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Review Article

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Application of Biomaterials in Tissue Engineering: A Review

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ABSTRACT

Degeneration or loss of organs, tissue component or cell unit remains the consequences of home or sport injuries, trauma, wear and tear of various diseases in human beings. The transplantation of tissue for the treatment of these diseases in different forms like autograft, allograft or xenograft posed potential benefits as well as risks. Due to the presence of many risk factors over health benefits of using allograft and others techniques, an alternative field termed as Tissue Engineering (TE) and Regenerative Medicine (RM) has been employed to enhance healthcare delivery in the core areas of regenerating, replacing and repairing of worn out or diseased tissues and organs. The most relevant areas of Human Tissue Engineering include cells, biomolecules, manufacturing factors, safety and performance issues, informatics, modelling, clinical data and most particular, biomaterials. This study concentrates on the various biomaterials and their applications in tissue engineering. Biomaterials (natural, synthetic or composite) have been used for various tissue engineering applications such as bone (to produce bone graft), cardiac (to develop bioartificial heart, cardiac patches and artificial heart valves), peripheral nerves, cartilage and skin repair, replacement and maintenance in order to enhance healthcare delivery based on physical, chemical or mechanical properties.

Keywords: Biomaterials; Tissue Engineering; Applications; Relevance

INTRODUCTION

Home or Sport Injuries, trauma, toxic substances, wear and tear and most in particular majority of various diseases in human beings of this global population result to failure, damage, degeneration or loss of one or more organs, tissue component or cell unit which requires different therapeutic measures to promote the regeneration, repair and replacement of worn out or damaged tissues or organs [1-4]. A typical study was the case of a liver failure where toxin was ingested and the only treatment options were supportive measures and transplantation as recorded by SN Bhatia et al. [4]. The transplantation of tissue for the treatment of the disease in different forms including autograft, allograft or xenograft, posed potential benefits as well as risks. The risks involved in applying those techniques were issue of rejection by the victim's immune system, infection, hematoma, pain and also cost. Due to the presence of many risk factors over health benefits of using allograft and others techniques, an alternative field termed as Tissue Engineering and Regenerative Medicine (TERM) was introduced to enhance healthcare delivery in the core areas of regenerating, replacing and repairing of worn out or diseased tissues and organs.

Tissue Engineering and Regenerative Medicine (TERM) are fascinating interdisciplinary subfields in Biomedical Engineering and Technology which combine cellular and molecular biology, chemistry, medicine, engineering and many other subject areas to curb or reduce the mortality and morbidity rates linked with worn out or damaged tissues and organs of the Human body [3]. TERM can also be defined as a growing multidisciplinary field that focuses on regenerating functional cells, tissues as well as organs for augmentation, repairing and replacement of lost function of biological materials. There is distinct difference in Tissue Engineering (TE) and Regenerative Medicine (RM). TE emphasizes on engineering and manufacturing part of tissue replacement whereas RM gives an alternative treatment to change medical practice today and involves in cellular regenerative area of tissue replacement [5]. Nevertheless, both of them restore body function and sometimes used interchangeably. This review focuses on the various biomaterials used in tissue engineering.

TISSUE ENGINEERING IN SPECIFIC AREAS

The relationship between TE and RM are illustrated in Figure 1. RM is seen as a bigger and more generalized field than TE which is quite narrower. TE contributes ample knowledge to cell and molecular biology through the generation of tissues *in vitro* or regeneration of tissues *in vivo* with grown cells in 3-D scaffolds. In vitro reveals the study of phenotypes of various cells and their behaviour [6]. TE regenerates an individual's organs or tissues that are biocompatible and bio-functional with little or no immune rejection to replace worn out ones [7]. This field acts as an alternative medical treatment. The tissue engineered skin and cartilage were the first to be produced and used to treat severe burns, wounds and joint injuries. Some other regenerative tools have been produced and are still being produced for the repair of bones, bladder and other medical challenges [8]. The most relevant areas of human tissue engineering include cells, biomolecules, manufacturing factors, safety and performance issues, informatics, modelling, clinical data and most particular, biomaterials (e.g. scaffolds), which is the focal point of this review article as illustrated in Figure 2.

