International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Biomimetic Approach for Treatment of TMJ Disorders Using Recent Tissue Engineering Advances

Dr Abhidha Tripathi[1], Dr Kratika Rastogi[2], Dr Shitij Srivastava[3], Dr Abhishek Singh[4]

[1,2,3,4]Department of Prosthodontics, Crown and Bridge/ Sardar Patel Postgraduate Institute of Dental and Medical Sciences/ Atal Bihari Vajpayee Medical University/ India

ABSTRACT:
Orofacial discomfort is mostly caused by temporomandibular disorders (TMD), which are among the most prevalent maxillofacial symptoms. Alternative tissue engineering alternatives are much sought after, despite the fact that present therapies offer both short- and long-term relief. Developing treatment plans that offer long-term relief from TMD and enable patients to resume normal function is of utmost importance. Understanding normal structure and function is a must for tissue engineering. Following a brief overview of the present state of TMD therapy, the morphological, mechanical, and biochemical properties of the temporomandibular joint (TMJ) and related tissues will be examined. The major focus is on the latest advancements in tissue engineering, whether or not a scaffold is needed, for the regeneration of TMJ tissue components. It is anticipated that tissue engineering would yield biomimetic TMJ tissues that accurately replicate the natural structure and function of the TMJ, hence providing appropriate management of TMD.

KEYWORDS: Condylar fibrocartilage, Scaffold-based tissue engineering, Scaffold-free tissue engineering, Temporomandibular joint disc, Temporomandibular joint disorder, TMD treatment methods

INTRODUCTION:

The temporomandibular joint (TMJ) is a synovial joint that facilitates mandibular mobility in relation to the cranial base and disperses typical function-related and parafunction-related stressors, such as speaking and chewing (clenching and bruxism). Because of its hinging and sliding properties, it is frequently referred to as the ginglymoarthrodial joint. The temporal bone of the skull and the mandibular condyle, or lower jaw, are joined by the TMJ. A fibrocartilaginous disc separates the joint space into superior and inferior compartments, each of which is filled with synovial fluid. The disc is positioned between the mandibular condyle and the glenoid fossa-articular eminence of the temporal bone.

Numerous conditions combined together are called temporomandibular disorders (TMD), and they all impact the TMJ. TMD refers to a diverse range of diseases and dysfunctions that are clinically significant and affect either the related jaw muscles, the TMJ, or both. Reduced range of motion, painful or painless joint noises, and joint and/or muscle discomfort are all signs of TMD. The alternatives for treating TMD differ depending on how severe the condition is. For people with TMD in its early stages, non-invasive

and minimally invasive therapies are recommended, whilst more intrusive methods should be saved for patients with the condition in its later stages. Regretfully, no therapy reliably results in a lasting recovery, and many patients need additional procedures or rounds of treatment. The development of innovative treatments, such as tissue engineering-based techniques, is necessary due to the absence of consistently viable therapeutic options. The tissue structure and function of the TMJ are covered in this overview in relation to the TMD treatment options available today. The production of the TMJ tissue components thus becomes the subject of significant advancements in the field of tissue engineering. In particular, cell-based techniques for scaffold-free and scaffold-based procedures are covered.

TMJ STRUCTURE AND FUNCTION:

It is essential to obtain all design parameters from the native tissue due to the intricate stress patterns that synthetic tissues would encounter in the TMJ. The high incidence of TMD and limited regenerating ability of TMJ disc, condyle, and condylar fibrocartilage replacements in particular have created a need for these tissues[1,2].

Condylar fibrocartilage has different biochemical characteristics depending on the zone. Unlike hyaline articular cartilage, which has a small amount of type II collagen, the superficial fibrous zone has a high concentration of type I collagen[3]. Subordinate to the fibrous zone is the proliferative zone, which serves as a reservoir for cells. Collagen type I is more prevalent in this layer, just like it is in the fibrous zone[4]. Chondrocytes fill the mature and hypertrophic zones, where collagen type II predominates in the extracellular matrix (ECM) but collagen types I and X are also present[5]. Mandibular condylar fibrocartilage has much less glycosaminoglycan (GAG) by weight than hyaline articular cartilage[6]. The composition of collagen and GAG affects the mechanical qualities of tensile and compressive strength[7]. In terms of tissue engineering, this idea of imitating the characteristics of original tissue is crucial.

