Revolutionizing Healthcare: Advances in Biomaterials and Biomedical Devices

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Abstract

Biomaterials and biomedical devices have seen significant advancements, playing a crucial role in modern healthcare. Biomaterials, including natural, synthetic, and hybrid substances, are designed to interconnect with body system for diagnostic and curative motives. They form the foundation of biomedical devices, which range from simple contact lenses to complex implants and artificial organs. Integrating biomaterials in medical devices has led to enhanced patient implications, particularly in tissue engineering, drug delivery systems, and regenerative medicine. Latest growth in nanotechnology and biotechnology has promoted the functionality of biomaterials, enabling the development of devices with better biocompatibility, durability, and targeted action. Innovations such as 3D-printed tissues, bioresorbable stents, and smart drug delivery systems exemplify the transformative potential of biomaterials. Moreover, this technology is useful in gene editing and set the foundations for new treatments of genetic disorders and cancer, as well as personalized therapies based on individual genetic profiles. Furthermore, these platforms are improving access to healthcare by enabling remote consultations, monitoring, and management of chronic conditions. However, the development of these materials and devices has many challenges such as immune response, long-term stability, and ethical considerations in using certain biomaterials. The present review focuses on the advancements in biomaterials and biomedical devices and their contribution in transforming healthcare, offering new possibilities for treatment, and enhancing the quality of life for patients.

Keywords: Biomaterials, Biomedical Devices, Healthcare, Nanotechnology, Biotechnology.

1. Introduction

Biomaterials are those materials that interconnect with the biological tissue or system and are utilized in medical devices for their introduction into the biologic tissues. Biomaterials are used for the purpose of diagnosing, treating, healing and replacing any damaged tissue or cell by interacting with the living system. Biomaterials can be classified into the following types; (a) Synthetic (includes metals, polymers, ceramics and composites); (b) Natural (includes animal and plant derived biomaterials) and; (c) Semi-synthetic or hybrid materials. These biomaterials are extensively used in healthcare from a long period of time but there advancement has led to improvement in their usefulness. Eventually, biomaterials have contributed as an essential part in biomedical engineering domain that enhanced the overall healthcare outcomes of the population [1-2]. Due to the strength, elasticity and, outstanding mechanical dependence of the metals, metal materials are predominantly used in medical implants. About 70-80% implants being used globally are made up of metal. In heart, oral, orthopedic disease and angioplasty; ceramics and metals are generally used because of their

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biocompatibility and quality. Polymers are utilized in the construction of tissues, drug conveying systems and dressing of wounds because of their versatile nature and adaptability. Biomaterials are mostly utilized in medical practice but they are also being used in other practices which involve the interaction with biological system, inclusive of analysis of blood protein in laboratories, spreading cells in culture, processing of biological molecules for biotechnological applications like fertility implant, diagnostic gene array, aquaculture of oysters and biochips. Biomaterials are the innate part of medical gadgets but are also used as secluded system in drug delivery approach, dental and bone defect fillers. The success rate of the biomaterial depends upon the response of the biological tissue towards the biomaterial [3]. Biomaterials that are intended for human healthcare use should be non-carcinogenic, non-pyrogenic, non-toxic, possess non-inflammatory effect and compatible with blood. So, the strength and productiveness of the biomaterial highly depends upon the biologic and mechanical characteristics of insertion, biocompatibility of implant, patient's health state and compatibility of the surgical method. Numerous studies revealed that insertion of biomaterial is not an easy task every time with respect to the response of human body against foreign invaders. Introduction of adverse immune response, destruction of biological tissue, and wrap-up of fibers that support process of healing may take place. Hence, one must have deep knowledge of the nature and behavior of the biomaterials for utilizing them in healthcare and bypassing their shortcomings [4]. Biomaterials have undergone a remarkable development and now became an important part of current biomedical devices [5]. Various changes in the area of medical science are visible from the last few years. These revolutionizing changes have remarkably enhanced the recognition, therapy, and control of the disease enhancing the patient end results and quality of life. These developments include generation of novel medicine, tissue engineering, development of therapeutic implants, and treatments that use innovative technology. For example, gene modifying technology like CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats associated protein 9) has paved a way for better treatment of genetic illness and developing mRNA vaccine provided a vital solution to the outbreak of coronavirus disease 2019. Besides, for maintaining health, wearable technologies and telemedicine came into existence with enhanced ease of access, comfort and individualized care. Evolution of 3D printing and nanotechnology has facilitated the creation of customized implants and drug conveying systems [6]. This review was conducted through a systematic literature survey of recent research and review articles followed by their analysis and selection on the basis of their relevant data. The articles from the last decade (2015-2025) were included in this study; however 2-3 older articles were also included due to their relevant data. The novelty of this work lies in its interdisciplinary approach, which brings together knowledge of material science, biomedical engineering, and healthcare. This combination allows for a deeper understanding of how advanced biomaterials and medical devices can be developed and applied in real world clinical settings.

2. Tissue Engineering (TE) and Regenerative Medicine (RM)

TE is a multifaceted area putting in application the fundamentals of engineering and life sciences (biomedical engineering) for developing biological material or device that can replace damaged tissue or organ. This conquers the problem of organ transplantation such as the need of immunosuppressant and lack of donor. It helps in rehabilitating, sustaining and enhancing tissue function [7]. TE focuses on three major design approaches; (a) using cells alone, (b) using scaffolds alone, (c) using cells with scaffolds. Scaffolds are 3D structures that are made up of natural or synthetic material and should be compatible with particular cell type and specific surrounding in human body. They imitate the natural environment that is ECM (extracellular matrix) where cells and tissues grow rapidly and sustain their conformation. Scaffolds gradually break down when cells generate their own ECM. They should be manufactured with specified characteristics like size of pores, geometry, permeation ability and spatial arrangement. Cellular behavior may be affected by bulk and surface properties of these materials. Latest developments in the fabrication of scaffolds have assisted TE advancement in the direction of aspiring goal. There are 4 levels of complications in which manufacturing of tissues and organ is divided. First one includes flat tissues like skin, followed by tube shaped organ like blood vessels and trachea. Third one comprises of hollowed non-tubular organ like bladder, and the utmost complex structures to fabricate include heart, kidney, and liver. Tissue engineering being a part of regenerative medicine includes other important areas like Stem cell therapy, gene therapy, cellular reprogramming, and soluble molecules **(Fig. 1)**. Additive manufacturing, micro and nanotechnologies have also played a great role in tissue engineering **(Fig. 1)** [8].

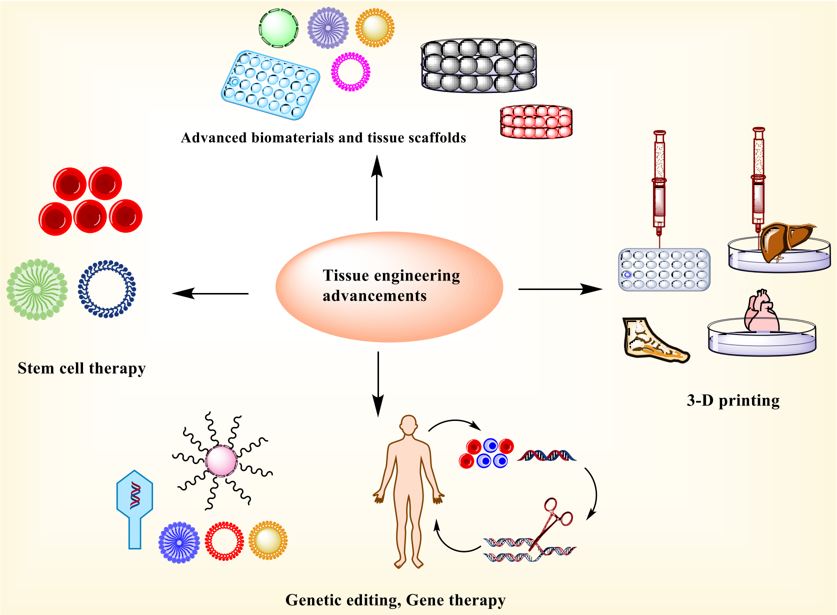

Figure 1. Illustration of advancements in tissue engineering.

