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Factors influencing osseointegration: A review

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Abstract

Nowadays, additive manufacturing is becoming more and more widespread and has also entered medical practice. Many implants are made using AM technology, which allows implants to be fully customisable. However, the osseointegration of prostheses is influenced by a number of factors, such as the material of the prosthesis and the size of the pores in the prosthesis. The aim of this study is to present the potential of different additively manufactured prostheses and to illustrate the limitations of their application based on a comprehensive literature review. This will provide a comprehensive overview of engineering and the latest manufacturing technologies and medical applications.[1-21]

Keywords: additive manufacturing (AM), medical implants, prosthesis materials, osseointegration, pore size

Introduction

Implants must promote load distribution, thus ensuring optimal mechanical stress on bones. Nowadays, implants are increasingly made using some form of additive technology, creating diverse structures. Different prostheses are most commonly produced using SLS technology. Prostheses made from various materials have different pore sizes, but in manufacturing, efforts are always made to create a connection between the bone and prosthesis, meaning the size of the prosthesis pores should be close to the size of the bone pores.[1,2,3,9,11-16,20,21]

Research methodology

We started to investigate the factors influencing bone integration based on currently available studies. We started by searching for key words that were important to us, such as pore size, porosity, implant material, etc. Based on this, we selected approximately 70 studies and processed them. In many of the studies we

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found similarities in the results and methods of the experiments, so we subsequently relied on data that reached similar conclusions to each other. On this basis, we analysed the results of the literature cited in the reference. Most of the keyword papers were published by Elsevier, ScienceDirect and ResearchGate.

Factors influencing osseointegration

The manufacturing process of implants The process begins with digitization, based on CT scans[21] of the patient for implants and bone replacements. Subsequently, a virtual model of the relevant replacement or the combination of bone and implant is created. The implant is then designed and subjected to various calculations and loads before manufacturing begins. The selection of suitable materials and finite element modeling are important steps in determining critical points and stresses. Following this are the test constructions and in-vitro tests. Biomechanical tests then follow.[1,5] Several factors must be taken into account for implants and tissues. For implants placed directly into bone tissue, the following factors are significant:

- biocompatibility
- porosity
- surface properties
- osseoconductivity
- mechanical properties
- biological degradability
- grain separation[2]

The most important factors are described below.

Biocompatibility

It is a crucial factor, as it can trigger pathological processes in the body (inflammation, rejection, infection). Therefore, only materials that do not release harmful substances into the body should be used. For example, copper, when used as an alloy at a certain percentage, has antibacterial properties. Porosity is also a major influencing factor for integration. For example, in the case of a hip prosthesis, it is important for the head of the prosthesis to fit properly with the bones and have a surface able to embed into the bone tissue. This way, the implant can fully assume the role of the damaged bone. For bone tissue, the ideal porosity is between 200-900 μm. Surface chemical and topographical regulation is necessary for creating proper bonds. This is mostly achieved with various grid designs, allowing the bone tissue to not only bind to the surface of the implant but also embed between the grids and initiate tissue growth. Therefore, the material of the implant is also taken into account, specifically osseoconductivity, which characterizes the regeneration and formation of new tissues. Mechanical properties are also important, as the implant must have properties similar to bone, including matching tensile strength, elongation at break, and viscoelastic behavior, being a non-corrodible material.[2]

Pore size

From the perspective of bone integration, the most favorable design is a surface with some porous or roughness, as we will see later. The most important parameters for implant integration are pore size, density, and shape.[5] Van Bael and colleagues carried out a study on how the shape and size of the pore affects bone formation. The study was carried out with three different pore shapes (triangular, hexagonal and rectangular) and two different pore sizes (500 μm and 1000 μm). For the study, the test pieces were fabricated from titanium alloy using SLM technology.[6] In the case of larger pores, cells and tissues were attached to a single strand. It was found that a larger pore size is more advantageous, as it does not block cell growth in smaller pores, thus preventing further cell growth. Pore sizes in bones vary, with sizes ranging in the macro and nano range, so AM implants must follow this porosity to ensure proper osseointegration. For AM components, this structure can be easily achieved, unlike traditional manufacturing. This porosity is necessary for cell attachment, growth, and division. In the case of additively manufactured components, two types of pores occur. One type is between particles, the other type is pre-determined pores resulting from the lattice structure, as shown in *Figure 1*. Connections can be formed between these pores, open and closed pores can be formed. In general, pores between particles are not desired during production, as errors may occur around them. The pore size is essential from the perspective of bone integration, so the implant and bone pore sizes should be close to each other to initiate bone tissue growth on the prosthesis surface. The ideal pore size is between 100 and 400 μm.[3] Above this size range, it is more difficult for bone tissue to attach. Deviations can be observed compared to the values found in the literature. According to other studies[7], a 500 μm pore size is more favorable than 700 and 1000 μm pores. The optimal range has been determined to be approximately 300-600 μm.

