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Tissue engineering of the temporomandibular joint : Where do we stand now?

Camille HADDAD

Dalia FLEIHAN

TISSUE ENGINEERING OF THE TEMPOROMANDIBULAR JOINT: WHERE DO WE STAND NOW

Camille Haddad* | Dalia Fleihan**

Abstract

Tissue engineering is an alternative to traditional strategies to repair and regenerate temporomandibular joints (TMJ). Nowadays, patients suffering from severe dysfunctions of the TMJ may undergo discectomy, a procedure that consists of removing the damaged disc in hopes of reducing the symptoms. However, tissue engineering presents a potential solution for patients suffering from these disorders, due to the lack of safety and effectiveness of TMJ disc implants.
Since 1991, several studies have investigated the possibility of regenerating the articular disc.
This literature review aims to expose the new challenges and techniques in TMJ disc tissue engineering whether it concerns cell sourcing, scaffold or bioreactors. As these challenges are overcome, the goal of future studies remains to create a functional biological replacement of the TMJ components.

Keywords: Tissue engineering - tissue regeneration - temporomandibular joint – disc – materials – bioreactors – scaffolds - cell sourcing.

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INGÉNIERIE TISSULAIRE DE L'ARTICULATION TEMPOROMANDIBULAIRE : OÙ EN SOMMES-NOUS MAINTENANT ?

Résumé

La regénération tissulaire est une alternative aux stratégies traditionnelles pour réparer et regénérer les articulations temporo-mandibulaires (ATM). De nos jours, les patients souffrant de dysfonctionnements graves de l'ATM peuvent subir une discectomie, une procédure qui consiste à retirer le disque endommagé dans l'espoir de réduire les symptômes. Cependant, l'ingénierie tissulaire présente une solution potentielle pour les patients souffrant de ces troubles en raison du manque de sécurité et d'efficacité des implants du disque de l'ATM.
Depuis 1991, de nombreuses études ont investigué les possibiltés de regénération du disque articulaire.
Cette revue de la littérature vise à exposer les nouveaux défis et techniques dans l'ingénierie tissulaire du disque de l'ATM tell l'approvisionnement en cellules, l'échafaudage et les bioréacteurs.
À mesure que ces défis seront surmontés, l'objectif des futures recherches reste de créer un remplacement fonctionnel et biologique des composants de l'ATM.

Mots-clés: regénération tissulaire - ingénierie tissulaire - articulation temporomandibulaire – disque - cellules souches – bioréacteurs - échaffaudage.

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* DCD, DUO, DUP, CES, MSM, DEA
Chargé de cours ,
Service de prothèse fixée et d'occlusodontie
Université Saint Joseph, Beyrouth, Liban
camhaddad@hotmail.com

** DCD, DU occlusodontie
Université Saint Joseph, Beyrouth, Liban.

Introduction

Tissue engineering of the temporomandibular joint (TMJ) is a newly emerging topic with intense impact. The first attempt of tissue engineering of the TMJ disc cells was led in 1991 [1]. However, the information provided at that time was little. It wasn't until the last decade that multiple studies have emerged and investigated thoroughly the disc characterization and gave solid conclusions about TMJ disc tissue engineering. In fact, the disc is affected in as many as 70% of temporomandibular dysfunctions (TMD) cases [2].

TMDs are most frequently accompanied by displacement of the TMJ disc, called "internal derangement" (ID)[3]. As patients seek treatment, the management of ID slides from non-invasive to total joint reconstruction. In patients expressing TMD symptoms, non-invasive treatment should always be explored first [4). While traditional treatment methods for advanced ID cases like allografts and autografts have been used, many disadvantages limit their application. Autografts that require a transplant of a small portion of a cartilage into defected sites have disadvantages like donor site morbidity and limited cartilage tissue availability [5 – 7]. Allografts issued from tissue banks, may induce immune responses [6, 7]. In more advanced cases, people suffering from osteoarthritis, a total joint replacement is indicated. This technique presents many disadvantages such as inflammation, infection and implant loosening [7].

Given the inferior characteristics of synthetic implant materials in response to the complex wear experienced by the articular disc, tissue engineering offers a promising approach to enhance this clinical need. It presents a natural and permanent solution to restore joint function and eliminate pain caused by TMDs [8]. The purpose of this literature review is to overview new findings in tissue engineering of the TMJ disc whether it concerns the scaffold, stem cells or bioreactors.

