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TISSUE ENGINEERING AS AN REGENERATIVE MEDICINE AS ENORMOUS APPLICATION: 3D PRINTING

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ABSTRACT
3D printing is a crucial technology in tissue engineering, as it allows the creation of intricate 3D printed constructions using biocompatible materials, cells, and supporting elements. The cytocompatibility properties of 3D printed structures composed of various synthetic and natural materials are the main topic of this review. The goal of the developing discipline of regenerative medicine is to repair and regenerate damaged tissue's functioning components. A branch of regenerative medicine called tissue engineering aims to grow whole organs and functional tissue fragments. Biomaterials and living cells can be used to construct native tissue mimics through the use of 3D printing technologies. Regenerative medicine has recently started using 3D bioprinting techniques to produce highly customized tissue models, which are an improvement over traditional tissue engineering techniques. In this article, we examine how 3D bioprinting has advanced tissue engineering by outlining its benefits over alternative tissue engineering techniques as well as how it works. The materials and methods used in bioprinting are also addressed, along with the field's future directions, obstacles, and clinical applications.

KEYWORDS: 3D Printing, Tissue Engineering, Regenerative Medicine, Bioprinting, Clinical Applications.

1. INTRODUCTION

The human body's capacity for regeneration is the source of recent advancements in the 3D printing technique. An estimated 31 million Americans were estimated to be affected by physical defects.[8] Globally, the number of individuals with different kinds of physical deformities resulting from traumas and degenerative processes of different origins is rising annually.[9,10] Support is needed for critical flaws in order for the cells to grow.[11] The human body's capacity to regenerate itself is restricted by a number of factors, including the availability of growth hormones and the functionality of the damaged tissue. For a long time, the accepted medical practice in these situations has been the implantation of an endoprosthesis that mimics the lost organ or autologous transplantation (less frequently, allologous). The aforementioned techniques enable the restoration of the lost organ's function, either fully or partially (tissue defect); nevertheless, it should be highlighted that they have numerous drawbacks that negatively impact the patient's quality of life. Thus, the concept of creating techniques that enable the complete regeneration of tissue abnormalities emerged; these techniques, known as tissue engineering (TE), are based on lab cell cultures.

Many researchers have been working on building cell-seeded implants that mimic native tissues in terms of anatomical geometry, cell location, and cell microenvironment in an effort to improve the functionality of tissue-engineered structures in recent years. The creation of designed structures will facilitate the integration of various cell types for tissue regeneration, sufficient mechanical support, and the transportation of nutrients appropriate for integration with systemic circulation.[8,9] Scaffolds with an innovative small- and large-scale design were produced using the three-dimensional printing (3DP) process.[10] This method of fabrication may create the geometries of 3D objects and their interior architectures in a controlled way, including pore size.[11, 12] With improved control over material and cell placement in 3D technology, this fabrication process has been widely applied to the construction of scaffolds or cell-laden constructs in tissue engineering and regenerative medicine.[11] The technique

of designing human tissue architectures using 3D bioprinting is far more intricate than the natural extracellular matrix synthesis[13] and simple cell layer[14] Nonetheless, in contrast to 2D constructs[13], several studies have demonstrated a discernible influence on cell characteristics as migration, differentiation, and proliferation.[14,15] It was proposed that in order to activate native extracellular matrix, 3D bioprinted constructions were necessary.[14] The two biomaterial types that are most thoroughly studied for 3D printed constructs are hydrogels[16, 17] and porous structures.[14] Furthermore, it has already been demonstrated that 3DP of physiologically adequate tissue reconstructions is a crucial instrument for prosthetics and surgery.[18] In the realm of tissue engineering, 3DP technologies enable the personalized production of complex multi-material implants for patient-specific geometries used in medical prosthesis.[19] The production of materials, such as ink, is one of the main issues with the topic.[20] For printable materials to expand into mechanically robust three-dimensional imprinted structures, they must possess rheological properties that facilitate extrusion and solidification. For medical implants, the materials used need to be fully biodegradable and biocompatible, allowing for tissue regeneration and maintaining the device's performance over its lifetime. In order to enable the incorporation of biological elements (such as cells, biologic cytokines, and growth hormones) into printed structures, it is necessary to maintain biocompatibility during any pre- or post-processing steps.[21] Studies revealed that while manufactured 3D printed structures have intricate geometry, they lack cell distribution. It was discovered that seeding different cell types onto a solid porous material is physically challenging. This includes uneven cell dispersion due to ineffective static scaffold cell seeding. Organ printing, then, is a novel method in cell-based tissue creation that uses rapid prototyping (RP) to create a hydrogel scaffold loaded with cells that has a certain exterior shape and reproductive interior morphology. Conversely, the utilization of 3D printing technology will facilitate the creation of vascular beds and improve the viability and survival rates of cells following implantation.[8,9] Tissue designers have also employed RP techniques to create three-dimensional (3D) permeable frameworks. The design and production of intricate framework geometries with fully interconnected pore arrangements are made possible by RP advances.[10] It was discovered in another study that tissue engineering research is extensively examining musculoskeletal tissue, bone, and ligament. Many biodegradable and bioresorbable materials have been studied and provisionally explored for usage as framework architectures. A scaffold should ideally possess the following attributes.

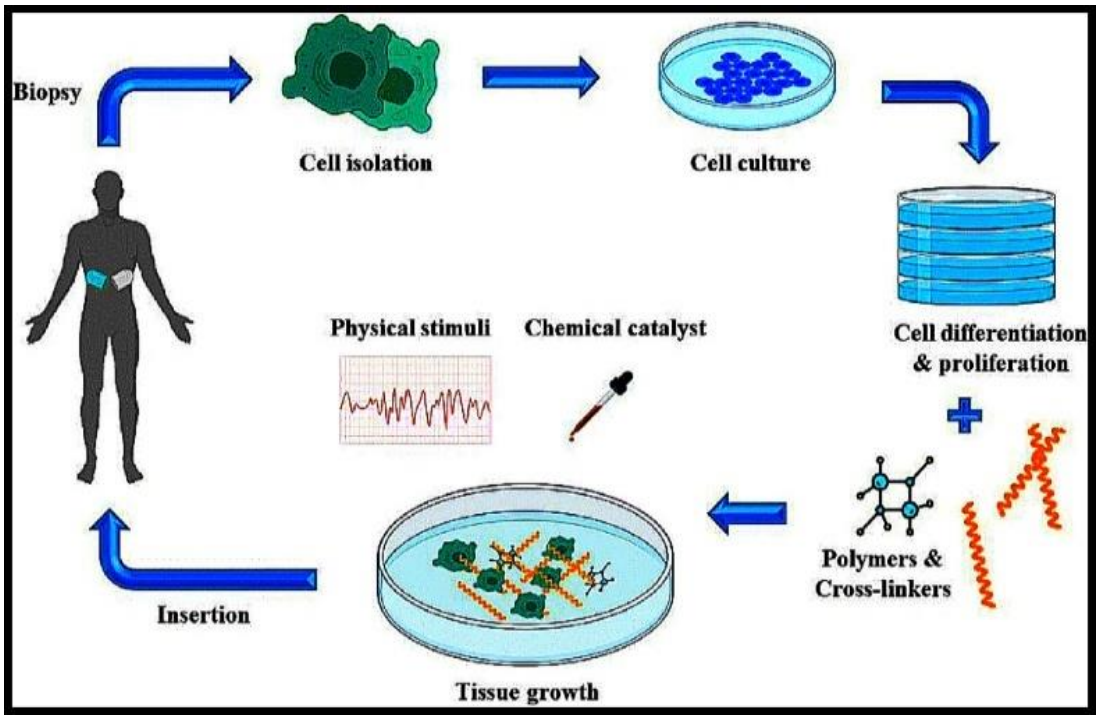

Figure 1: Schematic Diagram of Tissue Engineering.

- Biocompatible and bioresorbable with a controllable debasement and resorption rate to coordinate cell/tissue development in vitro or potentially in vivo.
- Reasonable surface science for cell connection, expansion, and differentiation;
- Mechanical properties to coordinate those of the tissues at the site of implantation.[22, 23]
- Three-dimensional and profoundly permeable with an interconnected pore arrange for cell development and stream transport of supplements and metabolic waste.

