Pre-Clinical Evidence of Biodegradable Osteosynthesis Systems

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A biodegradable osteosynthesis system should meet two intertwined criteria to be used as an osteosynthesis system: (1) the biomaterial needs to be biocompatible with the host tissue and (2) the mechanical properties should be sufficient for stable fixation of fracture or osteotomy segments during the surgical procedure (primary stability) and during the degradation of the biomaterial, with a gradual transfer of stress to the healing bone

Keywords: biocompatible materials ; absorbable implants ; polymers ; orthopaedic fixation device ; fracture fixation ; reconstructive surgical procedures

1. Biocompatibility

1.1. Initial Host Response

Implanted materials evoke an initial host response after implantation that includes inflammation, proliferation and tissue remodeling, and, in the case of biodegradable biomaterials, is affected by the degradation products [1]. This host response is mediated by both the innate and adaptive immune systems. Macrophages are the most important innate immune cells during the host response and also play a main role in the outcome of biodegradable implants [1]. The phenotype of macrophages ranges from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages [2][3]. After tissue injury, M1 macrophages secrete several inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) to initiate the healing process [1][4]. After the initial inflammatory phase, macrophages switch to a wound-healing phenotype (M2a), secreting growth factors (e.g., platelet-derived growth factor) that promote angiogenesis and cell proliferation [4][5]. Subsequently, macrophages switch to an anti-inflammatory phenotype (M2c) and produce anti-inflammatory cytokines (e.g., IL-10) that leads to the inhibition of the inflammatory response [6].

The adaptive immune system is also involved in the host response. Through antigen presentation, macrophages and dendritic cells can activate $CD4^+$ T-cells of the adaptive immune system. T helper 1 (T_H1) cells can induce M1 macrophages by producing interferon-γ and IL-2 [7]. Subsequently, M1 macrophages can produce cytokines and chemokines (e.g., IL-12, CXC-chemokine ligand 9) that intensify the T_H1 response by recruiting additional T_H1 cells [1]. In contrast to T_H1 cells, T_H2 cells produce anti-inflammatory cytokines (e.g., IL-4 and IL-10) that induce polarization of macrophages towards M2 macrophages. M2 macrophages in turn secrete cytokines (e.g., CC-chemokine ligand 17) that recruit additional T_H2 cells that temper the inflammatory response [7]. Imbalances of M1 over M2 macrophages or prominent presence of M1 macrophages may lead to (chronic) foreign body reactions (e.g., a sterile abscess formation with fibrous encapsulation) [1]. Therefore, it is essential that a well-controlled and timely switch of M1 to M2 macrophages occurs as this then leads to implant degradation and tissue remodeling, to eventually replace the implant by host tissue (biodegradable systems) or to controlled fibrous encapsulation (titanium systems) [1].

1.2. Synthetic Biodegradable Polymers

The most commonly used (co)polymers in biodegradable osteosynthesis systems consist of poly(α-esters) such as poly(L-lactic acid) (PLLA), poly(D,L-lactic acid) (PDLLA), poly(lactic-*co*-glycolic acid) (PLGA), or poly(L-*co*-D,L-lactic acid-*co*-trimethylene carbonate) (P(LLA-co-DLLA-co-TMC)) [1].

Biodegradation

Synthetic polymers undergo biodegradation via two different modes depending on the rates of bond cleavages and water diffusion into the polymer: bulk and surface degradation. In bulk degradation, the degradation occurs in the complete implant resulting in a decrease in molecular weight and molecular strength with time. Since the complete implant degrades at a similar rate, disintegration of the implant with generation of polymeric debris can occur. In contrast, surface

degradation occurs on the surface of the implant, resulting in a decrease in size and mass of the implant with time. Here, the molecular weight and mechanical properties of the material remain relatively unchanged [1].

Extracellular degradation of poly(α-esters) occurs through hydrolysis (two phases), enzymatic degradation, and oxidation. During hydrolysis, cleavage of the ester bonds by water results in oligomers and monomers, such as lactic acid and glycolic acid (primary hydrolysis) [8][9], that can enter the tricarboxylic-acid cycle (secondary hydrolysis) to form carbon dioxide and water that can be excreted in the lungs or via urine. Secondary hydrolysis is the rate-limiting step and depends highly on the crystallinity and hydrophobicity of the intermediate products [10]. Enzymes secreted by macrophages and derived from the blood can contribute to hydrolysis through extracellular hydrolysis [1]. Macrophages can also phagocytize biomaterial particles. In addition, inflammatory cells (e.g., macrophages and neutrophils) can induce depolymerization of polymers by oxidation via the release of reactive oxygen species [11]. Macrophages can also undergo fusion to improve their efficiency and form multinucleated giant cells [12] which can remain for up to 24 months after implantation [13]. Although the phagocytosis capacity of multinucleated giant cells is reduced compared to macrophages, the capacity of extracellular degradation is increased by secreting higher concentrations of enzymes and reactive oxygen species into the interface between the multinucleated giant cells and implant [12].

Late Host Response

Biodegradable osteosynthesis systems should, preferably, be completely resorbed within 12 months [14]. However, foreign body reactions to polymeric biodegradable materials remain a major concern, even years after implantation [15]. Factors that influence foreign-body reactions are implant related (e.g., polymer composition, crystallinity, geometry, and surface topology), recipient related (e.g., blood supply), and plate location related (e.g., epiperiosteal versus subperiosteal) [1][16][17].

The progression of the host response is affected by the acidic degradation products of the poly(α-esters). A lowering in pH intensifies the inflammatory response that results in fibrous encapsulation of the implant [18][19]. Furthermore, the acidic degradation products are autocatalytic, resulting in progressive degradation of the remaining polymers and an increase in the inflammatory response. Additionally, bulk degradation leads to fragmentation of the polymer that may result in phagocytized particles within the fibrous tissue [1]. Demineralization of the surrounding bone can occur whenever the degradation occurs too quickly and the surrounding tissue fails to eliminate the degradation products [20]. Therefore, the possibility to induce a foreign body reaction is dependent on an equilibrium between the levels of degradation products, the degree of fibrous encapsulation, and the ability of the host to eliminate the degradation products [1]. Short-term foreign body reactions are mainly caused by fast-degrading polymers (e.g., PGA) [21] while delayed foreign body reactions are often associated with slow-degrading polymers (e.g., PLLA) with high crystallinity and crystalline degradation fragments [22][23][24]. Foreign body reactions to polymeric biodegradable materials can occur to particle sizes of <2 µm, even years after the implantation (**Table 1**) [15].

Currently, two main hypotheses regarding the etiology of foreign body reactions to these synthetic polymeric biomaterials exist. After implantation, the biodegradable polymers are encapsulated by fibrous tissue that acts as a semi-permeable membrane [16]. The first hypothesis is that, as the polymer degradation continues over time, the size of the polymeric fragments decreases while the number of particles increases. These particles cannot pass the semi-permeable membrane. Subsequently, the osmotic pressure within the area surrounded by the fibrous layer increases and this results in a clinically observable swelling that, without an intervention, remains [22]. An alternative hypothesis is that, eventually, the acidic polymeric fragments become small enough to pass the membrane. This results in a decrease in pH of the surrounding tissues which then causes excessive sterile inflammation [25][26] accompanied by phagocytosis of any residual fragments [16]. However, since crystalline fragments are stable and more resistant to further hydrolytic degradation, they accumulate in the macrophages and multinucleated giant cells, and then remain in situ. Furthermore, extra- and intracellular residual fragments can lead to the accumulation of crystalline oligomeric stereo-complexes over time that are resistant to further hydrolytic degradation [1][27]. These two hypotheses could also occur simultaneously.

Differences in vascularization also contribute to inducing foreign body reactions. Sufficient vascularization is necessary for adequate bone healing, but it is also essential to eliminate the acidic degradation products of the hydrolyzed poly-α-esters (e.g., polylactide), thereby affecting the equilibrium between the levels of degradation products and the ability of the host to eliminate the degradation products [1]. Accumulation of acidic degradation products may result in decreased pH [1], bone demineralization [20], and may damage the surrounding cells such as macrophages [28][29][30]. Whenever micromovements are present, fibrous encapsulation can entrap the acidic degradation products, resulting in reduced elimination of the degradation products [1]. The acidic degradation products have an autocatalytic effect and cause further degradation of the remaining polymer resulting in a vicious circle that eventually leads to a more severe inflammatory

reaction [1]. Since the mandible has lesser vascularization and is exposed to higher forces, mandibular osteosyntheses are more prone to these (accumulating) effects compared to those in other parts of the facial skeleton.

In a recent study, the long-term (i.e., up to 4-year follow-up) biocompatibility and degradation of four commonly used biodegradable copolymeric osteosynthesis systems was compared using a goat model [13]. The study included the BioSorb FX [poly(70LLA-*co*-30DLLA)], Inion CPS [poly([70–78.5]LLA-*co*-[16–24]DLLA-*co*-4TMC)], SonicWeld Rx [poly(DLLA)], and LactoSorb [poly(82LLA-*co*-18GA)] biodegradable osteosynthesis systems. The copolymer of the SonicWeld Rx system was the only one that was amorphous; all the other assessed systems were semi-crystalline. All the biodegradable systems were safe to use and well-tolerated. The SonicWeld Rx system showed the most predictable degradation profile. In addition, together with the LactoSorb system, new bone percentages similar to negative controls were observed after 18 months while the two other included systems reached these levels after 36 months. However, nanoscale residual polymeric fragments, predominately accumulated in adipocytes, were observed at every system's assessment.

