Chapter 1

Introductory Chapter: Multi-Aspect Bibliographic Analysis of the Synergy of Technical, Biological and Medical Sciences Concerning Materials and Technologies Used for Medical and Dental Implantable Devices

Leszek A. Dobrzański

Additional information is available at the end of the chapter

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1. General role of the regenerative medicine and dentistry

In many scientific centres, the World intensive research is under way related to the significant development of science in the field of Materials Engineering in connection with cell biology, thus expanding the new groups of advanced materials and technologies finding their application in regenerative medicine and dentistry. The author has already published on this topic studies [1–4] as well as books [5–9], monographs [10–24], scientific papers [25–76], patents [77–84] awarded in international fairs and exhibitions of research, invention and innovation [85–102]. In this area, several of author's own scientific and research projects have also been realised [103–107]; some are in progress [108], and others are planned for implementation [109]. Generally, one of the main reasons of this activity is the dynamic growth of post-injury defects, post-resection defects, as well as those originating from the operative treatment of cancerous tumours, whereas the number of cases is systematically increasing, or inflammation processes and as a result of other disorders of the human population, including the consequences of tooth decay, in particular due to local and systemic complications. Surgical treatment, often saving human lives, causes the necessity to replace losses in such organs or tissues, including in the dental system, to prevent biological and social degradation of patients and to restore their living functions. A growing number of road accidents and severe injuries of more and more people frequently requires a surgical intervention with replacement or supplementation of losses in organs or tissues and numerous interventions in the stomatognathic system. For example, the data of the Association for Improving Safety of Road Traffic reveal that about 1.7 million people suffer injuries in the EU every year. The growing number of sports accidents and bodily injuries frequently requires a surgical intervention with supplementation of lost tissues, also in the dental system. For example, according to EU IDB catalogue, annually, an average 6.1 million people in the EU are treated in hospitals for sports injuries. The number of people aged over 65 will have systematically grown, e.g., in EU by 70% to 2050. Systematically proceeding population ageing, which considerably increases the number of patients requiring surgical intervention with supplementation of losses in organs or tissues, often in the stomatognathic system.

One of the fundamental tasks globally, considered also to be one of the European Union's priorities, is to improve the society's condition of health, medical care and health safety. The numerous tasks related to this topic include the prevention of health risks, early recognition of diseases, rapid and effective implementation of medical procedures, comprehensive and continued therapies leading to an improved health condition and the improved health condition and improved quality of the society's life [1]. For example, the European Health Strategy regards health-related aspects to be a central focus of the Community's policy and proposes a programme of actions for citizens, by recognising their right to own health and healthcare and through the promotion of the ageing society's health, through the protection of citizens against risks for their health and life and through supporting dynamic health care systems and new technologies, related to technical support for medicine, including dentistry. The idea is to protect against serious health risks, especially such as civilisational diseases, pandemics and bioterrorism and to support research, especially such applying advanced technologies, to ensure the fullest prophylactics of diseases and safe treatment of patients, taking into account the relationships between health and economic well-being. A significant and costly problem of modern medicine is the necessity to replace or supplement organs or tissues, in particular in orthopaedics and traumatology and maxillofacial surgery and restorative dentistry, to prevent the biological and social degradation of patients and to restore their living functions [1]. It also applies mostly to the elimination of consequences of tooth decay, considered to be an exceptionally burdensome civilisational disease, also one of the costliest ones, in particular, due to local and systemic complications [110–125].

A relatively new branch of medicine is regenerative medicine and dentistry. The achievements of modern implantology depend not only on the knowledge and experience of medicals, but it also requires the application of advanced engineering problems, both in the field of engineering design, material engineering, nanotechnology and material technology. These are very responsible research, and the most avant-garde trends concern the offering of personalised medical devices manufactured according to individual anatomical features of the patient, according to complex and advanced original technologies and ever newer biomaterials used for implantable devices. These issues are the subject of many years of scientific interest of the Author, and they belong to the group of the most avant-garde, so far relatively little known, but extremely promising technical problems for use in regenerative medicine and dentistry. This study presents the results of previous studies and own research, derived from previously published original own work done by the Author with a team of co-workers [1–19]. As in all other cases, in material engineering and material science, in order to satisfy the functional functions of implantable devices as well as all other products, it is necessary to design and apply engineering materials that, subjected to the appropriate technological processes of shaping the geometric form, and especially the structure, will ensure appropriate physico-chemical properties of the material. This book presents exhaustively the achievements of numerous teams from different countries of the world, inscribing itself in the discussed European Health Strategy, in advanced research areas related to biomaterials used in regenerative medicine and dentistry. In the overall analysis of the issue concerning biologically active cellular structures and a substrate with an engineering composite material matrix used for scaffolds and for newly developed implantable devices applied in regenerative medicine and dentistry, further in this description all the aspects are analysed separately, because the lack of holistic approach and general references is in the literature, apart from own works.

2. Importance of regenerative medicine and dentistry and tissue engineering

The development of regenerative medicine, whose technical aspects are covered by the book with the first reports dating back to 1992 [126], is a relatively new field of medicine. Implantable biomedical devices encompass numerous solutions eliminating various dysfunctions of a human organism and are currently aggregately considered to be medical bionic implants. The development of regenerative medicine, whose technical aspects are covered by the book, previously described in author's theoretical study [1], started with the first reports dating back to 1992 [126], as a relatively new field of medicine. Implantable biomedical devices encompass numerous solutions eliminating various dysfunctions of a human organism and are currently aggregately considered to be medical bionic implants. Bionics is understood as production and investigation of biological systems to prepare and implement artificial engineering systems which can restore the lost functions of biological systems [127, 128]. Autographs, allografts or metal devices or such made of other engineering materials are primarily the current methods of organ and tissue replacement employ [129]. The purpose of the regenerative medicine is treatment—by replacing old and sick cells with young cells, also using tissue engineering methods and cell-based therapies or organism regeneration using a gene therapy. It raises numerous new challenges, notably in counteracting the symptoms and consequences of diseases, and even their causes [130–133]. The application of therapies based on living cells in medicine is a relatively new concept. The first successful allogeneic transplantation of human haematopoietic stem cells (HSC) was seen as late as in 1968 [134] (29), then the cells were used for other therapeutic applications [135, 136]. The therapies based on living cells were intensively developed in the 1990s [137], in particular for skin and cartilage implants. Tissue engineering provides technical support for regenerative medicine and is an interdisciplinary field employing the principles of engineering and life sciences for development of biological substitutes, for restoration, maintenance and improvement of functions of tissues or entire organs [138, 139]. Tissue engineering, introduced in 1985 [140], as a field of technical sciences, utilises medical knowledge and materials engineering methods to develop biological materials capable of restoring, maintaining or improving the functions of particular tissues or organs [138] and to produce their functional substitutes [141, 142]. Tissue engineering is based on understanding the principles of tissue growth and on applying this for functional production of a replacement tissue for clinical use [143].

An overview of the present situation points to a diversity of the currently available therapeutic methods based on cells, undergoing the phase of clinical studies [144]. The global market of cell-based therapies boasts a revenue of more than a billion USD per year [145]. Therapeutic strategies include direct transplantation of the desired type of cells collected using biopsy or such originating from cultures of stem cells, both in the autologous and allogeneic system. Multipotent and self-renewing stem cells (MSCs), depending on the tissue development stage, can be grouped into adult and embryonic cells [136, 146, 147]. Embryonic cells exist in umbilical cord blood [148, 149], in the placenta [150], in amniotic fluid [151] or deciduous teeth pulp in infants, termed as multipotent stromal cells (MSCs). The clinical application is most beneficial, especially of autologous cells [136], as they do not cause an immunological response and do not require immunosuppressive treatment [151–154], and, nevertheless, such application is limited [155]. There is a much greater potential for somatic and especially haematopoietic stem cells (HSC) from bone marrow stromal [156–158], supporting bone marrow stromal cells (BMSCs) as a standard [136, 158]. Adult stem cells also occur, in particular, in synovial fluid, tendons, skeletal muscles [158, 159] and adult muscles, fat tissue—ASCs (adipose-derived stem cells ASCs) [158, 159], the stroma of cornea [149], peripheral blood, nervous tissue and dermis and have an ability of transformation into multiple tissues.

The efficiency of cell-based therapies depends on the preservation of their viability after implantation [160, 161], to prevent the ischaemia of tissues and necrosis [162–167]. Stem cells originating from bone marrow and fatty tissue may be used for breeding mesenchymal cells and tissues, in adipocytes, chondrocytes, osteoblasts and skeletal myocytes and can be used for producing tissues, e.g., muscles fat, gristle and bones [168–171]. Stringent safety requirements must be considered in cell-based therapies because raw materials of the animal origin are used, which poses a potential threat of transmitting a pathogen to a recipient or of immunological complications [172] and as post-production cleaning is required [173]. Progress in this domain seen since 2004 requires further detailed considerations concerning the mechanism of *in vivo* therapeutic activity, to facilitate the development and optimisation and for the development of automated processes, with improved efficiency and with quality control and with reference standards established [174–177]. About 100 companies specialised in this area are operating at the American and European market. For better characterisation, the conditions of cell-based therapies must be realised more intensive the basic research. The introduction of the new clinical regenerative procedure having no competition requires the development of breeding techniques of human stem cells. However, the adult stem cells could be used to a limited extent [178]. The fabrication of the majority of therapeutically meaningful cell types (except the mesenchymal stem cells) has not yet been mastered at a technologically satisfactory scale. However, it should be emphasised that the outcomes achieved to date in this area be promising. Therefore, a wide commitment of the scientific environment is generated for the elaboration and explanation of the phenomena accompanying the growth of tissue structures in conditions allowing their industrial production. The purpose is the development of the adequately organised therapeutic processes, introduction appropriate engineering materials and obtaining the technological processes for them, including nanotechnology. A very important cognitive task is the explanation the interaction between the surface structure of engineering materials forming the substrate and the tissue structures deposited onto it and explication the role of a substrate for culturing tissue structures.

Opposite to pure therapies, in which stem cells are injected directly into peripheral circulation or located in particular tissues, in numerous clinical cases it is necessary to use stem cells' carriers to transport them, and especially scaffolds for their three-dimensional grouping in a particular place of an organism, and such research is being constantly developed [179–188]. It should be noted that the notion of scaffolds is quite comprehensive, as it may not only refer to engineered extracellular matrices 'scaffolds', but also to rigid microporous materials into which osteoblasts may grow, and also to microporous mats made of polymer nanofibres, into which living cells are growing and may be used as specific plasters, to treat for example burns or to reconstruct large fragments of skin [7]. The latest publications [5, 6] also note the relevance and need of developing such therapeutic methods for the dental system. A microscopic, porous structure of scaffolds is required, enabling the diffusion of nutrients and metabolism products through them. Scaffolds, including also bone scaffolds, must enable the adhesion and migration of cells and facilitate their development to form a three-dimensional tissue structure in conditions simulating a natural micro-environment [187, 189]. Scaffolds should exhibit adequate mechanical properties for ensuring an appropriate environment of development for cells and ensure the mechanical preservation of living tissues in a three-dimensional structure. The task of scaffolds is to ensure also the necessary conditions of cells growth by the creation of new blood vessels [190–193].

Two separate aspects need to be considered: a porous structure, especially the size of pores and manufacturing technologies of appropriate porous materials, and the selection of engineering materials of which scaffolds are produced. Both aspects are of primary importance for the undertaking's success, and hence each of them has been analysed based on the state-of-the-art.

3. Designing of geometric properties of porous materials

Porous materials have been used for not too long in orthopaedic procedures to replace damaged bones, and porous scaffolds are geometrically similar to natural hard tissues made up of a skeleton penetrated by interlinked pores [194], thus solid metals are unsuitable because they are, by nature, non-permeable and prevent the adhesion and proliferation of living cells. Porous materials, mainly metals, are implanted to repair damaged bones having a critical size and in the majority of cases are used as carrying devices [195]. It is vital that an implant has properties similar to a recipient bone and the surrounding tissue [196]. A human bone has a hierarchical structure with three major anatomic cavities of different sizes which are Haversian canals (50 μm) [197], osteocytic lacunae (few micrometres) [198–201] and canaliculi (<1 μm) [201, 202]. All the three cavities play an important role in the mechanical integrity of the bones and the processes reconstruction [203]. A porous structure ensures appropriate space for the transport of nutrients and the growth of living cells [204, 205]. A bone elasticity modulus, much smaller than for non-noble metals, is regarded to be one of the major problems in the construction of implants because, as a result, the screening of stresses would often lead to implant damages. Porous metals can duplicate bone properties if their structures are digitally designed and are produced using advanced manufacturing technologies [205]. A bone, despite its anisotropy [206], is being replaced by porous engineering materials with similar rigidity, making them efficient for transmitting loads and for alleviating the effect of stress screening and for regeneration of bone tissue in the damaged place [195]. The following is therefore required: (1) biocompatibility; (2) appropriate surface for adhesion, proliferation and differentiation of cells; (3) a very porous structure with a network of open pores for the growth of cells and for the transfer of nutrients and metabolic wastes; (4) mechanical properties adjusted to the requirements of the surrounding cells to reduce or eliminate excessive stresses and meeting anatomic requirements to avoid a mechanical damage [207–211]. The key features for the design of porous metallic implants include careful selection of porosity, size of pores and mutual connections between pores, aimed at achieving satisfactory clinical results. Such constructional features have a large effect on the mechanical properties and biological activity of scaffolds [195]. Bone regeneration *in vivo* porous implants consists of recruitment and penetration of cells from the surrounding bone tissue and vascularisation [212]. Higher porosity may facilitate such processes and enable bone growth [213, 214]. The influence of the pore size on the growth of cells, e.g., bone cells, is, however, still controversial [195, 215]. Pore sizes of artificially produced scaffolds should be adapted to the specific cell type. They should be small, because then they ensure more space for cells' growth, e.g., bone tissue [195], but small enough to prevent the sealing of pores in a scaffold [187]. They should also be large enough to prevent blood clots [216], enable the migration of cells and ensure conditions to fill up scaffold pores by the reconstructed cells, guaranteeing neovascularisation [217]. For this reason, the upper suggested limit is 400 μm [215], because it is no longer beneficial to increase it. It was found, though, that for pores sized 600–900 μm, the growth of bone cells is higher than for the pores sized 300 μm [195]. The permeability of a porous structure of a scaffold ensures the transport of cells, nutrients and growth factors as a result of blood flow, and a blood pressure gradient depends on the pore size and has also influence on vascularisation and accelerates the osseointegration process [195], although this requires further studies. It is thought that the optimum pore size for cells growth, and especially mineralised bone growth, is 100–400 μm [195]. The aspect is still important, because although increased porosity, pore size and mutual connection of pores are the key factors, which are having a large impact on facilitated bone growth and the transport of cells and nutrients, evidently ameliorating the quality of biological processes, nevertheless they may considerably reduce rigidity and strength of scaffolds [195]. Although the shape and size of pores can be adjusted by changing the conditions of even traditional fabrication processes, e.g., casting or powders metallurgy; however, only a randomly organised porous structure can then be obtained, which is not fully open or is not open at all [218]. To produce porous scaffolds as well as other medical implants, including dental ones, additive technologies are used most often in combination with prior CAD/CAM, as highly competitive against traditional manufacturing methods, such as casting or machining [219–224]. Such technologies can be applied for various engineering materials, not only metals and alloys which are prepared, respectively, as powder or liquid, rolled material or thin fibres. Additive technologies have been widely used for fabricating diverse, customised elements applied in medicine, in particular, scaffolds with required porosity and strength with living cells implanted into an organism [225–227], models of implants and dental bridges [228–230], implants of individualised implants of the upper jaw bone, hip joint and skull fragments [231–238]. Considering the additive technologies applied most widely, the following have found their application for scaffold manufacturing, in implantology and prosthetics, i.e., electron beam melting (EBM) [222, 239–243], and also 3D printing for production of indirect models, although selective laser sintering/selective laser melting (SLS/SLM) and its technological variants offers broadest opportunities [220, 222, 244–253], which was noted in discussing each group of materials. SLS/SLM techniques permit to produce a structure with open pores, e.g., with a lattice structure promoting osseointegration, while maintaining different external shapes of the whole implant [254]. The determination of optimum geometric features of scaffolds as a result of computer-aided design in conjunction with the optimisation of technological conditions of the applied additive technology, and broad experimental verification in the engineering and biological aspect, is of key importance.

4. Selection of materials of implantable devices in regenerative medicine and dentistry

The selection of appropriate materials for application in the regenerative medicine and dentistry, in conjunction with the optimisation of technological conditions of fabrication of implantable devices, including porous scaffolds and implant-scaffolds, are the important aspects of the analysed problems, previously just described in author's own theoretical study [2]. It occurs as a synergy of classical prosthetics/implantation of bone and organ post-injury or post-resection losses together with the methods of tissue engineering in the connection (interface) zone of bone or organ stumps with prosthetic elements/implants. It calls for the use of porous and high-strength non-graded metal and/or composite and/or polymer materials (which is strongly, but not exclusively, dependent on the specificity of the clinical application) together with using at the same time biodegradable materials for tissue scaffolds. One of the solutions strives to achieve bioactive connections, as most advantageous regarding bond strength, which is formed between bone tissue and implants/scaffolds made or coated with bioactive materials, considerably improving the stability and durability of connection, especially for porous scaffolds/implants. Another acceptable approach is a very durable biological connection characteristic for porous implants/scaffolds whereby the bone tissue is growing through the material pores and is mechanically "anchored" in the bone. Porous resorbable bioglass may be used for scaffold fabrication [255], e.g., from the CaO-SiO_2-P_2O_5 system, Hench bioglass [256], produced both, with classical melting methods and with sol-gel methods, and also bioglass from the SiO_2-Al_2O_3 system endowed with silver, due to their biocompatibility [257, 258] and bacteriocidity, and with pore walls coated with hydroxy carbonate apatite (HCA) [259], ensuring enhanced activity of osteoblasts [260] and expression of genes connected with bones [261]. The formation methods of porous structures from ceramic materials, in particular such as aluminium oxide, zirconium oxide, calcium carbonate, hydroxyapatite (HA), titanium oxide, include casting of sections from mass containing a fine-grained ceramic material with additives facilitating foaming and then material sintering, and also the use of other methods, e.g., an organic matrix and lyophilisation of ceramic slip [255]. The basic bioactive ceramic materials used for scaffolds is calcium phosphate (CaPs), as the main component of bone, and in hydroxyapatite (HA), β-tricalcium phosphate (β-TCP) or a mixture of HA and b-TCP, known as biphasic calcium phosphate [262–264]. A classical solution in the domain of ceramics, are porous scaffolds/corundum implants completely biocompatible, growing through the fully valuable bone tissue. They possess mechanical strength sufficient for many types of clinical procedures and ensuring freedom of manipulation during a surgical procedure. After growing through, have an appropriate modulus of elasticity, which ensures their good interworking with the bone and also allow for sterilisation with any method. Both, bioactive and biodegradable polymers can be employed [193, 265, 266], including in particular natural polymers such as: alginate, chitosan, collagen, fibrin, hyaluronic acid and silk, and used, e.g., for bone reconstruction [267], as well as synthetic ones, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and polycaprolactone (PCL) and poly(propylene fumarate) (PPF) with high compressive strength, comparable to this of a cortical layer of bone [266]. Some of them, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) may cause negative tissue reactions [268]. Composite materials satisfy mechanical and physiological requirements, e.g., CaP-polymer scaffolds, interconnected tricalcium phosphate (TCP) scaffolds coated inside pores with polycaprolactone (PCL) [269], hydroxyapatite HA/poly(ester-urethane)(PU) [270] or a nanocomposite of collagen and Bioglass [271].

Metallic materials represent one of the largest groups of engineering materials used for this purpose and comprise, among others, titanium, tantalum, niobium and their alloys, and in dentistry also cobalt-matrix alloys and alloys of noble metals, for which, SLS/SLM technologies were especially applied [272, 273], irrespective of stainless steels often used until now. The SLS/SLM technique has been used successfully for production of complex porous and cellular structures made of austenite stainless steels [218]. One of the main grades of stainless austenitic steel which can be used for medical purposes is nickel, now thought to be one of the main allergens [274], with 17% of adults [275] and 8% of children [276] being sensitised to it, approx. 50–60 million people altogether in the EU. Apart from many disorders [277, 278], this chemical element causes rejection of orthopaedic gradients [279], and dental implants [280] and, for this reason, Directive 94/27/EC [281] was put into force prohibiting the use of nickel and materials containing it for prosthetic and implantological purposes. Co-matrix alloys such as Co-Cr-Mo, Co-Cr-W and cast Co-Cr-W-Mo alloys, for machining or manufactured by powder metallurgy methods, for which the SLS/SLM technology was successfully employed [272, 273, 282–289], can be seen as the basic classical materials for dental prosthetic restorations [290–296], despite their high density, which is more and more often considered as counter-indicative for their application for such purposes.

Porous metal materials, though not biodegradable, are used for scaffolds, mainly Ti and Ta [297], also after treatment of pores' surface [298]. Therefore, interest in light metals and their alloys have been on the rise. Ti and its alloys represent engineering materials which are particularly suitable for use in additive technologies, e.g., for selective laser sintering [5, 6, 10, 77–81, 85–91, 299–305]. Porous Ti [297] can be utilised for non-biodegradable scaffolds, including such after treatment of the pore surface, applied primarily due to relatively high compressive strength and fatigue strength [193, 306]. It was proven that structures of porous Ti6Al4V are also effective in aiding the growth of cells and bone tissue [307–311]. Ti and its alloys with Al, Nb and Ta and Ti alloys with Al, V and Nb, well tolerated by a human organism, are the metallic materials more and more often used these days for joint prostheses and for various implants, also intramedullary wires and for prosthetic restorations and dental implants [33, 312–322]. When used for dental crowns, though, they have a significant disadvantage, consisting of porcelain reactions with titanium oxide, causing bruising and colour darkening, which - for aesthetic reasons - practically eliminates such prosthetic restorations, but does not exclude their use for a root part of the implant [323]. Titanium-matrix materials do not cause allergic reactions and are stainless and feature high strength and hardness, and also thermal conductivity several times lower than traditional prosthetic materials [324]. Titanium is a very thrombogenic material [240]. The biocompatibility, especially thrombocompatibility, of Ti can be enhanced by introducing alloy elements [325]. Some publications [326–334] provide limited information on the toxic activity of V as an alloy element in the Ti6Al4V alloy, because it was found that V could be regarded as a potentially toxic factor [335, 336], which is, however, true only for a considerable concentration of V in a body, due to development of its undesired immunological response, when the freed V ions migrate from the material surface to a soft tissue, binding with proteins [337, 338]. Some research on cells implies that Ti6Al4V exhibits high cytotoxicity [307–311, 339]; there are reports that V may cause sterile abscesses, and Al may cause scarring, while Ti, Zr, Nb and Ta show good biocompatibility [340]. Some publications argue that a risk associated with an unfavourable effect of Ti alloys can be limited by replacing V, as in, e.g., Ti6Al4V alloy, by Nb, e.g., in Ti6Al7Nb alloy, which would show better properties, e.g., corrosion resistance and bioavailability [334, 341–346]. It was revealed, however, by direct comparison in the same conditions that differences between Nb and V in Ti alloys are not too high [334], and even that Ti6Al4V alloys exhibit better properties than Ti6Al7Nb alloy [334, 347–349], such as thrombocompatibility, more intensive antibacterial activity and resistance to colonisation of Gram-positive bacteria, although worse for colonisation of Gram-negative bacteria [334]. Other alloys, with a higher concentration of Nb, are however employed successfully, e.g., Ti24Nb4Zr8Sn, including those manufactured by selective laser sintering, with an elasticity modulus better adapted to a bone than Ti6Al4V alloy, which prevents bone resorption and does not cause implant loosening in use [350]. Although porous Ti6Al4V was comprehensively studied, the potential release of toxic ions has led to a search for alternative Ti alloys, including, among others, Ti24Nb4Zr8Sn, Ti7.5Mo and Ti40Nb, with comparable mechanical properties as their counterparts manufactured traditionally [350–353].

The concept of the synergic use, for this purpose, of the existing achievements in tissue engineering in the scope of selection of materials and scaffold fabrication technologies, in materials engineering and production engineering in the scope of design and manufacture of prostheses/implants with different engineering materials, and in surgery and regenerative medicine in the scope of prosthetics/implantation in the treatment of the above-mentioned civilisational diseases and their effects have been outlined in the earlier works and projects by the author [1–109].