The ideal pore size for orthopedic implants is still a subject of debate, with no uniformly accepted size, only recommendations for the optimal range.[9] Some suggest 100-400 μm[9], however, Itala and colleagues[10] found this value to be 50-125 μm when studying rabbit bones. Kuboki and colleagues[20], determined the pore size in HA (hydroxyapatite) samples to be 300-400 μm, while smaller (90-120 μm) pores may induce cartilage formation, larger (~350 μm) pores initiate bone formation. Karageorgiou and group[11] found that the minimal pore size is ~100 μm, while the larger pore size can be ~300 μm. This shows that there is no consensus on pore size. In a study by Taniguchi[12] on the formation of bone and blood vessels using titanium with pore sizes of 300, 600, 900 μm, it was found that 600 μm proved suitable for implantation after 2 weeks, but 300 μm was more suitable 4 weeks later. The mechanical properties of SLM printed Ti6Al4V alloy are similar to those of bones, so the next study will examine the pore sizes of this material. Cell differentiation can occur with small pores (401 ± 26 μm), but to promote bone tissue growth, it is recommended to increase the pore size, with 607 ± 24 μm being found suitable based on studies.[9] Various manufacturing processes can cause surface defects on the component, and these must be removed before application. When implanting the implant, a connection is established between the bone and the surface of the implant. At this connection, a boundary interface is formed with different properties. Surface morphology affects the speed and quality of bone tissue formation. Various post-treatment solutions are available to optimize surface morphology.[8]

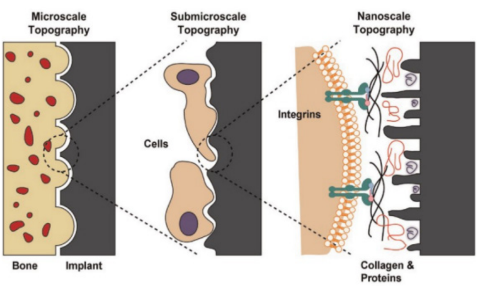

Figure 1. Formation of the connection between the implant and cells

Porosity

The porosity shows the percentage of voids compared to the solid material, and its value is influenced by pore size, pore thickness, and pore thickness. Higher porosity is favorable for the formation and growth of bone cells, as more porous material results in a larger surface area.[3]

Lattice topologies

The most popular grids include the cube, center-centered cube, and surface-centered cube, as well as their combinations. The different lattice structures have different mechanical properties and can withstand different directions of loads.[3]

Materials for implants

Several types of materials can be used in additive manufacturing.[3-5,13-19] Metals, polymers, ceramics, composites, and other special materials can be used, including biomaterials, memory-shape materials, etc.

Metals: Metals are important in various implant applications due to their corrosion resistance, load-bearing capacity, and fatigue limit being higher than those of polymers and ceramics, resulting in longer lifespan and better load capacity approaching that of the human skeleton. Another important consideration is biocompatibility. In orthopedic implants, important properties include modulus of elasticity, toughness, and hardness. Surface roughness is also important for implants, as it greatly influences bone integration, i.e., osseointegration.[5]

There are special alloys among metals, such as biodegradable metals, which have the advantage of not requiring secondary surgical removal as they are absorbed along with healing. Magnesium alloys are the most commonly used, primarily in cardiovascular stents, bone screws, and fixation plates. For example, Fe-Mg-Si alloy, known for its shape memory effect, high hardness, strength, and resistance to fatigue.[4,13]

Another group of special metals are shape memory alloys, which regain their original shape and size after the stress is removed within a specific temperature range through heating or martensitic transformation. A porous fixation can be made from the alloy using AM technology, providing adequate stiffness until complete healing. Once the bone is fully healed, it returns elastically to normal stress distribution. This property is also used in the production of spine implants due to its good corrosion resistance, wear resistance, and biocompatibility.[4,13] Based on the above requirements, the following materials are commonly used for implants among metals:

