REVIEW ARTICLE

# Bioengineered TMJ Replacement: The Futuristic Approach

Neha Singh[1], Savitha Dandekeri[2], K.Kamalakanth Shenoy[3]

1- P.G Student, Department Of Prosthodontics,Yenepoya Dental College, Deralakatte, Mangalore,India.

2-Professor,Department Of Prosthodontics,Yenepoya Dental College, Deralakatte, Mangalore, India.

3- Senior Professor And H.O.D Department Of Prosthodontics,Yenepoya Dental College, Deralakatte, Mangalore,India,

Correspondence to:
*Dr. Neha Singh*
*Yenepoya Dental College , Deralakatte, Mangalore-575018*
*E-mail:- drneha1709@Gmail.Com*
*Phone :- 09987193626 , 8147470955*

Contact Us : editor@ijdmr.com
Submit Manuscript : submissions@ijdmr.com
www.ijdmr.com

## ABSTRACT

TMJ is a ginglymoarthroidal joint capable of both rotational and translational movements while masticating, swallowing or speaking. During masticatory function, the both-side joints work in harmony with adjacent structures including masticatory muscles, teeth (occlusion), tongue, etc. and sustain heavy and repeated bite force or loading. The function of the articular disc is the absorption of the compression load to the joint. It is susceptible to forward displacement due to the increase of the friction coefficient and the degeneration of the collateral ligaments. An anteriorly displaced disc will lead to higher compressive and tangential stresses in the posterior band of the disc and to a fibrotic change or eventual perforation of that zone of the disc. This disharmony may culminate to a more severe stage of degenerative osteoarthritis, and joint replacement leading to limited mouth opening , compromised function and speech. TMJ prosthesis has evolved as a successful alternative for more than 30 years and served to restore the function of temporomandibular joint disorder (TMD) patients. Recent advances in tissue engineering may provide an alternative to traditional strategies to repair and regenerate the TMJ. Study of the biomechanism of TMJ prostheses could enhance our knowledge in the pathogenesis of TMD and success in the regeneration of TMJ.

KEYWORDS: Biomechanism , Temporomandibular joint disorder (TMD) , Temporomandibular joint (TMJ) , Tissue engineering , TMJ prosthesis.

## INTRODUCTION

Temporomandibular joint disorder (TMD) is a collective term that involves temporo-mandibular joint, masticatory muscles and associated structures. It has been claimed that 6 to 12 percent of the adult population suffer from temporo-mandibular disorders or myofascial pain dysfunction syndrome (MPDS).[1] The various contributing factors are occlusal disturbances, para-function, psychological or emotional factors. Hence TMD has multifactorial yet elusive etiology.[2]

Signs and symptoms include pain, joint sounds (click or crepitations), trismus (limited range of motion), impaired jaw function, deviation or deflection upon mouth opening, malocclusion, and closed or open locking.[3] Painful disorders involving the temporo-mandibular joint (TMJ) have a prevalence ranging from 15-60% for reported symptoms and 30-80% for clinical signs.[4] Approximately 25% of those individuals experiencing temporo-mandibular pain are pertinent to the pursuit of treatment as it the

*How to cite this article:*
Singh N, Dandekeri S, Shenoy KK. Bioengineered TMJ Replacement: The Futuristic Approach. Int J Dent Med Res 2014;1(3):118-128.

most common chief complaint of the patients.[5]

The Research Diagnostic Criteria for TMD, classifies TMD into three categories, internal derangement, myogenic disorders and arthritis or arthrosis.[6] Articular disc displacement (internal derangement) is the most common articular disorder.[7,8] Myogenic disorders include myalgia (myofascial pain, fibromyalgia), myospasm, splinting, and fibrosis/contracture. TMJ pain from an articular disorder may conversely lead to myofascial pain due to reflex muscle contractions in the muscles of mastication.[9] In a classification of disc displacement by magnetic resonance imaging (MRI), Wilkes promotes the theory that internal derangement logically progresses to degenerative joint disease.[10]

The progressively deleterious stages of pathoses and clinical dysfunction such as osteoarthritis, osteoarthrosis and, in late stages, ankylosis are some of the possible sequelae to internal derangement (ID). Arthroplasty and joint replacement are generally the choice of treatment for these late stage sequelae. TMJ reconstruction and total joint replacement have been developed for more than 30 years. In the 1970s, Kent-Vitek TMJ prosthesis failed due to the foreign body reactions to proplast and Teflon used in the manufacture of the glenoid fossa component.[11] Until now, TMJ replacement is rare in reconstructive surgery as compared with hip and knee joint replacement. The difficulties encountered today underline the importance of collective research efforts from four major categories: tissue engineering, biomechanics, clinical community, and biology.[12]

In this review, the plethora from pathogenesis of TMD's to the biomechanics of TMJ prosthesis and the innovations of TMJ bioengineering tissue which have emerged recently for TMJ replacement has been significantly explored.

