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Review article

# Metallic biomaterials in biopharmaceuticals and biomedical applications

**Yuvaraj Sivamani[1], Afrah Kounain P[2], Siddhant Yadav[2], Leya Elsa Sebastian[2], Sumitha Elayaperumal*[2]**

[1] Department of Pharmaceutical Chemistry, Cauvery College of Pharmacy, Mysore, Karnataka, India

[2] Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysore, Karnataka, India

**Corresponding author:** Sumitha Elayaperumal, ✉ sumithae@jssuni.edu.in, **Orcid Id**: https://orcid.org/0000-0003-0740-8415

Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysore, Karnataka, India



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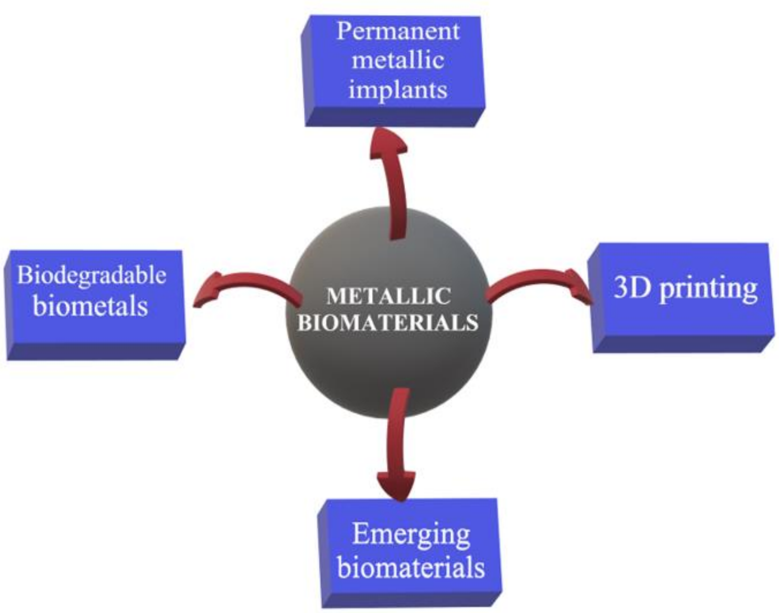
## ABSTRACT

Metallic biomaterials have captured a lot of interest because of their distinct mechanical characteristics, biocompatibility, and usefulness in biopharmaceutical and biomedical applications. These materials are essential for the creation of several medical equipment and treatment strategies. They include titanium, cobalt-chromium alloys, stainless steel, and biodegradable metals. Metallic implants in orthopaedics offer strong support for bone mending and joint replacement; they have outstanding load-bearing capacity and are resistant to corrosion and wear. Metallic heart valves and stents provide structural integrity and functionality in cardiovascular applications, enhancing patient outcomes in heart valve and coronary artery illness. Metallic biomaterials are manufactured systems created to give biological tissues intrinsic support, and they are commonly employed in stents, dental implants, orthopaedic fixations, and joint replacements. Increased implant-related issues are linked to higher biomaterial utilization because of weak implant integration, infections, mechanical instability, necrosis, and inflammation, as well as ensuring extended patient care, discomfort, and functional loss. The performance and integration of metallic biomaterials inside biological systems have been improved by developments in surface modification techniques, such as coating with biocompatible polymers and drug-eluting technology.



Researchers are exploring the possibility of using biodegradable metals that eventually dissolve within the body reducing the risk of long-term issues and repeat procedures. Metallic nanoparticles have also demonstrated potential in increasing therapeutic efficacy, minimizing systemic adverse effects, and selectively targeting disease locations when included in drug delivery systems. The main metallic biomaterials will be briefly discussed in this review, along with the most important established and new methods for modification, which are used to enhance the durability, flexibility, biointegration, and of the biometals, and boost their suitability for 3D printing.