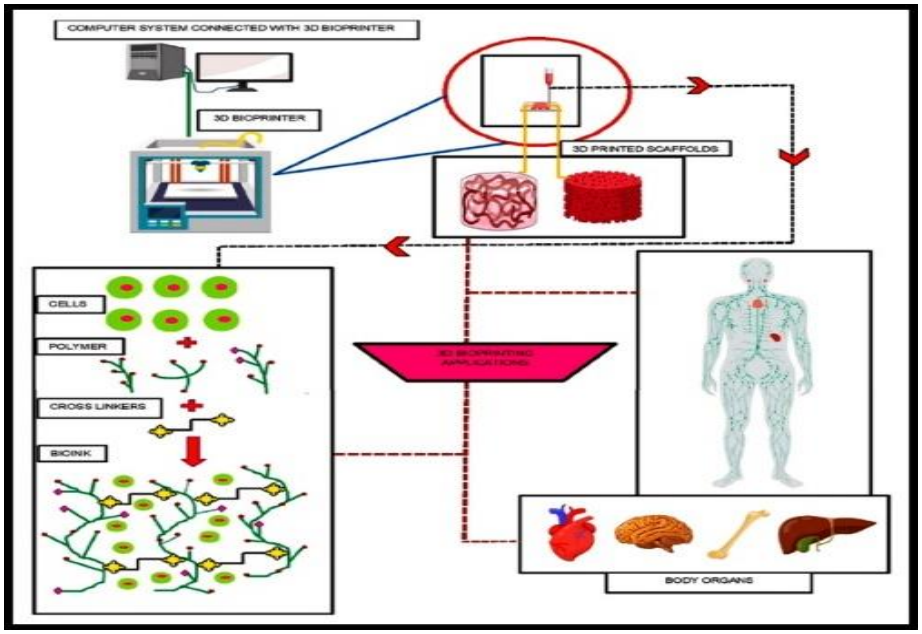

Figure 2: 3D printing in Tissue Engineering.

1.1. Tissue Engineering and Regenerative Medicine

The capacity to regenerate tissue has grown in significance as a cutting-edge technique to replace damaged tissues and organs' functioning components.[24] Tissue engineering is a branch of regenerative medicine that attempts to restore normal biological functions by regenerating certain tissues using in vitro and in situ techniques.[25,26] In order to mimic the body's natural extracellular matrix (ECM) and advance tissue engineering, the three traditional approaches to tissue engineering are as follows: (a) scaffolds alone; (b) isolated cells and other bioactive molecules; or (c) a combination of cells implanted within or on scaffolds.[25,26,27] Each strategy has unique benefits and possible applications. One way that is frequently employed is the combination technique, which involves seeding cells onto scaffolds and then implanting the 3D structural support the cells have created inside the body. This method allows for the culture of cells and the observation of their maturation process outside the body.[27]

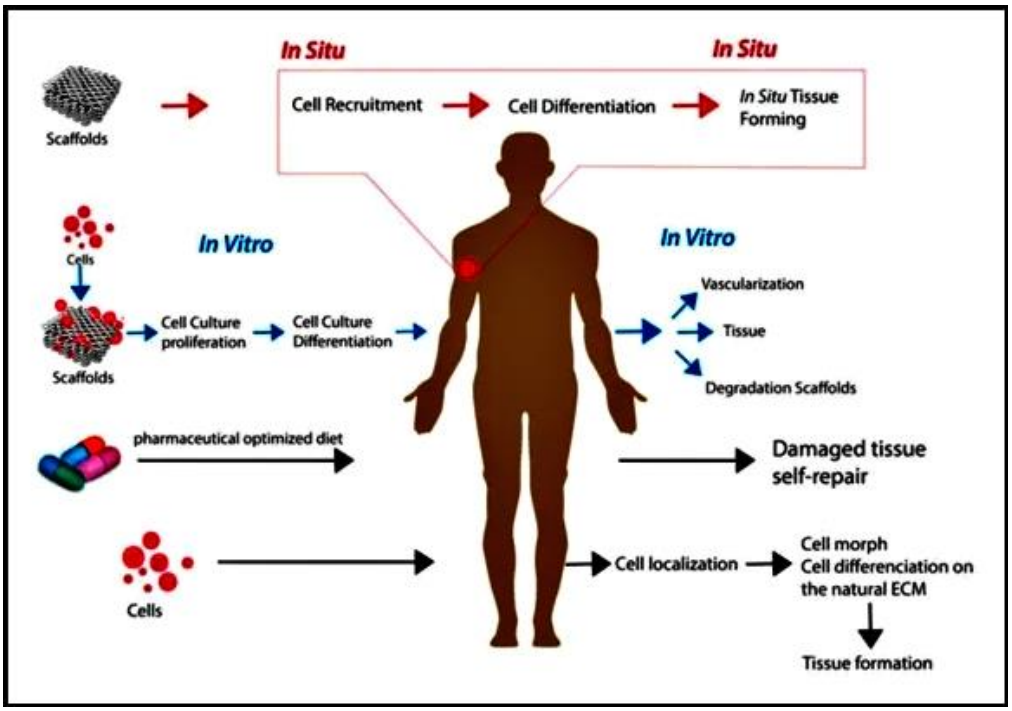

Figure 3: Approach of Tissue Engineering, Reproduce under open access.

However, the simple act of implanting a scaffold by itself can support the structure and encourage the in situ recruitment of normal cells. The goal of regenerative medicine is to enhance the body's natural capacity for self-healing in order to encourage the creation of cells and issues in vivo.[28] In addition to various in vivo therapies like cell or gene therapy, pharmaceutically adjusted diets, or immunomodulation, tissue engineering techniques are used to achieve this.[26,27,29]

Since both fields are concerned with returning the body's tissues to functional state, the words "tissue engineering" and "regenerative medicine" (TERM) are essentially synonymous due to their merger of bioengineering and medicine. Even though TERM research has been done over many years, its application is still relatively young. It is a fast-growing field of study that is being extensively used in almost all medical specialties.

By introducing biomaterials and cells into the body, tissue regeneration is accomplished. This process rebuilds tissues and encourages the body's natural capacity for self-healing to encourage tissue growth.[30] In order to encourage cell proliferation, stem cell technology is frequently employed in biomaterials. It is possible to generate tissue mimics outside of the body through in vitro tissue engineering, which allows one to anticipate how the tissue will grow before implantation.

Tissue engineering presents a great deal of promise for improving outcomes in many organ systems where it is not possible for injured tissue to regenerate on its own.[30] By employing our own cells, tissue engineering allows us to regenerate our own tissue.[31,32,33,34,35] For instance, spontaneous regeneration is not possible when nerve or cartilage cells have died. Thus, for effective regeneration, surgery or the insertion of specific stem cells are required. Furthermore, tissue defects range from localized injury to complete organ failure and can be hereditary or acquired as a result of aging, sickness, birth deformities, or accidents.[36,37] Depending on the degree of tissue injury, tissue engineering plays a different role. In order to advance the field of TERM, we explore here the application of 3D bioprinting in particular preclinical models both in vitro and in vivo, with particular emphasis on the materials and methods that make up 3D bioprinting.

Tissues are the fundamental unit of function in the body, and tissues are made up of cells. Extracellular matrix is a term for the support structures that groupings of cells often create and produce on their own. In addition to providing support for the cells, this scaffold, or matrix, serves as a conduit for several signaling molecules. As a result, messages that are available from the surrounding environment are received by cells from many sources. Every signal has the power to initiate a series of reactions that control the cell's fate. Researchers can repair damaged tissues or even grow new ones by manipulating the way individual cells respond to signals, interact with their surroundings, and organize into tissues and organisms. Building a scaffold from a variety of potential sources, such as proteins or polymers, is often the first step in the process. Cells with or without a "cocktail" of growth factors can be added to scaffolds after they are made. A tissue forms in the proper conditions. Sometimes the scaffolds, growth factors, and cells are combined simultaneously to enable tissue to "self-assemble."

An existing scaffold Is used in another technique to generate new tissue. After removing the donor organ's cells, new tissue is grown on the collagen scaffold that remains. Tissue from the heart, liver, lung, and kidney has been bioengineered using this technique. With the right patient cells and scaffolding made from human tissue that is lost during surgery, this method has a lot of potential for creating tailored organs that the immune system won't reject.

Clinical Application of Stem Cells

The potential of stem cells presents regenerative medicine with a promising future. Human ESC-derived oligodendrocyte progenitor cells (OPCs), dubbed GRNOPC1, was the first human ESC-derived therapeutic product to be used for treating spinal injuries in 2010.[104] Two positive outcomes of treating age-related macular degeneration with the first human ESC-derived terminally differentiated cells have been reported for later in 2012.[105,106] However, there are still a number of issues with cell therapy, such as cell rejection that prevents the cells from interacting with the surrounding internal tissues, the inability of the cells to reach the diseased site and perform as planned, and the potential for negative outcomes like undifferentiated stem cell-induced tumor development.[107,108] Numerous research have suggested using a combination of cells and materials, particularly cell/tissue transplantation for organ damage locations, to increase the effectiveness of regenerative medicine.[109] Furthermore, as was indicated in the earlier sections, materials have the ability to control the function of stem cells and create tissue-like structures at both the macro and micro levels.[110] We shall thus go into more detail on the functions of materials in regenerative medicine.