## PATHOGENESIS OF TMD'S

The temporo-mandibular joint is a cranio-mandibular articulation formed by the mandibular condyle and squamous portion of the temporal bone. The TMJ is a load-bearing articulation that is connected to its contralateral counterpart by a single bone (i.e., the mandible connects both TMJs with the cranium). The articular surfaces of the TMJ are composed of fibrocartilages.[3,12] The articular disc is a fibrous tissue composed of bundles of collagen fibres and accommodates the condyle's movement. The main function of the disc is the absorption of compressive loads from the mandible and thus protect the thin temporal bone of the mandibular fossa.[13] The condyle both rotates within the fossa and translates anteriorly along the articular eminence. The translational ability of the condyle helps in achieving maximal incisal opening as compared to the rotation alone.[14]

In internal derangement, the disc is displaced anteriorly. Therefore, there is excessive stretching of the retro-discal tissue, which causes continuous loading force from the mandibular condyle. In many patients, the disc is recaptured while opening the mouth and is known as "disc displacement with reduction." This recapture usually results in TMJ sounds like clicking or popping and results in the full translational movement of the condyle. The reciprocal (closing) click represents the condyle returning to the retro-discal tissue and the disc returning to an anterior position during the mandibular closure. As the disease progresses, the disc are pushed more forward and the retro-discal tissue is stretched and loosened. Anterior displacement without reduction resumes eventually and is known as the closed lock.

The condyle's forward translation is limited by the disc's anterior position and is unable to reduce onto the disc, thus allowing only for rotational and not translational movement. Patients with acute or sub-acute closed lock typically report a sudden onset of pain and inability to open more than 20 to 30 mm. The patient may give a history of joint noise that suddenly cease with the onset of signs and symptoms. Clinically, the mandible deviates on opening to the affected side due to the ability of the unaffected joint to translate. Additionally, excursive mandibular movements to the contralateral side are limited. Recovery of function is due to stretching the retro-discal tissue over weeks to months, restoring translational movement.[7,14]

The retro-discal tissue has shown to have some capacity to adapt to the compressive forces and may transform into a "pseudodisc." However, the adaptive ability of the disc may be compromised and a progressive degenerative joint disease may result.[3,14]

## FEA STUDIES ON TMJ KINEMATICS

Various researchers suggested that one of the causative factors of TMD's is excessive loading of the joint. Stress loading may be attributed to clenching, bruxism, trauma, and stress induced by muscle tension. Studying the kinematics of TMJ might aid in proper understanding of the pathogenesis of TMJ disorders. The TMJ is a clinically critical and inaccessible location in the face that is not amenable to any invasive exploration or experiment.[4-16]

Therefore, computational investigations analysed and predicted the regional stresses and strains in TMJ.[17] In 1990s, some investigators started to create finite element eminence.[18-20] Chen et al. obtained the geometry of TMJ from MRI and measured the tissue proportions from cadaver TMJs.[21] The contours of TMJ components were digitized into a computer-aided engineering software for FEA modelling. Their results demonstrated that, with 9 mm incisor opening, the stress in the condyle was dominantly compressing and in the fossa-eminence complex was dominantly tensile. Both stresses were concentrated near the articulating contact area. To evaluate the validity of FEA models, DeVocht et al. measured the stress in the TMJ by insertion of a small strip of pressure-sensitive film in a cadaver's joint spaces.[22] The recorded maximum stresses were between 5.6 and 9.9, which was in accordance with the FEA prediction of between 6.4 and 8.2. They concluded that the finite element model of the TMJ provide a reasonable approximation of the actual physical situation of the articulating contact area.

Tanaka and Koolstra analysed stress distribution during jaw opening using a three-dimensional finite element model of human temporomandibular joint.[23] They noticed differences in the stress distribution between a normal control and the internal derangement patients. In their later studies, they suggested that increase of the frictional coefficient between articular surfaces may be a major cause of the onset of disc displacement. Nitzan proposed a theoretical concept that the process of lubrication impairment in TMJ may be involved in the pathogenesis of disc displacement.[24]

Other researchers compared the stress distribution in the healthy joint and in two pathologic situations, one joint affected with an anterior disc displacement with reduction (ADDWR) and one without reduction (ADDWOR), during an opening movement of the mouth with clinical TMJ FEA model.[25] Finally, the results suggested that an anterior

displacement of the disc led to higher compressive and tangential stresses in the posterior band of the disc than in the healthy one eventually perforating the disc.

