Chapter 10

Progress in Bioactive Metal and, Ceramic Implants for Load-Bearing Application

Mohammed Elbadawi, James Meredith,
Lynne Hopkins and Ian Reaney

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62598

Abstract

The field of biomaterials is an exuberant and enticing field, attracting interest across a number of scientific disciplines. Synthetic materials such as metals and ceramics have helped civilisation accomplish many feats, and this can also be said for the achievements in orthopaedic applications. Metals and ceramics have achieved success in non-load-bearing applications and attempts are made to translate the accomplishments into weight-bearing applications. For this, a material needs to be porous but with sufficient strength to withstand daily loading; however, both properties are mutually exclusive. The implant must also avoid causing adverse reactions and toxicity and, preferably, bond to the surrounding tissues. Metals such as stainless steels and chromium-cobalt alloys have been used due to their excellent mechanical properties that can withstand daily activities, but retrospective studies have alluded to the possibilities of significant adverse reaction when implanted within the human body, caused by the elution of metal ions. Lessons from metals have also demonstrated that materials with significantly higher mechanical properties will not necessarily enhance the longevity of the implant—such is the complexity of the human body. Ceramics, on the other hand, exhibit excellent biocompatibility, but their mechanical properties are a significant hindrance for load-bearing use. Thus, the chapter herein provides a select overview of contemporary research undertaken to address the aforementioned drawbacks for both metals and ceramics. Furthermore, the chapter includes a section of how metals and ceramics can be combined in a multi-material approach to bring together their respective properties to achieve a desirable characteristics.

Keywords: Bioactive Metals, Osseointegration, High Strength, Fabrication, Ceramics

1. Introduction

The orthopaedic implant market is expected to grow from its current $30 billion value due to the rising demands for orthopaedic implant procedures in a universally aging civilisation. A plethora of synthetic materials capable of encouraging bone growth are available in the market, referred to as bioactive materials. The clinical success rates of bioactive orthopaedic implant validate the concerted research undertaken to enhance their abilities, underpinned by their propensity to alleviate pain, expedite recovery, and ameliorate quality of life for the patient. Applicable artificial implants can be in the form of plates, rods, screws, or scaffolds (a porous structure used to substitute missing osseous tissue). Indeed, artificial implants can be fabricated from metals, ceramics, polymers, and composites; however, due to the complexity of the human skeleton, no one class of materials is suited for all applications. Moreover, bioactive materials are not without their drawbacks. The aim of this chapter is to provide an overview of how material science and engineering techniques are employed to maximise their potential and thus ensuring long-term efficiency.

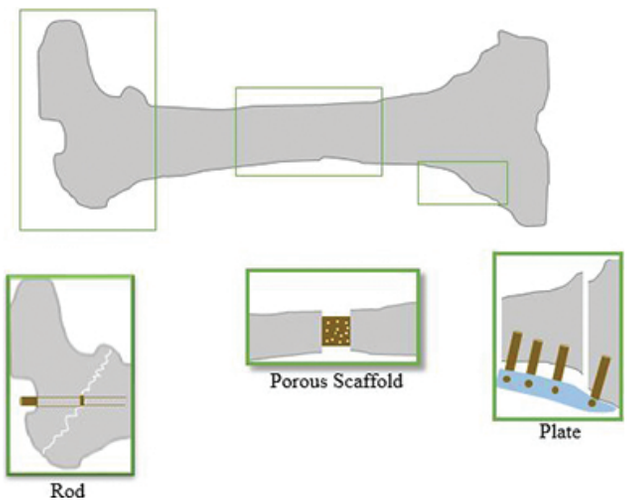

Figure 1. Schematic to show how implants are used for load-bearing applications.

1.1. Background

Bone resides in a perpetual resorption-regeneration state dictated by osseous cells and, like the skin, has a natural tendency to heal when fractured over time. There are instances when the healing cannot be accomplished, such as non-union fractures, which leads to medical intervention. Bone grafting is considered a strong candidate in such cases. A graft can either be natural or synthetic in its form but serves the purpose of encouraging the bone to grow. Bone grafts can be retrieved from the patients' own skeleton (autograft) or from a donor (allograft); however, concerns including but not limited to histocompatibility, disease transfer, and lack of availability necessitate the use of synthetic materials—of which metals and ceramics have been extensively researched.

http://dx.doi.org/10.5772/62598

Synthetic materials can exert several responses within physiological environment. If no adverse reaction occurs, then the material is said to be biologically compatible, or "biocompatible." This can further be subdivided into two groups: bioinert and bioactive, where the former is used to refer to a material that does not interact with the surrounding tissues. A bioactive implant can elicit an efficacious reaction that induces a phenomenon where a bone-like layer is formed around the implant providing an initial rapid and robust bond between the bone and implant that can culminate in complete integration. This type of response is technically referred to as *osseointegration*. Materials can recruit pre-existing bone cells to lay the groundwork for the integration, which is referred to as *osteoconduction*. Others stimulate undifferentiated cells into bone cells are referred to as *osteoinduction.* Implants eliciting such a response are associated with high success rates in clinical settings. Such exceptional attributes are inherent in some materials, and others need additional processing to implement the trait. An assortment of bioactive materials is capable of dissolving gradually within the human body, under physiological environment. The concept of a synthetic material inducing bone growth and vanishing, so to speak, when a new bone is remodelled is very attractive as it can avoid added patient inconvenience and healthcare costs. Materials that can dissolve or degrade under the physiological conditions are referred to as "biodegradable" or "bioresorbable." The aim for bioresorbable materials in load-bearing applications is for the implant to bear the majority of the load when implanted, and as the bone heals and more bone tissue is formed, the load is shared between the implant and healing tissues. As the scaffold is resorbed and consequently weakened, the healing bone sustains the majority of the load until the scaffold is completely resorbed and bone is fully restored. Preferably, if the graft resorption occurs in tandem with bone regeneration, structural weakness can be mitigated and minimising premature graft failure. A porous structure is also favoured because opportunities for bone to grow within the implant (as opposed to solely on the surface) can be achieved that leads to enhanced osseointegration and early implant stabilisation. Therefore, designing an artificial implant should incorporate as many of the aforementioned attributes.

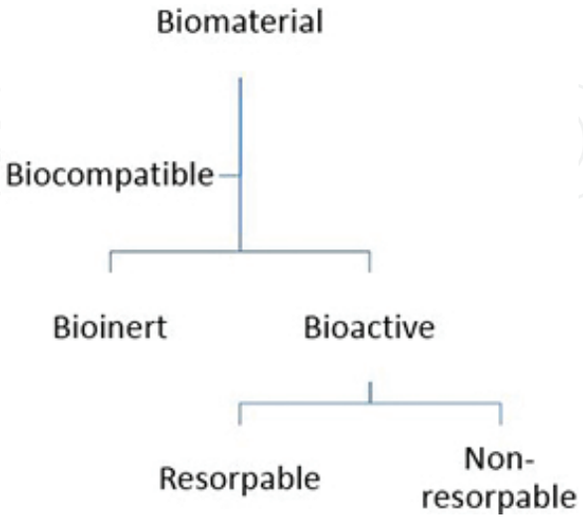

Figure 2. Figure depicting the hierarchy of biocompatible materials.

A material's characteristics (e.g. its resorbability in the body, and at what rate) is ultimately determined by their composition and the fabrication process employed. The overall process involves multiple steps that determine the structure and properties of the final product, ranging from structural modifications at the atomic level through to the gross level visible to the eye, such as colour and surface roughness. All materials have their atoms arranged in some manner, which can be altered through, for example, heat treatment. If the arrangement is homogenous throughout the material's microstructure, then it is referred to as homogenous, or single phase. However, if two or more discrete zones are evident within the microstructure, then the additional zones will be referred to as secondary, tertiary, etc., phases. Alternatively, a complete change in atomic orientation can occur, resulting in a transition of phases. Greek letters are used to denote between different phases of a material, e.g. α-titanium, β-tricalcium phosphate, etc.

