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Recent Advances in Biomaterials for Bone Scaffolds and Tissue Engineering Applications challenges and Future Prospects

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Abstract

Over the last few years, there has been an increasing demand of bone tissue engineered biomaterials for diseased or damaged bones. In this review the structure and mechanical properties of natural bone introduced. The strategies of fabrication of scaffolds for bone tissue engineering are described. The paper focuses on biomaterials used in the fabrication of scaffolds, which includes types, properties, and applications. Naturally derived biomaterials were discussed in particular due to their advantage.

Keywords: Bone tissue engineering, Natural biomaterials, Protein based biomaterials, Bone scaffolds.

1. INTRODUCTION

Bone tissue plays important multiple roles in our daily functionality. As number of accidental bone damage and disorder is increasing worldwide, the need for artificial bone implants increased. Naturally human bones have a certain self-healing ability, but are powerless for large bone defects. To solve this problem, bone tissue engineering (TE) is introduced to restore, improve, and heal damaged tissues [1].

Natural bone consists of cells; extra cellular matrix (ECM) assembled from collagen and hydroxyapatite (HAP) and bound minerals. Collagen and HA account for 95% of natural bone under dry conditions. It contains certain amounts of ions such as Na+, Mg2+, Cl-, K+, F-, and Zn2+. The mechanical properties of natural bone vary with the age and the body part [2].

TE always need the development of biomaterials that compiles the design approach and novel surface nature in order to enhance cellular activities as cell adhesion, proliferation, differentiation, and improve biocompatibility for formation of complex tissue. Medical implants in TE that work to restore damaged or support existing tissues or organs in the human body can cause inflammatory or immune response that severely affects their performance and function in vivo [3]. Bone tissue engineering aims to induce new tissue repairing and regeneration by cells and scaffolds [4]. A scaffold prepared from biomaterials act as a carrier of cells and signals. It represents a main factor in bone tissue engineering. It is necessary to design a temporary support to help cell proliferation, differentiation, and growth. An ideal scaffold should have biocompatible, suitable mechanical properties, high porosity, and gradient pore structure. The fabricated scaffold gradually degrades with cell growth until the new tissue completely replaces it [5].

2. SCAFFOLD MANUFCTURING

There are several manufacturing technologies that have been shown to produce scaffolds for bone tissue engineering, we discuss her some techniques:

2.1 Solvent Casting and Particulate Leaching

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In this technique, the biomaterial solution dissolved by a solvent combined with uniformly distributed salt particles of a certain size. By evaporation of solvent the salt particles remain in the mixture. Second step is submersion of the mixture in water where the salt dissolved in the water leaving a structure with high porosity [6]. This technique is easy, low cost, and permits tuning the pore size, but soluble particles cannot be separated from the mixture matrix [7].

2.2 Freeze-Drying

In this process biomaterial is dissolved in an appropriate solvent. The solution is then cooled under the freezing point, and then evaporated leaving a solid scaffold with numerous interconnected pores [8]. This technique does not need high temperatures that could decrease the activity of biological factors. The pore size is controlled by changing the freezing method [9]. The technique uses water and ice crystals instead of an organic solvent during scaffold fabrication which is more suitable in biomedical application. It is not preferred in certain medical applications as vascular systems in biomedicine [10].

2.3 Thermal-Induced Phase Separation

Thermal-Induced Phase Separation (TIPS) is a low-temperature method that sets the homogeneous polymer solution with high temperature in a decreased temperature environment to induce phase separation so that a polymer-rich phase, as well as a poor polymer phase is achieved [11]. This technique permits the adjustment of pore sizes to allow inclusion of fillers and drugs, but it is not very suitable for seeding of the osteoblasts or for bone-tissue growth.

2.4 Gas Foaming

In this technique inert gas foaming agents such as carbon dioxide is used to perform pressure on biodegradable polymer with water until they are saturated or full of gas bubbles. The disadvantage of this technique is the presence ability of a closed pore structure [12].