## BIOMECHANICS OF TMJ PROSTHESES

TMJ prostheses function as total replacement systems for condylar replacements, fossa-eminence replacements, and total joint prostheses. The articular disc replacement is indicated for severely deformed disc or disc perforation. TMJ fossa-eminence prostheses are used as inter-positional devices in the case of TMJ ankylosis. In cases of severe osteo-arthrosis, condylar prostheses or total joint prostheses can be used to restore the lost height of the condyle.[26]

Although many individuals and research groups have introduced different designs of the TMJ prosthetic devices, only three TMJ implants (from three manufacturers) are currently approved by the FDA for clinical applications

- TMJ Implants/Christensen total/partial joint replacement system (TMJ Implants, Inc., Golden, CO, USA).[27,28]
- TMJ Concepts Customized computer-assisted design/computer-assisted manufacture (CAD/CAM) total TMJ reconstruction system (Techmedica, now TMJ Concepts Inc., Ventura, CA, USA).[29]
- Biomet/Lorenz Microfixation Total TMJ prosthesis (Biomet/Lorenz, Warsaw, IN, USA).[30]

The TMJ Implants/Christensen total/partial joint replacement system is the only replacement sytsem that has metal-to-metal combination. It demonstrated various disadvantages like increased frictional torque that could result in loosening of the prosthesis, cellular toxicity and carcinogenicity. While TMJ Concepts (Ventura) and Biomet-Lorenz Microfixation system consist of a mandibular component made of Co-Cr-Mo alloys that articulates with the glenoid fossa component made of ultra-high molecular weight polyethylene.

In cases of unilateral joint replacement, the restricted translational movements forced the mandible to the prosthetic side, leading to unnatural movements of the natural joint. Von Loon et al. suggested that these unnatural movements can cause overloading of the natural joint and the eventual development of osteoarthritis and internal derangements in the joint, leading to replacement of the natural joint as well.[26,30] In cases of bilateral replacement of the joints, translational movements of the whole mandible are restricted. Due to the lack of translational movement the incisal opening is reduced leading to decreased chewing efficiency.

In TMJ replacement follow-up studies, Mercuri et al. obtained the measures of mandibular inter-incisal opening and lateral excursions from direct measurements by patients themselves. They noted a 24% and a 30% improvement in mouth opening after two years and ten years, respectively. On the other hand, at two years post-implantation, there was a 14% decrease in left lateral excursion and a 25% decrease in right lateral excursion from the pre-implantation data.[31-34]

Kashi et al. used an FEA model to quantify the stress distribution in the Christensen implant and bone.[35] A 300-N force was applied at the top of the implant vertically. The investigators found that the maximum stresses occurred at the location of the first screw hole (closest to the condyle) and the highest microstrains were observed in the bone adjacent to the first screw hole. .

The articular disc is designed to distribute joint forces as well as to limit the depth to which the condyle is compressed into soft tissues covering the temporal bone without distorting the surface[36]. Al-Sukhun et al. evaluated biomechanical loading of the temporomandibular joint when using a biodegradable laminate implant to replace the articular disc.[37] The authors concluded that the use of bio-resorbable laminate implants proved to be an efficient technique to replace the articular disc and promote normal function of the temporomandibular joint as they observed a remarkable reduction in the Von Mises stresses acting on the mandibular condyle. Some workers focused primarily on calculating absolute magnitude of TMJ loading with finite element models. The reported magnitudes of TMJ loading differ significantly from one another because of differences in simulation conditions. Therefore, a more comprehensive biomechanical analysis of the TMJ is essential for better understanding of the movements, applied forces, and resultant stresses in natural and/or artificial joint components.[38-39]

## TISSUE ENGINEERING FOR TMJ RECONSTRUCTION

The primary methods used to reconstruct the TMJ included autogenous bone grafting, such as harvesting from the rib, or the use of alloplastic materials, with neither being ideally suited for the task and sometimes leading to unwanted adverse effects.[40] Collectively, grafting procedures as well as prosthetic implants share certain drawbacks, such as implant wear, dislocation, suboptimal biocompatibility, donor site limitation and morbidity, immunological challenge, and potential pathogen transmission.[41] With the recent advances in the understanding of stem cell biology and biomaterials, it is more promising to construct a bioengineered TMJ replacement that is bio-compatible and capable of withstanding the physiologic loads required of this joint.