Since the crystalline regions of synthetic (co)polymers, the intermediate degradation products and the crystalline oligomeric stereo-complexes that can be formed in vivo over time are hydrophobic [14][27][31], this could explain the remarkable accumulation of polymeric birefringent fragments in adipocytes within the medullary bone cavity up to 4-year follow-up [13]. Similar birefringent fragments, derived from as-polymerized PLLA, were observed in a case report [22] and experimental studies up to the 5-year follow-up [32][33]. Such particles were found intracellular after 3 and 4.5 years of implantation, although the particles decreased in size over time [32]. Crystalline fragments derived from as-polymerized PLLA can induce foreign body reactions even up to 5.7 years after implantation [22][34]. Another clinical study that focused on the efficacy of an osteosynthesis system composed of unsintered hydroxyapatite/PLLA composite, with a 12-month follow-up, showed that the removed symptomatic systems included up to 65% crystalline regions in the explanted polymers [35]. In a study that implanted the Resorb X osteosynthesis system (PDLLA) at the condyle of sheep mandibles, no foreign body reactions and complete bone formation were observed after 12 months [36]. Another study showed complete bone formation 18 months after implanting the LactoSorb system in the maxillofacial area of Göttingen minipigs without signs of foreign body reactions [37]. In contrast, after implanting the Inion CPS system in sheep, the system was surrounded by a fibrous capsule with granulomatous foreign body reactions after 52 weeks [38]. In the literature, foreign body reactions have predominately been reported for biodegradable osteosyntheses with a high proportion (i.e., >70%) of PLLA [1][22][24][39] or poly(glycolic acid) (PGA) [1]. More amorphous copolymers such as PDLLA (e.g., 50LLA/50DLA ratio) are more hydrophilic, and degrade and resorb more quickly and predictably [40]. These findings, as well as those of different (pre-)clinical studies [1][13][15][41], emphasize that the (co)polymers used in biodegradable systems should be completely amorphous. Future research should focus on amorphous (co)polymers with a minimum follow-up of ≥24 months so that a proper degradation assessment can be performed. Furthermore, it remains unknown whether the observed nanoparticles after 4-year follow-up [13] may be harmful in the long run (i.e., >4 years). Since microplastics have been shown to be toxic in vitro, with a potential impact on human health (e.g., effects on the gastrointestinal tract, lungs, immune system, and blood components) [42][43], the effects of the observed nanoparticles need further research.

Other than (co)polymer composition, the geometry and surface topography of the implanted materials also affect biocompatibility in vivo [41]. Thick biomaterials, especially with points and sharp edges, can increase the risk of foreign body reactions [15][44][45]. In contrast, thinner biomaterials, as well as smaller sized polymeric particles used to engineer a biomaterial, allow for quicker degradation and a lower risk of foreign body reactions [41][46][47]. A smooth well-contoured shape without acute angles induced macrophage polarization towards macrophages with an immune regulatory phenotype [48][49]. In vivo biocompatibility of medical devices, such as implants, can be significantly improved by tuning the spherical dimensions [41]. Furthermore, low implant volume reduces the amount of acidic degradation products and thus reduces the risk of (late) foreign body reactions [1]. The fact that screws possess acute angles, while welded pins do not, may explain the favorable degradation profile of the SonicWeld Rx system compared to the BioSorb FX, Inion CPS and LactoSorb biodegradable systems [1][13][50][51]. Novel biodegradable system development should incorporate geometry and surface topography into the design-phase as these characteristics are tunable and may be efficient ways to decrease foreign body reaction risk, hasten degradation, enhance quicker bone formation, and balance the degradation and regeneration equilibrium (**Table 1**) [15].

Table 1. Different aspects of biodegradable osteosynthesis systems accompanied with the ideal properties and the potential solutions to accomplish these properties.

Aspect	Ideal Properties	Method	Potential Solutions	Refs
Surgical handling	Easy perioperative adaptation of plates	3D engineering	Patient specific osteosynthesis systems	[1][15] [52]
		Production process	Plate adaption at room temperature	[53]
	No risk of perioperative screw breakage	Alternative application method	Ultrasound welding of thermoplastic pins instead of using conventional screws	[53]
Elastic modulus of materials	Enough elastic modulus to avoid micromovements, but not stiffer than bone to avoid stress-shielding of the underlying bone	Production process	Create composites to tailor the elastic modulus to the application of interest	[15]
			Self-reinforcing of polymers to increase the elastic modulus of systems	[53]
		Alternative application method	Ultrasound welding of thermoplastic pins to increase the maximum tensile load and stiffness, and side-bending stiffness	[53]
Bacterial infection	Preventing bacterial adhesion to implant surface	Coating	Hydrophobic coatings	[15]
	Eliminating surrounding bacteria without antibiotics	Surface modification	Adjusting the nano-scale surface topography (e.g., pillars on the surface)	[54]
	Eliminating surrounding bacteria with local antibiotics		Polymer coating containing stabilized gas bubbles loaded with antibiotics that can be released locally using ultrasound	[55]
Foreign body response (FBR)	Materials that do not elicit an FBR	Selection of materials	Materials with non-toxic degradation products (e.g., derived from silk)	[1]
		Production process	Avoid thick materials, especially with points and sharp edges	[15] [44] [45]
	Tailor the host response so that FBR are avoided	Production process	Avoid particle sizes < 2 µm	[15]
	Avoid micromovements (max. 28–150 µm), that can result in fibrous encapsulation of the implant	Selection of materials, production process, and 3D engineering	Osteosynthesis system with material properties that matches with the mechanical properties of the target tissue (e.g., by using ultrasound welding)	[15]
Degradation profile	Predictable degradation, preferably after 3–12 months	3D engineering	Thinner materials degrade quicker	[14]
		Production process	Balance the degradation and regeneration equilibrium by, e.g., using L- and D-chirality or by copolymerization	[13] [15]

1.3. Biodegradable Metals

Biodegradable metals are promising alternatives to polymeric osteosynthesis systems due to their mechanical properties that are closer to bone than (co)polymeric materials [1] and their less harmful degradation products. The tensile strength, elastic modulus, axial pull-out force, and maximum torque of magnesium alloys are higher than that of (co)polymers, but lower than that of titanium alloys [1][56]. To date, three biodegradable metal groups have been researched to be used for biodegradable osteosynthesis systems, i.e., magnesium (Mg), iron (Fe), and zinc (Zn) and their alloys [1]. Mg-based biodegradable metals have been studied most extensively. The available research for Fe- and Zn-based degradable metals is limited due to the low degradation rate of Fe-based metals while Zn-based metals have been introduced only recently [1].

Biodegradation

Biodegradable metal degradation is driven by anodic and cathodic reactions that result in the production of oxides, hydroxides and/or hydrogen gas [1][57]. Once biodegradable metals come into contact with body fluids, they are oxidized into metal cations combined with producing electrons via an anodic reaction. The electrons generated by implanting Mg-

based biodegradable metals are consumed by cathodic reactions with water to form hydrogen gas and hydroxide. For Fe- and Zn-based metals, oxygen reduction only produces hydroxide without hydrogen gas. Hydroxide then reacts with the adjacent metal to form a metal-hydroxide layer on the surface of the implant. The protective layer can be eroded by high levels of chloride ions in the body fluids resulting in continuation of the degradation process. However, in Fe-based biodegradable metals, the protective layer consists of $Fe(OH)_2$, $Fe(OH)_3$, and Fe_3O_4, that inhibits further degradation. As a result, the degradation rate of Fe-based metals is very slow [1]. These ongoing reactions cause an oversaturation of calcium and phosphate ions in the surrounding body fluids that result in a layer of calcium-phosphate on the metal-oxide layer, that is able to induce bone formation [1].

A major challenge of biodegradable metals, particularly Mg-based materials, is the unpredictable degradation profile in vivo with subcutaneous emphysema due to the accumulation of hydrogen gas [1]. The degradation rate of biodegradable metals can be controlled by tailoring the microstructure, surface properties and coatings of the materials. For example, a recent study included gallium (i.e., a bone resorption inhibitor) in a magnesium alloy and showed promising results with inhibition of bone porosity formation, mechanical properties matching cortical bone, and low corrosion rate resulting in less hydrogen gas formation compared to other available magnesium alloys for orthopedic surgery [58]. In addition, surface modifications and coatings can be used to tune the degradation rates. For example, Mg-alloys and polymers can be combined to form Mg–polymer composites. These composites include high strength and elastic modulus derived from biodegradable metals while the surrounding biodegradable polymer matrix improves the corrosion resistance of the underlying metal [59].

Late Host Response

The degradation products of degradable metals such as hydroxide ions, hydrogen gas, metal-oxides, abraded particles, and calcium-phosphate affect the host response [60][61]. In a bone environment, the formation of the calcium-phosphate layer induces new bone deposition, making it a unique feature as base material for an osteosynthesis system. In addition, the Mg-ions can induce new bone formation in cortical bone by increasing calcitonin gene-related peptide 1 levels in periosteum-derived stem cells [62]. However, current Mg-based biodegradable metals often show a burst release of Mg-ions that can lead to excess formation of hydrogen gas resulting in gas pockets, tissue displacement, and subcutaneous emphysema. The fast degradation rate can also induce osteolysis, hemolysis, and rapid reduction of the mechanical properties [63].

1.4. Silk

Silk is the most recent addition to biodegradable materials [1]. Silk is a natural biodegradable polymer that is usually derived from the silkworm *Bombyx mori*. Although the evidence is still limited to pre-clinical evidence, the current evidence shows excellent biocompatibility and unique mechanical properties combined with easily and environmentally friendly processing into mechanically robust three-dimensional bulk materials with excellent machinability [1][64]. To date, it is the only natural polymer that has been used to prepare an osteosynthesis system [64].