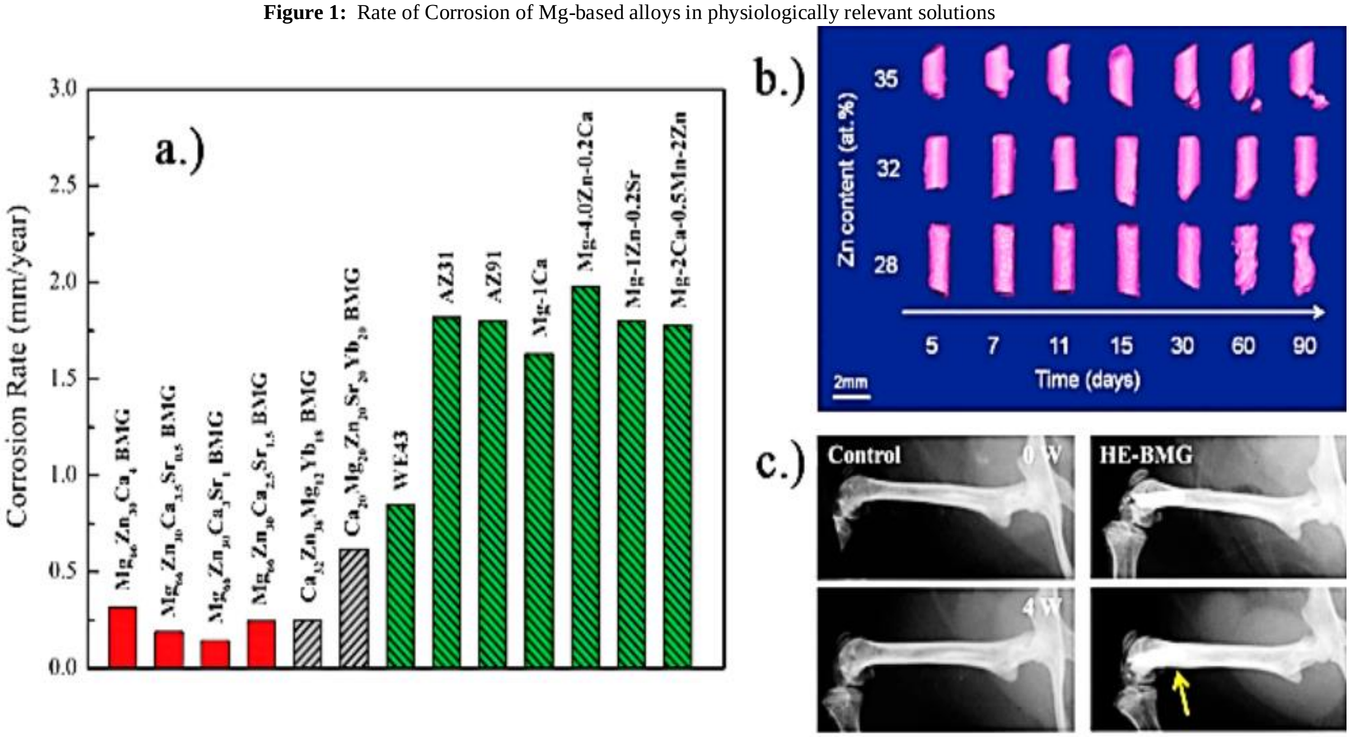
**Keywords**: Surface modification, Inflammation, Tissue engineering, Biomaterial, Implant

## INTRODUCTION

Metallic or metal-type biomaterials are synthetic mechanisms created to give biological tissues intrinsic support. Stents, dental implants, orthopaedic fixations, and joint replacements frequently use metallic biomaterials. Because of poor inflammation, integration of implants, necrosis, and infections along with the accompanying prolonged care of the individual, discomfort, and loss of functionality, there is a correlation between increased implant-related difficulties and higher biomaterial utilization. In this study, the primary metallic biomaterials will be briefly described, along with the most significant established and novel approaches for stock and surface modification, which are utilized in enhancing the biometals' mechanical toughness, flexibility, and compatibility with 3D printing. The variety and usefulness of provided biomaterials, and also the techniques of manufacturing and combining them into the implanted device, have all considerably developed due to the enormous variety of natural, hybrid, and synthetic materials that are now available in the market. With a variety of choices, it is feasible to select the material that will best help the treatment achieve its objectives, such as using highly electroconductive metals as electrodes in man-made organs, unreactive substances to replace lost operation permanently, or biodegradable materials as a contextual feature in circumstances in which can regrow lost tissue or function [1].