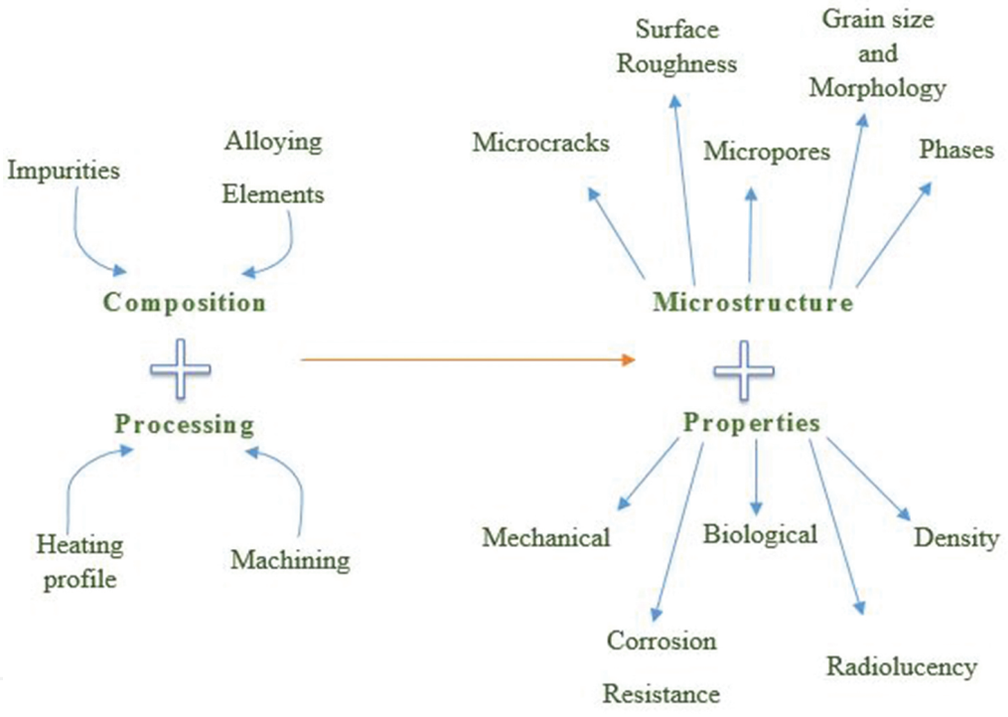

Figure 3. Figure illustrating examples for composition, processing, microstructure, and properties.

Metals are a popular choice for synthetic implants and their strength lies in the various processing routes available—owing to their mechanical properties. Their mechanical properties are either comparable or exceed that of bone. Contrarily, their chemical makeup is a limiting factor for both load and non-load-bearing orthopaedic implants. Ceramics, on the other hand, offer far more options with respect to their excellent bioactivity, but the manufacturing processes are a limiting factor that prevents them from producing the mandatory physical and mechanical properties for load-bearing applications. Therefore, the scientific interest varies for metals and ceramics. The chapter herein draws from contemporary research to provide examples of how material engineering is capitalised to tackle the challenges faced.

http://dx.doi.org/10.5772/62598

2. Metals

In general, metals possess a versatility that extends their application beyond that of other material classes, ranging from mechanical strength to bioactivity. A favourable characteristic of metals is the diversity of both the manufacturing processes available for shaping complex, porous structures, and the range of properties attainable. Metals show appreciable plasticity that allows them to be shaped either cold (ambient temperatures) or hot (high temperatures). Equally, altering their chemical composition can be achieved through a number of engineering routes. Alloying, from Old French to "combine," is a useful method of altering a metal's characteristics, including mechanical and chemical characteristics. Essentially, conventional methods entail two metals melted and combined together. A *solvent* metal (the parent metal) is combined with a *solute* metal where mixing occurs at the atomic level. The chemical outcome results in either a homogenous distribution of the combined atoms, or heterogeneous mixture with dissimilar atomic orientation.

Not all metals can be alloyed together due to factors such as atomic size, electrochemical behaviour, and valency, as well as temperature discrepancies.[1] As stated, the new changes at the atomic level can lead to profound changes to the metal's properties, such as mechanical, thermal, and wear-resistance behaviours. Moreover, subsequent fabrication processes are able to influence the final performance of the metals such as shaping, work hardening, and coating. Modifications can be made only on the surface, without a global change to the metal's structure. Treatments to the surface are effective in improving biological properties and can be both straightforward as well as cost-effective.

Metals used for implants are frequently formed from iron-, titanium-, and cobalt-based alloys. However, common iron- and cobalt-based implants (steel and cobalt-chromium alloys, respectively) are bioinert and possess mechanical properties that are deleterious to implant fixation. Titanium-based implants can be made bioactive through alloying and surface treatments, and their mechanical properties are less detrimental than steel and cobalt-chromium. Furthermore, a few metals yield degradable behaviour under physiological environment. The section herein illustrates examples of biodegradable and non-biodegradable metals, starting with the metal considered as the gold standard of metallic implants.

2.1. Non-degradable metals

2.1.1. Titanium

Titanium (Ti) and its alloys, such as the widely used Ti-6Al-4V (shortened to TAlV; contains aluminium and vanadium contents), have long been the favoured alloy for load-bearing applications [1]. While priced higher than other metals, titanium contains standout properties that make it a suitable choice for implants such as high specific strength, good corrosion resistance and biocompatibility. The latter two are attributed to the titanium oxide (TiO_2) layer

[1] As an example, the boiling temperature of magnesium is lower than the melting temperature of titanium and attempts to use the melt-driven alloy process results in partial evaporation of magnesium.

produced in the presence of oxygen that reforms within milliseconds when damaged [2]. Ti and its alloys exhibit high strength and good biocompatibility in contrast to 316L stainless steel, cobalt-chromium implants (Co-Cr). Pure titanium is stronger but also lighter with respect to steel; however, it possesses a stiffness (referred to as elastic or Young's modulus) that is several times higher than cortical bone.[2] The problem therein produces a phenomenon known as "stress shielding"—where the implant absorbs the applied stress instead of the bone which leads to the tissue resorption (i.e. dissolved). The dynamic state of bone regeneration-resorption is dictated by stress, among other factors. Tissue resorption around the implant leads to loosening and consequently a surgical revision is needed. Therefore, to ensure the longevity of titanium-based implants, the stiffness should be reduced as much as possible.

Alloying of Ti allows the compressive strength and weight benefit to be maintained above the threshold value but reduces the elastic modulus of the implant to lessen the effects of stress shielding. Furthermore, although non-modified pure Ti is unable to, TAlV can in fact bond with tissues, further securing the implant to the host's bone. Additionally, the alloy exhibits mechanical properties that are more suited for implantation than ceramics and, considering that pure titanium exhibited no cytoxicity, was conjectured to do the same. Clinical application of the alloy include fixation plates, fasteners (screws, nails, etc.), and bone replacement; however, it has been documented that aluminium and vanadium ion release from the surface can induce a plethora of side effects, such as neuropathy, Alzheimer's disease, and immunological responses, to name a few [1, 3].

In search of new alloying elements, potential metals have been evaluated in vitro, in their pure form. Niobium (Nb) and zirconium (Zr) were found to have low toxicity and higher cell proliferation detected with respect to other alloying elements, such as aluminium and molybdenum [1]. Thus, a surge of interest was generated in Ti alloys that incorporated both Zr and Nb (termed TNZ alloys). The improved biocompatibility of the TNZ alloys stems from the fact that the added elements produce a metal with ions that are less likely to elute from the implant surface as the elements are less soluble than aluminium and vanadium in biological fluids. In addition, the spontaneous coating formed (technically referred to as self-passivation) that provides greater protection to the substrate [4].

For load-bearing applications, TNZ alloys display excellent fatigue results that make them compelling for long-term load-bearing application. They could also be fabricated with a lower Young's modulus with adequate compressive strength and exhibit superior cold-forming ability with respect to other TAlV. Moreover, the alloys are cheaper to manufacture. Most of these qualities can be attributed to the rich β-phase found in TNZ. As mentioned, metals can be composed of more than one phase. Titanium can exist in a number of forms, of which the β-phase (not ordinarily seen at ambient temperatures), has been demonstrated to possess a lower elastic moduli than its counterparts, including the (α + β) phase produced in Ti-6Al-4V [4–6]. Furthermore, studies have demonstrated how porous TNZ alloys can be fabricated with a physical structure and mechanical strength suitable for load-bearing applications. Indeed,

[2] The human bone is truly a complex structure. It comprises of two sections referred to as cancellous and cortical bone. The latter has the greater mechanical properties and thereof is used as a reference for load-bearing.

http://dx.doi.org/10.5772/62598

TNZ has inherited the versatility seen in other Ti-based alloys and is a likely candidate to replace TAlV [7–9].

Surface treatments are an alternative to ensuring a firm bone-implant bond, and can be applied to both dense and porous titanium. Considering that host tissues first point of contact is with the surface, such treatments are designed to avoid altering the bulk properties of the material and, as is the case in titanium, can be an alternative to avoiding toxicological concerns. They can be designed, however, in combination with desirable bulk attributes to further enhance biological properties. There are more than one surface treatments available that can be used to coat both dense and porous titanium, such as plasma surface modification [10] and hydrothermal treatments [11, 12] that result in an improvement to the coverage of the bone around the implant. One interesting method is ultraviolet (UV) light treatment to bioinert pure titanium. The treatment is technically simple as it does not require any additional chemical, high temperatures, or mechanical processing [13, 14], and can be applied to a range of Ti and its alloys [15]. The process involves a chemical reaction where hydrocarbons that form on the surface of titanium under ambient conditions are reduced and results in an osteoinductive metal with good osteoconductive properties. Furthermore, the coverage of bone tissue on the implant was found to be almost 100%, which is unprecedented for a titanium implant, and thus the term "superosteoconductive" has been coined for such an accomplishment [14, 16, 17]. UV-light treatment was also found to prompt a similar biological effect on chromium-cobalt alloys [17].