Biodegradation

As with most natural polymers, silk is degraded enzymatically, e.g., by protease XIV, matrix metalloproteinase and collagenase [8]. These enzymes cleave silk protein chains into peptide fragments with decreased molecular weight and strength [65]. Immune cells, especially macrophages and FBGCs, play an important role during degradation of silk. Immune cells mediate silk degradation through (1) phagocytosis and (2) extracellular degradation mediated by proteolytic enzymes derived from macrophages and FBGCs. The degradation products are tightly packed aggregates or amino acids for metabolism [1]. The degradation time depends on implant-related factors (e.g., molecular weight, porosity, crystallinity, and surface topography) and host-related factors (e.g., species and implantation site). The degradation times can be tailored from minutes to years by controlling the material variables such as molecular weight, surface topography, β-sheet content, and porosity [1]. Although in vivo research in animal studies showed complete silk degradation, a thorough understanding of the degradation pathways and clearing mechanisms as well as degradation in humans is still lacking [1].

Late Host Response

After implantation of silk materials, a mild inflammatory response occurs that decreases within a few weeks. This host response involves recruitment and activation of macrophages and the formation of FBGCs. The silk implant can be degraded and replaced by host tissue (e.g., bone), but it can also be integrated within the tissue or encapsulated by fibrous tissue. There is currently limited data regarding the short- and long-term host response in vivo. In the currently only available study that prepared a silk-based osteosynthesis systems for fracture fixation in maxillofacial surgery, the in vivo assessment of the 4- and 8-week host response by rats showed more favorable mechanical properties than

biodegradable synthetic polymers and excellent biocompatibility accompanied with bone remodeling [64]. These results are promising but additional research is necessary to unravel the complete degradation pathways as well as the host responses that this natural-derived polymer elicits.

1.5. Titanium and Its Alloys

Late Host Response

Titanium osteosynthesis systems are commonly made of pure titanium or titanium alloys [53][66]. The most frequently used titanium alloy for maxillofacial osteosynthesis systems consists of 90% titanium, 6% aluminum, and 4% vanadium (Ti6Al4V, also called titanium alloy grade 5) [66][67][68][69]. However, although titanium and its alloys are presumed to be completely bioinert, there is growing evidence that wearing of particles occurs that can accumulate in surrounding tissues and different organs of which the consequences are still largely unknown [66][68][70].

In a study that explanted titanium osteosynthesis plates from patients that underwent craniofacial surgery, titanium particles (7.9 to 31.8 µg/gram of dry tissue) could be detected in the regional soft tissue and lymph nodes after 24-month follow-up [71]. Similarly, a recent study showed that the tissue surrounding titanium plates after fracture and osteotomy fixation contained 1.03 and 1.09 ppm titanium particles, respectively [72]. Meningaud et al. revealed a large variation in titanium levels within the surrounding tissue (4–8000 µg/gram) after titanium fixation of osteotomies, but concluded that almost all of these particles were produced at the moment of applying the osteosynthesis system [73]. Other studies reported on the presence of dark-grey pigmentation accompanied with fibrosis of the surrounding tissue and macrophages containing intra-cellular titanium particles [74][75][76]. Zaffe et al. have also shown the presence of titanium in the surrounding tissue as well as that erythrocytes and lymphocytes contained titanium particles [77]. In addition, explanted osteosynthesis plates analyzed with scanning electron microscopy showed defects and irregularities most likely due to in vivo substance loss [75]. Titanium debris has also been found throughout the body suggesting hematogenous dissemination, with traceable amounts of titanium particles within the liver, spleen, and lymphatic system [68][70].

To determine the effect of such titanium particles, Coen et al. assessed the cytotoxicity of Ti6Al4V particles on human fibroblast cells in vitro, and showed chromosomal instability, reproductive failure and decreased clonogenic survival 10 generations postexposure [78]. Studies that analyzed the periosteum surrounding titanium plates as well as blood samples in patients after mandibular fracture fixation showed redox abnormalities, and increased oxidative stress and damage [79][80]. Furthermore, an association between aluminum and the pathogenesis of Alzheimer's disease has been suggested. In addition, increased levels of circulating aluminum are associated with microcytic anemia and osteomalacia [68][81][82]. These findings indicated that there is a need for long-term epidemiological studies that assess the effect of these particles in the long run.

Surface modifications (e.g., oxygen plasma immersion ion implantation) have been proposed to reduce metal ion release from the implant (**Table 2**) [83]. In addition, they are an important aspect of biocompatibility [68][83]. Titanium, without surface modifications, has a positively charged surface and will, therefore, tend to covalently bond to negatively charged proteins such as fibronectin [84]. Fibronectin promotes bacterial adhesion and, thus, increases the risk of infection [85]. Besides bonding to autologous proteins, most of the cell surface of bacterial species (e.g., *Staphylococcus aureus*, the most common etiological pathogen of infections surrounding osteosyntheses [86]) is negatively charged, and thus also adheres to positively charged surfaces such as titanium [87]. By modifying the surface charge, adhesion of various bacteria (e.g., *Staphylococcus aureus* and *Escherichia coli*) is inhibited and, ideally, the risk of infection is reduced [83]. These properties of titanium systems can also be tuned by other surface modifications (**Table 2**).

Table 2. Different aspects of titanium osteosynthesis systems accompanied with the ideal properties and the potential solutions to accomplish these properties.

Aspect	Ideal Properties	Methods	Potential Solutions	Refs
Surgical handling	Easy perioperative adaptation of plates	3D engineering	Patient specific osteosynthesis systems	[88][89]
		Production process	Adaption of the production process to alter the mechanical properties of plates (e.g., lower stiffness)	[53][90][91][92][93]
	No risk of perioperative screw breakage	3D engineering	Adjusting the screw head to improve the grip on the screws	[53]

Aspect	Ideal Properties	Methods	Potential Solutions	Refs
Elastic modulus	Enough elastic modulus to avoid micromovements, but not stiffer than bone to avoid stress-shielding of the underlying bone	Production process	Adaption of the production process to alter the mechanical properties of plates	[53][90] [91][92] [93]
Bacterial infection	Preventing bacterial adhesion to implant surface	Coating	Hydrophobic coatings	[15]
			(Nano)gel coatings	[94][95]
		Surface modification	Plasma immersion ion implantation (surface modification)	[83][96] [97]
			Physical vapor deposition	[98][99]
			Increasing surface energy by acid etching	[100]
	Eliminating surrounding bacteria without antibiotics	Coating	Titanium Nitride (TiN) coating	[101][102]
		Surface modification	Adjusting the nano-scale surface topography (e.g., pillars on the surface)	[54]
			Plasma immersion ion implantation	[83][103]
			Physical vapor deposition	[104]
			Laser surface modification	[105]
			Anodization	[106][107]
			Micro-Arc oxidation	[108][109]
	Eliminating surrounding bacteria with local antibiotics	Coating	Polymer coating containing stabilized gas bubbles loaded with antibiotics that can be released locally using ultrasound	[55]
			(Nano)gel coatings	[95][110]
		Surface modification	Chemical vapor deposition	[111]
		Coating	(Nano)gel coatings	[110]
			Plasma spraying with hydroxyapatite	[112][113] [114][115] [116]
Osteogenesis	Improving bone growth surrounding the implant	Surface modification	Plasma immersion ion implantation	[117][118]
			Physical vapor deposition	[119][120]
			Chemical vapor deposition	[121]
			Increasing surface energy by acid etching	[100]
			Laser surface modification	[105][122] [123]
			Anodization	[124]
		Coating	Titanium Nitride (TiN) coating	[125][126]
Wear resistance	No wearing of titanium (alloy) particles	Surface modification	Plasma immersion ion implantation	[83]
			Physical vapor deposition	[68]
			Laser surface modification	[123][127]
			Anodization	[107][128] [129]

2. Mechanical Properties

2.1. Minimally Required Mechanical Properties

Several studies assessed the mechanical forces surrounding osteosyntheses applied to maxillofacial fractures [130][131][132][133][134][135][136], osteotomies [137][138] and reconstructions [139], so that the minimally required mechanical properties of an osteosynthesis system can be estimated. After maxillofacial trauma, the reported bite force increases up to 64 N by the second postoperative fracture fixation day, 92 N after 1 week, 187 N after 4 weeks, and up to 373 N at the 3-month follow-up [130]. Other studies focusing on trauma patients showed that 100 N forces were measured after 4 weeks of fixation [132][134]. The mechanical forces around maxillofacial osteotomies have been reported to increase from 21 ± 14 N (i.e., after 1 week) to 65 ± 43 N (i.e., after 6 weeks) [133] while other studies reported forces ranging from 82.5 to 132 N [137][138]. The masticatory forces after mandibular reconstructions ranged from 28 to 186 N [139]. However, the mechanical stress surrounding osteosynthesis systems is multi-factorial and is affected by the location of the fracture [140], differences in interfragmentary stability [140], mandibular height [140], degree and direction of movement [141], and preoperative masticatory forces [132][142][143]. Load-sharing osteosynthesis allows sharing of the load between bone segments and the osteosynthesis system (e.g., fractures with interfragmentary stability) whereas in load-bearing osteosynthesis, the complete load at the fracture site is carried by the osteosynthesis system without interfragmentary stability [140][144]. In a load-bearing situation, the osteosynthesis system is exposed to substantially higher loads and, thus, the biomechanical requirements for an optimal osteosynthesis system are higher compared to load-sharing osteosyntheses [39][145]. Although it would be of high clinical value to determine the exact cut-off value of the transition from load-sharing to load-bearing osteosyntheses, this is currently unknown. Since the mandible is exposed to considerably higher biomechanical forces compared to the maxilla [140], load-bearing osteosynthesis of the mandible requires even higher mechanical properties of the used osteosynthesis system compared to load-bearing osteosynthesis of the maxilla or load-sharing osteosynthesis of the mandible [146][147]. Furthermore, as bone healing progresses, the forces will be shared by the osteosynthesis system and the underlying healing bone. Thus, it remains difficult to estimate the least mechanical properties an osteosynthesis system has to meet. Therefore, researchers have mainly focused on relative differences between the available osteosynthesis systems [53].