TMD AND RECENT TREATMENT MODALITIES:

The pathophysiology of TMD is poorly known, and its aetiology is multifactorial and complicated[8]. It is appropriate to classify the variables that lead to TMD development and progression as predisposing, initiating, and perpetuating[9,10]. Trauma[11] , malocclusion[12] , oestrogen impact[13] , bruxism[14] , genetic differences[15] , and even psychological elements[16] are a few examples of these issues. Regardless of the exact mix of reasons causing the condition, they all result in mechanical stress on the joint's constituent parts, which in turn causes osteoarthrosis and degenerative changes to eventually emerge[17,18] . Therefore, finding and removing the main cause of TMD would be the best course of action.

There are now non-invasive, minimally invasive, and invasive TMD treatment methods available. In order to address the possible aetiology of TMD as well as its associated symptoms, a combination of these therapies is typically used. Physical therapy, acupuncture, pharmaceuticals, and occlusal splints (orthotics)[19] are a few non-invasive therapeutic options. Patients with TMD may be offered several classes of oral or topical drugs to treat pain and discomfort, depending on the severity of their condition[20]. Arthrocentesis, arthroscopy, and intra-articular injections are examples of minimally invasive therapy techniques. Medication such as corticosteroids alone or in combination with high molecular weight sodium hyaluronate can be injected directly into one or both joint compartments using intra-articular injections[21,22]. The direct access to the joint space provided by these procedures is a benefit. Even though several studies have shown a considerable reduction in TMD symptoms, recurrent injections and/or

arthroscopies are not advised, and as a result, the long-term effectiveness of these therapies is still debatable.

Surgical procedures involving open joint replacement (arthrotomy) or partial replacement of the joint with alloplastic or autogenous prosthesis (arthroplasty) are examples of invasive therapies. Disc relocation and repair are not recommended because to the procedure's transient success[23]. On the other hand, discectomy, or the whole removal of the TMJ disc, is still often performed and has the potential to significantly improve patients' long-term quality of life when they are treated for severe TMD and do not respond to non-invasive methods[24].

Approaches to total joint replacement and reconstruction that make use of metallic prostheses or autologous tissues have also been investigated[25]. Said another way, alloplasty is recommended for adults, but autologous reconstruction is suggested in children because of the capacity of autologous implants to develop and remodel[26]. While alloplastic devices have been linked to degradation and heterotopic bone development [26,27] more recent, custom-made prostheses appear to provide good results for up to 15 years.

TISSUE ENGINEERING APPROACHES FOR TMJ TISSUES

A possible alternative for replacing or repairing the damaged tissues of the physiologically complex and physically demanding TMJ is tissue engineering. Historically, scaffolds, stimuli, and cells have been the main components of tissue engineering. A recent technique that does not require a scaffold is cell-based[28]. This section covers the engineering of condylar fibrocartilaginous and TMJ disc tissues, categorised into scaffold-based and scaffold-free approaches. Cells and stimuli specific to each tissue type are also described in relation to the methodology under discussion.

TMJ DISC:

Alginate hydrogels[29] , polylactic acid (PLA)[30] , polyglycolic acid (PGA)[31,32], poly–L–lactic acid (PLLA)[33] , decellularized native extracellular matrix materials[34] , polytetrafluoroethylene (ePTFE) monofilaments[35] , poly (glycerol sebacate) (PGS)[36] , and, more recently, polycaprolactone (PCL) polyester are some of the scaffolds utilised in TMJ disc tissue engineering. Although matrix production was enhanced by the inclusion of transforming growth factor-β1 (TGF-β1), basic fibroblast growth factor (bFGF), and insulin-like growth factor-1 (IGF-1), the scaffold still breaks down quickly. Consequently, the significantly slower degradation rate of PLLA, an alternative scaffold material, was investigated.

New manufacturing methods might make it possible to create scaffolds that more precisely resemble the distinct features of TMJ components, such as tissue anisotropy. In order to do this, PCL scaffolds with an anisotropic internal structure were 3D printed using additive manufacturing. TMJ discs that have been designed to have better mechanical and biochemical characteristics have been conditioned using mechanical stimuli that approximate physiological loading patterns. During joint movement, the native TMJ disc is subjected to tension, compression, shear, and hydrostatic pressure. Stress-shielding is a possible drawback of employing scaffolds when applying mechanical stimulation. More research is required to optimise pertinent growth factors, dosages, and regimens because there aren't many studies on the effectiveness of growth factors for scaffold-based engineering of TMJ discs.