2.1 Advanced smart biomaterials;

Smart biomaterials **(Table 1)** or constructs are those materials that can interact, trigger or stimulate cells and tissues in specified ways, have rational customized characteristics and functions that help in promoting tissue regeneration. They are capable of responding internal and external signals that help in healing of tissue. This advanced technology shows promising effects in urgent therapeutic needs. The smart material based methods comprises of (1) smart scaffolds and stem cell constructs for bone tissue engineering, (2) smart drug delivery systems, (3) smart pH sensitive dental materials for particularly inhibiting acid producing bacteria, and (4) smart polymers for regulating biofilm species apart from infectious constitution and towards healthy composition [9].

Table 1. Different smart biomaterials along with their advantages and applications**.**

Sr no.	Smart biomaterial	Description	Application	Advantage	References
1.	Smart scaffold for bone tissue engineering	Created by adding bioactive particles and nanoparticles together and by modifying their physical and chemical properties.	Tissue engineering	Enhance the interaction with cells, response better to the body environment, help in replacing and repairing bone defects, enhances efficacy of tissue regeneration.	[9, 10]
1.1	Biomimetic and bionic	Development is based on how biological materials are structured, generated and functions. Biomimetic materials mimic biological structures and properties and bionic materials create artificial system that mimics biological functions. Various techniques used to develop biomimetic smart materials are 3D printing, 4D printing, electro-spinning, and melt electro-writing.	Cardiac, Heart valve, Bone, and Nerve tissue engineering. Biosensors	Enhances survival of cells and regulate many cellular activities that include migration and differentiation.	[9, 10]
1.2	Immune-sensitive	They are prepared by incorporation of interleukins within the scaffold. These with osteoimmunomodulatory ability provide an osteocoductive micro-surrounding to improve regenerative function and survival of stem cells.	Tissue engineering.	Facilitate osteogenic differentiation and bone regeneration.	[9]
1.3	Shape-memory polymers	They are capable of coming back in their	Bone tissue engineering.	They can be predesigned and	[9]

		original shape from contort shape by external signals like change in temperature, electric or magnetic field, and light.		disfigured to comfortably introduce into the bone defects by slightly invasive surgical procedure, then extended to adjust to an asymmetrical bone defect.	
1.4	Electromechanical-stimulus	Include piezoelectric materials like ceramics, some crystals, biological tissues like bone, tendon, ligament, cartilage, skin, collagen and some biological macromolecules like protein, nucleic acid, and mucopolysaccharide.	Bone tissue engineering.	Improve tissue generation by supplying an electrically active microenvironment in the absence of external supply of electricity for electrical inducement	[9]
2.	Smart drug delivery for bone tissue engineering	Tiny molecules, cytokines, peptides, genes, and proteins are used to load in drug delivery systems.	Tissue engineering.	Controlled drug release, synergistic effect and improve osteoblast multiplication and separation to foster tissue regeneration.	[9, 11]
2.1	Stimuli responsive tunable drug delivery system	They can switch their characteristics influenced by a small signal that can be exogenous or endogenous and are able to deliver desired quantity of drug.	Tissue engineering	Allow real time drug delivery and monitoring.	[9, 12]
2.2	Smart multifunctional nanoparticle based DDS	Nanotechnology is applied in this and nanoparticles ranging from 10-200 nm are taken as potential drug transporting carriers because of their minute size, large surface area,	Tissue engineering.	Better interaction with living environment, on demand delivery of the drug on required site.	[9]

		good biological properties, and surface chemistry.			
2.3	Biomimetic DDS	They mimic the ECM constitution and geometry thus improving the controlled delivery of drug. Biomimetic hydrogels, micelles, liposomes, dendrimers, polymeric carriers and nanomolecules were formed.	Tissue engineering.	Provide required biological surrounding that support cell enlargement and breakdown.	[9, 13]
3.	Smart biomaterial for promoting dental and periodontal regeneration	These materials (multiphasic scaffolds) are made in accordance with the unique periodontium structure accompanied by the attempts to mimic the structure for regenerating the periodontal ligament. Multiphasic and multi-layered scaffolds were developed by methods like 3D printing, electrospinning, and electrospray.	Tissue engineering, dental and periodontal regeneration.	Tackle and revive the self-healing ability of periodontal regeneration. Stimulate orientation of the PDL into the cementum and alveolar bone that provide osteogenesis signal for bone development.	[9, 14, 15]
4.	Smart dental resins responsive to pH	They counter pH and safeguard tooth structures from dental caries. These resins liberate Ca^{2+} and PO_4^{3-} ions in higher level and neutralize the acids at lower pH required for stoppage of caries.	Dental application, dental bone regeneration, and Enamel re-mineralization,	Protect tooth structures, suppress osteoporosis.	[9, 16]
5.	Smart resins for regulating biofilm species towards good	These materials regulate mouths biofilm composition by conquering cariogenic	Dental applications	Have power of regulating the biofilm composition by shifting it from	[9]

	composition	and bacterial types assisting non-cariogenic and healthy species. Quaternary ammonium methacrylate is co-polymerized with resin matrix to introduce itself in the polymer lattice with extended role.		cariogenic condition to healthy condition.	

2.2 Additive manufacturing (AM)/3D printing;

AM is a modern fabrication method that has empowered the progression in designing and manufacturing of personalized or user specified biomaterials and biomedical devices like implants, prosthetics, and orthotics with complicated inner microstructure and adjustable features. It is also known as 3D printing **(Fig. 1)**. It reduces waste and manufactures lightweight material with complicated structure that is frequently hollow and porous and hence needs minimum energy and material for the manufacturing process [17]. 3D printing is a process that utilizes CAD (Computer Aided Design) software for designing a 3D model and then sections the model into cross sectional layers. Subsequently, printer accumulates these slices with each other layer by layer (LbL) to construct the object [18]. Biomaterials that are utilized in 3D printing are ceramics, polymers, metals and composites. Ceramic-polymer mixture is widely used to improve the printing ability. Extrusion grounded printing is majorly used for 3D printing of polymeric materials and show wider utility in tissue engineering. Generally used methods of 3D printing in bioprinting are inkjet and extrusion. For RM and TE, 2 types of fabricates are acellular and cell-laden scaffolds that carry living constituents and mimics tissue respectively. A blend of various techniques of bioprinting is required for manufacturing a complicated multipurpose scaffold. 3D printing involves various techniques **(Table 2)** like bioprinting, inkjet, extrusion printing, laser beam melting, stereolithography, fused deposition modeling (FDM), selective laser sintering (SLS), digital laser printing (DLP), and polyjet. All of these techniques utilize one principle that involves placing materials in a LbL style until complete 3D scaffold is formed. Customized 3D scaffolds can be fabricated utilizing patient's information from CT scan and MRI. CAD could be utilized to add up porosity and architecture for vasculature to build up these models [19-20].

A methodology was introduced that could be utilized to transform data of medical imaging that is produced by CT scan to 3D printed prototypes. New developments in segmentation software have made it easy to generate 3D models of body tissues from their medical images and models can be produced using a normal computer deprived of much medical knowledge. Besides, 3D printers are economical these days thus making 3D printing easy and accessible for their use in therapeutics [21].