2.2. Mechanical Properties of Osteosynthesis Systems

The mechanical properties of osteosynthesis systems depend on several factors including composition (i.e., titanium (alloys) or (co-)polymers), the production processes (e.g., stamping versus laser cutting of titanium systems) [90][91][148], dimensions, polymer self-reinforcement [149], the application method (i.e., screws or ultrasound welded pins) [150], ageing, and sterilization methods [151][152][153]. The tensile, bending and torsional stiffness of an osteosynthesis system are a more clinically relevant outcome than maximum tensile load since this affects adequate fixation and bone healing (i.e., malunion and non-union) [154] while maximum tensile load is only relevant whenever the bone segments are already separated by more than a few millimeters. In the latter case, this will certainly result in compromised bone healing or malunion.

In a recent in vitro study, the maximum tensile load as well as the tensile, bending and torsional stiffness of 13 biodegradable and 6 titanium straight, four-hole osteosynthesis systems derived from static mechanical tests of the initial materials were assessed and compared [53]. The titanium systems' tensile loads were higher than those of the biodegradable systems. The bending stiffness of the 1.5 mm titanium systems was comparable to all the biodegradable systems whereas the 2.0 mm system's bending stiffness was higher. Regarding the biodegradable systems, Inion CPS 2.5 mm had the highest tensile load and torsional stiffness, SonicWeld 2.1 mm the highest tensile stiffness, and BioSorbFX 2.0 mm the highest bending stiffness. Regarding the titanium systems, the CrossDrive (2006) systems had the highest tensile, bending and torsional stiffness. It must be noted, though, that although high mechanical osteosynthesis properties are sought for adequate fixation, the extreme stiffness of the titanium systems can be a disadvantage due to the stress shielding of the underlying bone [155]. Stress shielding occurs when the underlying bone is exposed to less stress than it should endure, leading to an increase in osteoclast activity and bone resorption, that can, in turn, lead to decreased bone density and aseptic loosening [68][156]. This has led to the development of new titanium osteosynthesis systems with a lower elastic modulus to reduce stress shielding of the underlying bone by adjusting the production process (**Table 2**) [53][157][158].

Within the limitations of finite element analyses (e.g., assuming the masticatory forces are fixed), three-dimensional analyses indicated that the biomechanical stresses surrounding osteosynthesis systems remain far below the threshold of their ultimate strength of both biodegradable and titanium osteosynthesis systems [136][146][159][160]. In addition, the empirical evidence of fracture [161] and osteotomy [162] osteosyntheses shows that the efficacy of titanium and biodegradable osteosyntheses is similar (e.g., absence of malunion), indicating that the less favorable mechanical

properties of biodegradable osteosynthesis are still sufficient to achieve similar healing outcomes. However, as also observed from the empirical evidence, the mechanical properties of biodegradable osteosyntheses of mandibular osteotomies may be insufficient to avoid micromovements [162]. Future research should also focus on these micromovements since they play an important role in developing foreign body reactions [15].

Finite element analyses also demonstrated that the stress surrounding conventional screws is much larger compared to those of plates, indicating that material complications may arise from the screws rather than the plates (e.g., screw loosening or fractures) [159]. The positive effect of ultrasound welding of biodegradable, thermoplastic pins instead of using conventional screws was demonstrated by the superior mechanical properties of the SonicWeld Rx (PDLLA with thermoplastic pins) compared to the Resorb X system (identical system with screws) [53]. Additionally, ultrasound welding caused a shift of the weakest link of the complete osteosynthesis system from the screw-plate interface to the plate itself. Therefore, ultrasound welding may reduce screw-related material complications, but this has to be investigated by future research.

References

1. Li, C.; Guo, C.; Fitzpatrick, V.; Ibrahim, A.; Zwierstra, M.J.; Hanna, P.; Lechtig, A.; Nazarian, A.; Lin, S.J.; Kaplan, D.L. Design of biodegradable, implantable devices towards clinical translation. Nat. Rev. Mater. 2020, 5, 61–81.
2. Mantovani, A.; Biswas, S.K.; Galdiero, M.R.; Sica, A.; Locati, M. Macrophage plasticity and polarization in tissue repair and remodelling. J. Pathol. 2013, 229, 176–185.
3. Sica, A.; Mantovani, A. Macrophage plasticity and polarization: In Vivo veritas. J. Clin. Investig. 2012, 122, 787–795.
4. Wynn, T.A.; Vannella, K.M. Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity 2016, 44, 450–462.
5. Willenborg, S.; Lucas, T.; van Loo, G.; Knipper, J.A.; Krieg, T.; Haase, I.; Brachvogel, B.; Hammerschmidt, M.; Nagy, A.; Ferrara, N.; et al. CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair. Blood 2012, 120, 613–625.
6. Shouval, D.S.; Biswas, A.; Goettel, J.A.; McCann, K.; Conaway, E.; Redhu, N.S.; Mascanfroni, I.D.; Al Adham, Z.; Lavoie, S.; Ibourk, M.; et al. Interleukin-10 receptor signaling in innate immune cells regulates mucosal immune tolerance and anti-inflammatory macrophage function. Immunity 2014, 40, 706–719.
7. Biswas, S.K.; Mantovani, A. Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. Nat. Immunol. 2010, 11, 889–896.
8. Nair, L.S.; Laurencin, C.T. Biodegradable polymers as biomaterials. Prog. Polym. Sci. 2007, 32, 762–798.
9. Middleton, J.C.; Tipton, A.J. Synthetic biodegradable polymers as orthopedic devices. Biomaterials 2000, 21, 2335–2346.
10. Da Silva, D.; Kaduri, M.; Poley, M.; Adir, O.; Krinsky, N.; Shainsky-Roitman, J.; Schroeder, A. Biocompatibility, biodegradation and excretion of polylactic acid (PLA) in medical implants and theranostic systems. Chem. Eng. J. 2018, 340, 9–14.
11. Xie, F.; Zhang, T.; Bryant, P.; Kurusingal, V.; Colwell, J.M.; Laycock, B. Degradation and stabilization of polyurethane elastomers. Prog. Polym. Sci. 2019, 90, 211–268.
12. Xia, Z.; Triffitt, J.T. A review on macrophage responses to biomaterials. Bio. Mater. 2006, 1, R1–R9.
13. Gareb, B.; van Bakelen, N.B.; Driessen, L.; Buma, P.; Kuipers, J.; Grijpma, D.W.; Vissink, A.; Bos, R.R.; van Minnen, B. Biocompatibility and degradation comparisons of four biodegradable copolymeric osteosynthesis systems used in maxillofacial surgery: A goat model with four years follow-up. Bioact. Mater. 2022, 17, 439–456.
14. Vacaras, S.; Baciut, M.; Lucaciu, O.; Dinu, C.; Baciut, G.; Crisan, L.; Hedesiu, M.; Crisan, B.; Onisor, F.; Armencea, G.; et al. Understanding the basis of medical use of poly-lactide-based resorbable polymers and composites–a review of the clinical and metabolic impact. Drug Metab. Rev. 2019, 51, 570–588.
15. Dewey, M.J.; Harley, B.A.C. Biomaterial design strategies to address obstacles in craniomaxillofacial bone repair. RSC Adv. 2021, 11, 17809–17827.
16. Chandorkar, Y.; Ravikumar, K.; Basu, B. The Foreign Body Response Demystified. ACS Biomater. Sci. Eng. 2019, 5, 19–44.
17. Amini, A.R.; Wallace, J.S.; Nukavarapu, S.P. Short-term and long-term effects of orthopedic biodegradable implants. J. Long. Term. Eff. Med. Implants 2011, 21, 93–122.