TMJ CONDYLAR FIBROCARTILAGE

Scaffold-based studies predominate over scaffold-free research when it comes to engineering condylar fibrocartilage. The few attempts that exist to create condylar tissue without the use of scaffolds are

restricted to the formation of a single phase (such as cartilage) by scaffold-free methods. For instance, scaffold-free cartilage was adhered to MSC-seeded alginate in the form of a condyle using fibrin glue to create an osteochondral, condyle-shaped construct. Following an 8-week period of subcutaneous implantation into nude mice, vascularized bone growth and endochondral ossification were noted in the alginate scaffold, but the cartilage phase maintained its characteristic[37]. Histological examination revealed that the integration between the two phases was preserved, however the mechanical integrity of the interface was not examined.

Future attempts at condyle tissue engineering should take integration into account, since it is anticipated that achieving a mechanically strong interface between the designed cartilage and bone is a prerequisite for a condylar implant to withstand the mechanically demanding environment of the TMJ.

CONCLUSION

TMD sufferers may benefit from tissue replacement engineering, which is a promising strategy for developing biological remedies for these now unsolvable issues. While there isn't a commercially available tissue-engineered product to treat TMD at the moment, a number of experiments have been conducted in an effort to create suitable instruments for creating TMJ tissues. Using a biomimetic technique to create new tissues from scratch (neotissues) with properties resembling those of the original TMJ is the ideal course of action.

A significant difficulty for the future is the building of shape-specific structures with dimensions close to the particular TMJ tissues that need to be replaced, on top of the tissue engineering challenges already discussed. The majority of research on tissue engineering looks at tiny, flat neotissues.

The surgical access to the failing TMJ tissues and the integration of the neotissues into the native environment provide a significant difficulty, even in the case of massive biomimetic structures. Indeed, it's critical to establish suitable surgical techniques for treating the TMJ, particularly when it comes to implanting tissue-engineered prostheses. Achieving neotissue integration into the TMJ is crucial and should be done in tandem with surgical methods. Although its effects have not been investigated in vivo, LOXL2 appears to have integrative effectiveness in vitro, as was previously reported. Finding elements that can strengthen the interfacial bond between neotissues and native tissues should be a priority.

The science of tissue engineering is about to transition from bench to bedside treatment of TMD, thus it's critical that the FDA provide the right regulations to support the successful creation of acceptable therapeutic treatments. Though there are numerous obstacles to overcome, tissue engineering presents a fantastic potential to address TMD, one of the most infamously challenging musculoskeletal issues, with meaningful remedies.

ACKNOWLEDGEMENTS

All authors contributed equally to this manuscript. The study was fully funded and carried out by department of prosthodontics, crown & bridge of sardar patel post graduate institute of dental and medical sciences, Lucknow, Uttar Pradesh, India.

ABBREVIATIONS

TMJ- Temporomandibular Joint
TMD- Temporomandibular Disorder
ECM- Extracellular matrix

GAG- Glycosaminoglycan
PLA- Polylactic acid
PGA- Polyglycolic acid
PLLA- Poly–L–lactic acid
PTFE- Polytetrafluoroethylene
PGS- Poly (glycerol sebacate)
PCL- Polycaprolactone
TGF-β- Transforming growth factor-β1
BFGF- Basic fibroblast growth factor
IGF-1- Insulin-like growth factor-1