Cells

These are the smallest units of life that could be autologous (from the same patient), allogenic (from a donor), xenogeneic (animal cells), stem cells or some cells with certain degree of differentiation. The cell source selection is a very critical decision to make when designing biomaterials in TE for clinical applications. The cells, however, must be able to fulfil basic requirements including integrating themselves in the specific tissue and secrete different growth factors and cytokines that could activate the endogenous tissue regeneration program. A typical example of the cell used in cell based techniques is the progenitor cell. Some alternative cell types such as embryonic stem cell (ESC) and adult stem cell (ASC) are also used for TE [9-11].

Biomolecules

These are signalling molecules that represent an important tool in TE to modulate areas of cell biology, from proliferation to specific phenotypic features of fully differentiated cells which could be termed as the differentiation factors, growth factors and other major factors.

Manufacturing Factors

Majorly include 3D tissue growth, cell expansion, the utilization of bioreactors, cell and tissue storage. The controlled release of various factors from scaffolds permits the constant renewal, having a great potential to direct tissue regeneration and formation [12].

Biomaterials

These are materials that augment, replace or repair worn out tissues and it can be influenced by physical or chemical methods, the growth, organization, differentiation of cells in the formation of the desired tissue. One of the most promising and important biomaterials in TE is the scaffold and ability to design as well as develop suitable biomaterials for remaking the in vivo microenvironment, usually provided by the extra cellular matrix (ECM) is the ultimate goal. Therefore, the right biophysical, biomechanical and biochemical procedures and signalling should be imbibed and explored for absolute proliferation, differentiation, maintenance and function [12]. In biophysical signalling, the ECM provides anchorage to cells. The ECM highly porous nanostructure gives the material a 3-Dimensional (3D) environment and biochemical signalling via two (2) mechanisms such as the binding of a wide variety of soluble growth factors (GF), enzymes and other effector molecules that control their diffusion and local concentrations, and the exposure of specific motifs that are recognized by cellular adhesion receptors [13-20]. For mechanical signalling to occur, the cells will be able to notice the matrix stiffness. TE specifically delves into the mimicking of the most important ECM properties to design and develop well customized scaffolds which are solely dependent on the recreation of the tissues [21-26]. For accurate and precise design of the scaffold, parameters such as scaffold dimensions pore size, chemical signalling motives and stiffness should be investigated.

The biomaterial designed should possess some specific properties for proper clinical applications. These properties include biocompatibility and biodegradability which permits the replacement of scaffold by proteins synthesized and secreted by native or implanted cells [1]. Biomaterials should also be easily produced, purified and processed [1]. Above all, the materials must be clinically compliant. Scaffolds for TE accommodate and guide cells in 3D space until their physiological matrix environment is produced [27-30]. These scaffolds act as a vehicle to deliver exogenous cells, growth factors and genes into the body. This can also be classified into two categories, namely, natural and synthetic [12]. Among all these areas of tissue engineering, the engineered biomaterials which will be discussed in full details play a significant role of providing cells with a microenvironment for specific growth and differentiation [31-35].

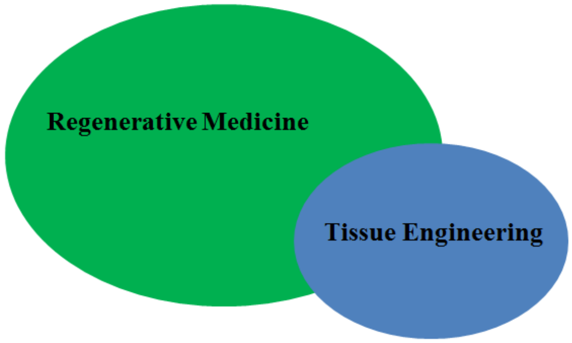

Figure 1. Tissue Engineering and Regenerative Medicine [43]