Uniqueness of TMJ: The difficulties of TMJ disc tissue engineering raises from the complexity of the TMJ system

Engineering tissues geometrically, biochemically and biomechanically similar to native tissue requires a profound knowledge of the properties of a healthy joint and its characteristics. However, more detailed reports can be found in the literature about the anatomy, structure and function of the TMJ disc [9 – 11] (Figs. 1 & 2).

The TMJ cells are mainly cells with characteristics of fibroblasts and chondrocytes. According to Detamore and al. [12], these cells are distributed through the disc: 70% are fibroblast-like cells and the other 30% are chondrocyte-like cells [12]. Cells in the central part of the intermediate band are most primarily chondrocyte-like cells, while on the periphery of the disc, fibroblast-like cells are most likely to be found [12, 13]. Across species, cellularity is higher in the anterior and posterior bands [11, 14]. With age, the disc tends to become more fibrous [15] and acellular [16]. According to Berkovitz [15], researchers collected rats and marmosets from different ages in order to study any cellular age changes of the disc. However, they both showed that the intra-articular disc of the joint changed from fibrous to fibrocartilaginous with age, a condition similar to that encountered in humans. On another hand, Minarelli [16] studied the age changes by light microscopy dividing his sample into age categories: a foetuses and children group (GI), a dentate group of adults (GII) and an edentulous, elderly group of humans (GIII). Results were that the disc naturally cellular in foetuses and children; it becomes more fibrous with age. Chondroid cells are observed in all portions of the discs in groups GII and GIII. Elastic fibers are numerous in GI discs and decrease in number in the disc with age.

Biochemically, a disc is described to be highly fibrous, low in glycosaminoglycan (GAG) content and high in collagen type I content. Collagen fibers occupy 50% of the disc volume [15]. However, unlike hyaline cartilage, collagen type III, VI, IX, XIII can also be found but in low percentages based on a study done on bovine [17] and leporine models [18]. Water is also an important component of the disc as it covers up to 80% [19, 20]. 1-2% of the tissue mass is dominated by cross-linked elastin fibers [21] which play a role in restoring the disc's original shape after loading [22 – 24].

Beek and al. [25] performed a study on human TMJ disc. The viscoelasticity of the disc depends on four factors: amplitude, rate, location and time of deformation [25]. Other studies were done in order to find the best animal model to reproduce the human disc. The pig had most statistical similarities in terms of dimensions, GAG/collagen contents and compressive properties [26]. Evidence suggests that collagen density and organization might be determinant of compressive and tensile properties [26]. However, GAG-decorin were found to influence collagen organization [27]. In fact, unlike other self-repairing tissues (bone for example), cartilage has low regenerative capacities. Articular cartilage is composed mainly by a dense extracellular matrix (ECM) and a very small percentage of chondrocytes. Therefore the density of the extracellular matrix (ECM) prevents the mobility of chondrocytes. In addition, articular cartilage lacks lymphatic, vascular neuronal networks and progenitor cells, which highly affects tissue repair [7, 28, 29].

TMJ is different than other joints in the body. It is composed of fibrocartilage that contains both collagens type I and II. In other synovial joints of the body, articular surfaces are covered by hyaline cartilage in which only collagen type II was found [30].

Fibrocartilage was proven to withstand sheer forces more than hyaline cartilage, which makes it support the large amount of occlusal forces placed on the TMJ [31]. Fibrocartilage has other advantages: fibers are tightly

packed to support forces of movement, they are less likely to breakdown over time and have better ability to repair [32].

Another difference between TMJ and other joints is that the cartilage found in TMJ is a secondary cartilage [33]. Secondary cartilages develop from undifferentiated cells comprising mesenchymal tissue covering the prenatal or postnatal condyle, while primary cartilage (found in all other articulations) growth begins in the cartilage cells within the central layer of an epiphyseal plate. In this developmental stage, the cells undergo mitosis [34].

Tissue engineering TMJ disc

During 1994, the first TMJ tissue-engineered constructs to be tested biochemically and biomechanically were formed. Many studies have emerged about this topic but they mainly lacked characterization. However, they helped optimizing design norms. During the last decade, core studies revealed that tissue engineering is a promising approach for the creation of viable, effective implants. They mainly investigated the three most important elements of tissue engineering: stem cells, scaffold and biomaterial reactors (Fig. 3).