Table 2. Summarized table of 3D printing techniques**.**

Sr No.	**Techniques**	**Description**	**Advantage**	**Limitation**	**Research Work**	**Application**	**Ref.**
1.	Extrusion	Commonly used method	Simple, affordable,	Lower speed and resolution	Oxidized nanocellulose	Wound dressing, tissue	[22, 23]

		of 3D bioprinting. In this technique bioink is extruded via nozzle of a syringe that generates tiny filaments that are eventually set down on a substrate to form a required structure.	diverse and predictable technique, Offer great cell density and has good vertical printing capability.	than inkjet and applicability is limited to viscous liquid materials.	3D printed structures were developed, alginate was used in micro-fabrication approach that created tissue strand as a bioink, Collagen and gelatin alginate hydrogels were used in printing cell laden hydrogel for studying cell expansion.	and organ bioprinting, tissue engineering.	
2.	Inkjet	This technique generates tiny droplets in the range of picoliter, fire them 1000 times in a couple of seconds and print them lacking the touch with surface. This makes it fit for deposition of living components.	Speedy fabrication, high resolution, affordable price, and capable of printing low viscosity biomaterials.	Not able to deliver materials in continuous flow, provide low cell density, and bad printing ability for vertical structures.	Development of PEG based bioink used along with inkjet printer, Droplet generation and inkjet printing quality of a cell-laden alginate and fibroblast based bioink were studied.	Soft tissue generation, tissue engineering, drug development.	[22, 24]
3.	Stereolithography (SLA)	This technology utilizes computer regulated UV-	Better printing quality, speedy printing, and good cell viability,	UV light source used for polymerization causes toxicity to cells, skin	PEGDA and GelMA were used to develop affordable	Micro scale cell patterning, tissue engineering.	[22, 25]

		laser beam for photopolymerization. A solo beam of laser is focused on the tank of liquid resin to harden it layer by layer that produces a 3D model with good precision and smooth surface.	nozzle free technique, highly accurate result, affordable cost.	cancer, inability of printing multiple cells, low resolution.	printing system for visible light SLA solution.		
4.	Laser assisted	This 3D printing technique uses laser beam to produce 3D objects. SLS (Selective Laser Sintering) has gained interest because of its capability to effectively fabricate complex geometrical metal objects with less waste. It uses laser light to specifically blend powdered material to form 3D model.	Good resolution, deposition of materials in solid or liquid state.	Costly, thermal damage occurs because of nanosecond laser irritation, cell survival rate is below 85%.	LbL manufacturing effect on cell multiplication *in vitro* and *in vivo* was studied, Sodium alginate loaded with NH 3T3 mouse fibroblast cells as bioink and calcium chloride as linker was utilized for cell printing in matrix assisted pulsed laser evaporation.	Tissue engineering.	[22, 26, 27]

2.3 Stem Cell Therapy;

The impediments of autologous transplantation of patient's tissue are conquered by stem cell transplantation so stem cell therapy has gained attention of several investigators. Combination of stem cell therapy and tissue engineering has led to the generation of tissue scaffolds that improves the viability of cells, proliferation, specialization, and curative effect of stem cells. It has been documented that mesenchymal, embryonic, and induced pluripotent stem cells foster damaged tissue regeneration. Stem cells possess bad durability and differentiation power of the transplanted tissues and cells that lead to their restraint in the medical use. TE is used to defeat this barrier [28].

Directly transplanting stem cells (SCs) into the damaged tissues induced local ischemia and thrombosis so stem cell activating growth factors and peptides were developed that improved the viability, paracrine and medicinal effect of the transplanted cells. Studies revealed that BMP (Bone Morphogenetic Protein) and BFP (Bone Forming Peptide-3) excited specialization of MSC (Mesenchymal Stem Cells) to osteoblast in bone and cartilage regeneration [28-29].

Biomaterials are being progressively introduced in *in vitro* culture to copy the characteristics (biochemical and biophysical) of stem cells that aid in directing the differentiation and self-renewal of cells into particular cells. Introduction of natural biomaterials might out turn in different level of inductive signal, cell adhesion and scaffold solidarity. Synthetic polymers are enhanced with adding up cross-linkers. 3-D scaffolds with adjustable mechanical attributes influence the survival of the cell, their specialization and growth. They have the ability to engulf soluble factors like cytokines, growth factors and farther can be implemented with adhering molecules to facilitate cell attachment and growth that impart a foundation for building of ECM for self-renewal and specialization of SCs [30].

Specialization of SCs into the required cell type is achievable by recognizing the surrounding microenvironment and epigenetic system that maintain stem cells fate. For example, a hydrogel (biomaterial) was formed and used as crosslinking agent. It was experimented in a mice model and studies revealed that the material was biocompatible that can act as a promising nominee for biomedical use like tissue engineering. The porous nature of the hydrogel influenced MSC and their reaction to IGF-1 (Insulin like Growth Factor) [31].

Nanotechnology is distinctly the newest and powerful tool used in the stem cell therapy. Various experiments directed on interactivity of nanomaterial with stem cells have resulted in remarkable progression. Stem cells have the ability of self-renewal but their use is restricted because of the lack of productive methods that could observe time span and specialization of embedded cells and tissues *in vivo*. By merging nanotechnology with stem cells, understanding of the management of stem cells differentiation is remarkably enhanced, that might lead to greater perception of the disease, their avoidance and therapy. For stem cells differentiation and tissue engineering, nanotechnology dependent approaches were developed by using safe and compostable nano-fibres like collagen, carbon, graphene-oxide nanoparticle, tri-calcium phosphate, tri-calcium silicate, and auto-assembled peptides. Polymer scaffolds such as heparin-hydroxyl-apatite chitosan nanoparticle, PLGA-nano-hydroxyapatite, and chitosan based imageable nanoparticle had remarkably aided in specialization, labeling, and tracking of various types of stem cells. Nano-patterning is a newer method developed in stem cell nanotechnology**.** Nano-patterned coverings might be utilized for greater adhesion, proliferation, selfrejuvenation, and differentiation of pluripotent stem cells. Drug-nano-patterned coatings of medicinal cells imparted advanced approach in stem cell therapy to improve the therapeutic effect of the transplanted cells [32].

Nanotechnology based cancer stem cell therapy is a promising approach for cancer treatment because of its capability of exploiting cancer stem cells and delivering them with medicinal agent. Destruction of cancer stem cells promises the long-running recovery of the disease and decreases its growth. Various nanoparticles like transretinoic acid entrapped albumin nanoparticle exterior coated with hyaluronic acid (HA) were produced to attack the CD44 amplified cancer stem cell that resulted in specified transfer of cancer stem cell anticancer drugs [32].

2.4 Gene editing/Gene therapy;

Genome engineering is an area where a series of genetic DNA is created and altered. Gene editing is an approach that include site specified alterations into genomic DNA utilizing DNA restoration process. The difference between gene and genome editing is that genome editing deals with all the genes and gene editing with only one gene. Four types of customizable nucleases available in gene editing area are; (a) ZFN (Zinc Finger Nuclease), (b) TALEN (Transcription Activator Like Effector Nuclease), (c) meganuclease, and (d) CRISPR/Cas-9 system [33].

Advancement in gene editing approaches has paved the way for direct targeting and alteration of genomic arrangement in nearly all eukaryotic cells. It has improved our capability to interpret the genetic factors that contribute to diseases by elevating the development of specific biological models of morbid process and has possessed significant result in several areas of research, biotechnology, and biomedical field. This technology has advanced its use in engineering of HSC, and tumor targeted T cells. Various applications in which genome editing is considerably showing its potential are cancer research, cardiovascular disease, metabolic, neurodegenerative, viral, hereditary eye, hematological and various hereditary diseases [34].

CRISPR-CAS9 has attracted the attention of researchers widely as it is helpful in curing genetic disorders such as sickle cell anemia and cystic fibrosis that were previously believed untreatable [6]. It possess easy engineering, versatile and flexible nature. Main problem in its implementation is the absence of effectual delivery system due to its bigger size. Viral and non-viral vectors are used for the delivery of genes and gene editing systems like CRISPR-CAS9 but currently, biomaterials have proved to be promising candidates because of their more capacity, versatile nature, biocompatibility, and higher transformation efficiency overcoming the hindrance of viral and non-viral vectors. Biomaterials like lipid, polymer, dendrimers, exosomes and inorganic nanoparticles were investigated for delivery of various genes [35].

A dendritic polymer of flexible nature that can remarkably deliver larger plasmid (Cas9) with improved packing volume and effective transformation was developed. Nanoparticle based CAR-T cell engineering has also attracted attention because of its characteristics like higher efficiency, simple scale-up, cheap price, and personalized properties and avoidance of off target effects and poisoning. Combination delivery approaches of nucleic acid and drugs were also scrutinized to enhance the medicinal effect and decrease the adverse effects. A cationic peptide based nano pro-drug co-delivery system of Cisplatin and Beclin1 siRNA was developed to be used in tumor cell targeted delivery [35-36].

