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Bioceramic Scaffolds for Bone Repair and Regeneration: A Comprehensive Review

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A B S T R A C T

Bone diseases are a serious health problem such as arthritis and osteoporosis. Their effects on the bones, structures, and tissues affect human life. Therefore, developing novel materials to evolve bone damage therapy is required. Bio-ceramic synthesis witnessed increased interest and attention due to the progression of bio-ceramic as high-quality materials to enhance bone healing, replacement, or regeneration. Among the inorganic materials, bioglasses and ceramics showed promising applications in medicine fields due to their several biological properties; for example, biocompatible, their compositions are similar to those in bones osteoinductive and osteoconductive. Thus, they considered promising materials for scaffold manufacturing to promote bone healing. This review aims to present the recent advancements in various classes of bio-ceramics, including inert-ceramics, bioactive ceramics, and bio-resorbable ceramics, and their wide medical applications in bone regeneration, overhauling skeletomuscular, as well as their mechanical issues.

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1. Introduction

The skeletomuscular system consists of bones. Ligaments, cartilages, and tendons. They function together to support the body and maintain its shape and structure. Ligaments are recognised as the elastic tissues that bind one bone to another, surrounding and connecting the bones' ends to form joints. The elastic property of the ligaments allows flexibility in motions in specific directions and prevents dislocation. The bones are connected to the muscles by the tendons, which are the connective tissue. The skeletomuscular system acts as a shield to protect the interior organs [1]. Thus, the health of the skeletal system is vital for a better life. The last five decades shed light on bio-ceramics materials. Bio-ceramic is the term that refers to the ceramic used in living tissue treatment [2-5]. Bio-ceramics are characterised as hard, brittle, low tensile substances with high compressive strength, displayed wear resistance enhancement, and low frictional properties [6-8]. Therefore, they can be potential biomaterial sources used in biomedical applications and engineering. Bio-ceramics are employed in orthopaedic surgery as a strengthening substance for remediating defects in the bone and tooth, especially in older people who suffer from weakness and low-density bones due to the reduction of osteoblast capacity [9]. Thus, the requirement for bio-ceramics is increased [10]. This review provides a comprehensive overview of the utilization of ceramic-based scaffolds in orthopedics and related medical disciplines. The objectives of this review are twofold: Firstly, to

examine ceramic as a biomaterial with properties compatible with human bone tissue. This includes a review of the mechanical properties, bioactivity, nontoxicity, and potential allergic responses associated with the implantation of ceramic materials into the body. Secondly, the review aims to present the methodology employed in conducting a systematic literature review, encompassing the approaches used for literature search, study selection, data extraction, and critical appraisal. Additionally, the review outlines the types of test animals utilized in the experimental work, synthesizes findings from studies on bone defects, and discusses the scaffolding approaches evaluated for various bone defect applications.

The incorporation of ceramic materials into composite constructs has been shown to enhance their biological advantages and expand their potential applications in the development of biologically active scaffolds and bone tissue engineering. This review endeavors to consolidate the current understanding and state-of-the-art in the utilization of ceramic-based scaffolds within the field of orthopedics and related medical disciplines. Moreover, requiring an extensive overview of various scaffold types and their applications, the progress made in scaffold testing over the years is crucial. The review details the use of scaffolds in bone defect, repair, regeneration, and tissue engineering. Lastly, the review discusses the challenges associated with ceramics. It explores the potential for developing new ceramic-based scaffolds to meet the critical clinical demand for bone defect reconstruction.

2. Classification of Bioceramics

Bio-ceramics are biomaterials that represent 50% of the most used biomaterials worldwide. Bio-ceramics have been utilised for multiple purposes, such as cementing material, strengthening substances, and implants for repairing and replacing impaired bone or dental tissue engineering applications due to their compatibility with the biological systems of the skeletal and muscular system from toe to head (Fig. 1) [1]. Bio-ceramics are the first developed bio-ceramics involving bio-inert ceramics with some distinguished features. They do not show any side effects on the surrounding tissues interacting with the excepted system that maintains their physical and mechanical features after implantation [11, 12]. The most used bio-inert ceramics are Alumina (Al_2O_3) and Zirconia (ZrO_2) [13]. The second-developed bio-ceramics are bio-active and bioresorbable ceramics [14]. Bio-active ceramics such as glass ceramic, bio-glass, and Hydroxyapatite can chemically react with the tissues around the bones and form a bond [1]. Meanwhile, bioresorbable implants imitate the regeneration process of damaged tissues as new tissue grows. The rate of degradable bioresorbable ceramics must be compatible with newly formed tissue [14].

Ceramics as bone grafts have gained popularity due to their biomechanical properties and have made significant advancements, focusing on those that can form direct chemical bonds with bones and tissues. Regenerative bioceramics, developed at the turn of the millennium, became an integral part of tissue engineering. Designers design bioceramic scaffolds to stimulate bone formation and vascularisation, frequently incorporating various biomolecules or cells [15]. This review discusses the major types and properties of bioceramics suitable for tissue engineering, as depicted in Table 1.