Regeneration in a natural condition is forcing the removal of an artificial scaffold [354–356]. The topic of scaffolds and biodegradable implants, including porous ones, both made of polymers [193], despite doubts of Mg-Ca alloys [357], and of composite materials [269–271], as well as a concept of separating the redundant pieces of cell-based products after finishing a therapy performed with their use [7], were thoroughly analysed in the own works [5, 6, 10]. Relatively high compressive strength and fatigue strength [193, 306] are primarily the reason for the application of Mg and its alloys [358–360]. Introducing pure Mg with interconnected porosity onto bearing plates, bolts and networks made by rapid pressure assisted densification methods, such as rapid hot pressing/Spark Plasma Sintering (SPS) is an innovative approach [361]. Due to Mg biocompatibility, and the manufacturing technology ensuring good mechanical strength and recovery of the bone pure Mg gives an optimum solution. Mg with Ca, Zn and Mn alloys can be used, to reduce the rate of *in vivo* corrosion and prevent necrosis and the blocking of blood flow. A human organism well tolerates these alloys [362, 363] mainly with coatings adapted to bioresorbable implants [364–367]. Reinforcements of magnesium MMCs usually include, notably, HA [368–373], FA [374], calcium polyphosphate [375], and calcium [374] and well affect biocompatibility. Mg and its alloys can be used for non-biodegradable scaffolds [372]. Except for several studies, the application of Mg as a biomaterial has not won popularity as late as until the end of the 1990s, because this pure metal cannot ensure appropriate mechanical properties or corrosion resistance in orthopaedic uses [376, 377]. Such popularity, though, has risen exponentially since then [378], owing to major improvements in Mg production [378] and various techniques elaborated, including the use of Mg alloys, substrate surface treatment or coating technologies [379–381]. Generally speaking, such alloys contain Al or rare-earth elements (REE) [382–384], although there are reports about studies over additives of non-toxic elements, such as Ca, Mn, Zn and Zr, and even Li, Cd, Sn, Sr., Si, Ag and Bi [378]. Al is a common additive for Mg alloys, as it is conceded that it improves strength and resistance to Mg alloys' corrosion Mg (258), although Al is shown in numerous pathological conditions in humans [385–388]. The additives of rare-earth elements are used for increasing strength, plasticity and wear resistance of Mg alloys and their corrosion resistance [383] in environments with a high content of chlorides in connection with a passivation layer rich in oxygen [389, 390]. The influence of such elements on the physiological system is unknown, [378], although it was found that they possess both, anti-carcinogenic and anti-coagulation properties [391], and when used as vascular stents without side effects [392], and also without La and Ce, do not have an effect on cytotoxicity and have a positive effect on cellular life [393], although quite the opposite was also found, that at least some REEs are highly toxic [393, 394]. The value of the research carried out in this scope may be limited if it turns out that such elements are too toxic in use for biomaterials [377] and this requires further systematic studies. Magnesium synthesised by SLM is closely adapted to a human bone [395]. This technology was employed for producing complex porous/cellular structures of magnesium alloys [350, 396–398], although the results of such studies are normally not available in the available literature [254]. A selective laser sintered Mg2Mn alloy is predisposed to use for bone implants [254]. The use of Mn, as a component of Mg alloys, consists of the improvement of corrosion resistance and may increase the plasticity of Mg alloys [383, 399]. Zn improves the strength of Mg alloys [399, 400] and their corrosive resistance [401]. However, its influence on increased cytotoxicity was identified [402, 403]. Magnesium and its alloys feature a high potential for orthopaedic uses because it has proven to be fully bioresorbable, their mechanical properties are adapted to bones and do not cause an inflammatory response; moreover, they are osteoconductive, supportive to bone growth and play a positive role in the binding of cells [404]. The application of biomaterials made of Mg highly increases a risk of hypomagnesia and, probably, of the excessively stored and circulating Mg [378]. Corrosion analysis and Mg concentration monitoring in serum must be an important aspect of Mg-based biomaterials' assessment [378]. Due to an effect of diverse factors such as pH, concentration and type of ions, adsorption of proteins on orthopaedic implants and the biochemical activity of the surrounding cells in the presence of body fluids [405, 406], further research into biomedical uses of Mg is indispensable. Powders are serially manufactured for, in particular, SLS/SLM [407].

Third-generation scaffolds made of CaP, Si-TCP/HA [408] and collagen hydrogel [409] are osteoinductive and allow to create a new bone and also its biomineralisation. Substitute scaffolds of bones are often administered with medicines, including gentamycin, vancomycin, alendronate, methotrexate and ibuprofen [410, 411] and with growth factors and transcription factors [265, 412, 413].

5. Selection of technologies of implantable devices in regenerative medicine and dentistry

The issue was previously considered in the Author's own review work [2], and some of the information compiled there was used here. The traditional, and also the oldest fabrication technologies of scaffolds with a porous structure differentiate the method of emulsifying/lyophilisation [414], to thermally induced phase separation (TIPS) [415], solvent casting & particulate leaching (SCPL), where solvent residues may have an adverse effect on cellular structures [416]. The aforementioned classical methods being unable to control accurately a general shape of the scaffold as well as the size, shape, distribution and interconnections of pores. Nevertheless, these methods have not been completely abandoned. They are used as a modern method in tissue engineering replication technologies with micro-/nanopatterned-surfaces [417–419]. The master moulds are produced using a hard or soft material, for the reason of mould rigidity. The structures with small feature resolution and micro/nanofabricated moulds, including for hot embossing (also known as nanoimprint lithography) and soft lithography (micro-casting) for achieving patterns with dimensions about of 5 nm [420–423] can be cast using synthetic and natural biodegradable polymers [424, 425]. Currently used methods do not require moulds for fabrication of scaffolds (solid freeform fabrication SFF) made not only polymer materials and hydrogels but also ceramic and metallic materials [193, 426–429]. The particular fabrication methods find wide application for the processing both the mentioned biocompatible engineering materials and biological materials [430]. The particular layers of powder are sprayed with an adequate biocompatible binding agent, e.g., for merging powder to fabricate scaffold from collagen [431], and a 25% acrylic acid solution in a mixture of water with glycerine [432] using the three-dimensional printing method (3DP) [433]. This method is also used for the integration of hydroxyapatite used for bone regeneration, and an aqueous citric acid solution is used for integration of ceramics based on calcium phosphate [434]. A method of three-dimensional printing hot wax droplets [435] could be used for manufacture a replica of the scaffold surface, e.g., bone and gristle substitutes fabricated with the SFF method. The limitations of the method originate from wax impurities with biologically incompatible solvents [436], which are not exhibited by new generation materials such as BioBuild and BioSupport dissolving in ethanol or water [436]. The stereolithography method permits to shape three-dimensional form of liquid polymer [437], in particular using poly(propylene fumarate) (PPF) [438, 439], poly(ethylene glycol) (PEG) [440, 441]. Polymer materials without solvents, including poly(ε-caprolactone) PCL [429, 442], poly(ethylene glycol)–poly(ε-caprolactone)–poly(lactide), PEG-PCL-PLA [442, 443] acrylonitrile-butadiene-styrene (ABS) and hydroxyapatite-poly(ε-caprolactone) HA-PCL [442, 444] are used in fused deposition modelling (FDM) [445]. The particular layers are placed from a computer controller and using computer-aided design (CAD) methods. Selective laser sintering (SLS) is similar to 3D printing. The process is starting with uniform spreading of a thin layer of powder onto the surface and then followed by the merging of powder grains as a result of sintering with the neighbouring grains with partial pre-melting. The next layers are manufactured subsequently according to the same method until the full dimensions of the manufactured element are achieved. The manufactured element, including the scaffolds, shows the assumed constructional features. This technique, used commonly for additive manufacturing of products, includes scaffolds and implants for the dental purpose, from metallic and ceramic materials [5, 6, 10, 446]. This technology was also utilised for scaffolds preparation [426] from biodegradable polymers, e.g., polyether polymer, poly (vinyl alcohol), polycaprolactone [447] and poly(L-lactic acid) [448], and also hydroxyapatite [449] and from composites composed of some of such polymers and hydroxyapatite [448, 450, 451].

Nanofibrous scaffolds are manufactured by electrospinning, and the so obtained nanofibres with the diameter of 5 nm to over 1 mm are continuous and randomly interconnected [452, 453]. Due to the character of electrospinning, fibres are arranged in an orderly manner or are oriented randomly [454]. They have a large specific surface area, exhibit high porosity, the small size of pores and small density [453] and their structure is similar to the extracellular matrix (ECM). Natural and engineering materials can be used as a material, including, in particular, collagen, gelatin and chitosan [453]. Scaffolds are fabricated using of non-covalent interactions for spontaneous fabrication of a three-dimensional structure in response to the activity of environmental factors [455]. The ability of peptides and nucleic acids, to self-organisation, is utilised for scaffolds fabrication. Such types of scaffolds were used, e.g., for regeneration of nervous tissue to stop bleeding and repair infatuated myocardia, as well as in medical products for slow release of a medicine [456, 457] and for DNA, where the branched DNA particles are hybridising with each other in the presence of ligases in hydrogel [458]. The scaffold fabrication method employing self-organisable nanofibres is one of few allowing to produce biocomponents with their properties similar to the natural extracellular matrix (ECM), and scaffolds containing hydrogel, made using such technology, employ more advantageous toxicological properties and higher biocompatibility than traditional materials. Conventional hydrogels are particularly useful for three-dimensional placement of cells [459]. Hydrogels used in tissue engineering should have low viscosity before injection and should be gelling fast in the physiological environment of the tissue, and the most important is gelling (sol-gel transition) by cross-linking, which may take place when producing them *in vitro* and *in vivo* during injection. Physical cross-linking is used in particular in the case of poly(N-isopropylacrylamide) (poly(NIPAAM)), which may be used in tissue engineering after introducing acrylic acid (AAc) or PEG [460, 461] or biodegradable polymers, including such as chitosan, gelation, hyaluronic acid and dextran [462–466] to block copolymers, such as poly(ethylene oxide) PEO-PPO-PEO (Pluronic), poly(lactide-co-glycolide) PLGA-PEG-PLGA, PEG-PLLA-PEG, polycaprolactone PCL-PEG-PCL and PEG-PCL-PEG [467–471], and also agarose (a polysaccharide polymer material, extracted from seaweed as one of the two principal components of agar) [459], as thermo-sensitive systems [472], to avoid the use of potentially cytotoxic ultraviolet radiation. Poly(NIPAAM) and block copolymer hydrogels may undergo cross-linking as a consequence of temperature and pH acting at the same time, as in the case of acrylates [473, 474], such as 2-(dimethylamino)ethyl-methacrylate (DMAEMA) or 2-(diethylaminoethyl) methyl methacrylate. Self-assembling peptides hydrogels, including such containing peptide amphiphiles (PAs), can form nanofibres [475, 476] used for three-dimensional formation of tissue cultures [476–480].

Chemical cross-linking hydrogels having convalescent bonds include photo-cross-linkable poly(ethylene glycol)-diacrylate (PEGDA), poly(ethylene glycol)-dimethacrylate (PEGDMA), poly(propylene fumarate) (PPF) and oligo(poly(ethylene glyco) fumarate) (OPF) [481–485], and also natural hydrogels such as dextran, alginate, chitosan and hyaluronic acid synthesised from PEGDA/PEGDMA [486–489] and Michael-type addition reaction [490–492] and Schiff base-cross-linked hydrogels [465, 493–495]. In the case of enzyme-mediated cross-linking [458], transglutaminases (including Factor XIIIa) and horseradish peroxidases (HRP) [459] are used for the catalysis of star-shaped PEG hydrogels [496] and tissue transglutaminase catalysed PEG hydrogels [497]. This also applies tyrosinase, phosphopantetheinyl transferase, lysyl oxidase, plasma amine oxidase, and phosphatases [498]. It made it possible in particular to develop new gels by engrafting tyramine groups into natural and synthetic polymers such as dextran, hyaluronic acid, alginate, cellulose, gelatin, heparin and PEG-PPO [499–505, 509].

Ionic cross-linking hydrogels include calcium-cross-linked alginate [459] and chitosan-polylysine, chitosan-glycerol phosphate salt and chitosan-alginate hydrogels [506–508]. Different synthetic and natural polymers were used for this purpose, including polyethylene glycol (PEG), and copolymers containing PEG [486, 510], hyaluronic acid (HA) [511] after an oxidation reaction through HA-tyramine conjugates [505] and as a result of the formation between HA–SH [492, 512] and Michael addition [491, 513], collagen and gelatin hydrogels mostly cross-linked using glutaraldehyde, genipin or water- soluble carbodiimides [513–515], chitosan [516–519], dextran 192 [520, 521] and alginate [522]. Hydrogels were used for reconstruction of the retina [523], ligament [524], fatty tissue [465], kidneys [525], muscles [526], blood vessels [527, 528], and also heart, neural cells, invertebral discs, bones and gristle [459]. Hydrogels were used to prevent adhesions [529, 530, 531], to promote cellular adhesion [490, 532, 533]. So-called strong hydrogels were developed to improve mechanical properties [534]. The three-dimensional representation is possible of placement of cells with energy in the hydrogel to vascular structures using a laser [535, 536], notably for recording directly the endothelial cell [535].

The general criteria of materials selection for tissue scaffolds relate to the material type and its structure, osteoconductivity ability, mechanical strength, ease of production and manipulation in clinical applications. **Table 1** presents numerous examples of the application of various bioactive and engineering materials, and their respective materials processing and tissue engineering technologies for manufacturing of the hybrid personalised implants and scaffolds [2].

Many layers of different types of cells at present can be three-dimensionally printed to directly create an organ, ensuring the highest currently possible degree of control over the structure of the regenerated tissues [537–542]. The first production system for three-dimensional printing of tissues was delivered only in 2009 based on the NovoGen bioprinting technology [543]. China has invested nearly 0.5 billion USD to establish 10 national institutes for development of organ

Fabrication stage	Investigated materials	Technologies applied	Areas of application
Fabrication of implant bearing structure	Ti, Ti alloys with V or Nb, Mg (possibly with additives of Ca, Zn and Mn), ceramic materials Al_2O_3 and ZrO_2, TiO_2, resorbable bioglass, e.g., Hench bioglass, from the CaO-SiO_2-P_2O_5 and SiO_2-Al_2O_3 system, hydroxyapatites, polymers, composites	Selective laser sintering, sintering, the use of organic matrix, lyophilisation of ceramic slip, rapid pressure assisted densification methods, such as rapid hot pressing/spark plasma sintering (SPS), skeletal casting, plastic working, cutting micro-treatment, computer-aided manufacturing, sol-gel methods, 3D printing, electrospinning, atomic layer deposition, and physical vapour deposition	Filling the losses of long bones, hip and knee joints, facial-skull bone, losses of joint cartilage cells, oesophagus losses and/or blood vessel losses, dental restorations, and skin restorations
Fabrication of porous implant part	Ti, Ti alloys with V or Nb, Mg (possibly with additives of Ca, Zn and Mn), ceramic materials Al_2O_3 and ZrO_2, TiO_2, resorbable bioglass, e.g., Hench bioglass, from the CaO-SiO_2-P_2O_5 I SiO_2-Al_2O_3 system, hydroxyapatites, polymers, composites		
Fabrication of coatings inside pores of porous implant part	A natural protein, synthetic and polysaccharide polymers, including thermosetting, including collagen, fibrin, alginate, silk, hyaluronic acid, chitosan, poly (lactic acid) (PLA), poly(glycolic acid) (PGA), polycaprolactone (PCL) and poly(propylene fumarate) (PPF), polyethylene glycol, Al_2O_3, resorbable bioglass, hydroxy carbonate apatite (HCA), calcium phosphate (CaPs), hydroxyapatite (HA), B-tricalcium phosphate (B-TCP), biphasic calcium phosphate, composites: collagen + hydroxy - apatite CaP-polymer tricalcium phosphate (TCP)-polycaprolactone (PCL), hydroxyapatite HA/poly(ester-urethane)(PU), collagen-bioglass	Infiltration, 3D printing, selective laser sintering, electrospinning, atomic layer deposition, physical vapour deposition, pressing, and sol-gel methods	
Fabrication and application of tissue cultures	Adipocytes, chondrocytes, osteoblasts, fibroblasts and skeletal myocytes	Cell transplantation, matrix implantation, cell implantation with matrix, breeding of xenogeneic and autologous cells and the stage of clinical activities	

Table 1. Examples of the application of various bioactive and engineering materials, and their respective material processing and tissue engineering technologies for manufacturing of the hybrid personalised implants and scaffolds [2].

printing [544], in which the printing of ears, liver and kidneys from living tissues was started in 2013. It is expected that fully functional printed organs can be achieved over the next dozens of years or so [545, 546]. In the meanwhile, there were reports that an Australian team obtained a kidney tissue print with this method for the first time [547]. An American team confirmed in 2014 it is ready to print a heart [548]. A three-dimensional structure is obtained by subsequent formation of layers of living tissues on the gel or sugar matrix substrate [549]. To use the three-dimensional printing technique, a polymer-cell mixture can be dosed, leading to the formation of cell hydrogel [550]. Microfluidics allows for the creation of three-dimensional systems of cells [551]. It is possible to obtain such cell systems from hydrogels by photopolymerisation of polymer solutions [552]. Using SFF techniques, including stereolithography techniques can create scaffolds made of PEG hydrogels also [440]. Vascularisation for organ printing remains a significant challenge in tissue engineering. The development of a vascular network in metabolically functional tissues enables the transport of nutrients and removal of wastes, ensuring maintenance of cells' viability for a long time [553]. Micro-formation techniques, by the three-dimensional printing of templates made of agarose fibres, are used for the creation of a microchannel network inside hydrogel products, including, in particular, inside star poly(ethylene glycol-co-lactide)acrylate (SPELA), methacrylated gelatin (GelMA), poly(ethylene glycol) dimethacrylate (PEGDMA) and poly(ethylene glycol) diacrylate (PEGDA) with different concentrations. In the last several years, the efficient formation of endothelial monolayers within the fabricated channels has also been confirmed [554]. Unfortunately, the progress in vascularisation control is limited, despite immense progress in the production of complicated tissue structures.

6. Contents of the book on regenerative medicine and dentistry

The book on Biomaterials in Regenerative Medicine contains a total of 18 chapters. Selected issues discussed in the previous five sub-chapters were presented in it. The literature review, in this first chapter, deals with technical, biological and medical aspects concerning materials and technologies for medical and dental implantable devices. In the second chapter, the metallic biomaterials and their application in regenerative medicine are presented in detail by the literature review. In addition to these two chapters, all the rest contain the results of their scientific research done by the authors of these chapters. Indeed, the originality of the presented research results constitutes the real value of the book at this moment passed to the readers' hands. The next chapters contain issues about additive technologies and laser manufacturing of materials used in regenerative medicine and mainly in regenerative dentistry. The third chapter is on microporous titanium-based materials located inside the pores by biocompatible thin films to facilitate the implantation and proliferation of living cells in the scaffolds thus produced. In turn, the fourth chapter includes mechanical properties comparison of engineering materials produced by additive and subtractive technologies for dental prosthetic restoration application. It discusses both solid and milled sintered titanium and its alloy, Co-Cr alloy, and sintered ZrO_2. In the fifth and sixth chapters, properties of Co-Cr dental alloys fabricated using an additive, technologies were presented. The progress of the application of 3D printing for tissue regeneration in oral and maxillofacial surgery is presented in chapter seven. In the eighth chapter, the issues of the tissue engineering and use of growth factors in bone regeneration are discussed. Laser processing was analysed in chapter nine concerning silicon for its synthesis as better biomaterials. Prospective of characterisation of the skin models and associated with it measurements and simulation of permeation and diffusion in 3D tissues are presented in the tenth chapter. The eleventh chapter also contains the skin regeneration problems explanation and also a description of the biomaterials for tendon and ligament regeneration. The next few chapters deal with natural and artificial gels of polymeric materials. In the twelfth chapter, authors described the hydrogels for regenerative medicine. Natural rubber latex biomaterials in bone regenerative medicine are presented in the thirteenth chapter. A systematic study of ethylene-vinyl acetate (EVA) in the manufacturing of protector devices for the orofacial system was described in the fourteenth chapter. The next few chapters outline other issues regarding regenerative medicine and tissue engineering. The fifteenth chapter includes tailoring bioengineered scaffolds for regenerative medicine. Biomaterials and stem cells as promising tools in tissue engineering and biomedical applications are the content of the sixteenth chapter. Identification of Fe_3O_4 nanoparticles biomedical purpose by magnetometric methods is the title of the seventeenth chapter. The eighteenth chapter applies to biomaterials for tissue engineering applications in diabetes mellitus.

The editor, publisher and the whole team of authors, by making this book available to the readers, deeply believe that the detailed information collected in the book, largely deriving from own and original research and R&D works pursued by the authors, will be beneficial for the readers to develop their knowledge and harmonise specific information concerning these topics, and will convince the engineers and medicals about the advantages of using the manufacturing and tissue engineering and advanced biomaterials in regenerative medicine and dentistry. On one hand, it makes possible gaining positive effects in the economic manufacturing of biomaterials and implantable devices; on the other hand, it will ameliorate the fate of many people affected by severe diseases. This awareness justifies the involvement in the execution of research and the effort put in describing their results in this book.

Notice

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Author details

Leszek A. Dobrzański

Address all correspondence to: leszek.adam@gmail.com

Science Centre of the Medical and Dental Engineering Centre for Research, Design and Production Asklepios, Gliwice, Poland

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Chapter 2

Up-to-Date Knowledge and Outlooks for the Use of Metallic Biomaterials: Review Paper

Ildiko Peter, Ladislau Matekovits and Mario Rosso

Additional information is available at the end of the chapter

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Abstract

In all cases, when a material has to be used in medical applications, the knowledge of its physical, chemical and biological properties is of fundamental significance, since the direct contact between the biological system and the considered device could generate reactions whose long-term effects must be clearly quantified. The class of materials that exhibits characteristics that allow their use for the considered applications are commonly called *biomaterials*. Patients suffering from different diseases generate a great demand for real therapies, where the use of biomaterials are mandatory. Commonly, metallic biomaterials are used because their structural functions; the high strength and resistance to fracture they can offer, provide reliable performance primarily in the fields of orthopedics and dentistry. In metals, because of their particular structure, plastic deformation takes place easier, inducing good formability in manufacturing. The present paper is not encyclopaedic, but reports in the first part some current literature data and perspectives about the possibility of use different class of metallic materials for medical applications, while the second part recalls some results of the current research in this field carried out by the authors.

Keywords: biomaterials, metallic biomaterials, morphology, biocompatibility, implanted antenna

1. Introduction

1.1. Outline

Generally, materials are playing an important role in our society. Apart other materials, biomaterials became key elements for the human well-being. The beginning of biomaterials goes back to thousands of years (the use of metals in dental implants dates back to 200 A.D.), while after World War II, a real expansion of biomaterials can be considered [1].

Actually, biomaterials can be employed for both short-term or permanently, amplifying or partially or completely replacing some organs, tissues, or other elements of the body with the aim to save or to improve the people's well-being. The numbers of the aged people are quickly increasing that in turn requires a greater call to substitute failed body parts with artificial devices made of biomaterials. Additionally, the ongoing tendency to move in the direction of using short-term implants and/or degradable ones constitutes one of the key progresses in biomaterials research. Further important issues are correlated to the possibility to reduce as much as possible implant related infections by means of infection-resistant biomaterials, which usually involves the application of suitable coatings. The use of any biomaterial is influenced by different features, i.e., composition, mechanical strength, rate of degradation (in case of temporary application), growth rate of the human cells, osteoinduction, osteoconduction, etc. [2].

The present review is not encyclopedic and does not completely cover any features about biomaterials, regenerative medicine (RM), and tissue engineering (TE) aspects, but it shows some essential features belonging to such a wide-ranging subject. Some experimental results here presented deal with the outcome of some of the investigations performed by the authors on the development of metallic biomaterials and their possible use for medical implant development. It also includes the description of a multidisciplinary application where a data transmission system is referred to that has been possible to be developed because of the existence of large dimension implanted device. Nowadays, other similar applications are under focus: controlled drug delivery from swallowed capsules by means of external (to the body) control through a communication system that requires the use of an antenna, explicitly a metallic device, is just one of the many applications that could be nominated.

1.2. Metallic biomaterials

Metallic biomaterials show excellent structural functions, superior than ceramic and polymeric biomaterials and for a long time they have been usually employed to substitute unhealthy natural parts or to repair different organs of the human body. Extension of metal made implants was firstly determined by the request to repair bone and later on their application for orthopedic purpose has been increased together with the short-term applications of pins and screws, followed by the use of permanent implants for total joint substitution. Further evolution involves the use of metals and their alloys for dental applications and recently there is a higher tendency for their use in non-conventional reconstructive surgery of organs and hard tissue. There are only some areas where the use of metallic biomaterials is exploited such as joint prostheses, bone fixation plates, pins and screws, dental implants and materials, ocular, contact and intra-ocular lenses, vascular grafts, urinary and intra-vascular catheters, surgical meshes, and voice prostheses.

Within the different class of biomaterials, firstly, *stainless steel* has been used for medical purpose. This is principally due to their low cost, good corrosion resistance conferred by the presence of Cr, allowing the development of the passive and protective oxide layer. **Table 1** reports the composition of the most important/recommended stainless steels used for the manufacturing of orthopedic implants. ASTM F138 and F139 reveal higher biomedical interest because of a better fatigue strength, higher ductility, and better machinability [3], but the high Ni content determines possible toxicity and allergy [4].

Steels (ASTM)	C	Mn	P	S	Si	Cr	Ni	Mo	N	Cu
F138	0.03	2.0	0.025	0.01	0.75	17.0–19.0	13.0–15.0	2.25–3.0	0.10	0.50
F1314	0.03	4.0–6.0	0.025	0.01	0.75	20.5–23.5	11.5–13.5	2.0–3.0	0.20–0.40	0.50
F1586	0.08	2.0–4.25	0.025	0.01	0.75	19.5–22.0	9.0–11.0	2.0–3.0	0.25–0.50	0.25
F2229	0.08	21–24	0.03	0.01	0.75	19.0–23.0	0.10	0.50–1.50	0.90	0.25

Table 1. Composition (wt%) of some austenitic stainless steels [5].

However, according to some research, e.g., [6], stainless steels can suffer pitting, crevice, corrosion fatigue, stress corrosion cracking, and galvanic corrosion within the human body accelerated by their reduced wear resistance. Additionally, appearance of allergic reaction limits their use as orthopedic joint prosthesis [7, 8]. Release of metallic ions, as corrosion product, in the human body can reduce the lifetime of the implant leading to an additional surgical procedure [9–12]. If high amount of Ni ions is released in the tissues, development of the most common contact allergy [13, 14] and cancer [15, 16] can be favored.

The corrosion resistance of stainless steels can be modified by the (i) different oxygen concentration (generally, low oxygen content contributes to a higher corrosion rate, because the growth of the protective oxide layer is delayed on the surfaces of the metallic implant), (ii) pH value which can be altered from a neutral condition to lower values due to the inflammatory cell secretions, and (iii) presence of aqueous ions level in the surrounding body fluid. If possible, the concentration of the released metal ions has to be as reduced as possible, and it has to be innocuous for the human body during a long service period [17]. The high elastic modulus of stainless steel is considered as one of the highest difficulties leading to the damage of the bone by stress shielding which is directly connected to the failure of the implant.

During the time, *Cobalt-Chromium alloys* have been developed, which reveal some superior properties and some drawbacks relating to their production costs than stainless steels [18, 19].

The alloys belonging to this family show high corrosion resistance attributable to the natural growth of the passive oxide film on the top of the metallic device which is resistant also in the chloride-rich background [20–23].