2.1.2. Other non-biodegradable metals

Titanium belongs to a group of metals known as refractory metals that are acknowledged for their excellent corrosion resistance and, incredibly, biocompatibility—such as tantalum and niobium [18, 19]. Both metals have displayed improved bone-implant binding with respect to titanium, with tantalum (Ta) exhibiting rapid bond-binding abilities. Surface adhesion can be further enhanced using hydrothermal treatments that form a Ta-OH layer, which is effective for bonding to bone [20–22] without adverse effects. Porous Ta can be engineered using methods such as solid-free form (see next section) and conventional powder methods, with porosity of up to 85%, and pore sizes ranging from 400 to 600 μm. The compressive strength and elastic modulus can also be tailored to that of cortical bone values [23, 24]. Short-term clinical trials have shown immediate weight-bearing capabilities, as well as a high volume of patient satisfaction in multiple orthopaedic implants [25]. Current limitations of the tantalum are its high cost and high density (preventing development of larger implants). Tantalum also displays a high melting temperature (>3000°C) that makes it difficult for processing using traditional alloying methods, and thus relies on powder metallurgic[3] routes for shaping.

Niobium (Nb) has been largely used as an alloying element and a coating due to its excellent biocompatibility but has been researched recently as a possible implant candidate in its pure form due to its attractive properties [26]. Unsurprisingly, Nb can be surface treated to become

[3] Techniques were extremely high temperatures needed for traditional alloying can be circumvented. Briefly, the metal is mixed in its powder form, followed by compaction into a desired shape and sintered.

bioactive and thus form a bone-implant bonding. With regards to load-bearing applications, Nb can be combined with zirconia to form a metal-ceramic composite which is capable of bearing high loads; however, more work is needed to determine the potential of pure niobium [27].

2.2. Biodegradable metals

2.2.1. Magnesium

Unequivocally, refractory metals offer a flexibility as orthopaedic implants that are difficult to match; however, for temporary implantations, bioresorbable materials are preferred as they can prevent a second surgery. Magnesium (Mg), on the other hand, does exhibit biodegradable capabilities in physiological conditions due to the presence of chlorides that react with the surface's chemical structure. Degradation of magnesium occurs through corrosion where Mg^{2+} ions are released and hydrogen gas is produced. Incidentally, Mg^{2+} is one of the essential minerals found in our body [28], of which over half the average is located in our bone cells—and deficiencies of the element results in several bone deformities. In addition, the release of Mg^{2+} results in mineralised bone formed on the surface, with in vivo tests demonstrating strong bone-implant bonding [29]. Moreover, in its dense form, the mechanical properties are more akin with cortical bone, and, at 44 GPa, the elastic modulus of magnesium is much lower than Ti and its alloys [30]. Current interest in magnesium is directed towards fasteners and fixation plates; however, based on contemporary research, it may be conceivable to advance its usage towards bone substitution.

Although biodegradability is a sought-after property, this is found to be rapid and uncontrollable in Mg, which causes the implant to lose much of its mechanical strength rapidly due to the rate of corrosion [31]. In vitro studies of Mg have demonstrated that cracks are generated through pits created by corrosion. Furthermore, the hydrogen gas released during corrosion further exacerbates implant failure by causing brittleness to the metal [32], in what can be referred to as "self-corroding," along with damaging the surrounding cells. Fortunately, the surface of magnesium is covered by a partial oxide film when exposed to air and aqueous environments and is said that corrosion attacks are more likely to occur in interruptions in the film [33]. Therefore, taking advantage of this phenomenon can be used to combat corrosion.

Alloying is again a favourable method in addressing the corrosion-assisted failure of Mg. There are about 25 metals with an appropriate atomic size, but realistically, only a few are considered to be appropriate alloying elements, due to the restriction in solubility. This number is further reduced when considering the use of adverse-free elements. Mg can be alloyed with calcium, strontium, and zinc, which are a plausible choice from a biological perspective considering that all three alloying elements are naturally present within the human body, with both Ca and Sr involved in bone metabolism [34]. Remarkably, all three have been implicated in the retardation of corrosion in both short-term in vitro and in vivo studies, with a synergistic effect observed when Ca and Sr are incorporated simultaneously, with respect to their individual binary Mg alloys [35]. Such mechanisms included improvement to the surface coverage of the oxide film, and higher resistance to corrosion via microstructural changes (via a reduction to

http://dx.doi.org/10.5772/62598

the grain size). There are reports, however, that suggest that excess amount of calcium can lead to a decrease corrosion resistance due to the formation of an intermetallic phase, Mg_2Ca [36], hence, tailoring the degradation rate can be made to suit the lifespan of an implant. Further work is needed to elucidate the optimum composition for a suitable strike between good strength and corrosion.

Surface treatment options with emphasis on altering the chemical structure of the surface have not been studied to the same extend as titanium. Nevertheless, improving the thickness of the oxide layer can be achieved through alkaline and heat treatment on the surface, with results indicating a slower degradation rate without observable cytotoxic effects.

Corrosion pits are able to intensify crack propagation under loading. Defects formed during manufacturing can also worsen corrosion resistance [37], which is further attenuated in porous Mg due to the increased surface area (i.e. more area for the chlorine to react with the surface). Therefore, in order to be seen as a candidate for bone replacement, the aforementioned setbacks will need further investigations. Porous magnesium continues to be a matter of intensive research.

2.2.2. Other biodegradable metals

Intriguingly, magnesium is joined by both iron and zinc as part of the resurrection of biodegradable metallic implants seen over the past three decades. The metals also degrade via corrosion. Iron (Fe) from an engineering perspective offers many advantages—such as low cost, availability, and durability, to name a few. Fe is also one of the essential elements that the human body requires, which further boosts its appeal. With respect to Mg, Fe and its alloys exhibit a significantly lower degradation rate in physiological fluid [38] and higher mechanical properties [39], with an elastic modulus of ~210 GPa, which once more, can be reduced drastically by incorporating pores [40]. The degradation rate of iron can be controlled using manganese or silicon alloying elements, to either increase or reduce the rate, respectively [38, 41]. Alternatively, Fe can be prepared as a porous structure to manipulate the degradation rate.

Zinc has a biodegradability that is in between pure Mg and pure Fe and hence could offer an alternative option for biodegradable implants. Zn is generally used as an alloying element to improve magnesium's properties, including corrosion and biological, and is also important for numerous protein functions in the body [42, 43]. This has led to the notion of zinc as a possible orthopaedic implant. Pure zinc has a low strength, plasticity, and hardness that limit its usage as a biomedical implant, and thus it relies on alloying techniques to improve its strength. Unsurprisingly, investigations were conducted on incorporating magnesium, calcium, and strontium, and all were found to augment the mechanical strength of zinc [44, 45]. From an engineering perspective, zinc-based alloys possess a low melting point and low reactivity in molten state, thus can be prepared by simple melting techniques. As of yet, most research is concentrated on the use of zinc as a fixation implant, but with Zn-Mg alloys boasting a compressive yield strength double that of femoral cortical bone, its potential as a load-bearing scaffold is very promising.

2.3. Summary of metals with bioactivity

In summary, metals possess a versatility that extends their application surpassing other material classes. New techniques are being developed and added to the existing large repertoire, and clever processing tricks are used to address reservations that exist with traditional methods, such cost and complexity. The emergence of metals that can be relied on to degrade by way of corrosion as metallic grafts is encouraging, and further research could surprisingly open more avenues. There are over 90 metals found on the periodic table; however, only a select few find recurring usage as alloying elements, particularly those found naturally in the human body. However, there are concerns regarding the metallic ions released into the human body that can have debilitating consequences in the long term.

3. Ceramics and glasses

Bioactive ceramics and glasses are brittle in nature with poor tensile and fracture toughness properties, which limits their application as orthopaedic implants. However, their excellent biological properties and no cytoxicity cannot be discounted, and accordingly, there is ardent interest in producing bone graft substitutes using bioactive ceramics and glasses. In contrast to metals, there are a number of bioresorbable ceramics and bioactive glasses (BG) with excellent osseointegration where degradation occurs as a consequence of dissolution (solution-mediated) and cell-mediate degradation. Hydroxyapatite (HA) is the mineral component of human bone[4] and, alongside a number of other calcium phosphates (CaP), can induce bone regeneration. CaP are a non-toxic group of ceramics with excellent bioactivity, which can be modified based on the calcium-to-phosphate ratio present resulting in a different structure. For example, a Ca/P ratio of 1.66 is associated with hydroxyapatite, whereas a Ca/P ratio of 1.5 results in a CaP with a significantly faster rate of degradation, known as tricalcium phosphate. Synthetic HA, ($Ca_{10}(PO_4)_6(OH)_2$), can be synthesised in a number of ways, where the quantity of raw materials, as well as heat treatment applied, can modify the Ca/P ratio. Other ceramics are also biocompatible with the human body and have been extensively used as orthopaedic implants, such as alumina (Al_2O_3) and zirconia (ZrO_2), but despite having high strength and excellent corrosion resistance, they are not bioactive. BGs have excellent bioactivity, where implantation of the material is able to bind to bone by producing a layer of carbonated HA between the glass and the host's bone [46]. In general, they have better biological properties as they are both osteoinductive and osteoconductive (see chapter introduction). Clinical indications for ceramics and bioactive glasses include vertebral arthrodesis, tibial osteotomy, and for filling femur, tibia, and humerus voids caused by fractures, resection, or tumour resection. Ceramisys' ReproBone™ and Keramat's Keramedic® are commercially available ceramic bone substitutes.