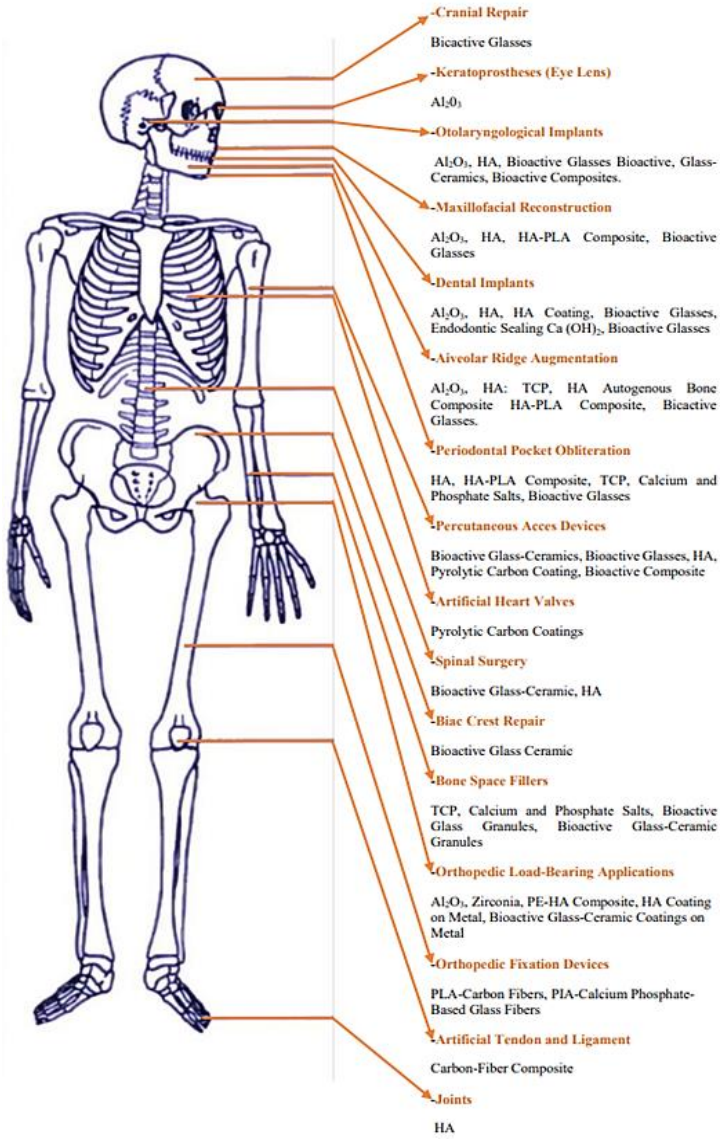

Figure 1: Clinical application of bio-ceramics reprinted and adopted from [15].

Table 1: Comparative key characteristics of bioceramics in bone tissue engineering applications [16].

Bioceramics	Features	Advantages	Disadvantages
Aluminum oxide	In physiological settings, alumina is highly resistant to corrosive conditions. Dental, orthopedic, and joint articulation applications have used this material.	- high compressive strength properties - bioinert	- high fracture rates -lack of biological activity
Zirconia	Due to its biological and chemical inertness, Zirconia has attracted much interest in orthopedic applications.	- good biocompatibility - excellent mechanical properties	need to improve the bioactivity further.
Hydroxyapatite	They closely resemble natural bone apatite and allow adequate bone growth.	- non-inflammatory responses - bioactive	They have poor mechanical properties, including low tensile strength and brittleness.
Bioactive glasses	They have osteoinductive and integrating properties because they connect with surrounding bone tissue.	- biocompatible - non-cytotoxic - ease of control over the chemical composition	Specific mechanical characteristics, like low toughness and strength, have limitations.
α,β-tricalcium phosphate	Their surface structure and chemical makeup are identical to bone minerals, making them naturally bioactive.	- good biodegradability osteoconductivity	- poor mechanical properties

2.1. Inert bioceramics

Alumina (Al_2O_3) and zirconia (ZrO_2) are two prominent examples of inert bioceramics that are frequently utilized in a variety of orthopedic and dental applications. These materials are commonly employed in hip and knee joint replacements, maxillofacial reconstructions, ossicular bone replacements, keratoprostheses, bone screws, and dental implants. The inertness of alumina and zirconia prevents direct chemical reactions between the material and bone tissue, which is a desirable characteristic. Additionally, these bioceramics exhibit favorable mechanical properties, including high compressive strength, elastic modulus, and hardness. They also demonstrate excellent corrosion resistance and biocompatibility, as well as low friction coefficients, making them stable and suitable for use in physiological conditions [17].

Because of their desirable mechanical features, as depicted in Table 2, zirconia and alumina-based biomaterials have gained significant attention for dentistry and orthopaedic applications.

Table 2: Alumina and Zirconia's properties [18].

Property	**α-Al_2O_3**	**ZrO_2**
Density (g/cm^3)	3-3.98	5-6.15
Melting point (Tm) (°C)	2004-96	2550-2700
Ultimate Flexure strength, (MPa)	152-800	177-1000
Elastic modulus (E) (GPa)	215-413	100-250
Resistance of crack (K1c) (MPa – $m^{1/2}$)	3.3-5.0	1-8
Vickers Hardness (HV) (GPa)	5.5-22.0	5.5-15.8

2.1.1. Alumina

Alumina or alumina-based components are widely utilised ceramics for replacing joints owing to their supreme coherence to human being cells without releasing cations and low wear under friction conditions. The first use of alumina was in the jaw and dental implants. Alumina was discovered by Boutin, who used a hip prosthesis for the first time. His study showed that bone growth was observed after eight weeks without any side effects from implantation. However, the tissue started forming within eight weeks because the implant separated from the tissue [19-21]. Alumina usage for hip arthroplasty was approved by the US Food and Drug Administration (FDA) in 1982. The most utilised commercial products in dental applications, such as ceramic crowns, are alumina-stabilized zirconia-based composites [19]. Historically, Peter Griss experimented with developing a bio-glass coated alumina in hip prosthesis in sheep. He noticed a chemical integration between the tissues and the implant [22]. Thornton-Bott et al. evaluated the osteolysis and the lifespan of alumina ceramic implants in full hip arthroplasties; their results documented that the alumina replacement in hip arthroplasties without using cement had a high persistence rate and, after 15 years, exhibited excellent performance and low wear rate, and no osteolysis symptoms [23]. Garcia-Cimbrelo investigated the long-term therapeutic of alumina substrates in orthopaedic implants. Their study examined 315 Cerafit cups of two generations. After 15 years, the results showed that the Cerafit alumina-on-alumina prosthesis performed flawlessly. The first generation of alumina cups often experienced loosening, but they have overcome these difficulties [24]. Camilo et al. established a methodology to understand how porous alumina substrates covered with bio-glass and HA bioactive compounds affect bone growth. The researchers implanted coated alumina substrates in rat tibiae and evaluated their influence on bone repair within 28 days. Alumina implants covered with bio-glass and HA can potentially improve osseointegration and bone formation, specifically in those with pores sized between 100 and 400 μm [25]. Mala et al. adopted an extensive study that reported a failure in the Al_2O_3 coated with bio-glass due to bio-glass coating separated from the Al_2O_3 substrate. Thus, the bonding was disturbed, leading to overall failure [1]. More studies are required to evaluate whether minimising wear between alumina-on-alumina implants leads to decreased osteolysis and loosening in load-bearing bones. Vidane et al. the study highlighted the potential of Al_2O_3/ZrO_2 scaffolds as bone graft substitutes. CaP coating enhances their bioactivity, biointegration, and biodegradation properties. The CaP-coated scaffolds have a very porous structure that resembles bone tissue, which impacts cellular activities, including movement, communication, signalling within cells, and exchanging nutrients. Their 56.38 ± 0.34% porosity is advantageous for bone biological activities, as shown in Fig. 2 [26].