Tissue engineering is composed of three critical elements, including cells, scaffold and bioactive molecules. It is complicated to engineer TMJ with all cellular components in the right place as it is composed of different tissues including bone, cartilage, ligament, muscle and synovial membrane. Although the tissue engineering of TMJ would give rise to future challenges like to design scaffolds that provide optimal environments for the progenitor or stem cells to replace the damaged tissue, or to stimulate indigenous cells; and to develop bio adhesives that promote tissue integration and prevent scaffold detachment during joint articulation.

### *Stem Cells*

The chondrocyte is the predominant cell type, but has limited potential for intrinsic repair because it is well differentiated. Embryonic stem cells and induced pluripotent stem cells have recently gained most attention. However, presently, it is the adult mesenchymal stem cell that is prime proponent in articular cartilage repair. Mesenchymal stem cells are stem cells derived from somatic tissue which can be differentiated into mesenchymal lineages such as bone, cartilage and fat.[42]

Unlike primary cells such as chondrocytes that have limited capacity to propagate, stem cells have the additional advantage of being stimulated by specific biological cues such as differentiating into osteoblasts, chondrocytes, fibroblasts, and myocytes. These cells types, in turn, generate cartilage, bone, ligaments, and muscles, respectively, to derive all key components of the TMJ complex. Synovial membrane-derived mesenchymal stem cells are regarded as particularly attractive for cartilage repair due to their close vicinity to cartilage,

their high chondrogenic capacity and easy availability during arthroscopy.[43-47]

The embryonic stem cells can provide a more unlimited supply of precusor cells for articular cartilage tissue engineering and regenerative medicine applications compared to the mesenchymal stem cells,. A recent study successfully induced human embryonic stem cells to differentiate to chondrocytes by adding bone morphogenetic protein 7 (BMP-7) and transforming growth factor beta 1 (TGF-1) to the culture medium without embryoid body formation.[48] However, the potential teratoma formation is a major concern for embryonic stem cells in clinical application. Mesenchymal stem cells are regarded to be safer than embryonic stem cells by most scholars at the present time. On the other hand, induced pluripotent stem cells (iPS) represent a very exciting possibility once the carcinogenic potential is eradicated.[49]

***Scaffolds***

A crucial requirement for joint repair is that the scaffolding should be attached to the cartilage lesions and should integrate with the tissue. Not only this but also the attachment must balance temporary mechanical function with mass transport to aid biological delivery and tissue engineering. In addition to being patient-specific , the scaffolds should facilitate cell attachment and regulate cell differentiation. Also they must be biodegradable, with non-toxic by-products, and exhibit favourable resorption kinetics to maintain initial stability.

The materials can be divided into natural or synthetic, based on the sources. Natural scaffolds may be subdivided into (1) protein-based matrices such as collagen and fibrin, (2) mineral-based matrices such as autogenous, allogenic and xenogenic bone grafts, and (3) carbohydrate-based matrices such as alginate, agarose, chitosan and hyaluronan. Synthetic materials have been used extensively both in vitro and in vivo. They include polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and their derivatives, for example poly (lactic-co-glycolic) acid (PLGA). The synthetic materials have been popular because of their easy moulding characteristics, relatively easy production, and the ability to control dissolution and degradation. However, their major weakness is biocompatibility. They are degraded by a hydrolytic reaction, thereby high concentrations of acidic by-products and particulates can be released, causing inflammation, giant cell reaction and chondrocyte death owing to a reduction in pH.[50]

Recently, “solid free-form fabrication” methods, such as electrospinning and selective laser sintering, have been studied extensively for their potential use in osteochondral tissue engineering applications.[51,52] But a major limitation of the electrospinning approach is the thickness it produces. One method for increasing overall scaffold thickness is to bond multiple electrospun scaffolds together with a biocompatible gel.[53] For the scaffolds to be patient specific new techniques such as computational topology design or image-based design were developed to match defect site geometry.[51-53]

Considering cell behaviour, both chondrocytes and mesenchymal stem cells face the problem with fibroblastic de-differentiation and terminal differentiation to a hypertrophic phenotype in vivo. It is therefore likely that these cell types require some degree of molecular modulation for successful application. This is fulfilled by signalling or bioactive molecules that stimulate the cells to more vigorous regeneration of new and normal tissue.

***Signalling or Bioactive molecules***……

An imbalance between the anabolic and

catabolic signalling factors has a significant impact on the development of osteoarthritis. This interaction therefore also plays a significant role in the regenerative process. The combination of growth factors with cells and scaffolds to produce more phenotypically suitable tissue-engineered constructs is highly promising.