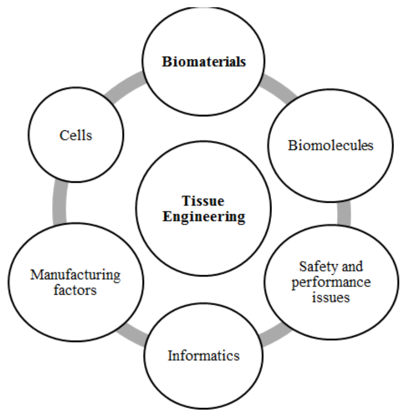

Figure 2. Relevant areas of Tissue Engineering

BIOMATERIALS FOR TISSUE ENGINEERING

Biomaterials are substances rather than drug either natural, synthetic or both in origins, which act as a whole or part of a system that augment, replace or repair any worn out tissue or organ of the human body [24]. In the first Consensus Conference of the European Society for Biomaterials (ESB) in 1976, a biomaterial was defined as 'a nonviable material used in a medical device, intended to interact with biological systems' [36]. The biomaterials create a biomolecular and spatial environment that is needed for cell proliferation and vascularization in TE and RM. Biodegradable scaffolds that aid in the formation of nouvelle tissues serve as a proffered solution in TE [37-39]. The various classes of biomaterials in TE include natural, synthetic and composite biomaterials.

Classification of Biomaterials

Natural biomaterials: Natural biomaterials which include protein-based biomaterials (collagen, silk fibroin, gelatin, fibronectin, keratin, fibrin, eggshell membrane) and polysaccharide-based biomaterials (e.g., hyaluronan, cellulose, glucose, alginate, chondroitin, and chitin and its derivative, chitosan), are promising subsets of biomaterials employed in tissue engineering because of their bioactivity, biocompatibility, tuneable degradation and mechanical kinetics and their intrinsic structural resemblance of native tissue ECM. They also promote biological recognition which helps cell adhesion, proliferation, cell differentiation and function. Protein-based biomaterials are made from animal and human sources which include bioactive molecules that mimic the extracellular environment whereas polysaccharide-based biomaterials usually received from algae, as in the case of agar and alginate or from microbial sources such as the case of dextran and its derivatives [19,20]. Another type is decellularized tissue-derived biomaterials made by the removal of all cellular and nuclear materials from native tissue/organs, as in decellularized dermis, heart valves, blood vessels, small intestinal submucosa (SIS) and liver, among others [15]. Natural biopolymers are often processed using environmentally-friendly aqueous-based methods [15]. These biomaterials possess poor mechanical strength and inconsistent in composition and properties. Another issue with naturally derived polymeric materials is the variability inherent in the production of the materials and the potential of the materials to evoke an immune response [15]. Advances in TE include the redesign and development of biomimetic and biocompatible scaffold to incorporate ligands mimicking the natural ECM is of utmost importance in enhancing healthcare delivery [40-49].

Synthetic biomaterials: Poly (α-hydroxy acids) include polylactic acid (PLA), polyglycolic acid (PGA) and their copolymer such as poly(lactic-co-glycolic acid) (PLGA) are synthetic biomaterials widely used as matrices and templates in biomedical engineering and bioengineering to mimic ECM systems of human beings that in other words control or coy the functions of the biomaterials. According to the report of Liu and Ma [50], these synthetic polymers have been nontoxic degrading products (lactic acid and glycolic acid) and produced via simple chemical hydrolysis of the polymers which cleared away by normal metabolic pathways. These materials possess tensile strength, mechanical modulus and degradation properties which can be utilized for target applications by changing the lactide/glycolide proportions and polymerization parameters. They have been used to produce urethral tissue as well as bladder material for replacement in patients suffering from idiopathic detrusor or neurogenic bladder [2,49]. They do not give an immune response due to lack of biologically functional domains. However, some synthetic polymer templates incorporate biologically functional domains in order to develop biomimetic scaffolds. For instance, collagen or serum coating and the synthetic polymeric scaffold allow initial cell attachment and ECM deposition while ceramic (calcium phosphate) and coating synthetic polymeric scaffolds work well for bone tissue engineering. Other relevant techniques have been applied and are still in the developmental process for proper treatment of diseases [15]. Some typical biomaterials (both natural and synthetic) for applications in TE are presented in Figure 3 and Table 1.

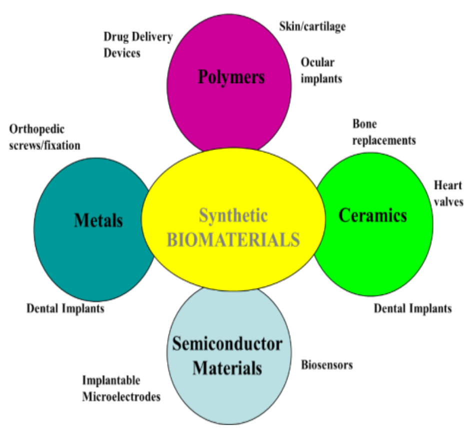

Figure 3. Synthetic biomaterials used for Tissue Engineering [24].

