Chapter 8
Applications of Hard and Soft Tissue Engineering in Dentistry

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1 Introduction

It is vital that teeth and oral tissues are protected since they play a crucial role in human function. Strong masticatory stresses and physical changes can result in changes in oral tissues, such as dental caries and periodontitis [1]. As a therapeutic measure, the use of biomaterials has played a role in helping to repair damaged oral tissue. Concerns are arising from exposure to body fluids within the mouth leading to a degradation of the material. Moreover, potential cytotoxic and harmful products can be released through the use of products in the oral environment. Therefore, tissue engineering has replaced more conventional biomaterial innovations.

Tissue engineering has been widely implemented to develop functional alternates for the damaged tissues [2–12]. Tissue engineering application can be based on three components—the cell source, scaffold, and bioactive molecules [9, 11, 13–19]. Research has been conducted with a vast amount of scaffold materials, such as natural polymers [20–29], natural silk [30], synthetic polymers [9, 15, 20, 31–33], and ceramics [34], as an attempt to regenerate dental tissues. Tissue engineering has been developed to be effective with pulp-dentin complex regeneration [20], guided tissue regeneration [35], and tooth [36] and salivary glands [37].

The increasing amount of research regarding tissue engineering and regeneration has made it an emerging field. However, due to many complications and challenges, only a few products have been used for clinical applications. We hope that concepts regarding tissue engineering and their applications toward dentistry are made aware to the public, and challenges regarding these applications are faced.

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L. Tayebi (ed.), *Applications of Biomedical Engineering in Dentistry*,
https://doi.org/10.1007/978-3-030-21583-5_8

2 Tissue Engineering Strategies

Tissue engineering is poised to have a significant and exciting impact in the field of dentistry. As it relates to dentistry, bone, cartilage, dentin, dental pulp, salivary glands, skin, and oral mucosa can be bioengineered via three primary methods—conduction, induction, and cell transplantation [38].

The conductive method employs the use of a polymeric barrier membrane, which seals off the intended area of tissue regeneration solely to cells that enhance tissue growth, while preventing unnecessary, or potentially harmful, cells from entering the site of the regeneration [38]. Nyman et al. demonstrated such a method, as they were able to enhance the growth of periodontal supporting cells while preventing gingival epithelial cells and connective tissue cells from entering the area of regeneration [39]. One significant benefit of this method is its ability to form bone in a well-controlled and usual manner [38].

Another approach to tissue engineering, known as the inductive method, sends biological messages to cells near the site of damage, facilitating the formation of new bone [38]. Urist demonstrated that BMPs can form new bone at places that usually are unable [40]. This process is made possible through polymeric carriers transporting inductive factors, like bone morphogenic proteins (BMPs), to the desired site of regeneration [38]. Major polymers include collagen of animal origin and synthetic polymers of lactic acid and glycolic acid [38]. The speed and quantity at which inductive factors are released are dictated by the rate of carrier breakdown [41]. Discoveries in this area of research have led to the widespread production of BMPs, now enabling individuals with bone defects to regrow and heal such wounds successfully [38].

The last method is cell transplantation, which transplants cells cultivated in a laboratory into the desired target [38]. This method requires interaction and cooperation between a doctor, engineer, and a cell biologist [38]. First, an individual is biopsied by a doctor to acquire information regarding the cells present in the individual [38]. Then, the biopsy is sent to the laboratory, where a cell biologist appropriately reproduces the specific cells [1]. Next, an engineer will fabricate a biodegradable polymeric scaffold, which is ultimately integrated with the cells of interest [38]. Finally, the scaffold is transplanted into the individual by the doctor [38]. After successful cell transplantation, the scaffold eventually breaks down but also guides the successful formation of healthy tissue [38].

The schematic representation of the cell-matrix tissue engineering strategy has been given in Fig. 8.1.

3 Application of Tissue Engineering in Dentistry

3.1 Tooth Regeneration

Whole tooth regeneration poses a difficult, yet vastly improving, area of research. Multiple studies have been performed with varying success in this area of study.