2.5 Electrospinning

It is the technique for making fibers from solution by using electricity. This technique is important for developing nanofibrous scaffolds. Electrospinning is the common methodology used to the manufacture of artificial vascular grafts [13]. Electrospinning technique is charging liquid under high voltage to cause interaction between the surface tension and electrostatic repulsion causing droplets on spinneret to erupt and stretch. A standard electrospinning system consists of four main components: a spinner with a syringe pump, a metallic needle, high-voltage power supply, and a grounded collector (FIG. 1).

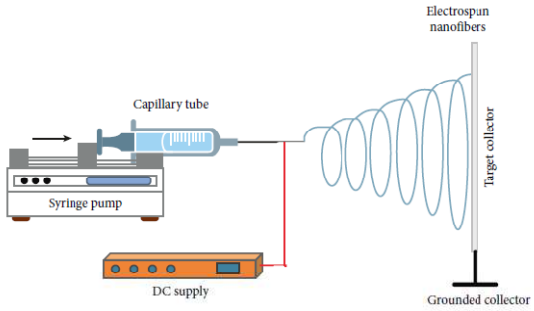

FIG. 1: Electrospinning technique

As the strength of the electric field exceeds the surface tension of the droplet a liquid jet is produced. Electrostatic repulsion extends the jet until it is deposited on the grounded collector. The jet is then solidified into a nonwoven fibrous membrane [6]. Electrospinning is a simple and quick method in fabrication of nanofibrous scaffolds, but it cannot be used in fabrication of scaffolds with complex structures [10].

2.6 Rapid Prototyping

Rapid prototyping (RP) technologies are a set of manufacturing processes that can generate direct forms from computer-aided design (CAD) models of an object without needing specific tooling or knowledge. RP can combine powder, liquid, and sheet materials to form scaffolds. RP machine can produce wood, ceramic, plastic and metal objects layer by layer using thin horizontal cross sections from a computer-generated model [14]. RP scaffold fabrication technique can be used in manufacturing with more control over polymer [15].

2.7 Three-Dimensional Printing (3DP)

3DP is a functional creating tool from the computer models. 3DP technique is performed by applying the material in powder form in layers over each other creating 3D object. This process is used to

form ceramic, metal, or composite scaffold. 3DP is a new fabrication method that controls the scaffold structure. The technique is very effective in producing nanoscale rough scaffolds. The disadvantage of 3DP is that scaffolds produced have limited ECM properties [16].

2.7.1 Fused deposition modeling (FDM)

In this technique, a solid polymer is fed into a hot extrusion nozzle where it is melted and extruded. The product of extrusion is casted on surface of 3D object under the control of computer. FDM has been used to process thermoplastic biopolymers.FDM is useful in the scaffold design in different fabrication techniques [17].

2.7.2 Selective laser sintering (SLS)

This technique uses laser as power source to sinter powdered material in any defined 3D model form in accumulated thin layers. The technique has been used to design scaffolds from various materials such as polymers, metals, and ceramics [18]. This technique is efficient in the fabrication of scaffold from ultrahigh-molecular-weight polyethylene [19] and in fabricating of bio-nanocomposite microspheres composing of PLLA that can efficiently produce microspheres carbonated hydroxyapatite (CHAP) nanospheres within a poly (L-lactide) (PLLA) matrix in order to build scaffold [20].

The SLS is very effective technique because it permits strong manufacture control over the microstructures of the scaffold using SLS process parameters to obtain the desired scaffold properties [19]. The main disadvantage of SLS is that it needs removal of injected powder after processing [19].

2.7.3 Bioprinting

Bioprinting is a technique which uses material transfer to develop biological patterns of materials, cells, molecules, tissues, and biodegradable biomaterials [21]. Bioprinting integrates cells with the material during the production process to fabricate living tissue constructs. These techniques have several advantages, such as low costs, high speed of printing, and high cell viability (80/90%). The major disadvantage is the narrow material; selectivity [21]. 3D bioprinting classified based on the working principle into [22]; the inkjet-based, the extrusion-based, the SLA based, and the laser-assisted printing (FIG. 2) [23].