Generally, two basic types of such alloys are commonly employed:

- Cobalt-Chromium-Molybdenum (CoCrMo) alloy and
- Cobalt-Nickel-Chromium-Molybdenum (CoNiCrMo) alloy.

Table 2 reports the composition of the most important alloys belonging to these classes used for the production of orthopedic implants.

CoCrMo has been used for many years in dental applications and for the manufacturing of artificial joints, while for prosthetic stem productions, for hip and knee joints the alloy containing Ni has been employed [21]. CoCrMo alloy, because of its high corrosion and wear resistance, is used for joint prostheses for the femoral head in combination with an ultra-high molecular weight polyethylene cup.

Alloys (ASTM)	Cr	Mo	Ni	Fe	C	Si	Mn	W	P	S	Other
F15	27–30	5–7	1.0	0.01	0.35 max	1.0	1.0	0.2	0.02	0.01	0.25N 0.3Al 0.01B
F799 (low C)	26–30	5–7	1.0	0.01	0.05	1.0	1.0	-	-	-	0.25N
F799 (high C)	26–30	5–7	1.0	0.01	0.25	1.0	1.0	-	-	-	0.25N
F563	18–22	3–4	15–25	0.01	0.05	0.5	1.0	3.0–4.0	-	0.01	0.50–3.5 Ti
F562	19–21	9–10.5	33–37	0.01	0.25 max	0.15	0.15	-	0.015	0.01	1.0 Ti
F90	19–21	-	9–11	0.01	0.05–0.15	0.40	1.0–2.0	14–16	0. 04	0.03	-
F1058	19–21	6-8	14–16	0.01	0.15	1.2	1.0–2.0	-	0.015	0.015	0.10 Be 39.0-41.0 Co

Table 2. Composition (wt%) of some CoCrMo and Co-Ni alloys [5].

However, Ni and Co ions, when released, are susceptible to induce allergic responses: Ni is carcinogenic and causes a toxicity problem, which can be avoided using an as much as possible low level of Ni.

Actually, *Ti and its alloys* have been received much more attention, even if they have been used since the late 1960s. Due to the fact that Ti is completely inert and resistant to corrosion in any fluids in the human body and tissues, these alloys exhibit the best biocompatibility among metallic biomaterials combined to good fatigue resistance, excellent in vivo corrosion resistance which is acquired by the growth on their surface of the stable passive oxide layer. In addition, showing some properties which are close to the human bones, i.e., strength, density, and relatively low elastic modulus, these alloys began to be extensively employed for joint replacements. Lower elastic moduli than other metallic biomaterial allow obtaining less stress-shielding phenomenon. Generally, Ti and its alloys are used for bone fixation, joint substitution, pacemakers, implants for dental, artificial heart valves, components and stents in rapid blood centrifuges due to their chemical stability and particular high strength [24]. Central position has been made for a commercially *pure Ti* (cp-Ti, ASTM F67), *Ti6Al4V alloy* (ASTM F136) strengthened by alloys obtained by the modification of them and *Ti-based shape memory alloys* (SMA) [25, 26]. Cp-Ti is typically used in dental and spinal surgery, Ti6Al4V for the manufacturing of artificial knee, hip and shoulder joints and for bone fixators, while SMAs are employed as orthodontic equipment and temporary spine and long bones fixations.

According to ISO 5832-2, four grades of cp-Ti are recognized for medical applications. Cp-Ti can contain a minor level of interstitial elements (O, N, and H) affecting the mechanical properties by interstitial solid solution strengthening. Cp-Ti is available in four grades, where (i) grade I corresponds to the lowest O content and yield strength and at the same time to the highest ductility and (ii) grade IV reveals the highest O content and the highest strength combined with the lowest ductility. **Table 3** reports the grades of different cp-Ti with the maximum limits of the interstitial elements and some mechanical properties. Due to the capacity for stimulating fast osseointegration, coming from the incorporation of OH^- ions inside the passive TiO_2 layer and due to the reaction of the hydroxylated surface area with the inorganic phase constituents (prevalently $Ca^{2+}$and $(PO_4)^{3-}$) present in the bone, cp-Ti is principally used for endosseous dental implants manufacturing.

Ti6Al4V alloy reveals outstanding mechanical strength, high biocompatibility and consents good implant-bone integration. However, over the years, some weaknesses during the use of such alloy have been noticed: (i) it has higher elastic modulus than bone, producing stress-shielding effect, (ii) it shows lower wear resistance too, and (iii) the release of Al and/or V can determine permanent diseases, i.e., osteomalacia and Alzheimer's disease [27].

The research community has dedicated high attention to these problems, and the trend is to develop new Ti alloys, by alloying the basic alloy and reducing as much as possible or even totally removing the release of any toxic elements. In this scenario, alternatives alloy with $(\alpha + \beta)$ structure, without V have been obtained, i.e., Ti6Al7Nb, Ti5Al2.5Fe, Ti6Al6Nb1Ta, and Ti5Al3Mo4Zr, which at the beginning have been developed for airspace application. These alloys reveal higher corrosion resistance, fatigue properties than other biomaterials, principally governed by the size and the distribution of the α and β phases [28]. Such structure can be obtained during mechanically working till to obtain the preferred form followed by fast cooling at room temperature and annealing for recrystallization within the $(\alpha + \beta)$ two-phase field and determine a fatigue strength more than 650 MPa.

β-Ti and near β-Ti alloys, i.e., Ti12Mo6Zr-2Fe, 35.5Nb7.3Zr5.7Ta, and Ti13Nb13Zr, introduced in the 1990s and their continuous improvement have been one of the leading topics of orthopedic materials research, because they contain superior amount of β-stabilizing elements and they are characterized by a considerably lower elastic modulus than other biometals (44–51 GPa for water-quenched and cold-worked Ti-13Nb-13Zr alloy compared to 110 GPa for Ti6Al4V). Additionally, good formability, high hardenability, excellent corrosion resistance, and better notch sensitivity (measure of how sensitive a material to notches or geometric discontinuities is) than the $(\alpha + \beta)$ Ti alloys characterize such alloys. In order to amplify the wear resistance, surface hardening can be carried out by aging in an oxygen-rich environment

Ti grade	O	N	H	σ_{yield} (MPa)	$\sigma_{ultimate}$ (MPa)	%E
1	0.18	0.03	0.015	170	240	24
2	0.25	0.03	0.015	275	345	20
3	0.35	0.05	0.015	380	450	18
4	0.40	0.05	0.015	483	550	15

Table 3. Maximum limits of the interstitial elements and mechanical properties of different cp-Ti grades.

determining the growth of a hard oxide film on the surface with an interstitial solid solution strengthening of the subsurface section atmosphere [29].

A class of special Ti alloys, developed in Japan, with exclusive physical-mechanical properties and large range of possibilities in medical applications are Gum alloys, belonging to the β-type of Ti alloys, fundamentally expressed as Ti (Ta, Nb, and V) + (Zr, Hf, and O). These alloys have excellent mechanical behavior at room temperature: an ultra-low Young's modulus (60–70 GPa) and a non-linear elastic behavior, an extended elastic limit, ultra-high strength (>1 GPa), superplastic-like deformability, Invar-like thermal expansion, and Elinvar-like thermal dependence of the elastic modulus making available several prospects for their application [30]. Such alloy, with no hazardous elements, combines extremely low elastic modulus with extremely high strength and can be considered a perfect candidate for many medical implants.

The capacity to return to the initial memorized shape varying the temperature is the most important features of *shape memory alloys*. Such a particular characteristic can be exploited in critical medical application, when recovering the original shape after large deformations induced by mechanical load and for conserving the deformed shape up to the heat-induced recovery of the original shape has primary importance [31]. Generally, in orthopedic, dental, and cardiovascular uses NiTi alloy (Nitinol) is employed because its good corrosion resistance and pseudoelastic property (reversible elastic response to an applied stress). However, the study [32] reports that at temperatures equal to the human body the formation of a passive layer on NiTi is not as much protective than the passive layer on Ti6Al4V. Additionally, there are some limitations too in the widespread use of such alloy because even if some studies have revealed that NiTi alloy is biocompatible [31, 33, 34], the possible release of Ni ions represents a serious apprehension [13, 15] because Ni is highly allergenic element, and it can induce intense inflammatory reactions.

Zr, Ta, and Nb have been employed as constituent elements of Ti alloys for medical applications because of their good biocompatibility and high corrosion resistance. Zr belongs to the same group as Ti and exhibits similar properties [35]. Recently, Zr-Nb [36, 37] and Zr-Mo [38] have been developed. Ta and Nb are non-toxic elements, and they exhibit very similar physical and chemical properties. Ta exhibits excellent chemical stability and good biocompatibility similar to that of Ti:Ta has been employed in dental and orthopedic applications such as radiographic bone markers, vascular clips, and as a material for cranial defect repair and nerve repair since the 1940s [39, 40]. In particular, porous Ta has been developed for bone in-growth applications, i.e., hip and knee arthroplasty, spinal surgery, and bone graft substitutes [41, 42]. Introduction of Ta in TiNi shape memory alloy determines a low incidence of artefacts, according to [43, 44], the blood compatibility of Ta is higher than that of other metals.

Recently, among other research, *biodegradable metals and their alloys* have attracted high interest, because of their possibility of degradation in biological surroundings. The main benefit of this class of materials is related to the fact that after the tissue has appropriately restored and they are no longer useful, the removal of follow-up surgery is avoided allowing higher protection since physical irritation and chronic inflammatory local reactions are totally excluded [45–47].

Fe, Mg, and Zn are all vital nutritional elements for a healthy body and generally reveal excellent biocompatibility in the human body, with no any sign of local or systemic toxicity biodegradable materials than polymers for load-bearing applications. Both pure Fe and pure Mg have been reported to possess excellent biocompatibility in the human body and show no signs of local or systemic toxicity [45, 48, 49].

Mg and its alloys (i.e., (AZ91, WE43, AM50, and LAE442) can be considered as favorable alloys for medical applications, and they have already been positively verified *in vivo* and in clinical studies and it has been reported that development of new bone is facilitated [50–52], when they are implanted as bone fixtures. The elastic modulus of Mg (41–45 GPa) is closer to that of natural bone (3–20 GPa). However, the mechanical properties of such alloys, i.e., strength and the elongation to fracture are not always acceptable which combined to the development of significant quantities of hydrogen limits their widespread use. Some studies [53–55] have reported as alternative solution the use of Fe-based alloys. However, the implants realized using such alloys reveal some reactions like those developed in long-term uses which is predominantly due to the low-degradation rate of pure Fe in biological atmosphere [56].

In Refs. [53, 54] the authors have developed Fe35Mn alloy with a higher degradation rate compared to the pure Fe; however, compared to Mg-based alloys, the interested value is still at least one order of magnitude inferior.

Even with the significant evolution carried out over the time on the implants made of by biodegradable alloys, many tasks are still unexplained.

1.3. Biomaterials in tissue engineering and regenerative medicine

Current evolutions of biomaterials and the constantly increasing demand for new technologies have transformed the field of TE and RM too. In such areas, biomaterials have received more and more attention and can be placed in pole position for repairing tissue functions by joining materials design and engineering with cell therapy. RM is considered new frontline of medical research; however, the idea of generating synthetic tissues is not so recent, since it goes back to 1938 [57]. Biomaterials can offer physical sustain for engineered tissues and can control and guide the cells. RM involves the replacement or restoration of human cells, tissue or organs, to repair or create typical function [58, 59].

Biomaterials engineering involves production, processing, characterization, and knowledge of innovative materials, including metallic ones. The most important limitations of RM is related to the generally health-care programs: the inclination to substitute conservative methodologies with new therapies is not so immediate. A large use of RM would be possible when a deep knowledge related to all connecting aspects (positive and negative outcomes) will be absolutely solved [60]. For the use on large scale RM, the ideas developed at laboratory level have to be inserted and totally transformed into widespread commercial products. In the past century, achievements in medicine have included different approaches and fundamentally, three different lines can be really able to follow the objective of RM: (i) cell-based therapy (meaning of introducing new and healthy cells in pathologic tissues), (ii) use of both biological or synthetic materials (use of cells and extra cellular matrix providing structural and functional support), and (iii) implantation of scaffolds seeded with cells (mixture of the earlier mentioned two possibilities) [61].

Generally, metallic ions have a significant role for some day-to-day living biological processes, being essential for many biochemical reactions: i.e. K, Na, Ca, Mg. Ca^{2+} ions level governs the intra- and inter-cellular communications, blood coagulation and muscle contraction, Mg^{2+} ions support photosynthesis, the electron transfer routes are generally based on Fe proteins, transport of oxygen requires Fe and Cu containing proteins, Zn has the main role in regulation of DNA transcription are only some cases which highlight the importance of them [62–66].

In addition, metallic ions have interesting capacity and can be exploited as therapeutic agents in tissue engineering. There are a large number of metallic ions which are vital cofactors of enzymes (Co, Cu, Fe, Mn, Zn, Ag, Sr, V, and Ga), and their specific properties can be correlated to their use for therapeutic purpose. The geometry and valence of metal ions, their hydrolytic and redox activity, Lewis acidity, radiochemical properties directly involve fast kinetics, higher affinity to interact with other ions with high flexibility to be inserted in engineered biomaterials allowing the modification/revision of cellular functions and their metabolism. Actually, there is a continuous growth in medical field of the use of metal ions in RM and tissue engineering, with a special attention concerned to their therapeutic properties. However, the possible toxicity of metal ions in case of their eventually local release has to be carefully considered, when exploiting them [67–70].

2. Real case study

Some fundamental aspects related to metallic biomaterials and their use in RM and TE are integrated with some experimental results obtained by the authors [71–75] during the years spent studying the development and characterization of metallic materials for medical purpose. In particular, some results, (1) prevalently related to the corrosion resistance, which can be directly associated with their biocompatibility of some (i) Ti-enriched Co-based traditional alloys to be submitted for dental application and (ii) TiNb alloys for load-bearing implant production will be reminded here; (2) the third line (iii) involves the possibility of using an implanted two-element antenna array placed on a metallic cylinder (metal made implant) embedded in a polymer dielectric that acts as the substrate between the ground plane and radiators with the purpose to use it for in-body communications.

2.1. Some details and the corrosion resistance of the experimentally prepared biometals

Cold crucible levitation melting technique with induction heating system has been used for the metallic alloys manufacturing, which guarantee high purity melts, important features for materials used for surgical implants. Enhancement with Ti has been performed in the case of the Co-based basic alloy. **Table 4** reports the chemical compositions of the alloys for dentistry, while **Table 5** reports the composition of the alloy used for load-bearing implant production.

Alloys	Chemical composition (wt%)					
	Cr	Mo	Si	Ti	Other	Co
CoCrMoTi4	26.5	6.0	1.0	4.0	1.5	bal.
CoCrMoTi6	28.0	4.5	1.0	6.0	0.5	bal.

Table 4. Chemical composition of the experimentally developed alloys.

Alloy	Ti	Nb	Ta	Zr	O
TiNb	71.4	24	1	3	0.6

Table 5. Chemical composition (at %) of the Ti-Nb alloy.

Wirobond®280 (Co60.9, Cr25, Mo4.8, W6.2, Ga2.9) and Ti6Al4V have been considered as reference material. The microstructures of the alloys investigated are reported in **Figure 1**, where a relatively homogeneous structure has been observed. Major details are reported in Refs. [71–73].

Following some structural and microstructural characterization (**Figure 1** reports the general morphology of the investigated alloys) combined with some mechanical properties evaluation, which can be found in [71–73], some words are spent about the corrosion behavior, verified by static immersion test, of the metallic alloys prepared, because such line is directly associated to the biocompatibility behavior of the metal alloys. The test has been carried out according to the route specified in the Standard ISO 10271/2011 at 37°C (±1°C). According to the standard, immersion of the samples has been realized in acid solution (7.5 ml lactic acid, 5.85 g NaCl, 300 ml H_2O di grade 2 purity, and 700 ml H_2O) simulating the biological environment. The pH value has been corrected to arrive to the neutral situation. The samples have been monitored after the permanence in the acid solution for 28 days. As a reference solution, an acid solution maintained in the same condition without any metallic alloy inside has been used. The sample surfaces, following corrosion test, have been investigated by scanning electron microscopy

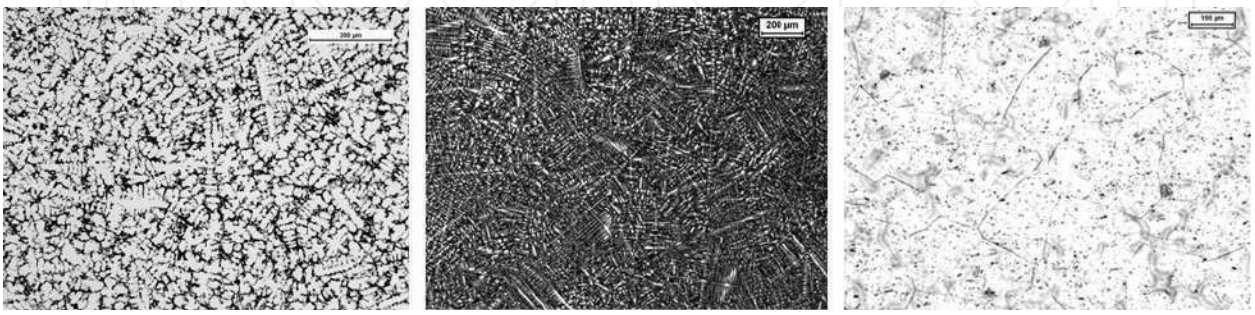


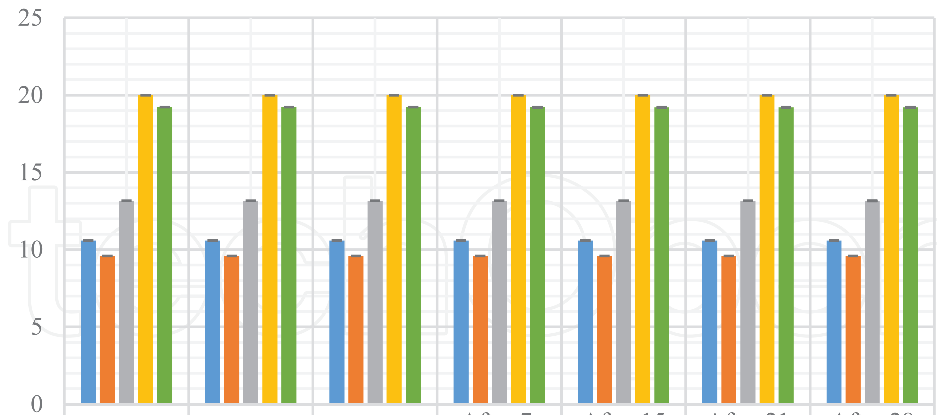
Figure 1. Optical micrographs of the investigated alloys.

analysis. The hydrogen ions measurements in the solution with the metallic alloys inside and the weight loss measurements are directly correlated to damage arisen and indicate the progress of the corrosion which involves the metallic alloys. After a regular time, the weights of the metallic samples have been measured, and the pH values have been monitored. Comparison of the results obtained for the solution with and with no metallic alloys inside has been carried out. The investigated alloys do not present any significant weight alteration after 28 days and no significant release of metal ions was observed (**Figure 2**). The same results have been confirmed by the pH value measurements (**Figure 3**). When the dissolution of the passive film developed on the surface of the alloy has a very low rate, the layer is able to protect the alloy. The release of metal ions is lower than 0.1% within the week, and this is below the threshold level indicated in the Standard (according to the Standard ISO 10271/2011 the allowed deviation from the original state could be only 1%).

Microstructural observation and compositional analysis after corrosion test confirm the analytical results, since on the surface of the alloys extracted from the physiological solution, no evidence of corrosion product has been found. The experimental alloys are used for some crown (**Figure 4** left) and load bearing implant (**Figure 4** right) manufacturing. The research in this direction is ongoing to further investigate additional performance of the alloys as much as possible in functional environment.

2.2. Some details about the use of the implant itself as ground plane for implanted antenna

Biotelemetry, increasingly exploited in the recent healthcare systems, involves the application of telemetry in medicine and health care, allowing remote checking of various vital functions



	Initial	After 24 h	After 48 h	After 7 days	After 15 days	After 21 days	After 28 days
CoCrMo6Ti6	10.588	10.588	10.588	10.588	10.588	10.588	10.588
CoCrMo6Ti4	9.5857	9.5857	9.5856	9.5855	9.585	9.585	9.5846
TiNb	13.1669	13.1638	13.16	13.16	13.16	13.16	13.1581
Ti6Al4V	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Wirobond	19.2316	19.2316	19.2316	19.2205	19.2187	19.2185	19.2181

CoCrMo6Ti6 CoCrMo6Ti4 TiNb Ti6Al4V Wirobond

Figure 2. Weight loss measurement evaluation results during 28 days of investigation.

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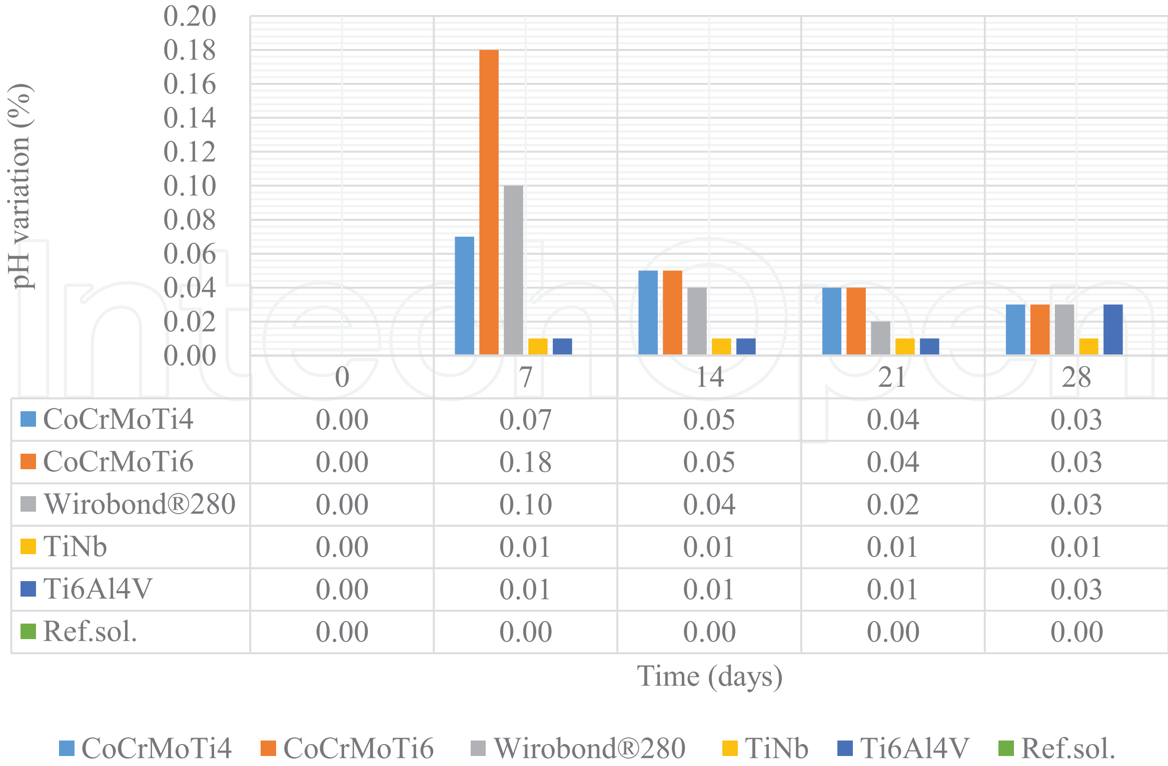

	0	7	14	21	28
CoCrMoTi4	0.00	0.07	0.05	0.04	0.03
CoCrMoTi6	0.00	0.18	0.05	0.04	0.03
Wirobond®280	0.00	0.10	0.04	0.02	0.03
TiNb	0.00	0.01	0.01	0.01	0.01
Ti6Al4V	0.00	0.01	0.01	0.01	0.03
Ref.sol.	0.00	0.00	0.00	0.00	0.00

Figure 3. Variation of the pH value during 28 days of investigation.

(i.e., temperature, blood pressure, and cardiac beat) in patients. The use of such technologies, firstly, can considerably decrease hospitalization time and then allows the constant collection of the patient's biological data. When the information has to be obtained from inside the body, it should be firstly revealed by a dedicated sensor and in a second step to be transmitted to an external (to the body) receiver. This operation requires the use of antennas that are made of conductive materials, i.e., metal. Such devices are in a direct contact with the different tissues, so special attention to their biocompatibility has to be paid. On the other hand, to increase the efficiency of the transmission, directive antennas are to be used, which implicitly means a large dimension. Such space is not always available inside the body. An alternative solution consists of using low-profile printed antennas, but they require the use of a large ground

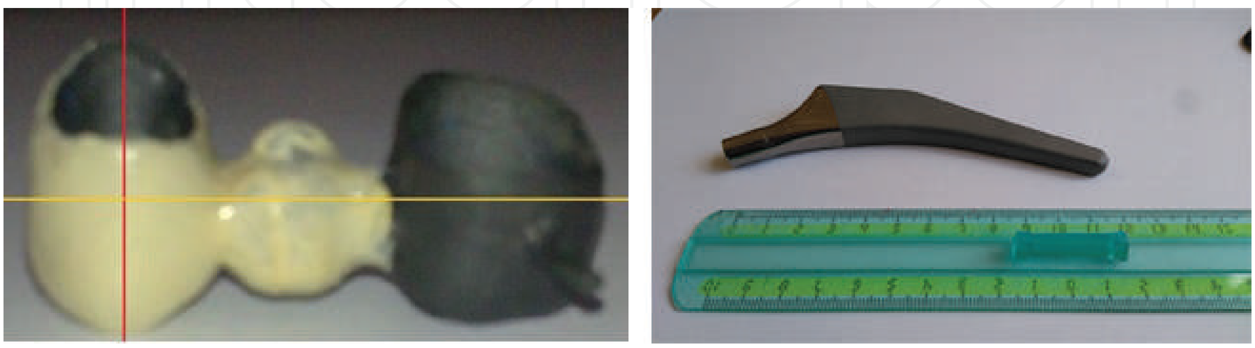

Figure 4. Photographs of the produced elements for medial application.

plane. A recently proposed solution by the author consists of the use of the implant itself as ground plane for the antenna. The rectangular radiator is made of a similar metal as the implant, i.e., biocompatible, and it is conformal to the cylindrical bone structure. The reported results in [74] refer to the case when a piece of bone is fully substituted by a biometallic cylinder. To maintain the distance between the ground plane and radiator constant, a biocompatible polymer, namely polydimethylsiloxane (PDMS), has been considered both as dielectric and superstrate. The geometry is presented in **Figure 5**.