[4] In its carbonated form.

http://dx.doi.org/10.5772/62598

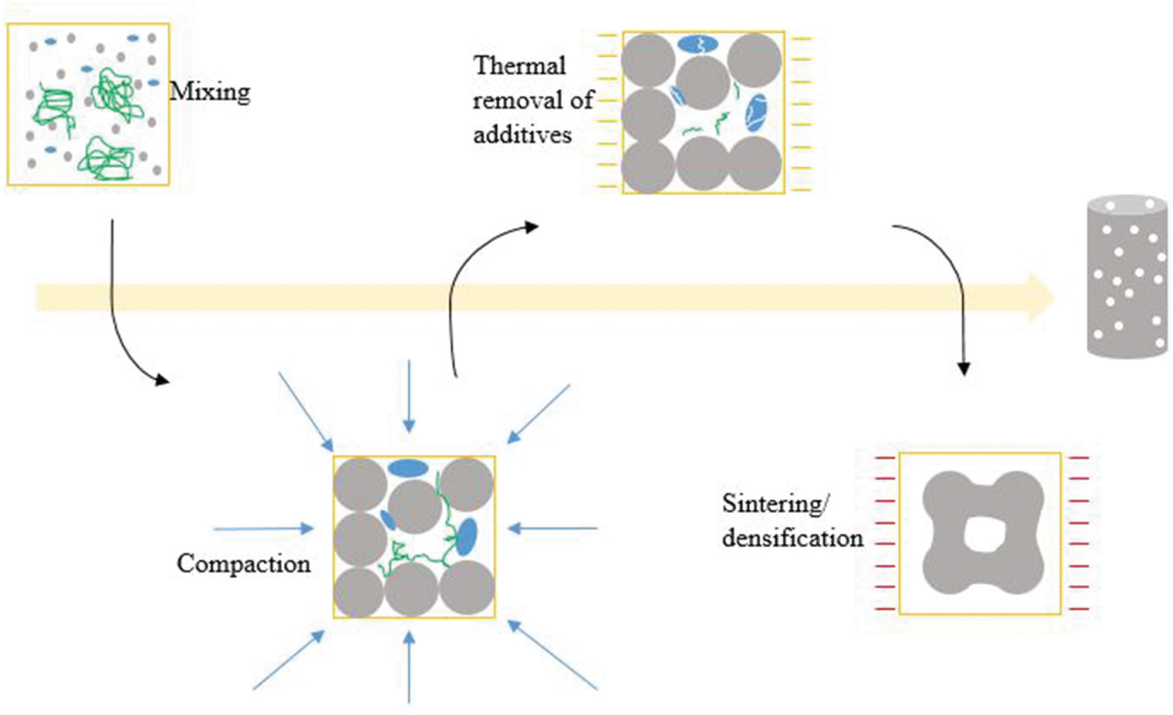

Figure 4. Schematic to illustrate the steps involved in forming ceramics using additives.

3.1. Fabrication of porous grafts

Dense hydroxyapatite displays a compressive strength that is markedly higher than cortical bone, and although it degrades at a rate well below the threshold for clinical use, it can be expedited with the implementation of pores. The quid pro quo for increased resorption due to porosity results in a substantial loss in mechanical strength. Moreover, as brittle materials with no appreciable plastic deformation (as anyone who has dropped a ceramic plate or glass beaker can attest to!), shaping of ceramics and glasses is difficult. Consequently, the outcome is a catastrophic failure in material due to microstructural flaws introduced throughout the processing stages. One possible solution is to use near-net shaping methods. Ceramic and glass in their powder form are combined with additives that introduces plasticity leading to complex, porous shapes produced. The powders are then evolved into a single solid mass through heating to remove the additives, and then subsequently heated at elevated temperatures to densify the solid mass—a process known as sintering. Plasticised ceramics with additives and a solvent are referred to as slurry or pastes. It has to be noted that removal of the non-ceramic contents presents its own problems.

Of relevance is not only complex shaping of the ceramics but the degree of porosity. Porosity and mechanical strength are mutually exclusive. The inclusion of pores contributes towards structural failure, as they are sites for crack initiators and propagation. Traditional fabrication routes have resulted in a porous scaffold with compressive strength well below the prescribed

value. Such techniques are also difficult for producing a porous structure in a controllable manner because the pores are formed randomly. Moreover, the pores generated tend to have a spherical or ellipsoidal shape, where both pore morphologies experience tensile forces under compression loading—and it is the tensile forces established that give rise to crack nucleation. Preferably, engineering a scaffold where the majority of pores are in the shape of a columnar profile (i.e. parallel and aligned) is desired as the tensile forces are limited [47], and thus improve mechanical integrity. Moreover, a scaffold with interconnected pore channels leads to enhanced bone-binding abilities, hence is also sought after in pore designs. Therefore, there is pressing concern in seeking new fabrication routes with well-defined pore architecture. The knowledge can then perhaps be used to better the commercially available scaffolds. The section hereafter details innovative methods used to improve the compressive strength.

3.1.1. Freeze casting

Freeze casting is a novel method that provides a highly porous ceramic with a well-controlled structure. Initially developed for highly dense ceramics. A porous scaffold with an aligned interconnectivity can be attained, with the added option for a hybrid porous structure if needed [48]. Freezecasting is a cost-effective method that provides a wide range of porosity in ceramics [48] and does not require the use of complicated equipment with minimal additives needed. The method entails preparing a colloidal slurry of ceramic powder with a liquid (aqueous or not), then pouring it into a mould where one end is attached to a cooling mechanism able to initiate freezing. The frozen solvent acts as a temporary binder holding the suspension together before demoulding [49]. During the freezing step, the liquid portion pushes and packs the ceramic particles as the ice crystals grow until further packing cannot occur. The frozen slurry is subjected to sublimation (i.e. converted from solid to gas state) in a freeze-dryer where the ice crystal remnants form the porous phase of the structure. The final step is sintering of the powder. Freezing liquids have a tendency to expel impurities and ceramic solutes rather than incorporating them into the crystal lattice during crystal growth which results in a preferential arrangement where spaces between ice grains are enriched with solutes [50].

One distinguishable benefit of the technique is that benign liquids can be used [51], including water and camphene without the use of solid polymeric additives, which can limit pre-sintering defects (although they can be incorporated for additional modification or improving the green strength of the scaffold). Each liquid vehicle allows for further modification of the final product as different liquids can produce a different crystal structure when frozen, thus different pore morphologies can be achieved. Opting for camphene can further reduce the complexity and the overall cost of the technique as it can form its frozen crystals at room temperature and therefore does not require complex operations below 0°C. Other processing parameters, including freezing rate, time, and holding temperature, can be adjusted to control the scaffold, along with solid loading and particle size. Particles have an extra role in that the particle surface is able to influence the nucleation of the ice crystals, thus particle morphology can be assigned to generate different pores.

http://dx.doi.org/10.5772/62598

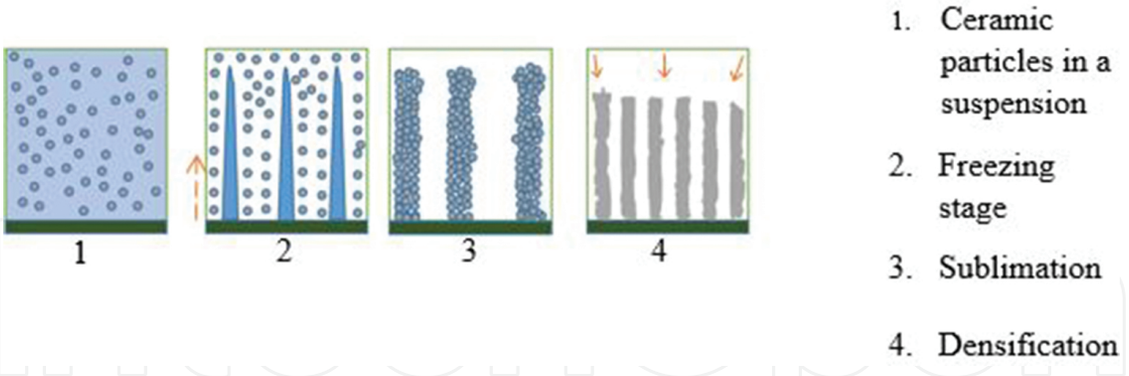

Figure 5. A schematic of the steps involved in freeze casting. The dashed arrow represents the direction of crystal growth, and the solid arrows represent the direction of densification.