Importantly, recent research has focused a lot of attention on the flexibility of particular biomaterials. As an example, the temporary material of the scaffold may be incorporated with biological agents, such as materials of chemotherapy, which are specifically aimed at carcinoma cells that were not eliminated at the time of the surge. These biological agents may include bone transforming growth factor-beta (TGF-beta), morphogenetic protein-2 (BMP-2), vascular endothelial growth factors (PDGF, FGF, and VEGF), platelet-derived growth factor (PDGF), and fibroblast. A notable example of this adaptability is seen in magnesium implants. Magnesium is lightweight, fracture-resistant, and strong enough to handle heavy applications such as minor fractures. Additionally, when it degrades, Magnesium ions are released. These ions are necessary for metabolism and were found to stimulate the growth of new bone tissue. The alloying metal composition, as picturized in Figure 1, as well as coating methods and particular mechanical functioning, can control how quickly the magnesium scaffold degrades [2].

**Figure 1:** Rate of Corrosion of Mg-based alloys in physiologically relevant solutions



Caption: [a] Mg-based alloy corrosion rates in physiological fluids; [b] Reconstructed pictures of implanted Mg95-nZnnCa5 (at %) in rat femurs. Note that the n = 28 sample shows evident degradation after 30 days, whereas the n = 32 and n = 35 samples show minimum or no degradation; [c] radiographs of the distal femora of mice with and with no implants of high-entropy Ca Mg Zn Sr Yb alloy, taken right after the process of implantation and 3-4 weeks later. In the implanted bone, the sample exhibits improved circumferential osteogenesis (yellow arrow), which denotes the production of new bone, and no gas generation, inflammation, or pain [1]

A few examples of bio-inert metals that can have additional functions added to them include Ti and Co-based alloys. These metals can be surface-structured or plated with bioactive ceramic and polymer nanostructures. For many load-bearing functions, biologically inert substances, typically rooted in titanium, steel, and cobalt are crucial. With no long period of toxicity to the host either locally or systemically, their corrosion resistance gives long-term stable mechanical power. These materials have been used for a range of medical devices over the decades, including artificial fracture joints and screws, etc. along with cardiovascular plus neurological devices like wires, stents, and staples used in artificial hearts. These substances have proper toughness and tensile strength in addition to stress-induced. Titanium is frequently the best material among bio-inert materials due to its variety of beneficial combinations.

The use of implantable metals presents several significant difficulties. As an illustration, improper decomposition kinetics for metals like Fe may result in an initial loss of mechanical force before the tissue has recovered completely. The chance of having hypersensitive reactions is increased when metals like steel, Ti alloys or Co-Cr, are present inside the body for an extended period. In addition, these metals create stress shielding as compared to normal bone tissue. The risk of infection associated with implants might dramatically diminish their use. This could cause a significant loss of tissue in the area near the implant when a load-bearing implant reaches its fatigue strength, septic loosening of the implant may prevent forces from being transferred, leading, for instance, to the improper transfer of biting pressure toward the dental implant its nearby bone. Such complications are expensive for the patient's health as well as for the healthcare system, as 20% of patients experience peri-implantitis 8–10 years after surgical intervention.

Several surface modification methods have been designed for a range of materials. These methods include laser ablation, surface functionalization, plasma and acid etching ion implantation, grain refinement, and coating, Along with the material's chemical makeup, the technique of turning it into an implant is also changing dramatically. Three-dimensional printing of biomaterials has lately made it possible to build complex features that are specifically tailored to the requirements of each patient. Importantly, the process used in 3D printing might enable the implant's anatomical structure and macroscopic dimensions to match the missing tissue. Bio-inert implants, like those constructed of solid, polished Co-Cr alloys and Ti, are usually linked with poor osteopenia and osseointegration brought on by stress shielding, as was previously mentioned. Incorporating size- and distribution-maintained permeability in Computer-assisted layer assembly could produce a structure that more closely resembles the extracellular matrix found in healthy tissue, making it more osseointegration-friendly, but it could significantly reduce elastic modulus, reducing strain protection [3].

**Permanent Metallic Implants**

The most popular metals for fractures and remodelling bone among biologically stable metals are cobalt, stainless steel, titanium alloys, and chromium alloys. This is primarily because of their superior mechanical characteristics and high durability under extremely engaging in-vivo settings. While these materials are thought to have a small amount of corrosion, it is important to keep in mind that friction and a highly aggressive microenvironment can cause the substances to degrade and release metallic ions. This results in tissue injury and inflammation, like gradual osteolysis of surrounding tissues and system-wide damage. Osteolysis can also compromise the implant's attachment and its pressure transmission, which could result in implant failure and require corrective surgery [4].