The thickness of each of the two PDMS layers is of h_{PDMS} = 2 mm with respect to the radius of the overall geometry of 106 mm (similar to an adult arm). Details on the dielectric properties of the tissues and materials involved in the numerical experiment can be found in [74].

As a result, a wide beam, approximately 100° half power beam width (HPBW) radiation pattern in the orthogonal to the bone axis plane has been obtained. Such characteristics allow a significant freedom to the patient to move without losing the communication link between the implanted antenna and fixed external base station.

However, considering the low efficiency, basically due to the lossy medium, and of the deep positioning of the antenna (with respect to subcutaneous solutions), and exploiting the low profile configuration, as a second step two radiators have been inserted, aiming to realize a two-element array with scanning possibility. It should be mentioned that this solution does not require additional space, since the second radiator is embedded in the already present

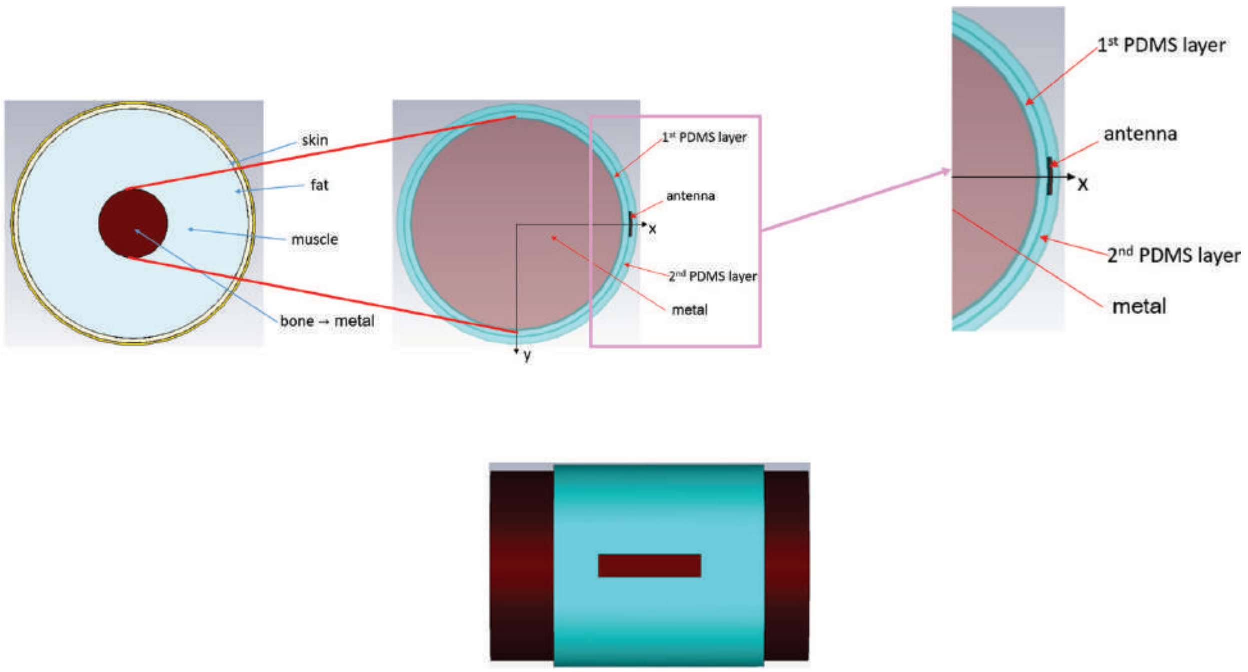

Figure 5. Numerical adult leg model: the bone is substituted by an equal diameter cylinder (left); the conformal antenna is positioned on a constant thickness PDMS dielectric layer of ring shape around the biometallic implant (central), side view of the structure (with removed tissues and outer PDMS layer for a better rendering (right).

PDMS layer. Because of the available space, different configurations have been tested to reduce the mutual coupling between the two radiators. The parametric study allows quantifying the coupling for different angular distances between the two radiators in the presence and absence of the coupling reduction elements. In all cases, metallic parts made of the same biometal have been considered. Due to the low coupling a more directive, i.e., higher gain, system can be built. The higher gain associated to the possibility to scan the beam further increases the freedom of movement of the patient the system is implanted in. All these features could be obtained at a very low extra space demand, basically due to the exploitation of the metallic implant as ground plane of the planar antennas.

From the manufacturing point of view, the proposed solution, i.e., antenna and coupling reduction structure, can be implemented on the biometallic cylinder before it is implanted. Moreover, the metallic cylinder could also incorporate the necessary electronics, sensors, beam forming network, etc. and power supply (batteries).

Similar solution using two dipole antennas has also been discussed in Ref. [75] where conical implant has been considered. The presence of the bone surrounding the implant eliminates the use of any additional materials, i.e., the PDMS layers, in the previous case. In particular, two orthogonal dipoles in turn-style like configuration have been considered. This solution allows to generate a circularly polarized radiated field, further increasing the freedom of movement of the patients.

3. Conclusions

The aim of this chapter was twofold. The first section was dedicated to offering a short outlook and to demonstrating on how metals and their alloys can be used for medical purpose focusing on their role and their influence on the surrounding body environment. The chapter has illustrated some significant features which are appropriate to such a widespread topic. Secondly, some experimental results achieved by the authors over time and illustrated here were proposed to partially support the theoretical line by providing a real case study.

In particular, some results about the biocompatibility of Ti enriched Co-based traditional alloys and TiNb alloy for medical implant production and the possibility of using an implanted two-element antenna array placed on a metal made implant inserted in a polymer dielectric acting as substrate among the ground plane, and radiators with the purpose to use it for in-body communications were highlighted.

There is a continuous need to obtain a deep understanding about the roles and the effect of the metallic ions in body environment. The interdisciplinary character of such research was pointed out with the aim to encourage the teamwork between material scientists, electromagnetic engineers, biologist, tissue engineers, and biomedical and medical researchers to develop new biomaterials and to acquire sufficient data about biological processes as a function of foreign biomaterial introduced in the human body.

Author details

Ildiko Peter[1]*, Ladislau Matekovits[2] and Mario Rosso[1]

*Address all correspondence to: ildiko.peter@polito.it

1 Department of Applied Science and Technology, Politecnico di Torino, Torino, Italy

2 Department of Electronics and Telecommunications, Politecnico di Torino, Torino, Italy

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Chapter 3

Microporous Titanium-Based Materials Coated by Biocompatible Thin Films

Anna D. Dobrzańska-Danikiewicz,
Leszek A. Dobrzański, Marek Szindler,
Lech B. Dobrzański, Anna Achtelik-Franczak and
Eugeniusz Hajduczek

Additional information is available at the end of the chapter

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Abstract

This chapter presents the outcomes of numerous own works concerning constructional solutions and fabrication technologies of a new generation of custom, original, hybrid, microporous high-strength engineering and biological materials with microporous rigid titanium and Ti6Al4V alloy skeletons manufactured by Selective Laser Sintering (SLS), whose pores are filled with living cells. The so constructed and fabricated implants, in the connection zone with bone stumps, contain a porous zone, with surface treatment inside pores, enabling the living tissues to grow into. As the adhesion and growth of living cells are dependent on the type and characteristic of the substrate it is necessary to create the most advantageous proliferation conditions of living cells inside the pores of a microporous skeleton made of titanium and Ti6Al4V alloy. In order to improve the proliferation conditions of cells ensured by a fully compatible substrate, internal coatings with TiO_2, Al_2O_3 oxides and $Ca_{10}(PO_4)_6(OH)_2$ hydroxyapatite of the surface of pores of a microporous skeleton made of titanium and Ti6Al4V alloy with SLS was used. Two technologies have been chosen for the deposition of thin coatings onto the internal surfaces of pores: Atomic Layer Deposition (ALD) and the sol-gel of deep coating from the liquid phase.

Keywords: implant-scaffold, scaffold, engineering biological composite, titanium, SLS, thin film, ALD, dip coating

1. The basis of biological interaction of living cells with a substrate made of metallic micro-skeletons manufactured by selective laser sintering and coated inside pores using atomic layer deposition or the sol-gel methods

The continuity of tissues requiring tissue regeneration in order to restore their normal condition is disrupted as a result of bodily injuries related to numerous accidents, most often work accidents, traffic accidents and sports accidents, as well as due to surgical interventions resulting from the employed therapeutic methods of treating numerous disorders, most often cancerous diseases or removal of inflammatory conditions [1]. One of the most significant and costly problems of modern medicine is the necessity to replace or supplement organs or tissues to prevent the biological and social degradation of patients and to restore their living functions, either normal functions or such acceptably similar to normal, resulting from a growing number of cases of organ or tissue loss or damage in the human population due to post-injury or post-resection losses as well as those originating from the operative treatment of cancerous tumours or inflammation processes and as a result of other disorders, and also work, traffic and sports accidents. The most widespread cases are caused by a strong development of civilisational diseases, including cancer, and the incidence rate of malignant cancers has been regularly rising. The number of traffic accident victims has been growing substantially, as well [2]. One of the fundamental tasks globally is to improve the society's condition of health, medical care and health safety. The idea is to overcome problems which occur more and more often and to protect against serious health risks, especially such as civilisational diseases, pandemics and bioterrorism and to support research, particularly research into the development of modern technologies, serving to advance medicine and healthcare, most of all to replace the lost tissues and organs by technical means, to ensure more complete prophylactics of diseases and safe treatment of patients, which are one of the important indicators of economic welfare. Bone reconstruction, for example, of legs and hands and in the craniofacial area, as well as skin and other soft tissue reconstruction, and also the reconstruction of oesophagus and blood vessels, are often required due to the consequences of civilisational diseases and accidents, including malignant cancers. Patients' healthcare expectations are also growing, and economic aspects at the global scale call for the efficient elimination of disabilities, in particular motoric disabilities, and the restoration of the previously handicapped persons to physical fitness and usually most often to full, or at least partial, professional activity, which considerably lessens pressure on the diminishing resources of social insurance funds. It is vital to reduce waiting times for treatment, to lower prices and to improve availability of medical products or services and therapy, to reduce the risk of treatment failure, in particular by tailor-made personalised medical products according to a patient's individual anatomical features, and ultimately to reduce therapy discomfort for patients and their family.

The development of regenerative medicine started nearly a quarter of century ago along with the works [3], consisting of treatment by replacing old and sick cells with young cells using tissue engineering methods and cell-based therapies or gene therapy and creating numerous new opportunities in counteracting diseases and their consequences [4–8]. On the other hand, tissue engineering – introduced somewhat earlier [9] – consists of the development of biological substitutes for restoration, maintenance or improvement of functions of tissues or entire organs [10, 11], involving the construction and fabrication of scaffolds maintaining the developing tissues and involving the production of a replacement tissue for clinical use [12] as a substitute of damaged tissues or entire organs [13, 14], capable of restoring, maintaining or improving the functions of particular tissues or organs [10]. It is obviously a continued endeavour to develop an engineering material with its properties corresponding to the tool being replaced, supplemented or aided, which does not cause an immunological response of the immunity system and expediting wound healing and not causing implant rejection. The advancement of tissue engineering methods poses further challenges for biomaterials which should not only be fully compatible, but when used for three-dimensional scaffolds, should ensure conditions for cellular cultures, taking into account the possibility of controlled growth, division and differentiation of different types of cells and the impact of various environmental factors on their living functions, and also for transporting medicines in a patient's organism.

Among the biocompatible materials currently and widely used in many branches of industry are titanium and its alloys. These materials are characterised by excellent corrosion resistance in the majority of aggressive environments. Titanium has two allotrope types: Tiα and Tiβ. The α allotrope type endures to the temperature of 882°C and crystallises in a hexagonal structure with a compact lattice (A3). The β allotrope type endures to the temperature of 882–1068°C being a melting point and it crystallises in a regular structure with a centred spatial lattice (A2) [15]. Titanium alloys are classified as single-phase α and β, double-phase $\alpha + \beta$ and pseudo-α and pseudo-β. Double-phase $\alpha + \beta$ alloys are the most popular, widely used group of titanium alloys with good strength and plastic properties. This group includes the most popular Ti6Al4V titanium alloy. Titanium and titanium alloys, conventionally manufactured by casting and plastic treatment [16], are used in the arms, chemical, automotive, aviation, power and transport sector, as well as in architecture and sports [17–20]. Pristine titanium and its alloys, independent of the wide engineering application, are often used in medicine in order to replace damaged tissues. From many years, these materials have been used for endoprosthesis of hip-joints and knee-joints, bone plates, screws for fracture repair and heart valve prostheses [21–24]. Moreover, artificial heart is currently developed using these materials [25]. Recently, for medical applications, materials sintered from powders of pristine titanium, Ti6Al4V and Ti6Al7Nb are also applied [21–25]. **Table 1** shows comparative analysis of these materials.

A structure of the extracellular matrix (ECM) occurring in living organisms, and acting as a natural scaffold of cells [26], can be imitated by biomaterials which, for this reason, can find their application as a substrate for the controlled breeding of living cells. Capable of growth, division and differentiation are such living cells only, which are attached to a substrate and have undergone adsorption on a substrate surface. In natural conditions, this is possible owing to the presence of the extracellular matrix. The coincidence of a metallic substrate with living cells is a very vital aspect. It is also vital to determine the potential favourable effect of indirect layers – in the form of thin coatings deposited onto the inner surfaces of pores of a metallic

No.	Evaluation criteria	Ti	Ti6Al4V	Ti6Al7Nb
1	The current use of this material in medicine	High	Very high	Minor
2	Powder granulation, μm	10–45	15–45	0–100
3	Density, g/cm^3	4.51	4.43	4.52
4	Melting point, °C	1600–1660	1660	1520–1580
5	Price, €/kg (state for 2014 year)	400	500	250
6	Availability	High	High	Low
7	Powder application in SLS/SLM process	Yes	Yes	No

Table 1. Comparative heuristic analysis of pristine titanium, Ti6Al4V and Ti6Al7N powders.

skeleton made of titanium and its alloys produced by SLS – on the potential adhesion and proliferation of living cells. Not all the factors are known, which are decisive for the influence of a substrate made of engineering materials on the attachment, division and growth of living cells, despite the fact that intensive research has been conducted in this field. A material's specificity is one of the most essential factors crucial for the breeding or growth of cells on the surface of engineering materials [27, 28]. The domains ensuring the adhesion of cells to a substrate are very important in interactions between living organisms and engineering materials in cultures of living stem cells and in implantology. The one which is best recognised is arginyl glycyl aspartic acid (RGD), which is a tripeptide composed of L-arginine, glycine, and L-aspartic acid, as well as other proteins, including integrins, cadherins, selectins and immunoglobulin-like proteins [29–37]. After placing an implant in an organism, its surface is covered with a thin layer of water within a few seconds, and then, within a few seconds to several hours, with a layer of specific proteins [38] from those contained in physiological fluids [39]. A weakly vascularised, fibrous layer of cells [29, 40] is growing on such cells within several minutes to several days, and finally a cytoskeleton of cells is reorganised, leading notably to the flattening of cells [41]. Surface wettability influences the ability of adhesion proteins to attach to the substrate, and their affinity to the material surface has influence on the structure and composition of a layer of proteins [38]. The free enthalpy of surface and its wettability influence the growth of cells, but do not have an effect on their shape and orientation [42–44]. The adhesion domains placed on the surface of engineering biomaterials influence the behaviour of cells due to an effect on the functioning of integrins [29]. Cells' material attachability depends on proteins' substrate adhesion [29–35, 37–39, 42, 45]. An excessively hydrophilic and hydrophobic character of the surface with the wetting angle of over 80 or below 15° [46] is sometimes unfavourable for the growth of cells, although surface hydrophobicity may, in the initial phase, support cells' adhesion, when hydrophilicity may support their division and multiplication [47]. In general, cells are preferentially attaching, dividing and growing on hydrophilic surfaces of a material, whilst their ability of adhesion to a substrate material is diminishing on hydrophobic surfaces [38, 39, 47–53].

As flexibility of different types of cells varies [54–66], their morphology and living functions depend on the stiffness of the substrate on which they are grown [54–69]. Usually cells' differentiation ability increases due to increased material stiffness, although exceptions to this rule exist [55, 57, 58, 60–66]. Because cells are interacting with the substrate surface [55, 57, 58, 60–66, 70], the cells growing on a stiff substrate exhibit greater rigidity [64, 67, 71], a more organised cellular cytoskeleton [55, 59, 63–67] and greater flattening [55, 57, 60, 63–66, 70, 72] than those growing on a more elastic substrate. Cells, especially fibroblasts and cells of smooth muscles, exhibit mechanotaxis (durotaxis), moving towards a substrate with greater rigidity [57, 62, 64–66, 72, 73]. Increased substrate rigidity is decisive for the reduced ability of cells to migrate [65], and different types of cells react differently to differentiated rigidity of a substrate made of engineering materials [54]. A material's surface topography influences cells' adhesion ability [74, 75], and they show an ability of adaptation to a material's surface specificity [53, 76–79]. Surface topography is dictating proteins' adhesion and creation of bonds, which is essential for material biocompatibility, influencing also morphology, spatial orientation, division and differentiation of cells [38, 80]. Cells' behaviour is also influenced by surface texture and smoothness [2, 38, 74, 76, 77, 81–84]. Cell adhesion is more difficult on less developed surfaces with higher smoothness [85], whereas the division of osteoblasts is faster on surfaces with smaller smoothness [86–88], opposite to fibroblasts which are proliferating fastest on smoother surfaces [56, 89–92]. The flattening of cells is decreasing as the smoothness of the substrate surface is deteriorating [86, 88, 91, 92].

Additive technologies [93–95] can be employed, in particular, for producing different implants, including dental implants and bridges, individualised implants of the upper jaw bone, hip joint and skull fragments using suitable biomaterials. An exceptional usefulness of additive technologies of producing solid and microporous materials in medicine and dentistry has been confirmed by comparing powder metallurgy technologies, casting technologies, metallic foam manufacturing technologies and additive manufacturing technologies with procedural benchmarking techniques [96, 97] using a universal scale of relative states for comparative evaluation [96–99]. Considering the additive technologies applied most widely in industry, only few have found their application in prosthetics, especially in prosthodontics, that is, electron beam melting (EBM) [100–105], and also 3D printing for production of indirect models, although selective laser sintering/selective laser melting offers broadest opportunities (SLS/SLM) [100, 106–125]. The sintering/melting of grains takes place by remelting the particles of a new powder on the surface with the existing piece of an item being constituted by a laser beam moving in a programmed fashion in line with the pre-defined geometrical characteristics of a metal element being produced. SLS/SLM technologies are so attractive due to the opportunities offered by 3D design with the use of CAD methods and due to the related overall control over the materials fabricated, both, in terms of the structure, sizes and repeatability of geometric features. Microskeletons with controlled sizes and shapes of pores can also be manufactured.

A microporous element manufactured by SLS can be further worked and combined with other materials, for example, by infiltration or internal treatment of pores' surface in an appropriately chosen technological process [117–121, 126–128]. Titanium and titanium alloys from Al, Nb and Ta [1, 2, 15, 26, 127–138], well tolerated by a human organism, have been long used in medicine and dentistry for prosthetic and implantological purposes, also fabricated by SLS. Titanium matrix materials do not cause allergic reactions and are stainless, feature high strength and hardness and also thermal conductivity several times lower than traditional prosthetic materials [139]. Titanium is a very thrombogenic material [140], and biocompatibility, especially thrombocompatibility [141] of this material can be enhanced by introducing alloy elements. Pores are dimensionally adapted to be filled by the reconstructed cells and their migration and also neovascularisation [142] for preventing blood clots [143]. Their section cannot be too small to prevent their sealing [144]. A porous structure of scaffolds should secure the diffusion of nutrients and metabolism products. Permanently fixated scaffolds do not ensure scaffold removal as is the case with scaffolds removable during regeneration in the natural condition [143–145]. Other metallic materials can also be utilised for this purpose, for example, polymer materials [40, 81, 146–153] or polymer matrix composite materials with a fraction of metals or ceramic particles [81, 150]. Unlike metals and their alloys, polymer materials can be not only biocompatible, but also biodegradable and bioresorbable [29, 46, 154, 155], and also in some cases osteoinductive [156] and can reduce thrombogenic properties of the material [40]. Another concept relates, however, to covering the surface of metallic materials with other materials, also as a result of working an internal surface of pores [125, 157]. Porous metallic materials, chiefly Ti and Ta [158] and Mg [159], are used for non-biodegradable scaffolds primarily due to relatively high compressive strength and fatigue strength [160, 161]. Coatings of internal surfaces of pores are used, however, because they meet the imposed requirements better than metals and their alloys [40, 162, 163]. The following is necessary, especially, not to cause disease-related changes: the lack of a toxic effect of the implant material, the lack of its mutagenic properties, the lack of its effect on the composition of body fluids, both by the material being implanted as well as in the case of polymer materials, also by its decomposition products [40, 81, 147].

Original own works [117–120, 126, 164–180] have been undertaken concerning constructional solutions and fabrication technologies of a new generation of custom, original, hybrid, microporous high-strength engineering and biological materials with microporous rigid titanium and titanium alloy skeletons manufactured by selective laser sintering, whose pores are filled with living cells (**Figure 1**). This will ensure the natural ingrowth of a living tissue, at least in the connection zone of prosthetic/implant elements, with bone or organ stumps, and will eliminate the need to apply for patients the mechanical elements which are positioning and fixating the implants. The so constructed and fabricated implants, in the

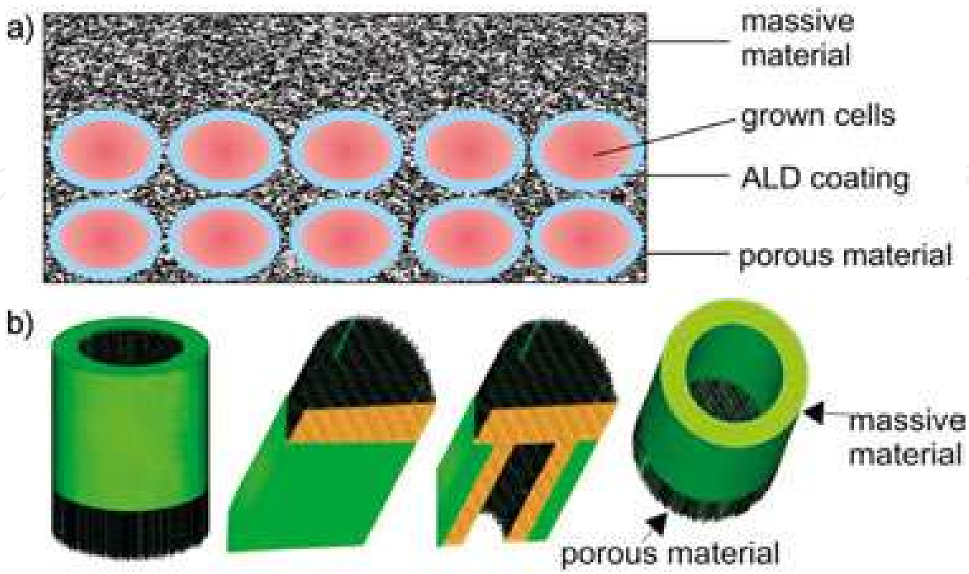

Figure 1. Chart of constructional assumptions (a) hybrid and multilayer biologically active microporous composite engineering materials consisting of biologically active cellular structures and of implant-scaffolds; (b) implant-scaffolds with microporous zones acting as scaffolds.

connection zone with bone stumps, contain a porous zone, with surface treatment inside pores, enabling the living tissues to grow and they remain in an organism permanently and do not require re-operation.

As the adhesion and growth of living cells are dependent on the type and characteristics of the substrate, in order to implement the planned concept of manufacturing engineering and biological materials and implant-scaffolds, it is required to seek the most advantageous proliferation conditions of living cells inside the pores of a microporous skeleton made of titanium and titanium alloys, which is the underlying scope of the research presented in this chapter. It appears that the improvement of proliferation conditions of cells is ensured by a substrate made of fully compatible materials, including TiO_2, Al_2O_3 oxides and a hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. For this reason, it was decided to employ these materials as coatings of internal surfaces of pores of a microporous skeleton fabricated by SLS. Two technologies have been chosen, respectively, for the deposition of thin coatings onto the internal surfaces of pores, ensuring the uniform thickness of coatings on all the walls and openings of a substrate being coated, even with highly complicated shapes, that is, the so-called atomic layer deposition (ALD) [96, 124, 126, 128, 181–184] (**Figure 2**) and the sol-gel technology of coating deposition from the liquid phase by the immersion method [96, 181, 185–194] (**Figure 3**).

