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Tissue Engineering for the Temporomandibular Joint: An Updated Review

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Abstract

Introduction: Tissue engineering potentially opens new hope for the treatment disorders of the temporomandibular joint which frequently afflict patients. Damage or disease in this area interferes with masticatory function and speaking, reducing patients' quality of life. Effective treatment options for patients suffering from severe temporomandibular joint disorders are in high demand because surgical options are restricted to removal of damaged tissue or complete replacement of the joint with prosthetics.

Tissue engineering techniques for the temporomandibualr joint opens new horizons for the clinical management of temporomandibular disorders.

Materials and methods: Website search (Pubmed, PMC) using the key words, Temporomandibular joint disorder; Condylar fibrocartilage; Temporomandibular joint disc; Scaffold-based tissue engineering; Scaffold-free tissue engineering; TMD

Conclusion: Tissue engineering of the TMJ is still an area of research due to the prevalence of TMD. Tissue engineering is a rapidly evolving field with the ongoing development in scaffold fabrication, cellularization strategies, and growth factor delivery; and many of these techniques have beenapplied to the TMJ. However, there are still challenging problems that remained unsolved.

Keywords: Temporomandibular joint disorder; Condylar fibrocartilage; Temporomandibular joint disc; Scaffold-based tissue engineering; Scaffold-free tissue engineering; TMD

Introduction

The human body has is unable to correctly regenerate most, if not all, of its major tissues and organs once the original tissue integrity has been exposed to damage as a result of medical disorders involving tissue dysfunction or trauma leading to tissue loss [1,2].

Amongst the increasing incidence of trauma, congenital,and degenerative disease tissue engineering and regenerative medicine provides new horizons of biological therapeutics for the management of chronic intractable diseases. This new approach of treatment is based on stimulating the patient's inherent healing potential or regeneration of damaged tissues or more optimistically replacement of the whole organ [3,4].

Research is going on to apply the concepts of tissue engineering in oral and maxillofacial region to induce the regeneration or *de novo* formation of dental, oral, and other structures of the maxillofacial region lost due to trauma, degenerative or congenital disease [5].

Anatomical and Physiological Overview of the TMJ

The TMJ is a ginglymoarthrodial joint consisting of three structures listed from inferior to superiorly: The mandibular condyle, the articular disc, the articular eminence and glenoid fossa **(Figure 1)** [6]. The function of the TMJ is to act as the pivot point for mandibular motion during movements such as chewing and speaking [7]. During maximal opening, the range of motion consists of condyle rotation in the glenoid fossa and anteroposterior translation over the articular eminence. The mandible can also be translated laterally and anterior-posteriorly such as in retrusion and protrusion during mastication. The connective tissue that surrounds the joint is termed the capsule that is lubricated by synovial fluid. The joint capsule is divided into two compartments by the anchor points of the articular disc. The articular surfaces of the TMJ are covered by fibrocartilage instead of the typical hyaline cartilage found on the articulating surfaces such as the knee and hip joints [8]. The primary blood supply runs through the retrodiscal tissue termed the maxillary artery, but also, branches from blood vessels within a 3 cm radius contribute to the TMJ disc [9].

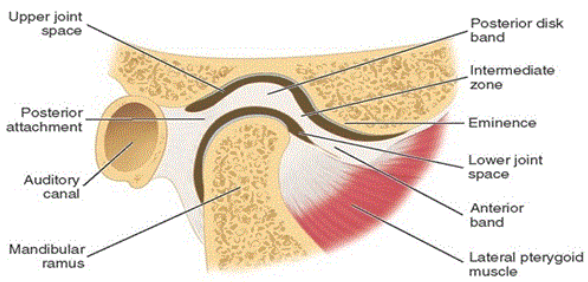

Figure 1: Anatomic structure of TMJ.