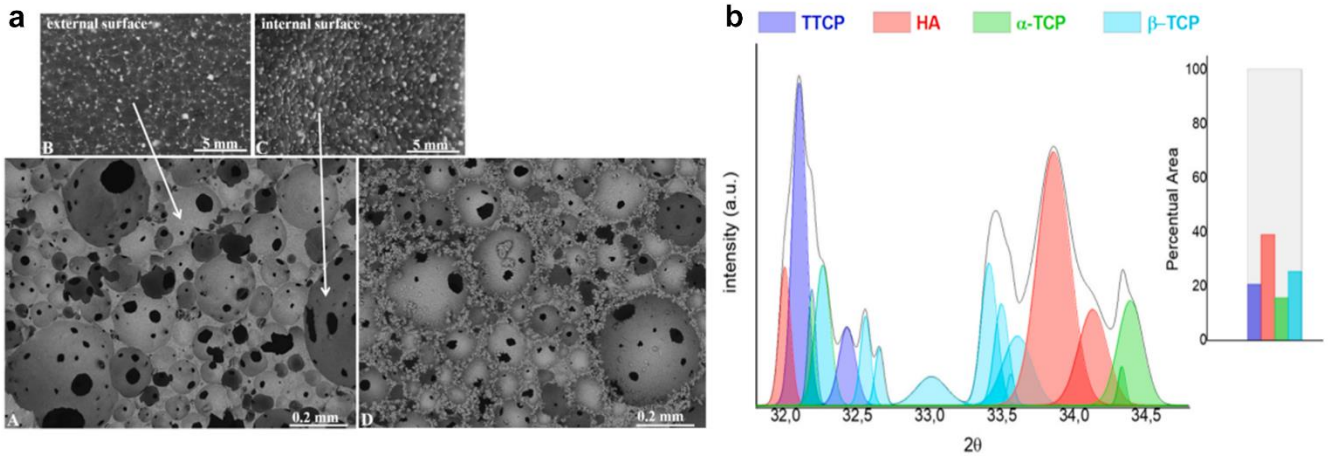

Figure 2: (**a**) SEM images of the scaffolds surface of Al_2O_3/ZrO_2. (A) Polished surface overview; (B) A magnified image of a pore outer surface; (C) A magnified image of a pore inner surface; (D) The Al_2O_3/ZrO_2 scaffold SEM image after 14 days of biomimetic coating. (**b**) The XRD patterns of the formed calcium phosphates on the porous Al_2O_3/ZrO_2 scaffold treated with chemicals after 14 days of biomimetic coating. The graph displayed the total area percentage for each presented calcium phosphate phase, as determined by after-treatment curve analysis [26].

2.1.2. Zirconia

There are three polymorphic forms of pure zirconia under atmosphere pressure: monoclinic at room temperature until 1170°C and the transformation into the tetragonal phase, which occurs at approximately 2370°C. The stable form is represented by transforming the tetragonal crystal lattice into the cubic form [27]. The mechanism of zirconia transition from the tetragonal shape to the monoclinic shape is done by nanoparticle diffusion. The early investigations highlighted the mechanical properties of zirconia, but the latter investigation emphasised the biocompatibility of zirconia for biomedical applications [28]. Zirconia ceramics are broadly utilised in various industries, especially in orthodontics, because of their special characteristics such as magnificent chemical, temperature, and corrosion resistance, low thermal conductivity, low friction coefficient, high rigidity and density, exceptional flexural strength and fracture toughness [29]. Scarano et al. used zirconia ceramic implants in rabbit tibias. Notably, after four weeks, newly generated bone was contacted directly with the implants and osteoblasts in certain spots, leading to osseointegration without inflammation [30]. Hoffmann et al. study revealed that all of the zirconia dental implants and the modifying surface of titanium implants in the four rabbits' femurs displayed significant bone apposition during the early recovery [31]. Depprich et al. examined the fusion of zirconia and titanium implants with the bone throughout 1, 4, and 12 weeks [32, 33]. The results documented the compatibility between the bone tissues and the rough surface of zirconia implants; thus, the ultrastructural results were similar to tissues surrounding the bone. Bachelli et al. investigated ZrO_2 surface implants, which are another common surface treatment, and they used mechanical titanium, titanium oxide plasma sprayed (TPS), and alumina sandblasted (Al-SL). The tibia cortical bone was implanted in 12 lambs, distributed among three groups. The implants were monitored at different periods via histology, histomorphometry, SEM, and microhardness testing. After two weeks, the best substantial bone ingrowth was noticed in Zr-SL implants, and the newly formed bone showed higher microhardness than that of Ti. ZrO_2 treatments. Additionally, it exhibited superior results in the peri-implant newly formed bone compared to Ti or TPS processing [34]. Kohal et aldocumented that changing the surface of Zirconia did not impact the histological or biomechanical results compared to a standard titanium implant surface. Overall, surfaces showed biocompatibility and Osteoconductive, which aids the bone tissue growing onto the implant surface [35]. Wang et al. conducted a study on osteoblast behaviour in nanostructured monoclinic zirconia coatings [36]. After six days of soaking in SBF, bone-like apatite residues were found on the coating surface, and the cells showed adequate adhesion and proliferation during cellular differentiation of osteoblast-like MG63 cells. Wang et al. created nano-composite coatings on titanium using electrodeposition, containing fluorinated HA and zirconia, demonstrating high strength bonding, a low rate of dissolution, and has promising in vitro bioactivities [37]. Mai et al. tested the biocompatibility of a zirconia implant surface termed "mds" made by Maxon Motor GmbH. The study examined the osseointegration of ZrO_2 mds implants in surgically

induced cranial deficits in adult male rats. The histomorphometric results reported that after 28 days of recovery, the bone regeneration rate was 36.3%. While after 56 days of recovery, the bone regeneration rate had risen about 1.6 times (58.2%). Furthermore, only 1% and 39.9% of contacted bone-implant were obvious following both recovery periods. After 28 days of recovery, connective tissue/marrow gaps had taken over 99% of the implant-contact area increased to 60.1% after 56 days [38]. The researchers discovered that the modifying surface of zirconia implants was biocompatible and osteoconductive. Möller et al. study on osseointegration in domestic pigs over 4 and 12 weeks found good biocompatibility between zirconium and titanium implants [39]. Histomorphometry showed a direct contaction between bone-implant and implant surfaces. Zirconium implants showed a slight delation in osseointegration, with a difference of 59.3% ± 4.6% after four weeks and 67.1 ± 2.3% after 12 weeks. There was statistically insignificant difference between both of the groups. The study concluded a comparable biocompatibility and osseointegration between zirconium and titanium implants. In 2012, An et al. [40] studied in vivo the fabrication of a zirconia-hydroxyapatite (HA) compound. The authors developed zirconia/HA scaffolds using the conventional replication (polyurethane foam scaffold) technique. Fig. 3a presents the succeeded bone formation in eight-week-old male SD rats. Thus, the formation of bioactive HA composite aids in the effective use of bioinert Zirconia as a bone-generation material for larger bone defects. In 2013, Kohal et al. [41] looked into how surface-modified zirconia implants might fuse with bone by either milling (TZP-A-m) or heating and etching them with hydrofluoric, nitric, and sulfuric acids (TZP-proc). They discovered that TiUnite® had a greater bone-implant contact rate after 14 and 28 days of recovery, but the modifying method did not boost the osseointegration ability of the zirconia material. Park et al. revealed that PIM zirconia implants had significantly higher contraction in bone-implant than mechanical titanium implants ($P < 0.001$) [42].