- Cobalt-chromium alloys
- Tantalum alloys
- Titanium alloys
- Stainless steels 5

Stainless Steels: Common materials for orthopedic implants due to their mechanical strength, corrosion resistance, and biocompatibility, primarily used to make screws and plates for fracture fixation.[4,5,14-17]

Cobalt-Chromium Alloys: Widely used as prosthetic materials, such as knee, shoulder, and hip prostheses. With the advent of AM technology, better mechanical properties have been achieved. Currently, CoCrMo and CoNiCrMo alloys are used as implants. They are corrosion-resistant alloys but not suitable for use as hinge implant materials due to poor friction conditions.[3-5,15-17]

Tantalum Alloys: Excellent corrosion resistance and biocompatibility, with mechanical properties similar to bone. Used as an insert material in hip prostheses. The use of porous tantalum rods in knee prostheses prevents femoral bone necrosis. The AM technology makes production more economical than traditional method.[3,4]

Titanium Alloys: Well-established alloys in orthopedics due to their high strength-to-density ratio, excellent corrosion resistance, and biocompatibility.[15] Various AM technologies affect the mechanical properties of the alloy.[4,5] Vanadium, when released into the body, can cause toxic side effects, leading to the development of alloys that retain favorable properties but without toxicity. Mechanical properties are higher than stainless steel, with lower bending stiffness compared to stainless steel and cobalt-chromium-molybdenum alloys.[4]

Ceramics: Inorganic compounds with ionic or covalent bonding. Ceramic materials used in medicine are generally bio-ceramics, either bioinert (aluminum oxide, zirconium oxide), bioresorbable (tricalcium phosphate), biologically active (hydroxyapatite, bioactive glasses), or porous ceramics (hydroxyapatite).[5,15,17,18] Ceramics are commonly used in orthopedic implants, such as bone plates, screws, spinal prostheses, spacers, with more frequent use in dental applications like implants and orthodontics.[17]

The implants were classified into three groups based on their biocompatibility by Barfeie et al:

- Biotolerant: The material does not reject the tissue, but a fibrous "capsule" forms around it.
- Bioinert: The materials closely interact with the bone surface.
- Bioactive: New bone formation starts on the surface, and chemical bonds form at the interface[18]

Polymers: Natural polymers such as collagen, fibrin, and hyaluronic acid are found in living organisms, making them highly biocompatible. Synthetic polymers like PGA (polyglycolic acid), PLA (polylactic acid), PCL (polycaprolactone), PLGA (poly(lactic-co-glycolic) acid), and PLLA (poly-L-lactic acid) are commonly used due to their flexibility and durability, tailored to the application needs.[13]

Composites: Ceramics have bone-like properties, while polymers enhance ceramic fragility and increase the strength of the bone-matrix interface. Adding nanoparticles can improve material structure and promote cell integration. Using ceramic and metal composites simultaneously can leverage the beneficial properties of both materials. An example is the printable diamond-polymer composite. Various composites can be created by combining different components. Nylon and its variations are commonly used polymers in SLS (Selective Laser Sintering). PCL(polycaprolactone) has good biocompatibility and biodegradability, making it ideal for cartilage tissue replacement. Cellulose can be used in pharmaceuticals as a drug coating.[13]

Clinical applications of additive manufacturing technologies

In clinical practice, there may be a need for bone replacement or the replacement of organs and tissues, as summarized in *Figure 2*. Today, there are numerous possibilities available due to the advancement of additive technology and the wide range of materials. Below are some examples of various clinical applications. *Figure 3* illustrates the location and structure of replacements.

External fixation may be done with a polymer stiffener made using FDM technology, or in more severe cases, surgical fixation may be necessary. In these cases, the fractured bone is supported with nails or plates during the healing process. Bone defect: In cases of larger congenital or acquired bone defects, the missing bone may need to be replaced. This is surgically implanted and typically made of non-absorbable material as a permanent replacement. In cases of accidents or other abnormalities, replacement of a piece of the skull bone may be necessary. Like all replacements, this is a completely customized device that fits