The research for studies selected in this literature review were conducted on key resources including PubMed, The Cochrane Library, Medline, major health technologies agencies and a focused Internet search using the keywords: "tissue engineering in dentistry", "tissue engineering in TMJ disc", "tissue engineering in TMJ". After filtering, the selected articles were limited to systematic reviews, meta-analyses and health technology evaluations. The search was also limited to English and French languages published in the last decade.

"Tissue engineering is a multidisciplinary field that aims to construct biological tissues such as the disc. Tissue engineering strategy generally involves the expansion of cell lines in vitro, followed by seeding the cells onto a three-dimensional (3D) biodegradable and biocompatible scaffold that provides structural support and can also act as a reservoir for bioactive molecules such as growth factors. Bioreactors and scaffolds including hydrogels play critical role in tissue engineering, former by provision of the physiological environment to control environmental conditions such as oxygen, pH, temperature, and aseptic operation, and latter by acting as temporary artificial extracellular matrices" [35, 36).

Unfortunately, there is a lack of literature listing specific indications for the use of TMJ tissue engineering solutions. Irreparable condylar trauma, developmental or acquired TMJ pathology in skeletally immature patients, hyperplasia, and documented metal hypersensitivities could be indications for bioengineered condyle and ramus TMJ components. There was consensus that Wilkes stage III internal derangement might be an indication for use of a bioengineered TMJ disc or possibly even a disc-like bioengineered "fossa liner." There was some controversy as to whether TMJ arthritic disease (osteoarthritis) and reconstruction after failed alloplastic devices should be indicated [37].

Yet, patients with TMJ disorders and multiple failed surgeries, parafunctional oral habits, persistent TMJ infection, TMJ rheumatoid arthritis, and ankylosis were contraindicated to benefit from tissue engineering [37].

Cell Sourcing

Selecting cell source is the most important strategy of tissue engineering. These cells are responsible of producing the ECM and therefore, developing a functional replacement of the TMJ disc. TMJ disc cells, articular chondrocytes and recently costal chondrocytes are the most commonly used [38, 39]. In fact, primary disc cells have been mostly studied. Two main problems were found: lack of donors' cells and donor site morbidity. TMJ disc cells dedifferentiate rapidly in culture and their phenotype is difficult to recover [40, 41]. This technique is currently abandoned. Recently, highly potent human stem cells, such as multipotent mesenchymal stem cells, umbilical cord matrix stem cells and pluripotent embryonic stem cells have appeared. These cells are known to be: 1) pluripotent; 2) can be isolated (from fat, bone marrow, skin, blood, muscles, biopsies); 3) proliferate in culture without losing their phenotype and 4) differentiate into bone, cartilage, muscle, tendon, ligament or fat. Embryonic stem cells (Fig. 4) are derived from embryos' eggs that are donated for research purposes with an informed consent of the donor whereas induced pluripotent stem cells are prelevated from the body and cultured in the lab. The purpose of the studies was to generate constructs with more of a chondrocytic phenotype with rounded morphology and positive staining for proteoglycans than a fibroblast phenotype [38]. When chondrocytes were encapsulated in a scaffold and cultured in biomimetic environment, cells survived well and secreted newly synthetized matrix consisting of GAG and proteoglycans, therefore leading to an enhancement of chondrogenesis to potential disc implant.

Scaffold

Scaffolds are an important element in tissue engineering, as they restore function and shape to mimic natural joint and provide mechanical integrity for cell attachment. They provide biological and mechanical structural support for tissue reconstruction so that the cells attach, migrate, proliferate and differentiate. Scaffold requirements include high porosity and surface area, mechanical stiffness and strength, controlled degradation, and biocompatibility. First TMJ disc tissue engineering study used a porous collagen scaffold [38]. It produced constructs with acceptable size and ECM [38]. Similar achievement was obtained with porous polylactic acid (PLLA) [38], polyglycolic acid (PGA) [38], polyglycerol sebacate [38], chitosan, fibrin and hydrogels.