Etiology and diagnosis of TMD

The primary symptom of TMD is the presence of pain in the TMJ area, and additional symptoms include popping, grinding, and locking in the joint [10]. These problems can result in disturbances in joint function and reducing maximum mouth opening from 52 mm of a normal adult to less than 20 mm [11]. TMD includes disc dislocation, osteoarthritis, degenerative joint disease, and muscle pain [12]. Also, there have been multiple studies that focus on the link between TMD and depression, but whether mental disorders are a cause or a result of TMD is still debatable [11, 12]. To diagnose TMD, researchers recently revised the diagnosis criterion which consists of 81 questions which focus on the location of the pain, joint function, and psychological distress. Joint disease can be confirmed by computed tomography (CT) scans or magnetic resonance imaging (MRI), especially in the case of disc displacement [12].

The causative factors of TMD has been associated with gender, parafunction, malocclusion, trauma, and psychological factors, yet often the underlying cause is often unknown. Chisnoiu et al. recently published a review that detailed the etiology of TMD [13]. Gender is the most prominent risk factor for TMD with symptoms occurring four times as often in females as compared to males. However, the reason for the discrepancy has not been linked to hormonal or behavioral factors. It is worth noting in a rat model, elevated levels of testosterone do decrease pain in the TMJ after formalin induction [14]. A heavily debated topic is the relation between TMD and malocclusion. Many publications have postulated that malocclusion is not an underlying cause of TMD, but actually may result from TMD [15]. Parafunctions such as bruxism and excessive gum chewing have also been linked to increasing the risk of TMD [16]. This correlation is likely due to the increased loading of the TMJ as evident by finite element analysis [17]. Trauma due to fracture or whiplash has also been postulated as a contributing factor for TMD, and both types of injuries contribute to an increased risk of TMD [16].

Treatment modalities of TMD

TMD in most of the cases is treated by conservative options as the symptoms often spontaneously disappear. Exercise consisting of stretching and manual movement of the TMJ has been demonstrated to improve maximal mouth opening and reduce pain; however, these activities have not been shown to restore the morphology of the TMJ [18]. The role of splints is to reduce muscle strain and temporarily correct mandible malalignment and come in a variety of materials and styles [19]. The use of stabilization splints has yielded debatable results in treating TMD. There is controversy regarding the use of splints to reduce pain, and element analysis suggests these splints do not reduce pressure on TMJ components [20]. On the other side, anterior repositioning splints have been shown to provide relief to patients suffering from disc displacement and general TMD symptoms [21]. Another treatment is the use of therapeutic agents such as NSAIDs, muscle relaxers, corticosteroids, and antidepressants to reduce TMD pain [22]. Even though clinical studies of drugs to treat TMD are rare, most evidence suggests that medications are effective in lowering TMD symptoms but are often associated with side effects such nausea and dizziness [22].

If conservative treatments are ineffective, minor procedure scan be employed to improve TMD symptoms such as arthrocentesis, arthroplasty, and hyaluronic acid injections. Arthrocentesis is an office based procedure performed by lavaging the joint capsule with a solution that may contain steroids. A systematic review concluded that arthrocentesis improved symptoms in over 83% of TMD cases making arthrocentesis a viable treatment option [23]. Arthroscopy is another commonly used treatment option, which involves inserting a small camera into the joint along with other tools to remove debris, lavage, and reposition the articular disc. Arthroscopy is a safe procedure and is equally effective in treating TMD as arthrocentesis with the added advantage of visualization of the joint for more accurate diagnosis [24]. Hyaluronic acid injections are also being considered for use in treating TMD, although not commonly used. The role of hyaluronic acid injections is compared to stabilization splints in managingTMJ disc displacement with reduction, both groups decreased pain significantly, and the hyaluronic acid injections were significantly more effective than the stabilization splints.

When the symptoms are too severe and are not responding to conservative treatments, open surgery may be required. Surgical procedures for TMD include discectomy, condylectomy, and in extreme cases, total joint replacement (TJR) may be necessary. Discectomy, or the removal of the articular disc, has been shown to reduce pain and improve joint function over at least five years [25]. To further reduce crepitus and degradation of the condyle, a lot of materials to protect the joint after disc removal although with limited success [26]. Condylectomy is a commonly used procedure to repair damage to the mandibular condyle including bony erosion, and joint immobility, also called ankylosis [27]. The procedure often consists of resecting the upper portion of the condyle and replacing it with a cost ochondral autograft that has been tissue harvested from a rib of the patient. Many studies supported the conclusion that condylectomy treats TMD in over 80% of cases when the patient presents with joint ankylosis or with failure of conservative treatment [28].In most of the post condylectomy cases, ipsilateral deviation is a possible complication to the affected site. Not only in condylectomy, other orthopedic procedures such as arthroplasty and total joint

replacement surgery, post operative complications such as malunion and non-union, as well the most devastating one, the unexpected nerve injury can also occur. To prevent all these devastating complications, the best alternative is tissue engineering that is the 3D printing of biological tissues.