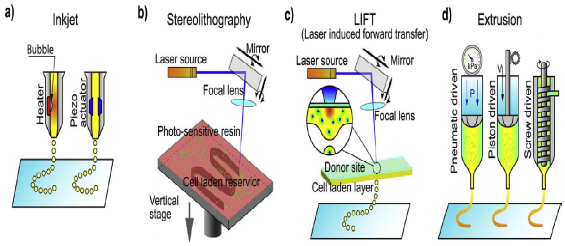

FIG. 2: Illustration of 3D printing processes: (a) inkjet-based 3D printing, (b) stereolithography-based 3D printing, (c) laser-assisted 3D printing, and (d) extrusion-based 3D printing. Image reprinted with permission from Jiang et al. 3D, three-dimensional.

2.7.3.1 Stereolithography (SL)

Stereolithography method is basically used to create solid and 3D objects by printing thin layers of ultraviolet (UV) curable material layer-by-layer. A stereolithography system has four main components; a tank with a photosensitive liquid resin, a transferable built platform, a UV laser for radiating resin, and a dynamic mirror system. The manufacturing process begins by putting a layer of photosensitive liquid resin on the platform and let it to solidify. A second layer is placed on the first layer then third layer and so until a 3D scaffold is created. It is used in many applications such as biosensing, drug discovery, and energy harvesting. The disadvantages of this method are the need of more treatment and dependence of size of the scaffold on the width of laser beam [24, 25].

2.7.3.2 Inkjet bioprinting

Inkjet-based bioprinting is a non-contact process technology based on the conventional inkjet process used by desktop inkjet printers, Inkjet bioprinting involves dispense of droplets of dilute solutions driven by thermal, piezoelectric, or microvalve processes [26]. It is classified as thermal inkjet bioprinting, electrostatic inkjet bioprinting, and piezoelectric inkjet bioprinting [27].

2.7.3.3 Extrusion-based bioprinting

Extrusion-based bioprinting has been extensively used in scaffold fabrication for TE in recent years [28]. The material is extruded through a printhead to build 3D shape in a layer-by-layer. The Extrusion takes place based on two main mechanisms: pneumatical force (gas or pres- surized air) and mechanical force (screw or piston).
The advantages of this technique are maintaining control over the deposition of cells, rate of cell distribution, and the ability to print very high cell densities with a fast fabrication rate [29]. 17 This technique provides excellent structural integrity due to the continuous deposition of the bioink [30]. This

is an important method in formation of high-viscous biomaterials. When compared with inkjet bioprinting, extrusion-based bioprinting offers higher cell densities but lower speed and resolution [31].

2.7.3.4 Laser-assisted bioprinting (LAB)

This bioprinting technique was developed for printing of metals, this technique successfully applied in bioprinting of nucleic acids such as DNA or organ cells [32]. The technique depends on a laser-induced vaporization effect of a thin layer of gold/titanium that coats the donor-slide. A bubble is formed that flashes the material onto the receiver-slide. This technique allows high resolution deposition of material in solid or liquid phase [33].

3. MATERIALS USED IN BONE TISSUE EBGINEERING

Types of materials used in scaffolds manufacture:

- Inorganic materials, e.g., metals, bioactive glasses, tricalcium phosphate (TCP), hydroxyapatite (HAP) and their combinations.
- Organic materials as polymers (natural (polysaccharides, proteins), and synthetic (e.g., poly (lactic acid) (PLA), poly (glycolic acid) (PGA)).

3.1 Inorganic Materials

3.1.1 Metals

Metals considered the oldest material used for implants [34]. The first recorded use of metal implants was in ancient Egyptian period [35]. At present, titanium and its alloys are the most frequently used metallic biomaterials for dental and orthopedic implants because of their biocompatibility [36], non-toxicity [37] and corrosion resistance [38]. Pure titanium is biocompatible but with poor strength. Titanium alloys have superior strength, but contain ingredients that can be toxic [39]. Metal alloys are commonly used for joint replacements and fracture-fixation implants, because of their good biocompatibility, corrosion resistance and high strength [40]. Magnesium alloys have good modulus of elasticity that approaches that of native bone (10−40 GPa). Its degradability rate can be controlled to keep up with the healing rate of bone [41]. The most disadvantages of using magnesium implants are the high corrosion rate that could produce hydrogen gas pockets, hemolytic reactions, and mechanical weakness at the implant site in vivo [42]. In general, the main disadvantages of metals could limit their use are the reduced cell adhesion, toxic metallic ions, corrosive action, and absence of biodegradable so metal implants must be removed especially in the case of children.