Table 1. Some examples of biomaterials used in TE discipline [24]

S/N	Material	Applications
1	Silicone rubber	Catheters, tubing
2	Dacron	Vascular grafts
3	Cellulose	Dialysis membranes
4	Poly(methyl methacrylate)	Intraocular lenses, bone cement
5	Polyurethanes	Catheters, pacemaker leads
6	Hydrogels	Ophthalmological devices, Drug Delivery
7	Stainless steel	Orthopedic devices, stents
8	Titanium	Orthopedic and dental devices
9	Alumina	Orthopedic and dental devices
10	Hydroxyapatite	Orthopedic and dental devices
11	Collagen (reprocessed)	Ophthalmologic applications, wound dressings

Biocomposites as biomaterials: Biocomposites are materials made up of two or more chemically or physically distinct with synergistic properties, suitably arranged or distributed materials with an interface separating them. Biocomposites have a continuous bulk surface termed as the matrix and the dispersed, non-continuous phase called the reinforcement which normally has superior mechanical or thermal properties to the matrix. The region between both of them is called the interphase. The bulk phase accepts the load over a large surface area and moves it to the reinforcement phase, which altered the mechanical properties (strength, toughness, stiffness or fatigue resistance) of the composite comfortably in order to meet the needs [37]. A typical example is in structural polymer composite where the reinforcement is more stiffer than the matrix which in other words makes the composite much more stiffer than the bulk polymer and leads to a reduction in bulk strain on deformation. The three (3) classes of composite materials include polymer-matrix composites (PMCs), ceramic-matrix composites (CMCs) and metal-matrix composites (MMCs). The later composite is a well advanced one which is not so common in biomedical applications and may be used for high-temperature applications [37].

Properties of Biomaterials

In the past few years, the utilization of biomaterials as medical implants progressively increased the life expectancy, lifestyle and enhancement in implant technology [33]. Biomaterials' development with specific characteristics speed up the recovery process of the damaged tissue either caused by accident, disease or also tries not to stimulate any allergenic or inflammatory response [45]. The characteristics of biomaterials include bio-inertness, bioactivity, chemical and mechanical stability, biodegradability, bio-functionality, bio-stability and bio-tolerance [31], which falls into various properties including physical, chemical and mechanical. The biomaterial could also be sterilisable so as to prevent rejection, irritation or any form of problem at the locus of the implant [50-60].

The biocompatibility of the biomaterial is dependent on the response of the human body when in contact with the foreign body. It ensures that there is no harmful effect at its locus of operation. Biocompatibility of the biomaterial works well with other characteristics like hemocompatibility, toxicity, tissue compatibility, bio-functionality [59] and typical examples are the synthetic polymer and metallic materials [31]. Bio-inert materials are also tolerated by the body and do not cause any chemical reaction between the material and the tissue. Some examples include zirconia, titanium, alloys, carbon and alumina [61, 62, 63,…, 66]. The bioactive materials cause an interaction between the implanted material and bone tissue, thereby, promoting the coating of the bone cells. Typical examples include hydroxyapatite, calcium phosphate, vitroceramics and calcium phosphate compound based glasses materials [31]. The biodegradable biomaterials like biopolymers are degrade, solubilize or get absorbed when in contact with the body for a particular period of time. Sterilization of these biomaterials possessing all these characteristics keeps them free from microorganisms and makes the biomaterial ready and available for implant [67, 68, 69]. These biomaterials also have some basic properties including physical, chemical and mechanical biological that make them suitable for implant.

Physical properties: This property aids cell adhesion where there exists a basically physical interaction between the biomaterial and cell. This interaction could most definitely be influenced by environmental factors, cell behaviour and biomaterial surface properties (roughness, wettability, filler, softness and chemical composition [14]. The cell responses to surface and architecture of tissue engineering scaffolds was examined by Chang and Wang [14]. The study employed positive and negative charged ions. It was observed that biocompatibility, cellular affinity and cellular differentiation on clean biomaterials surfaces of implant were improved. In the report, a 2-hydroxyethyl methacrylate (HEMA) gel having positive charges yielded better adhesion and spreading of osteoblasts and fibroblasts rather than when using the neutral or negative charges [70, 71, 72,…., 81].