18. Kim, M.S.; Ahn, H.H.; Na Shin, Y.; Cho, M.H.; Khang, G.; Lee, H.B. An in vivo study of the host tissue response to subcutaneous implantation of PLGA-and/or porcine small intestinal submucosa-based scaffolds. Biomaterials 2007, 28, 5137–5143.
19. Jones, K.S. Effects of biomaterial-induced inflammation on fibrosis and rejection. Semin. Immunol. 2008, 20, 130–136.
20. Böstman, O.; Pihlajamäki, H. Clinical biocompatibility of biodegradable orthopaedic implants for internal fixation: A review. Biomaterials 2000, 21, 2615–2621.
21. Bostman, O.M.; Pihlajamaki, H.K. Adverse tissue reactions to bioabsorbable fixation devices. Clin. Orthop. Relat. Res. 2000, 371, 216–227.
22. Bergsma, J.E.; de Bruijn, W.C.; Rozema, F.R.; Bos, R.R.; Boering, G. Late degradation tissue response to poly(L-lactide) bone plates and screws. Biomaterials 1995, 16, 25–31.
23. Seino, D.; Fukunishi, S.; Yoshiya, S. Late foreign-body reaction to PLLA screws used for fixation of acetabular osteotomy. J. Orthop. Traumatol. 2007, 8, 188–191.
24. Jeon, H.B.; Kang, D.H.; Gu, J.H.; Oh, S.A. Delayed Foreign Body Reaction Caused by Bioabsorbable Plates Used for Maxillofacial Fractures. Arch. Plast. Surg. 2016, 43, 40–45.
25. Van Bakelen, N.B.; Buijs, G.J.; Jansma, J.; de Visscher, J.G.A.M.; Hoppenreijs, T.J.; Bergsma, J.E.; Stegenga, B.; Bos, R.R.M. Comparison of biodegradable and titanium fixation systems in maxillofacial surgery: A two-year multi-center randomized controlled trial. J. Dent. Res. 2013, 92, 1100–1105.
26. Grizzi, I.; Garreau, H.; Li, S.; Vert, M. Hydrolytic degradation of devices based on poly
27. Vert, M.; Li, S.; Garreau, H. New insights on the degradation of bioresorbable polymeric devices based on lactic and glycolic acids. Clin. Mater. 1992, 10, 3–8.
28. Athanasiou, K.A.; Niederauer, G.G.; Agrawal, C.M. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. Biomaterials 1996, 17, 93–102.
29. Athanasiou, K.A.; Agrawal, C.M.; Barber, F.A.; Burkhart, S.S. Orthopaedic applications for PLA-PGA biodegradable polymers. Arthroscopy 1998, 14, 726–737.
30. Gredes, T.; Kunath, F.; Gedrange, T.; Kunert-Keil, C. Bone Regeneration after Treatment with Covering Materials Composed of Flax Fibers and Biodegradable Plastics: A Histological Study in Rats. Bio. Res. Int. 2016, 2016, 5146285.
31. Vert, M.; Mauduit, J.; Li, S. Biodegradation of PLA/GA polymers: Increasing complexity. Biomaterials 1994, 15, 1209–1213.
32. Laitinen, O.; Pihlajamäki, H.; Sukura, A.; Böstman, O. Transmission electron microscopic visualization of the degradation and phagocytosis of a poly-L-lactide screw in cancellous bone: A long-term experimental study. J. Bio. Mater. Res. 2002, 61, 33–39.
33. Pihlajamäki, H.; Böstman, O.; Tynninen, O.; Laitinen, O. Long-term tissue response to bioabsorbable poly-l-lactide and metallic screws: An experimental study. Bone 2006, 39, 932–937.
34. Bergsma, E.J.; Rozema, F.R.; Bos, R.R.; de Bruijn, W.C. Foreign body reactions to resorbable poly(L-lactide) bone plates and screws used for the fixation of unstable zygomatic fractures. J. Oral Maxillofac. Surg. 1993, 51, 666–670.
35. Sukegawa, S.; Kanno, T.; Katase, N.; Shibata, A.; Takahashi, Y.; Furuki, Y. Clinical evaluation of an unsintered hydroxyapatite/poly-l-lactide osteoconductive composite device for the internal fixation of maxillofacial fractures. J. Craniofac. Surg. 2016, 27, 1391–1397.
36. Rasse, M.; Moser, D.; Zahl, C.; Gerlach, K.L.; Eckelt, U.; Loukota, R. Resorbable poly(d,l)lactide plates and screws for osteosynthesis of condylar neck fractures in sheep. Br. J. Oral Maxillofac. Surg. 2007, 45, 35–40.
37. Wiltfang, J.; Merten, H.-A.; Schultze-Mosgau, S.; Schrell, U.; Wénzel, D.; Keler, P. Biodegradable Miniplates (LactoSorb): Long-Term Results in Infant Minipigs and Clinical Results. J. Craniofac. Surg. 2000, 11, 239–243.
38. Nieminen, T.; Rantala, I.; Hiidenheimo, I.; Keränen, J.; Kainulainen, H.; Wuolijoki, E.; Kallela, I. Degradative and mechanical properties of a novel resorbable plating system during a 3-year follow-up in vivo and in vitro. J. Mater. Sci. Med. 2008, 19, 1155–1163.
39. Buijs, G.J.; van der Houwen, E.B.; Stegenga, B.; Bos, R.R.M.; Verkerke, G.J. Mechanical Strength and Stiffness of Biodegradable and Titanium Osteofixation Systems. J. Oral Maxillofac. Surg. 2007, 65, 2148–2158.
40. Xue, A.S.; Koshy, J.C.; Weathers, W.M.; Wolfswinkel, E.M.; Kaufman, Y.; Sharabi, S.E.; Brown, R.H.; Hicks, M.J.; Hollier, L.H., Jr. Local foreign-body reaction to commercial biodegradable implants: An in vivo animal study. Craniomaxillofac. Trauma Reconstr. 2014, 7, 27–34.

41. Veiseh, O.; Doloff, J.C.; Ma, M.; Vegas, A.J.; Tam, H.H.; Bader, A.R.; Li, J.; Langan, E.; Wyckoff, J.; Loo, W.S.; et al. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. Nat. Mater. 2015, 14, 643–651.

42. Shi, Q.; Tang, J.; Liu, R.; Wang, L. Toxicity in vitro reveals potential impacts of microplastics and nanoplastics on human health: A review. Crit. Rev. Environ. Sci. Technol. 2021, 195, 1528.

43. Hwang, J.; Choi, D.; Han, S.; Jung, S.Y.; Choi, J.; Hong, J. Potential toxicity of polystyrene microplastic particles. Sci. Reports 2020, 10, 7391.

44. Vallés, G.; González-Melendi, P.; González-Carrasco, J.L.; Saldaña, L.; Sánchez-Sabaté, E.; Munuera, L.; Vilaboa, N. Differential inflammatory macrophage response to rutile and titanium particles. Biomaterials 2006, 27, 5199–5211.

45. Stankevich, K.S.; Gudima, A.; Filimonov, V.D.; Klüter, H.; Mamontova, E.M.; Tverdokhlebov, S.I.; Kzhyshkowska, J. Surface modification of biomaterials based on high-molecular polylactic acid and their effect on inflammatory reactions of primary human monocyte-derived macrophages: Perspective for personalized therapy. Mater. Sci. Eng. C 2015, 51, 117–126.

46. Bose, S.; Roy, M.; Bandyopadhyay, A. Recent advances in bone tissue engineering scaffolds. Trends Biotechnol. 2012, 30, 546–554.

47. Deshayes, S.; Kasko, A.M. Polymeric biomaterials with engineered degradation. J. Polym. Sci. Part A Polym. Chem. 2013, 51, 3531–3566.

48. Matlaga, B.F.; Yasenchak, L.P.; Salthouse, T.N. Tissue response to implanted polymers: The significance of sample shape. J. Bio. Mater. Res. 1976, 10, 391–397.

49. Salthouse, T.N. Some aspects of macrophage behavior at the implant interface. J. Bio. Mater. Res. 1984, 18, 395–401.

50. Soundararajan, A.; Muralidhar R, J.; Dhandapani, R.; Radhakrishnan, J.; Manigandan, A.; Kalyanasundaram, S.; Sethuraman, S.; Subramanian, A. Surface topography of polylactic acid nanofibrous mats: Influence on blood compatibility. J. Mater. Sci. Mater. Med. 2018, 29, 145.

51. Mann, G.S.; Singh, L.P.; Kumar, P.; Singh, S.; Prakash, C. On briefing the surface modifications of polylactic acid: A scope for betterment of biomedical structures. J. Thermoplast. Compos. Mater. 2019, 34, 977–1005.

52. Guillaume, O.; Geven, M.A.; Varjas, V.; Varga, P.; Gehweiler, D.; Stadelmann, V.A.; Smidt, T.; Zeiter, S.; Sprecher, C.; Bos, R.R.; et al. Orbital floor repair using patient specific osteoinductive implant made by stereolithography. Biomaterials 2020, 233, 119721.

53. Gareb, B.; Roossien, C.C.; Van Bakelen, N.B.; Verkerke, G.J.; Vissink, A.; Bos, R.R.M.; Van Minnen, B. Comparison of the mechanical properties of biodegradable and titanium osteosynthesis systems used in oral and maxillofacial surgery. Sci. Rep. 2020, 10, 18143.

54. Lee, S.W.; Phillips, K.S.; Gu, H.; Kazemzadeh-Narbat, M.; Ren, D. How microbes read the map: Effects of implant topography on bacterial adhesion and biofilm formation. Biomaterials 2021, 268, 120595.

55. Keskin, D.; Zu, G.; Forson, A.M.; Tromp, L.; Sjollema, J.; van Rijn, P. Nanogels: A novel approach in antimicrobial delivery systems and antimicrobial coatings. Bioact. Mater. 2021, 6, 3634–3657.

56. Kozakiewicz, M.; Gabryelczak, I.; Bielecki-Kowalski, B. Clinical Evaluation of Magnesium Alloy Osteosynthesis in the Mandibular Head. Materials 2022, 15, 711.

57. Shuai, C.; Li, S.; Peng, S.; Feng, P.; Lai, Y.; Gao, C. Biodegradable metallic bone implants. Mater. Chem. Front. 2019, 3, 544–562.

58. Bazhenov, V.; Koltygin, A.; Komissarov, A.; Li, A.; Bautin, V.A.; Khasenova, R.; Anishchenko, A.; Seferyan, A.; Komissarova, J.; Estrin, Y. Gallium-containing magnesium alloy for potential use as temporary implants in osteosynthesis. J. Magnes. Alloys 2020, 8, 352–363.

59. Sezer, N.; Evis, Z.; Kayhan, S.M.; Tahmasebifar, A.; Koç, M. Review of magnesium-based biomaterials and their applications. J. Magnes. Alloys 2018, 6, 23–43.