2. Evolution of 3D Bioprinting

Currently, 3D bioprinting of completely functional organs for transplantation is not entirely feasible. It is undeniable, nonetheless, that bioprinting methods have advanced dramatically. Many years ago, pioneers like Vladimir Mironov, Gabor Forgacs, and Thomas Boland saw the natural blending of technologies like commercial inkjet printing and cell patterning to create living structures that might one day be used in human organ transplantation[43], [44], and.[45] Figure 3 shows a chronology of the development of bioprinting technology up to the current state of the art.

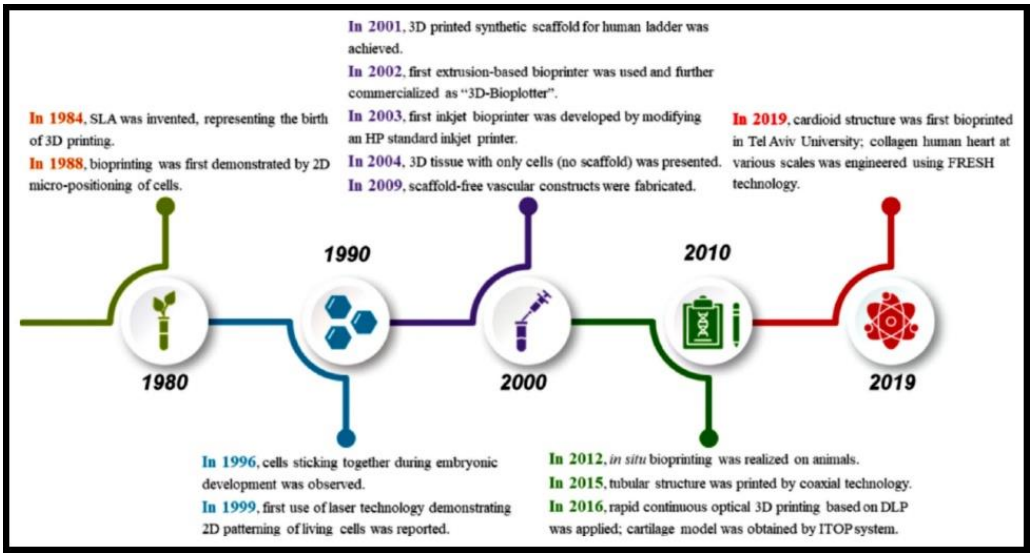

Figure 4: Evolution of 3D Bioprinting.

2.1. A Brief History of 3D Bioprinting

The first 3D printer, stereolithography (SLA), was created in 1984 by Charles Hull and allows for the creation of three-dimensional objects from digital data. The first instance of bioprinting was in 1988, when Klebe used a typical Hewlett-Packard (HP) inkjet printer to deposit cells via a process called cytoscribing.[46] Forgacs and colleagues came to the conclusion in 1996 that apparent tissue surface tension was a quantitative indicator of tissue cohesion and the macroscopic expression of molecular adhesion between cells.[47] Odde and Renn used laser assisted bioprinting for the first time in 1999 to deposit living cells in order to create analogs with intricate anatomical features.[48] Human cells were seeded into a bladder-shaped scaffold that was directly printed in 2001.[49] Landers et al. reported on the first extrusion-based bioprinting method in 2002; it was subsequently made available for purchase as the "3D-Bioplotter".[50] By altering an HP ordinary inkjet printer, Wilson and Boland created the first inkjet bioprinter in 2003.[51] Their group used a commercial SLA printer to execute cell-loaded bioprinting a year later.[52] The same year, 3D tissue made entirely of cells without a scaffold was created. Living cells were deposited by electrohydrodynamic jetting in 2006.[53] 2009 saw the development of scaffold-free vascular tissue using bioprinting by Norotte et al.[54] Skardal et al. attempted in situ bioprinting on mouse models in 2012.[55] Numerous more bioprinting items were introduced in the years that followed, including prosthetic liver and articular cartilage in 2012, tissue integration with the circulatory system in 2014, and so forth.[56,57] Gao et al. used coaxial technique in 2015 to fabricate tubular structures.[58] Pyo et al. used DLP-based quick continuous optical 3D printing in 2016.[59] Anthony Atala's research group used an integrated tissue-organ printer (ITOP) to create a cartilage model that same year.[60] A perfusable scale-down heart was successfully manufactured in 2019 by Noor et al.[61] And a few months later, Lee et al.[62] succeeded in bioprinting human hearts made of collagen at different scales using the freeform reversible embedding of suspended hydrogels (FRESH) method.

3. Process of 3D Bioprinting

a) **Data Acquisition:** X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and other scanning and reconstruction methods can be used to create 3D models, or they can be generated directly with computer-aided design (CAD) software. Then, using specialized software, 3D models would be split into 2D horizontal slices with movable size and orientation. Depending on the various bioprinting techniques used, these data would then be further processed into filaments or particles.

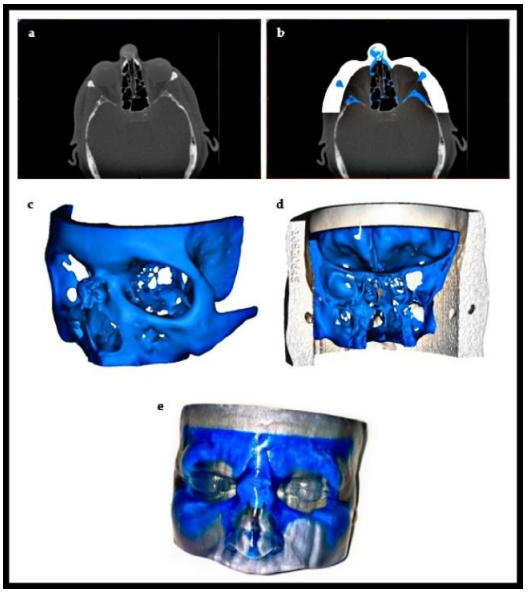

Figure 5: 3D Model of Bioprinting.

b) Material Selection: Materials such as hydrogels, growth factors, cells, and other materials should be carefully selected in accordance with the needs of printed structures and methodologies. The

combination of these biomaterials is technically referred to as "bioinks," though they are typically just thought of as cell-filled hydrogels. To ensure biocompatibility, printability, and mechanical properties—discussed in more detail in the final section of this review—the choice of bioinks is essential.

c) **Bioprinting:** It is necessary to validate that the printing parameters are configured appropriately before bioprinting. Additionally, monitoring the printing process is required in order to make adjustments in the event that issues arise.

d) **Functionalization:** The goal is to use physical and chemical stimulation to cause distributed cells to form connections and initiate some functions of a natural tissue or organ after printing.

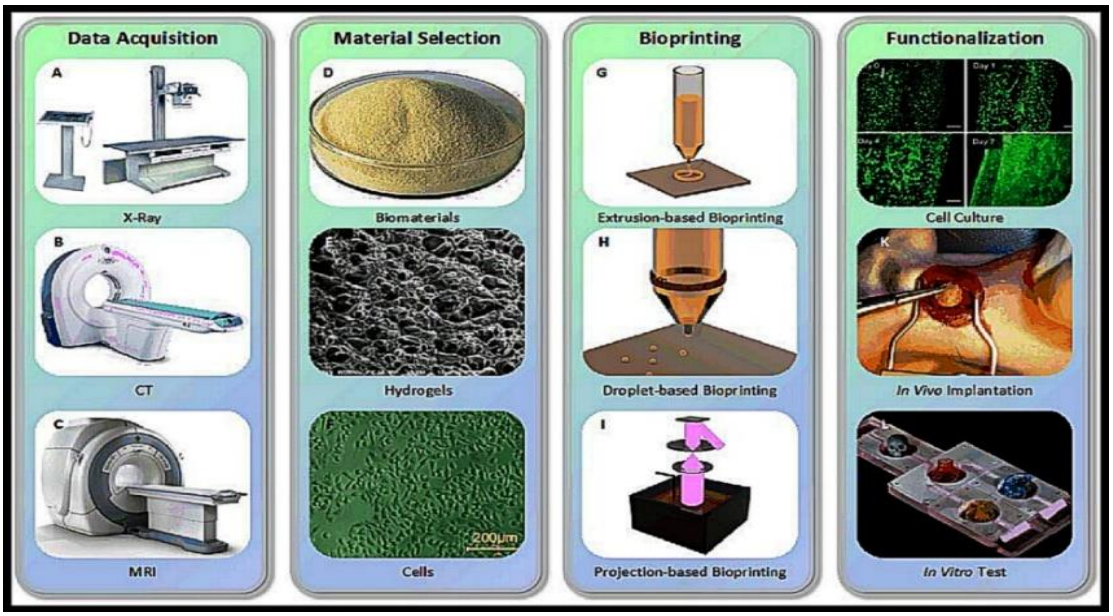

Figure 6: Process of 3D Bioprinting.