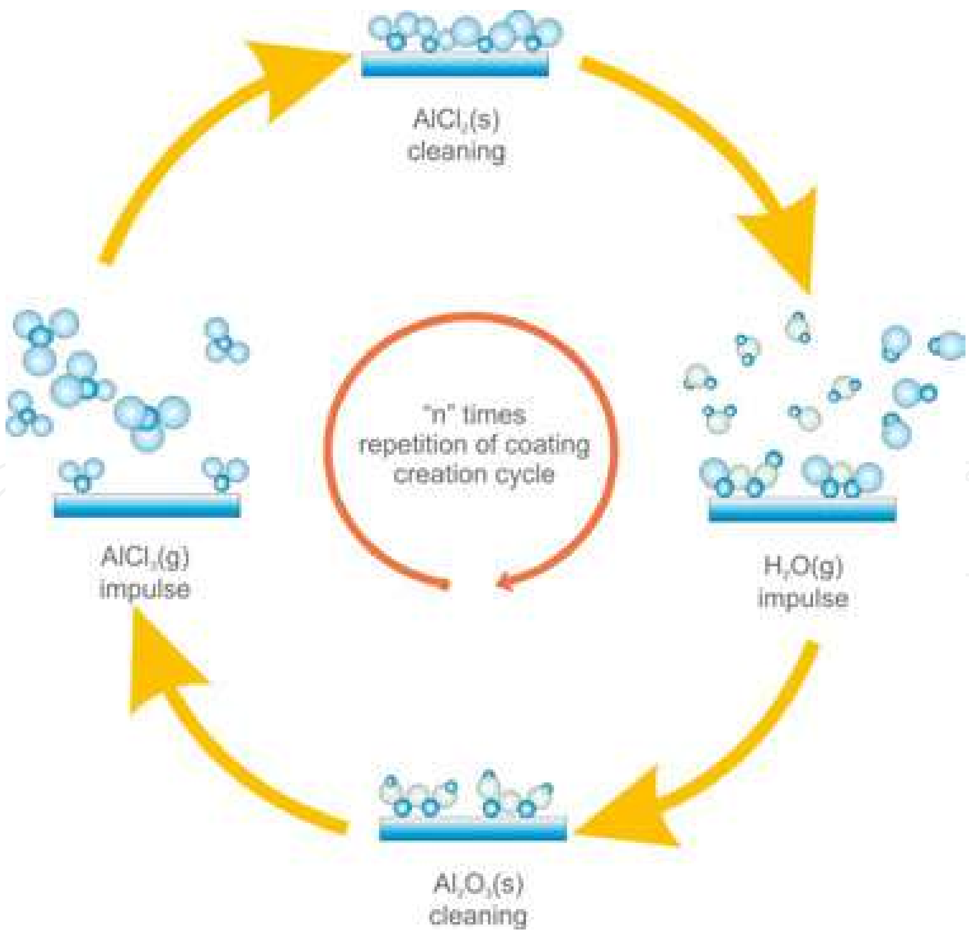

Figure 2. Sequence of the phenomena associated with ALD technology [96].

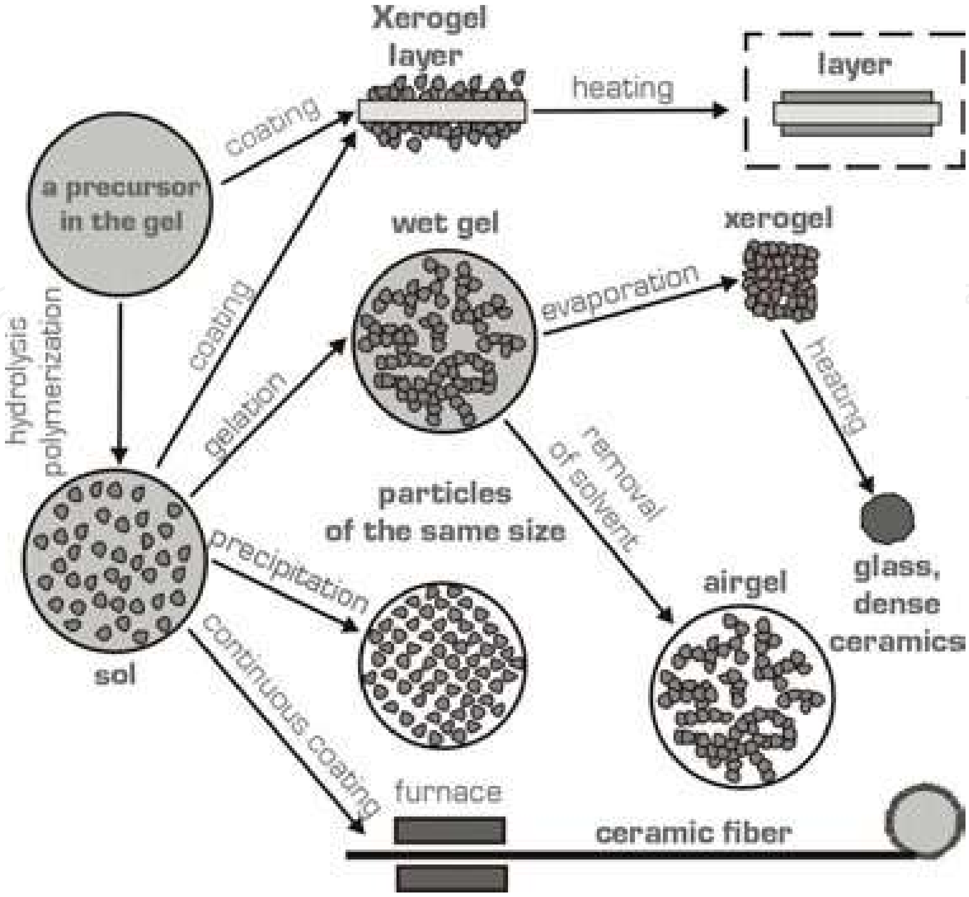

Figure 3. Sequence of the phenomena associated with the sol-gel technology of coating deposition [96].

2. Structure and properties of selectively laser sintered microskeletons made of titanium and Ti6Al4V alloy

The elements used for the research were produced by an additive method by powder sintering in an SLS process. Selective laser sintering can be grouped into a stage of designing a given element, the outcome of which is a 3D CAD model in the *.stl* format, then transferred into a machine's software, and another stage, at which an item designed virtually in advance is produced for real, a layer by layer, until a final product is obtained (**Figure 4**).

The following was used for model designing: Solid Works 2015 Pro and 3D Marcarm Engineering AutoFab (Software for Manufacturing Applications) software, version Autofab MCS 2.0 and Autofab MTT 64 and the CAD/CAM tools available in, respectively, SLM 250H system by MTT Technologies Group and in AM 125 system by Renishaw for selective laser sintering. The software enables to select model dimensions, constructional features, the type of the model volume filling either as solid or porous and to choose the size of a cell unit making up the entire model. A set of "hexagon cross" unit cells was used, selected in a geometrical analysis, and as a result of preliminary studies, from the set available in the software. By duplicating them, the entire elements were designed, consisting of nodes and single lattice fibres, linking the particular skeleton node (**Figure 5**). Fabrication conditions were also selected, at the stage of virtual design of elements, achievable in, respectively, SLM 250H

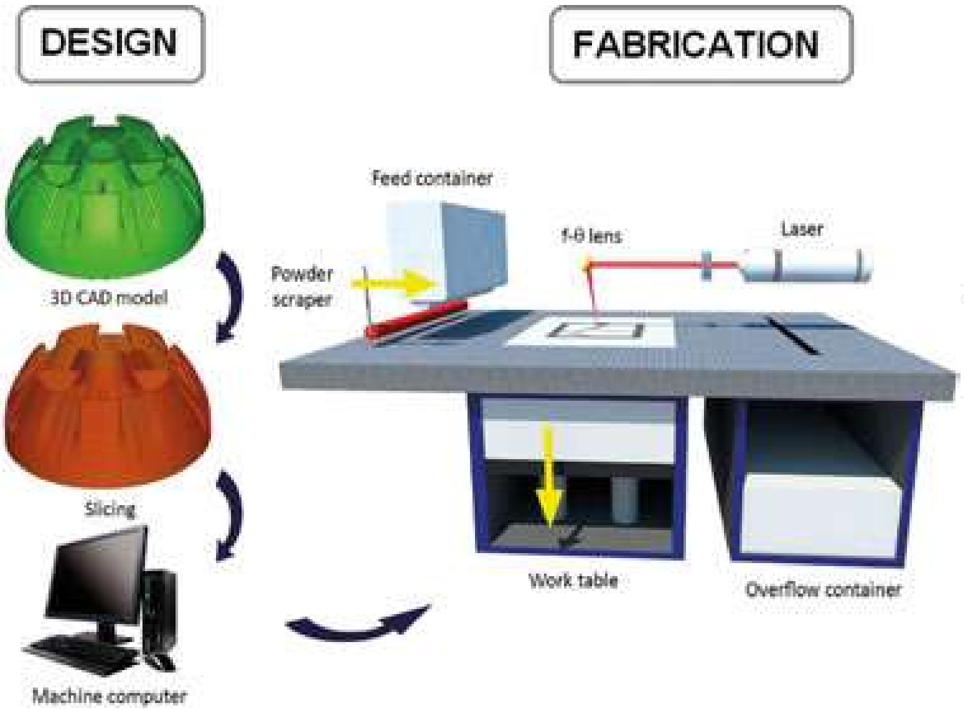

Figure 4. Selective laser sintering technology process diagram [195].

system by MTT Technologies Group and AM 125 by Renishaw for selective laser sintering, including layer thickness, laser power, laser beam diameter, scanning rate, distance between particular remelting paths. A spatial orientation of unit cells of 45° relative to the x-axis of the system of coordinates was also chosen experimentally, because other orientations analysed initially turned out to be less advantageous due to the mechanical properties of the elements produced (**Figure 5**). The structures of microporous skeletons with appropriately differentiated average sizes of pores of ~450, ~350 and ~250 μm, with suitable sizes of a unit cell of 700, 600 and 500 μm, were defined by reproducing and assuming suitable values characterising the spatial lattice, such as height, depth and width. Solid specimens were also made for comparative purposes.

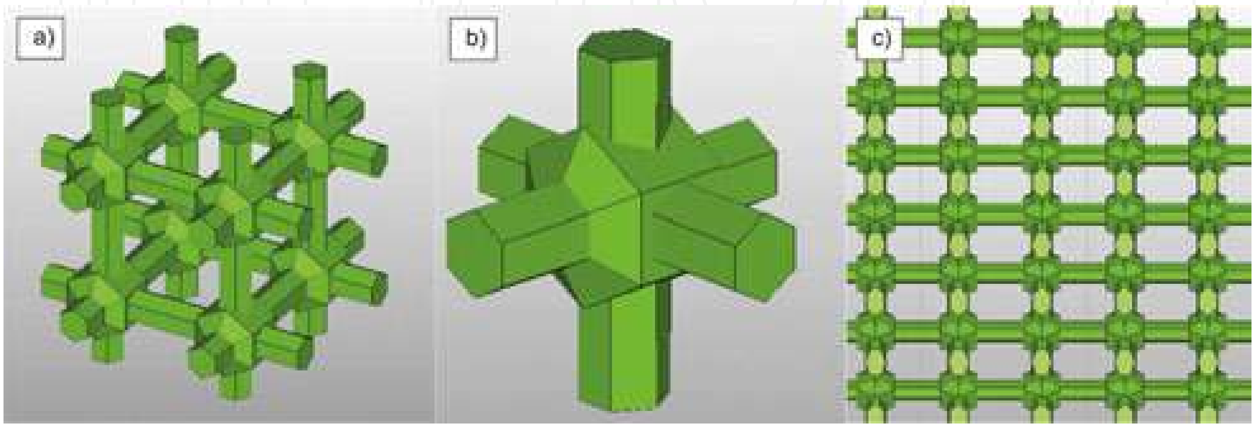

Figure 5. (a, b) Hexagon cross unit cell; (c) image of structure of computer models presenting the arrangement of unit cells in the space of the system of coordinates at the angle of 45° relative to the x-axis.

It was very important to establish the correct laser power value, ranging between 50 and 200 W, and the laser beam diameter, of 30–150 μm, and also the distance between laser beams and distance between laser remelting paths equal to or smaller than the laser beam diameter in case of solid elements, as opposite to the variant when it is larger than the laser beam diameter, which is decisive for the porosity of the produced element. Such conditions were selected as a result of preliminary studies.

When a model is designed and the selected fabrication conditions are taken into account, it is transferred to the software of the SLM 250H system machine by MTT Technologies Group or AM 125 by Renishaw, where selective laser sintering takes place. The YFL fibre laser, with an active material doped with Ytterbium and the maximum power of, respectively, 400 and 200 W, was used in the devices. The skeleton microporous materials, fabricated by SLS, exhibit porosity which depends on the manufacturing conditions, including mainly laser power and laser beam diameter and the distance between laser beams and the distance between laser remelting paths. Solid titanium with the density of 4.51 g/cm^3, corresponding to the density of solid titanium given in literature, can be achieved if the laser power of 110 W is applied. The smallest porosity of 61–67% corresponds to the selectively laser sintered elements with the highest mass and the average pore size of ~250 μm, whereas the highest porosity of 75–80% corresponds to elements with the smallest mass and the average pore size of ~450 μm. The porosity of 70–75% was obtained for the average pore size of ~350 μm.

Two types of powders with a spherical shape were used, respectively, for selective laser sintering to produce solid specimens and microporous skeletons (**Figure 6a**,**b**) and with the composition shown in **Table 2**, also confirmed with spectral examinations with the energy dispersive spectrometry (EDS) method (**Figure 6c**,**d**):

- titanium powder with Grade 4 and grain size of up to 45 μm, oxygen concentration reduced to 0.14%, the aim of which is to ensure process safety,
- Ti6Al4V alloy powder with the grain diameter of 15–45 μm, for medical applications.

Figure 7a and **b** and shows a surface structure of pristine titanium and Ti6Al4V alloy manufactured by selective laser sintering with laser beam size of 50 μm and laser power of 110 W. Chemical composition, examined with an EDS spectrometer, shows that Ti only exists in the first case in the sample (**Figure 7c**), and Ti, Al and V (**Figure 7d**) were identified in the other case, which corresponds to the data given in **Table 2** for chemical composition of powders used for selective laser sintering. It was revealed in both cases that, apart from the completely sintered materials with revealed paths of laser beam transition, fine powder particles exist, as well, which – after sintering – should be removed mechanically or by chemical etching. On the surface of porous titanium microskeletons (**Figures 8–10**), apart from sintered titanium, there are grains of powder loosely bonded with a skeleton, which were not fully melted with a titanium microskeleton; the results of local remelting also exist, as indicated by the surface topography of porous titanium skeletons for the different arrangement of cell units. In order to remove such unfavourable surface effects, porous titanium, after selective laser sintering, was subjected to preliminary cleaning in an isopropyl alcohol solution with an ultrasound

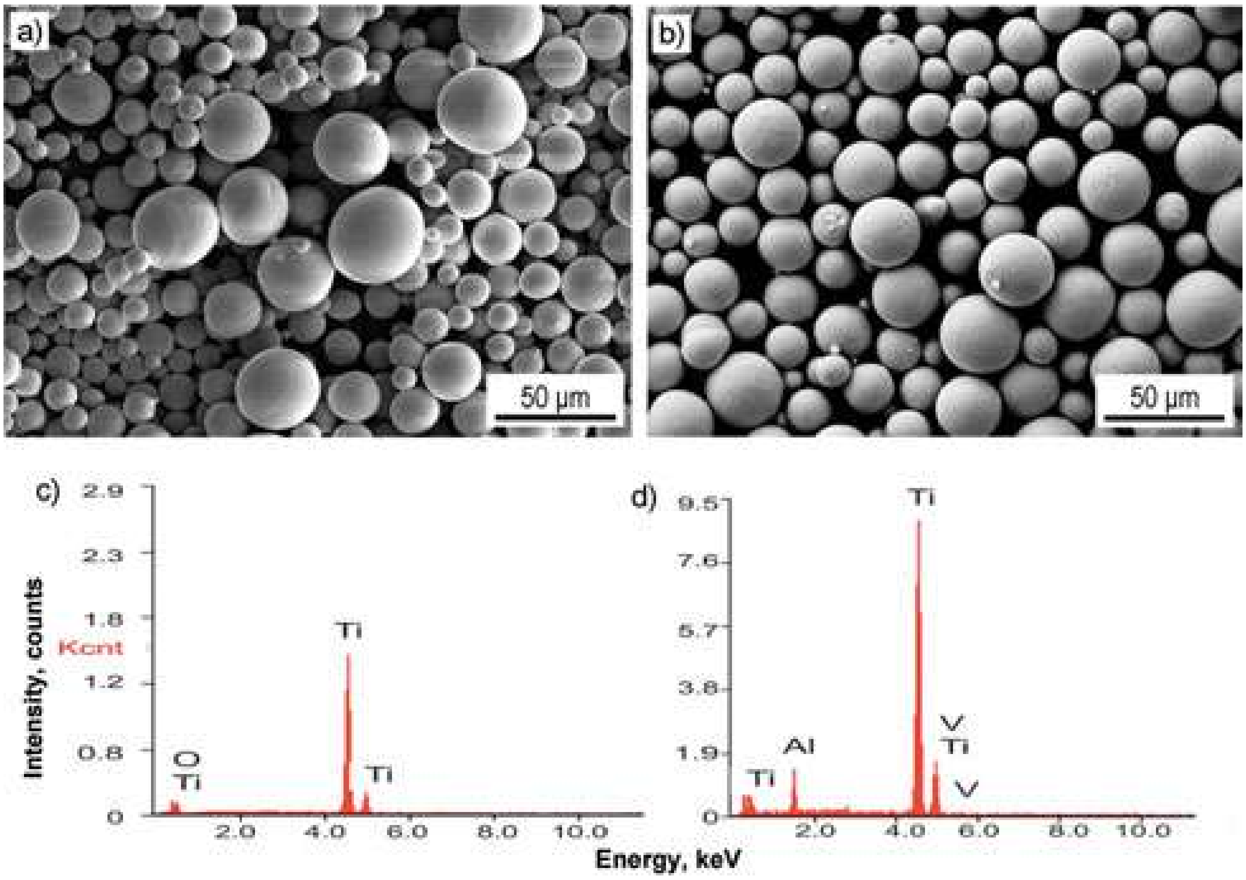

Figure 6. Powder of (a) Ti, (b) Ti6Al4V alloy (SEM), (c, d) relevant diagrams of EDS [119].

Powder	Mass concentration of elements, %									
	Al	V	C	Fe	O	N	H	Others total	Others each	Ti
Ti	–	–	0.01	0.03	0.14	0.01	0.004	<0.4	<0.01	Remainder
Ti6Al4V	6.35	4.0	0.01	0.2	0.15	0.02	0.003	≤0.4	≤0.1	

Table 2. Chemical composition of the powders used for selective laser sintering.

washer. After getting rid of excessive powder from the pores of the titanium skeleton, it was subjected to etching in an aqua regia solution with the fraction volume of 3:1 $HCl:HNO_3$, for 1 hour with an ultrasound washer, to etch the surface remelting not removed in preliminary cleaning and the fine powder particles not attached permanently to the previously constituted titanium microskeleton. The samples were subjected to etching in an aqua regia solution, as a result of which about 3% of the sintered material mass was removed (**Figure 11**). The roughness of skeletons before etching is much higher than after etching **(Figure 11).** A 14% aqueous hydrofluoric acid solution can also be used alternatively for etching.

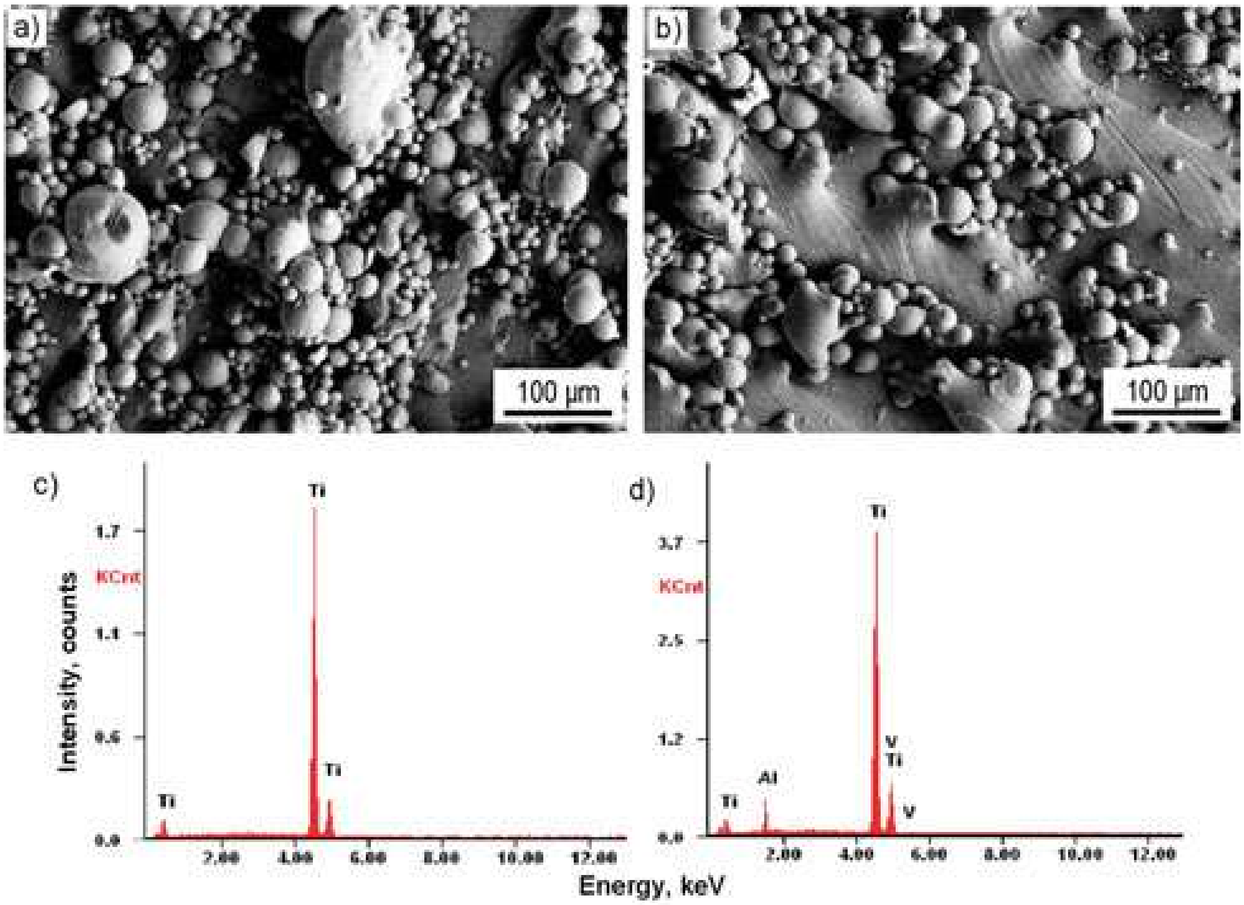

Figure 7. Surface structure of solid samples manufactured by selective laser sintering with the use of laser beam of 50 μm with laser power of 110 W; SEM of (a) solid titanium, (b) Ti6Al4V alloy, (c, d) respectively, EDS charts [119].

The structural examinations of selectively laser sintered titanium and Ti6Al4V alloy were carried out in a transmission electron microscope, TITAN 80–300, by FEI. Titanium and Ti6Al4V alloy have a crystalline structure, hence for the appropriately high microscope resolution, one can observe the rows of atoms arranged parallel to each other, both, when the microscope is in the TEM transmission mode and in the STEM scanning-transmission mode (**Figure 12**).

It is not possible to use standard normalised conditions of mechanical tests due to a porous structure of the analysed materials, which are not covered by the system of EN standards, and also due to the manufacturing costs and time of the samples for tests of mechanical properties and due to a limited size of a working chamber and manufacturing device efficiency. A custom, own method was therefore established for performing such examinations with a universal tensile testing machine, Zwick 020, in the conditions principally corresponding to static tensile tests, three-point bending and compression tests. Moreover, specially adapted miniaturised samples were also produced for examinations of strength properties (**Figure 13**), with the dimensions of measuring parts of, respectively, 3 × 3 × 15 mm, 3 × 10 × 35 mm (for support spacing of 30 mm) and 10 × 10 × 10 mm.

The mechanical properties of solid and porous materials fabricated by SLS, that is, sintered titanium and sintered Ti6Al4V alloy, were compared each time. The results of examinations of, respectively, tensile strength, bending strength and comprehensive strength were presented in

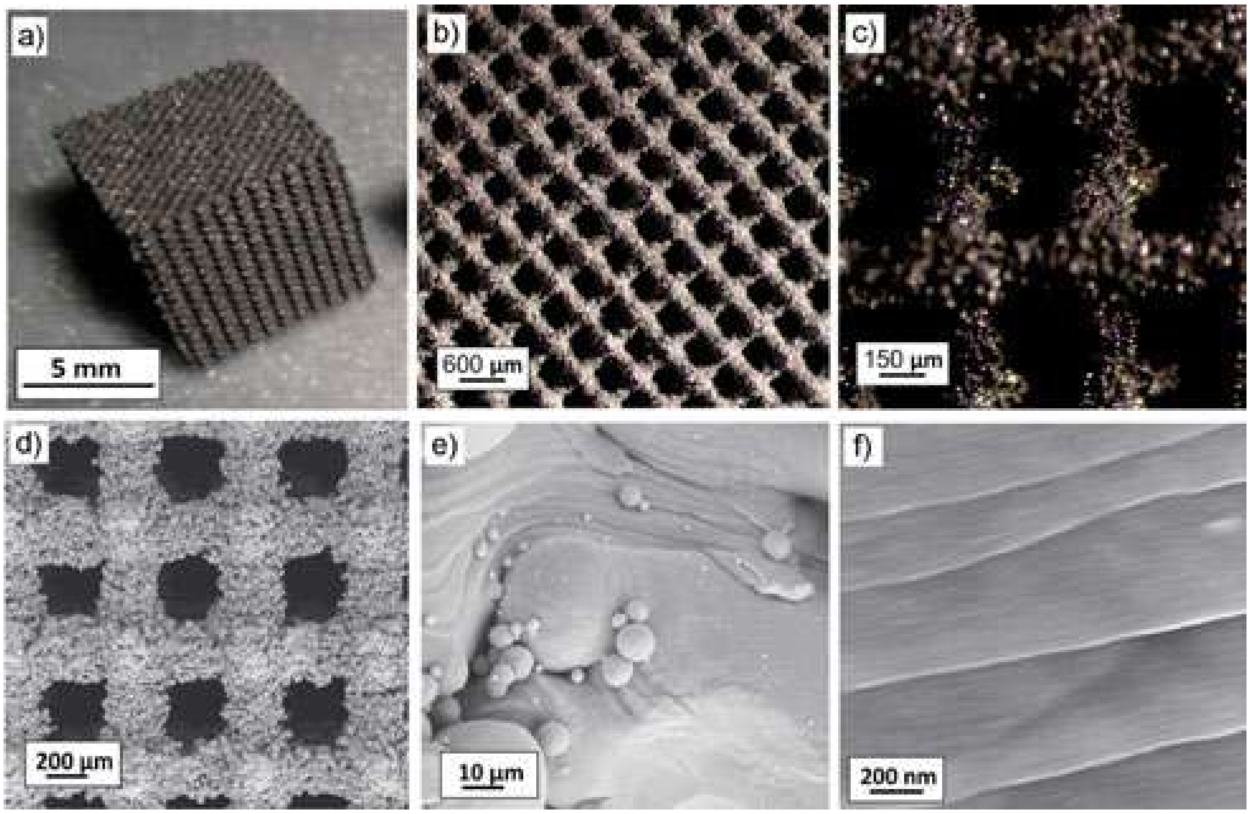

Figure 8. Titanium scaffold (a) visible with bare eye, (b, c) stereoscope microscope, (d–f) SEM.