60. Gu, X.; Zheng, Y.; Cheng, Y.; Zhong, S.; Xi, T. In vitro corrosion and biocompatibility of binary magnesium alloys. Biomaterials 2009, 30, 484–498.

61. Seitz, J.M.; Eifler, R.; Bach, F.W.; Maier, H.J. Magnesium degradation products: Effects on tissue and human metabolism. J. Bio. Mater. Res. Part A 2014, 102, 3744–3753.

62. Zhang, Y.; Xu, J.; Ruan, Y.C.; Yu, M.K.; O'Laughlin, M.; Wise, H.; Chen, D.; Tian, L.; Shi, D.; Wang, J.; et al. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. Nat. Med. 2016, 22, 1160–1169.

63. Sheikh, Z.; Najeeb, S.; Khurshid, Z.; Verma, V.; Rashid, H.; Glogauer, M. Biodegradable Materials for Bone Repair and Tissue Engineering Applications. Materials 2015, 8, 5744–5794.

64. Perrone, G.S.; Leisk, G.G.; Lo, T.J.; Moreau, J.E.; Haas, D.S.; Papenburg, B.J.; Golden, E.B.; Partlow, B.P.; Fox, S.E.; Ibrahim, A.M.S.; et al. The use of silk-based devices for fracture fixation. Nat. Commun. 2014, 5, 3385.

65. Numata, K.; Cebe, P.; Kaplan, D.L. Mechanism of Enzymatic Degradation of Beta-sheet Crystals. Biomaterials 2010, 31, 2926.

66. Riviș, M.; Roi, C.; Roi, A.; Nica, D.; Văleanu, A.; Rusu, L.-C. The Implications of Titanium Alloys Applied in Maxillofacial Osteosynthesis. Appl. Sci. 2020, 10, 3203.

67. Gupta, K.; Laubscher, R.F. Sustainable machining of titanium alloys: A critical review. Proc. Inst. Mech. Eng. Part B J. Eng. Manuf. 2017, 231, 2543–2560.

68. Quinn, J.; McFadden, R.; Chan, C.W.; Carson, L. Titanium for Orthopedic Applications: An Overview of Surface Modification to Improve Biocompatibility and Prevent Bacterial Biofilm Formation. iScience 2020, 23, 101745.

69. Elias, C.N.; Lima, J.H.C.; Valiev, R.; Meyers, M.A. Biomedical applications of titanium and its alloys. JOM 2008, 60, 46–49.

70. Urban, R.M.; Jacobs, J.J.; Tomlinson, M.J.; Gavrilovic, J.; Black, J.; Peoc'H, M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. J. Bone Jt. Surg.—Ser. A 2000, 82, 457–476.

71. Jorgenson, D.S.; Mayer, M.H.; Ellenbogen, R.G.; Centeno, J.A.; Johnson, F.B.; Mullick, F.G.; Manson, P.N. Detection of titanium in human tissues after craniofacial surgery. Plast. Reconstr. Surg. 1997, 99, 976–981.

72. Opris, H.; Armencea, G.; Manea, A.; Mitre, I.; Baciut, M.; Onișor, F.; Imre-Lucaci, F.; Vulpoi, A.; Vacaras, S.; Simion, B.; et al. Titanium Periimplant Tissue Alterations: A Prospective Cohort Plate Retrieval Study. Appl. Sci. 2021, 11, 6315.

73. Meningaud, J.-P.; Poupon, J.; Bertrand, J.-C.; Chenevier, C.; Galliot-Guilley, M.; Guilbert, F. Dynamic study about metal release from titanium miniplates in maxillofacial surgery. Int. J. Oral Maxillofac. Surg. 2001, 30, 185–188.

74. Armencea, G.; Gheban, D.; Onisor, F.; Mitre, I.; Manea, A.; Trombitas, V.; Lazar, M.; Baciut, G.; Baciut, M.; Bran, S. Histological Change in Soft Tissue Surrounding Titanium Plates after Jaw Surgery. Materials 2019, 12, 3205.

75. Acero, J.; Calderon, J.; Salmeron, J.I.; Verdaguer, J.J.; Concejo, C.; Somacarrera, M.L. The behaviour of titanium as a biomaterial: Microscopy study of plates and surrounding tissues in facial osteosynthesis. J. Cranio-Maxillofac. Surg. 1999, 27, 117–123.

76. Lalor, P.A.; Revell, P.A. T-lymphocytes and titanium aluminium vanadium (TiAlV) alloy: Evidence for immunological events associated with debris deposition. Clin. Mater. 1993, 12, 57–62.

77. Zaffe, D.; Bertoldi, C.; Consolo, U. Element release from titanium devices used in oral and maxillofacial surgery. Biomaterials 2003, 24, 1093–1099.

78. Coen, N.; Kadhim, M.A.; Wright, E.G.; Case, C.P.; Mothersill, C.E. Particulate debris from a titanium metal prosthesis induces genomic instability in primary human fibroblast cells. Br. J. Cancer 2003, 88, 548–552.

79. Borys, J.; Maciejczyk, M.; Antonowicz, B.; Kretowski, A.; Waszkiel, D.; Bortnik, P.; Czarniecka-Bargłowska, K.; Kocisz, M.; Szulimowska, J.; Czajkowski, M.; et al. Exposure to Ti4Al4V titanium alloy leads to redox abnormalities, oxidative stress, and oxidative damage in patients treated for mandible fractures. Oxid. Med. Cell. Longev. 2018, 2018, 3714725.

80. Borys, J.; Maciejczyk, M.; Krętowski, A.J.; Antonowicz, B.; Ratajczak-Wrona, W.; Jabłońska, E.; Załęski, P.; Waszkiel, D.; Ładny, J.R.; Żukowski, P.; et al. The redox balance in erythrocytes, plasma, and periosteum of patients with titanium fixation of the jaw. Front. Physiol. 2017, 8, 386.

81. Kawahara, M.; Kato-Negishi, M. Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses. Int. J. Alzheimer's Dis. 2011, 2011, 276393.

82. Schifman, R.B.; Luevano, D.R. Aluminum Toxicity: Evaluation of 16-Year Trend Among 14 919 Patients and 45 480 Results. Arch. Pathol. Lab. Med. 2018, 142, 742–746.

83. Xue, T.; Attarilar, S.; Liu, S.; Liu, J.; Song, X.; Li, L.; Zhao, B.; Tang, Y. Surface modification techniques of titanium and its alloys to functionally optimize their biomedical properties: Thematic review. Front. Bioeng. Biotechnol. 2020, 8, 1261.

84. Do Nascimento, R.M.; de Carvalho, V.R.; Govone, J.S.; Hernandes, A.C.; da Cruz, N.C. Effects of negatively and positively charged Ti metal surfaces on ceramic coating adhesion and cell response. J. Mater. Sci. Mater. Med. 2017, 28, 33.

85. Ribeiro, M.; Monteiro, F.J.; Ferraz, M.P. Infection of orthopedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. Biomatter 2012, 2, 176–194.