According to different prototyping principles and printing materials, 3D bioprinting is mainly based on three central approaches: extrusion-based, droplet-based and photocuring-based bioprinting. Extrusion-based bioprinting extrudes bioinks to form continuous filaments for building constructs; droplet-based bioprinting produces discrete droplets to stack into structures; and photocuring-based bioprinting takes advantage of photo-curing materials, to solidify and stack layer-by-layer to achieve 3D models.

4. Scaffolds for Tissue Engineering-

Thirteen individuals die per day on average as a result of lengthy organ transplant waiting lists.[63] Tissue compatibility is another troubling issue that exists. Tissue engineering can provide different and effective ways to construct scaffolds in this kind of scenario, allowing the tissue compatibility problem to be readily resolved. Using the patient's own cells, the concept and objective are to provide a functional, compatible organ. However, given the various variables pertaining to the physiology of the organism, including the need to cultivate a variety of cell types, this approach could prove to be extremely difficult.[64] Scaffolds are generally required for the construction of graft structures. TE scaffolds serve as a foundation for the migration and differentiation of cells as well as the production of newly regenerated tissue. Therefore, the design, morphology, and qualities of the materials—particularly the chemical and physical ones—are essential for the viability and proliferation of cells.[65,66] Furthermore, restoration of many coexisting tissues, including bones, glands, muscles, arteries, ligaments, nerves, and cartilage, may be necessary for the successful repair of the abnormalities. At the macro, micro, and nanoscales, the architecture and morphology of the scaffolds are critical. From the standpoint of the size and form of the defect, which are crucial for the contact and interactions between the scaffold and the native tissues, matrix-cell interactions, and the transport of nutrients, the architecture is related to the scaffold size and shape at the macro level.[67] Scaffold porosity, pore shape, or pore spatial distribution are the micro-level characteristics that determine overall scaffold permeability. The morphology is connected to the fiber surface properties at the nanoscale, which are thought to be in charge of cell differentiation and proliferation.[68]

The type of fabrication technology and the biomaterial selection are the two most important elements in 3D printing scaffolds. Biomaterials are substances that interact with biological systems and can be categorized based on a number of factors, including their physical and chemical makeup, application of specific changes, and biodegradability.[69] The nature of the injured tissue influences the biomaterial selection. Biodegradable and

piezoelectric biomaterials are typically preferred materials. Ceramics, composites, and polymers—both natural and synthetic—make up the three primary categories of these materials. In orthodontic applications, ceramic scaffolds are the preferable material; in dental tissue engineering, composite scaffolds are useful, while in soft tissue engineering, polymers are employed.[70]

5. Different Tissue Engineering Strategies

When treating tissue abnormalities using tissue scaffolds in TE, two different approaches are typically employed.[71] Each involves seeding the created scaffold with cells (occasionally the cells are incorporated in the scaffold matrix), culturing the cells in a bioreactor, and then implanting the scaffold containing the newly produced tissue into the defect site. The selection of the implantation moment makes a difference. The first approach involves implanting fully developed and modified tissue into the problem site. In this instance, the scaffold ought to undergo total breakdown and metabolization prior to the implantation process. The second approach involves implanting a scaffold that is full of immature tissue. The implanted scaffold should exhibit distinct deterioration (erosion) dynamics based on the selected approach.

The construction of TE scaffolds is typically followed by suitable surface alterations to provide the structure and/or qualities that the cells want. During the cell culture, different hormones or growth agents are typically added. The procedure for producing the tissue engineering product is depicted in Figure 5.

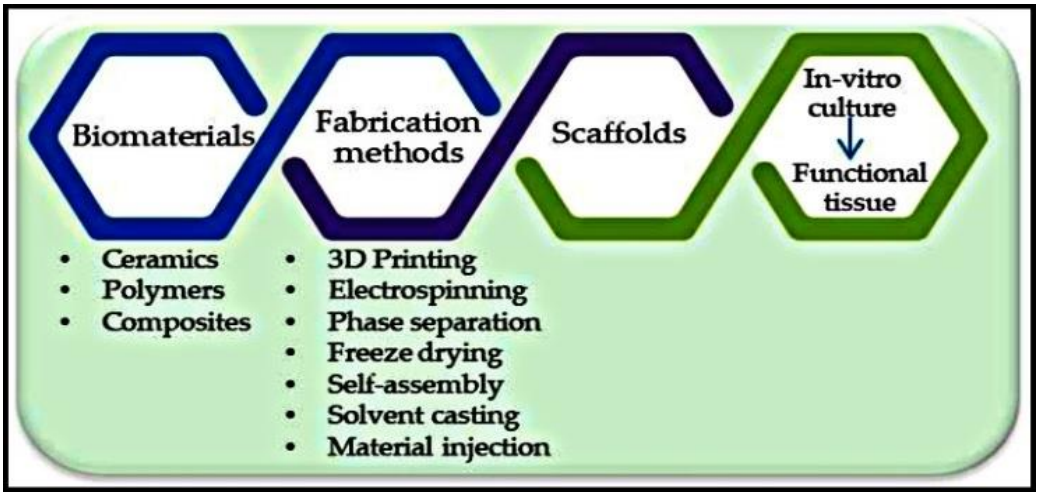

Figure 7: Tissue Engineering Process.

5.1. Conventional TE Scaffold Fabrication Techniques vs 3D Printing Techniques

There are numerous scaffold formation techniques that enable them to satisfy the specifications in a wide range of particular applications. Furthermore, a lot of biomaterials are continuously being enhanced for better tissue engineering applications. Figure 8 is a schematic illustration.

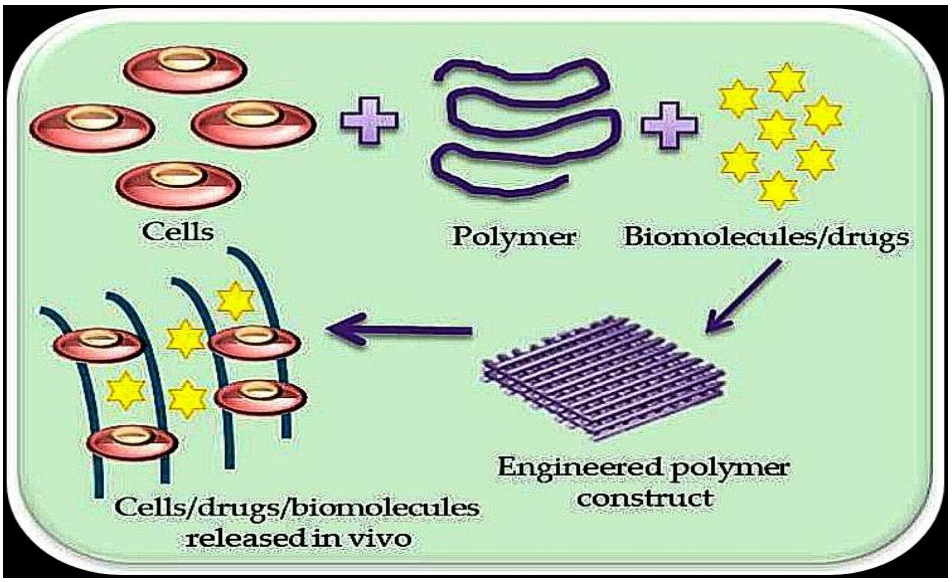

Figure 8: Scaffold with Biomolecules Formation.

The mostly used scaffold fabrication methods include: electrospinning, additive manufacturing, phase separation, solution casting, foaming, extrusion, and self assembly.[72] In order to limit some disadvantages of the methods, a combination of them is often used, which sometimes leads to very interesting and promising effects.[73] Figure 9 shows various techniques to fabricate three-dimensional scaffolds while some of them are described further.