Chemical properties; Most compositions, chemical and physical properties affect the type of cell bond and determine the reactivity as well as chemical stability of the biomaterial. Chemical stability is a crucial property to note with regards to biocompatibility [82]. When corrosion occurs, it causes severe reactions to the surroundings of the implant. This caused by increase in concentration of ions around the implanted material, thereby, causes swelling and pain. Besides, the corrosion wastes could move to other body regions thereby causing unbearable reactions for the implant and the tissue. Corrosion affects chemical stability as well as mechanical integrity of the both implant and tissue [82]. It has been reported that corporeal ambience caused biodegradation of the biomaterial due to corrosion and degradation can also be influenced by the sterilization process in which the material is subjected to [34, 35, 47].

Mechanical properties: Young's modulus, ductility, tensile strength, yield strength, compression strength and fatigue, and wear debris are some of mechanical properties of biomaterials and solely depend on the type of human tissue involved. For instance, soft elastic material is used for brain tissues (0.1-1 kPa) and hard ones are used for mineralized bones (30 kPa and above) [72]. Young's modulus enables uniform tensile distribution and prevents stress shielding and attaching the implant. Biomaterials possess high value of yield and properties of compression strength which prevent fractures but enhance functional stability. Ductility aids in modelling the formation of the biomaterial and dental biomaterials too. Increase in hardness of biomaterials results to a decrease in wear incidence as well as the increase in tenacity reduces any form of fracture [76-93]. These properties evaluate the success and biocompatibility of the material. Some biomaterials that have the potential to bear the cyclic efforts without cracking in the process are comprised of polyester, polyurethane and metals. They are chiefly used for dental, orthopaedic and cardiovascular implants [22]. For the replacement of intervertebral disk, the biomaterials needed must have fair properties of compression strength since the backbone undergoes compression usually caused by body weight or contraction loads of the muscles surrounding the bones. For example, compression forces during dynamic lifting were estimated in up to 2500 N and the intradiscal pressure of approximately 1 MPa during routine activities such as climbing steps (0.5-0.7 MPa) and jogging (0.35-0.95 MPa) [88]. The development of bio-adaptive materials having mechanical properties similar to those of damaged tissues or organs could favour cell adaptation [92]. The design and development of more relevant properties play a major role for advances in medicine and engineering.

APPLICATION AREAS OF BIOMATERIALS IN TISSUE ENGINEERING

Biomaterials have been used in various areas of TE to regenerate tissues for augmentation, repair or replacement. These biomaterials have been vastly applied in bladder, tendons, ligament, kidney, liver, heart valves, myocardial patches, bone, cartilage, pancreas, cardiac, islet of Langerhans, vascular and skin [12,75**].** Some of these developments are further described below.

Bone TE

In biology, a bone is classified as a calcified connective tissue that contains natural organic mineral composed by collagen type I and calcium phosphate, hydroxyapatite specifically known to give the basic structure and protection to the internal organs [78]. The inner layer has high porosity (between 50 and 90%) and less mechanical strength whereas the outer layer has low porosity (between 10 and 30%) and high mechanical strength. Bones possess high vascularized network that permits the supply of oxygen and nutrients as well remove waste products which makes it difficult for scaffold, an *in vitro* model, to be produced for Bone TE [7,25,60,78]. Interestingly, bones have the capability to regenerate, remodel and repair in response to injury. In order to avoid using autograft, allograft or xenograft due to infection, immunological rejection, disease transmission and many other reasons, the development and application of 3D porous scaffold with bone mimicking features was considered. Bio-ceramic scaffolds consisting of hydroxyapatite (HA) have been produced and used because it is biocompatible, bioactive, support and promote new bone formation and mimics the mineral component of the natural bone [11]. However, the low mechanical property puts the biomaterial at risk of being fractured when heavy load applied which may result to no regeneration of large bone defects, thereby, caused use of composite biomaterials (HA and collagen I) and improved potentials using *in vivo* analysis [93]. Others such as HA and alginate, gelatin or chitosan have been investigated to generate the most suitable bone substitute [15,39]. More research is carried out to produce a biomimetic material that provides a better environment for cell-matrix interaction, adhesion and proliferation of bone cells (differentiated osteocytes) [75], osteo-inductive, promote the formation of new bone through biomolecular signalling and progenitor cell recruitment [12]. Nanoparticles have been developed to release osteogenic factors such as Bone Morphogenic Proteins (BMPs) as well as improve *in vitro* and *in vivo* osteogenic differentiation in bone defect models [78]. Also, Mesenchymal Stem Cells (MSCs) had stabilized vascularization and form functional bone in vivo, which resembles an autologous bone graft [10, 17, 85].