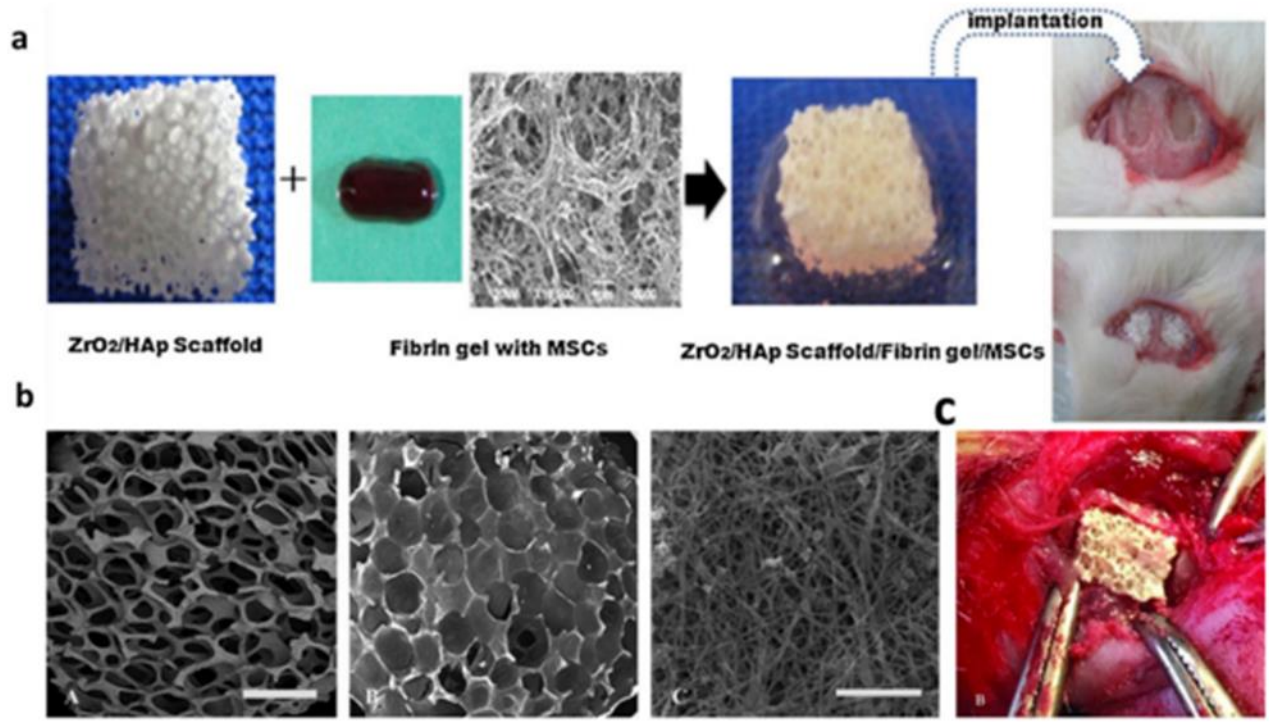

Figure 3: (**a**) zirconia/HA scaffold fabrication by using the technique of polyurethane foam-scaffold and successfully regenerating bone in eight weeks age eight-week-old male Sprague Dawley (SD) rats. (**b**) The scheme of PRP-impregnated HA/zirconia: (A–C) the outputs of high-resolution SEM of the PRP-impregnated HA/zirconia scheme. (C) The scheme of the in vivo experiment of PRP-impregnated HA/zirconia; (B) A rabbit mandible with a rectangular bone defect was used for the in vivo experiment, and the defected bone was replaced with intentionally designed rectangular scaffolds [48].

Kohal et al. examined a novel procedure to treating the surface of alumina-toughened zirconia (ATZ) implants using pore-building polymers [43]. They determined the implants to be both biocompatible and osteoconductive. Biocompatible and osteoconductive. TiUnite® and ATZ stimulate bone-to-implant contact and biomechanical

anchoring between the second and fourth weeks of the recovery process ATZ reduced histomorphometric test scores in week two but not in week four; thus, the osseointegration process of ATZ with the ATZ surface progress slowly in the early implant integration phase. Numerous researchers have explored the utilisation of ZrO_2 as a bone substitute material in biomedical applications, including orthopaedic prostheses and substitutes [44, 45]. The research teams of Latifi et al. and Shahsavari-pour et al. developed zirconia scaffolds using the polyurethane foam replication technique. Latifi et al. coated the scaffolds with hydroxyapatite (HA) and fluoroapatite (FA) using a slurry coating method. Shahsavari-pour et al. further impregnated these HA-coated zirconia scaffolds with platelet-rich plasma (PRP) and heparin sulfate (HS) to create an HA/zirconia/PRP composite scaffold. SEM revealed that the HA/zirconia/PRP scaffolds had a high porosity at the nanoscale, with the PRP gel uniformly infiltrating the pore spaces, as shown in Fig. 3b. Latifi et al. conducted in vivo studies for eight weeks using the HA/zirconia/PRP scaffolds implanted in rabbits, as depicted in Fig. 3c. The studies found that while the HA-coated zirconia scaffolds, both with and without the addition of PRP, were able to replicate the bone features of the rabbit mandible, the inclusion of PRP did not further enhance the scaffolds' regenerative properties synergistically. Overall, the HA/zirconia composite scaffolds showed promise for bone tissue regeneration applications but the addition of PRP did not provide additional benefits based on the results obtained [46, 47].