**Titanium-Based Alloys**

Due to the former's 50% higher ratio of strength to weight, it is a good solution for processes that require high starting rates, pharmaceutical grade titanium alloys perform better than stainless steel. The amount of pain that the neighbouring bone will experience depends in large part on the alloy's weight. The titanium dioxide layer's high dielectric constant, which quickly forms on the disclosed titanium, engages cell incorporation and results in a significantly stronger bond between titanium-based implants and tissues than steel does. The strength of Ti alloy can be further increased by annealing, quenching, and thermal ageing [5].

Titanium is frequently alloyed to increase its mechanical strength. The Ti-6Al-4V alloy contains 5.5–6.5 wt% of aluminium and 3.5–4.5 wt% of vanadium is one of them and is frequently employed because compared to commercially available unalloyed titanium, it has a better power profile. Aluminium may be added to Titanium without appreciably changing its other properties, increasing its hardness by 32%. Niobium is known to boost Ti's durability and wear resistance, as seen in the Ti15Nb4Ta4Zr alloy, the latter of which is because of a strong, less friction coating of $Nb_2O_5$. For situations where bending could be a function of the implant, though, alloying may also diminish

Ti's ductility, which may be desired and for which Ti may give a better choice.

Restoring anatomic integrity complicated phases with proper requirements, such as craniomaxillofacial surgery, has considerable promise for 3D-printed titanium implants. Maxillary and orbital level restoration as well as the single-operation correction of bifrontal skull abnormalities have both been demonstrated to be suitable candidates with one 3D-printed titanium implant. These implants were faithfully rendered, took less time to place, and produced better results. Patients with these implants did not experience trigeminal or facial dysfunction, and the implants displayed adequate long-term stability. In comparison to the traditional approach of plates and screws, the 3D configuration may also offer enhanced durability following fixation of fractures, such as mandibular fractures, because of configuration than the increased thickness of the sheet or screw lengths. It might help the bone tissue receive better blood flow. However, as demonstrated by the method by which the titanium mesh implants were created by 3D printing, these were prone to subclinical infection which required the prescription of antibiotics. The 3-dimensional titanium implants utilized in the restoration of traumatic zygomatic-orbital abnormalities, that necessitated removal of the implant, were also demonstrated to be susceptible to infection [6].

Dental implants made in this way are stress resistant than porous titanium made using traditional spraying plus coating processes, in which the latter might cause a 30% reduction in fatigue resistance. Furthermore, unlike methods like solid-state foaming or ductility growth of argon-filled pore spaces, particle plasma splattering over a closely packed central nucleus, Using preceding particle or titanium fibres sintering, SLS offers essential condition over the nano size and micro-structural in the bulk as well as the entire morphology of the implant. It is significant to remember that some of the above-mentioned technologies also result in implantation with comparable biocompatible and osteoconductive qualities. A debate on Beagle dogs transplanted with Ti-implants for 1, 3, and 6 weeks, for instance, showed that only specific stages of implantation led to considerably higher biomechanical responsiveness and osteoconductivity in comparison to alumina-blasted/acid-etched implantation [7].

Cobalt-based bio metals

The extensive use of cobalt-based implants in hip connections, where the femoral head's persistent direct engagement with the bone or plate could induce attrition over time, is justified by the better resilience they provide than titanium alloys. Co-Cr-Mo is one of the alloys that is used most commonly in clinical settings because of its excellent combination of outstanding ductility and outstanding strength. Worked Co-Cr alloys containing Ni, including such Co-Ni-Cr-Mo, offer better durability in comparison to cast Co-Cr alloys; nevertheless, since Ni is potentially poisonous, it is only utilized in specific applications. Furthermore, Co-Cr alloys have a greater elastic modulus than commercially available pure Ti or Ti alloys. Co-Cr alloys have yields and tensile characteristics in the phase of 448-1606 MPa and 655-1896 MPa, respectively, whereas Ti has compositions and ultimate strength of 896-1034 MPa and 965-1103 MPa[8]. The Co-Cr alloys have a higher stress intensity factor than Ti and Ti alloys or Mg because they have a higher elastic modulus and are dense when compared to bone.