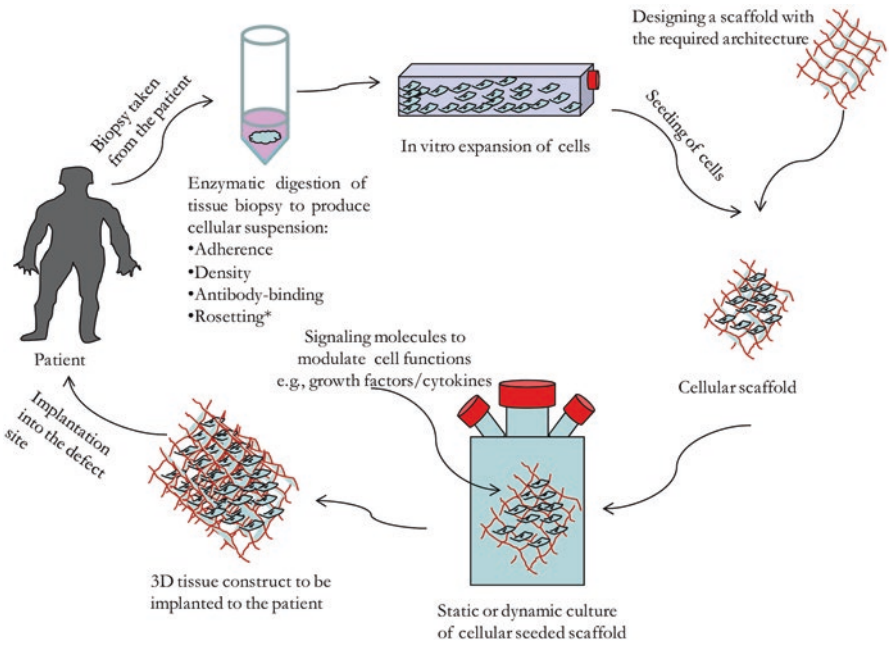

Fig. 8.1 Schematic representation of cell-matrix tissue engineering strategy [42]

Using tooth buds from the third molars of pigs, Young et al. were the first to successfully regenerate tooth structure containing enamel and dentin [43]. Biodegradable scaffolds containing pig tooth bud cells were transplanted into rats, and 20–30 weeks later, defined tooth structure was present, although the size of the tooth was very small [43]. Likewise, Duailibi et al. were able to regenerate teeth using tooth buds from rats [44]. Tooth bud cells were isolated from the rats between 3 and 7 days postnatally and grown in vitro for 6 days with polyglycolic acid (PGA) and polylactic-co-glycolic acid (PLGA) scaffolds [44]. It was determined that tooth bud cells isolated from rats 4 days postnatally and seeded onto PGA and PLGA scaffolds resulted in the most mature tooth structure [44]. Xu et al. designed a novel silk scaffold, with specified pore sizes of 250 and 550 μm, to facilitate the growth of tooth bud cells from a 4-day postnatal rat [45]. It was determined that scaffolds with pore sizes of 550 μm best supported the development of osteodentin-like tissue and the intended tooth shape; however, no enamel was detected [45]. With a more unique approach, Nakao et al. placed epithelial and mesenchymal cells within collagen gel drops for 2 days, promoting growth before transplantation into mice; after 14 days, ameloblasts and odontoblasts were detected in the mice teeth [46].

Although many complex factors are required to achieve a structurally sound and morphologically acceptable tooth, research is currently progressing towards this desired outcome. Imagine a world where teeth can be regenerated with relative ease to replace missing teeth—it surely will be a revolutionary advancement.

3.2 Bone Tissue Regeneration

Bone damage is a serious health concern that may result from injuries, infections, and birth defects [38]. Conventional surgical methods—like autografts, allografts, and synthetic biomaterials—are not without their shortcomings; as a result, bone tissue regeneration has become an area of research interest to offset the inadequacies of conventional bone repair methods [38].

All three primary methods of tissue engineering may be employed for successful bone regeneration [38]. Conductive and inductive methods may be used to regenerate areas of minor bone damage [38]. When conductive measures cannot sufficiently repair bone, BMPs are then inductively bioengineered [38]. Lastly, cell transplantation uniquely enables researchers to create large bony structures, like the mandible, before surgery. Bone precursor cells are cultured onto scaffolds with careful consideration for the essential environment and factors needed for proper functioning. Gradually, the scaffold will break down, leaving bone shaped in the form of a mandible [38].

3.3 Cartilage Tissue Regeneration

Cartilaginous tissue has become an area of interest for researchers in developing cartilage transplantation methods, as this tissue has a limited ability to repair itself. Trauma and degenerative diseases, such as osteoarthritis, can lead to cartilage destruction, precisely at the temporomandibular joint (TMJ). Polymer scaffolds have been constructed to mimic the same mechanical properties as cartilage, leading to a novel discovery in cartilage reconstruction. At the forefront of this engineering project is the development of cartilaginous cell transplantation to counteract the limited regeneration capability of the tissue and its lack of inductive molecules. The newest technique in cartilage transplantation is to use cells without a carrier to repair small defects. Animal models have proven that new cartilaginous tissue relating to the maxillofacial region, such as the nasal septum and temporomandibular joint, can be scientifically engineered using biodegradable scaffolds to transplant these new cells [38].