Reasonable results were obtained with Total joint replacement(TJR) devices with some achieving over 90% success. Patients reported alleviation of pain and an increase in maximal opening as compared to pre-surgery immediately, as well as 3, 5, and 20 years post-surgery [29].

Despite many conventional treatment methods exist to fix the tempomandibular disorders, tissue engineering is emerging as a novel and potential solution for a permanent cure.

The role of tissue engineering

Tissue engineering may provide improved solutions to disc replacement materials, structural degradation, and alternatives to TJR. Regarding disc replacements, the infamous Teflon-protoplastic implants of the 1960s provided patients with immediate relief from the symptoms associated with TMD [30]. These implants undergo degradation leading to implant failure, osseous degeneration, foreign body granulomas, and pain [31]. Use of adipose tissue to cushion the joint has a major disadvantage of rapid reduction in the volume of the graft. A tissue engineering procedures may overcome the defects of limited longevity by generating viable tissue capable of self-renewal with normal function. For bone regeneration, tissue engineering may facilitate the restoration of complex structures such as the condyle and fossa through anatomically accurate and osteo inductive scaffolds. Eventually, tissue engineering devices may reduce or even obviate the need for TJR devices by giving surgeons the tools to regenerate the damaged structures of the TMJ completely. Obstacles for this approach include an optimal selection of cells, scaffold materials, and growth factors that work together. The purpose of this review is to throw light on the current strategies used in tissue engineering for each component of the TMJ.

TMJ Condylar Fibrocartilage

Numerous types of scaffolds for engineering the TMJ condylar fibrocartilage have been examined and reviewed elsewhere [32]; the most common of these include PLGA, PGA (polygylcolic acid), PCL, and poly(ethylene glycol) (PEG). Rat bone-marrow MSCs(mesenchymal stem cells), induced to differentiate into chondrogenic and osteogenic lineages were seeded into a condyle-shaped PEG hydrogel [33]. Unfortunately, the functional properties of the engineered tissue were not confirmed by mechanical testing, but there was histological and immunohistochemical evidence for both cartilage and bone. In general, engineering the condyle may require generating both cartilage and osseous tissue, so characterization of the mechanical properties of each component is essential.

Different cell types, from chondrocytes to stem cells, have been compared to TMJ condylar cells with respect to engineering condyle fibrocartilage using scaffolds [34]. Chondrocytes from the ankle were compared to fibrochondrocytes from the mandibular condyle seeded on PGA and treated with IGF-1; the anklechondrocytes outperformed condylar fibrochondrocytes and produced 10- and 6-fold more GAG and collagen, respectively [35]. When human umbilical cord matrix stem cells were compared to TMJ condyle fibrochondrocytes, PGA constructs seeded with the stem cells contained significantly higher GAG (glycosaminoglycans) and cell number, but there was no increase in collagen content [36]. It is of no wonder in saying that even stem cells derived from the umbilical cord matrix are not extremely efficient in increasing the collagen content which is very essential in reconstructing the injured or damaged tissue. Therefore, the tissue engineering would be more advantageous than the traditional treatments. Notably, collagen types I and II were observed for the stem cell-seeded constructs, but not for the cultures seeded with condylar fibrochondrocytes. From these studies, it is clear that more work is needed to optimize the culture of condylar fibrochondrocytes. As presently reviewed,various cell types have demonstrated greater promise than TMJ condylar cells for the tissue engineering of condylar fibrocartilage.

