Review:

Temporomandibular Joint Reconstruction: from Alloplastic Prosthesis to Bioengineering Tissue

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Abstract

Pain and dysfunction of the temporomandibular joint (TMJ) may affect more than 10 percent of the adult people in developed countries. TMJ is a unique jaw joint with 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 and is susceptible to displacement forward 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. The disease thus may progress to a more severe stage of degenerative osteoarthritis, and joint replacement is indicated for the destructed disease entity. TMJ prosthesis has evolved for more than 50 years and served to restore the function of temporomandibular joint disorder (TMD) patients. There are some limitations in the function of the implanted TMJ prosthesis, such as lack of translational motion of the condyle and reduction in opening of the mouth. Recent advances in tissue engineering may provide an alternative to traditional strategies to repair and regenerate the TMJ. For the patient or defect-specific purpose, a three-dimensional (3D) image-based design and multi-phasic tissue fabrication technique is under development and could offer a sophisticated approach to the TMJ reconstruction. The biomechanical analyses of the TMJ prosthesis and the newly developed bioengineering constructs are still very rare. Study of the biomechanism of TMJ could improve our knowledge in the pathogenesis of TMD and success in the regeneration of TMJ.

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

1. Introduction

Temporomandibular joint disorder (TMD) is a disease with pain and dysfunction affecting the jaw joints and related structures. It has been claimed that 6 to 12 percent of the adult population, or approximately 10 million Americans, suffer from temporomandibular disorders or myofascial pain dysfunction syndrome (MPDS) [1]. In Taiwan, it was found that 42.9% of college students had one or more signs of TMD, and girls suffered slightly more often [2]. Occlusal disturbances, parafunction, psychological or emotional factors all have been suggested as contributing factors. However, the etiology is not elucidated exclusively, and TMD is referred to as a disease with multifactors or causes. TMD has a complex of signs and symptoms. Signs and symptoms of TMDs may include pain, joint noise, 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 temporomandibular joint (TMJ) and associated soft tissues are relatively common, with prevalence ranging from 16-59% for reported symptoms and 33-86% for clinical signs [4]. Pain is the most common chief complaint of patients pertinent to pursuit of treatment. Approximately 25% of those individuals experiencing temporomandibular pain will eventually seek treatment [5].

According to the research diagnostic criteria (RDC) for TMD, the complex of TMD includes 3 categories, internal derangement, myogenic disorders and arthritis or arthrosis [6]. Articular disc displacement (internal derangement) is the most frequently encountered articular disorder [7]. The incidence of

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articular disc displacement is unknown. Numerous radiographic, clinical, and cadaveric studies of asymptomatic subjects have shown rates up to 30% [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 (DJD) [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). The treatment of choice for these late-stage sequelae might be arthroplasty and joint replacement. TMJ reconstruction and total joint replacement have been developed for more than 50 years. In the 1980s, due to the materials used having improper wear properties, some TMJ prosthesis were taken off the market [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, we will explore the pathogenesis of TMD from the point of view of biomechanics. Although, the treatment of TMD tends to be conservative nowadays, TMJ replacement is indicated in osteoarthrosis (OA), TMJ ankylosis, etc. We will also review the biomechanism of TMJ prosthesis and the innovations of TMJ bioengineering tissue which have emerged recently for TMJ replacement.

2. Pathogenesis of TMD

The temporomandibular joint is a synovial-lined 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]. The articular disc is a fibrous tissue composed of bundles of collagen fibers and accommodates the condyle's movement. The main function of the disc is the absorption of compression loads from the mandible for protection of the thin temporal bone of the mandibular fossa [13]. The TMJ functions uniquely in that the condyle both rotates within the fossa and translates anteriorly along the articular eminence. Because of the condyle's ability to translate, the mandible can have a much higher maximal incisal opening than would be possible with rotation alone [14].

Internal derangement means the disc is displaced, and mostly anteriorly. When the articular disc becomes displaced anteriorly, there is excessive stretching of the retrodiscal tissue, which then bears the repeated 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 noise (clicking or popping) and full translational movement of the condyle. With mandibular closure, a reciprocal (closing) click represents the condyle returning to the retrodiscal tissue and the disc returning to an anterior position.