The TMJ is a bilateral joint connecting the mandibular condyles and temporal bones of the skull, with a fibrocartilaginous disc between these two bones. This disc functions as the support of the joint and absorbs any stresses and trauma. Due to the complex structure of the TMJ, there are minimal treatment options available for the management of disorders relating to this joint. In 1991, Thomas et al. [47] produced the first in vitro cartilage tissue analog in an animal model by way of organ culture. The tissue produced had the same clinical appearance and physical properties of the TMJ disc; this experiment provided a method for in vivo autografting as an alternative way to treat TMJ disc problems. Three years later, Puelacher et al. [48] tested the effectiveness of the newly engineered tissue growth of the TMJ disc by placing

dissociated chondrocytes on a synthetic biodegradable polymer in vitro and then transplanting this into mice, and the resultant engineered cartilage was visualized. At the conclusion of the study, all implants that were seeded with the chondrocytes displayed hyaline cartilage, while still allowing the scaffolds to maintain their original shape. This study proved the imminent possibility of scientifically engineered synthetic TMJ disc tissue.

The research conducted in the 1990s was followed by studies targeting TMJ tissues. Abukawa et al. [49] successfully reconstructed the mandibular condyle by using similar tissue-engineered bone constructs that were made by combining biodegradable polymers and porcine mesenchymal stem cells (pMSCs). Weng et al. [50] determined in their study that bone and cartilage composites can be successfully engineered to serve as substitutes to the mandibular condyle. The junction of bone and cartilage was proven to be similar to the common junction of these composite tissues in articulating joints.

Although these studies have shown many advances in engineering synthetic TMJ disc tissue, the presence of multiple tissues on the TMJ (bone, cartilage, fibrocartilage) presents a challenge. Researchers must be able to engineer the TMJ to withstand normal pressure and shock that the TMJ disc bears typically to have any reliable clinical application [1].

3.4 Enamel Regeneration

Enamel is the outer surface of a tooth; it is avascular, acellular, and non-vital, making it a problematic tissue to attempt to regenerate. Enamel is subject to many forces to the tooth, such as chewing forces, temperature, pH, caries, bruxism, and chemical erosion. Ameloblasts, the enamel-forming cells, form a protective layer on the outer surface of the enamel before the eruption. However, at the eruption, ameloblasts are lost, therefore leaving behind a highly mineralized acellular enamel structure. Due to the difficulty in regenerating an acellular, avascular, and non-vital tissue, very little research has been published on tissue engineering of enamel. Therefore, the focus of enamel regeneration research is mainly concerned with the remineralization of demineralized or defective enamel [1].

In a study conducted by Fan et al. [51], amelogenin was used with a modified biomimetic deposition method to remineralize the surface of etched enamel, forming mineral layers containing hydroxyapatite crystals. Amelogenin was an essential modulator in the study, as it promoted bundle formation of fluoridated hydroxyapatite as the dose was increased. The biomimetic synthesis of amelogenin-fluoridated hydroxyapatite crystals is one of the initial steps necessary in developing biomaterials that would be applied in future applications for enamel regeneration in restorative dentistry. Although the research conducted in this study was novel in promoting remineralization of affected enamel in its earliest stage, producing enamel tissue itself is a significant challenge to researchers today. Many factors must be considered: the highly mineralized state of the enamel (96% mineralized); the

arrangement, morphology, and size (2–3 mm) of the hydroxyapatite crystals; and the acellularity of enamel. Additionally, ameloblasts originate from epithelial cells and require the differentiation of odontoblasts before they can form the enamel. This epithelial-mesenchymal interaction is very complex and necessary for adequate enamel and dentin formation. Thus, although there has been some research conducted in the regeneration of the enamel, there are still many barriers present in achieving this new feat.

3.5 Dentin and Dental Pulp Regeneration

Animal and laboratory studies have successfully engineered dentin and dental pulp production. The biggest need for regeneration in this field of dentistry would be due to damage to the dentin and other structures in the dentin from tooth decay. Dental caries cause significant damage to the tooth structure, with the most insult to dentin. Caries is one of the most prevalent diseases in children and young adults; successful dentin regeneration through tissue engineering could be a potential future breakthrough solution to this epidemic [38].