3.1.2 Bioceramics

Bioceramics are ceramic material specially designed to tolerate and encourage the regeneration of tissues and healing damaged body tissues [43]. Bioceramics have high tensile strength, inert, and good adhesion to host tissues so it is used and combined with other biomaterials to develop composite scaffolds for bone tissue engineering [44].

Ceramic scaffolds applied for bone TE are characterized by high mechanical stiffness, very low elasticity, and brittleness. Bioceramics is similar to natural bone in chemical composition so they have excellent biocompatibility. Bioceramics on the other hand is brittle cannot withstand mechanical loading and degradation-rate control [45]. Bioceramics shows many properties as being mechanically strong, bioactive [46], biocompatible, have corrosion resistance, resistance to compression, and weak to shearing and tensile forces [47]. The most commonly used bioceramics in bone-tissue engineering are HAP, TCP and their composites [40]. HAP has excellent properties for TE as it is a major natural inorganic component of bone. It has excellent bioactivity, biocompatibility, controlled degradation, osteoconductivity, non-toxicity, and non-inflammatory characteristics. Its mechanical properties affected by the size of the HAP particles, porosity, and density [47]. HAP is very useful for reconstructing damaged bone tissues, as it stimulates growth factors and encourages alkaline phosphatase (ALP) in mesenchymal stem cells (MSCs) [44]. HAP is very hard but brittle, with a very slow degradation rate in vivo so it must be combined with natural or synthetic polymers to manufacture TE scaffolds. HAP can be combined with natural or synthetic polymers to form composite biomaterials to enhance its mechanical properties.

TCP is another popular bioceramic commercial product already available used in TE. TCP supports in vivo osteogenic differentiation and used for the production of TE scaffolds. Collagen combined with TCP scaffolds used in a rabbit femur bone showed better bone regeneration than collagen-HAp scaffolds [49].

3.2 Organic Materials

Organic materials as polymers classified into natural (proteins, polysaccharides), and synthetic poly lactic acid (PLA), poly glycolic acid (PGA). Use of polymers in TE scaffolds has many advantages. Natural polymer biomaterials have good properties as excellent cell attachment, growth, adhesion, ductility, biocompatibility, and biodegradability. But they have disadvantages as immune-response problems, poor mechanical properties [50], the presence of impurities as endotoxin [51], and lack of organized degradation rates. Crosslinking of polymers can enhance structural properties [52, 53].

Natural biomaterials include substances which are natural in origin or need certain chemical modifications to be used for development of scaffolds or any other implants. Based on the nature of their origin, natural biomaterials can be broadly classified into two main categories, protein based (soy, collagen, fibrin gels, silk) and polysaccharide-based biomaterials (starch, alginate, chitin/chitosan, and hyaluronic acid derivatives).

Synthetic polymers based on polyesters have tailored pore size, porosity, and degradation rate that can be controlled easily [54]. Their disadvantages are reduced bioactivity, hydrophobic, and lack cell recognition sites. Synthetic and natural polymers in general have relatively poor load bearing capacity, low elastic modules [55, 56].
Combining polymers with bioceramics or bioglasses produce composite scaffolds that can reduce or overcome these limitations. Bioceramics or bioglasses may be added as a coating or filler to a polymer matrix to improve bioactivity and mechanical properties [57, 58]. Porosity can modify in composite polymer-ceramic scaffolds with varying levels of precision using techniques including 3D printing and electrospinning [59].

3.2.1 Natural polymers

3.2.1.1 Protein based natural biomaterials

Protein based biomaterials consists of certain recombinant proteins with amino acids as the major constituent [60]. They have certain mechanical and biological pattern derived from natural proteins that provide structural support.