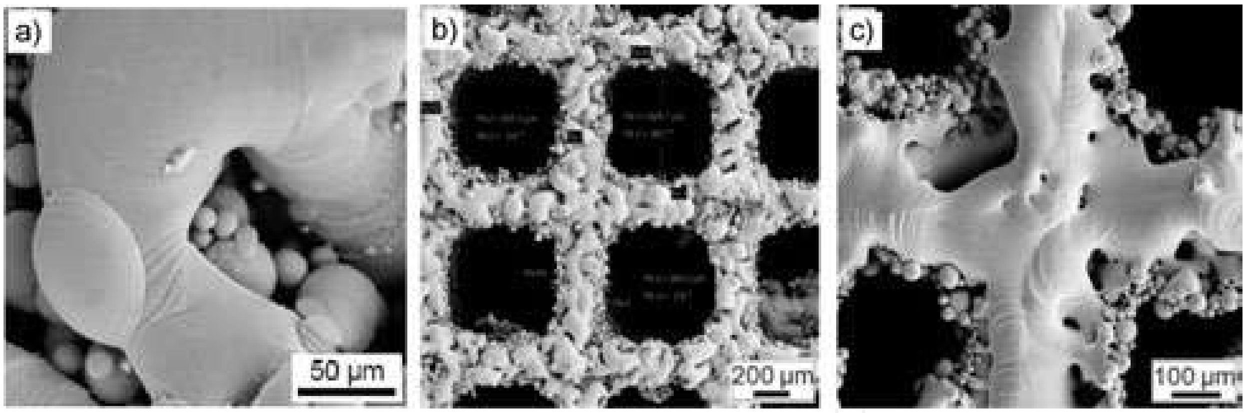

Figure 9. Surface typography of porous titanium skeletons with different pore size: (a) 350 μm, (b) 450 μm, (c) 630 μm; SEM.

such order. The impact of laser power ranging 70–110 W was investigated in the first place on tensile strength values of sintered titanium and sintered Ti6Al4V alloy. The results of examinations for five samples, for each treatment option of each of such materials, are presented in **Figure 14**.

Figure 15 presents the comparison of diagrams of dependency between tensile stress and elongation for solid and porous laser sintered Ti and Ti6Al4V alloy samples with the pore size of approx. 250 μm, subjected to static tensile tests. The results were obtained to compare the conditions of

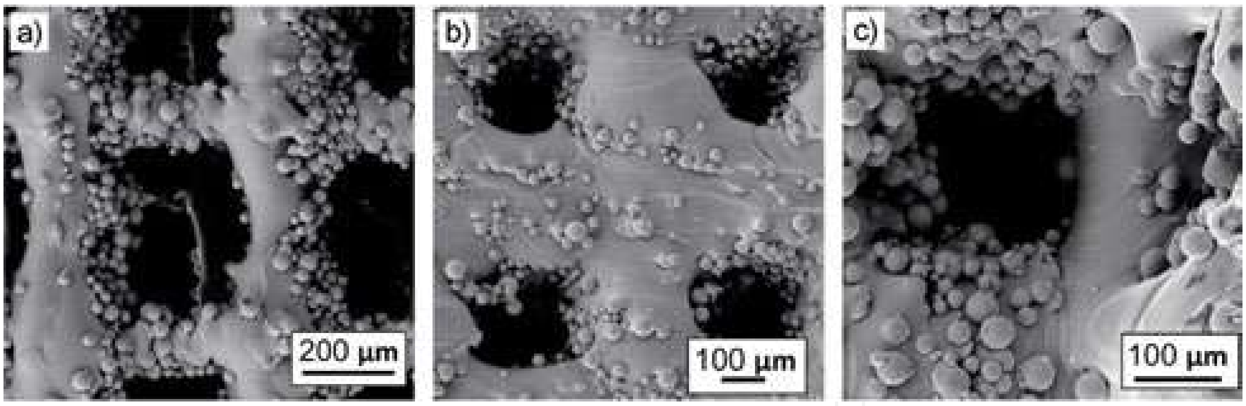

Figure 10. Surface topography of microskeletons made of Ti6Al4V alloy manufactured as multiplication of different unit cells presented with different magnificence (a, b, c); SEM images.

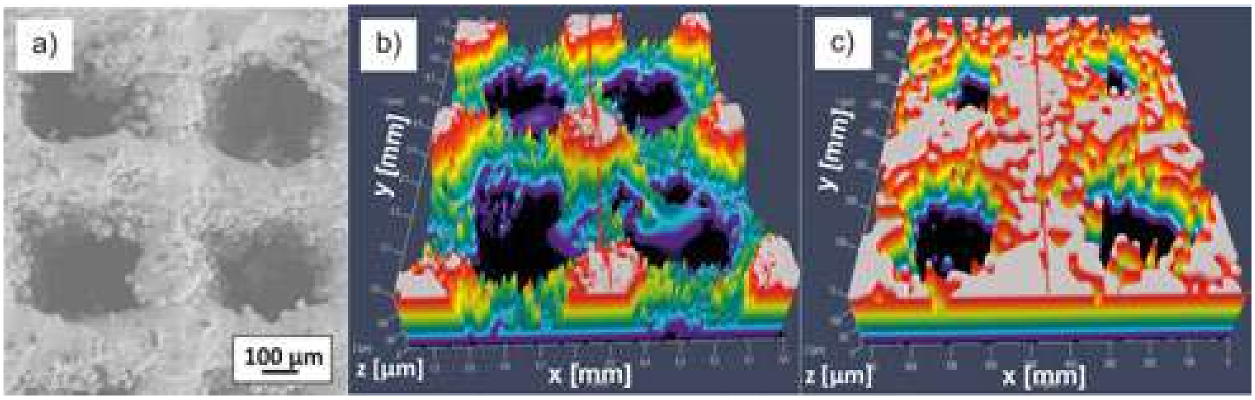

Figure 11. Surface topography of porous titanium skeletons with the pore size of ~450 µm (a) after etching in aqua regia solution (SEM), (b) after ultrasound cleaning, (c) after etching in aqua regia solution; (b, c) laser confocal microscope.

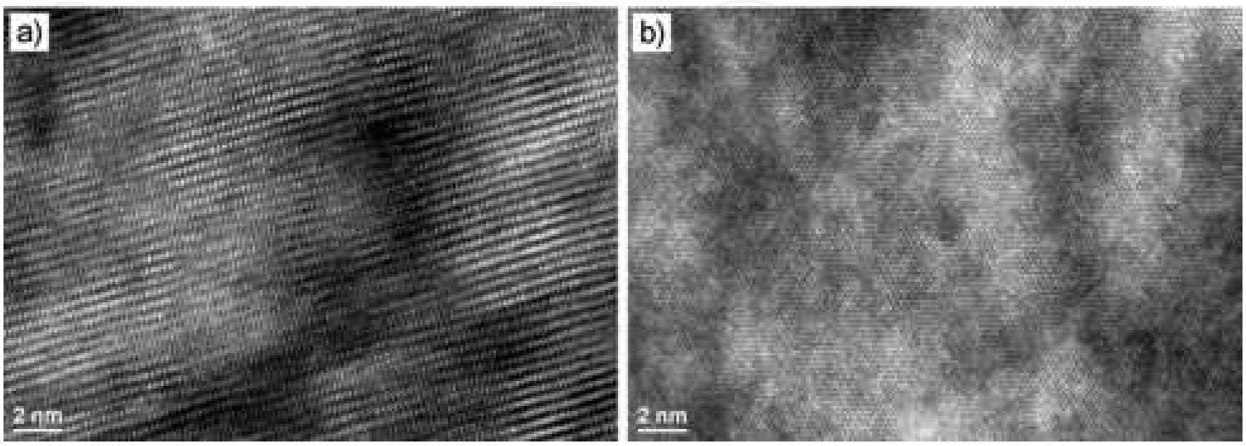

Figure 12. Crystalline structure of: (a) pristine titanium, (b) Ti6Al4V alloy; HRTEM image.

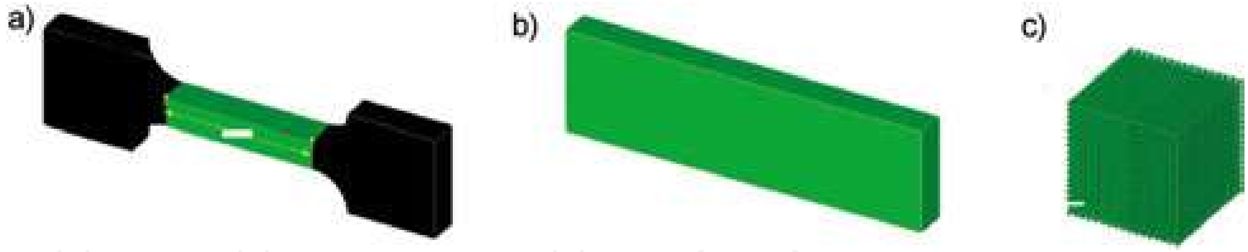

Figure 13. Image of computer model of solid samples for static test: (a) tensile test, (b) three-point bending test, (c) compression test.

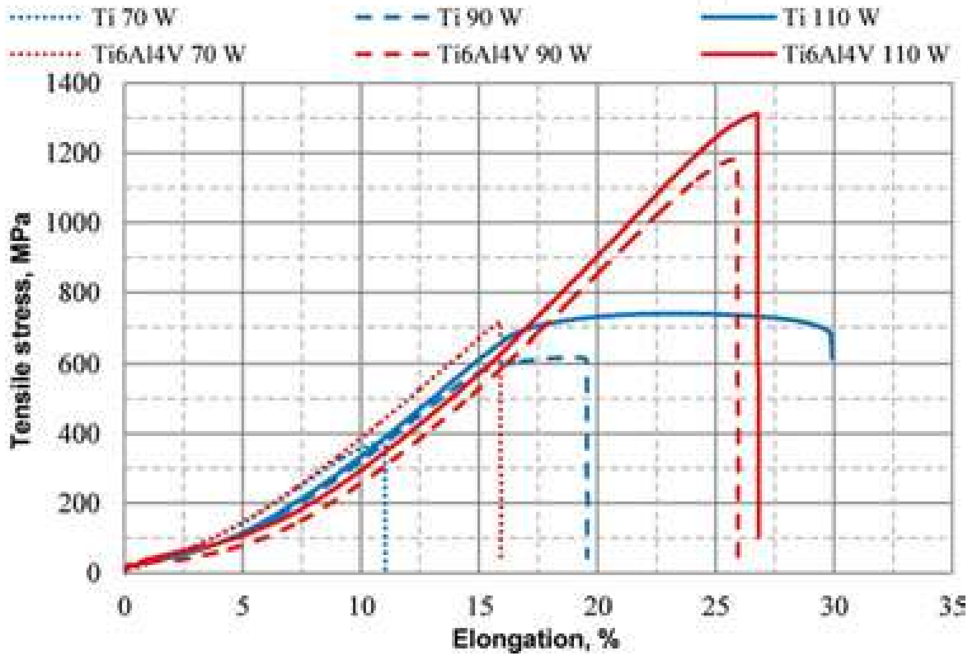

Figure 14. Comparison of diagrams of dependency between tensile stress and elongation for solid samples made of Ti6Al4V alloy and pristine titanium sintered at different laser powers [119].

selective laser sintering, that is, with the laser power of 60 W, which is favourable for porous materials. The examinations pinpoint, however, they are completely unacceptable for solid materials.

Bending strength tests were performed the same as tensile strength tests. The geometrical characteristics of the samples given in **Figure 13** were selected. The tests were carried out in relation to the investigated solid materials, that is, sintered titanium, sintered Ti6Al4V alloy as well as in relation to porous materials manufactured by SLS. The results concerning such tests were obtained as previously, for comparable conditions of selective laser sintering, that is, for the laser power of 60 W. The impact of laser power ranging 70–110 W on bending strength values of sintered titanium and sintered Ti6Al4V alloy for five samples for each treatment variant of each of the materials is shown in **Figure 16**. **Figure 17** compares the diagrams of dependency between bending stress and deflection for solid and porous Ti and Ti6Al4V alloy samples with the pore size of approx. 250 μm, selectively laser sintered in the given conditions.

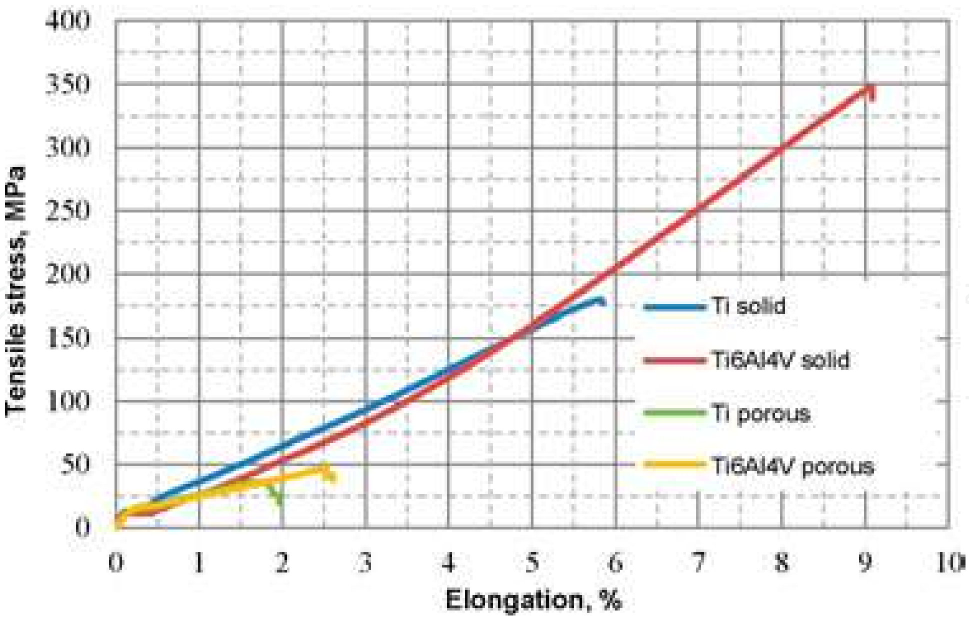

Figure 15. Comparison of diagrams of dependency between tensile stress and elongation for solid and porous laser sintered Ti and Ti6Al4V alloy samples with the pore size of approx. 250 μm [119].

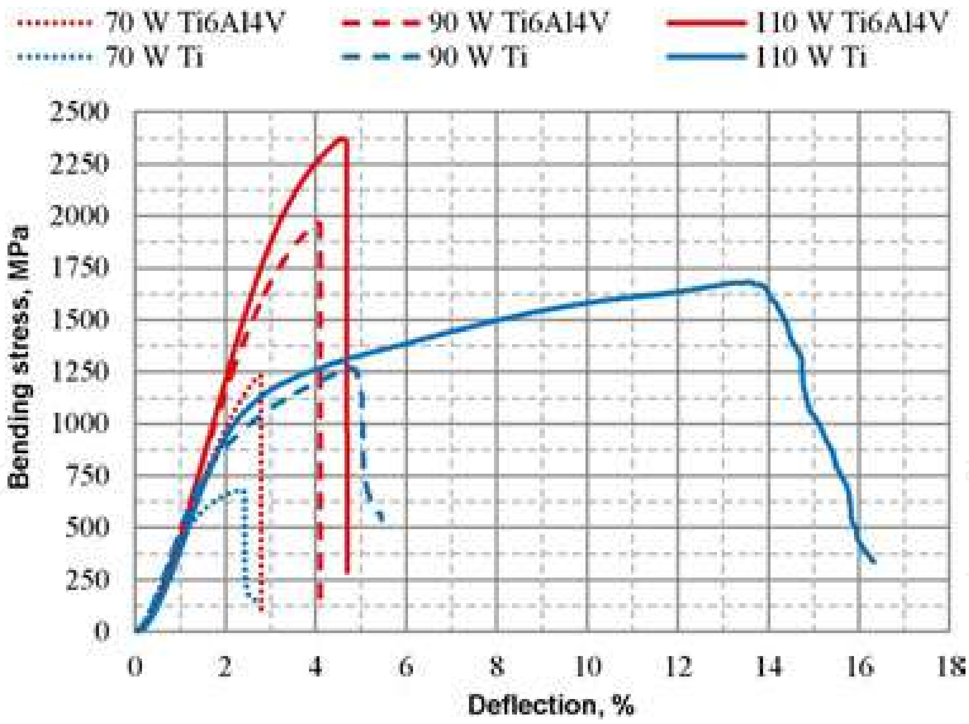

Figure 16. Comparison of diagrams of dependency between bending stress and deflection for solid samples made of Ti6Al4V alloy and pristine titanium sintered at different laser powers [119].

The results of compressive strength tests are also presented for solid and porous Ti and Ti6Al4V alloy samples with the pore size of approx. 250 μm, selectively laser sintered with the laser power of 60 W (**Figure 18**).

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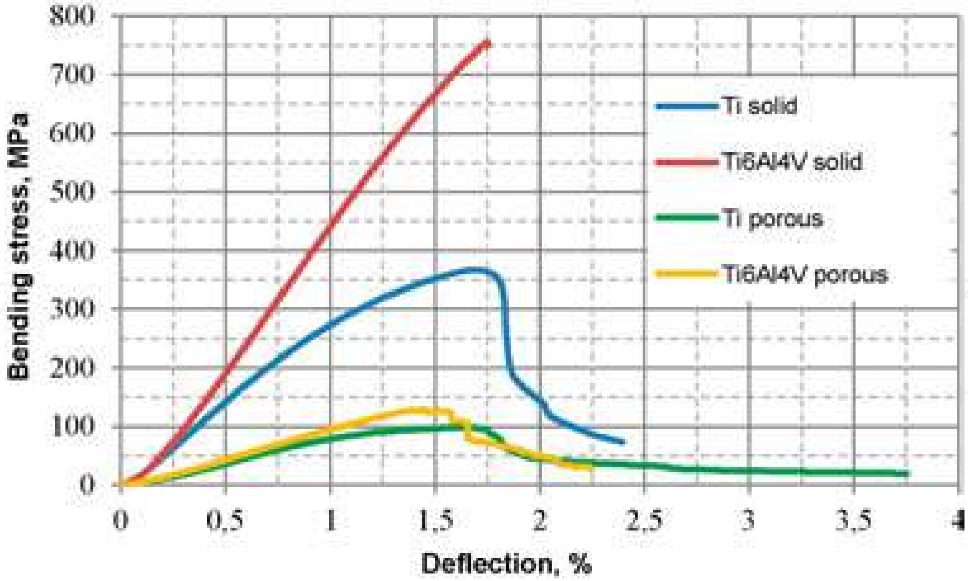

Figure 17. Comparison of diagrams of dependency between bending stress and deflection for solid and porous selectively laser sintered Ti and Ti6Al4V alloy samples with the pore size of approx. 250 μm [119].

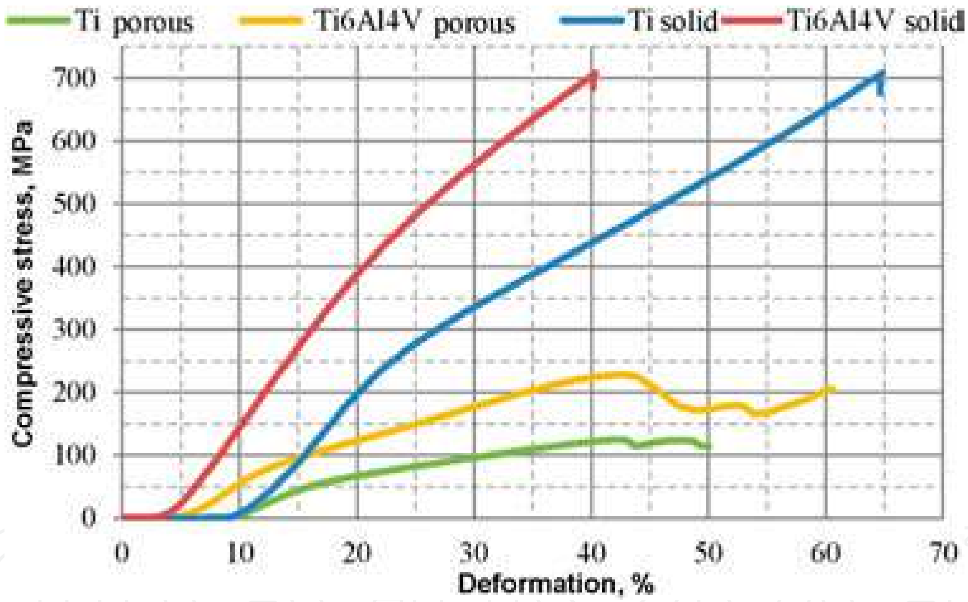

Figure 18. Comparison of diagrams of dependency between compressive stress and deformation for solid and porous selectively laser sintered Ti and Ti6Al4V alloy samples [119].

3. Structure and properties of ALD coatings on the substrate from selectively laser sintered microskeletons made of titanium and Ti6Al4V alloy

The ALD technique enables to deposit a chosen TiO_2 coating very uniformly across the entire surface of a part being treated, also if this part has a porous structure, as is the case with scaffolds. Changes in the sample colour, depending on the number of the executed ALD cycles, hence depending on the thickness of the deposited TiO_2 layer, is an interesting phenomenon observed with a bare eye (**Figure 19**) and in a light stereoscopic microscope, Discovery V12 Zeiss, allowing to view colourful magnified images. An uncoated element has silver-metallic colour, and when subjected to surface treatment by the ALD method, it becomes, respectively: brown-gold (500 cycles), navy blue (1000 cycles) and light blue with silver shade (1500 cycles) (**Figure 19**).

Scaffolds manufactured by the selective laser sintering method from powders of titanium and biocompatible Ti6Al4V titanium alloy, then coated with a thin layer of Al_2O_3 in the process of deposition of single atomic layers, ALD, were examined – analogously as TiO_2 layers – by means of a stereomicroscope, Discovery V12 Zeiss, allowing to identify that – along with the changing deposition thickness of an ALD layer – the colour of scaffolds is changing. The scaffolds, onto which Al_2O_3 layers were deposited in 500 cycles, are dark brown; such onto which Al_2O_3 layers were deposited in 1000 cycles are navy blue, and such onto which Al_2O_3 layers were deposited in 1500 cycles are dark blue (**Figure 20**). The differences in colours are also visible with a bare eye.

The measurements of layers' thickness with a spectroscope ellipsometer for each sample with deposited TiO_2 layers were performed in 25 places and statistical calculations were carried

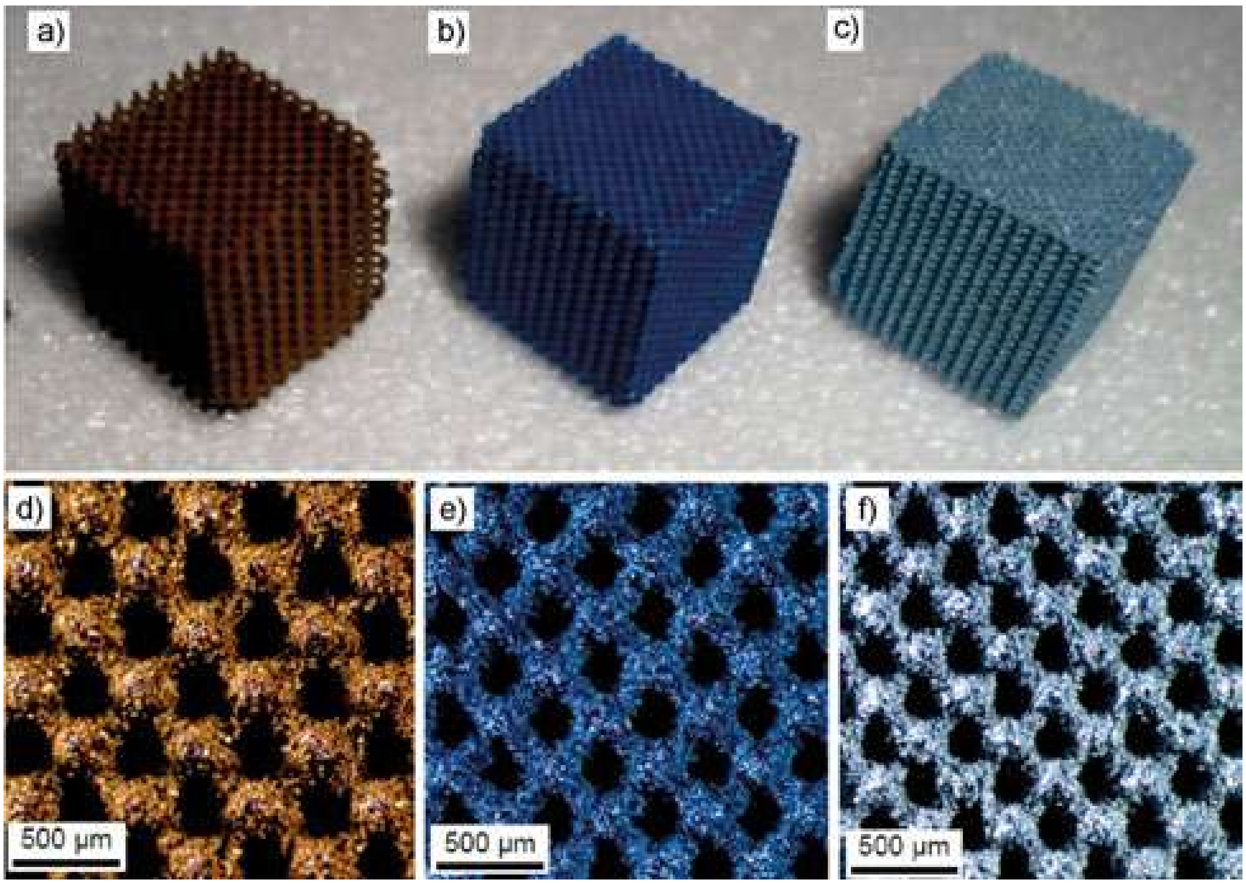

Figure 19. Titanium scaffolds coated with TiO_2 layers deposited by ALD; (a–c) cubic scaffolds viewed with bare eye, (d–f) stereoscopic scaffold images made with the magnification of 32× after: (a, d) 500 cycles, (b, e) 1000 cycles, (c, f) 1500 cycles.