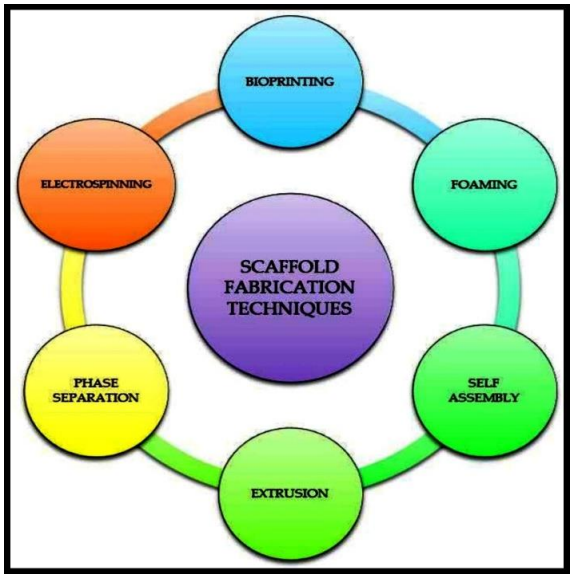

Figure 9: Scaffolds' Fabrication Techniques.

6. Organ Transplantation

Since the middle of the 20th century, organ transplantation has been a mainstay of care for patients with end-stage organ failure. A kidney was successfully transplanted in 1954, marking the first organ transplantation success.[38] Organ transplants have been utilized extensively in clinical practice ever since. But as the need for organ transplants has increased over the years, it has become more challenging to keep an adequate supply of organs on hand. The World Health Organization (WHO) estimates that only roughly 10% of people who require an organ transplant ever get one, and the number of people on the waiting list for organs has been rising steadily over the years.[39] With around 40,000 organ transplant procedures performed in 2019, the United States reached a record high for both organ donors and transplants, according to the United Network for Organ Sharing (UNOS).[40,41] By the end of the year, it is predicted that over 110,000 individuals will still be waiting for an organ transplant, despite this noteworthy accomplishment.[18] The Health Resources and Services Administration (HRSA) estimates that around 17 persons pass away each day while awaiting an organ.[42] Since more and more patients are joined to the UNOS waiting list every year, these statistics will only rise. These factors make it imperative to investigate alternate sources of organs.

7. 3D Printing of Tissue Engineering Scaffolds

Numerous techniques for creating tissue engineering scaffolds have been developed since the idea of using these products in reconstructive medicine first surfaced. These techniques range from the most basic, like leaching sugar or salt crystals from a solid structure, to the most sophisticated, like rapid prototyping (RP) and rapid manufacturing (RM). Rapid manufacturing techniques are a field that is currently evolving extremely quickly. Practically every day, new gadgets and methodologies are developed, old ones are modified, and the RM sector is currently fueled by both commercial hardware and software producers and scientific organizations. Unfortunately, systematizing current methodologies is challenging due to the dynamic nature of industry development. Since many of the common names for RM techniques are registered trademarks, it is common for multiple manufacturers to create quite comparable devices under different names while essentially employing the same manufacturing process. There is a great deal of confusion caused by the simultaneous popular usage of these names. It is important to understand that phrases like 3D printing, rapid prototyping/manufacturing, additive manufacturing, and solid free-form fabrication are practically interchangeable. For the rest of this work, we will refer to it as 3D printing. It is a relatively novel technique for creating controlled-architecture TE scaffolds. Stereolithography, bioprinting, inkjet printing, fused deposition modeling (FDM), PED (Precision Extruding Deposition), laser beam melting, polyjet, electron beam melting, digital laser printing (DLP), and selective laser sintering (SLS) are just a few examples of the many different 3D printing techniques available.[74] However, all of these techniques share the general idea of material deposition layer by layer until the finished product is created.[75]

As a result, the 3D TE scaffold is created by layering on top of one another in successive 2D layers of material. Several benefits come with additive manufacturing, including the capacity to build intricate structures and the potential to use computer-aided design (CAD) techniques. It makes a variety of biomaterials usable.[76] It is possible to develop new techniques and approaches for the creation of complex tissues and, maybe in the future, entire organs by using living cells and biodegradable polymers.[77] Patient-specific data can be used to design a 3D-printed TE scaffold. The 3D organ or any missing portion can be precisely designed thanks to the CAD technology. Certain characteristics of living organs, such vasculature or porosity, could be included in the CAD 3D model. Owing to these outstanding benefits, 3D printing is becoming increasingly popular in tissue engineering and regenerative medicine.[78]

Binder 3D printing and direct 3D printing are two categories into which 3D printing procedures can be divided. The older method (Figure 10) is also referred to as the "drop on powder technique".[79] An inkjet liquid printing binder solution on a powder foundation is used to create objects.[80,81, 82] The powder coating is first

spread out throughout the building platform. The design is printed using positioning software by depositing droplets onto the powder layer. The following layer can then be applied once the building platform, powder, and portion are lowered. After the powder is taken off, the printed portion is visible. The method's drawbacks include printhead reliability issues and rather low resolution. Although a smaller nozzle may be of higher quality, it is more likely to clog. As a benefit, the surrounding powder supports items, making the manufacture of intricate scaffolds with internal channels possible.

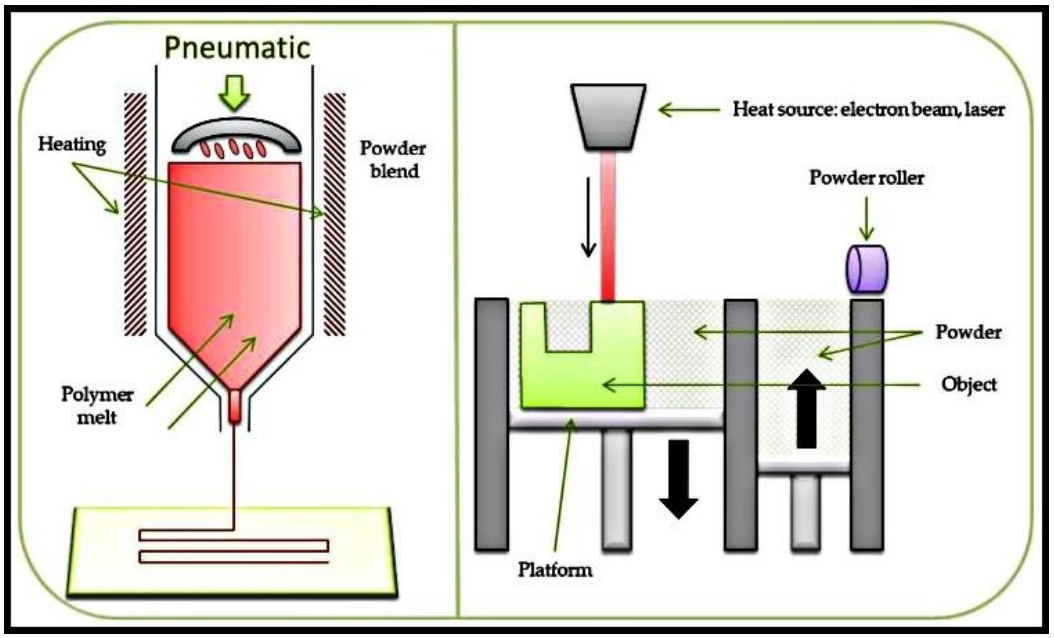

Figure 10: Drop on Powder Technique.

In the case of direct 3D printing, which is shown in Figure 10, the nozzle of a 3D printer moves back and forth dispensing waxes or plastic polymers, which solidify to form consecutive layers of the fabricated 3D object.

7.1. Tissue Engineering-related Applications of 3D Printing Techniques

There are few most known applicable techniques of 3D printing for Tissue Engineering.

- **Bioprinting:** Soft 3D tissue scaffolds including biomaterials, living cells, and growth factors can be created with this technique. It makes it possible to create biomedical components that most closely resemble the properties of actual tissue. Generally speaking, 3D bioprinting builds tissue-like structures by layer-by-layer depositing substances called bioinks. Inkjet bioprinting, extrusion bioprinting, laser-assisted bioprinting, and stereolithography are the four primary subcategories of 3D bioprinting.[83]
- **Inkjet Bioprinting:** A combination of living cells and a bioink is kept in a chamber that is connected to the printhead in this kind of bioprinting technique.[84] The printhead is deformed by the piezoelectric transducer during the process. Tissue constructions are established by spatially specified droplets (Figure 6). The technique's primary benefits are its low cost and great cell survivability.[85] However, there are a lot of issues with this technique, like clogged printheads, uneven cell distribution, and inability to print viscous materials. In recent years, researchers have given inkjet bioprinting less thought as a result of these issues.[86]
- **Laser- Assisted Bioprinting:** In order to produce structures, typical laser-assisted bioprinting (LAB) uses specialized layers such as a collecting layer, an energy-absorbing layer, a donor (quartz/glass), and a bioink layer.[87] The energy-absorbing layer is the focal point of a laser beam during the procedure. This layer then vaporizes, causing an air bubble to form between the donor and bioink layers. The required quantity of bioink is ejected onto the collecting layer upon the development of a bubble. Drop by drop, a tissue structure is generated (Figure 6).[88] It is possible to employ LAB with viscous materials and high cell density. It has also been noted that the procedure clears the clogging problems and exhibits good cell viability (95%). However, LAB is a costly procedure that adds significantly to the cost of large-scale projects. As a result, very few printer prototypes were made.[90, 89]
- **Extrusion Bioprinting:** The liquid extrusion (paste, solution) from a pressurized syringe through a needle to a solution with regulated density is the basis of the extrusion bioprinting technology. To produce complicated structures, the materials are extruded as long strands or dots.[91] Natural biomaterials, particularly hydrogels, can be printed using this method at room temperature (Figure 11).[92]