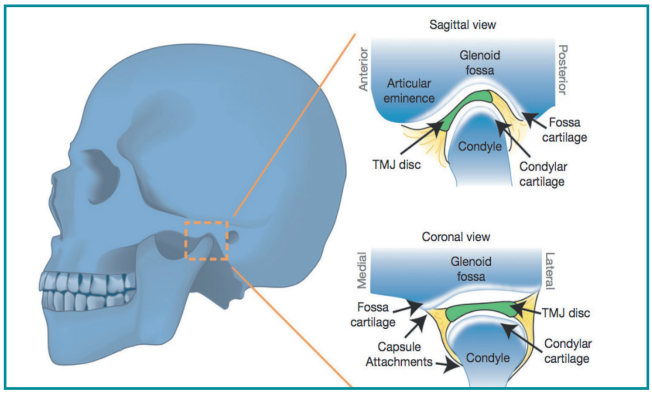

Fig. 1: Location and anatomy of the TMJ in the sagittal plan. The TMJ is capable of both rotational and translational movement and is composed of three articulating structures: the mandibular condyle, the TMJ disc, and the glenoid fossa. The mandibular condyle and glenoid fossa are both covered by fibrocartilage and the TMJ disc is positioned between these two structures.

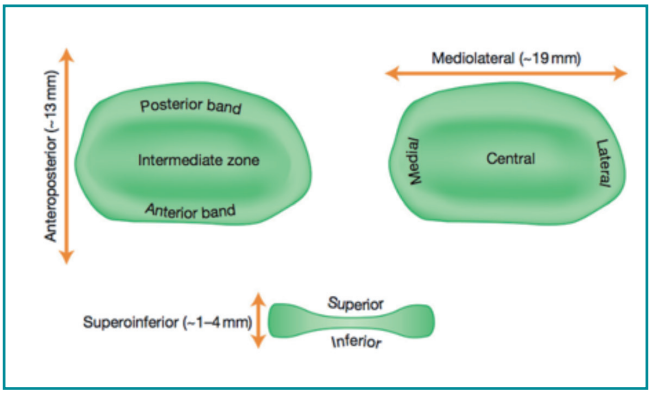

Fig. 2: Regional variations and approximate dimensions of the TMJ disc. The TMJ disc is commonly classified into posterior band, intermediate zone, and anterior band in the anteroposterior direction. In the mediolateral direction, the disc can be separated into medial, central, and lateral regions. The disc exhibits a biconcave shape in the superoinferior direction, with each surface having distinct properties. Source: V P Willard, L Zhang and KA Athanasiou; Tissue Engineering of the Temporomandibular Joint, p.224.

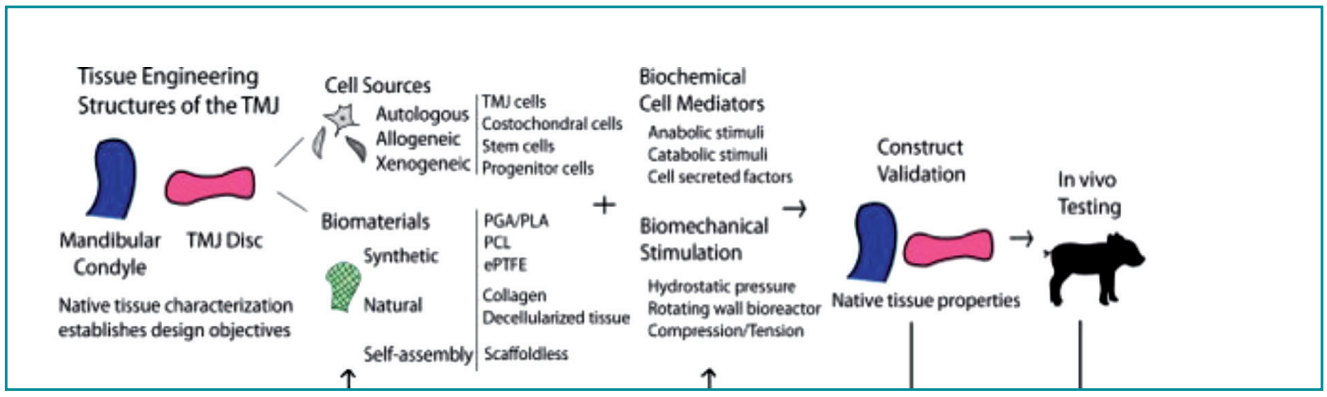

Fig. 3: TMJ tissue engineering strategy. Tissue engineering approach to repairing or replacing the mandibular condyle and TMJ disc [4].