There are many approaches to engineer lost dentin and pulp. Even if the odontoblasts (dentin-producing cells) have been lost due to the carious process, these odontoblastic cells still can be regenerated, unlike ameloblasts (enamel-producing cells). Specific bone morphogenetic proteins can be utilized, allowing the newly synthesized odontoblasts to form new dentin. A study conducted by M. Nakashima [52] proved this hypothesis correct. Reparative dentin was developed in the cavity of an amputated pulp and capped with a bone morphogenetic protein, allowing for a cell-mediated immune response, resorption of the BMP, and vascular invasion. Four weeks post-op, osteodentinoblasts were found in the matrix, and other parts of the pulp were filled with pulpal tissue. It was determined that the osteodentine found in this study may be involved in the differentiation of odontoblasts into dentin and dental pulp. This study was followed by a survey conducted by Lianjia Y et al. [53]; it was determined that the primary inductive factor in odontoblast differentiation has not been identified, but BMP, which induces the formation of cartilage and bone when implanted in muscle tissue, is found in dentin matrix, hence the reason why BMPs are used in this area of research. BMP exists in odontoblasts, ameloblasts, and dentin matrix and induces the formation of osteodentin, as found in the previous study. Thus, BMP plays a tremendous role and could be the primary inductive factor in odontoblast differentiation.

In addition to dentin, the dental pulp can be scientifically engineered by using fibroblasts and synthetic polymer matrices. The ability to successfully apply regenerated dentin and pulp is a future breakthrough to restorative dentistry, as it can potentially be the solution to dental caries, a disease common to many around the world.

3.6 Periodontal Tissue Regeneration

Periodontal disease is the result of accumulated bacterial biofilm and a subsequent inflammatory response that leads to the progressive destruction of the supporting tissues surrounding teeth and can eventually lead to tooth loss. Conventional therapy aims to decrease bacterial loads to a level tolerable by the body, thereby halting the disease process and allowing periodontal tissues to heal. However, traditional treatment is unlikely to result in the regeneration of lost periodontal structures. Tissue engineering techniques are alternative or adjunct treatments aimed at regenerating lost periodontal tissues. As with other tissue engineering approaches, periodontal tissue regeneration requires cells, growth factors, and scaffold or extracellular matrix. Effective treatment should result in the formation of cementum, ligament fibers, alveolar bone, and reattachment of the epithelial seal [1, 54].

A technique, termed guided tissue regeneration (GTR), involves the use of a physical barrier, either a resorbable (polylactic acid, polyglycolic acid, collagen) or non-resorbable (methylcellulose acetate, polytetrafluoroethylene) membrane that prevents the migration of the more rapidly forming epithelial and connective tissues, providing a space for the migration of cells onto the affected root surface and promoting the formation of bone. There is no clinically significant difference between the use of resorbable and non-resorbable membrane [55]. GTR is an established and widely used treatment for periodontal defects. Guided bone regeneration (GBR) is another technique used for the treatment of bone defects, such as dehiscence, apical fenestration, and socket defects [56].

Tissue engineering approaches may be improved by the use of bioactive molecules or growth factors, which may result in better cell migration and behavior [57]. A study by Nevins et al. [58] demonstrated the effect of purified recombinant human platelet-derived growth factor BB (rhPDGF-BB) on Class II furcations and interproximal intrabony defects. rhPDGF-BB incorporated into bone allograft resulted in histologically evident regeneration of the periodontal attachment apparatus, including new cementum and PDL, in four of the six interproximal defects and four of four furcation defects treated with PDGF. A subsequent randomized control trial demonstrated the safety and efficacy of rhPDGF-BB in the treatment of periodontal osseous defects, and the results showed a significant increase in the rate of CAL gain, reduced gingival recession at 3 months post-surgery, and improved bone fill at 6 months [56].

3.7 Oral Mucosa Regeneration

Soft tissue defects are commonly repaired using autologous grafts taken from a different part of the patient's own oral cavity. In these cases, rejection of the graft is not a risk, as the patient's own tissue is used, yet autologous grafting is not without limitations. Potential issues with autologous grafting include donor site morbidity,

tissue shortage, and retention of donor tissue characteristics. An alternative approach to oral mucosal regeneration is the use of tissue-engineered products, produced by cultured keratinocytes on dermal matrices in vitro [59].