Cartilage TE

Cartilage is a human connective tissue that is stiff and flexible, made up of chondrocytes embedded in a highly hydrated ECM. The different classes of cartilage are hyaline, elastic and fibro with different components of ECM have been developed using TE techniques for the purpose of cartilage repair, joining of cells with scaffolds, mechanical stimulation and growth factors (GFs) are developed [57]. Natural scaffolds such as collagen [59], fibrin [23,81], agarose or gelatin and synthetic scaffolds including polyurethane [29], polyethylene glycol [8,9] and elastin based polymers [55] have been significantly used to incorporate signalling motives that can recreate cartilage ECM [13]. With the aging members of our communities and the entire world, degenerative joints challenges have been on the increase and may also affect the young sport players as a result of sport injuries. TE has enabled these players to smile again by producing TE cartilage from the victim's chondrocytes grown on many substrates which definitely reduced the need for implants for such victims [75].

Cardiac TE

The heart is a muscular organ in the human body that pumps blood throughout the arteries and veins so as to supply oxygen and nutrients in the whole body. The organ comprises of epicardium, myocardium and endocardium that perform specific functions including self-contraction [13]. The ability to contract is so much required for blood pumping and hence, dysfunction or loss of cardiomyocytes leads to heart failure (HF) which is one of the leading causes of death and danger in the entire world. Heart transplantation has been a most promising and alternative solution where the drug therapies failed [13]. Due to the unavailability of transplants from potential donors as well as the immune response of the host recipient, cell therapies and tissue engineering have promising future in the area of cardiac regeneration or repair. The three therapeutic approaches include direct injection of isolated cells suspension [58,63,64,90]; injection of biomaterials with or without cells and/or GFs [16, 36, 40, 41, 48, 51, 73] and implantation of biomaterials previously prepared with or without cells and/or GFs [66, 68, 86, 87]. Some cells have proven to be good ingredients for Cardiac TE. Embryonic Stem Cells (ESC) differentiate into cardiac lineage but the implantation of them *in vivo* might lead to the production of teratomas [18, 44] or arrhythmias [52]. Chitosan has been utilized as soft and injectable material to improve myocardial infarction microenvironment [51]. Chitosan has been modified in several ways to improve its mechanical property or its effect on cell differentiation [53] while maintaining its biological properties [73]. Proteins such as collagen, gelatin, silk, vitronectin, fibrin and laminin with or without modifications have been studied for their effect on cell behaviour both in 2D and 3D microenvironment through *in vitro* study [53, 73]. Nanoparticles or micro encapsulations for growth factors or cell delivery gives slow release and a safe refuge to escape recognition by the host immune system [12, 13]. Hydrogels due to its advantages such as substrate immobilization for its administration as a strong tool for regenerative in cardiac TE could be investigated as alternative vehicles for release or immobilization of growth factors. Stamm et al. [84] reported that the important factors to be considered for cardiac TE include choice of cells, other materials, growth factors, patient selection, cell transplantation and survival, dose, age, regulatory body and funding.

Pancreas TE

Pancreas is an essential organ in the human body composed of the exocrine and endocrine. The endocrine is made of 5 types of cells namely α, β, δ, ε and polypeptide cells in the islets of Langerhans which aids in secreting hormones into the bloodstream. The most existing cells are the β cells (80%) which produce insulin into the bloodstream. The malfunctioning or destruction of β cells by the immune system results to Type I Diabetes [62]. The most prevalent method of treating this disease is to use a daily injection of exogenous insulin. Based on this reason, TE can be used to regenerate and replace the damaged cells for regulated insulin-producing cells [62]. A scaffold, Matrigel™ had been used to get nouvelle sources of functional β cells knowing well that a major issue of islet transplantation is the lack of donor tissue [46]. Bonner et al. [6] reported that human ductal cells grown in 2D as an epithelial sheet and covered with a thin layer of Matrigel™ could be differentiated into insulin positive cells. The regeneration as well as transplantation of pancreatic islets has improved over the years to the understanding of complex microenvironment that surrounds β cells as well as the advances made in the field of Biomaterials and immunology. Nevertheless, long term survival of transplanted islets and shortage of islets (more challenges) should be visited and tackled.