Gold nanoparticles were also produced for delivering CRISPR Cas9-gRNA (guide-RNA) ribonucleoprotein (RNP) and HDR (homology directed repair) template. CRISPR gold is made up of gold nanoparticles combined with DNA, that are entangled with donor DNA, Cas9 RNP and the polymer Poly L Aspartic acid for endosomal disorganization. When it reaches to the cytoplasm, DNA from the gold coating of CRISPR-gold is released by glutathione that lead to fast release of Cas9 RNP and donor DNA. Baculoviral molecule combined with magnetic nanoparticle (MNP-BV) is also used for delivering CRISPR-Cas9 with geometrically management of genome editing. Magnetic field applied after delivering the MNP-BV helps to mitigate the problem of inactivation of baculoviral molecule that leads to geographically controlled gene editing in the target tissue [37].

Various nanotechnology based delivery approaches for gene editing technology that have gained attention are Gold/lipid-CRISPR system for PLK-1 gene editing in melanoma, lipid-CRISPR approach for human hepatitis B virus PCSK9 editing and polymer-CRISPR system for MTH1 gene editing in ovarian cancer. Incorporating CRISPR-Cas9 component in unit nanocarrier can be a better approach for delivering CRISPR-Cas9 to the same cancer cell at same time. CRISPR-Cas9 have negative charge on their surface, so to encapsulate it nanoparticles having positive charge (like cationic LNP, polymers and polypeptides) can be interacted with it by electrostatic force of attraction [38].

3. Implantable medical devices (IMDs)

IMDs are generally used in medical field for diagnosis and treatment of the disease. They are used in a variety of pathological conditions like in diabetes for monitoring glucose level, high BP telemetry device, cardiac reporter and defibrillator. IMD interconnects with the anatomical process like heart beat and arbitrate sensing and regional stimulus, recording of details, and drug delivery. Advanced IMDs have the ability to transfer essential values (BP, blood glucose level, and electrocardiogram) from internal of the body to outside. These outputs help in creating a therapeutic decision and provide a customized clinical method for diagnostic and therapeutic purpose. For instance, self-reporting cardiovascular stents. Execution of these devices faces some limitations that need to be addressed. Various advancements have been made in IMDs like low energy miniaturization of the devices, microelectronic power efficiency, establishing long lasting life and enhancements in biocompatibility, transmission methods aided the devices with live tracking to be implanted and transmit information wirelessly for reporting pathological conditions **(Fig. 2)** [39].

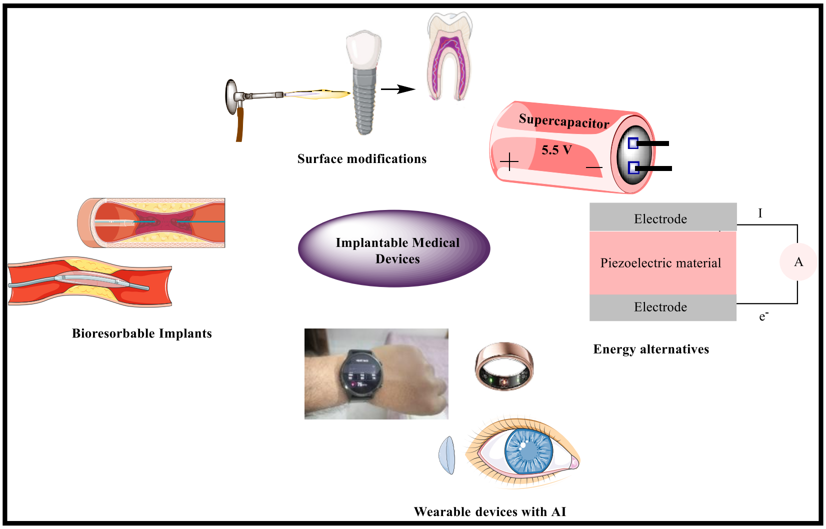

Fig. 2. Advancements in implantable medical devices.

3.1 Advancements in better energy alternatives for implantable and wearable bio-electronic biomedical devices;

Implantable bioelectronics are categorized in two types, 1) active, and 2) passive depending on the fact that they have an energy source or not. Active implants use traditional Li-ion (lithium ion) batteries. The drawback of these batteries is that they are large, stiff, need stubborn packing, and hold a huge space in the device. The batteries require surgical removal when their work is done or exchanged regularly because of their restricted volume. In passive implants, power is used by the exterior source (wired or wireless). This may cause skin wire interface infection. Advancements like miniaturization, low weight, sufficient volume, mechanical distorted characteristics, biodegradability, and biocompatibility etc. in modern power solution for implant devices has been proved to be potential substitutes for traditional batteries. Potential energy substitutes that have gained attention include; supercapacitor (energy storage device), piezoelectric/bioelectric power generator, thermoelectric and biopotential energy harvester, biofuel (interior power scavenging system), and inductive coupling, ultrasound-induced, photovoltaic device (exterior wireless energy transfer technology) [40].

Energy storage device (Super-capacitors);

Super-capacitors are energy storage systems (EES) that are used because of their supreme property like specified energy, fast charging and discharging degree and better life cycle. They require minimum time for charging and hence used widely in renewable power applications. SCs overcome the obstacles related to batteries like rate of charging and discharging, life span, and cold prejudice. SCs possess 10,000 folds more capacitance than conventional capacitors because of the advancement of electrolytes, current collector, large electrode SSA (specific surface area) and narrow dielectric separator [41]. Materials that are appropriate for electrodes are activated carbon, Carbon Nano Tubes, graphene, transition metal oxide, and conducting polymers. Diverse electrolytes such as aqueous, non-aqueous, polymer and ionic liquid based could be utilized in super-capacitors. Activated carbon is widely used in electrodes because it increases the surface area of SC and hence improves the capacitance [42]. The advancements in super-capacitors that have been reported to improve the capacitance include development of nano-porous materials or stratified micro to nanostructures, improvement of wet electrode surface subjected to the electrolyte, adjustment of the mass transport mechanism, and use of novel and active materials that permit higher mass transfer like graphene-nickel cobaltite nano-composite or activated carbon. Various types of super-capacitors that are in industrial use include hybrid capacitors (asymmetric, composite, battery type hybrid), pseudo-capacitors (metal oxide, conducting polymer), and electric double layer capacitor (CNT, grapheme, activated carbon) [43]

Internal energy scavenging device (Piezoelectric, triboelectric, thermoelectric nanogenerators and biofuel cells);

As discussed above batteries have several limitations like restricted capacity, bulkiness, short life span, and high cost because of the spending on surgical procedures that are done to replace the battery when its work is done. To mitigate these limitations, high tech self-powering approaches have come out that include piezoelectric nanogenerator implants (iPENG) and triboelectric nanogenerator implants (iTENG). These technologies empower for self-governed working by utilizing the little impulsive actions of internal organs like heartbeat, blood flow, inhalation-exhalation, muscle twitch and vibration of lungs. They produce energy by gathering biomechanical energy from motion of inner body parts. Various promising benefits of these systems above batteries include lower price, miniaturized dimension, greater biocompatibility, flexible nature, long lasting energy source, and higher environmentally conscious. The ability of iPENG and iTENG for producing electrical energy from biomechanical power allow them to act as self-powered implantable devices for distinct utilizations like sensing (cardiac, bladder, GI, and ligament strain sensing), tracking and inducement of cells and tissues (stimulation of nerve cell, muscles, cartilage, bone and drug delivery) [44-47].

Nanotechnology integrated with the tribo and piezo-electric generators resulted in the potential advancements like nanostructured polytetrafluoroethylene (nPTFE) was developed as a triboelectric layer for enhancing the power output signals. A kapton film was fixed on n-PTFE layer for improving the device's stretch ability and a very thin aluminum foil was used for electrode as well as triboelectric layer. Two degradable polymer layers were combined with the nanomaterial as contacting section and whole system was enclosed in a bulk drug product so that it does not get affected by the biological environment. Another approach in the advancement of these devices was the development of core shell cover for achieving tight and flexible packing for improving the stability of the device [48].