3.2.1.1.1 Silk

Silk is a protein-based polymer that is produced in the form of fibers by lepidoptera larvae such as silkworms, spider, scorpions, mites, and flies [61]. The most widely used silks are from the domesticated silkworm-Bombyx mori and from spiders-Nephila clavipes [62]. A silk protein is a promising biomaterial due to its biocompatibility, biodegradability, self-assembly, mechanical stability, and ability to tailor its structure and morphology. Silk protein combined with organic/in-organic solvents and water-soluble gelatin materials have been used for fabrication of 3D porous composite scaffolds for regeneration of bone, ligament and skin tissues.
Silk used to coat TE scaffolds gives encouraging results. Silk composite is promising for orthopedic applications. Silk serve as filler materials for small invasive surgeries of vertebral fractures. Silk can be transformed into various material formats such as, films, scaffolds, fibers, and sponges. Silk manufacturing forms are useful for many specific bone applications. Until now, silk films have been investigated to study the osteogenic differentiation of human MSCs for regeneration and healing of cortical bone lamellae [63].
In a further study, trials were made to enhance the mechanical properties of silk scaffolds by uniformly dispersing HAp nanoparticles into silk nanofibers [64]. Addition of HA increase the mechanical properties of the composite scaffolds. Further increases of HA concentration cause disruption in the polymer chain networks within silk nanofibers and weakened the overall mechanical strengths.

3.2.1.1.2 Collagen

Collagen is very important abundant protein in the body. It provides strength and structural stability to all body tissues. Collagen has good biocompatible, biodegradable, good mechanical strength, and cell-binding properties [65]. 89% of the organic matrix of bone is composed of collagen-I combined with HAP. Collagen crosslinked with HAP, chitosan fibers and mesenchymal stem cells have been used to produce porous scaffolds for bone TE [66, 67].

Collagen is maybe the most frequently adapted material into TE scaffolds. Type I collagen has been used most frequently within TE due to the lack of immune response associated with its use [68]. Collagen has mechanical properties that are insufficient for manufacturing a load-bearing scaffold as other natural polymers [69]. The mechanical and degradation properties of collagen can be enhanced through the processes of crosslinking [70]. Collagen needs the combination with robust materials to create composite scaffolds. Collagen can be combined with HA as the major inorganic component of bones in composite scaffolds.

3.2.1.1.3 Fibrin

Fibrin is a protein based natural polymer produced from fibrinogen that supports numerous living tissues and permits wound healing by inducing angiogenesis and promoting cell attachment and proliferation [71, 72]. It has strong adhesive properties to biological surfaces so coating on scaffold has been found to improve scaffold adhesion properties which promote early tissue regeneration [73, 74]. Studies report addition of fibrin with cells seeded into biodegradable scaffolds which have poor cell adhesion properties for cell delivery and tissue engineering applications [75]. Fibrin based hydrogel scaffolds have been widely used for TE applications of cartilage and bone tissues [76].

3.2.1.1.4 Bovine Serum Albumin (BSA)

As mentioned before natural biomaterials as polysaccharides or proteins provide excellent cell attachment, growth, adhesion, good ductility, biocompatibility, and biodegradability [51]. But they have poor mechanical properties [50].
Albumin is simple, water-soluble protein. It is found in egg white, blood serum, milk, and many other animal and plant tissues. Albumin is one of the most abundant proteins; chair about 55% of blood plasma protein. Rhodes and Zolle prepared human serum albumin microspheres used for the determination of abnormal pulmonary circulation [77, 78].

Albumin microspheres have been investigated for drug targeting to various organs and tissues [79, 80]. The albumin tissue scaffold possesses an extremely porous structure, and moderate mechanical strength as well as cell grown [81]. The different advantages and disadvantages of biomaterials with can be used either an additives or base matrix are presented in Table 1.

Table 1: Advantages and disadvantages for biomaterials

Material	Advantages	Disadvantages
Metals	Biocompatibility, non-toxicity and corrosion resistance	Not biodegradable
Bioceramics Bioactive glasses	Improve differentiation and osteogenesis	Low strength and brittleness
Hydroxyapatite (HAP)	Bioactivity, biocompatibility, osteoconductivity, non-toxicity and non-inflammatory	Brittle, very slow degradation
Tricalcium phosphate	Supports in vivo osteogenic differentiation	Slow degradation, incompressible nature
Natural (polysaccharides, proteins)	Biocompatibility Biodegradability Abundant sources	Poor mechanical properties
Synthetic polymers (e.g., poly (lactic acid) (PLA), poly (glycolic acid) (PGA)	Biodegradable, non-toxic, a low melting point good mechanical properties, good biocompatibility	Slow degradation. Poor cell adhesion.
Bovine Serum Albumin (BSA)	Abundant sources. Very compatible as it may be extracted from patient blood. Biodegradable. Low cost synthesized	