Similar to Ti implants, the high structural stiffness of Co-Cr alloy poses a significant obstacle that 3D printing can aid in overcoming. The elastic modulus and rigidity gaps between both the alloy and bone may be reduced by adding nano- and micro-geometry to the alloy. By using the electron beam melting (EBM) technique, Co-Cr alloys can be 3D printed, producing Co-Cr implants with the necessary macro-morphology and bulk cross-linking architecture. These implants showed acceptable total bone-implant contact of about 27% after 26 weeks of implantation into adult sheep femora. Its outcome was marginally inferior to that of Ti the identical inner and outer geometries. The mineral crystallinity, apatite-to-collagen, and carbonate-to-phosphate ratios, as well as the designing tissue surrounding the implant and gradually growing, were identical between the two implant types. A higher osteocyte density was also present close to the Co-Cr porous structure's edge, which would point to a different rate of bone remodelling [9].

In addition to printing foam monoliths, EBM can also manufacture solid and mesh implants. In terms of structure, tabular directed Cr23C6 precipitate structures spaced by around 2 m in the principal directions were formed using both Co-29Cr-6Mo alloy fibre and bubble microstructures. This was a sign that solid cylindrical parts that had been assembled in melt pools had begun to solidify. Solid Ti-6Al-4V implants created employing phase acicular platelets largely displayed ′-martensite phase while mesh and foam implants primarily displayed residual phase [10].

Strong temperature gradients during the selective laser melting (SLM) process and quick cooling afterwards of the alloy produced a fine cellular structure in the CoCrMo implant, with fences that were enriched in Mo and depleted in Co. Additionally, the procedure reduces martensitic surface phase development and carbide precipitation. Compared to traditional cast alloy, this gives the 3D-printed implant improved corrosion resistance. These characteristics also reduce the incidence of metallosis by limiting the discharge of metal ions in the peri-implant environment. The quantity of laser melt pool boundaries was related to the rates of both corrosion and ion release [11].

**Challenges with Permanent Metals**

We now know that 3D printing can support damaged musculoskeletal tissue effectively and more closely match the unique anatomical characteristics of each patient. Furthermore, we have discussed the purposeful addition of porosity to connect the implant's rigidity and Young's modulus to the neighbouring hyaline cartilage and cortical bone and so minimize stress shielding, a significant issue that frequently leads to the already brittle bone to fracture anew [12]. In actuality, bone formation and density are directly impacted by the forces put on that area of bone tissue. Using titanium alloys could significantly lower the pressures that cortical bone is exposed to, which could prevent the bone from deteriorating and losing density because they are up to 10 times stronger than cortical bone. Increased osseointegration, adequate compressive strength, high fatigue resistance, other benefits can all be used to achieve these benefits [13].

**3D Printing**

The use of 3D printing has grown dramatically and is now widespread, with applications in fields as diverse as engineering, aviation technology, and fashion. In the medical and healthcare industries, 3D printing has the potential to transform organ and tissue engineering by enabling the printing of living cells, as well as fulfilling the needs of medical technology. Medical uses of the first usage have led to the development of personalized orthopaedic surgery and stomatology therapies. In actuality, 3D printing makes use of computational design and modeling to analyze high-quality 3D visual data of the anatomic structures acquired from the patient using a computer scan (CT) and to produce a model that mirrors the tangible surfaces and corrects any errors [14]. The implantation is then correctly and swiftly prototyped utilizing the model's data. In addition to describing the macroscopic features of the implant, the model can be utilized to give the material's bulk the required structure. For instance, introducing porosity will promote tissue in-growth, vascular creation, and nutrient replenishment to support the emerging tissues since the structure, diameter, alignment, and pore connection of the pores may be regulated [15]. Significantly, it is theoretically possible to print many materials at once, creating intricate structures that resemble tissues and organs in a single step. Metallic, natural as well as synthetic polymers, glassware, ceramics, active chemicals like proteins, and biological molecules can all be used to carefully and correctly build a single structure.

**Biodegradable Biometals**

The use of disposable alloys rather than everlasting metal implants may also result in much more sophisticated ways of fracture fixation in circumstances wherein total tissue regeneration is anticipated. Because of their appropriate in vivo biological properties, controlled degradation profile, and appropriate mechanical strength to support bone regeneration, iron (Fe), magnesium (Mg) and zinc (Zn) alloys are the degradable materials for cardiovascular and orthopaedic programs that have been the subject of the most research. While bioresorbable polymers like polyglycolide (PGA), polylactide (PLA), and polylactic-glycolic acid (PLGA) copolymers are fragile and may not be ideal for programs involving full-size stresses at the implant, bioresorbable metals, on the other hand, have enhanced mechanical properties [4]. In contrast to Mg, Fe, and Zi biodegradation products, which are typically metabolized by host cells, polymer breakdown through products can also cause necrosis and inflammatory tissue reactions [16].