Oral mucosal equivalents have been developed for clinical applications and for use in in vitro studies of biocompatibility, mucosal irritation, disease, and other fundamental oral biology phenomena [60]. Such equivalents have been used in the surgical reconstruction of the lips, oral vestibule, and tongue and have been proposed for use in tissue engineering of other mucocutaneous structures [61].

3.8 Salivary Gland Regeneration

Salivary glands may be damaged by diseases such as Sjogren's syndrome or radiotherapy, as they are particularly sensitive to radiation. The loss of salivary gland tissue or function has a significant impact on quality of life for those affected individuals, as saliva has a vital role in aiding food digestion and moistening and protecting the oral mucosa. Hyposalivation can cause dysgeusia, dysphagia, increased dental caries, and increased incidence of candidiasis, among many other sequelae [38]. Currently available therapies, which include saliva substitutes and sialagogues, are mostly supportive and are often insufficient. Tissue engineering of glands could improve treatment but is complicated by the intricate anatomy and histology of salivary glands [1]. Inductive gene therapy has been used to treat salivary gland deficiencies. The goals of this type of treatment include repair of hypofunctional gland tissue, production of secretory transgene products, and induction of a phenotypic change in existing ductal epithelial cells. This approach has demonstrated success in animal models [62]. In cases of extensive loss of salivary gland tissue, an alternative treatment is the transplantation of artificial salivary glands. This was demonstrated in a study by Baum et al. [63], in which synthetic salivary gland substitutes were developed from polymer tubes lined by epithelial cells. These devices could be grafted into buccal mucosa and would have the ability to deliver aqueous fluid into the oral cavity. These regenerative approaches have the potential to treat patients with insufficient saliva production due to salivary gland tissue dysfunction and/or destruction, thereby treating and preventing the sequelae of hyposalivation.

3.9 Temporomandibular Joint Regeneration

The temporomandibular joint (TMJ) is a bilateral synovial joint composed of, in part, a shock-absorbing fibrocartilaginous disc located between the mandibular condyles and temporal bones of the skull. It is a complex structure consisting of many tissue types, including bone, cartilage, and ligament, which are bound posteriorly by blood vessels and nerves. There are only a few treatments available for the

management of TMJ disorders, including pharmacotherapy, physiotherapy, and surgical intervention. Tissue engineering has a potential application in the treatment of TMJ dysfunction resulting from degeneration [1].

A study by Thomas et al. [47] from 1991 reported the in vitro development of TMJ cartilage using type I collagen meshes to culture chondrocyte-like cells. The study indicated that the "resultant tissue analog had the clinical appearance and characteristics of the temporomandibular joint disc" and concluded that such an analog could alternatively be used in vivo for disc repair. Not long after, another study by Puelacher et al. [48] engineered the fibrocartilaginous disc of the TMJ. TMJ disc replacements were made by seeding dissociated chondrocytes on synthetic, bioresorbable polylactic (PLA) and polyglycolic (PGA) acid fiber scaffolds. The constructs were incubated in vitro and then transplanted into test animals. The scaffolds maintained their shape, and all implants seeded with chondrocytes showed gross evidence of histologically organized hyaline cartilage. This study demonstrated the potential use of tissue-engineered cartilage grown on scaffolds in reconstructive surgery of the TMJ and also in craniomaxillofacial, plastic, and orthopedic surgery.

Engineering of other TMJ tissues followed the previously discussed studies. Abukawa et al. [49] proposed the fabrication of bone to eliminate donor site morbidity. Engineered constructs that closely resembled a modeled condyle were made using porcine mesenchymal stem cells and porous polymer scaffolds of biodegradable PLGA. A study by Bailey et al. [64] compared engineered condylar cartilage made from human umbilical cord matrix (HUCM) stem cells and TMJ condylar chondrocytes seeded onto PGA scaffolds. Samples were cultured either in a medium containing chondrogenic factors or in a control medium. The HUCM constructs showed increased levels of biosynthesis and higher cellularity, demonstrating that the HUCM stem cells outperformed the TMJ condylar cartilage cells.

Another study by Schek et al. [65] demonstrated the engineering of osteochondral implants using biphasic composite scaffolds to simultaneously generate bone and cartilage in discrete regions and a stable interface between cartilage and subchondral bone. Due to the presence of multiple tissues in addition to the complex anatomy of the TMJ, tissue engineering to treat TMJ dysfunction is challenging. Additionally, for engineered constructs to have a clinical application, they must be biologically and mechanically functional and can remodel according to functional loading stresses.