With freeze casting, the removal of non-ceramic segments diminishes the drying stresses and shrinkage that are detected in other fabrication methods, therefore subsequently mitigating cracks and other defects observed before sintering [52]. Moreover, the technique allows for complex shapes to be generated, including a graded porosity where the scaffold comprises of regions with varying porous morphology [53], which is more representative of human bone. The process does not depend on chemical but on physical interaction and accordingly can be used to engineer other materials, such as bioactive glasses—or composites of bioactive glass/ceramic [54–56].

A remarkable compromise between porosity and compressive strength can be obtained using freeze casting, with recent research illustrating pore sizes ranging from 200 to 500 μm with a relatively high compressive strength comparable to that of cortical bone [49, 51, 57]. The controllable manner of porosity, as well as a high solid loading[5] of ceramic powder, is a contributory factor [58]. Equally impressive, high levels of porosity and powder loading were achieved in glass-only casts, in conjunction with compressive strength comparable to that of cortical bone [56]—hence, freeze casting is an encouraging technique for load-bearing applications.

3.1.2. Solid free form

Solid free form (SFF) is a relatively new technique developed towards the end of the last century and has gained tremendous attraction because of their ability to address key barriers faced by conventional fabrication methods. Although significant measures have been taken in mould-based fabrication routes with respect to mechanical properties, the lack of realising complex geometries, high spatial resolution of scaffold architecture, and labour-intensive procedures are considered a hindrance. Fortunately, SFF methods, also referred to as rapid prototyping or additive manufacturing, are able to address such shortcomings. SFF is an assortment of computer-controlled processes that build a scaffold from powders based on an iterative method, using a 3-dimensional (3D) computer-aided design (CAD). The computer-

[5] A high solid loading, or ceramic content, equates to improved powder packing and subsequently a densified structure with minimum unwanted gaps.

ised assistance delivers excellent reproducibility of outstanding spatial resolution. The CAD design can be based on an accurate reconstruction of the fractured site, using popular non-invasive imaging modalities such as computed tomography and magnetic resonance imaging scans, obtaining the geometry of the defect site. Thus, the techniques eliminate the need for post-processing machining of the scaffold to the desired, or incorporating "pockets" for the addition of protein carriers for a synergetic effect on healing rate if needed. The final outcome is a reduction in surgical time and cost before surgery, despite SFF techniques themselves are, by and large, more expensive than the conventional techniques used to manufacture biocer-amics.

As mentioned in the previous section, SFFs can be used to engineer metallic structure, which is a testimony to their versatility. There are distinct methods for SFFs to assemble an implant, which are divided into two classes: extrusion based or powder based. In general, the latter offers improved flexibility for complex 3D shapes and their internal architecture but it is the former, extrusion based, that has been known to realise high compressive strengths sufficient for load-bearing use. Notably, a technique known as robocasting, colloidal HA pastes with compressive strengths reaching approximately 300 MPa were achieved, whereas direct ink writing and freeze-form extrusion fabrication attained 136 MPa and 140 MPa, respectively, for bioactive glass (13–93). All three SFF techniques are capable of attaining porosity of over 40%, but the range of pore size is restricted with respect to other techniques [59–61]. Direct ink writing fabrication of the primordial 45S5 Bioglass® has also been attempted, but the com-pressive strength was insufficient for bearing loads [62]. SFFs are rapid and can incorporate other processing conditions such as porogens for additional customisation [63, 64]. The high spatial finesse of SFF leads to superior mechanical properties because of their structured architecture [65]. Although bespoke grafts for clinical use can be developed, whether such complex geometries are able to maintain their structural strength will need to be investigated. SFF are still in their early stages and their potential is yet to be realised.

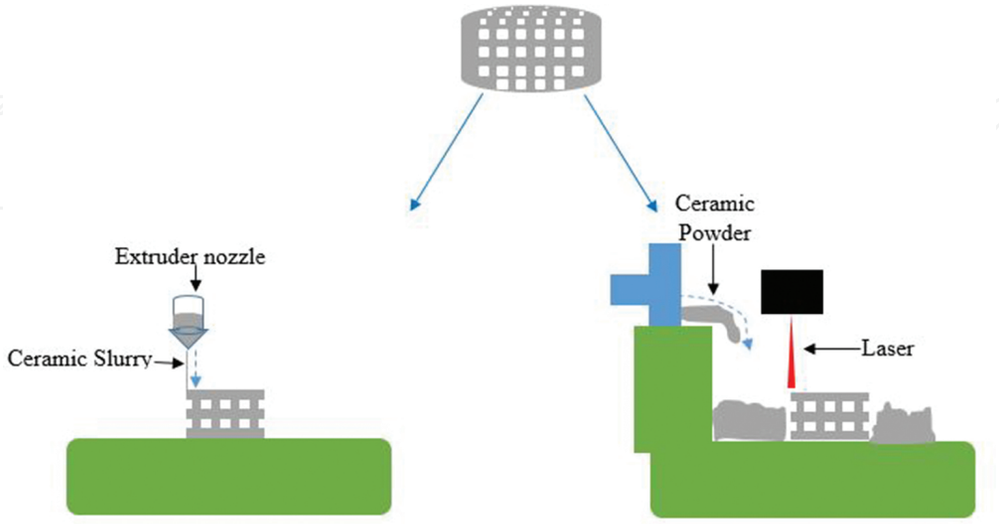

Figure 6. Schematic representing the two forms of solid free form.

http://dx.doi.org/10.5772/62598

3.2. Ionic substitution

Ionic substation, also known as doping, is analogous to alloying in metal in that essentially, elements are incorporated to produce a material where the base is still a ceramic but with a modified (and desirable) atomic structure that consequently results in altered properties. Doping of CaP is a simple technique, and more than one ionic substitution can be readily incorporated to occur simultaneously (i.e. double- or multi-substitution). Doping with fluorine is particularly favoured due to the improvement to both mechanical and biological properties in contrast to un-doped hydroxyapatite.

3.3. Summary

The strength can be enhanced if microstructural defects can be avoided, and hence the pressing concern is to seek a fabrication route that can eliminate such flaws. The section introduced examples of engineering routes capable of attaining sought-after compressive strengths, and despite their difference, the resultant research has elucidated structured porosity results in improved mechanical attributes.

Strengthening bioresorbable ceramic and glass can be achieved through minimising the processing steps in obtaining the final design, and/or minimal inclusion of non-ceramic components. The techniques described reveal that arranged pores are less susceptible to early fracturing. Such techniques carry a positive outlook and whence the fabrication methods have been perfected, they can be applied to other bioactive materials not mentioned in this section, such as calcium silicates. Incorporation of pores in a tightly controlled manner is of scientific interest because of the results on mechanical and biological properties are affected by pore morphology, and an aligned porous structure that allows for a high compressive strength to be achieved.

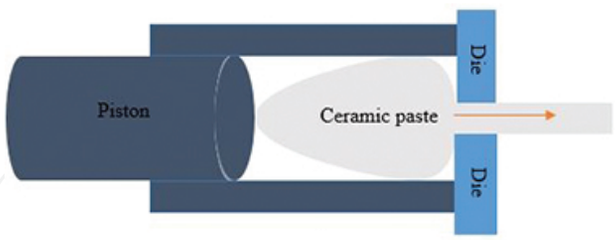

Figure 7. Extrusion schematic.

The fabrication of such pore architecture using traditional ceramic extrusion is of significant interest to the author. Extrusion is the technique of choice for imparting high strengths to ceramic in the catalyst support industry, and the aim is to transfer the accomplishment to bioactive ceramics. Essentially, a ceramic paste is forced through a honeycomb die followed by removal of additives and sintering. The desirable columnar and interconnected pores can be generated spanning the length of the scaffold as the cross-sectional features are maintained throughout the paste; and the die opted for can be designed to alter pore size, shape, and orientation. Large pressures can be generated to extrude a high solid-loading (67+ wt%)

ceramic paste that also compacts and reorients the ceramic particles for improved particle packing—thus minimising defects associated with shrinkage during drying and sintering.

4. Combined metal-ceramic approach

The human bone is fundamentally a biological composite composed of two phases where one instils strength and the other flexibility. Hence, it infers the use of synthetic composites. In principle, synthetic composites can be used to prevent elution of alloying elements in metals by applying a coating. If an enhanced bioactivity is desired throughout the implant then powder blending can be employed to embed CaP throughout the implant. The aim, once again, is to engineer an implant with both excellent mechanical properties and excellent osseointegration. Composites differ from alloying or ionic substitution in that the two amalgamated materials maintain their individualistic properties. Therefore, synthetic composites can provide an alternate route to developing new bioactive materials for load-bearing applications. The section herein provides examples of how osseointegration is improved in metallic implants through coating and powder blending.