Bioreactors for engineering condylar fibrocartilage have been reviewed elsewhere [35]. A few studies have also looked at the effects of biomechanical stimuli on other cell types, but not all the results are positive. For example, applying sinusoidal, dynamic loading at 0.3 Hz and a 15% amplitude strain to condyle fibrochondrocytes in PEG hydrogels resulted in inhibition of cell proliferation and proteoglycan synthesis [37]. In another study, applying hydrostatic pressure up to 90kPa for 720 minutes to rabbit mandibular fibrochondrocytes in monolayer increased cell proliferation; however, alkaline phosphatase activity was also elevated, which might induce an undesirable mineralization effect when engineering fibrocartilage [38].when it is viewed from the side of potential benefits, rise in alkaline phosphatase doesn't seem to be an issue clinically as the liver being an amazing organ with a sophisticated machinery can itself heal swiftly.Bioreactors have also been used for engineering bone in a condylar shape [39]. In this respect, rotational [40] and perfusion [41] bioreactors were used to culture porcine MSCs in PLGA and human MSCs in a cellular bone, respectively. The rotational bioreactor experiment was a pilot study that did not compare the tissues generated with other bioreactors or static controls, so the utility of a rotational bioreactor remains unclear for engineering bone constructs for the condyle. A perfusion bioreactor was shown to improve cell attachment by 2-fold compared to static culture [41]. Bioreactors that have shown efficacy in cartilage and bone tissue engineering may also be beneficial for condyle fibrocartilage tissue engineering [34], though this has yet to be confirmed. Due to the limited studies on engineering the condyle, a robust conclusion on the effectiveness of bioreactors is premature.

Research on the role of growth factors in increasing cell proliferation and biosynthesis in condylar fibrochondrocytes, both in a monolayer and seeded in scaffolds. In monolayer, 10 ng/mL basic fibroblast growth factor (bFGF) resulted in the highest increase (65%) in proliferation of human mandibular condylar fibrochondrocytes, compared to increases due to 10 ng/mL TGF-β1 (13%) and 10 ng/mL IGF-1 (24%) [42]. When comparing hyaline chondrocytes to condylar fibrochondrocytes,

only the chondrocytes were responsive to IGF-1, forming a fibrocartilage-like tissue with types I and II collagen, with about an 8-fold increase in both GAG and collagen contents over unstimulated controls [35]. Although the data on the use of growth factors in engineering the condyle are scarce, bFGF and IGF-1 have emerged as effective stimuli for cell proliferation and biosynthesis, respectively.

TMJ Disc

Scaffolds used in TMJ disc tissue engineering include alginate hydrogels [43], polylactic acid (PLA) [44], polyglycolic acid (PGA) [71, 73, 74, 20], poly−L−lacticacid (PLLA) [45], decellularized native ECM materials [46], polytetrafluoroethylene (ePTFE) monofilaments [47], poly (glycerol sebacate) (PGS) [48], and, recently, polycaprolactone (PCL) polyester [49]. As noted above, scaffold characteristics must be tailored to the cell types used to engineer the tissue. For example, porcine TMJ disc cells seeded on PGA scaffolds result in constructs that contract severely because the PGA degrades much faster than the matrix is produced. Although the addition of insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), and transforming growth factor-β1 (TGF-β1) improved matrix synthesis [43], the scaffold still degrades fast. As a result, a different scaffold material, PLLA, was examined for its much slower degradation rate [45]. Overall, PLLA scaffolds seeded with porcine TMJ cells and treated with TGF-β1 demonstrated higher collagen and GAG contents and improved mechanical properties (1.4 MPa Young's modulus) when compared to constructs seeded on PGA [45]. Maintaining the desired shape and size during tissue engineering can be challenging not only for the disc [50], but other tissues as well [51], and scaffold optimization toward this parameter remains an ongoing endeavor.

The advent of new manufacturing techniques may allow for the production of scaffolds that more closely mimic the unique structures of TMJ components, including tissue anisotropy. Toward this end, additive manufacturing was used to 3D print PCL scaffolds with an anisotropic internal structure [49]. Seeded with mesenchymal stem cells (MSCs), anisotropic properties were observed. However, given the short time points examined in this study, it is unclear if the anisotropic properties would be retained long-term, since the observed anisotropy was likely due to the scaffold as opposed to the matrix produced. The goal of using scaffolds, to engineer anisotropic TMJ tissues composed of only cell-generated matrices, is yet to be realized.