86. Arciola, C.R.; Campoccia, D.; Ehrlich, G.D.; Montanaro, L. Biofilm-Based Implant Infections in Orthopaedics. Adv. Exp. Med. Biol. 2015, 830, 29–46.
87. Katsikogianni, M.; Missirlis, Y.F.; Harris, L.; Douglas, J. Concise review of mechanisms of bacterial adhesion to biomaterials and of techniques used in estimating bacteria-material interactions. Eur. Cells Mater. 2004, 8, 37–57.
88. Kraeima, J.; Glas, H.H.; Witjes, M.J.H.; Schepman, K.P. Patient-specific pre-contouring of osteosynthesis plates for mandibular reconstruction: Using a three-dimensional key printed solution. J. Cranio-Maxillofac. Surg. 2018, 46, 1037–1040.
89. Kraeima, J.; Schepers, R.; Spijkervet, F.; Maal, T.; Baan, F.; Witjes, M.; Jansma, J. Splintless surgery using patient-specific osteosynthesis in Le Fort I osteotomies: A randomized controlled multi-centre trial. Int. J. Oral Maxillofac. Surg. 2020, 49, 454–460.
90. Gupta, R.K.; Kumar, V.A.; Mathew, C.; Rao, G.S. Strain hardening of Titanium alloy Ti6Al4V sheets with prior heat treatment and cold working. Mater. Sci. Eng. A 2016, 662, 537–550.
91. Koike, M.; Greer, P.; Owen, K.; Lilly, G.; Murr, L.E.; Gaytan, S.M.; Martinez, E.; Okabe, T.H. Evaluation of Titanium Alloys Fabricated Using Rapid Prototyping Technologies—Electron Beam Melting and Laser Beam Melting. Materials 2011, 4, 1776–1792.
92. Venkatesh, B.D.; Chen, D.L.; Bhole, S.D. Effect of heat treatment on mechanical properties of Ti-6Al-4V ELI alloy. Mater. Sci. Eng. A 2009, 506, 117–124.
93. Yang, F.; Pi, Z.Q.; Zhao, Q.Y.; Raynova, S.; Liu, Q.; Sharp, K.; Brandt, M.; Bolzoni, L.; Qian, M. Strong and Ductile Ti-6Al-4V Alloy Produced by Hot Pressing of Ti-6Al-4V Swarf. JOM 2019, 71, 1056–1061.
94. Guo, L.; Feng, W.; Liu, X.; Lin, C.; Li, B.; Qiang, Y. Sol-gel synthesis of antibacterial hybrid coatings on titanium. Mater. Lett. 2015, 160, 448–451.
95. Keskin, D.; Tromp, L.; Mergel, O.; Zu, G.; Warszawik, E.; van der Mei, H.C.; van Rijn, P. Highly Efficient Antimicrobial and Antifouling Surface Coatings with Triclosan-Loaded Nanogels. ACS Appl. Mater. Interfaces 2020, 12, 57721–57731.
96. Yu, L.; Tian, Y.; Qiao, Y.; Liu, X. Mn-containing titanium surface with favorable osteogenic and antimicrobial functions synthesized by PIII&D. Colloids Surf. B Biointerfaces 2017, 152, 376–384.
97. Shanaghi, A.; Chu, P.K. Investigation of corrosion mechanism of NiTi modified by carbon plasma immersion ion implantation (C-PIII) by electrochemical impedance spectroscopy. J. Alloys Compd. 2019, 790, 1067–1075.
98. Fabritius, M.; Al-Munajjed, A.A.; Freytag, C.; Jülke, H.; Zehe, M.; LeMarchand, T.; Arts, J.J.; Schumann, D.; Alt, V.; Sternberg, K. Antimicrobial silver multilayer coating for prevention of bacterial colonization of orthopedic implants. Materials 2020, 13, 1415.
99. Bergemann, C.; Zaatreh, S.; Wegner, K.; Arndt, K.; Podbielski, A.; Bader, R.; Prinz, C.; Lembke, U.; Nebe, J.B. Copper as an alternative antimicrobial coating for implants—An in vitro study. World J. Transplant. 2017, 7, 193–202.
100. Jäger, M.; Jennissen, H.P.; Dittrich, F.; Fischer, A.; Köhling, H.L. Antimicrobial and Osseointegration Properties of Nanostructured Titanium Orthopaedic Implants. Materials 2017, 10, 1302.
101. Scarano, A.; Piattelli, M.; Vrespa, G.; Caputi, S.; Piattelli, A. Bacterial adhesion on titanium nitride-coated and uncoated implants: An in vivo human study. J. Oral Implantol. 2003, 29, 80–85.
102. Zhao, J.; Cai, X.M.; Tang, H.Q.; Liu, T.; Gu, H.Q.; Cui, R.Z. Bactericidal and biocompatible properties of TiN/Ag multilayered films by ion beam assisted deposition. J. Mater. Sci. Mater. Med. 2008, 20, 101–105.
103. Soares, T.P.; Garcia, C.S.; Roesch-Ely, M.; da Costa, M.E.M.; Giovanela, M.; Aguzzoli, C. Cytotoxicity and antibacterial efficacy of silver deposited onto titanium plates by low-energy ion implantation. J. Mater. Res. 2018, 33, 2545–2553.
104. Ewald, A.; Glückermann, S.K.; Thull, R.; Gbureck, U. Antimicrobial titanium/silver PVD coatings on titanium. Bio. Eng. Online 2006, 5, 22.
105. Chan, C.W.; Carson, L.; Smith, G.C.; Morelli, A.; Lee, S. Enhancing the antibacterial performance of orthopaedic implant materials by fibre laser surface engineering. Appl. Surf. Sci. 2017, 404, 67–81.
106. Tsuchiya, H.; Shirai, T.; Nishida, H.; Murakami, H.; Kabata, T.; Yamamoto, N.; Watanabe, K.; Nakase, J. Innovative antimicrobial coating of titanium implants with iodine. J. Orthop. Sci. 2012, 17, 595–604.
107. Feng, W.; Geng, Z.; Li, Z.; Cui, Z.; Zhu, S.; Liang, Y.; Liu, Y.; Wang, R.; Yang, X. Controlled release behaviour and antibacterial effects of antibiotic-loaded titania nanotubes. Mater. Sci. Eng. C 2016, 62, 105–112.
108. Sedelnikova, M.; Komarova, E.; Sharkeev, Y.; Tolkacheva, T.; Khlusov, I.; Litvinova, L.; Yurova, K.; Shupletsova, V. Comparative investigations of structure and properties of micro-arc wollastonite-calcium phosphate coatings on titanium and zirconium-niobium alloy. Bioact. Mater. 2017, 2, 177–184.

109. Li, Y.; Wang, W.; Liu, H.; Lei, J.; Zhang, J.; Zhou, H.; Qi, M. Formation and in vitro/in vivo performance of “cortex-like” micro/nano-structured TiO2 coatings on titanium by micro-arc oxidation. Mater. Sci. Eng. C 2018, 87, 90–103.

110. Yu, S.; Li, Z.; Han, L.; Zhao, Y.; Fu, T. Biocompatible MgO Film on Titanium Substrate Prepared by Sol-gel Method. Xiyou Jinshu Cailiao Yu Gongcheng/Rare Met. Mater. Eng. 2018, 47, 2663–2667.

111. Martin, T.P.; Kooi, S.E.; Chang, S.H.; Sedransk, K.L.; Gleason, K.K. Initiated chemical vapor deposition of antimicrobial polymer coatings. Biomaterials 2006, 28, 909–915.

112. Shahali, H.; Jaggessar, A.; Yarlagadda, P.K.D.V. Recent Advances in Manufacturing and Surface Modification of Titanium Orthopaedic Applications. Procedia Eng. 2017, 174, 1067–1076.

113. Sun, L. Thermal Spray Coatings on Orthopedic Devices: When and How the FDA Reviews Your Coatings. J. Therm. Spray Technol. 2018, 27, 1280–1290.

114. Fox, K.E.; Tran, N.L.; Nguyen, T.A.; Nguyen, T.T.; Tran, P.A. Surface modification of medical devices at nanoscale—Recent development and translational perspectives. Biomater. Transl. Med. A Biomater. Approach 2019, 163–189.

115. Guimond-Lischer, S.; Ren, Q.; Braissant, O.; Gruner, P.; Wampfler, B.; Maniura-Weber, K. Vacuum plasma sprayed coatings using ionic silver doped hydroxyapatite powder to prevent bacterial infection of bone implants. Biointerphases 2016, 11, 011012.

116. Ullah, I.; Siddiqui, M.A.; Liu, H.; Kolawole, S.K.; Zhang, J.; Zhang, S.; Ren, L.; Yang, K. Mechanical, Biological, and Antibacterial Characteristics of Plasma-Sprayed (Sr,Zn) Substituted Hydroxyapatite Coating. ACS Biomater. Sci. Eng. 2020, 6, 1355–1366.

117. Lai, H.; Qiao, S.; Cao, H.; Zhao, X.; Lo, H.; Zhuang, L.; Gu, Y.; Shi, J.-Y.; Liu, X. Ag-plasma modification enhances bone apposition around titanium dental implants: An animal study in Labrador dogs. Int. J. Nanomed. 2015, 10, 653–664.

118. Hanawa, T.; Kamiura, Y.; Yamamoto, S.; Kohgo, T.; Amemiya, A.; Ukai, H.; Murakami, K.; Asaoka, K. Early bone formation around calcium-ion-implanted titanium inserted into rat tibia. J. Bio. Mater. Res. 1997, 36, 131–136.

119. Hong, Z.; Mello, A.; Yoshida, T.; Luan, L.; Stern, P.H.; Rossi, A.; Ellis, D.E.; Ketterson, J.B. Osteoblast proliferation on hydroxyapatite coated substrates prepared by right angle magnetron sputtering. J. Bio. Mater. Res. Part A 2010, 93, 878–885.

120. Hauschild, G.; Hardes, J.; Gosheger, G.; Stoeppeler, S.; Ahrens, H.; Blaske, F.; Wehe, C.; Karst, U.; Höll, S. Evaluation of osseous integration of PVD-silver-coated hip prostheses in a canine model. Bio. Res. Int. 2015, 2015, 292406.

121. Giavaresi, G.; Ambrosio, L.; Battiston, G.A.; Casellato, U.; Gerbasi, R.; Finia, M.; Aldini, N.N.; Martini, L.; Rimondini, L.; Giardino, R. Histomorphometric, ultrastructural and microhardness evaluation of the osseointegration of a nanostructured titanium oxide coating by metal-organic chemical vapour deposition: An in vivo study. Biomaterials 2004, 25, 5583–5591.

122. Chien, C.S.; Liao, T.Y.; Hong, T.F.; Kuo, T.Y.; Chang, C.H.; Yeh, M.L.; Lee, T.M. Surface microstructure and bioactivity of hydroxyapatite and fluorapatite coatings deposited on Ti-6Al-4V substrates using Nd-YAG laser. J. Med. Biol. Eng. 2014, 34, 109–115.

123. Chen, J.; Bly, R.; Saad, M.; AlKhodary, M.; El-Backly, R.; Cohen, D.; Kattamis, N.; Fatta, M.; Moore, W.; Arnold, C.; et al. In-vivo study of adhesion and bone growth around implanted laser groove/RGD-functionalized Ti-6Al-4V pins in rabbit femurs. Mater. Sci. Eng. C 2011, 31, 826–832.

124. Popat, K.C.; Leoni, L.; Grimes, C.A.; Desai, T.A. Influence of engineered titania nanotubular surfaces on bone cells. Biomaterials 2007, 28, 3188–3197.

125. Chouirfa, H.; Bouloussa, H.; Migonney, V.; Falentin-Daudré, C. Review of titanium surface modification techniques and coatings for antibacterial applications. Acta Biomater. 2019, 83, 37–54.

126. Van Hove, R.P.; Sierevelt, I.N.; Van Royen, B.J.; Nolte, P.A. Titanium-Nitride Coating of Orthopaedic Implants: A Review of the Literature. Bio. Res. Int. 2015, 2015, 485975.