4.1. Ceramic-metal composites

Combining ceramics and metals can be achieved through many routes, including coatings and powder blending. To reiterate, the first contact made between implant and the host occurs on the surface of the material, and thus, coating an implant can alter the host's response. This is an alternative method to addressing the ions released from metallic implants as coating with, for example, a CaP layer prevents the release of the harmful ions, effectively acting as a shield. Such coatings can be achieved either through physical or wet-chemical deposition methods. As the name suggests, physical deposition coats the designated substrate using a physical process that vaporises a solid form of CaP under vacuum (to eliminate contamination and ensure directional control). The atoms are then transferred to the surface where condensation of the vaporised atoms occurs culminating in a film coating of the substrate. Suffice it to say, this method of coating is costly as some methods require high power, and not to mention extra care is needed to ensure the method of vaporisation does not conduce decomposition of the specific CaP desired. Moreover, the physical deposition techniques are associated with "line-of-sight" coating, where the vaporised atoms coat the surface that is in-plane, and complex shapes with corners and holes are not well coated, if at all. Wet-chemical deposition on the other hand is less complex and better suited for coating intricate shapes. These techniques involve immersing or spraying a solution of highly saturated CaP to form the coating. The process does not require the same level of high temperatures allowing for organic components, such as antibiotics, to be incorporated into the process.

The two coating categories offer a range of techniques that allows for a range of possibilities —such as coating multi-doped HA, nano-range thickness, controlled porosity, and incorporating polymers, to name a few. Similarly, the substrates can be dense or porous, biodegradable, or non-biodegradable. In any case, the key considerations for a coating is to ensure

http://dx.doi.org/10.5772/62598

excellent long-term adhesion with the surface of the implant and to resist delamination due to stresses caused during the processing stage, or stresses caused by degradation under physiological milieu that will expose the substrate surface. Additionally, the purity of the CaP will need to upheld and not decompose during the process, and in the case of load-bearing application, the mechanical properties are met. Hydroxyapatite and its doped derivatives have been comprehensively used to coat metals in order to alter their biological responses—such as imparting bioactivity to a pure Ti scaffold to elicit tissue bonding [66], and on Mg and its alloys to reduce their rapid corrosion and safeguard against localised toxicity of hydrogen gas [67, 68]. Coatings are able to act as a protective layer and stop the dissolution of harmful alloying elements, in the case of Ti-6Al-4V alloys, and can also be added to ceramic-metal composites (see Section 4.3). Relatively straightforward techniques with low temperature and low energy consumption requirement, as well as environmentally conscious are available—such as electrolytic deposition—and have been experimented with positive outcomes. Nevertheless, the added processing steps of applying the coating result in the overall fabrication process incurring costs.

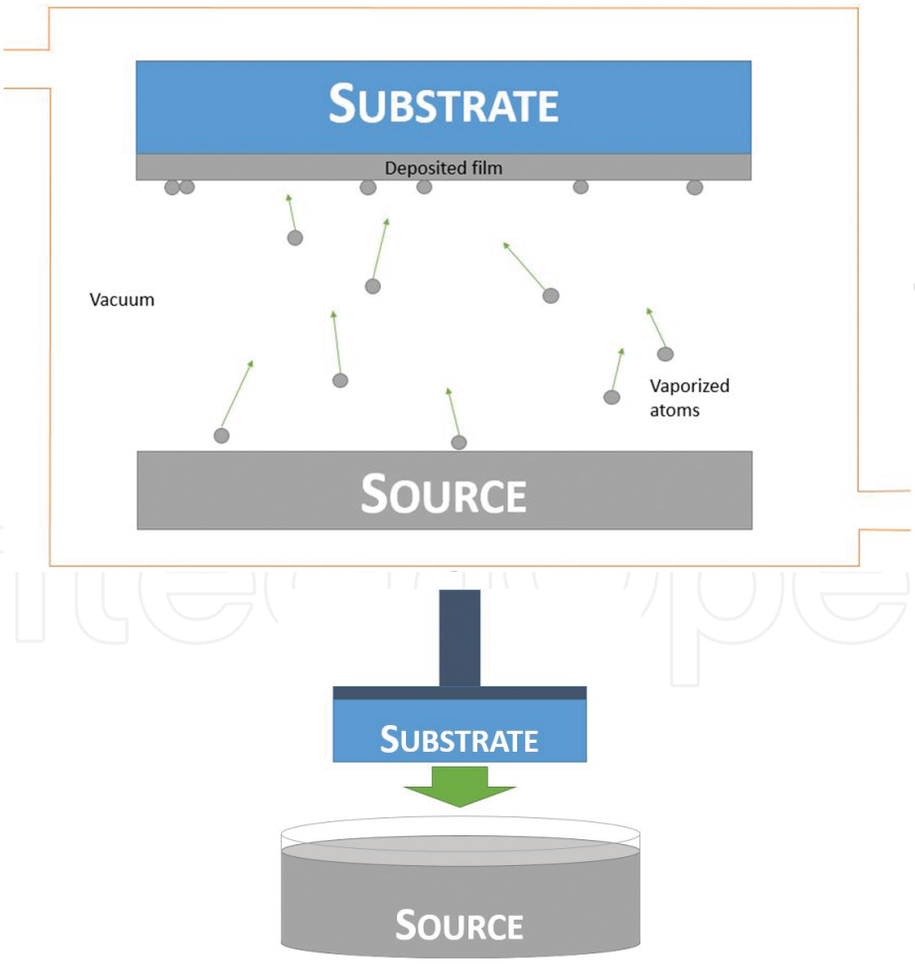

Figure 8. A representative of (a) physical and (b) wet deposition.

Other forms of ceramic-metal composites can be attained through the powder blending route. Metallic powders of iron and magnesium can be homogenously mixed with CaP powders, followed by consolidation and densification. This can be an ideal method if the strategy is to impart the desired qualities (e.g. ductility) throughout a porous structure rather than purely on the surface. Considerations such as mixing time and sintering temperatures need to be determined without resulting in contaminations by milling apparatus[6] or decomposition of CaP, respectively. In order to avoid the latter issue, Choy et al. [69] used microwave synthesis of a Ti-CaP composite to avoid using high temperatures, where materials absorb electromagnetic energy that are produced by the microwave and subsequently convert it into heat energy. Additional benefits of the technique include fast reaction rate and efficient energy transformation. A Ti-CaP composite with excellent mechanical properties comparable to cortical bone was fabricated by mixing and reacting Ti with two precursors of HA (calcium carbonate and dicalcium phosphate dihydrate in this case). Interestingly, it was discovered that the in situ synthesis method chosen resulted in the presence of Ti, HA, TTCP, and $CaTiO_3$, indicating that the calcium precursors were able to react indiscriminately with the Ti. Incidentally, $CaTiO_3$ was claimed to facilitate apatite formation in vitro.[7]

4.2. Same material composites

A titanium-magnesium porous composite is one example of two metals combined, and can be achieved in a number of ways to form a semi-biodegradable metallic implant—including powder blending, melt infiltration casting, or as a layered structure. Porosity and compressive strength suitable for bearing loads are attainable, but this depends on the amount of magnesium, which is significantly altered in situ as corrosion of Mg takes place.

5. Conclusion

Contemporary research in bioactive metals and ceramics for load-bearing application is focused on bridging the gap between mechanical properties and biocompatibility. The fabrication techniques detailed in this chapter have demonstrated that great strides have been made and in doing so, can potentially be applied to improve on existing orthopaedic implants. The chapter also presented materials that are yet to be used in load-bearing application, such as zinc and niobium, but have great potential in doing so. With regards to metals, mitigating the toxicity of their respective ions is the major focus. This can be achieved through alloying with elements that are less toxic, or improving the coating on the implant to ensure ion release is minimised. Emerging biodegradable metals, such as magnesium and iron, are highly promising as they can reduce the overall healthcare cost. These metals degrade in the body through corrosion, and, as they are naturally found in the body, they can be excreted. The message from bioactive metals is that if the metal is naturally found in the body, then it is

[6] Wear from the container for example in which the powders are mixed can form into the mixture.

[7] Intriguingly, this is a clear example of how an attempt to address an issue results in more questions and possibilities in biomaterial engineering.

http://dx.doi.org/10.5772/62598

corroded and thus resorbed. If not, then if binding should occur, improved binding is achieved if a ceramic coating is formed, for example, TiO_2 on titanium-based implant. This is interesting considering that metals such as titanium and tantalum are extracted in their oxide form and are followed by arduous processing to achieve high levels of purity, for only osseous tissues to show preference to their oxide form. Perhaps if certain steps necessary for achieving high purity can be avoided, then this could lessen the costs associated with the manufacturing steps, and thus implant fabrication.