2.1.3. Carbon

Carbon nanomaterials (CNMs) such as carbon nanohorns (CNHs), graphene, and carbon nanotubes (CNTs) are widely attributed in biomedical applications due to their unique biocompatibility, physical properties, and chemical steadiness; thus, they represent potential base materials for scaffolds development and consider a suitable parameters stimulator for the bone regeneration [49, 50] (Fig. 4). The scaffold evolution is essential for medication evolvement; therefore, much attention is paid to the CNTs' applications as scaffolds and in the field of bone regenerative medication [51]. Several in vitro investigations documented that the CNT/Polycarbonate urethane composites and CNTs improve and enhance osteoblast proliferation [52, 53]; author in vitro study investigated that CNT/polylactic-co-glycolic acid (PLGA) improve osteoblast adhesion [54]. Several in vitro studies investigated and documented to evince further studies on the bone-related cells [55]. Li et al. documented the ability of MWCNTs to adsorb and concentrate some proteins (i.e., rhBMP-2), induce the alkaline phosphatase (ALP) along with the *cbfa1* and *COLIA1* gene expression, stimulate the osteogenic differentiation that coated with the diamond-like carbon via the laser ablation such as chemical and physical vapor deposition [56]. Choudhury et al., to reduce the orthopaedic implant friction, the titanium alloy coated with ZrO_2 that contains inter-layers, combined with diamond-like carbon (DLC), followed by a substrate coated with three layers, each one with a particular aim. The first layer of Zr:ZrN provides corrosion resistance and maintains the load-bearing capacity. Meanwhile, the second layer of Zr:DLC provides stress resistance. The third layer of N-doped DLC provides lubrication [57]. Another study by the same researcher explained the imitated hip movement after one year and the effects of diamond-like coating in minimising friction within the orthopaedic implants [58]. The nanocrystalline diamond showed remarkable effects of providing extra hardness to the surface and preventing sound making, especially while walking [59, 60]. The studies of nanocrystalline diamond coating of implants have taken priority in recent years, mainly due to their biocompatibility [61-65]. The diamond-like nanocrystalline composite bio-compatibility for the knee implant is documented [66]. Catledge et al. stated the implication of DLC coating in minimising the wear rate [67]. Gorzelanny et al. coated the Ti discs with DLC saturated with silver nanoparticles to provide bacterial resistance and prevent infections. They proved that the mammalian cells regenerate around the Ti disc and its antibacterial activities [68].

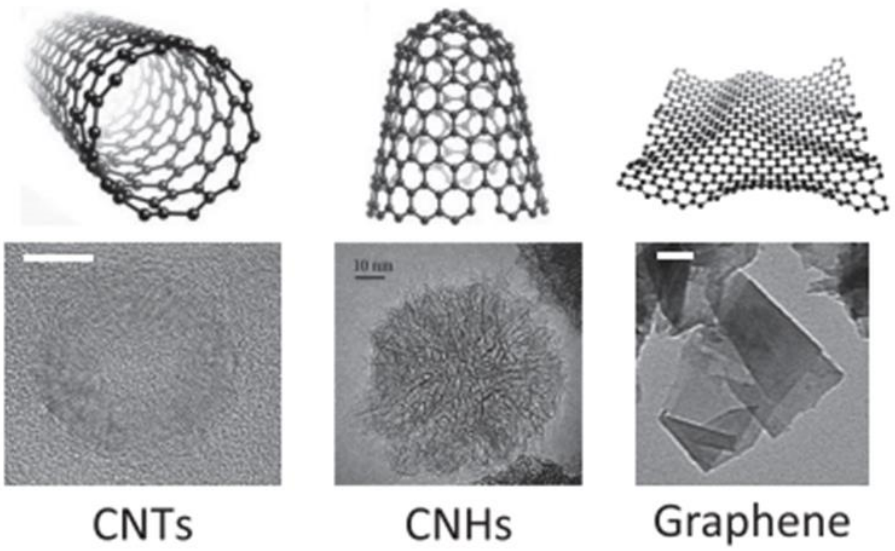

Figure 4: Schematic models and TEM observation of carbon nanomaterials [50].

2.2. Bioactive Ceramics

Hydroxyapatite (HA), glass, glass-ceramic, and composites are bioactive ceramics that showed interactions with biological environments to improve the host's responses and bind damaged tissues. These components gradually degrade simultaneously as the new tissue regenerates [17].

2.2.1. Hydroxyapatite (HA)

Hydroxyapatite is similar to the composition and structure of the bone inorganic components [69]. The studies of HA applications in bone tissue engineering represent a promising field of investigation [70]. Therefore, improving HA biochemical and biological characteristics is necessary for bone tissue engineering [71]. Hydroxyapatite is used as a potential material for tissue engineering because of its similarity with the minerals found within the teeth and many desirable features such as osteoconductive, bioactivity, and biocompatibility. In addition, it can be used as a bone scaffold, bone filler, and osteoconductive implant. Achieving optimal HA biocompatibility, performance, and mechanical properties depends on the interaction with additional collagen supports, metals, and minerals [70-73]. Moreover, HA revealed high thermodynamic stability and low solubility under physiological conditions because the functional and structural features of bio-minerals are identical to those of the bone and teeth. HA has been extensively studied to address dental and bone abnormalities [74]. Furthermore, utilising fabricated implant materials displayed crucial advantages for bone restriction, especially HA, due to the significant bio-mimetic of structural and functional properties when interacting with human bones [75]. In addition, HA is produced by simple industrial methods at low cost. Therefore, it is appropriate to manufacture scaffolds and implants and use drug transporters to treat different bone syndromes [76]. However, using HA as an implant material exhibited a few disadvantages, mostly regarding its susceptibility to damage. Therefore, further studies are required to explore new and alternative material combinations and introduce optimal synthesis procedures [77]. Hydroxyapatite has been used to coat bone implants for a long time to strengthen the implant materials and is considered a composites material with other bolstering substances [78-80]. The recent investigations cross the limitations of using HA as coatings only to explore other combinations to improve the implants' osseointegration, mechanical, and antibacterial features [81, 82]. Yamasaki [83] research on the subcutaneous dog model revealed no evidence of new bone growth at the HA ceramic implantation site, which was thick, granular, and porous due to irrigational reactions. Yuan et al. [84], Two forms of macroporous (HA) (rough pore walls and smooth walls) were created by various intramuscular implants in dogs. They discovered bone structures in rough pore walls. Chu et al. [85] combined HA and Ti particles to form a composite, enhancing the mechanical characteristics and introducing high porosity in rabbits. After three weeks, the composite could partly integrate with newborn bone tissues, predicting bone integration after twelve weeks. 2006 In their study, Rumpel et al. [86] showed that osteoclasts with ruffled frames and acid-phosphatase action break down HA with SiO_2 implants in pig bone defects, creating resorption trails and lacunae. Dorozhkin et al. [87] demonstrated the speed of bone regeneration