Vascular TE

Vascularization is a means by which blood vessels and capillaries are made in living tissues. The anatomy of blood vessels has three layers namely the Tunica Intima, Tunica Media and Tunica Adventitia. They maintain a specific balance in blood distribution to avoid an insufficient or excessive delivery of oxygen and nutrients that may result to the development of several diseases such as tumours which are associated with new blood vessel growth to fulfil the metabolic demand of the altered cells [30]. The technique employed to vascularize engineered tissues may include scaffold design, angiogenic factor delivery and also in vitro or in vivo pre-vascularization [12]. According to Dahl et al. [21], Wang and Guan [91] reports, the development of vascularized grafts as structures contribute to the repair of the damaged vasculature. The use of an optimized technique in TE should be greatly considered in this area of specialization for safe delivery of oxygen, nutrients and soluble effector molecules as well as removal of metabolites in order to improve regeneration of the damaged tissue.

Skin TE

The human skin has a structure that specifically provides water, electrolyte and bacteria proof barrier to the outer world as shown in Figure 4 [54]. The human skin may no longer perform its specific functions due to high susceptibility of the patients to bacterial infections emanating from some fatal illnesses including chronic non-healing ulcer and burns as shown in Figures 5 and 6. The cells have already been grown on several substrates for the treatment of severe burns or difficult conditions such as diabetic ulcers. The biocompatible and physical barrier potentials to loss of fluid and infection have reported to aid regeneration of the skin for the patient [75].

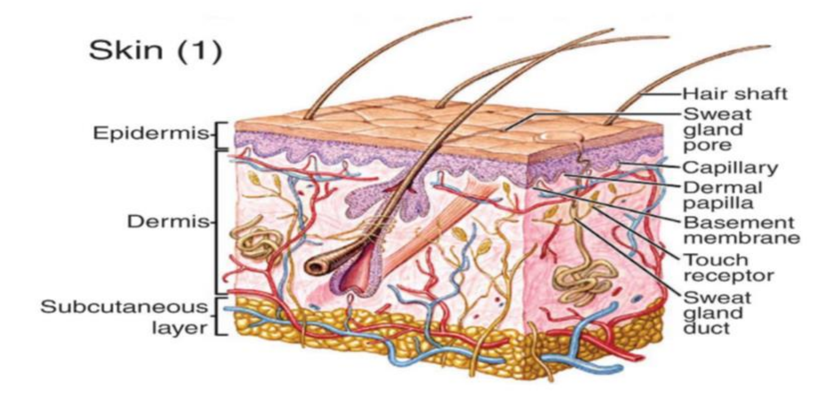

Figure 4: The structure of the human skin [54].

Figure 5: The neuropathic diabetic ulcer of a patient's foot (a) failed to heal for 3 years and (b) healing of the same foot after 8 years of applied patient's own cells [54]