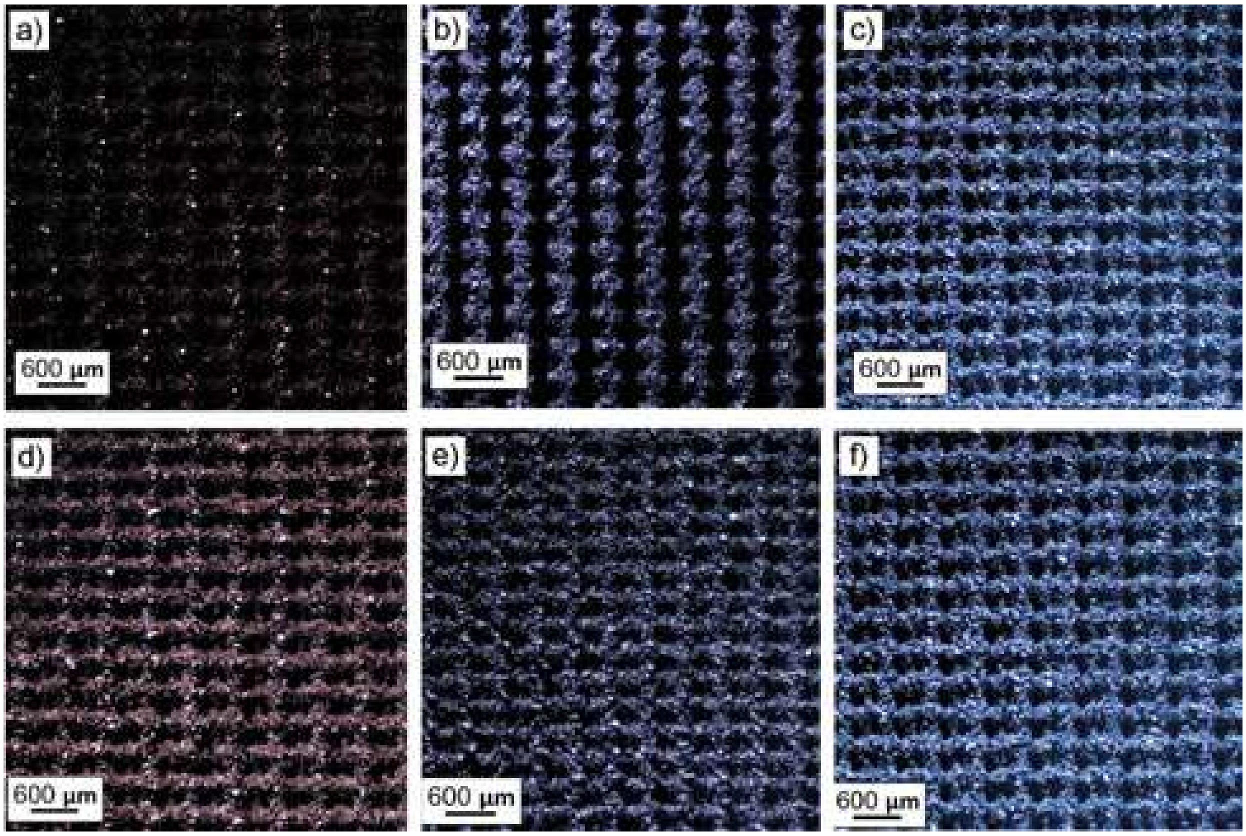

Figure 20. Surface topography of scaffolds manufactured from: (a–c) pristine titanium; (d–f) Ti6Al4V alloy; and coated with a layer of Al_2O_3 in: (a, d) 500; (b, e) 1000; (c, f) 1500 cycles; stereoscope microscope.

out, which has permitted to create a series of 2D maps of thickness distribution of the deposited atomic layers (**Figure 21**). The average thickness of TiO_2 layers deposited by ALD technique for the analysed cases of 500, 1000 and 1500 cycles is, respectively, 56, 99 and 149 nm. The difference in the thickness of the deposited TiO_2 layers on the studied area does not exceed 2 nm, which can be analysed in detail by studying layer thickness distribution maps. The best results were obtained for a layer deposited in 1000 cycles. A difference in the thickness of the deposited layer in this case does not exceed 1.1 nm across the entire area of the surface-treated item.

The topography of the scaffolds' surface coated with TiO_2 layers, deposited by the ALD method, was examined by means of an atomic force microscope, AFM XE-100 Park System, in two and three dimensions (**Figure 22**). There are irregularities with a nanometric scale on the scaffold surface, the number of which is rising proportionally to the number of the deposited layers. In particular, a layer deposited in 500 cycles has a rather uniform granular structure and the larger clusters of atoms are occurring on it only occasionally. In the case of a layer deposited in 1000 cycles, clusters of atoms with a diameter of about 1 µm occur every several microns. The biggest clusters of atoms, forming "islands" with the length of up to several micrometres, occur in the case of a layer deposited in 1500 cycles.

The detailed surface morphology examinations of the produced TiO_2 layers were performed with an electron scanning microscope, Supra 35, by Zeiss, with the accelerating voltage of

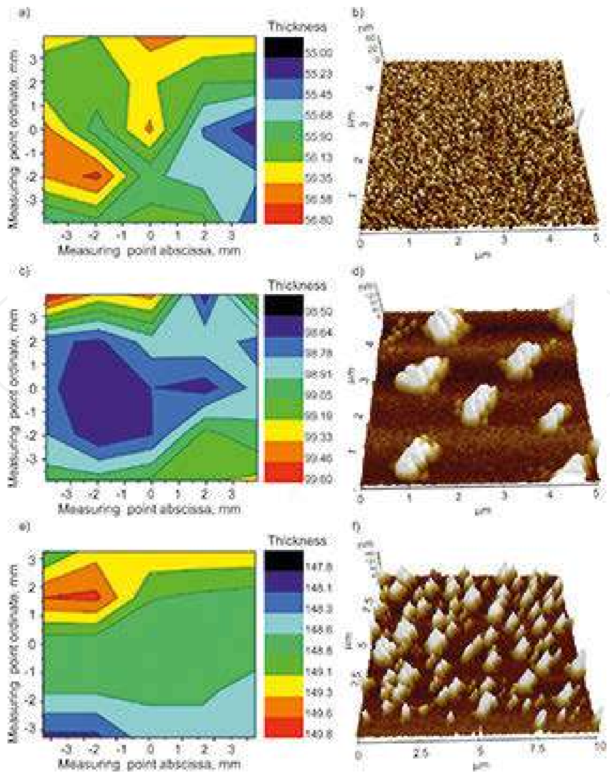

Figure 21. Titanium scaffolds coated with TiO_2 layers deposited by ALD after: (a, b) 500 cycles, (c, d) 1000 cycles, (e, f) 1500 cycles; (a, c, e) thickness deposition maps; (b, d, f) AFM image of 3D surface topography.

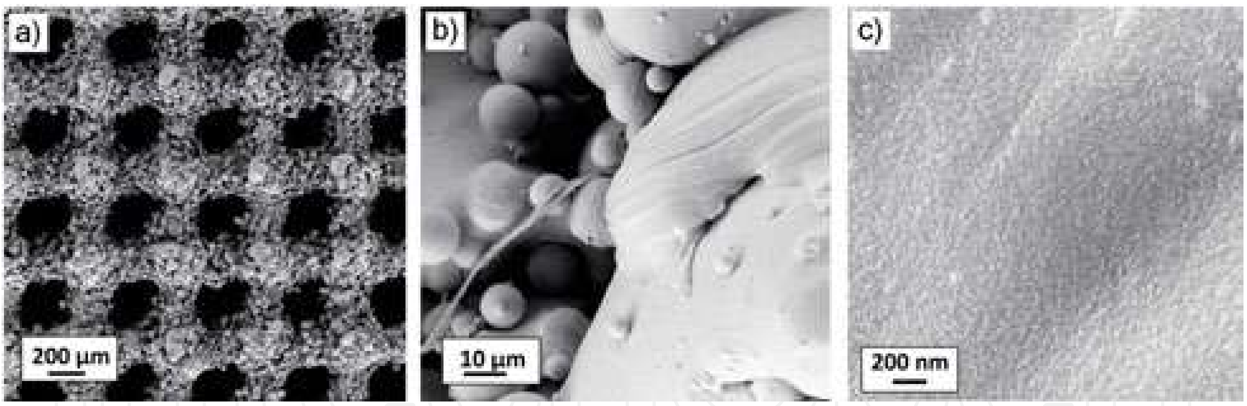

Figure 22. Scaffold surface with TiO_2 layer deposited in 1500 cycles presented with different magnificence (a, b, c); SEM images.

10–20 kV (**Figure 22**). Secondary Electrons detection with SE detectors by In Lens was used to obtain surface topography images. A nanometric thickness of TiO_2 layers deposited by ALD results in the fact that the layers can be observed in a scanning electron microscope only for very high magnifications of 150kx (**Figure 22**). A clear difference between a scaffold surface without surface treatment and scaffold surface covered with a TiO_2 layer in an ALD process can be observed only when such high magnifications are used. The scaffold surface, immediately following fabrication, is smooth with clear longitudinal bands arranged every several dozen/several hundreds of nanometres, corresponding to the laser activity direction.

The deposited atomic TiO_2 layer, when magnified by approx. 150kx, is visible as a "sheep", that is, a set of numerous adjacent oval granules of which only a few have a larger diameter.

The detailed surface morphology examinations of thin Al_2O_3 layers produced in a process of deposition of single atomic ALD layers, the same as TiO_2 layers, was examined by means of a scanning electron microscope, Supra 35, by Zeiss, with the accelerating voltage of 2–10 kV (**Figures 23** and **24**) with different magnification of up to 100kx inclusive. The examinations performed with the highest magnification allow to spot a clear difference between the scaffold surface without surface treatment and the scaffold surface with a deposited layer of aluminium oxide, which is coated with convexities with the size of up to approx. 10 nm if 500 cycles are used, to approx. 200 nm if layers are deposited in 1500 cycles (**Figures 23** and **24**).

A TiO_2 layer deposited by ALD onto a surface of a scaffold made of pristine titanium is of an amorphous structure, opposite to a crystalline titanium structure clearly shown in TEM images (**Figure 25**), as confirmed by TiO_2 layer examinations with a transmission electron microscope, TITAN 80–300 by FEI. Depending on the number of cycles, the thickness of a TiO_2 layer deposited by ALD varies between several dozens to hundred and a few dozens of nanometres. The examinations of TiO_2 layers with a transmission electron microscope on samples in a form of thin foils prepared with a focused ion beam microscope (FIB) with the use of gallium arsenide with deposition of a thin layer of platinum show that the both chemical

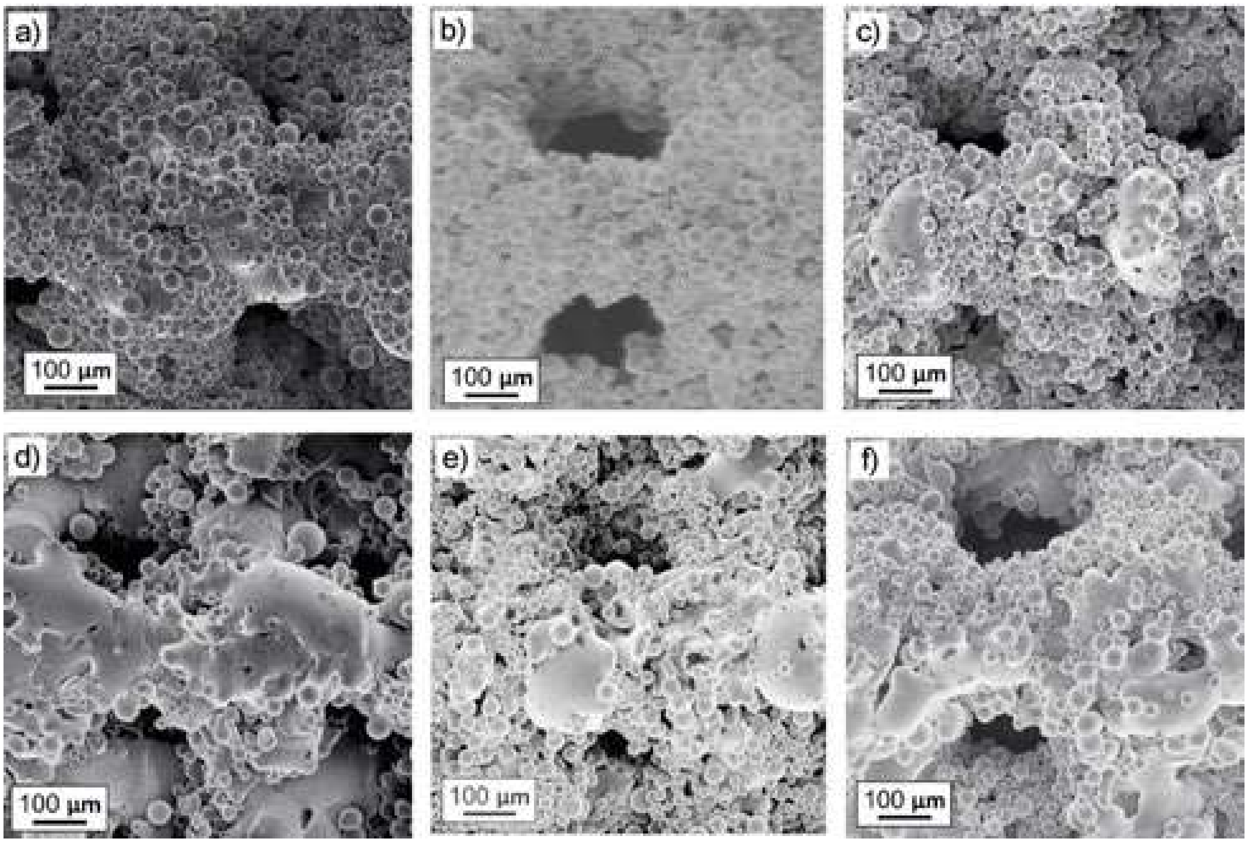

Figure 23. Surface topography of scaffolds manufactured from: (a–c) pristine titanium; (d–f) Ti6Al4V alloy and coated with Al_2O_3 layer in: (a, d) 500; (b, e) 1000; (c, f) 1500 cycles; SEM.

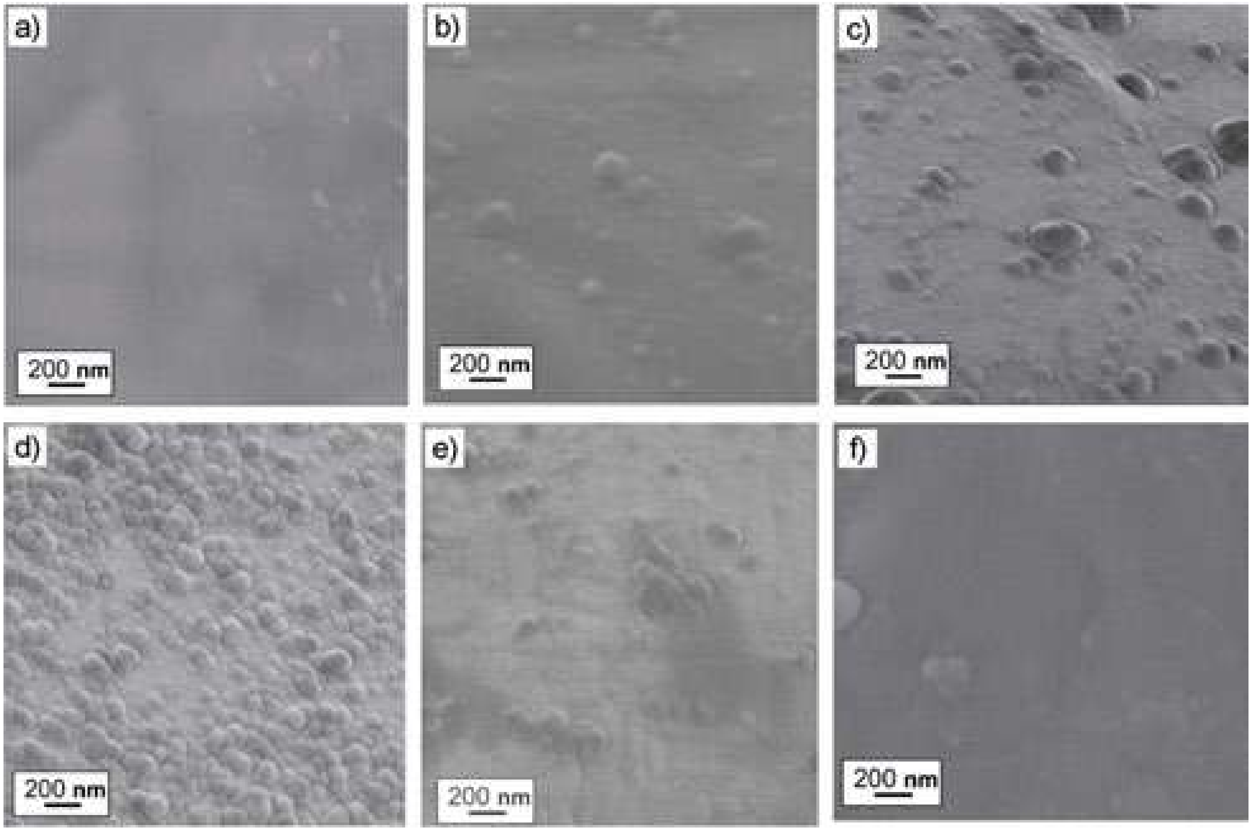

Figure 24. High-resolution surface topography of scaffolds manufactured from: (a–c) pristine titanium; (d–f) Ti6Al4V alloy and coated with Al_2O_3 layer in: (a, d) 500; (b, e) 1000; (c, f) 1500 cycles; SEM.

elements, apart from titanium and oxygen, are found on the EDS chart from an area situated on the periphery of the deposited layer, located in the direct neighbourhood of the protected layer of platinum (**Figure 25**). The EDS examinations of the deposited layers carried out in the region closer to the substrate reveal the presence of titanium and oxygen only (**Figure 25**), as is also confirmed by a prepared distribution map of chemical elements (**Figure 26**).

In order to confirm the presence of layers consisting of TiO_2 on the surface of a scaffold fabricated from TiAl6V4 powder, qualitative examinations of chemical composition were performed with the EDS scattered X-ray radiation spectroscopy method using an EDS (energy dispersive spectrometer), and a scaffold not containing a TiO_2 layer was considered a reference material. An analysis of the diagrams shown in **Figure 27** indicates that a spectrum was recorded in both cases with reflexes distinctive for titanium, aluminium and vanadium, whereas a reflex coming from titanium and oxygen exists additionally in a material covered with a layer of ALD, which corresponds to the occurrence of a TiO_2 layer on the surface of this material. Examinations were also undertaken using the inVia Reflex device by Renishaw, being an automated Raman system. A Raman spectrum obtained with the wave dispersion method, after base line correction, within the spectral range of 150–3200 cm^{-1}, is coming from a material being a scaffold, while a Raman spectrum coming from a material coated with a thin layer of titanium dioxide is shown in **Figure 27**, which – just like an EDS analysis – confirms the presence of titanium, aluminium and vanadium in the reference material; moreover

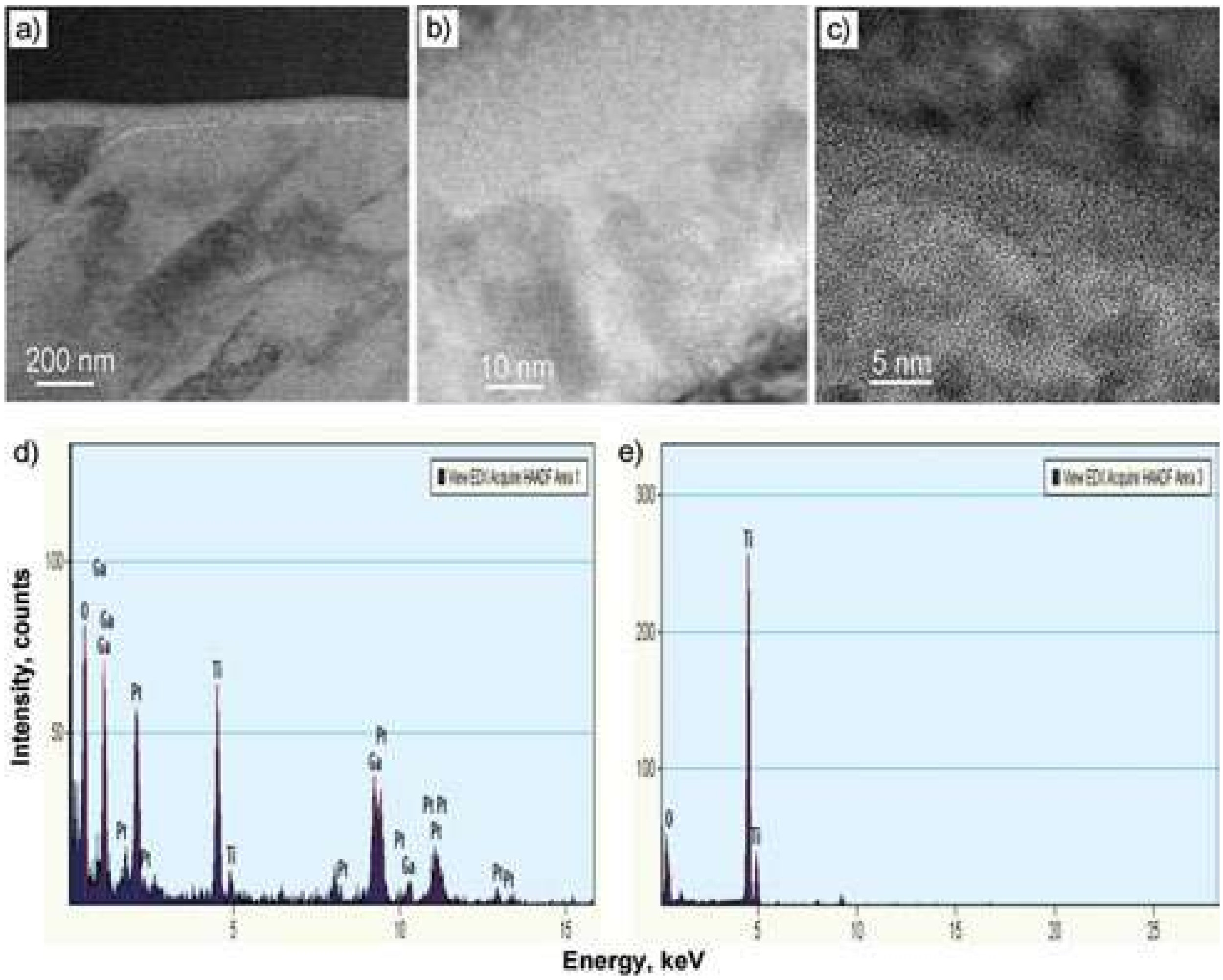

Figure 25. Amorphous TiO_2 layer deposited onto pristine titanium with a crystalline structure in a technological process lasting 1500 cycles; (a–c) HRTEM; (d, e) qualitative analysis of EDS chemical composition of TiO_2 layer: (d) from the peripheral region contiguous to the protective platinum layer; (c) near a titanium substrate.

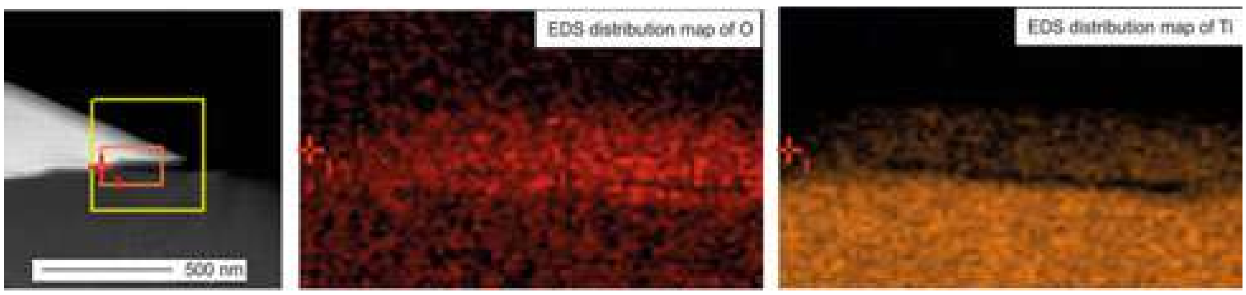

Figure 26. Distribution map of chemical elements present in the TiO_2 layer situated near titanium substrate.

oxygen, present in the surface layer, is found – apart from such chemical elements – in a material coated with a TiO_2 layer.