Novel protein-based plastic derived from Bovine Serum Albumin (BSA)

Protein-based materials (from vegetable or animal origin) are proposed as a potential solution to provide new biodegradable plastics. Proteins are very practical materials because of its possible modifications to requirements of many specific applications. The development of protein-based plastics from vegetable or animal origin solves the problem of resources and costs. Subsequent polymerization for Bovine Serum Albumin (BSA) results in the formation of a biodegradable plastic with a strong polymer matrix remains [82] (FIG. 3).

Such plastic could be synthesized commercially from the bovine serum albumin of the animal blood to offer a novel biodegradable plastic. The produced plastic BSA (PBSA) could be used in many biomedical applications [82].

3.2.1.2 *Polysaccharide based natural biomaterials*

Polysaccharide based biomaterials are natural polymers consisting of sugar monomers. Polysaccharides derived from plant or animal sources have many tissue engineering applications. Chitosan, alginate, hyaluronan, and agarose are polysaccharide biomaterials used in fabricating scaffolds for tissue engineering [83].

3.2.1.2.1 *Chitosan*

Chitosan is a linear polysaccharide derived from partial deacetylation of chitin. Chitinis found in the cell walls of fungi and yeast [84]. Chitosan is a promising biomaterial due to its excellent biological properties as biocompatibility, biodegradability, and support for cell attachment, proliferation, and antimicrobial activities [85]. Chitosan-HAP composite scaffolds are used for regeneration of bone tissues because of their improved bioactivity and bone bonding ability [86].

3.2.1.2.2 *Alginate*

Alginate or Alginic acids are biopolymers composed of non-repeating unbranched exopolysaccharides derived from certain seaweeds, bacteria and brown algae [87]. Alginate is hydrophilic, biocompatible, relatively economical, and biodegradable [88]. Composite scaffolds have been found successful with alginate combined with different other biomaterials like HAP, chitosan, collagen and silk fibroin for bone regeneration.

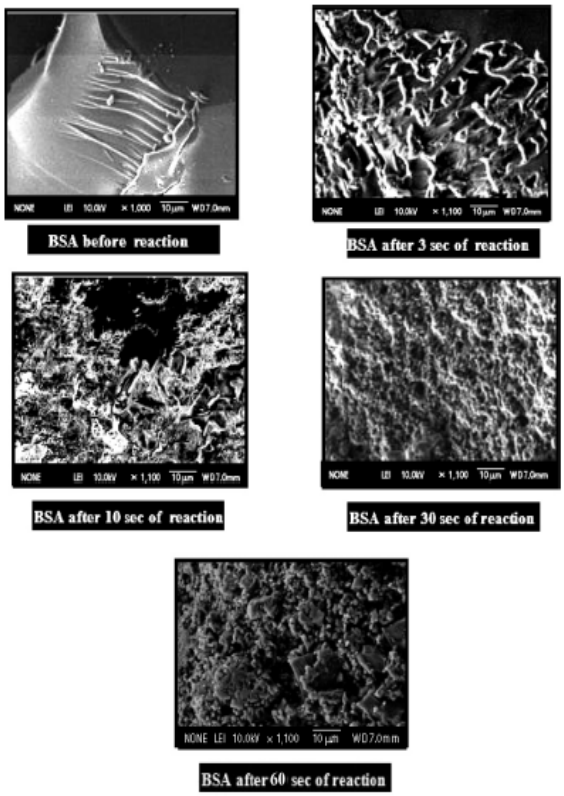

FIG. 3: SEM micrograph of the native BSA and the formed PBSA after sub-CW reaction at 523 K for different interval times

3.2.1.2.3 Hyaluronan acid

Hyaluronic acid or Hyaluronan is a major glycosaminoglycan polysaccharide present in the extracellular matrix of tissues that promotes early inflammation critical for wound healing [89], Hyaluronan found widely in connective, epithelial, and neural tissues. Hyaluronan has good biocompatibility, biodegradability, and ability to

maintain a hydrated environment conducive for cell infiltration [90]; it has a very large molecular weight and has been used in TE in both hard and soft tissue. The mechanical properties of Hyaluronic acid can be improved through crosslinking [91, 92], Composite scaffolds based on hyaluronan combined with synthetic polymers, collagen, and HAP have been developed for bone and cartilage regeneration.
Hyaluronic acid has also been used as a delivery agent to improve bioactivity in bone substitute materials. The addition of hyaluronic acid to bone grafts helps osteoconduction and improves handling characteristics in clinical situations.