**Magnesium Alloys**

Magnesium has a low density of 1.74 g/cm3, a very low Young's modulus of 41 GPa, and a relatively high specific strength among biodegradable materials. It can be shaped into metal plates, rods, and screws that gradually break down after implantation to provide mechanical support and make room for the growth of bone tissue [17]. The bone tissue is subjected to greater forces as the condition progresses, increasing its density and strength. Biodegradable implants eventually dissolve and are removed from the body, reducing the risk of metal intolerance in comparison to permanent Ti and Co implants.

Magnesium corrodes quickly in physiological environments, particularly biological fluids, despite its promising mechanical and biological properties [18]. The majority of $Mg^{2+}$ ions are ejected as a result, prematurely reducing the implanted material's mechanical strength. Gas pockets around the implant and the release of hydrogen gas can result from a lack of corrosion resistance. It's also important to remember that too much corrosion resistance can make it harder to fix bones. Magnesium-based staples degrade in both in vitro and in vivo environments. Magnesium staples' optical shape after being submerged in a pH 4 simulated body fluid [19]

**Zinc Alloys**

The collapsing of protein subdomains like the DNA-restricting spaces of eukaryotic record factors, RNA polymerases, and embellishment proteins engaged with nucleic corrosive replication, as well as the reactant effectiveness of north of 300 compounds, are reliant upon zinc, a second minor component and helps in body adjustment [20]. Additionally, protein design and capability are fundamentally impacted by zinc. Because of the way that most tissues endure an overabundance of Zn particles, zinc compounds are as of now being considered for bioresorbable metal stent applications. Anodic disintegration and cathodic decrease of broken-up oxygen are the major cycles of zinc consumption, and the pH of the general climate is vital. At a pH of 7.3, for example, zinc oxide (ZnO) and zinc chloride (ZnCl) start the erosion interaction. When utilized as stents in rodent courses for as long as a half year, uncovered Zn wires didn't cause critical apoplexy or immune system responses, and, surprisingly, somewhat debased stents showed huge tissue reconciliation [21].

**Iron Alloy**

Dissolved oxygen, which, unlike Zn implants, does not produce hydrogen gas, is the cause of localized corrosion in Fe alloys.

Iron's rate of degradation is comparable to that of vascular remodelling, making it the biodegradable metal with the lowest tendency to dissolve. The formation of a protective surface oxide layer that prevents rapid deterioration is one factor contributing to the low corrosion rate. No signs of thrombosis, excessive toxicity, or other adverse inflammatory reactions have been observed in numerous studies on bioresorbable Fe stents in rats, pigs, or rabbits. Fe stents allow for the use of extremely thin stent struts and are easy to insert into arteries due to their high radial strength [22].

During analysis, mending, and follow-up, attractive reverberation imaging (X-ray) is regularly used to envision patient life structures and physiological cycles. Iron in careful inserts can obstruct X-rays. Inserts can change shape and position when warmed by strong attractive fields. The way that these impacts can be utilized to further develop helpful results should be underscored. For instance, iron nanoparticle-based porous magnetic scaffolds are capable of attracting potential growth factors, hormones, and polypeptides, encouraging cell adhesion and proliferation, relieving compressive and tensile stresses on nearby cells, and reducing stress on cells [23]. It has been demonstrated that it increases bone tissue production through carryover and cytoskeletal deformation. Stimulation of intracellular signalling pathways that are required for the normal formation of bones. Drug release for implant-related infections and cancer can be initiated by targeted heating and external magnetic fields [24].