It was found, with special WiRETM 3.1 software, that a layer deposited by the ALD method is anatase, being a polymorphous type of titanium dioxide. **Figure 28** shows the images of

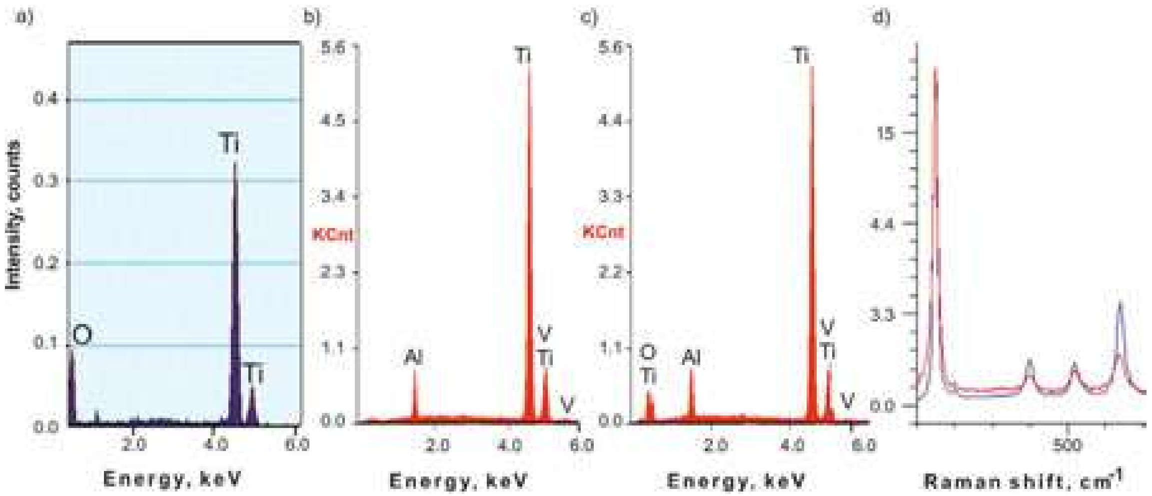

Figure 27. (a) Qualitative analysis of EDS chemical composition of TiO_2 layer; (b, c) results of qualitative analysis of chemical composition of: (b) TiAl6V4 without ALD layer, (c) TiAl6V4 with TiO_2 layer deposited by ALD method after 1500 cycles; (d) Raman spectrum of Ti6Al4V scaffold deposited by ALD method with TiO_2 layer [124].

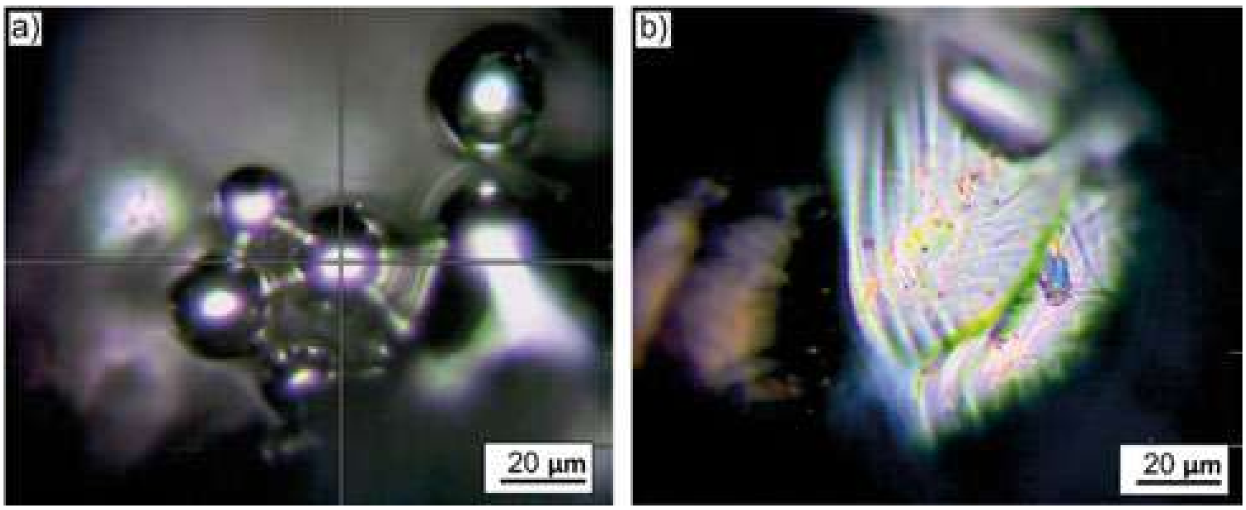

Figure 28. Points where Raman spectra were recorded, originating from: (a) reference Ti6Al4V scaffold, (b) Ti6Al4V scaffold covered with a layer of TiO_2; images coming from a confocal microscope.

points where spectra were recorded, originating from a reference Ti6Al4V scaffold and a scaffold covered with a layer of TiO_2; the images were made with a confocal microscope being a constituent part of the inVia Reflex device.

Structural examinations were performed with the X-ray diffraction (XRD) method (**Figure 29**) with an X′Pert Pro X-ray diffractometer by Panalytical (CuKα radiation, $\lambda = 1.54050 \cdot 10^{-10}$ m) using filtered radiation of a copper lamp with the voltage of 45 kV and a filament current of 35 mA, and the deposited TiO_2 layers were examined with the razing-incidence method due to the small thickness of not more than 150 nm, thus extinguishing

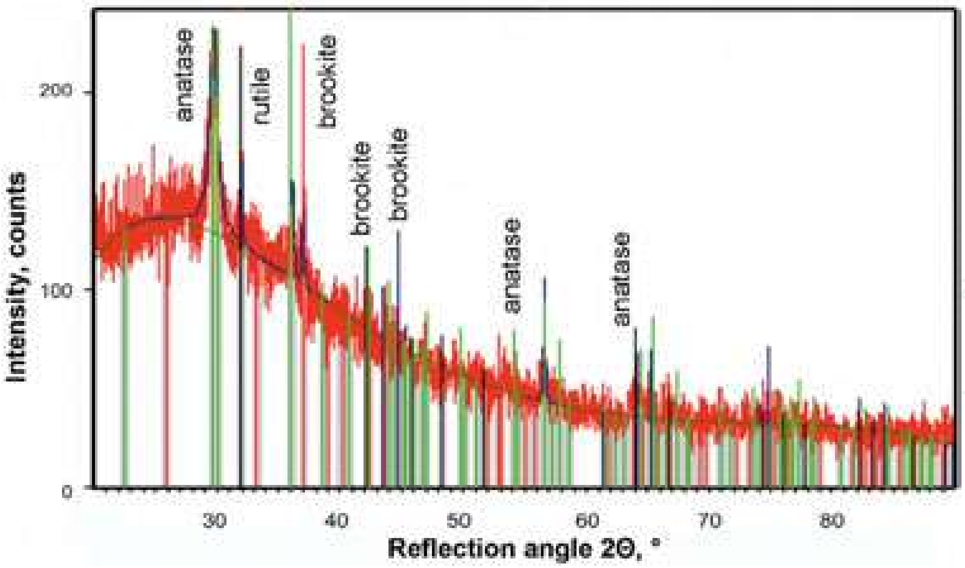

Figure 29. X-ray diffraction pattern of TiO_2 layer applied by atomic layer deposition (ALD) performed with the razing-incidence X-ray diffraction method.

the peaks coming from the substrate. Reflexes coming from three polymorphous variants of titanium dioxide, that is, anatase, rutile and brookite, were identified in the examinations.

In order to confirm that the observed ALD layers are fabricated from Al_2O_3 aluminium oxide, qualitative examinations were performed of chemical composition with the EDS scattered X-ray radiation spectroscopy method and were displayed as diagrams in **Figure 30**. For thin Al_2O_3 layers, deposited on a scaffold made of titanium, spectra were recorded with reflexes characteristic for aluminium and oxygen, coming from a layer and for titanium coming from the substrate (**Figure 30a**). A spectrum was recorded for a Ti6Al4V scaffold, with

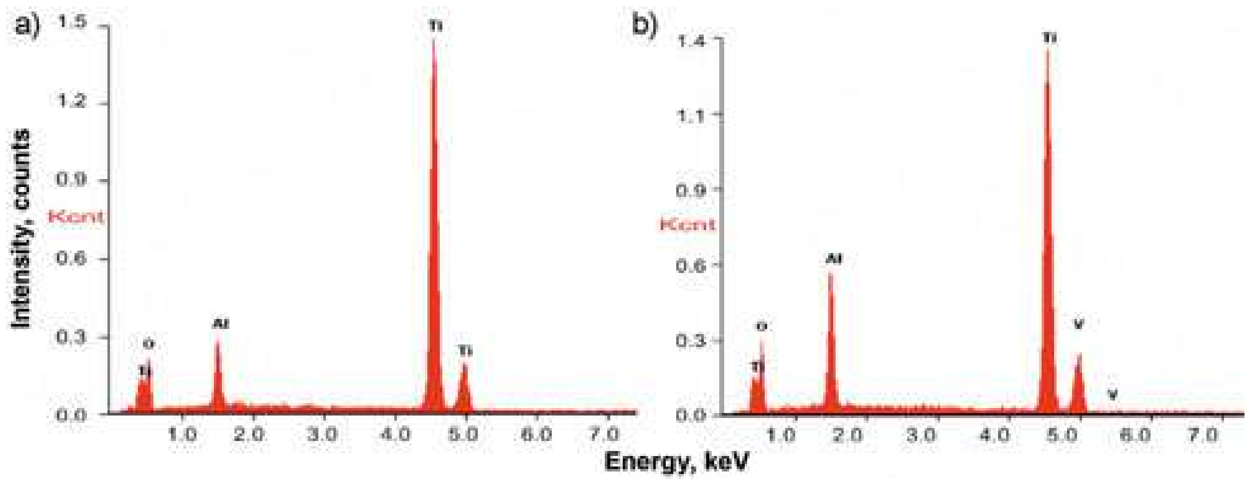

Figure 30. EDS spectrum made for scaffolds manufactured from: (a) pristine titanium; (b) Ti6Al4V titanium alloy; and coated with Al_2O_3 layers in 500 cycles.

reflexes characteristic for titanium and vanadium, coming from the substrate and oxygen from the layer. The reflex recorded from aluminium comes from the coating and substrate (**Figure 30b**). Distribution maps of chemical elements were additionally performed in the investigated materials. The presence of titanium, aluminium and oxygen was found in a titanium scaffold coated with aluminium oxide, and additionally vanadium is also found in a scaffold produced from Ti6Al4V. Supplementary X-ray examinations were also performed as a result of which no crystalline phase of aluminium oxide was found for ALD layers, which indicates their amorphous form. Such a result is expected due to the analogy with TiO_2 layers – deposited with the same method – subjected to examinations at a nanometric scale. An amorphous structure of the deposited layers is clearly seen in TEM images as opposed to crystalline titanium being the substrate.

4. Structure and properties of layers of hydroxyapatite deposited with the sol-gel immersion method on microporous selectively laser sintered skeletons made of titanium and Ti6Al4V alloy

Thin layers of hydroxyapatite were deposited with the immersion sol-gel technique (dip coating). The solution was prepared using hydroxyapatite nanopowder (HA), polyethylene glycol (PEG), glycerine and ethyl alcohol. The scaffolds manufactured from pristine titanium and Ti6Al4V alloy, coated with a layer of hydroxyapatite, manufactured by the sol-gel technique, were examined by means of a stereomicroscope microscope, Discovery V12 ZEISS. The detailed surface morphology examinations of the produced layers were undertaken with an electron scanning microscope Supra 35 by Zeiss. SEM images of thin layers were presented, on which hydroxyapatite particles are visible (**Figures 31** and **32**). The shape of the majority of hydroxyapatite particles is oval, however, a large content of particles with an elongated shape, with rounded, sometimes sharpened edges, is observed. The size of hydroxyapatite particles can be estimated at 20–80 nm. In case of sol-gel layers deposited on a scaffold made of titanium, spectra were recorded with reflexes characteristic for calcium, phosphorus and

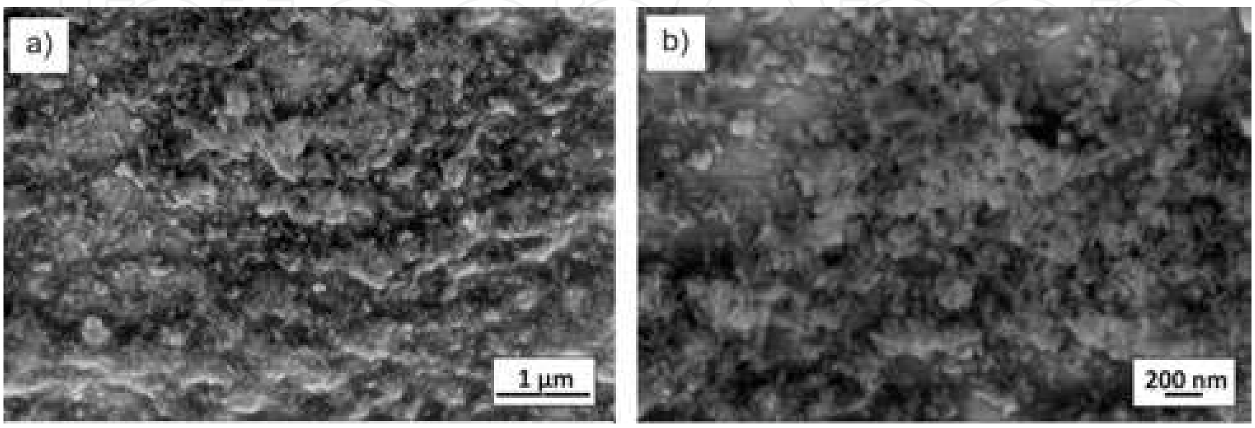

Figure 31. Scaffold made of Ti with the sol-gel layer of hydroxyapatite deposited after 10 immersions presented with different magnificence (a, b); SEM images.

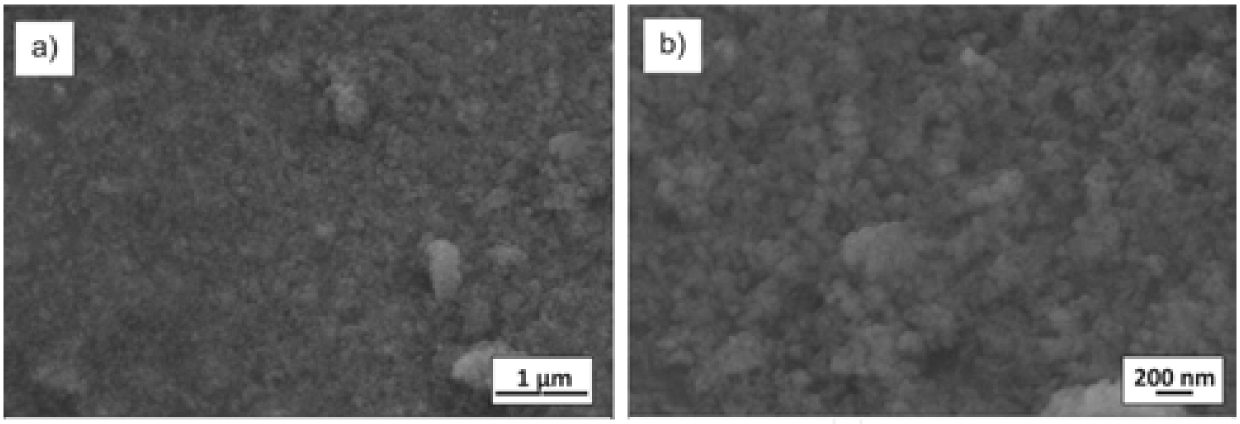

Figure 32. Scaffold made of Ti6Al4V alloy with the sol-gel layer of hydroxyapatite deposited after 10 immersions presented with different magnificence (a, b); SEM images.

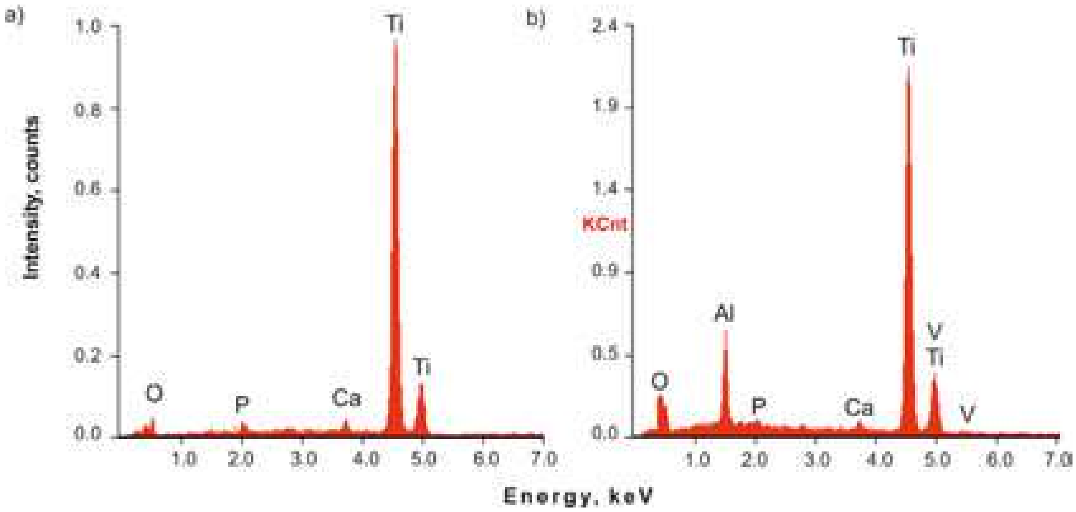

Figure 33. EDS spectrum of scaffold made of: (a) Ti, (b) Ti6Al4V: With a sol-gel layer of hydroxyapatite deposited after 10 immersions.

oxygen coming from a layer, and being the main hydroxyapatite components, and a reflex for titanium coming from the substrate (**Figure 33**). Similarly, for a scaffold made of Ti6Al4V alloy, spectra were recorded with reflexes characteristic for calcium, phosphorus and oxygen coming from the layer, and titanium, aluminium and vanadium, coming from the substrate. In addition, distribution maps of chemical elements were additionally performed in the investigated samples. Titanium was identified in a pure Ti scaffold, and also vanadium if Ti6Al4V alloy was also used. In the samples covered with a sol-gel layer, apart from the chemical elements coming from the substrate (e.g. titanium or titanium, aluminium and vanadium), calcium, phosphorus and oxygen were additionally identified, coming from a layer of hydroxyapatite (**Figure 33**). Structural examinations of sol-gel layers were performed by means of an X-ray structure analysis. Reflexes were identified coming from hydroxyapatite (**Figure 34**).

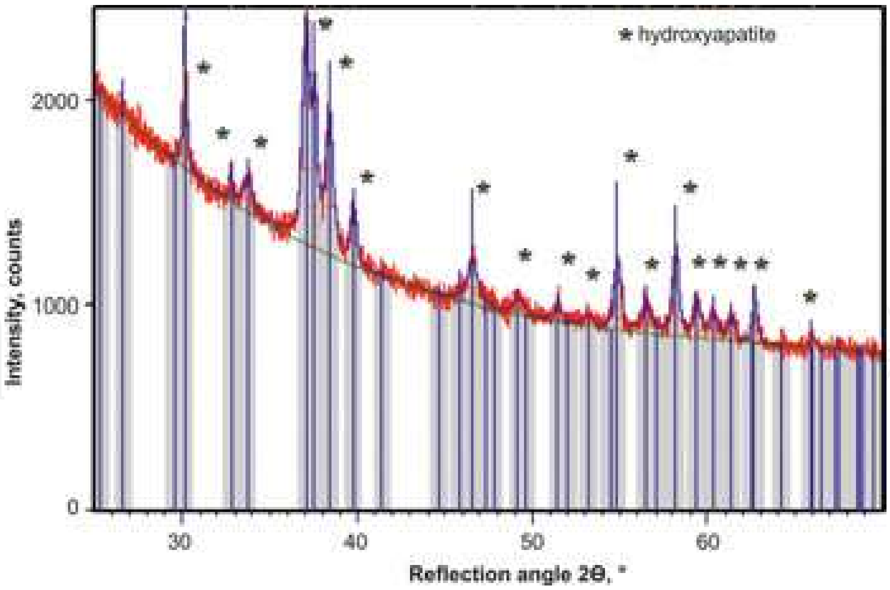

Figure 34. X-ray diffraction pattern of hydroxyapatite layer made with the sol-gel method.

5. Final remarks

One of the many elements largely influencing the quality of the society's life is the standard of healthcare. For this reason, all the activities in this sphere are considered as priorities in social policy in many countries and by international organisations. The life quality of patients after mechanical injuries, with tumorous and genetic diseases and with lost teeth greatly depends on the technical level, innovativeness and avant-garde solutions for medical and dental implants. It is obvious that the successfulness of the medical care provided depends on competencies of the doctors performing diagnostics, taking relevant decisions, applying appropriate therapies and related surgical procedures. The issue is a synergy of the actions jointly undertaken by medical doctors and engineers. The aspects of engineering-assisted medicine relate, both, to the constructional, material and technological design of, in particular, medical and dental implants. The development of medical implants is largely dependent upon advancements in biomaterials engineering, characterised by the required biological compatibility and harmonious interaction with living matter, without acute or chronic reactions, nor an inflammatory condition of the surrounding tissues after introduction into an organism. The advanced research efforts described in this chapter concern the engineering aspects of development of innovative implant-scaffolds, which enable the adhesion and proliferation of a patient's living cells into an intentionally designed porous structure of an implant which, on one hand, acts as an element transferring high stresses existing in an organism, and on the other hand acts as a scaffold into which a patient's cells are growing into. Metallic materials, despite their disadvantages, such as insufficient corrosive resistance and insufficient biotolerance in some areas of applications, are characterised by a pool of very advantageous mechanical properties. High fatigue corrosion resistance, brittle cracking resistance and tensile and bending strength should be considered especially significant. However, weak susceptibility of metallic materials as a substrate for cells' development is undoubtedly an issue. An effect of a substrate on the proliferation of living cells has been described in detail based on comprehensive literature studies. This aspect is very complex. Porous metallic materials are an attractive implantation material due to better, as compared to traditional alloys, accommodation of the elasticity modulus to the bone and because bone tissue can grow on pores and by ensuring appropriate implant fixation to the bone. Dedicated technologies ensuring surface treatment inside pores with the size of 200–400 μm are fully innovative and require very advanced nanotechnological instrumentation. Titanium and titanium alloys belong to a group of metallic materials applied for many years in the fabrication of implants for bone surgery, maxillo-facial surgery and prosthodontics. The principal reasons include relatively low density, a beneficial strength-to-yield stress limit ratio, good corrosive resistance and best biocompatibility in this group of biomaterials. Titanium and titanium alloys are considered as such allowing to eliminate the risk associated with a harmful effect of chemical elements occurring as alloy additives in metallic materials, and concerns and controversies around some of them have not been scientifically proven until now.

A porous scaffold, with its dimensions and shape perfectly suited to a patient's tissue loss, made of a biocompatible material (Ti or Ti6AlV4), additionally coated with a nanometric layer of osteoconductive titanium oxide, aluminium oxide or hydroxyapatite inside pores, seems to be a breakthrough solution. It is a highly hybridised and composite engineering material, fabricated by a hybrid technology combining avant-garde and experimental additive technologies of selective laser sintering SLS, in conjunction with ALD and sol-gel technologies appropriate for nanotechnology. Modern CAD/CAMD software allows to convert the data acquired at a clinical stage into a 3D solid model of a patient's lost tissues. The model is then converted into a porous model through the multiplication of a unit cell whose dimensions and shape may be designed according to a patient's individual preferences. The pores existing in the material structure have the diameter of up to 500 μm and should be open, because a scaffold, in its intended conditions of use, is to grow through a patient's living tissue.

This chapter presents the outcomes of numerous author's complementary technological, structural and strength investigations which are a basis for optimised selection of engineering materials, adequate technologies and constructional assumptions for completely new and innovative products. Biomimetic, light, porous, rough and biocompatible materials with unique mechanical and functional properties finding their application for completely innovative scaffolds and implant-scaffolds can be manufactured owing to a custom combination of advanced methods of computer aided materials design and selective laser sintering (SLS) of titanium and Ti6AlV4 alloy powders with avant-garde deposition methods of single atomic ALD or sol-gel methods. A series of the investigations performed to date, in which technological conditions were established for the fabrication of this type of coatings inside pores, was completed successfully, which is presented thoroughly in this chapter. The role of the manufactured layers, with their thickness which can be programmed in advance, and not only controlled *post factum*, is to enhance osteoconduction of the materials which are to be ultimately placed in a human organism. The application of the technologies and materials described is of fundamental significance to ensure the synergy of clinical effects obtained by medical doctors and dentists by classical prosthetics and implantation and the natural nesting and proliferation of living tissues in a microporous bonding zone with scaffolds or implant-scaffolds created from the newly developed engineering materials. It is the authors' intention to launch such new products soon for broad application in medicine and regenerative and intervention dentistry. Scaffolds will be fabricated this way in the form of microporous skeletons, and, optionally, implant-scaffolds consisting of a solid core and a microporous, strongly developed surface layer, connected in a hybrid way into the solid whole. The results of the investigations conducted allow to perform the currently pursued author's biological research pertaining to the nesting and proliferation of living tissues in the micropores of the created porous microskeletons and to assess the deposition of internal surfaces of micropores with layers supporting the growth of living tissues. Another report will be drafted following the completion of the research, concerning the details of the biological and clinical investigations performed, supplementary to the research and engineering works presented in this chapter.

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Author details

Anna D. Dobrzańska-Danikiewicz[2*], Leszek A. Dobrzański[1], Marek Szindler[3], Lech B. Dobrzański[1], Anna Achtelik-Franczak[1] and Eugeniusz Hajduczek[3#]

*Address all correspondence to: anna.dobrzanska.danikiewicz@gmail.com

1 Medical and Dental Engineering Centre for Research, Design and Production Asklepios, Gliwice, Poland

2 University of Zielona Góra, Faculty of Mechanical Engineering, Zielona Góra, Poland

3 Faculty of Mechanical Engineering, Silesian University of Technology, Gliwice, Poland

Deceased author

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