Central to the efforts of tissue engineering are identifying a suitable source of cells and seeding density. TMJ disc cells, as well as articular chondrocytes derived from the condyle, fossa-eminence and shoulder, in addition to dermal fibroblasts have all been examined for engineering the TMJ disc [52]. For example, dermal fibroblasts showed chondrogenic potential when treated with IGF-1. These cells are particularly promising since they are clinically relevant for autologous therapy without significant donor site morbidity. Cell seeding density is another important factor that influences the composition of the resultant construct [53]. Increasing cell seeding density does not always improve functional or biomechanical properties, so seeding density must be carefully controlled. For example, TMJ disc cells seeded from 15-120M cells/ml of scaffold volume onto PGA scaffolds show variable results. Increasing the cell number up to 120M cells/ml of scaffold volume increased GAG and collagen content without significant improvement in the compressive properties of the engineered tissue. For each new cell source, identified for engineering the TMJ disc, the lowest seeding density that yields desirable functional properties must be determined.

Mechanical stimuli approximating physiological loading profiles have been used to condition engineered TMJ discs to improve their mechanical and biochemical properties. In situ, the native TMJ disc is exposed to tension, compression, shear, and hydrostatic pressure during joint movement. When applying mechanical stimuli, a potential disadvantage in using scaffolds is stress-shielding. For example, applying tension and compression onto cell seeded scaffolds can result in the scaffold bearing the load as opposed to having the load propagate down to the cellular level [54]. Spinner flask and orbital shaker cultures have both been used to apply fluid-induced shear [43]. When cultured in spinner flasks, TMJ disc cells seeded on PGA showed higher ECM production 4 weeks after seeding compared to constructs in static culture. However, no significant improvement was observed in mechanical properties in comparison with static conditions [55]. Hydrostatic pressure at 10 MPa, applied either constantly or intermittently for 4 hours a day, using a duty cycle of 2 days on, 1 day off for 1 week, showed that the constantly applied load led to the highest amount of collagen and number of cells per construct [56]. The use of these bioreactors results in enhanced GAG and collagen synthesis, but corresponding improvements in mechanical properties must be demonstrated.

Biological signals have been used to promote collagen and GAG synthesis in engineered TMJ discs, with the expectation that this approach would lead to improved mechanical properties of the engineered tissues. Effects elicited by bioactive signals depend greatly on conditions of the experiment. For example, in a study that compared platelet derived growth factor-AB (PDGF), bFGF, and IGF-1 at various concentrations in monolayer, bFGF was shown to result in the greatest improvements in GAG and collagen production (2 and 4.5 fold increases, respectively, compared to control) [57]. However, when examining IGF-1, bFGF, and TGF-β1 on cell-seeded PGA scaffolds in spinner flasks, the results suggested that IGF-1 elicited the greatest collagen production [43]. Both studies used porcine TMJ disc cells, but the conditions varied, the former was a two-dimensional, static culture, while the latter was a three-dimensional culture subjected to fluid-induced shear. Due to the limited number of studies on the efficacy of growth factors for scaffold-based engineering of TMJ discs, additional work is needed to optimize relevant growth factors, doses and regimens. However, a comprehensive picture will not emerge until this characterization is performed for each scaffold and culture condition.

Conclusion

Tissue engineering of the TMJ is, and will continue to be, an area of active research due to the prevalence of TMD. Tissue

engineering is a rapidly evolving field with the ongoing development in scaffold fabrication, cellularization strategies, and growth factor delivery; and many of these techniques have been applied to the TMJ.

This literature review, shows that there are enormous efforts and advances in fabricating scaffolds in the correct anatomical shape, and the materials utilized have been shown to increase tissue regeneration in models for TMD. However, there are still obstacles that need to be solved or overcome. Other difficulties facing tissue engineering of the TMJ include restoration and incorporation of the fibrocartilage on the articulating surfaces, displacement of the implant material, and evaluation of long-term outcomes from the use of regenerative approaches. Moreover, tissue engineering strategies have yet to be applied directly to the glenoid fossa and articular eminence.Further studies will shed light on a future when TMJ pathologies can be treated effectively and thus improve patient outcomes.

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