In vitro studies have shown TGF-1 to induce mesenchymal stem cell differentiation to chondrocytes.[54] However, it does have negative effects such as fibrosis and osteophytosis if given in higher doses.[55] Therefore, the dosage of different growth factors is a critical issue. Research has shown that BMPs, particularly BMP-4, -6 and -7, have a positive effect on the chondrogenic phenotype, increasing the amount of collagen type II and proteoglycan production and reducing collagen type I.[48,56,57] Insulin-like growth factor (IGF-1) is the main anabolic growth factor of articular cartilage. It aids to increase proteoglycan and collagen type II synthesis as well as provide chondrocyte phenotypic stability. IGF-1 is stored in the extracelluar matrix, bound to proteolgycans via IGF-1-binding proteins. It is likely that the interaction between it and the binding proteins regulate its activity, as an increase in catabolic activity causes proteolysis of these proteins, thereby modulating its release.[58] FGF-2 is an important mitogen for cells of mesodermal origin and is a chemo-attractant for endothelial cells.[59] It is also shown that FGF-2 inhibits terminal differentiation of chondrocyte, which is of particular interest with regard to mesenchymal stem cells, as being able to stimulate chondrogenic differentiation and inhibit terminal differentiation is essential. Although most attention has been paid to FGF-2, FGF-18 also has great potential in articular cartilage tissue engineering, with a number of recent studies showing the potential to stimulate cell proliferation and differentiation and matrix production both in-vitro and in-vivo.[60]

### *Biophysical Stimulation Of Cells By Bioreactors*

Conventional rotating bioreactors only provided convective flow around graft surfaces but not in the graft interior.[61] New generations of bioreactors that perfuse through the cultured constructs have been preferred for engineering bone, because they can provide micro-environmental control and biophysical stimulation of the cells in the large constructs.[62] This new bioreactor can provide interstitial flow and therefore enhance the mass transport and generate hydrodynamic shear, which are critically important for bone development and function.

### *Futuristic Summons*

It has been reported that transplanted stem cells kept a high versatility during chondrogenic differentiation and responded to the shift from chondrogenic medium to in vivo exposure under non-joint like conditions by changing their differentiation , thus hampering the stability.[63] How to lock the transplanted cells in a reached differentiation state remains a problem. The ability to engineer large and viable bone grafts customized to the specific defects and meet the clinical demands of diverse craniofacial and orthopaedic applications with great precision is complicated and difficult.

With the advance of computational topology design and solid free-form fabrication, the specificity is gradually improved. However, the long-term shrinkage rate after in vivo transplantation deserves more investigation. Engineering of vascularized graft in a way that allows immediate connection to the vascular supply of the host is another issue critical for the clinical application. Additionally, the

engineered osseous grafts do not replicate the entire joint anatomy inclusive of the cartilage layer and the joint disc. Multipotent stem cells may provide part of the solutions. It has been demonstrated feasible to construct an entire articular condyle with stratified cartilaginous and osseous components from a single population of adult mesenchymal stem cells.[64]

## CONCLUSION

Biomechanical studies help to explore and understand the disease entity as the etiology of the disease remains unknown. Combination of clinical researches and biochemical studies can get full understanding of the disease. Though the majority of TMD conditions can be successfully managed by various non-surgical and less-invasive treatments, joint replacement becomes the only potential remedy for certain TMD circumstances such as Osteoarthritis, ankylosis, etc. The mechanical failure of the implant material has been a major drawback of TMJ prosthesis. Now we are facing the crossroad of alloplastic prosthesis and bioengineering implant of TMJ. Tissue engineering by stem cells and biodegradable scaffold seem to hold the prospective of TMJ replacement in the future.