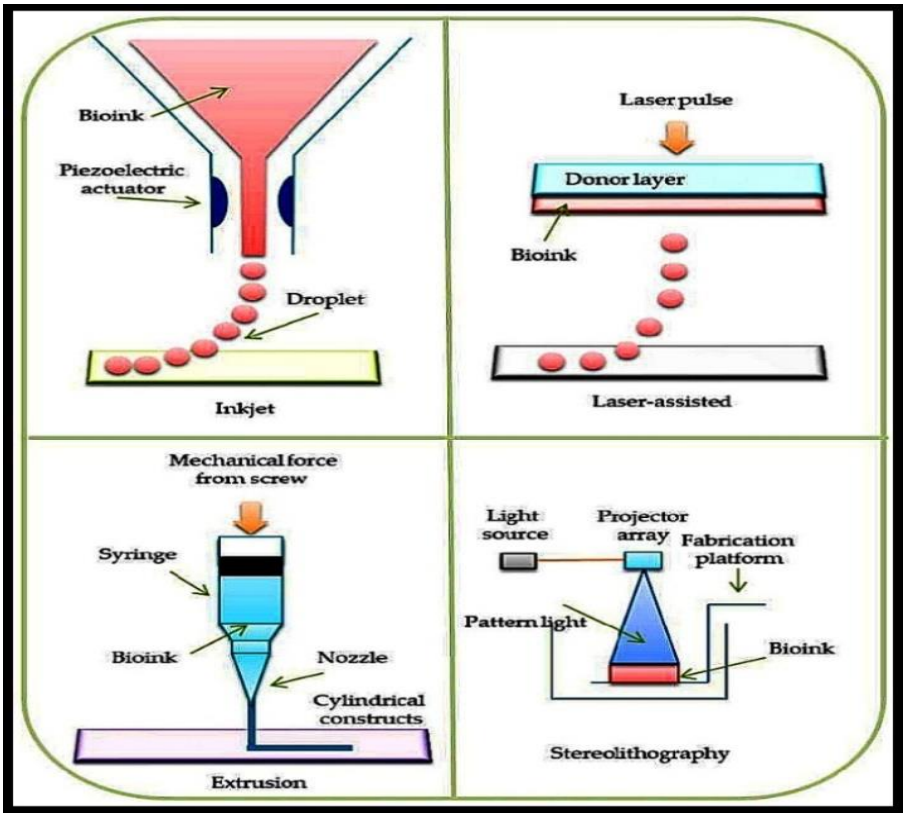

Figure 11: Natural Biomaterials used for printing at room temperature.

- **Stereolithography:** The first technique for rapid prototyping was stereolithography (SLA), which gained popularity in the late 1980s.[93] A laser beam is used by stereolithography rasters to regulate the bioink polymerization process in a two dimensional layer. Curing happens after a material is deposited in layers. A photosensitive hydrogel is exposed to UV or visible light during the curing process. Once a layer has reached the polymerization stage, the procedure is carried out again, covering the preceding layer until the scaffold is finished in its whole. The following hydrogel materials (Figure 11)[94] can be used with this method: gelatin methacryloyl (GelMA)[95] and polyethylene glycol diacrylate (PEGDA).[94] Photo-initiators can also be added.[96, 97] A high-quality (including resolution) output can be achieved by adjusting a number of polymerization process parameters, such as light energy and intensity, printing speed, layer thickness, and exposure duration.[98,99,100,101,102,103] However, the SLA procedure is more time-consuming than the other approaches, which makes it feasible for things with minute details.

8. Design Strategies of 3D Printed Scaffolds

8.1. Idea of Computer Aided Tissue Engineering (CATE)

It's likely impossible to imagine modern tissue engineering without the use of various computer-aided techniques; nonetheless, the benefits of computer-aided TE scaffold design were not completely realized until the advent of numerically controlled 3D printers in TE. They are involved in practically every step of the process that goes into making the so-called tissue engineering product. The purpose of this chapter is to describe a few specific computer-aided design methodologies and explain their function in the design and manufacture of tissue scaffolds using 3D printing methods. In general, computer-aided design plays such a significant part in tissue engineering that the name CATE (Computer-Aided Tissue Engineering) has been around for a while and is used in the literature.[114, 115]

A simplified block diagram Illustrating the CATE system's functioning is presented in Figure 12. The individual system modules are represented by the blocks in the diagram. To put it briefly, the CATE system's job is to provide a tissue scaffold design that is understandable for numerically controlled production equipment like 3D printers, depending on the defect geometry and a set of suitably chosen criteria.

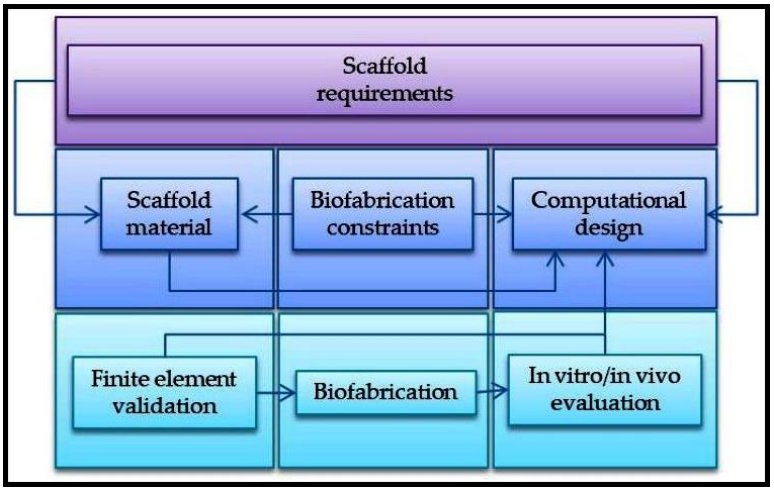

Figure 12: General Idea of CATE System.

8.2. Tissue Engineering Scaffold CAD Geometry Development

CAD software can be used to create scaffold geometry from beginning to end. Typically, a collection of solid virtual objects with surfaces that accurately characterize its shape are used to describe such a model. It is important to remember that the scaffold's geometry is a depiction of the tissue defect, which is typically shaped irregularly. In this situation, using reverse engineering techniques—which allow one to precisely specify the shape of the defect based on the results of medical imaging using computed tomography (CT) or magnetic resonance imaging (MRI)—would be a more appropriate way to obtain the geometry of the constructed scaffold. Tomograms, or a series of cross-sectional pictures of the object under inspection, are the end product of the CT scan. The tomograms often need to have all types of noise and method-specific anomalies filtered out. The binarization of grayscale tomograms is the following step. Using commercial or free tools (Materialise MIMICS, 3DSlicer, InVesalius), one can generate a CAD model of the intended scaffold based on the series of binarized tomograms. Typically, one of the neutral file types used by additive manufacturing systems is where the CAD model is saved. Standard Tessellation Language is arguably the most widely used format in additive manufacturing systems (STL). The Standard Tessellation Language (STL) is used in additive manufacturing systems. After being created initially for stereolithography, it gained popularity in other additive manufacturing techniques. Since an object's shape is approximated in the STL format by a mesh of triangles, an STL file's contents consist of the vector normal to the triangle plane and the x, y, and z coordinates of each vertex. Other less popular geometric storage formats, such as SLC (a format with sequential portions denoted by polylines), HGPL (HP Graphical Language), and CLI (Common Layer Interface), exist in addition to STL.