Fuel cells convert chemical into fuel and then into electric energy by various chemical reactions. Biofuel cells utilizes microorganisms, enzymes and metal as catalyst to generate electricity through biochemical reactions of organic renewable assets such as glucose and amylum that makes them ample for various IMDs like pacemaker, heart defibrillator and transmitter devices for various therapies. Biofuel cells in comparison to batteries are better energy source as they are ecofriendly, and energy generation can be amplified, long shelf life and higher biocompatibility [49]. Basic idea of biofuel cells rely on the arrangement of system that permit redox reaction to occur at electrocatalytic electrodes separated by a spacer. The reaction is promoted by biocatalytic microorganisms and enzymes. Various developments are done to make them more effective like long life, miniaturization of cells, and enhanced energy delivery. Enzymatic biofuel cells in comparison to other biofuel cells are mostly applied in pacemakers, glucometers, and smart contact lenses because of their higher activity at optimum conditions. But they have short shelf life so non enzymatic biofuel cell are utilized to overcome the limitation of enzymatic ones. Nanotechnology showed promising advancements in the field of biofuel cell power production [50].

Hybrid biofuel cells were produced that achieved paramount energy output. It utilized gold nanoparticles for modifying carbon nanotubes as electrodes that increased the energy output when anode was immobilized with an enzyme [50-51]. Nano materials enable the transfer of charge from catalyst to electrodes, they have greater surface area that furnish fast flow of intermediaries in the electrodes and possess suitable microenvironment that enhances the stability and life of enzymes. Various nanostructures that are utilized to produce bio electrodes of enzymatic biofuel cells include silver nanoparticle graphene oxide, graphite, carbon nanotubes, and nitrogen doped hollow nanosphere with huge holes [52].

Thermoelectric generator is a concrete device that scavenges the heat energy of human body and converts it into electricity. Due to their efficiency of gathering energy from low heat, solid, and stable nature, they are widely utilized in IMDs and wearable electronics. They convert temperature difference to electrical power by seedbeck mechanism. Traditional TEGs were composed of thermocouples on a hard substrate that makes them insufficient for applying into the human body so flexible TEGs are used human use [53]. Generally, thermoelectric materials should have higher electrical conductivity and lower thermal conductance for better performance. This poses a challenge to discover such a material with both characteristics. So, several researchers have worked on developing novel thermoelectric materials to enhance the power translation ability.

Semiconductors are used for balancing the electrical conductance. Nanotechnology has proved to be beneficial for developing thermoelectric materials with enhanced performance. Nanocrystalline materials improved the activity of TEGs. Nanostructured BiSbTe bulk alloy manufactured by hot pressing BiSbTe nanopowder proved to be effective. Silicon nanorod structure exhibited 100 times more deduction in the thermal conductance. Incorporation of CNT and inorganic nanomaterials in the polymer is a documented approach for improving energy factor. Synthesis of paste like inorganic structures is considered to manufacture flexible and screen printable thermoelectric generators [54].

External wireless power transfer (WPT) technology;

WPT has attracted potential observation for tracking and energizing IMDs without the need of interfering methods. This strategy enables the concurrent transference of the energy and data between an alterable exterior source and internal implant device without utilizing percutaneous wires and batteries. This system support distinct wearable and implantable devices like contact lenses, brain, neural and cardiac implant medical devices. Numerous WPT techniques that include inductive coupling, magnetic resonant coupling, radiofrequency and mild field WPT were developed focusing on the factors like efficient power transfer, transmittance distance, and frequency of operating. Due to their several advantages over conventional batteries and other energy systems they are widely used in cardiovascular implantable medical devices (cIMDs) like leadless pacemaker, cardioverter defibrillator, cardiac stent, and ventricular assist device (VAD) [55]. WPT comes under WBAN that creates a link between the thing worn on the surface of body to the implant or other surface attached device. Implant to surface implant communication is utilized for diagnosing the cause or problem in which sensed signal is transferred to the exterior of human body and surface to implant communication system is utilized with therapeutic implants to transfer signals from exterior source to implanted device [56].

Radiofrequency technology used in IMDs transmits the radiofrequency signals from human body to a receiver that is outside the human body. The receiver might be worn on the human body surface or positioned at a distance [56]. Radiofrequency identification device receive the radiofrequency power from the monitor and excites the chip present in the tag and transfer an identification code to the monitor. This code is then linked with specified information about the tag to which thing it is attached with. The data is then stored and updated in a database to be utilized in various applications. High frequency device communicate energy with near field inductive coupling and ultra-high frequency device transfer and receive energy with far field backscattering. Chip less RF device have also gained attention because of its shift resonance frequency. These sensors convert the radar profile of RF device tag to transfer sensed data without the requirement of complicated integrated circuit. When antenna receives the signal from the monitor, the resonant circuit produces specified frequency and amplitude based on the sensor data. The monitor then decodes the data by analyzing these changes and if the tag is positioned on a material that is under test, resonant frequency will shift on the basis of the changes in the properties of material [57]. Our surrounding environment is full of electromagnetic signals like WiFi, FM radio, mobile phase stations, TV, digital TV etc. that also aid for the energy harvesting for RF devices [58].

A small wireless IMD that utilizes radio near frequency WPT method was developed for tracking increased intracranial pressure. Device contains Rx antenna, Styrofoam spacer, dummy photo electro-chemical elements and an aluminum vessel. The PTE (power transmission efficiency) was calculated in accordance to distance variation that was found to be improved [59].

A compact transmittance method in the midfield RF was developed that could condense magnetic field into human tissue. Its work was evaluated through implanted PIFA (planar inverted F antenna) that was placed in the heart tissue layer at 55 mm separation distance between transmitter (TX) and receiver (RX). Its PTE was also justified by an assessment setup utilizing pork muscle, and the result was found to be very precise compared to the computer simulations. Utilizing 1W of energy generated by a transmitter, the sent energy was more than 5.6 milliwatts of power to the implantable antenna that was away at a short distance [60].

Ultrasonic is also one of the arising technologies for transfer of energy to the implantable devices like neural, cochlear, and cardiovascular implant devices because of its improved efficiency and less propagation loss. It can transfer energy to larger distances. This technology transmits energy by propagation of energy as sound or vibration waves. It can penetrate deeply into the depth and travel through electrically conductive material that is opaque to electromagnetic energy. Work was done on ultrasonic projection that illustrated that ultrasonic power transmission is a reliable approach for implantable devices for human body [61].

A study demonstrated that small and low power devices can effectively generate and receive ultrasonic waves. Regardless of the transformation loss induced by ultrasonic transducers, the ultrasonic waves are less influenced by attenuation of 2.4 GHz radiofrequency. It was illustrated that IoMT (Internet of Medical Things) need remarkably less power to transmit data with credibility over long distances in comparison with radiofrequency. For instance, at same bit error rate (BER), IoMT could utilize 35 dBm less energy than RF at distance over 12cm. This results in lower consumption of power and long shelf life of the device. It was also proposed that RF links could not work at distance more than 12cm, whereas ultrasonic links can function at up to 20cm with minimum energy transmission rate and low BER (Bit Error Rate) [62].

In spite of the fact that there are various techniques for diagnosing, monitoring and imaging of the disease like MRI, Ultrasound, X-ray, wireless implantable sensors has attracted the interest of the researchers because of their real time monitoring, safety, ease of use and efficiency. They are applied in distinct clinical areas for diagnostic and therapeutic purpose. For instance, incorporation of implantable strain sensor into orthopedic and prosthetic for characterization of force acting on these joints for developing superior prosthetics, incorporation of implantable cardiovascular flow and pressure sensors for providing prior warning of immoderate clotting or obstructed flow in the patients who have more risk, and implantable neurostimulator for treating muscular and neurological injury [63].