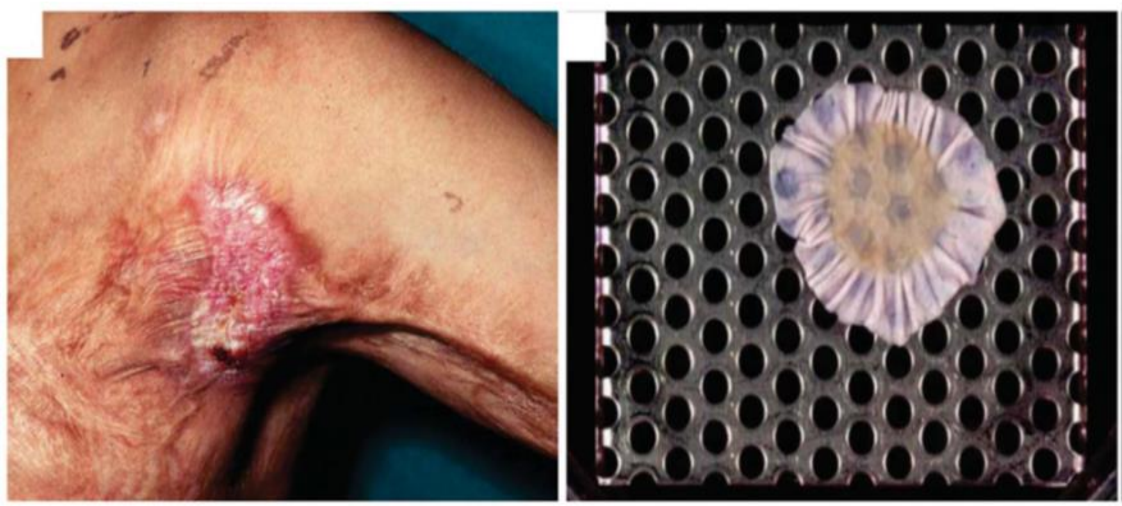

Figure 6: (a) The application of TE skin to care for extensive contraction on a patient's burn injury (b) Keratinocytes contract human allodermis in the laboratory [54]

Peripheral nerve TE

A severed peripheral nerve from an accident may lead to a gap between the severed nerve endings. This may be too wide for conventional microsurgery to be considered. Biomaterials needed to provide a conduit in order to enable regeneration-promoting Schwann cells to grow in a guided manner to bridge such injuries [75].

Cornea TE

The fact that the cornea is avascular is a major challenge that obtained its physiological needs from lachrymal fluids at the front and aqueous humour due to need for donor corneas and rejection. The use of suitable scaffold and the patient's limbal cells to colonise the substrate was considered in the recent research for a new cornea by tissue engineers [75].

PROS AND CONS OF BIOMATERIALS FOR TISSUE ENGINEERING

Biomaterials either natural or synthetic (collagen, metals, ceramics and polymers) are applied in the medical field for tissue repair or replacement, heart valves and implants. These materials are chosen appropriately due to its benefits over demerits. Some metals such as gold, nickel-titanium alloy and stainless steel are usually considered and used after proper sterilization for pacemaker challenges, dental implants, bone and joint replacements which are quite resistant to fatigue and degradation but sometimes corrode due to chemical reaction with the body enzymes and acids [79]. Thus, result to toxicity of the body. Cotton, silicones and nylon are polymeric materials used in tissue repair, breast implants and heart valves due their characteristics such as easily manufactures, modify, and absorb relevant nutrients and water from the blood, but wear and tear due to intensive interaction with the human body and biodegradability [79]. Ceramics such as zirconia, alumina and pyrolytic carbon are used for dental and orthopaedic implants. This is because they are strong and chemical inert, compressive strength needed for bone implants, biodegradable due to chemical and structural properties that mimic the mineral phase of human bone, exhibits very low elasticity and hard brittle surface [61]. Unfortunately, there is difficulty in manufacturing forms, the implants become loose as well as dislodged and reduces the bone ingrowth. Then, composites including allograft, xenograft or bioglass-ceramic produced from two or more materials have combine properties from all individual property [79]. Composites are usually strong with low density and high resistant to corrosion, but relatively high cost and rigidity in shape. Collagen, a natural biomaterial provides strength as well as structural stability to tissues in the body (tendon, cartilage, blood vessel and bone) [61]. The transplantation of islets allows the control of glucose level but the major challenge in this situation is the need to use immunosuppressive drugs to overcome rejection of cross-patient transplanted islet cells [12]. Other challenges such as acute toxicity, genotoxicity, neurotoxicity, immunotoxicity, carcinogenicity, genotoxicity and endotoxins have been reported by Domin [24].

FUTURE PERSPECTIVE

The development of the use of biomaterials has contributed significantly in improved properties, but more challenges still exist in the areas of engineering well vascularized bone that resembles and acts as the natural bone blood vessels, proffering better solutions to treat cardiomyopathies, body toxicity, integrating the engineered construct with the native host tissue and more efficient biological processes during bone tissue regeneration.

CONCLUSION

The potential benefits of application of biomaterials to tissue engineering outweigh the risks involved. Therefore, more improved technologies and tools should be developed in areas of bone, cartilage, skin, vascular, peripheral nerves, cardiac and dental tissue engineering for enhancement of healthcare delivery.

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