## Emerging metallic biomaterials and future trends

### Shape memory alloys

Biomaterials that can undergo phase changes that can be reversed in response to stress-induced properties like temperature, pressure, or superelasticity are known as shape memory alloys. The "shape memory effect" and apparent elasticity are two examples of their distinct mechanical and functional properties. Pseudoelasticity is the capacity for a substance to regain its initial shape following severe mechanical deformation. The "shape memory effect" is the capacity of a material to modify its flexible structure below its transformation temperature [25]. This material regains its original form as the temperature rises. Two distinct solid phases characterize shape memory alloys. The first type of solid is the primary part of austenite, which is highly symmetrical and stable at high temperatures. Another solid body with limited symmetric and durability even at relatively low temperatures is the martensite phase [26]. Applications place a significant emphasis on obtaining the necessary mechanical properties, shape memory, and pseudoelastic behaviour at temperatures suitable for biological systems.

Thermoelastic and based on Ti, Nitinol is a biomaterial with 50% atomic Ni. Nitinol gained popularity in the medical industry when the most promising shape memory alloys based on Ti became available. Nitinol is distinguished by its mechanical stability, decreased stiffness, thermoelasticity, and resistance to biodegradation and corrosion. Due to its promising properties, nitinol is a viable alternative to stainless steel implants [27]. Wires, palatal arches, intravertebral implants, intramedullary pins, scoliosis-treating staples, spinal spacers, and self-expanding vascular stents are all examples of things that can be made with nitinol. However, how Nitinol is utilized is determined by the body's capacity to regulate Ni release. This is typically accomplished by altering the alloy's surface to preserve its bulk shape-recovery capability [28].

## Limitations of biomaterials and strategies for improvement

Understanding the limitations of the materials that can make these prosthetic body parts and the existing solutions to these limitations is essential in light of the growing demand for artificial limbs, joints, and other body parts. Although the most of persistent and biodegradable metals currently in use are biocompatible, severe wear and early disintegration could jeopardize their biocompatibility, impede healing, and result in long-term harm. Techniques routinely employed to enhance mechanical and tribological or corrosion resistance may also reduce its biocompatibility. For instance, it is proven that the addition of Al or Ni raises the possibility of inflammation in the adjacent tissues. By decreasing the quantity of direct communication that cells have with the implantation, as is the case with Co-Cr rods that can be fastened to the bone using more biocompatible Ti screws, this issue can be partially minimized. Osteointegration may potentially be hampered by antibacterial actions altering host cell-surface contacts [29].

One of the best ways to improve the surface biocompatibility of these implants is surface modification. On a titanium sheet, titanium nanotubes were created, purified with nitric acid, and dried. The Ti was employed as an electrode and a platinum sheet as the cathode throughout anodic oxidation in 0.50 weight % $NH_4F$ + 10 vol. % $H_2O$ in glycerol at 10 V, 30 V, and 60 V for 5 hours. The maximum biocompatibility was shown by Ti nanotubes on these surfaces that underwent a lower power during anodization, as evidenced by the increased proliferation and improved adherence of bone mesenchymal stem cells (BMSCs) [30].

Surface porosity and roughness are introduced to facilitate cell adhesion and osseointegration. Traditional techniques comprise laser ablation, acid etching, and sandblasting. For instance, roughening the implant surface by large-grit acid sandblasting can provide micro-level topography for cell proliferation and adhesion. It has been established that nano-scale topography boosts wettability, which promotes cell adhesion. The effect of nanostructured titanium is that nanostructured surfaces exhibit greater adhesion than conventional titanium surfaces. It is still important to consider that these modifications to surface topography might potentially have an immense effect on how harmful bacteria interact with surfaces [31].

## CONCLUSION

The currently employed biomaterials have been addressed in this review along with potential limitations and enhancement suggestions. The problems that currently plague existing implants can be solved by using new or modified materials, which can also provide patients with biomaterials that give more accurate results. Future biomaterials can probably benefit from materials engineering, and multipurpose nanomaterials can be used to make the next generation of implants.

The fabrication of patient-specific metallic implants via 3D printing has enormous promise for producing complex constructions with managed interior nano-, micro-, and macro-scaled characteristics with unique geometry. But before these modern implants can be used in clinical settings, several problems need to be resolved. These include enhancements in modelling and visualization techniques. Even though CT scans are created by incredibly thin slices, the imaging technique can produce the accumulation of many slices, which is a source of error. Even though this error might not have a big impact on macroscale features, it can have a big impact on micro and nano features. For accurate reconstruction of modelled buildings, the precision of the assembly operations must also be improved. The 3D printing of metallic implants can become a fully developed modality in personalized medicine once these difficulties are overcome.

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