3.2 Surface modifications in IMD;

Surface modifications are done for improving the limitations, enhancing mechanical characteristics, and biocompatibility of implants. Various methods are utilized for coating and synthesizing the surface of metal implants with polymer layer that leads to enhanced performance of the implant. Generally physical and chemical modifications were used for the surface modification of implants. Physical methods include plasma spray technology, physical vapor deposition, and plasma immersion ion implantation and deposition. However, chemical approaches include chemical vapor deposition, sol-gel, and micro arc oxidation. In chemical methods, the surface is immersed into chemically active solution that lead to the coating formation on surface and in physical technique energetic charges and other physical tools like flame and plasma are subjected to the surface of implants. Chemical modifications on the surface of implants enhance the adherence of the implants to the biological cells by supplying greater area for binding. Various functional groups like carboxyl, amino, and hydroxyl can be introduced only by replacing the terminal group in SAM. They are utilized to alter the surface and self-assembled molecules (SAM) are generally used for modifying the surface by adding thiol group [64-65]. Physical vapor deposition is used to coat implant's surface by depositing metal and ceramic materials and it imparts better adherence, accurate stereochemistry, higher density, and better steadiness. Various materials that are used for coating the surface are PEEK (polyether ether ketone), titanium dioxide, transition metal nitride, carbon based materials, calcium phosphate, zirconia, and bioactive glass [66]. To mitigate distorted surface topography, low adhesion of surface coating, contamination risk, and bad maintenance of coating thickness, laser technology has been developed. This technique is used to design uniform and non-porous microstructure, metallurgical binding to the substrate and generate less dilution and less heat to the material coating. These techniques involve PLD and laser cladding that are advantageous in terms of low cost, fast technique, versatile nature and ease of use [67].

Plasma spraying technology (PST), a physical method of surface modification utilizes a plasma arc that is operated by direct current as a power source to ionize the plasma (inert gas) and produce energy. The heated plasma flame melts the coating material (ceramics, metals, alloys, and other materials) and then sprays on the surface of implant at elevated speed to produce a uniform coating. This technology possess rapid deposition rate, less price, and huge deposition thickness [68].

A gradient hydroxyapatite (HA) coating on Ti6A14V (a titanium alloy) by LENS using PST technique was developed. Magnesium oxide and silver oxide to the HA were added for enhancing biological and antibiotic effects of the implant. The study revealed that the intermediate layer produced by LENS strengthened the adhesion of coating and titanium. The presence of silver oxide and magnesium oxide did not affect the strength of adhesive bond. When the LENS layer was present, the release of silver ions from the coating declined by 70% because of enhanced crystallization HA layer. *In vitro* test revealed that the presence of silver oxide did not show detrimental effect on the growth and specialization of human osteoblast cells and also exhibited antimicrobial properties against *E.coli* and *S.aureus* pathogens. This research provides a novel method for improving mechanical and antimicrobial properties of plasma sprayed HA coatings for orthopedic and dental implants [69].

3.3 Bioresorbable implants;

Implantable medical devices are utilized for prolonged or permanent disease monitoring and therapy and they cannot be regarded for temporary or brief implementations because patients have to go through surgical procedures for reclamation of the implants. So, various advancements in bioresorbable materials instigated the design of short-lived implantable devices. They are implanted next to the intended tissue for pre-planned period with a goal of estimation of pressure, strain, temperature and at that time the device revive specific tissues. For the development of temporary and miniaturized bioresorbable implantable devices, various materials, new manufacturing approaches, and device design schemes have been utilized. Bioresorbable IMDs overcome various limitations of conventional IMDs like patient pain because of surgery, high cost, and infection possibilities [70].

Bioresorbable materials break down gently in the body and yield by products that are entirely soluble and compatible with the body fluids. They do not leave behind any leftover and show minimum harmful effects that remove the requirement for recovery surgeries. Disintegration of these materials into non-harmful molecules that after some time get absorbed is assisted by hydrolytic and enzymatic degradation. The materials used for bioresorbable implants involve metals, semiconductors, polymers, insulators and nanocomposites. The choice of material to be selected for manufacturing of bioresorbable IMD relies on the physical and chemical characteristics of materials. Development of bioresorbable implantable devices has been facilitated by material science, micro and nanotechnology advancements. These implants comprise of biocompatible sensors that recognize the changes in physiological variables like pressure, blood circulation, pH, and electrical signals generated in the body. These devices are created by utilizing Complementary metal oxide semiconductor manufacturing technique in the absence of increased cost and reorganization of system. Bioresorbable metals have been visible in distinct orthopedic uses like bone fracture fix screw, nails, plates and pins. In balloon angioplasty process, cylindrical mesh materials of magnesium and iron stents acted as short-term vascular stents [71-72].

Development of magnesium rooted bioresorbable stents was a significant discovery in the area of bioresorbable stents. Despite their potential, prior experiences with theses stents raised a problem of rapid destruction and excess release of magnesium ion and H2 gas. Numerous experiments in novel magnesium alloys, fabrication techniques, and surface modifications and coating have been conducted to enhance the regulation of magnesium degradation. Surface functionalization was done through bioactive modifications and biomolecule immobilization, surface nano and micro patterning for improving endothelialization. Alloying magnesium with molecules such as calcium, manganese, tin, zinc, aluminum, zirconium, strontium, and earth metals can enhance mechanical strength as well as corrosion resistance. For example, a magnesium-zinc-calcium alloy was produced with higher strength, low-alloy and higher purity. It exhibited remarkable mechanical characteristics because of the factors like advancement of grain size refining, precipitation strengthening, and slow degradation rate [73].

Absorbable implants have also enhanced orthopedic surgeries, decreased complexities, and stimulated bone regeneration. Magnesium acts as a potential orthopedic implant because of its promising biocompatibility and biodegradable nature. Its mechanical characteristics imitate natural bone that aids in preventing strain resistance and improves osteoblast adhesion. Magnesium degrade rapidly that causes an obstacle in prolong bone proliferation so various advancements have been done for enhancing corrosion resistance of magnesium for its utilization in bone regeneration. Magnesium rooted metallic glass with more power, elasticity, and greatly corrosion resistant nature have been developed to be associated as bioresorbable implant for orthopedic application [74].

An implantable device was manufactured utilizing bioresorbable materials that were absorbable in biological fluid. It was able to track intracranial pressure and temperature during the therapy of traumatic brain injury. The device was attached with a near field communication (NFC) through molybdenum wires [75].

A bioresorbable PLLA (poly-l-lactic acid) based pressure sensor for measuring pressure of intra organs was produced. It was evaluated by incorporating into mouse abdomen for measuring contraction pressure in diaphragm to determine breathing impression. This piezoelectric sensor offered potential alternative to current bio-electronic devices for tracking of intra organ pressure. It showed promising use in drug delivery, medical devices and regenerative medicines [76].

In cardiovascular disease like atherosclerosis**,** blocked arteries were generally treated with metal stents, but the metal stents sometimes were blocked because of in-stent restenosis in which inner lining of the vessel gets leaned due to excess growth of smooth muscle cells. Development of absorbable stents mitigated this limitation of metal stents. After the incorporation of BRS, they gradually disintegrate and absorb in the blood that overcomes the requirement for prolonged antiplatelet treatment, eliminating the chances of local hypersensitivity and chronic inflammation. When dissolved, the stents leave a normal, unobstructed vessel with steady blood flow. The elimination of stent also has the power to restore the vessel's constriction ability that helps to regulate normal blood circulation [77].

3.4 Wearable and implantable biomedical devices with artificial intelligence (AI);

AI is an advanced computer science technology that creates program and algorithms for performing task easily and efficiently that typically require skilled human expertise. AI uses approaches like machine learning, deep learning, neural network, speech recognition and fuzzy logic to improve the area of medical science. In addition to enhance human healthcare, IoMT unite with networked medical devices via software. IoMT techniques relate medical officials with patients through medical devices like implants, allowing remote data communication as discussed above in wireless technology for implantables. This approach involves wearable devices like smart wristwatch, electronic textile and garments, and smartphone incorporated devices for real time monitoring of patients health indicators and fitness [78-79]. Advancements in these electronic devices have assisted in customized health tracking and accurate treatments. They have been investigated to track electrophysiological procedure associated with the brain activity (EEG), heart (ECG), and muscle tissue (EMG). Helping in prior diagnosis of the disease, these devices could decrease patients' health risk and prolonged treatment cost. Flexible bioelectronics were developed to overcome the limitation of traditional rigid electronics. Flexible and soft bioelectronics devices have the ability to conform to the human body's curved surfaces and easy incorporation with the tissues. Progress in the fabrication strategies and materials has enabled the integration of cost effective sensors in small space [80].

A wireless binodal wearable patch for infants at risk was developed. It has the ability of evaluating PPG (Photo Plethysmo Graphy) and ECG and painless attachment of the sensor to the skin. Its miniaturized size and wireless system minimized the tenderness for infants and clinicians [81].