throughout the human osteoblasts' attachment and proliferation. The benefit of nano-HA was documented in numerous investigations that revised of the nano-HA's crystal size and morphogenic inrole in bone tissue engineering. Shin et al. [88] study highlighted the low fracture toughness of HA compared to other substances with similar properties. Hao W. et al. [89] investigated osteoinduction and vascularisation of two different types of HA scaffolds in intramuscular dogs. They showed the pore structural properties are correlated to the formation of ectopic bone, resulting in outstanding biocompatibility. Chen et al. [90] prepared an RGD-CS/HA scaffold seeded with bone marrow stromal cells (BMSCs). The study displayed that an RGD-CS/HA scaffold showed high biocompatibility, cytocompatibility, histocompatibility, and osseointegration features and represented an effictive bone substitution for use in bone tissue engineering applications, as shown in Fig. 5. displays X-ray radiographs that compare rabbit radial bone defects in the RGD/CS/HA, CS/HA, and control groups after 2, 4, and 6 weeks. Wu et al. [91] developed a bonelike scaffold using HA nanocrystal composite and kind (I) collagen in three-dimensional form. Several researchers have investigated using HA as a material to replace bones in biomedical applications, such as orthopaedic prostheses and substitutes [92, 93]. Fazeli et al. utilized fused deposition modeling (FDM) 3D printing to fabricate porous polycaprolactone (PCL) scaffolds. Post-processing of the scaffolds was then conducted using coatings of hydroxyapatite (HA), bioactive glass (BG), and a HA/BG composite bioceramic [94]. Fazeli et al. explored the effectiveness of the fabricated scaffolds for bone regeneration in an in vivo rat calvaria bone defect model. Histological analysis, immunohistochemistry (IHC), and micro-computed tomography (micro-CT) imaging were employed to examine new bone formation, as illustrated in Fig 6. The results demonstrated that scaffolds coated with both HA and BG composites improved calvarial bone reconstruction compared to single coatings of HA or BG. This suggested the synergistic interaction between HA and BG bioactive materials enhances bone regeneration capabilities. Overall, the study provided evidence that 3D printed PCL scaffolds integrated with HA and BG coatings may be a promising approach for bone tissue engineering applications.

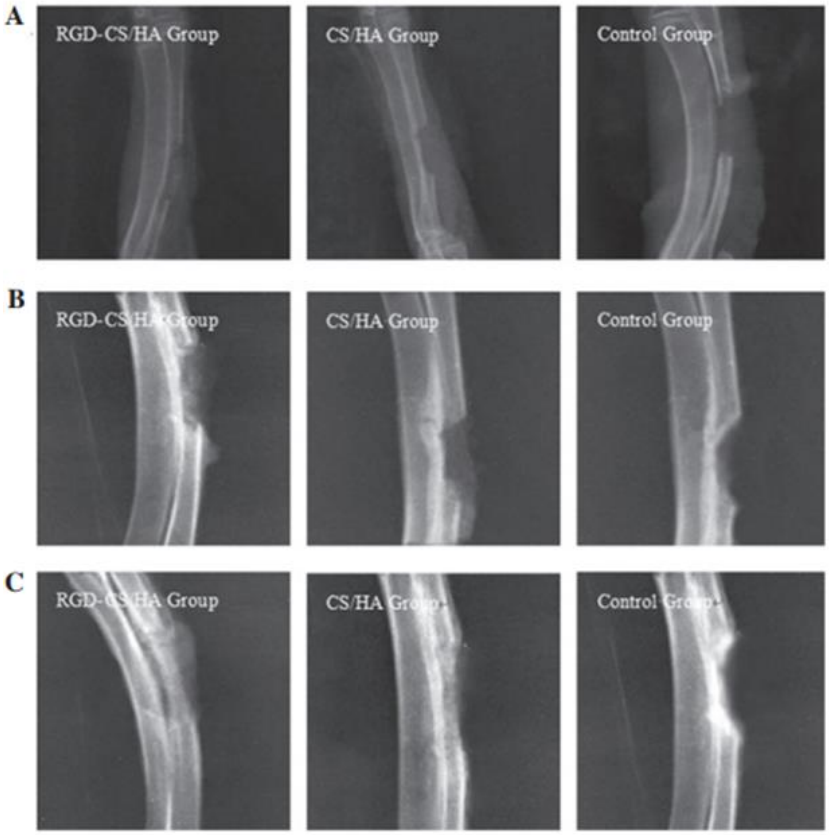

Figure 5: Figure 5: X-ray micrograph images showing radial bone defect repair in rabbit radii implanted with either arginine glycine aspartic acid (RGD)-modified chitosan/hydroxyapatite (CS/HA) scaffolds, unmodified CS/HA scaffolds, or no scaffold (control) after (A) 2 weeks, (B) 4 weeks, and (C) 6 weeks [90].