The scaffolds are classified into two main types (table 1):

Polysaccharide-based scaffolds

Polysaccharide-based (alginate, chitosan, and agarose) scaffolds usually require further cell-attachment modification to promote cell adhesion and proliferation. This type of scaffolds includes:

1- Polymer materials of polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic) acid (PLGA) polyglycerol sebacate (PGS), polyethylene glycol (PEG), polycaprolactone (PCL), polyurethanes, and composites. Polymers are flexible and biodegradable through their hydrolysis or by means of cellular or enzymatic pathways when implanted. Polymers have low mechanical strength and hence are often combined with high-modulus micro or nanoscale ceramic constituents like HA [42].

2- Hydrogels/ alginate: Alginate is often extracted from certain seaweed and produced by certain bacteria. In fact, hydrogels have demonstrated great scaffolding potential due to their high biocompatibility, efficient transport of nutrients and waste, ability to uniformly encapsulate cells and ability to be made into any shape.

3- Chitosan: Natural chitosan is a polysaccharide material used mainly in cartilage engineering due to its biocompatibility strength and shape persistency. However, cell seeding in this kind of scaffold is not homogeneous. Cells tend to adhere to the scaffold surface. Natural scaffolds like collagen type I, chitosan, calcium alginate, hyaluronic acid, composites have been

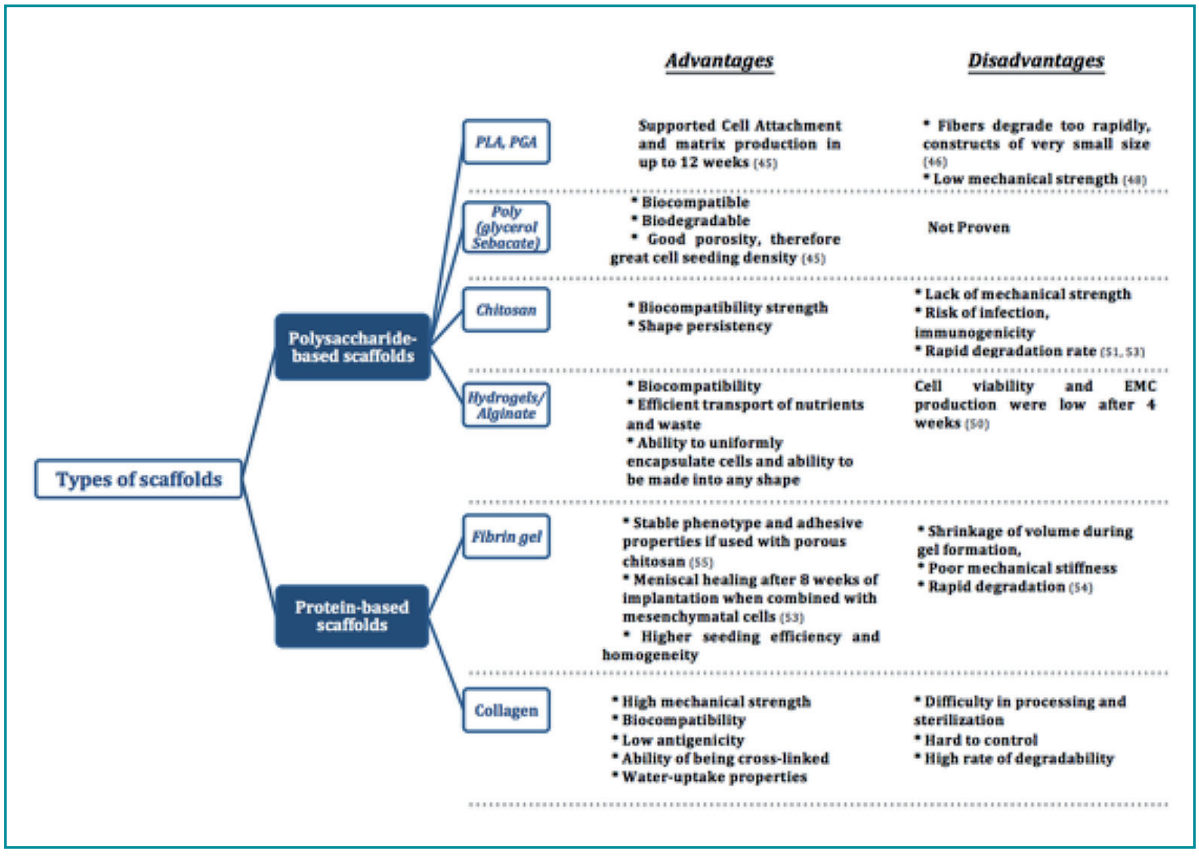

Table 1: Conclusive table summing the different types of material used in TMJ disc scaffolding with their respective advantages and disadvantages according to the literature.

shown problems like lack of mechanical strength when implanted, risk of infection, immunogenicity, and rapid degradation rate [43, 44].