Researchers outlined the integration of AI with human intelligence (HI) that would offer synergism for considerable discoveries and genuine possibilities for enhancing healthcare from prevention of disease to its diagnosis and therapy [82].

Conventionally, tattoos were considered as a body art only but nowadays because of their flexibility and compliancy they are being used for tracking and diagnosis of diseases. Presently, e-skins are broadly used for detecting physiological parameters like ECG, EEG, and EMG. Tattoo based ECG devices being modern approach for monitoring heart health overcomes the limitation of textile based ECG trackers like non stability and sensitivity because of their smaller size, congenial and flexible nature [83].

A tattoo based monitor that contains small electronic components built on graphene and polymethylmethacrylate double layer base was developed. The GET was manufactured by wet transfer dry patterning method and created a thin, transparent and stretchable device. This device could be pertained on the skin same as tattoo as it binds with the skin by Van der Waals force that makes it invisible and provide ECG measurement [84].

An advanced textile based skin wearable device for the monitoring of ECG was created. Conventionally, heartbeats were measured through gel based silver/silver chloride electrode cables which causes discomfort to the patient, so to overcome this problem, this device was developed using graphene implemented fabric incorporated with ECG biosensor. This approach proved to be more comfortable and convenient way of tracking the heart health [85-86].

Oura smart ring was used to speculate corona virus symptoms at a fast rate (within 24 hours). In the lab, SARS COVID fast test was developed with the aid of deep learning model using CNN and RNN algorithms for diagnosing corona virus precisely and quickly. The result showed value 0 (indicating that the person is not affected by SARS CoV) and 1 (indicating that the person is affected by SARS CoV). X-ray and CT scans were used to distinguish the condition of the patient from starting to serious stage. 0.5 threshold values indicated initial stage of the infection and 1 indicated severity stage [87].

Convenient and supple earphones for wireless and real time monitoring of electroencephalogram in daily schedule were designed. They consist of 3 electrodes which are composed of CNT, PDMS (polydimethylsiloxane), AgNW (silver nanowires). The electrodes are surrounded by a plastic frame with electronics like conductive elastomers, signal transducer, and metal strip with soft earbuds. Earphones have the ability to wirelessly send EEG signal to a smartphone via Bluetooth and distinguish between sleepiness and consciousness. Despite that, due to the crosstalk with music, EEG signals have lower SNR (signal to noise ratio) and need further amplification and support signal processing approaches for enhancing the signal quality [88].

Smart contact lens for tracking and diagnostic purpose of diabetes utilizing tears was developed. The lenses are composed of phenylboronic acid, a non-enzyme, HEMA (hydroxyethyl methacrylate) and a monomer for measuring concentration of glucose in tears. The lens swells, increasing its thickness when glucose is present in the tears. Thickness of the lens is directly proportional to glucose concentration. Despite the use of integrated energy or photosensors, the lens uses a smartphone for detecting thickness changes of the lens. The smartphone catches the light reflected images from the lens and analyses the images by utilizing software for determining glucose concentration [89].

4. Medical imaging devices

Medical imaging techniques create images that are used for diagnosis and prediction of the disease in human body that helps in their treatment [90]. Various imaging techniques used in the medical field are CT scan, X-rays, nuclear imaging, single photon emission computed tomography (SPECT), sonography/ultrasound, MRI and fluoroscopy. They are used in diagnosing variety of diseases like myocardial, cancer, nuerological, abdominal, bone fractures, congenital heart disease and many more. These techniques offer various benefit but also have some limitations like low resolution in some techniques, sensitivity problem and lack of specificity [91]. Various advancements in these technologies that overcome these limitations are listed below **(Fig. 3)**.

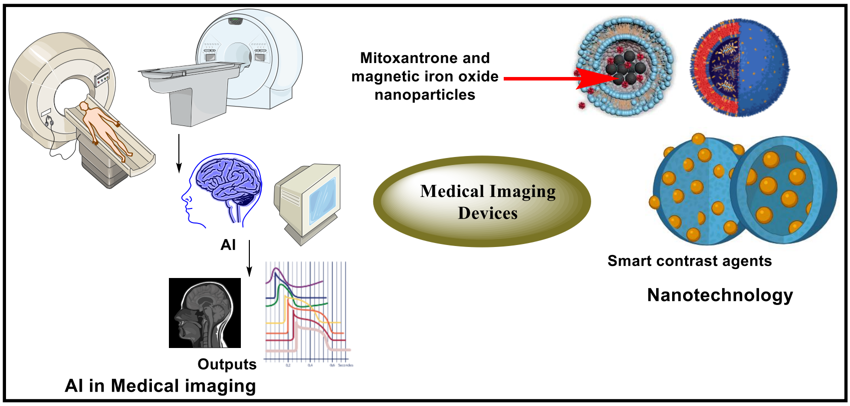

Fig. 3. Representation of advancements in medical imaging.

4.1 Nanotechnology in medical imaging;

Early disease detection and diagnosis demands advancements in imaging techniques and contrast agents like MRI, computed tomography, ultrasound, fluorescence, and positron emission tomography. Nanotechnology applied with these techniques provides detailed tissue information and characterize lesions [92]. Characteristics of nanoparticles like small size, prolonged circulation, high sensitivity, unique magnetic and optical properties, and the ability to conjugate with target ligand, improved permeability and retention effects in solid tumors make them potential structures for imaging techniques and contrast agents. Multifunctional nanostructures designed by incorporation of numerous functional agents enable multimodal imaging and therapy also known as theranostic [93-94]. Gold and silver nanoparticles are used in optical imaging and multiphoton plasmon resonance microscopy, mesoporous silica nanoparticles in ultrasound and targeted endoscopic detection of disease like colorectal cancer, and nanoparticles based contrast agents like iron oxide nanoparticles, magnetic nanoparticles (MNP), are used in thermal and nuclear imaging. In MRI, iron oxide and gadolinium based nanoparticles are used as contrast agents [95]. Contrast nanoparticles offer further information about the disease process and their effects. Manufacturing of these structures have developed a lot by integrating numerous functions in them like customization, targeted and efficient disease detection [96]. Smart contrast agents can respond to biochemical signals or can be targeted to a particular site using conjugate. Aptamer based smart contrast agents were developed by using both schemes. Aptamers are potential candidates for molecular imaging like MRI and PET due to their ease of chemical modification and better target affinity. As monoclonal antibodies are used to deliver contrast agents, aptamers also served as a vector for transporting contrast agents to desirable sites for in vivo MRI [97].

Magnetic iron oxide nanoparticles (MION, MRI contrast agents) and anticancer agent (mitoxantrone) were loaded in a multipurpose liposome that was developed for target specific cancer treatment and ultrasensitive MRI. When tested in mice with breast cancer, Mit-GML (gonadorelin-functionalizied MION/mitoxantrone loaded liposome) showed better targeting at breast cancer cells than liposomes that were gondaorelin free. They showed less harmful effect in the cancer therapy and also provided better imaging results that suggest that the combination of imaging and drug in these liposomes can enable targeted cancer treatment directed by images [98].

Workable, easy to use, cost-effective, and handmade NIR (Near Infrared) lymphatic imaging device was developed utilizing accessible constituents like personalized laser, a modified webcam for imaging lymphatic vessels. It was tested on 25 year old healthy women and image of lymphatic vessels in the forearm showed normal lymphatic vessels [99].