8.3. Computer-Assisted Optimization of TE Scaffolds

The ideal tissue scaffold ought to include numerous, frequently incongruous characteristics. Consequently, given that experimental evaluation of the design variations requires time-consuming and costly in vitro and in vivo testing, a trial-and-error design typically becomes laborious and inefficient due to the huge number of design variables describing the tissue scaffold structure. The mechanical characteristics of the material utilized, porosity, scaffold stiffness (which depends on the material and scaffold structure), biological activity, and chemical activity of the selected material are design elements that have a direct impact on the quality of the scaffold. Although there are a number of beliefs on the ideal scaffold, there have long been no tested techniques to support tissue scaffold design. The earliest attempts to apply computer-aided design approaches did not exist until the mid-1990s. Until recently, the only applications of computer methods in tissue engineering were either for the computer-aided design of the geometry of the TE scaffold or for the evaluation of the intended structure through the use of in silico models, primarily based on the finite element method (FEM). Approaches to the challenge of tissue scaffold design have changed significantly since the end of the first decade of this century.[116] During that period, the first attempts were made to use optimization techniques, including classical and AI-based algorithms.[117, 118, 119]

9. Biomaterials Used for Tissue Engineering Scaffolds 3D Printing-

A variety of distinct characteristics, including sufficient mechanical strength and stiffness, open porosity, biocompatibility, and biodegradability, should define the perfect TE scaffold. It is feasible to establish an environment that is conducive to cell growth by fulfilling the aforementioned conditions. All of the aforementioned requirements are somewhat attributable to the material that was used. Natural (chitin, collagen, cellulose) and synthetic (polycaprolactone, polyglycolide, and their copolymers) polymers, ceramics, and other additives (hydroxyapatite (HA), carbon nanotubes) are examples of materials frequently utilized for TE scaffolds. An attempt has been made to describe the principal categories of 3D printing materials below. First, since

polymers are the most commonly utilized class of materials for tissue engineering, they will be discussed.

9.1. Polymers

The primary class of materials with the most promise for usage in 3D printing TE scaffolds is polymers, which are also broadly applicable for imitating different tissues. Both biodegradable and non-biodegradable polymers can be used to create TE scaffolds. Biodegradable polymers typically offer more advantages than non-biodegradable ones in the context of tissue engineering.

9.1.1. Natural Polymer

Because of their bioactivity, biocompatibility, low immunological reaction, and inherent biodegradability, natural polymers are recognized as the best options for creating TE scaffolds. The work of detailing the manufacture of TE scaffolds for cartilage regeneration composed of bacterial cellulose serves as an illustration of the use of natural polymers in TE. Acetobacter xylinum cellulose is confirmed to be useful in cartilage regeneration by another investigation. Among the polymers that have been studied and used extensively in TE are collagen and chitosan. It is well known that each of the elements listed above promotes cell survival and proliferation.

Gelatine, which is an irreversibly hydrolyzed version of collagen, is another naturally occurring substance that is readily available and biocompatible. Gelatine has been the subject of multiple attempts to be used as a biomaterial for TE scaffold 3D printing. The gelatine/hydroxyapatite composite was studied by as a potential material for 3D printed scaffolds for the chondrogenic development of stem cells. It has been demonstrated that pure gelatine 3D scaffolds provide an optimal environment for hepatocyte cell survival and proliferation.

High vitality and multiplication of mesenchymal stem cells cultivated on/in collagen/agarose scaffolds were noted in the study by.[120]

9.1.2. Synthetic Polymer

For many years, researchers have examined the potential applications of biodegradable synthetic polymers, primarily aliphatic polyesters like PCL and PLGA, in tissue engineering. The very low toxicity of biodegradable aliphatic polyesters has been noted. Nevertheless, the release of acidic oligomeric compounds, resulting from the hydrolytic destruction of polymers, might trigger an inflammatory response, thereby impeding the process of tissue regeneration. Previous studies examining the degradation kinetics of 3D-printed TE scaffolds composed of different aliphatic polyesters have demonstrated that the degree of degradation varies depending on the material: for PLGA (40,000–75,000 Da) and PCL (Mw = 114,000 Da), the percentages are 18% and 56% on days 14 and 28 for PLGA, and 33% on days 21 and 39% on days 28 for PCL. It is well recognized that aliphatic polyester TE scaffolds can be used well to cure tissue loss including bone regeneration. Aliphatic polymer-based TE scaffolds have a fully controllable degradation time. For all bioresorbable polyesters utilized in bioengineering, hydrolysis under enzymatic conditions is the major degradation mechanism. Water, one of the primary elements of the physiological environment, enters the implant (such as TE scaffold) and begins to permeate the polymer matrix at different rates as soon as it is put in the living organism. Varies in its rate of penetration into the polymer matrix. Numerous factors, including the implant material's hydrophilicity, affect this penetration rate. The ester bonds that give polymer chains their cohesiveness are weakened by water molecules and eventually break. It was discovered that the center portion of some items formed of aliphatic polymers degrades more quickly than the parts that are in direct contact with the environment due to heterogeneous degradation. There are many instances of aliphatic polyesters being used in tissue engineering.[121]

9.1.3. Hydrogel

Hydrogels are crosslinked polymers with the ability to bind a sizable volume of water. Alginate and collagen are examples of natural or synthetic polymers that can be used to make them. Hydrogels have low mechanical characteristics and are very biocompatible due to their high water content. Hydrogels are one of the most promising materials from which tissue scaffolds can be made because of their great biocompatibility, mechanical resemblance to the genuine tissue, and transport/diffusion capabilities. Additionally, they make the immobilization of physiologically active compounds very simple and safe. Various crosslinking techniques, including click chemistry, ionic/hydrogen bonding, and chemical bonding, have been employed with a variety of bioink biomaterials, including gelatin-methacrylates, agarose, alginate, collagen, chitin, silk, hyaluronic acid, cellulose, and their combinations. Alginates are the most appealing among them for bioprinting, primarily because of their capacity to create a soft gel matrix that is low-aggressive for encapsulated macromolecules and living cells. The capacity of alginate to create gels through ionic crosslinking with calcium cations is one of its key characteristics. The condition of the hydrogel material and its deterioration, however, can be readily influenced by external factors like temperature or buffer acidity, which will ultimately result in the loss of the biomolecules contained in the hydrogel matrix. Hydrogels can also be made using polymers like natural gelatin methacrylate (GelMA) or poly(ethylene glycol) diacrylate (PEGDA). Hydrogels are frequently utilized in hybrid tissue engineering scaffolds to simulate soft tissues, such as muscular tissue.[122]

9.2. Other Materials

Organic calcium and phosphate salts are present in ceramic and composite scaffolds. The principal benefits of 3D-printed ceramic scaffolds are their exceptional

mechanical strength and excellent biocompatibility. Because of their capacity for mineralization, ceramic scaffolds become good candidates for bone tissue engineering. Bone-like hydroxyapatite (HA)[178] is a material of interest for the construction of intricate three-dimensional structures with bone-like mechanical characteristics. In the field of regenerative medicine, these kinds of 3D-printed scaffolds are being studied extensively. A composite material can be made by combining the aforementioned ceramic elements with a polymer. These materials' capacity to assist vascularization qualities has been demonstrated. Components of the TE scaffold are frequently made of materials with mechanical qualities comparable to those of bone, such as bioglass, silica, graphene oxide, and zirconium titanate. Numerous organizations looked into the feasibility of creating workable TE scaffolds out of polymeric composites containing the aforementioned ingredients. Freeze-drying and sintering are two methods used to enhance the mechanical and cytocompatibility of many 3D-printed ceramic materials. It was demonstrated that TE scaffolds printed from bioactive glass-ceramics with a special triphasic structure made up of hardystonite, gahnite, and strontium had 34% porosity and 110 MPa of strength, which is comparable to that of a bone.

Polymer scaffolds with added bioceramics provide superior qualities, increased biocompatibility, and controlled degradation. Furthermore, because of their superior osteogenic qualities, bioactive ceramics are becoming increasingly and more well-known.[123] Because of their chemical resemblance to bone, calcium phosphates (CaPs) are the most commonly utilized bioceramics in tissue engineering applications.

10. Advanced Examples of 3D Printing in Tissue Engineering

10.1. Bone and Cartilage Tissue Engineering-

One of the most popular regeneration treatments is the repair of bone and cartilage abnormalities. Replacing a broken bone is the main goal of bone and cartilage tissue engineering. As a result, 3D printing technologies attempt to produce an artificial bone structure with the necessary characteristics, including the right size, form, and mechanical qualities. Trauma, congenital abnormalities, and tissue excision from malignancy are the main causes of deficiencies in bone and cartilage. Autogenous bone grafting is one such procedure that has a number of drawbacks, including donor site morbidity or the inability to get adequate donor tissue. Conversely, the possibility of disease transfer makes allogeneic bone grafts unwise. The significance of therapies utilizing 3D-printed TE scaffolds has been steadily increasing during the last few years. Seeded cells can attach, migrate, develop, and differentiate into osteogenesis and chondrogenesis thanks to TE scaffolds.