## REFERENCES

1. L. LeReschel, "Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors," Crit. Rev. Oral Biol.Med.1997; 8(3): 291-305.
2. Y. Y. Shiau, H. W. Kwan and C. Chang, "Prevalence of temporomandibular disorder syndrome (TMD) in university students: a third year report of the epidemiological study in Taiwan," Chin. Dent. J.1989; 8: 106-116.
3. S. B. Milam, "Pathophysiology and epidemiology of TMJ," J. Musculoskel. Neuron Interact.2003; 3(2): 382-390.
4. G. E. Carlsson and L. LeResche, "Epidemiology of temporomandibular disorders," in: B. J. Sessle, P. S. Bryant and R. Dionne (Eds.), Temporomandibular Disorders and Related Pain Conditions, Seattle: IASP Press.1995; 211-226.
5. M. Von Korff, S. F. Dworkin, L. LeResche and A. Kruger, "An epidemiologic comparison of pain complaints," Pain.1988; 32(2): 173-183.
6. S. F. Dworkin and L. LeResche, "Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique," J. Craniomandib. Disord.1992; 6(4): 301-355.
7. K. Herb, S. Cho and M. A. Stiles, "Temporomandibular joint pain and dysfunction," Curr. Pain Headache Rep.2006;10(2): 408-414.
8. P. L. Westesson, L. Eriksson and K. Kurita, "Reliability of a negative clinical temporomandibular joint examination: prevalence of disk displacement in asymptomatic temporomandibular joints," Oral Surg. Oral Med. Oral Pathol.1989;68(23): 551-554.
9. O. E. Ogle and M. B. Hertz, "Myofascial pain," Oral Maxillofac. Surg. Clin. North. Am., 2000;12(3): 217-231.
10. C. H. Wilkes, "Internal derangement of the temporomandibular joint: pathological variations" Arch Otolaryngol. Head Neck Surg.1989; 115(44): 469-467.
11. G. J. Kearns, D. H. Perrott and L. B. Kaban, "A protocol for the management of failed alloplastic temporomandibular joint disc implants," J. Oral Maxillofac. Surg.1995; 53(31): 1240-1247.
12. M. S. Detamore, K. A. Athanasiou and J. Mao, "A call to action for bioengineers and dental professionals: directives for the future of TMJ bioengineering," Ann. Biomed. Eng.2007; 35(11): 1301-1311.
13. C. Marchetti, G. Bernasconi, M. Reguzzoni and A. Farina, "The articular disc surface in different functional conditions of the human temporo-mandibular joint," J. Oral Pathol. Med., 1997;26(9): 278-282.
14. M. C. Fletcher, J. F. Piecuch and S. E. Lieblich, "Anatomy and pathophysiology of the temporomandibular joint," in: M. M. Hamilton (Ed.), Peterson's Principles of Oral and Maxillofacial Surgery, Ontario: BC Decker.2004;933-947.
15. K. Brehnan, R. L. Boyd, J. Laskin, C. H. Gibbs and P. Mahan, "Direct measurement of loads at the temporomandibular joint in macaca

arctoides," J. Dent. Res.1981;60(14): 1820-1824, 1981.
16. R. L. Boyd, C. H. Gibbs, P. E. Mahan, A. F. Tichmond and J. L. Laskin, "Temporomandibular joint forces measured at the condyle of macaca arctoides," Am. J. Orthod. Dentofac. Ortho.1990;97(33): 472-479.
17. D. C. Hatcher, "Development of mechanical and mathematical models to study temporomandibular joint loading," J. Prosthet. Dent.1986;55(11): 377-384.
18. T. W. P. Korioth, D. P. Romilly and A. G. Hannam, "Three-dimensional finite element stress analysis of the dentate human mandible," Am. J. Phys. Anthropol.1992;88(31): 69-96.
19. E. Tanaka, K. Tanne and M. Sakuda, "A three-dimensional finite element model of the mandible including the TMJ and its application to stress analysis in the TMJ during clenching," Med. Eng. Phys.1994;16(3): 316-322.