4.2 Artificial Intelligence in Medical Imaging;

Artificial intelligence is transforming medical imaging by enhancing functions like image interpretation, processing, and reporting. AI is incredibly versatile in radiology, from capturing image to the data analysis. It is believed to remarkably affect the daily tasks of radiotherapist. The raising workload of medical images can limit the ability of radiologist to interpret them that leads to the shift in the focus of radiologist from clinical analysis to only detection and the clinical interpretation is left on other doctors. This might lead to misdiagnosis as non-radiologist may not fully understand the radiological context. AI provides a promising chance for these types of situations [100]. Artificial neural network (ANNs), a machine learning algorithm, inspired by brain of human has many layers or connected nodes that include input, output, and hidden layers. Machine learning algorithms recognize patterns in medical images by studying various examples. They create a mathematical model that can be trained to make accurate prediction when input data is fed. These models provide information about abnormal findings, generally in the form of probabilities that can be used for decision making. ANNs have progressed and enhanced with more complex structures leading to the development of deep learning. Deep learning uses multiple layers to automatically find necessary pattern in data. Deep neural networks are the modern machine learning models that are used for enhanced image analysis, diagnostics, and language processing [101]. They often exceed shallower networks in tasks like classification and regression. DNNs use techniques like restricted Boltzmann machine or residual neural networks with skip connection for preventing their stuck in local minima or over fit that is a limitation of ANNs. Deep learning is further advanced into Convolutional neural networks that have promising results in various areas. CNNs have convolutional, pooling, and connected layers. The prime goal of CNNs is to identify patterns, lines, and edges in images. Multiple kernels produce multiple feature maps which are then down sampled using pooling layers. Regardless of the size and shape of images, this process extracts important features from the images. [100-103].

In recent years, DL approaches proved effective for semantic segmentation. They were effectively utilized in medical imaging classification, segmentation, and detection. New deep learning models known as RU-Net and R2U-Net based on U-Net residual and recurrent convolutional networks were proposed. They were designed for medical image segmentation functions with various advantages like better training stability, enhanced feature representation, and smaller network size for better performance. These models were tested on three datasets like blood vessel, skin cancer, and lung lesion segmentations. The result showed better performance on segmentation than compared models like U-Net and ResU-Net [104].

DoubleU-Net model that combines two U-Net architectures was proposed. The initial U-Net utilized a pre-trained VGG-19 encoder with already learned patterns from ImageNet, and the second U-Net was added to capture more semantic information. Atrous Spatial Pyramid Pooling (ASPP) was also used for capturing contextual information. DoubleU-Net was tested on four medical image datasets and it was found that it performed better than U-Net and baseline models, especially on challenging images. These results showed the effectiveness of DoubleU-Net for medical image segmentation and suggested that it can serve as a strong baseline for further research [105].

5. Challenges and Future Prospects

Advancements in biomaterials and biomedical devices offer great potential for therapeutic applications, but their development and use are complex and multifaceted. They still face some translational barriers that need to be resolved. Material selection, regulatory compliance, cost, accuracy and precision, and standardization are the major challenges posed by additive manufacturing that need to be addressed for its global assumption in the clinical field. The materials should be biocompatible, sterilizable, safe, strong, and flexible and should have wear resistance. Biocompatibility and scalability also poses problems. It has been documented that after prolonged implantation, hydrogels containing cells may cause excessive cell growth. So, selection of biocompatible materials with appropriate size and stiffness is important to prevent adverse reactions. Techniques that work well in lab may be hard to scale on large production. So, there is a need to improve the scalability of the biomaterials [106].

For invasive devices, thorough safety testing like long term toxicity analysis is crucial. Wearable devices remain in contact with skin, so they should be made more adaptable to skin and undergo extensive evaluation to estimate electromagnetic radiation risk. For medical devices that are used for sensing and recording, accuracy and reliability is still a challenge. Implantable devices are particularly susceptible to accuracy loss due to factors like tissue scarring and immune response (inflammation and unstable chemical reactions). Energy harvesting and storage devices that have been introduced still need to extend the lifespan of implanted medical devices and minimize the necessity for replacement. Their energy density and safety also needs to be addressed [106-107].

In the growth of bio-implants market, high cost and reimbursement poses serious challenge. Research, testing, and manufacturing process are costly. Nanostructures are reported to offer unique properties that enhance the functionality of implants but mimicking living bone tissue still remains a challenge. Surface coating technique also faces a challenge like development of coating that dissolves at the same rate as bone growth, and allows direct implant-bone contact. The effect of nanomaterial on humans and animals when exposed to air and water is still not understood. Nanomaterial based bioimplants must be carefully tested during production and implantation before clinical approval to checkout possible health risks [108].

Battery powered wearable devices such as smart wrist watch, fitness band, and oura smart rings etc have limitations in sensing quality, patient comfort and compliance that needs to be addressed. Weight of batteries can cause motion artifacts and prevent accurate bio-signal recording. Daily charging requirements of battery requires removal of device that may lead to data loss and noncompliance. Large device can be uncomfortable during sleep or hot weather that may lead to removal of device and data loss ultimately leading to the prevention of detection of essential physiological changes. Sensing regions are often limited to small areas on the body that can restrict the functionality and accuracy of sensors [109].

For the execution of smart healthcare using wearable devices, integrating data from different sensors is a major challenge. Sensors produce various data types and it is important to convert these signals into a relevant format for health monitoring. Various data fusion approaches can be explored to combine information from different sensors and enhance signal reliability and minimize bandwidth required for cloud communication. Security and privacy are also great concerns in wearable devices [110]. Blockchain based frameworks can provide secure data communication. Remote patient monitoring faces challenge such as missing or incomplete information. Power cut or natural disaster can cause data loss before documenting it at cloud location. This is especially problematic for patients with serious illness at home. When a number of patients require urgent healthcare, medical teams may be overburdened. So, we need systems to send urgent patient requests to other healthcare providers. We further need methods to deal with missing data. Optimized algorithms, end to end architectures, and synthetic data generation can be utilized to address the data shortages. Feature selection algorithms can help to identify and remove unnecessary features that may degrade performance of the system [110].

Deep learning approaches in medical imaging are leading and often perform superior than traditional methods. A study reported that particular DL architecture may not be critical for success. For instance, in a diabetic retinopathy challenge, multiple researchers used the same network structure but achieved extensively different results. This highlights the importance of data preparation techniques like augmentation and preprocessing that significantly affects model performance and robustness [111]. Researchers must consider regulatory requirements, ethical suggestions, and technological advancements for ensuring safe and effective clinical translation of biomaterial based treatments. Regulatory approval, biocompatibility testing, and material characterization should be considered for ensuring safety and quality of biomaterials. Throughout the R&D process, ethical considerations like informed consent, privacy and equity must be prioritized. Intellectual property, environmental sustainability, public perception and acceptance are also crucial factors to be considered for successful adoption of biomaterial treatments [112].

Researchers must focus on these challenges and pursue future directions for contributing to the development of innovative biomaterials and biomedical devices for enhancing patient outcomes, healthcare delivery, and promoting sustainable future.

6. Conclusion

The field of biomaterials and biomedical devices has witnessed remarkable advancements in recent years followed by revolutions in tissue engineering, 3D printing, gene editing, stem cell therapy, energy alternatives, implantable and medical imaging devices, nanotechnology and artificial intelligence combined with human intelligence. These technologies have the potential to revolutionize healthcare by providing novel and better solutions for diagnosis, treatment and prevention of diseases. 3D printing and tissue engineering together have made it possible to create complicated biological structures like organs and tissues that can be used for transplantation and regenerative medicine. Gene editing approaches, particularly CRISPR-Cas9 offer precise tools for modifying genetic material, open doors for gene therapy and personalized medicine. Bioresorbable implants have improved the quality of life of millions of people. Nanotechnology and artificial intelligence have also proved promising in transforming healthcare with their unique properties and optimizing treatments. These advancements have improved the efficiency, precision, and personalization of medical treatments. The convergence of material science, biotechnology, and computer science with data driven intelligence not only enhances clinical outcomes but also promises to reduce costs and healthcare burdens all over the world. Overall, these developments are contributing to more effective, minimally invasive, and patient-centered solutions. Continued research and development in these areas will likely lead to more groundbreaking innovations that will improve healthcare.

Abbreviations: CRISPR-Cas9: Clustered regularly interspaced short palindromic repeats associated protein 9, PEGDA: Poly (ethylene glycol) diacrylate, GelMA: Gelatin methacryloyl, PLGA: Poly (lactic-co-glycolic acid), HSC: Hematopoietic stem cells, CAR-T: Chimeric antigen receptor T cell, WBAN: Wireless body area network,

IoMT: Internet of medical things, PLD: Pulsed laser deposition, LENS: Laser engineered net shaping, GET: Graphene electronic tattoo, CNN: Convolutional neural network, RNN: Recurrent neural network.

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Disclosure of Interests

The authors have no competing interests to declare that are relevant to the content of this article.

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