3.2.1.2.4 Agarose
Agarose is a marine algal polysaccharide obtained by isolation of red algae and seaweed [93]. Agarose has the ability to form into hydrogel providing a three-dimensional environment for cell proliferation and retention of their phenotype [94]. The physical structure of the gels can be changed by varying the agarose concentration which results in the desired pore sizes. Agarose based hydrogel scaffolds used in bone tissue engineering [95, 96].

3.2.1.2.5 Algae based polysaccharide
Algae are a rich source of different varieties of sulphated polysaccharides. Algae have antioxidant, anti-allergic, anti-inflammatory, and anti-coagulant properties ideal for TE applications [97]. Sulphated polysaccharides like Ulvan extracted from green algae Ulva, Carrageenans from red algae Rhodophyceae and Fucoidan from brown algae Phaeophycophyta [98] have been extensively used for synthesis of composite bone scaffolds.

3.2.2 Synthetic polymers
Natural polymers such as collagen used within scaffolds can have weak mechanical properties [99-100]. Significant research has therefore looked to optimise and improve scaffold properties by developing hybrid synthetic polymer/ceramic scaffolds for bone tissue engineering.
Many polyesters based synthetic polymers have been examined due to their high tensile properties in as suture materials in surgeries [101]. Synthetic polymers have been routinely used due to their high strength and durability in the fabrication of small diameter vascular conduits. Synthetic polymers that have been used frequently within TE include polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), and copolymers of PLA-PGA (PLGA). These poly (a-ester) s have key characteristics of being biodegradable, nontoxic and biocompatible [102, 103].

3.2.2.1 Polycaprolactone (PCL)
PCL has been wide utilized in TE for the fabrication of 3D scaffolds. PCL is biocompatible, has comparatively slow degradation rate, high mechanical strength, and fewer acidic breakdown merchandise that square measure necessary advantageous characteristics [104-108]. The high mechanical strength probably permits supporting inside native tissue in TE scaffold [109]. However, PCL has poor cellular adhesion properties. Addition of some materials to make PCL composites improves bioactivity [110, 111]. PCL/alginate composite scaffolds showed inflated bone-forming cell viability, Ca deposition, mountain activity, and bigger cell-seeding potency in culture. Hydroxyapatite (HAP) has conjointly been combined with PCL by many teams trying to make a lot of bioactive composite scaffolds for TE.

3.2.2.2 Poly (lactic acid) (PLA)
PLA is perishable and bioactive thermoplastic polyester that has been accustomed build variety of medical implants together with bone screws, fixation devices, and tube-shaped structure grafts [112]. PLA is created by the chemical process of carboxylic acid that may be obtained from renewable sources together with starch and sugar. many types of PLA exist because of the chiral nature of carboxylic acid, together with poly-L-lactide (PLLA) and poly-D-lactide (PDLA) that square measure made from the chemical process of L-lactide and D-lactide severally [113]. PLLA fibers have high crystallinity, rigidity, and a degradation behavior that may be altered preferentially to match the biological properties of host tissue [114]. PLLA suture materials square measure utilized in coating of assorted drugs/drug-loaded polymers. PLLA suture square measure medicinal drug and antifungal that enhance wound healing at the positioning of injury [115].