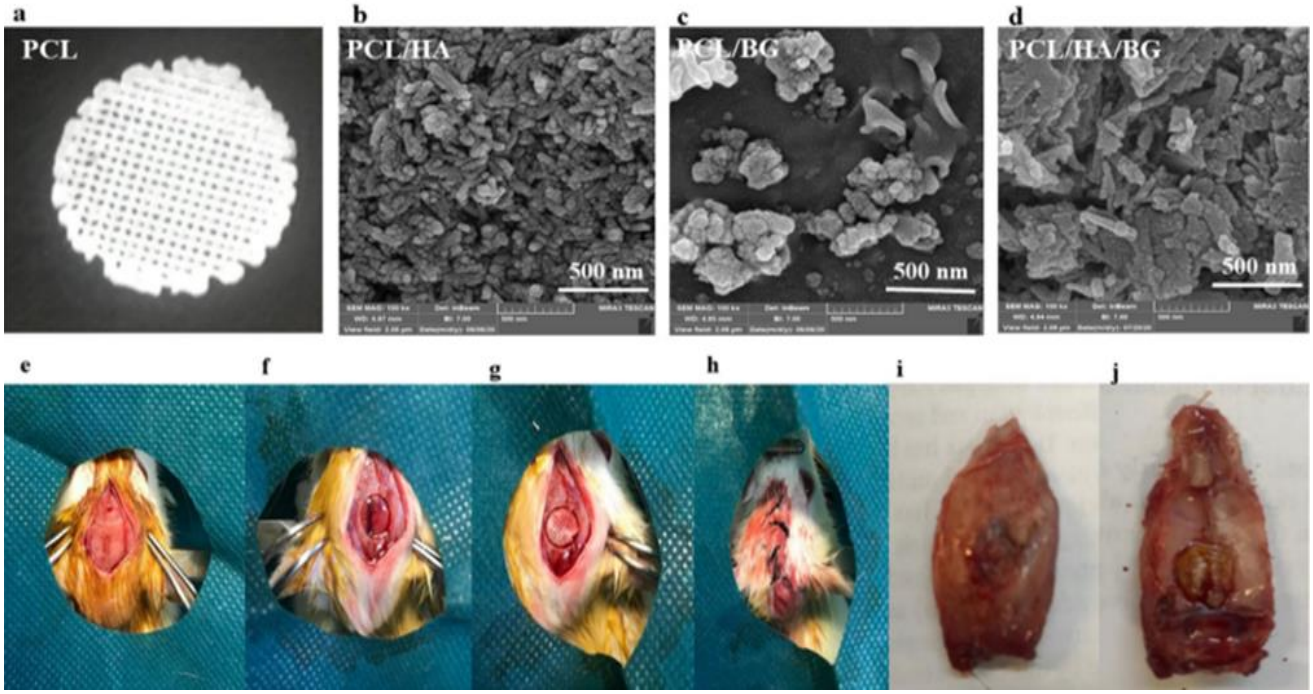

Figure 6: (a) Macroscopic view of the PCL scaffold and surface-deposited nanobioceramics. (b) Surface morphology of PCL/HA. (c) Surface morphology of PCL/BG. (d) Combined PCL/HA/BG scaffolds at high magnification. (e)–(h) Stages of lesion creation and implantation in rat calvaria. (i) Reconstruction of a defected calvaria in the control group after 30 days. (j) Regeneration within the 3D-printed scaffold graft in the experimental group after 30 days [94].

2.2.2. Bioglass and Glass-Ceramics

It is unknown when the word "bioactive glass" or "bioactivity" first emerged in the literature, but by 1982, Hulbert, Hench, Forbers, and Bowman had published a definition of a "bioactive material." The concept states: "A bioactive material elicits a specific biological response at the material's interface, resulting in the formation of a bond between tissues and the material." This notion eventually evolved into 'bioactivity' as it applies to glass and other biomaterials used as implants [95]. Ceramics and glass ceramics have been gradually utilised to renovate and regenerate bone. This broad category of 'bioceramics' introduces the range of the commonly defined implant-bone interactions [96]. Also, the glasses offer unlimited treatment options for repairing bone and tooth due to their benefits, such as osteoconductivity and osteoinductivity, and their higher level of angiogenesis compared to traditional bio-ceramics [97]. In addition, the compositions of modern glass-ceramics and bioactive glasses within ($CaO–P_2O_5–SiO_2–MgO–Na_2O$) could contain small amounts of SrO, K_2O, MgF_2, and CaF_2 [98]. Such glasses are utilised clinically to fill bone cavities, dental applications, maxillofacial reconstruction, and ear ossicles [99]. In 1990, Kokubo et al. developed bioactive glasses and other substances through in vitro experimentation in fluids that mimicked human blood plasma. The simulated body fluid (SBF) is a known solution for evaluating bioactive reactions [100]. Vallet-Regí. Conducted tests on creating an HCA nanocrystal layer on the glass surface, which showed a bioactive encouraging response, the glass after implanted bonded with living tissues, the initial silica-rich layer resulted from the ionic exchange of Na and Ca ions into the glass and protons into the solution, which attracted carbonate, Ca, and phosphate ions [76]. This process led to amorphous Ca phosphate crystals forming within HCA nanocrystals. This layer attracted inorganic components, promoting new bone formation. The bioactive glass coatings comprising 20% CaO and 80% SiO_2 (mol%) on Ti_6Al_4V were characterised [101]. Also, after two weeks into acellular SBF, the coatings were dissolved. Firstly, the coating silica and Ca ions were leaching into the solution. The ceramics have excellent thermal and mechanical properties appropriate for the orthopaedic uses. It resists the abrasion and scratching [102]. Livingston et al. researchers created porous glass bioactive scaffolds from 45S5 granules, which changed into Ca-P and replaced new bone in rats after twelve weeks of implantation [103]. Loredana M. et al. created three-dimensional scaffolds using glass fiber as a bone filler for bone remedy abnormalities in rabbit tibias. The scaffolds inserted new bone into the medullary cavities and

facilitated healing [104]. Nandi et al. compared the recovery of surgically produced radius abnormalities in goats using porous bioactive glass implantation with typical healing procedures. The control group was compared to the porosity of bioactive glass-stimulated bone forming over the damaged area [105]. The technological development led to create bioactive glass ceramics using nanoscale crystals [106]. Lianxiang et al. observed the bioactive glass scaffolds (1393B1 borosilicate and 1393B3borate) for rat calvaria defects and found that 1393B3 glass improved bone growth and healing [107]. Gabbi et al. studied a rabbit model using a bioactive glass coating on a titanium alloy plate. They observed the formation of new bone tissue upon contact [108]. Swati et al. glass scaffold Bioactivity 70S30C were implanted on the tibia of a rat model. After eleven weeks of implantation, they healed a rat tibia defect by regenerating new bone and degrading old scaffolds [109]. Lao et al. conducted a multimodal investigation of SiO_2-CaO bioactive glass scaffolds implanted in sheep mandibles, focusing on bone mineral variations and providing significant insights into bone minerality and construction [110]. Sych et al. studied the creation and description of mostly porous glass ceramics [111]. Steinhausen et al. concluded that bioactive glass was considered a suitable bone substitution for successfully controlling infection and defect filling and bone remedy regarded infected non-union, as shown in Fig. 7. Bioactive glass was comparable to autologous bone grafts in terms of both primary and secondary endpoints [112]. Further studies are required including large patients number. Dilshat et al. worked on 47.5B bioactive glass scaffolds in a rabbit's femur, revealing gradually resorption and significant bone osteogenic developed after surgery [113].

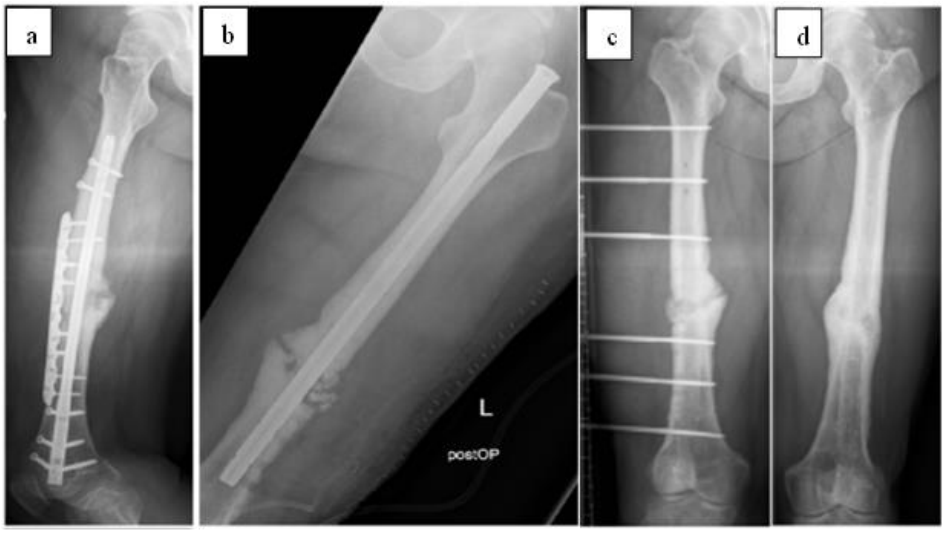

Figure 7: Bioactive glass in a patient with an infected non-union of the femur. (a) Infected non-union of the femur with loosened retrograde intramedullary nail and plate osteosynthesis. (b) Temporary stabilisation with an antegrade intramedullary nail. (c) Six months after defect filling. (d) The final result was a bony fusion after two years [112].