The following are some instances of newly released research on the use of 3D printing in the regeneration of bone and cartilage: The majority of suggested remedies rely on combining various materials, including hydrogels, polyesters, and ceramics. A hybrid scaffold is frequently created by combining an injectable hydrogel into a 3D-printed porous structure to increase osteoinductivity and cell-seeding efficiency. Biodegradable aliphatic polyesters continue to be the gold standard even if several materials are utilized to create 3D-printed bone scaffolds. Conversely, the most often used class of materials for the cartilage TE is hydrogels. For tissue engineering, osteochondral scaffolds continue to provide unique difficulties. Because osteochondral scaffolds are typically bi- or even tri-phasic, the construction of these scaffolds typically necessitates a mix of multiple printing processes and materials.[124]

10.2. Nervous Tissue

The hardest tissues to repair are those of the peripheral nervous system (PNS) and the central nervous system (CNS). Using needles and a 3D printing frame, collagen microchannels were created to create the in vitro 3D printed brain model. The brain microvasculature regenerate as a result of culturing mouse brain cells on collagen microchannels. This work has demonstrated the broad applicability of the brain-blood barrier model, including medication administration, tissue regeneration, and tissue engineering, as well as pathological and physiological testing. The 3D printing of nerve conduits is the subject of some studies. In a study by[125], cellularized adipose-derived stem cells (ASCs) on cryopolymerized gelatin methacryloyl (cryoGelMA) gel was utilized to 3D print cellularized conduits for peripheral nerve regeneration. The constructed conduits' capacity to re-innervate was demonstrated in vivo. It is important to note that casting molds customized for each patient were created using 3D printing.

10.3. Cancer Models

Advancements in bioprinting have made it possible to create three-dimensional in vitro models of several types of malignant tissue. These models facilitate the development of tailored treatments for individual patients and the study of carcinogenesis-related mechanisms, including tumor extravasation. Typically, bioprinted cancer models consist of several layers that house various cell types such as growth factors, extracellular matrix, tumor cells (which are typically obtained from patients), and vasculature.[127] Tumor heterogeneity should be accurately reflected in bioprinted tumor models. They make it possible to screen for anti-cancer therapies and look at interactions between cells and matrices. Compared to 2D in vitro models, which are unable to replicate the intricate structural makeup of tumors, bioprinted cancer models have several advantages.

10.4. Ocular Tissue

Though most 3D printing applications do not include tissue engineering, interest in these technologies is

nevertheless developing in the field of ophthalmology. The following are instances of projects that use 3D printing to regenerate eye tissue: A report on an attempt to recreate a 3D retina can be found in the work of. 3D printing was used to create the retina-like structure that houses adult rat retinal ganglion cells and glia. It has been demonstrated that these kinds of retinal cells can be successfully printed without losing some of their phenotypic characteristics or survival. The work by on the creation of the TE corneal scaffold, which is composed of collagen-based bio-ink including encapsulated corneal keratocytes, is another illustration of the use of 3D printing in ocular tissue engineering.

10.5. Skin

A skin was created using 3D printing with the aid of a laser. Fibroblasts and keratinocytes were cultivated with a combination of collagen type I and Matriderm (for matrix stabilization). By applying a bioprinted construct to the mouse skin, the experiment was likewise carried out in vivo. The result mostly showed the formation of an epidermis. The process of creating skin equivalents (SE) utilizing an open-market bioprinter with fibroblasts and keratinocytes suspended in a gelatin-based hydrogel was covered in. Direct extrusion of SE build layers onto the multi-well plate was done. The dermis, laminin/entactin base layer, and epidermis are the three tiers that make up the formed structure. It is possible to model skin diseases in vitro using the created SE.

10.6. Ear

The computer-aided design has been used to create the bionic human ear. A hydrogel matrix containing cells and a conductive polymer with the addition of silver nanoparticles were used during printing—bioprinted in the shape of a human ear. The studies allowed control of the signals from the cochlea-shaped electrodes. The in vitro culture was provided on the cartilage tissues on every side of the inductive coil. The printed ear was found to enhance the auditory sensing. Another study showed that the printed ear can be formed by 3D bioprinting with the subject's lipid tissue and an auricular cartilage. Adipocytes and chondrocytes differentiated from the adipose-derived stromal cells were enclosed in hydrogels and then placed at the lipid and cartilage tissue.

10.7. Kidney

Tests were conducted using PEGDA scaffolds that had calcium sulfate and sodium alginate added to them. Following construction, scaffolds were grown with human embryonic kidney cells (HEK) and crosslinked using UV radiation. It was demonstrated that the aforementioned composite materials had characteristics that promote the growth and vitality of the cells. Extrusion-based 3D bioprinting was used in Lawlor et al.'s work to create human kidney organoids, which are simplified in vitro replicas of living organs. Precise control over the size, quantity, and shape of organoids is possible because to the employed production technique. The kidney organoids model that was created in vitro may be utilized for illness modeling or medication testing.

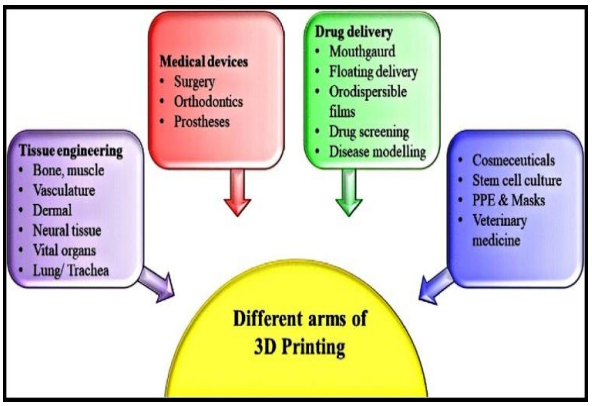

Figure 13: Different arms of 3D printing.

11. Advantage of 3D Printing

With their many benefits that traditional technologies cannot match, 3D printed scaffolds for bone tissue engineering have become more and more popular in the past several years for the application of stem cells, particularly for bone repair and cartilage regeneration of composite structures. Growing knowledge of the machining parameters influencing these structural attributes can aid in the creation of composites that are more and more optimal. Numerous materials and composite materials are used in 3D printing technology; these materials not only expand the range of materials covered by traditional technology but also enable the creation of materials that were previously unattainable through the use of technologies (e.g. scaffolds with regulated drug release. With 3D printing technology, intricate internal and external structures that adjust to the mechanical and biological properties of surfaces may be printed with extreme accuracy. A customized, patient-specific implant that is well suited for tissue and organ defects, as well as disease simulation platforms, stem cell research platforms, and other applications, can be prepared thanks to 3D printing technology's ability to print intricate and highly accurate internal and external structures that adapt to mechanical and biological surface characteristics.

12. Drawbacks of 3D Printing

3D printing technology has drawbacks and restrictions when it comes to stem cell research and applications. First off, while 3D printing may create accurate and customized scaffolds, it also comes with high expenditures associated with clinical and scientific research as well as a lack of mass production. Second, the use of 3D printed scaffolds in clinical, cell biology, and regenerative medicine is restricted due to the cytotoxicity of certain of the materials and the hazardous and pathogenic nature of the fabrication process. Furthermore, despite the versatility of 3D printing technology, there are still many obstacles to overcome in the creation of complicated geometric shapes for

composite materials, the processing of different materials, and the post-optimization of composite surface qualities. Lastly, given the speed at which stem cell regenerative medicine is developing, we should also give careful thought to the social ethics, legality, and regulatory concerns raised by the printing of organs and tissues.

13. Future of 3D Printing

It is looking more and more possible to construct efficient scaffolds for the use of extracellular matrix, bone, and cartilage for stem cells as a result of ongoing technological optimization and the development of new bio-ink materials. For tissue engineering, 3D printed scaffolds may hold the key to enhancing the quality of life for individuals suffering from organ dysfunction and defects brought on by injury or lesions. The future development path of 3D printing technology is the creation of novel printing materials, nanomaterials—particularly biocompatible materials—composite materials, and complex biomaterials based on varied application requirements. The development direction of 3D printing and stem cell production will also aim to support the systematization, standardization, non-toxic, harmless, green, and environmental protection of 3D printing materials, as well as to continuously expand the integration of 3D printing technology, stem cell technology, and traditional treatment. We anticipate that the natural marriage of additive manufacturing and regenerative medicine will greatly benefit humankind.

14. CONCLUSION

3D bioprinting has come a long way toward printing functional tissues since its debut. Despite difficulties, the preliminary research has amply demonstrated that bioprinting merits further study. The clinical potential of this technology will require more time, work, and multidisciplinary talent to realize, but the future seems promising. The field of individualized regenerative medicine is expected to benefit greatly from bioprinting.

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