20. J. Chen and L. Xu, "A finite element analysis of the human temporomandibular joint," J. Biomech. Eng.1994;116(35): 401-407.
21. J. Chen, U. Akyuz, L. Xu and R. M. V. Pdaparti, "Stress analysis of the human temporomandibular joint," Med. Eng. Phys.1998;20(7): 565-572.
22. J. W. DeVocht, V. K. Goel, D. I. Zeitler and D. Lew, "Experimental validation of a finite element model of the temporomandibular joint," J. Oral Maxillofac. Surg.2000;59(17): 775-778.
23. E. Tanaka and J. Koolstra, "Biomechanics of the temporomandibular joint," J. Dent. Res.2008;87(45): 989-991.
24. D. W. Nitzan, "The process of lubrication impairment and its involvement in temporomandibular joint disc displacement: a theoretical concept," J. Oral Maxillofac. Surg.2001; 59(23): 36-45.
25. P'erez del Palomarand and M. Doblare, "An accurate simulation of anteriorly displaced TMJ discs with and without reduction," Med. Eng. Physics.2007;29(11): 216-226.
26. J. P. von Loon, L. G. M. de Bont and G. Boering, "Evaluation of temporomandibular joint prostheses: review of the literature from 1946 to 1994 and implications for future prosthesis designs," J. Oral Maxillofac. Surg.1995;53(19): 984-996.
27. L. Guarda-Nardini, D. Manfredini and G. Ferronato, "Temporomandibular joint total replacement prosthesis: current knowledge and considerations for the future," Int. J. Oral Maxillofac. Surg.2008;37(16): 103-110.
28. D. C. Chase, J. W. Hudson, D. A. Gerard, R. Russell, R. Chambers, J. R. Curry, J. E. Latta and R. W. Christensen, "The Christensen prosthesis: a retrospective clinical study," Oral Surg. Oral Med. Oral Pathol.1995;80(21): 273-278.
29. L. G. Mercuri, L. M. Wolford, B. Sanders, R. D. White, A. Hurder and W. Henderson, "Custom CAD/CAM total temporomandibular joint reconstrucion system: preliminary multicenter report," J. Oral Maxillofac. Surg.1995;53(21): 106-115.
30. P. D. Quinn, "Lorenz prosthesis," Oral Maxillofac. Surg. Clin. North Am.2000;12: 93-104.
31. L. M. Wolford, D. A. Cottrell and C. H. Henry, "Temporomandibular joint reconstruction of the complex patient with the Techmedica custom-made total joint prosthesis," J. Oral Maxillofac. Surg.1994;52: 2-8.
32. R. D. Komistek, D. A. Dennis, J. A. Mabe and D. T. Anderson, "In vivo kinetics and kinematics of the normal and implanted TMJ," J. Biomech.1998;31(2): 13.
33. H. J. Yoon, E. Baltali, K. D. Zhao, J. Rebellato, D. Kademani, K. N. An and E. E. Keller, "Kinematic study of the temporomandibular joint in normal subjects and patients following unilateral temporomandibular joint arthrotomy with metal fossa-eminence partial joint replacement," J. Oral Maxillofac. Surg.2007;65(19): 1569-1576.
34. L. G. Mercuri, L. M. Wolford, B. Sanders, R. D. White and A. Giobbie-Hurder, "Long-term follow-up of the CAD/CAM patient fitted total temporomandibular joint reconstruction system," J. Oral Maxillofac. Surg.2002;60(7): 1440-1448.
35. Kashi, A. R. Chowdhury and S. Saha, "Finite element analysis of a TMJ implant," J. Dent. Res.2010;89(29): 241-245.
36. J. R. Fricton, J. O. Look, E. Schiffman and J. Swift. "Long-term study of temporomandibular joint surgery with alloplastic implants compared with nonimplant surgery and nonsurgical rehabilitation for painful temporomandibular joint disc displacement," J. Oral Maxillofac. Surg.2002;60(23): 1400-1411.
37. J. Al-Sukhun, N. Ashammakhi and H. Penttila, "Effects of tissue-engineered articular disc