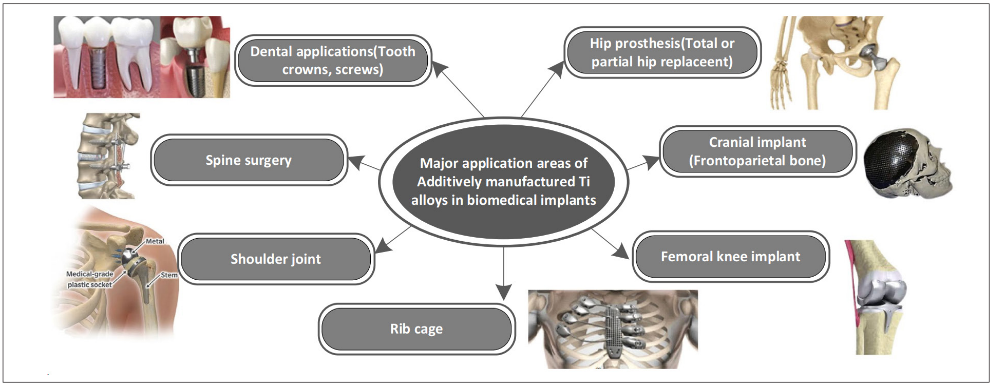

Figure 2. Various Implants Shoulder and other joint replacements[19]

the patient perfectly.[5] We can see several examples in the *Figure 4*.

In many cases, replacements of various joints such as ankle, wrist, knee, hip, etc., may be necessary surgically to improve the patient's quality of life. Spinal vertebrae replacement: Modern materials like shape memory alloys are now available, making the implant closely resemble the properties of the original damaged vertebra. Dentistry: Dentistry is one of the most common areas of application. Over the years, developments have been made in terms of materials, appearance, and embeddability.[5] The literature search has revealed that bone integration is influenced by pore size, porosity and lattice topology. In addition, a number of material properties and the physical condition of the patient also affect the success of implantation. Our study has provided an answer to the question of the ideal pore size for integration for different materials. In addition, a review of the studies reviewed found that, in addition to the widely known materials, a number of new materials suitable for implant manufacture have emerged, e.g. memory materials, which have much better mechanical properties and are therefore ideal as implant materials. We did not cover the application of these specific materials in this research, as this was not the aim of this study, but we would like to explore the medical applications of

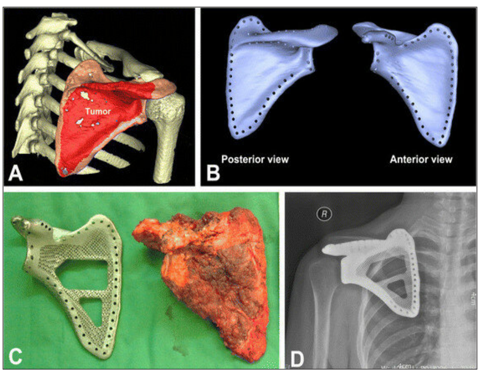

Figure 3. Shoulder Blade AM Prosthesis Fracture fixation[5]

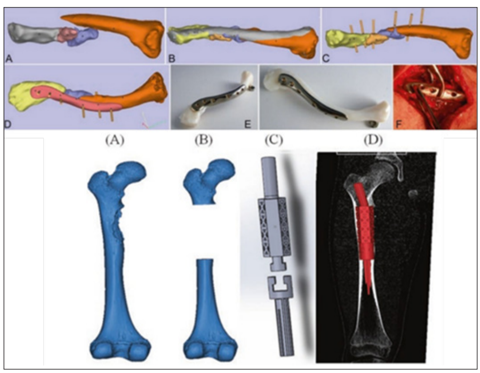

Figure 4. Various Bone Defect Replacements with AM Prosthetics Various joints[5]

these materials in the future. Due to the large amount of literature available, only the application of metal and metal alloys to implants was considered, and therefore polymers and special alloys were not discussed.

Summary

The use of prosthetics produced with additive technologies is becoming increasingly common. Prosthetics can vary in terms of materials, from various polymers to ceramics to different medical metals. Both the material of the prosthesis and the manufacturing, or additive manufacturing technology, affect the pore size and porosity. These characteristics are crucial for osseointegration, or the integration of the implant into the bone. The size of pores in bones varies from bone to bone, and even within the bone. Implants can only establish contact with the bone if both the bone and implant sizes fall within the same size range. The pore size range for bones is 200-900 μm, and cell growth on the surface of the prosthesis starts at approximately 100-400 μm pores. However, researchers have found different values for implants made of different materials, making this an ongoing subject of research. With these results, as engineers we are able to additively manufacture implants using alloys and parameters that are safer for patients. With this knowledge, healthcare personnel can produce completely customized, personalized prostheses, thus contributing to the advancement of medicine.

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