3.2.2.3 Poly (lactic-co-glycolic acid)/PLGA
PLGA could be an artificial co-polymer of poly-L-lactic acid (PLLA) and polyglycolic acid (PGA), with America Food and Drug Administration approval for human applications. Degradation rates of PLGA are often varied in restraint to vary from weeks to months supported the quantitative relation of PLLA to PGA within the composite structure [116].
PLGA is best than pure PLA and PGA within the vary of accessible solvents that may be dissolved in and also the easiness with that it is often shaped into structures of desired sizes and shapes. PLGA encourage a lot of growth factors for tissues. The foremost disadvantage that limits exploitation PLGA inside TE is low elastic modulus, inflicting status to elastic deformation additionally to poor osteoconductive properties [117].
Combining PLGA with ceramics and bioactive glasses to make composite scaffolds will overcome these limitations [118].
Combining nano-HAP that has high osteogenic properties and high modulus with PLGA will overcome and enhance PLGA properties [119]. On alternative hands high concentrations of nano-HAP in an exceedingly composite will cause decrease in mechanical properties because of non-uniform distribution, however lower concentrations square measure able to improve tensile and compressive properties of scaffolds [120, 121].
Composite scaffold containing nano-HAP helps cells and proteins attachment to scaffold materials [122]. Nano-HAP has some limitations as crispiness and slow degradation that can also be overcome or increased by the mixture of PLGA that may balance these limitations [123]. Electrospun scaffolds

composed of PLGA were utilized in nerve regenerative applications [124]. Combination of artificial polymers like PCL and PLGA with HAP has light-emitting diode to winning results. Natural polymers like albuminoid and chitosan have higher mineralization characteristics than artificial polymers. Natural polymers have various ionic molecular teams that permit mineralization rates improved by the negative surface charge. The surfaces of artificial polymers also are mostly hydrophobic. This property causes poor cell adhesion [125, 126]. Several procedures are created to boost the surface of artificial polymers to extend cell affinity.

4. Conclusions

Biocompatible materials or biomaterials and their synthesis techniques play a vital role in bone scaffolds and tissue engineering applications. The manufacturing techniques used to produce scaffolds for bone tissue engineering varies according to type of biomaterial or medical applications. The ideal manufacturing method is easy, low cost, and permits the control of shape and pore size. Natural polymeric biomaterials as Polysaccharides or proteins can be derived from enormous sources and have excellent cell attachment, growth, adhesion, ductility, biocompatibility, and biodegradability but have poor mechanical properties.

Bovine Serum Albumin is one of the most abundant proteins, because it is simple, water-soluble protein. It has been investigated in many medical applications as drug delivery to organs and tissues. The albumin tissue scaffold possesses an extremely porous structure. The albumin tissue scaffold possesses moderate mechanical strength, allows cell growth, and highly pores. Focus in future work need to be taken on the novel protein-based plastic derived from Serum albumin which has many biomedical advantages. Protein-based materials derived from vegetable or animal origin are potential solution to provide new biodegradable plastics. The development of protein-based plastics from vegetable or animal origin solves the problem of resources and costs. Polymerization for serum albumin of the animal blood results in the formation of a biodegradable. This novel biodegradable plastic could be used in many biomedical applications.

5. Abbreviations

TE: Tissue engineering; ECM: Extra cellular matrix; HAP: Hydroxyapatite; TIPS: Thermal-Induced Phase Separation; RP: Rapid prototyping; CAD: computer-aided design; 3DP: Three-Dimensional Printing; FDM: Fused deposition modeling; SLS: Selective laser sintering; CHAP: carbonated hydroxyapatite; PLA: poly (L-lactide); PGA: poly (glycolic acid); SL: Stereolithograph; UV: ultraviolet; LAB: Laser-assisted bioprinting; TCP: tricalcium phosphate; BCP:biphasic calcium phosphate; ALP: alkaline phosphatase; MSCs: mesenchymal stem cells.

6. Declarations

Ethics approval and consent to participate

Not applicable

7. Consent for publication

Not applicable.

8. Availability of data and materials

The materials used and analyzed in the study are available from the corresponding author on reasonable request.

9. Competing interests

The authors declare that they have no competing interests.

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11. Authors' contributions

Conceptualization, W.A.M. and A.M.Y.; Data curation, A.M.Y. and M.S.A.; Investigation, M.S.A. and T.E.W.; Resources, A.M.Y.; Supervision, M.S.A.; Validation, W.A.M. and T.E.W.; Visualization, A.M.Y., M.S.A.; Writing – original draft, A.M.Y.; Review & editing, M.S.A. All authors have agreed to the published version of the manuscript.

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