, L. Biomimetic surfaces coated with covalently immobilized collagen type I: An x-ray photoelectron spectroscopy, atomic force microscopy, micro-CT and histomorphometrical study in rabbits. *Int. J. Mol. Sci.* **2019**, *20*, 724. [CrossRef] [PubMed]
140. Roest, R.; Latella, B.A.; Heness, G.; Ben-Nissan, B. Adhesion of sol-gel derived hydroxyapatite nanocoatings on anodised pure titanium and titanium (Ti6Al4V) alloy substrates. *Surf. Coat. Technol.* **2011**, *205*, 3520–3529. [CrossRef]
141. Van Hooreweder, B.; Apers, Y.; Lietaert, K.; Kruth, J.P. Improving the fatigue performance of porous metallic biomaterials produced by Selective Laser Melting. *Acta Biomater.* **2017**, *47*, 193–202. [CrossRef] [PubMed]