Protein-based scaffolds

For biopolymer-based tissue engineering scaffolds, protein-based (fibrin, collagen) materials provide binding sites for cell adhesion to promote cell adhesion and proliferation. These include: fibrin gel and collagen scaffolds. An interesting pilot study done by Yang Wu in 2013 [45], combined fibrin gel to porous chitosan scaffold to form an hybrid scaffold. The authors hoped it would get fixed in the site of disc defect by the adhesive property of the fibrin gel [45]. Results were a higher seeding efficiency and a more homogenous cell distribution compared to fibrin-free scaffolds.

However, an ideal scaffold will show a balance of biocompatibility, mechanical ability and porosity. The concept of TMJ disc decellularization is now present. Results have shown that porcine discs treated with sodium dodecyl sulfate (SDS) most closely matched the energy dissipation capabilities and resistance to deformation of the native tissue [46]. Treatments using Triton X-100 caused the resultant tissue to become relatively softer with inferior energy dissipation capabilities, while treatment using acetone/ethanol led to a significantly stiffer and dehydrated material. However, these techniques have shown to retain native biochemistry, microenviromental architecture, and mechanical properties. The use of surfactant SDS to dellularize TMJ disc helped in retaining the mechanical integrity and molecular architecture of the native disc. The use of naturally derived scaffolds doesn't support cell function due to the lack of microvasculature. It has been proven that carbon dioxide laser micropatterning (LMP) into natural ECM structure of the acellular TMJ improves the permeability of the ECM matrix scaffold. This permeability will support homogeneous cell integration and provides a path of infiltration for metabolite diffusion without weakening the mechanical ability without a non-LMP.

Nowadays, the tendency is directed towards "scaffold-free or scaffoldless tissue engineering" [47]. "Scaffoldless tissue engineering refers to any platform that does not require cell seeding or adherence within an exogenous, three dimensional material". However, this technique requires a large cell

number. Limitations associated with number of primary cells and donor site morbidity led to the use of allogenic sources mainly (for immunological considerations, if not xenogenic).

Bioreactors

An important factor in tissue engineering is the use of growth factors to enhance cellular proliferation and biosynthesis. Bioreactors provide a method for maintaining cell viability and stimulating cells within three dimensional biomaterial scaffolds over periods of days to weeks. During this period, the cells are able to proliferate and mature.

So far, several growth factors have been investigated in TMJ tissue engineering: platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factors-β1 and β3 (TGF-β1 and β3), and insulin-like growth factor-I (IGF-I). TGF- β1, IGF-I and bFGF have demonstrated cell proliferation and biosynthesis [48, 49]. In 3D culture, the effects of growth factors have been investigated with different types of scaffolds. Using PGA scaffolds, IGF-I and TGF-β1 showed an increased collagen synthesis on porcine TMJ disc cells [50]. When using PLA scaffolds, only TGF-β1 showed favorable biochemical and mechanical properties [51]. It was also concluded that high concentration of growth factors favored cell proliferation while low concentrations favored biosynthesis [39]. Latest evidence suggests that using catabolic agent (like chondroitinase-ABC) in the midpoint of culture may improve construct properties and hence the tensile properties [52].

Future considerations / Conclusion

Tissue engineering remains the only natural permanent and promising remedy for disc replacement given the problems occurring with surgical solutions. There is a significant amount of work that should be done to produce functional displacement of the TMJ components. Yet, the studies directions right now should go towards engineering disc attachments, fossa cartilage and capsule. However, biomedical engineers must raise the specific indications that might demand TMJ bioengineered structures, so that they avoid developing technologies in search of problems that might not exist for patients and clinicians. They should focus instead on identifying the problems that need resolution and address those particular situations.

The ultimate goal of replacing TMJ can be reached and the future looks bright for this technology. One question yet remains, are we close to 3D print a TMJ disc? Future further studies will surely provide the answer to this question.

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