implants on the biomechanical loading of the human temporomandibular joint in a three-dimensional finite element model," J. Craniofac. Surg.2007;18(1): 782-788.

38. S. Ingawale and T. Goswami, "Temporomandibular joint: disorders, treatments, and biomechanics," Ann. Biomed. Eng.2009; 37(3): 976-996.
39. J. A. Lipton, J. A. Ship and D. Larach-Robinson, "Estimated prevalence and distribution of reported orofacial pain in the United States," J. Am. Dent. Assoc.1993;124(43): 115-121.
40. L. E. Ta, J. C. Phero, S. R. Pillemer, H. Hale-Donze, N. McCartney-Francis and A. Kingman, "Clinical evaluation of patients with temporomandibular joint implants," J. Oral Maxillofac. Surg.2002;60(21): 1389-1399.
41. J. J. Jacobs, J. L. Gilbert and R. M. Urban, "Corrosion of metal orthopaedic implants," J. Bone. Joint. Surg. Am.1998;80(12): 268-282.
42. B. Sacchetti, A. Funari and S. Michienzi, "Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment," Cell.2007;131(53): 324-336.
43. S. Fickert, J. Fiedler and R. E. Brenner, "Identification, quantification and isolation of mesenchymal progenitor cells from osteoarthritic synovium by fluorescence automated cell sorting," Osteoarthritis Cartilage.2003;11: 790-800.
44. M. Q. Wickham, G. R. Erickson, J. M. Gibmle, T. P. Vail and F. Guilak, "Multipotent stroma cells derived from the infrapatellar fat pad of the knee," Clin. Orthop. Relat. Res.2003; 412(91): 196-212.
45. H. Nakahara, V. M. Goldberg and A. I. Caplan, "Culture-expanded human periosteal-derived cells exhibit osteochondral potential in vivo," J. Orthop. Res.1991;9: 465-476.
46. M. M. Bailey, L. Wang, C. J. Bode, K. E. Mitchell and M. S. Detamore, "A comparison of human umbilical cord matrix stem cells and temporomandibular joint condylar chondrocytes for tissue engineering temporomandibular joint condylar cartilage," Tissue Eng.2007;13: 2003-2010.
47. M. Pei, F. He, B. M. Boyce and V. L. Kish, "Repair of full-thickness femoral condyle cartilage defects using allogeneic synovial cell-engineered tissue constructs," Osteoarthritis Cartilage.2009;17: 714-722.
48. T. Nakagawa, S. Y. Lee and A. H. Reddi, "Induction of chondrogenesis from human embryonic stem cells without embryoid body formation by bone morphogenetic protein 7 and transforming growth factor beta 1," Arthritis Rheum.2009;60: 3686-3692.
49. J. Yu, M. A. Vodyanik, K. Smuga-Otto, J. Antosiewicz-Bourget, J. L. Frane, S. Tian, J. Nie, G. A. Jonsdottir, V. Ruotti, R. Stewart, I. I. Slukvin and J. A. Thomson, "Induced pluripotent stem cell lines derived from human somatic cells," Science.2007;318: 1917-1920.
50. M. I. Gray, A. M. Pizzanelli, A. J. Grodzinsky and R. C. Lee, "Mechanical and physiochemical determinants of the chondrocyte biosynthetic response," J. Orthop. Res.1988; 6: 777-792.
51. R. M. Schek, J. M. Taboas, S. J. Hollister and P. H. Krebsbach, "Tissue engineering ostochondral implants for temporary joint repair," Orthod. Craniofacial. Res.2005; 8(3): 313-319.
52. J. M. Williams, A. Adewunmi, R. M. Schek, C. L. Flanagan, P. H. Krebsbach, S. E. Feinberg, S. J. Hollister and S. Das, "Bone tissue engineering using polycaprolactone scaffolds fabricated via selective laser sintering," Biomaterials.2005;26(11): 4817-4827.
53. S. McCullen, P. Miller, S. Gittard, B. Pourdeyhimi, R. Gorga, R. Narayan and E. Loboa, "In situ collagen polymerization of layered cell-seeded electrospun scaffolds for bone tissue engineering applications," Tissue Eng. Part C Methods, doi: 10.1089/ten.TEA.2009.0753, 2010. [Epub ahead of print]
54. R. Flaumenhaft, M. Abe, Y. Sato, K. Miyazono, J. Harpel, C. H. Heldin and D. B. Rifkin, "Role of the latent TGF-beta binding protein in the activation of latent TGF-beta by co-cultures of endothelial and smooth muscle cells," J. Cell Biol.1993;120(82): 995-1002.
55. P. Cassiede, J. E. Dennis, F. Ma and A. I. Caplan, "Osteochondrogenic potential of marrow mesenchymal progenitor cells exposed to TGF-beta 1 or PDGF-BB as assayed in vivo and in vitro," J. Bone Miner. Res.1996;11: 1264-1273.
56. H. M. van Beuningen, H. L. Glansbeek, P. M. van der Kraan and W. B. van den Berg, "Differential effects of local application of BMP-2 or TGF-beta 1 on both articular cartilage composition and osteophyte formation," Osteoarthritis Cartilage.1998;6: 306-317.

57. Sekiya, D. C. Colter and D. J. Prockop, "BMP-6 enhances chondrogenesis in a subpopulation of human marrow stromal cells," Biochem. Biophys. Res. Commun.2001;284(66): 411-418.
58. S. D. Cook, L. P. Patron, S. L. Salkeld and D. C. Rueger, "Repair of articular cartilage defects with osteogenic protein (BMP-7) in dogs," J. Bone Joint Surg.-Am. Vol.2003;85-A(3): 116-123.
59. C. Gaissmaier, J. L. Koh and K. Weise, "Growth and differentiation factors for cartilage healing and repair," Injury.2008;39(1): 88-96.
60. S. H. Lee and H. Shin, "Matrices and scaffolds for delivery of bioactive molecules in bone and cartilage tissue engineering," Adv. Drug. Deliv. Rev.2007;59(4-5): 339-359.
61. D. Davidson, A. Blanc and D. Filion, "Fibroblast growth factor (FGF) 18 signals through FGF receptor 3 to promote chondrogenesis," J. Biol. Chem.2005;280(21): 20509-20515.
62. H. Abukawa, "Reconstruction of mandibular defects with autologous tissue-engineered bone," J. Oral Maxillofac. Surg.2004;62: 601-606.
63. W. L. Grayson, M. Fröhlich, K. Yeager, S. Bhumiratana, M. E. Chan, C. Cannizzaro, L. Q. Wan, X. S. Liu, X. E. Guo and G. Vunjak-Novakovic, "Engineering anatomically shaped human bone grafts," Proc. Natl. Acad. Sci. USA.2010;107(8): 3299-3304.
64. Dickhut, K. Pelttari, P. Janicki, W. Wagner, V. Eckstein, M. Egermann and W. Richter, "Calcification or dedifferentiation: requirement to lock mesenchymal stem cells in a desired differentiation stage," J. Cell Physiol.2009;219(1): 219-226.

Source of Support: Nil
Conflict of Interest: Nil