Many ceramics and glasses display excellent bioactivity and are toxic-free. This is to be expected considering that they have been synthesised based on the composition of natural bone. Forming ceramics and glass into complex shapes is difficult irrespective of the application due to their inherent properties; however, progress is being made to eliminate such factors. The chapter on ceramics and glasses focused predominantly on fabrication routes with "ideal" porous structure. Such techniques have elucidated to how compressive strength for load-bearing application is attainable in porous CaP if excellent control over the physical properties can be achieved. However, the bone exhibits multiple stress states which will all need to be addressed before clinical application is considered. To achieve desirable flexural (bending) strength and fracture toughness, the fabrication method could use a CaP reinforced with ceramics that possess high toughness and flexural strength. Reinforcing dense β-TCP composite with varying amounts of the bioactive TiO_2 is known to increase the fracture toughness and flexural strength similar to that of cortical bone. Recent progress showed that an eight-fold increase in compressive strength in HA reinforced with TiO_2 above the required amount, with respect to TiO_2-free HA. Alternatively, hydroxyapatite rod-like particulates, also known as whiskers, can be incorporated into the CaP matrix. Although a form of CaP, the whiskers are able to preserve their morphology during sintering, forming a distinct phase from the surrounding CaP. When dispersed throughout the microstructure, whiskers improve the fracture resistance by deflecting microcrack propagation, as well as absorbing the energy generated by the microcrack. Factors such as the aspect ratio, whisker orientation, and content volume influence their effectiveness. Incidentally, natural bone exhibits crack deflection behaviour. Therefore, in theory, fabricating CaP using freeze casting or extrusion with reinforced whiskers or TiO_2 can enhance flexural strength and/or fracture toughness, and thus CaP implants can be made suitable for multiple stress states.

The final section of the chapter presented examples of how ceramics and materials can be combined to produce synthetic implants with excellent bioactivity and mechanical properties. A CaP coating can be applied to titanium or magnesium to impart bioactivity or improve corrosion resistance, respectively. However, the extra process required additional costs.

Titanium-based materials still remain as the exemplary implant for load-bearing application. The fatigue resistance and analysis of multiple stress responses of biodegradable materials have not been concluded, and indeed, there are concerns with their ability to reach the benchmark set by titanium-based materials. However, if they can be engineered to withstand the initial load and allow for natural bone to remodel, then what synthetic material currently available (and possibly for the very long foreseeable future) is able to outperform the natural bone? Furthermore, the great diversity in bone morphology means that there is no ideal

scaffold and thus each application requires a bespoke graft with matching mechanical properties, which will need to be addressed.

It is evident from this chapter that material engineers are exhausting their resources and developing ingenious methods in the process to improving bioactive implants. There are issues regarding the rate of degradation of bioresorbable implants; however, different materials (e.g. magnesium and zinc) degrade at varying rates. It will be interesting to see if technology can allow for a multi-layered bioresorbable implant can be engineered (the different layers corresponding to different bioresorbable materials). Investigations into finding ways of degrading titanium could be interesting. The conjecturing of future directions in the field is limitless and thus it can be said with confidence that the future of the field is very encouraging.

Author details

Mohammed Elbadawi[1*], James Meredith[1], Lynne Hopkins[2] and Ian Reaney[2]

*Address all correspondence to: melbadawi1@sheffield.ac.uk

1 Department of Mechanical Engineering, University of Sheffield, Sheffield, United Kingdom

2 Department of Material Science and Engineering, University of Sheffield, United Kingdom

References

[1] Stenlund P., et al., *Bone response to a novel Ti–Ta–Nb–Zr alloy.* Acta Biomaterialia, 2015. 20: p. 165–175.

[2] Velten D., et al., *Preparation of TiO2 layers on cp-Ti and Ti6Al4V by thermal and anodic oxidation and by sol–gel coating techniques and their characterization.* Journal of Biomedical Materials Research, 2002. 59(1): p. 18–28.

[3] Aguilar C., et al., *Synthesis and characterization of Ti–Ta–Nb–Mn foams.* Materials Science and Engineering: C, 2016. 58: p. 420–431.

[4] Henriques V., et al., *Production of Ti–13Nb–13Zr alloy for surgical implants by powder metallurgy.* Journal of Materials Science Letters, 2010. 45(21): p. 5844–5850.

[5] Bai Y., et al., *Characterization, corrosion behavior, cellular response and in vivo bone tissue compatibility of titanium-niobium alloy with low Young's modulus.* Materials Science & Engineering. C, Materials for Biological Applications, 2016. 59: p. 565.

[6] Ozan S., et al., *Development of Ti–Nb–Zr alloys with high elastic admissible strain for temporary orthopedic devices.* Acta Biomaterialia, 2015. 20: p. 176–187.

[7] Rao X., Chu C.L., and Zheng Y.Y., *Phase composition, microstructure, and mechanical properties of porous Ti–Nb–Zr alloys prepared by a two-step foaming powder metallurgy method.* Journal of the Mechanical Behavior of Biomedical Materials, 2014. 34: p. 27–36.

[8] Wang X., et al., *Porous TiNbZr alloy scaffolds for biomedical applications.* Acta Biomaterialia, 2009. 5(9): p. 3616–3624.

[9] Sheremetyev V., et al., *Functional fatigue behavior of superelastic beta Ti-22Nb-6Zr(at%) alloy for load-bearing biomedical applications.* Materials Science and Engineering C, 2016. 58: p. 935–944.

[10] Chu P.K., et al., *Plasma-surface modification of biomaterials.* Materials Science and Engineering: R: Reports, 2002. 36(5–6): p. 143–206.

[11] Hamada K., et al., *Hydrothermal modification of titanium surface in calcium solutions.* Biomaterials, 2002. 23(10): p. 2265–2272.

[12] Takemoto S., et al., *Corrosion behavior and surface characterization of titanium in solution containing fluoride and albumin.* Biomaterials, 2005. 26(8): p. 829–837.

[13] Tsukimura N., et al., *Synergistic effects of UV photofunctionalization and micro-nano hybrid topography on the biological properties of titanium.* Biomaterials, 2011. 32(19): p. 4358–4368.

[14] Hori N., et al., *Effects of UV photofunctionalization on the nanotopography enhanced initial bioactivity of titanium.* Acta Biomaterialia, 2011. 7(10): p. 3679–3691.

[15] Ishijima M., et al., *Enhancing osteoblast-affinity of titanium scaffolds for bone engineering by use of ultraviolet light treatment.* Biomedical Research (Japan), 2015. 36(1): p. 55–62.

[16] Hori N., et al., *Electrostatic control of protein adsorption on UV-photofunctionalized titanium.* Acta Biomaterialia, 2010. 6(10): p. 4175–4180.

[17] Att W., et al., *The effect of UV-photofunctionalization on the time-related bioactivity of titanium and chromium–cobalt alloys.* Biomaterials, 2009. 30(26): p. 4268–4276.

[18] Matsuno H., et al., *Biocompatibility and osteogenesis of refractory metal implants, titanium, hafnium, niobium, tantalum and rhenium.* Biomaterials, 2001. 22(11): p. 1253–1262.

[19] Levine B.R., et al., *Experimental and clinical performance of porous tantalum in orthopedic surgery.* Biomaterials, 2006. 27(27): p. 4671–4681.

[20] Godley R., StarosvetskyD., and GotmanI., *Bonelike apatite formation on niobium metal treated in aqueous NaOH.* Official Journal of the European Society for Biomaterials, 2004. 15(10): p. 1073–1077.

[21] Gao H., et al., *Bioactive tantalum metal prepared by micro-arc oxidation and NaOH treatment.* Journal of Materials Chemistry B, 2014. 2(9): p. 1216–1224.

[22] Kokubo T., et al., *REVIEW Bioactive metals: preparation and properties.* Official Journal of the European Society for Biomaterials, 2004. 15(2): p. 99–107.

[23] Balla V., et al., *Tantalum—a bioactive metal for implants.* The Journal of The Minerals, Metals & Materials Society (TMS), 2010. 62(7): p. 61–64.

[24] Arabnejad S., et al., *High-strength porous biomaterials for bone replacement: a strategy to assess the interplay between cell morphology, mechanical properties, bone ingrowth and manufacturing constraints.* Acta Biomaterialia, 2016. 30: p. 345–356.

[25] Long W.J. and Scuderi G.R., *Porous tantalum cones for large metaphyseal tibial defects in revision total knee arthroplasty: a minimum 2-year follow-up.* The Journal of Arthroplasty, 2009. 24(7): p. 1086–1092.

[26] Johansson C.B. and Albrektsson T., *A removal torque and histomorphometric study of commercially pure niobium and titanium implants in rabbit bone.* Clinical Oral Implants Research, 1991. 2(1): p. 24–29.

[27] Bartolomé J.F., et al., *In vitro and in vivo evaluation of a new zirconia/niobium biocermet for hard tissue replacement.* Biomaterials, 2016. 76: p. 313–320.

[28] Mochizuki A. and Kaneda H., *Study on the blood compatibility and biodegradation properties of magnesium alloys.* Materials Science & Engineering C, 2015. 47: p. 204–210.