127. Mukherjee, S.; Dhara, S.; Saha, P. Enhancing the biocompatibility of Ti6Al4V implants by laser surface microtexturing: An in vitro study. Int. J. Adv. Manuf. Technol. 2015, 76, 5–15.

128. Roy, P.; Berger, S.; Schmuki, P. TiO2 nanotubes: Synthesis and applications. Angew. Chem.—Int. Ed. 2011, 50, 2904–2939.

129. Kim, K.; Lee, B.A.; Piao, X.H.; Chung, H.J.; Kim, Y.J. Surface characteristics and bioactivity of an anodized titanium surface. J. Periodontal Implant Sci. 2013, 43, 198–205.

130. Gerlach, K. Elektrische Messverfahren zur Bestimmung der Belastbarkeit des Unterkiefers bei Patienten mit vollbezahntem Gebiss. Dtsch. Zahnarztl. Z. 1986, 39, 146–149.

131. Tams, J.; van Loon, J.-P.; Otten, E.; Rozema, F.R.; Bos, R.R.M. A three-dimensional study of bending and torsion moments for different fracture sites in the mandible: An in vitro study. Int. J. Oral Maxillofac. Surg. 1997, 26, 383–388.

132. Tams, J.; Van Loon, J.P.; Rozema, F.R.; Otten, E.; Bos, R.R.M. A three-dimensional study of loads across the fracture for different fracture sites of the mandible. Br. J. Oral Maxillofac. Surg. 1996, 34, 400–405.

133. Pistner, H.; Kukiz, P. Chewing forces after orthodontic therapy, osteotomies and fractures of the mandible. Dtsch. Zahnarztl. Z. 1998, 53, 528–531.

134. Tate, G.S.; Ellis, E.; Throckmorton, G. Bite forces in patients treated for mandibular angle fractures: Implications for fixation recommendations. J. Oral Maxillofac. Surg. 1994, 52, 734–736.

135. Feller, K.U.; Richter, G.; Schneider, M.; Eckelt, U. Combination of microplate and miniplate for osteosynthesis of mandibular fractures: An experimental study. Int. J. Oral Maxillofac. Surg. 2002, 31, 78–83.

136. Wu, W.; Zhou, J.; Xu, C.-T.; Zhang, J.; Jin, Y.-J.; Sun, G.-L. Biomechanical evaluation of maxillary Lefort I fracture with bioabsorbable osteosynthesis internal fixation. Dent. Traumatol. 2014, 30, 447–454.

137. Maurer, P.; Holweg, S.; Knoll, W.D.; Schubert, J. Study by finite element method of the mechanical stress of selected biodegradable osteosynthesis screws in sagittal ramus osteotomy. Br. J. Oral Maxillofac. Surg. 2002, 40, 76–83.

138. Maurer, P.; Holweg, S.; Schubert, J. Finite-element-analysis of different screw-diameters in the sagittal split osteotomy of the mandible. J. Cranio-Maxillofac. Surg. 1999, 27, 365–372.

139. Steffen, C.; Sellenschloh, K.; Polster, V.; Heyland, M.; Vollmer, M.; Morlock, M.M.; Heiland, M.; Huber, G.; Rendenbach, C. Biomechanical comparison of polylactide-based versus titanium miniplates in mandible reconstruction in vitro. J. Stomatol. Oral Maxillofac. Surg. 2019, 121, 377–382.

140. Haerle, F.; Champy, M.; Terry, B.C. Atlas of Craniomaxillofacial Osteosynthesis; Thieme: Stuttgart, Germany, 2009.

141. Huang, S.-F.; Lo, L.-J.; Lin, C.-L. Biomechanical interactions of different mini-plate fixations and maxilla advancements in the Le Fort I Osteotomy: A finite element analysis. Comput. Methods Biomech. Bio. Eng. 2016, 19, 1704–1713.

142. Proffit, W.R.; Turvey, T.A.; Fields, H.W.; Phillips, C. The effect of orthognathic surgery on occlusal force. J. Oral Maxillofac. Surg. 1989, 47, 457–463.

143. Tams, J.; Otten, B.; Van Loon, J.P.; Bos, R.R.M. A computer study of fracture mobility and strain on biodegradable plates used for fixation of mandibular fractures. J. Oral Maxillofac. Surg. 1999, 57, 973–981.

144. Ehrenfeld, M.; Manson, P.N.; Prein, J. Principles of Internal Fixation of the Craniomaxillofacial Skeleton: Trauma and Orthognathic Surgery; Thieme: Stuttgart, Germany, 2012.

145. Buijs, G.; van Bakelen, N.; Jansma, J.; de Visscher, J.; Hoppenreijs, T.; Bergsma, J.; Stegenga, B.; Bos, R. A randomized clinical trial of biodegradable and titanium fixation systems in maxillofacial surgery. J. Dent. Res. 2012, 91, 299–304.

146. Lee, J.H.; Han, H.S.; Kim, Y.C.; Lee, J.Y.; Lee, B.K. Stability of biodegradable metal (Mg–Ca–Zn alloy) screws compared with absorbable polymer and titanium screws for sagittal split ramus osteotomy of the mandible using the finite element analysis model. J. Cranio-Maxillofac. Surg. 2017, 45, 1639–1646.

147. Chang, L.-R.; Chen, C.-C.; Jeng, S.F.; Chen, Y.-R.; Hwang, L.-C.; Lin, T.-S. Investigation of a Modified Novel Technique in Bilateral Sagittal Splitting Osteotomy Fixation: Finite Element Analysis and in Vitro Biomechanical Test. Bio. Res. Int. 2020, 2020, 8707389.

148. Mutombo, K.; Rossouw, P.; Govender, G. Mechanical Properties of Mill-Annealed Ti6Al4V Investment Cast. Mater. Sci. Forum 2011, 690, 69–72.

149. Ashammakhi, N.; Peltoniemi, H.; Waris, E.; Suuronen, R.; Serlo, W.; Kellomäki, M.; Törmälä, P.; Waris, T. Developments in Craniomaxillofacial Surgery: Use of Self-Reinforced Bioabsorbable Osteofixation Devices. Plast. Reconstr. Surg. 2001, 108, 167–180.

150. Buijs, G.J.; van der Houwen, E.B.; Stegenga, B.; Verkerke, G.J.; Bos, R.R.M. Mechanical Strength and Stiffness of the Biodegradable SonicWeld Rx Osteofixation System. J. Oral Maxillofac. Surg. 2009, 67, 782–787.

151. Gorna, K.; Gogolewski, S. The effect of gamma radiation on molecular stability and mechanical properties of biodegradable polyurethanes for medical applications. Polym. Degrad. Stab. 2003, 79, 465–474.

152. Grabow, N.; Schlun, M.; Sternberg, K.; Hakansson, N.; Kramer, S.; Schmitz, K.-P. Mechanical properties of laser cut poly(L-lactide) micro-specimens: Implications for stent design, manufacture, and sterilization. J. Biomech. Eng. 2005, 127, 25–31.

153. Gogolewski, S.; Mainil-Varlet, P. Effect of thermal treatment on sterility, molecular and mechanical properties of various polylactides. 2. Poly(L/D-lactide) and poly(L/DL-lactide). Biomaterials 1997, 18, 251–255.

154. Engroff, S.L.; Blanchaert, R.H.; Von Fraunhofer, J.A. Mandibulotomy Fixation: A Laboratory Analysis. J. Oral Maxillofac. Surg. 2003, 61, 1297–1301.
155. Viljanen, J.; Kinnunen, J.; Bondestam, S.; Majola, A.; Rokkanen, P.; Törmälä, P. Bone changes after experimental osteotomies fixed with absorbable self-reinforced poly-l-lactide screws or metallic screws studied by plain radiographs, quantitative computed tomography and magnetic resonance imaging. Biomaterials 1995, 16, 1353–1358.
156. Arabnejad, S.; Johnston, B.; Tanzer, M.; Pasini, D. Fully porous 3D printed titanium femoral stem to reduce stress-shielding following total hip arthroplasty. J. Orthop. Res. 2017, 35, 1774–1783.
157. Niinomi, M. Low Modulus Titanium Alloys for Inhibiting Bone Atrophy; InTech: Rijeka, Croatia, 2011.
158. Kang, D.H.; Kim, T.W. Mechanical behavior and microstructural evolution of commercially pure titanium in enhanced multi-pass equal channel angular pressing and cold extrusion. Mater. Des. 2010, 31, S54–S60.
159. Park, B.; Jung, B.T.; Kim, W.H.; Lee, J.-H.; Kim, B.; Lee, J.-H. The Stability of Hydroxyapatite/Poly-L-Lactide Fixation for Unilateral Angle Fracture of the Mandible Assessed Using a Finite Element Analysis Model. Materials 2020, 13, 228.
160. Song, I.S.; Choi, J.; Kim, S.R.; Lee, J.H. Stability of bioresorbable plates following reduction of mandibular body fracture: Three-dimensional analysis. J. Cranio-Maxillofac. Surg. 2019, 47, 1752–1757.
161. Gareb, B.; van Bakelen, N.B.; Dijkstra, P.U.; Vissink, A.; Bos, R.R.M.; Van Minnen, B. Biodegradable versus titanium osteosyntheses in maxillofacial traumatology: A systematic review with meta-analysis and trial sequential analysis. Int. J. Oral Maxillofac. Surg. 2020, 49, 914–931.
162. Gareb, B.; van Bakelen, N.B.; Dijkstra, P.U.; Vissink, A.; Bos, R.R.M.; van Minnen, B. Efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery: A systematic review with meta-analysis and trial sequential analysis. Eur. J. Oral Sci. 2021, 29, e12800.