4 Tissue Engineering: Challenges and Opportunities in Dentistry

Tissue engineering introduces the exciting possibility of replacing lost or damaged tissue. This could be a reality for practitioners and patients in the near future, but there are undoubtedly many challenges before this approach can be regularly

utilized clinically. There have been many significant contributions made to the literature, but still, relatively few tissue-engineered products have reached clinical trials, and applications are primarily limited to the skin, bone, cartilage, capillary, and periodontal tissue [66]. More research and interdisciplinary collaboration are still needed to shift clinical treatment from repair and reconstruction to regeneration. Research to date has illuminated the fundamental processes of tissue engineering, but many issues remain, as tissue engineering is a field that involves many disciplines of the health sciences and bioengineering. This requires the collaboration of many research groups and professionals, including but not limited to dentists, dental biomaterial experts, physicists, bioengineers, and biotechnologists [1].

Key challenges that the field of tissue engineering faces include the complexity and current lack of knowledge of oral tissues, tissue-specific problems, ethical concerns of stem cell research, the cost-effectiveness of treatments using tissue-engineered products, regulation of such products, and the need for training and funding.

It is crucial to understand the composition of the tissue and how it is produced in nature before one can successfully engineer the tissues. An article by Zafar et al. [1] discusses an example of the challenging complexity of enamel, which is the hardest substance in the body due to its highly mineralized structure and is secreted by ameloblasts. Scientists are unable to stimulate ameloblasts to secrete enamel tissue in vitro with structure and properties similar to that of natural enamel. Besides, the enamel is acellular, avascular, and cannot remodel. Many tissue-specific challenges complicate tissue engineering efforts.

The use of stem cells brings up ethical concerns. Stem cells have great potential to reveal the mechanisms of cell and tissue development and differentiation. However, religious and legal dilemmas arise due to debates about when the cells in question are considered a human being, consent to donate biological materials, oversight of research, local and international regulations, and more. Also, these concerns differ depending on geographical location, creating a limitation for research groups that develop partnerships and potentially involve the transport of biological materials across the globe [67].

Cost-effectiveness is inevitably a concern with any medical therapy on the market. One must consider the costs of research and development and the comparative value of currently available treatments. These factors are essential to labs, patients, and practitioners alike. As the development of tissue-engineered products continues, the cost-effectiveness of these products is something to consider.

Biomaterials and the regulation of such materials are additional challenges. A fundamental component of tissue engineering is the use of scaffolds. While it does not yet exist, an ideal scaffold would match the mechanical, physical, and biological properties of the natural tissue of interest, be able to support the tissues' cells throughout their lifespan, and be non-immunogenic and non-allergenic. Of course, infected or contaminated biomaterials cannot be used; however, maintaining a sterile environment during the process of tissue engineering, which can take months, is very challenging. Conventional heat or chemical sterilization may harm cells and tissues or affect the integrity of scaffold materials [66].

Last, as engineered tissue products become available, dental providers will need training and experience in the use of these products. This would require the introduction of these materials in the dental school curriculum and additional continuing education courses for current practitioners to increase the familiarity of such treatments among those in the profession. Additional specialty training in oral surgery and periodontology would need to be introduced, as the use of tissue-engineered products often involves surgical procedures. There is a need for interdisciplinary collaboration to further tissue engineering research efforts, as well as financial support via government funding agencies and private industry.

While there are still many barriers to the clinical use of tissue-engineered products, the possibilities grow with continued research and the contributions of many different groups around the globe. The paradigm shift from simple repair and reconstruction to regeneration is an exciting prospect for the future of dentistry.

5 Conclusions and Future Trends

Although tissue engineering is an emerging field in the career of dentistry, many challenges must be faced before many applications can be clinically practiced. We must be able to solve how we can apply this type of technology as a whole into the field. Some of the major issues to this problem have come down to the cost of having these applications available and how we are going to distribute and apply this technology in healthcare centers. There will also be a new rise of training programs to utilize this type of technology.

Moreover, ethical issues have arisen regarding tissue engineering. When applying this technology, the source of the cells, whether they are the patient's own or donated, would need to be considered. Furthermore, the type of people receiving these therapies is questioned. Many concerns regarding the implementation of this technology exist and will take time for the application of this technology to be used in an actual clinical setting. Much research regarding the field is being accomplished at dental schools and postgraduate programs to make many more advances in this field. Using the basic sciences and incorporating that knowledge into a clinical setting—such as in oral surgery, periodontics, and oral medicine—has been implemented with the use of translational research. For practitioners, continuing education programs in the field of tissue engineering will allow a better understanding in this area, facilitating awareness of newer and better treatments.

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