[29] Berglund I.S., et al., *Peri-implant tissue response and biodegradation performance of a Mg–1.0Ca–0.5Sr alloy in rat tibia.* Materials Science and Engineering: C, 2016. 62: p. 79–85.

[30] Pompa L., et al., *Surface characterization and cytotoxicity response of biodegradable magnesium alloys.* Materials Science and Engineering: C, 2015. 49: p. 761–768.

[31] Jafari S., Singh Raman R.K., and Davies C.H.J., *Corrosion fatigue of a magnesium alloy in modified simulated body fluid.* Engineering Fracture Mechanics, 2015. 137: p. 2–11.

[32] Atrens A., Liu M., and Zainal Abidin N.I., *Corrosion mechanism applicable to biodegradable magnesium implants.* Materials Science & Engineering B, 2011. 176(20): p. 1609–1636.

[33] Atrens A., et al., *Advances in Mg corrosion and research suggestions.* Journal of Magnesium and Alloys, 2013. 1(3): p. 177–200.

[34] Guan, R.-g., et al., *Development and evaluation of a magnesium–zinc–strontium alloy for biomedical applications—alloy processing, microstructure, mechanical properties, and biodegradation.* Materials Science & Engineering C, 2013. 33(7): p. 3661–3669.

[35] Bornapour M., et al., *Magnesium implant alloy with low levels of strontium and calcium: the third element effect and phase selection improve bio-corrosion resistance and mechanical performance.* Materials Science & Engineering C, 2014. 35: p. 267–282.

[36] Harandi S.E., et al., *Effect of calcium content on the microstructure, hardness and in-vitro corrosion behavior of biodegradable Mg-Ca binary alloy.* Materials Research, 2013. 16: p. 11–18.

[37] Singh Raman R.K., S. Jafari, and S.E. Harandi, *Corrosion fatigue fracture of magnesium alloys in bioimplant applications: a review.* Engineering Fracture Mechanics, 2015. 137: p. 97–108.

[38] Xu Z., Hodgson M.A., and Cao P., *A comparative study of powder metallurgical (PM) and wrought Fe–Mn–Si alloys.* Materials Science and Engineering: A, 2015. 630: p. 116–124.

[39] Schinhammer M., et al., *Design strategy for biodegradable Fe-based alloys for medical applications.* Acta Biomaterialia, 2010. 6(5): p. 1705–1713.

[40] Čapek J., et al., *Microstructural, mechanical, corrosion and cytotoxicity characterization of the hot forged FeMn30(wt.%) alloy.* Materials Science and Engineering C, 2016. 58: p. 900–908.

[41] Fântânariu M., et al., *A new Fe–Mn–Si alloplastic biomaterial as bone grafting material: In vivo study.* Applied Surface Science, 2015. 352: p. 129–139

[42] Zakiyuddin A. and LeeK., *Effect of a small addition of zinc and manganese to Mg–Ca based alloys on degradation behavior in physiological media.* Journal of Alloys and Compounds, 2015. 629: p. 274–283.

[43] Zhou Y.-L., et al., *Microstructures, mechanical and corrosion properties and biocompatibility of as extruded Mg–Mn–Zn–Nd alloys for biomedical applications.* Materials Science and Engineering: C, 2015. 49: p. 93–100.

[44] Kubásek J., et al., *Structure, mechanical characteristics and in vitro degradation, cytotoxicity, genotoxicity and mutagenicity of novel biodegradable Zn-Mg alloys.* Materials Science & Engineering. C, Materials for Biological Applications, 2016. 58: p. 24.

[45] Liu X., et al., *Effects of alloying elements (Ca and Sr) on microstructure, mechanical property and in vitro corrosion behavior of biodegradable Zn–1.5Mg alloy.* Journal of Alloys and Compounds, 2016. 664: p. 444–452.

[46] Hoppe A., Güldal N.S., and Boccaccini A.R., *A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics.* Biomaterials, 2011. 32(11): p. 2757–2774.

[47] Huang T.S., et al., *Porous and strong bioactive glass (13–93) scaffolds fabricated by freeze extrusion technique.* Materials Science & Engineering C, 2011. 31(7): p. 1482–1489.

[48] Liu R., XuT., and Wang C.-A., *A review of fabrication strategies and applications of porous ceramics prepared by freeze-casting method.* Ceramics International, 2016. 42(2, Part B): p. 2907–2925.

[49] Deville S., Saiz E., and Tomsia A.P., *Freeze casting of hydroxyapatite scaffolds for bone tissue engineering.* Biomaterials, 2006. 27(32): p. 5480–5489.

[50] Pawelec K., et al., *Ice-templated structures for biomedical tissue repair: from physics to final scaffolds.* Applied Physics Reviews, 2014. 1(2): p. 021301-1 – 021301-13

[51] Wegst U.G.K., et al., *Biomaterials by freeze casting.* Philosophical Transactions of the Royal Society A, 2010. 368(1917): p. 2099–2121.

[52] Macchetta A., Turner I.G., and Bowen C.R., *Fabrication of HA/TCP scaffolds with a graded and porous structure using a camphene-based freeze-casting method.* Acta Biomaterialia, 2009. 5(4): p. 1319–1327.

[53] Tang Y., et al., *Two-step freeze casting fabrication of hydroxyapatite porous scaffolds with bionic bone graded structure.* Ceramics International, 2013. 39(8): p. 9703–9707.

[54] Mozafari M. and Moztarzadeh F., *Synthesis, characterisation and biocompatibility evaluation of sol–gel derived bioactive glass scaffolds prepared by freeze casting method.* Ceramics International, 2014. 40(4): p. 5349–5355.

[55] Mallick K.K., *Freeze casting of porous bioactive glass and bioceramics.* Journal of the American Ceramic Society, 2009. 92: p. S85–S94.

[56] Liu X., Rahaman M., and Fu Q., *Oriented bioactive glass (13–93) scaffolds with controllable pore size by unidirectional freezing of camphene-based suspensions: microstructure and mechanical response.* Acta Biomaterials, 2011. 7(1): p. 406–416.

[57] Deville S., *Freeze-casting of porous ceramics: a review of current achievements and issues.* Advanced Engineering Materials, 2008. 10(3): p. 155–169.

[58] Soon Y.-M., et al., *Compressive strength and processing of camphene-based freeze cast calcium phosphate scaffolds with aligned pores.* Materials Letters, 2009. 63(17): p. 1548–1550.

[59] Dellinger J.G., Wojtowicz A.M., and Jamison R.D., *Effects of degradation and porosity on the load bearing properties of model hydroxyapatite bone scaffolds.* Journal of Biomedical Materials Research Part A, 2006. 77(3): p. 563–571.

[60] Fu Q., Saiz E., and Tomsia A.P., *Direct ink writing of highly porous and strong glass scaffolds for load-bearing bone defects repair and regeneration.* Acta Biomaterialia, 2011. 7(10): p. 3547–3554.

[61] Huang T.S., et al., *Porous and strong bioactive glass (13–93) scaffolds fabricated by freeze extrusion technique.* Materials Science and Engineering: C, 2011. 31(7): p. 1482–1489.

[62] Eqtesadi S., et al., *A simple recipe for direct writing complex 45S5 Bioglass® 3D scaffolds.* Materials Letters, 2013. 93: p. 68–71.

[63] Leong K.F., Cheah C.M., and Chua C.K., *Solid freeform fabrication of three-dimensional scaffolds for engineering replacement tissues and organs.* Biomaterials, 2003. 24(13): p. 2363–2378.

[64] Cesarano J., et al., *Customisation of load-bearing hydroxyapatite lattice scaffolds.* International Journal of Applied Ceramic Technology, 2005. 2(3): p. 212–220.

[65] Doiphode N., et al., *Freeze extrusion fabrication of 13–93 bioactive glass scaffolds for bone repair.* Official Journal of the European Society for Biomaterials, 2011. 22(3): p. 515–523.

[66] Gopi D., Shinyjoy E., and Kavitha L., *Influence of ionic substitution in improving the biological property of carbon nanotubes reinforced hydroxyapatite composite coating on titanium for orthopedic applications.* Ceramics International, 2015. 41(4): p. 5454–5463.

[67] Zhang J., et al., *Effect of the addition CNTs on performance of CaP/chitosan/coating deposited on magnesium alloy by electrophoretic deposition.* Materials Science and Engineering C, 2016. 58: p. 992–1000.

[68] Zomorodian A., et al., *Biofunctional composite coating architectures based on polycaprolactone and nanohydroxyapatite for controlled corrosion activity and enhanced biocompatibility of magnesium AZ31 alloy.* Materials Science & Engineering C, 2015. 48: p. 434–443.

[69] Choy M., et al., *Microwave assisted-in situ synthesis of porous titanium/calcium phosphate composites and their in vitro apatite-forming capability.* Composites Part B: Engineering, 2015. 83: p. 50–57.

IntechOpen