2.3. Resorbable Ceramics

The 3rd class of bio-resorbable ceramics, made of Ca silicates, Ca phosphate cement, Ca carbonates, and CaPs, are slowly absorbed and replaced by new bone tissue in vivo [114].

2.3.1. Calcium Phosphate

Calcium bio-ceramics are unsuitable for heavy, load-bearing implants like hip prostheses due to their weak solidity and resistance to stress from activities such as exercise, walking, and jumping. They are suitable for coating implants, ear implants, and fillers in bone defects with less stress. Calcium phosphate is beneficial for minor bone repairs but unsuitable for larger bones due to its brittleness [115]. However, the CaP applications in the orthodontist are restricted due to pre-implantation infection and the patients' slow healing. The Ca phosphate was investigated for alveolar bone regeneration with a positive result [116]. The Ca phosphate's bio-compatibility, nontoxicity, and efficiency in periodontal diseases were investigated, and variable outcomes were documented [117, 118]. Kurashina et al. studied the application of calcium phosphate cement in rats' subcutaneous parts, observing its

conversion to Hydroxyapatite after implantation, which interacted with surrounding soft tissues [119]. Maddalena et al. studied the effectiveness of combining silicon stabilised with tricalcium phosphate in sheep for bone defect repair, revealing excellent regeneration and significant implant integration [120]. Song et al. put 3D-printed scaffolds with nano-biphasic calcium phosphate, platelet-rich fibrin, and polyvinyl alcohol into a rabbit's radius defect. They showed that they were biocompatible and biologically active [121]. A study by Abeer et al. investigated the potential use of a bone grafting composite (BCP) and a hyaluronic acid gel to repair femoral condylar deformities in rats. The findings demonstrated that the materials effectively produced new bone [122]. Owji et al. conducted in vivo studies to examine neo-bone formation at 4- and 8-week post-implantation, as shown in Fig. 8. The quantitative micro-CT and histological examination results showed that bone formation was not faster in CaP-filled CSMA composites compared to CSMA alone [123].

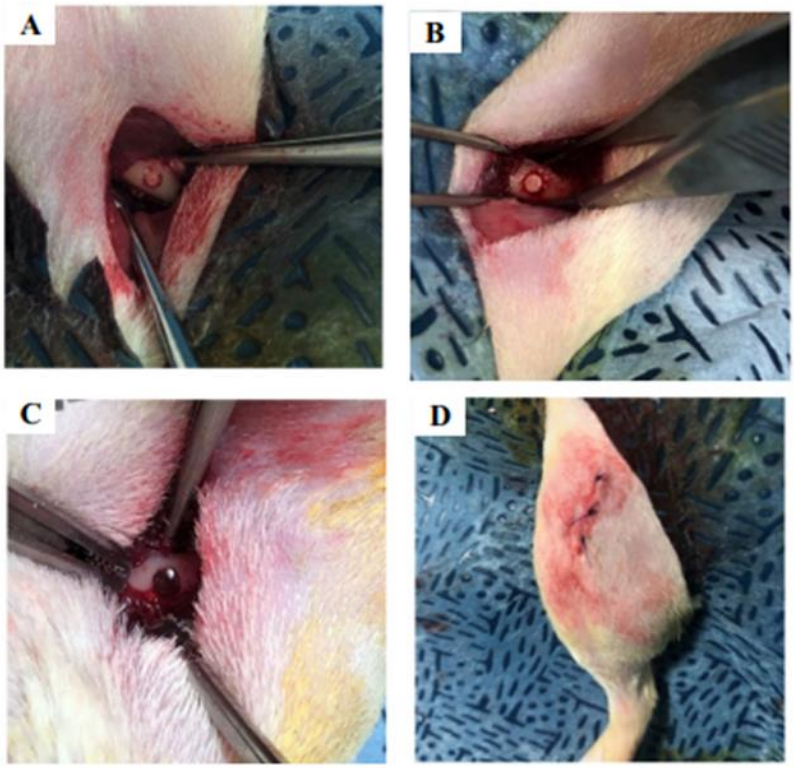

Figure 8: These images explained the surgical operation during the CSMA and CSMA+50% CaP implant inside the rat's femur. Initially, the implant was inserted into the femur of the rat. The images (A–C) describe the implant's implantation. Image D represents the surgery suturing before retrieving the specimens after 4 and 8 weeks of the surgical procedures [123].

3. Conclusion

Bio-ceramics play an essential part in bone regeneration, and they add value to human well-being. Numerous bio-ceramics classes are accessible for the orthopaedic use. Also, the bio-ceramics selection relies upon the nature of the overhauled defects. Bio-ceramic manufacturing develops fast to optimise fabrication with the desired characteristics. Also, the bio-ceramics mechanical property is planned to fit various applications, such as strengthening substances, implants, cement, etc. Resorbable bio-ceramics possess a huge potential in converting tissue engineering. They act as scaffolds and permit bone regeneration as a part of the natural tissue repair mechanism. These bioactive nanoceramic coatings confer key advantages for orthopedic implant applications. No surgical removal is required as the degraded ceramic products are non-toxic. Incorporating nanoscale bioceramics into implants has enhanced their utility in orthopedic procedures. Compared to bulk ceramics, nanomaterials demonstrate significantly higher osseoconduction and osseointegration efficiency due to their precise porous network which facilitates bone repair.

A critical design consideration is balancing mechanical properties to suit load-bearing function. While nanoceramic coatings have demonstrated lifespan up to 15 years maximum in vivo, further improving durability over even longer implant service lifetimes remains an important research focus. Additional studies are also warranted to optimize interfacial bonding between coatings and implant substrates. Overall, nanobioceramic technologies show promise for enhancing orthopedic implant fixation, resorption behavior, and lifespan; however, continued work is needed to realize their full potential to restore long-term bone health.

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Conflict of Interest
The authors declare that they have no conflict of interest.

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