REFERENCES

1. Athanasiou KA, Almarza AJ, Detamore MS, Kalpakci KN. Tissue engineering of temporomandibular joint cartilage. *Synthesis Lectures on Tissue Engineering.* 2009;1:1–122. [Google Scholar] [Ref list]
2. Kalpakci K, Willard V, Wong M, Athanasiou K. An interspecies comparison of the temporomandibular joint disc. *J Dent Res.* 2011;90:193–198. [PMC free article] [PubMed] [Google Scholar] [Ref list]
3. Ngan PW, Deguchi T, Roberts EW. *Orthodontic Treatment of Class III Malocclusion.* 2014 [Google Scholar] [Ref list]
4. Wang L, Lazebnik M, Detamore M. Hyaline cartilage cells outperform mandibular condylar cartilage cells in a TMJ fibrocartilage tissue engineering application. *Osteoarthritis and Cartilage.* 2009;17:346–353. [PubMed] [Google Scholar] [Ref list]
5. Kuroda S, Tanimoto K, Izawa T, Fujihara S, Koolstra J, Tanaka E. Biomechanical and biochemical characteristics of the mandibular condylar cartilage. *Osteoarthritis and Cartilage.* 2009;17:1408–1415. [PubMed] [Google Scholar] [Ref list]
6. Delatte M, Von den Hoff JW, Van Rheden RE, Kuijpers-Jagtman AM. Primary and secondary cartilages of the neonatal rat: the femoral head and the mandibular condyle. *Eur J Oral Sci.* 2004;112:156–162. [PubMed] [Google Scholar] [Ref list]
7. Detamore MS, Athanasiou KA. Structure and function of the temporomandibular joint disc: implications for tissue engineering. *J Oral Maxillofac Surg.* 2003;61:494–506. [PubMed] [Google Scholar] [Ref list]
8. Pullinger AG, Seligman DA. Multifactorial analysis of differences in temporomandibular joint hard tissue anatomic relationships between disk displacement with and without reduction in women. *J Prosthet Dent.* 2001;86:407–419. [PubMed] [Google Scholar] [Ref list]
9. Berger M, Szalewski L, Bakalczuk M, Bakalczuk G, Bakalczuk S, Szkutnik J. Association between estrogen levels and temporomandibular disorders: a systematic literature review. *Przeglad menopauzalny= Menopause review.* 2015;14:260–270. [PMC free article] [PubMed] [Google Scholar] [Ref list]
10. Bi RY, Ding Y, Gan YH. A new hypothesis of sex-differences in temporomandibular disorders: Estrogen enhances hyperalgesia of inflamed TMJ through modulating voltage-gated sodium channel 1.7 in trigeminal ganglion? *Med Hypotheses.* 2015;84:100–103. [PubMed] [Google Scholar] [Ref list]
11. Fischer DJ, Mueller BA, Critchlow CW, LeResche L. The association of temporomandibular disorder pain with history of head and neck injury in adolescents. *J Orofac Pain.* 2006;20 [PubMed] [Google Scholar] [Ref list]

12. Barrera-Mora JM, Escalona EE, Labruzzi CA, Carrera JML, Ballesteros EJC, Reina ES, Rocabado M. The relationship between malocclusion, benign joint hypermobility syndrome, condylar position and TMD symptoms. *CRANIO®* 2012;30:121–130. [PubMed] [Google Scholar] [Ref list]
13. Stemig M, Myers SL, Kaimal S, Islam MS. Estrogen receptor-alpha polymorphism in patients with and without degenerative disease of the temporomandibular joint. *CRANIO®* 2015;33:129–133. [PubMed] [Google Scholar] [Ref list]
14. Dias GM, Bonato LL, Guimarães JP, Silva JNN, Ferreira LA, Grossmann E, Carvalho ACP. A Study of the Association Between Sleep Bruxism, Low Quality of Sleep, and Degenerative Changes of the Temporomandibular Joint. *J Craniofac Surg.* 2015;26:2347–2350. [PubMed] [Google Scholar] [Ref list]
15. Meloto CB, Serrano PO, Ribeiro-DaSilva MC, Rizzatti-Barbosa CM. Genomics and the new perspectives for temporomandibular disorders. *Arch Oral Biol.* 2011;56:1181–1191. [PubMed] [Google Scholar] [Ref list]
16. Suvinen TI, Reade PC. Temporomandibular Disorders: A Critical Review of the Nature of Pain and Its Assessment. *J Orofac Pain.* 1995;9 [PubMed] [Google Scholar] [Ref list]
17. Jerjes W, Upile T, Abbas S, Kafas P, Vourvachis M, Rob J, Mc Carthy E, Angouridakis N, Hopper C. Muscle disorders and dentition-related aspects in temporomandibular disorders: controversies in the most commonly used treatment modalities. *Int Arch Med.* 2008;1:23. [PMC free article] [PubMed] [Google Scholar] [Ref list]
18. Wang X, Zhang J, Gan Y, Zhou Y. Current understanding of pathogenesis and treatment of TMJ osteoarthritis. *J Dent Res.* 2015;94:666–673. This short review paper gives a clear and comprehensive understanding on the pathogenesis and current treatment options of TMJ disorders. [PubMed] [Google Scholar] [Ref list]
19. Klasser GD, Greene CS. Oral appliances in the management of temporomandibular disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2009;107:212–223. [PubMed] [Google Scholar] [Ref list]
20. Hersh EV, Balasubramaniam R, Pinto A. Pharmacologic management of temporomandibular disorders. *Oral Maxillofac Surg Clin North Am.* 2008;20:197–210. [PubMed] [Google Scholar] [Ref list]
21. Dym H, Bowler D, Zeidan J. Pharmacologic Treatment for Temporomandibular Disorders. *Dent Clin North Am.* 2016;60:367–379. [PubMed] [Google Scholar] [Ref list]
22. Machado E, Bonotto D, Cunali PA. Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: a systematic review. *Dental Press J Orthod.* 2013;18:128–133. [PubMed] [Google Scholar] [Ref list]
23. Dolwick MF. Disc preservation surgery for the treatment of internal derangements of the temporomandibular joint. *J Oral Maxillofac Surg.* 2001;59:1047–1050. [PubMed] [Google Scholar] [Ref list]
24. Dimitroulis G. Condylar morphology after temporomandibular joint discectomy with interpositional abdominal dermis-fat graft. *J Oral Maxillofac Surg.* 2011;69:439–446. [PubMed] [Google Scholar] [Ref list]
25. Vega LG, González-García R, Louis PJ. Reconstruction of acquired temporomandibular joint defects. *Oral Maxillofac Surg Clin North Am.* 2013;25:251–269. [PubMed] [Google Scholar] [Ref list]

26. Sidebottom AJ. Alloplastic or autogenous reconstruction of the TMJ. *Journal of Oral Biology and Craniofacial Research.* 2013;3:135–139. [PMC free article] [PubMed] [Google Scholar] [Ref list]
27. Mercuri L. Alloplastic temporomandibular joint replacement: rationale for the use of custom devices. *Int J Oral Maxillofac Surg.* 2012;41:1033–1040. [PubMed] [Google Scholar] [Ref list]
28. Hu JC, Athanasiou KA. A self-assembling process in articular cartilage tissue engineering. *Tissue Eng.* 2006;12:969–979. [PubMed] [Google Scholar] [Ref list]
29. Almarza AJ, Athanasiou KA. Seeding techniques and scaffolding choice for tissue engineering of the temporomandibular joint disk. *Tissue Eng.* 2004;10:1787–1795. [PubMed] [Google Scholar] [Ref list]
30. Ahtiainen K, Mauno J, Ella V, Hagstrom J, Lindqvist C, Miettinen S, Ylikomi T, Kellomaki M, Seppanen R. Autologous adipose stem cells and polylactide discs in the replacement of the rabbit temporomandibular joint disc. *J R Soc Interface.* 2013;10:20130287. [PMC free article] [PubMed] [Google Scholar] [Ref list]
31. Detamore MS, Athanasiou KA. Evaluation of three growth factors for TMJ disc tissue engineering. *Ann Biomed Eng.* 2005;33:383–390. [PMC free article] [PubMed] [Google Scholar] [Ref list]
32. Almarza A, Athanasiou K. Evaluation of three growth factors in combinations of two for temporomandibular joint disc tissue engineering. *Arch Oral Biol.* 2006;51:215–221. [PubMed] [Google Scholar] [Ref list]
33. Allen K, Athanasiou K. Scaffold and growth factor selection in temporomandibular joint disc engineering. *J Dent Res.* 2008;87:180–185. [PubMed] [Google Scholar] [Ref list]
34. Brown BN, Badylak SF. Extracellular matrix as an inductive scaffold for functional tissue reconstruction. *Transl Res.* 2014;163:268–285. [PMC free article] [PubMed] [Google Scholar] [Ref list]
35. Springer IN, Fleiner B, Jepsen S, Açil Y. Culture of cells gained from temporomandibular joint cartilage on non-absorbable scaffolds. *Biomater.* 2001;22:2569–2577. [PubMed] [Google Scholar] [Ref list]
36. Hagandora CK, Gao J, Wang Y, Almarza AJ. Poly (glycerol sebacate): a novel scaffold material for temporomandibular joint disc engineering. *Tissue Eng Part A.* 2012;19:729–737. [PMC free article] [PubMed] [Google Scholar] [Ref list]
37. Sheehy EJ, Mesallati T, Kelly L, Vinardell T, Buckley CT, Kelly DJ. Tissue Engineering Whole Bones Through Endochondral Ossification: Regenerating the Distal Phalanx. *Biores Open Access.* 2015;4:229–241. [PMC free article] [PubMed] [Google Scholar] [Ref list]