As the disease progress, the disc is pushed more forward and the retrodiscal tissue stretched and loosened. Anterior displacement without reduction resumes eventually. Anterior displacement without reduction is also known as closed lock. The condyle's forward translation is limited by the disc's anterior position and is unable to reduce onto the disc, allowing only for rotational and not translational movement. Patients with acute or subacute 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 ceased 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. In chronic disc displacement without reduction, the patient can usually recount a history consistent with acute closed lock that resolved over time. Recovery of function is due to stretching the retrodiscal tissue over weeks to months, restoring translational movement [7].

When the articular disc becomes displaced anteriorly, there is excessive stretching of the retrodiscal tissue, which then bears repeated loading force from the mandibular condyle. This tissue has been shown to have some capacity to adapt to these 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].

3. Pathogenesis of TMD from the viewpoint of biomechanism

Previous research has shown that the TMDs are closely related to stress loading of the joint. Stress loading may be due to clenching, bruxism, trauma, and stress induced by muscle tension. Disc displacement or internal derangement is also correlated with TMDs. Studying the kinematics or biomechanisms of TMJ might lead to an understanding of the pathogenesis of TMJ disorders, and also to the improvement of the success of the TMJ implants. The TMJ is a clinically critical and inaccessible location in the face which is not amenable to any invasive exploration or experiment [15,16]. Therefore, computer modeling offers a promising approach to analyze and predict the regional stresses and strains in TMJ.

In the beginning, the analytical or computational investigations of TMJ biomechanisms focused on the reaction force on the condyle [17]. In 1990s, some investigators started to create finite element analysis (FEA) models for the TMJ, including the condyle, the disc and the articular fossa & 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 and input into a computer-aided engineering software for FEA modeling. Their results demonstrated that, with 9 mm incisor opening, the stress in the condyle was dominantly compressing and in the

fossa-eminance 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.

Tanaka and Koolstra used a three-dimensional finite element model of human temporomandibular joint to analyze the stress distribution during jaw opening [23]. They noticed there existed 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. This mathematical assumption is supported by the accumulated clinical data and laboratory investigations in the literature. Nitzan suggested that translation of the disc in the TMJ is enabled due to the presence of phospholipids and hyaluronic acid [24], which constitute an efficient lubrication system. This system may break down in the presence of uncontrolled free radicals [24]. There tended to be high friction generated in the TMJ the disc was sliding against the fossa and eminence slop. She proposed a theoretical concept that the process of lubrication impairment in TMJ may be involved in the pathogenesis of disc displacement.

Other researchers tried to compare the stress distribution in the healthy joint and in two pathologic situations [25], 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. They found that, while in the healthy disc, the highest compressive stresses were located in the intermediate zone, in the pathologic joints the maximum compressive stresses were located in the posterior band both in the ADDWOR case and in the ADDWR before the reduction. Due to a higher stress on the collateral ligaments, this could be a fact that leads to degeneration of these components and subsequently to the total anterior displacement of the discs. Finally, the results suggest that an anterior displacement of the disc would lead to higher compressive and tangential stresses in the posterior band of the disc than in the healthy one, and as a consequence, to possible perforations in that zone of the disc.

4. Biomechanism of TMJ prostheses

TMJ prostheses are used as implants for articular disc replacements, 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 interpositional devices in the case of TMJ disorders with little or no loss of condylar height; i.e., TMJ ankylosis. When there is also loss of condylar height, as for example in cases of severe osteoarthrosis, 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 [27]:

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

Generally speaking, the total TMJ replacement system is a ‘‘ball and socket’’ type prosthetic joint similar to a hip implant. When a single fossa-eminence prosthesis or a condylar prosthesis is implanted, the articular disc is removed in most cases. Without the disc to cushion between the bony parts of TMJ, resorption of the bone is likely to occur at the stress loaded point [26].

TMJ reconstruction using partial or total TMJ prosthetics, in most cases, improves range of motion and mouth opening in the TMJ patients. However, loss of translational movements of the mandible on the operated side has been reported, maybe due to various factors like loss of pterygoid muscle function, scarring of the joint region and the muscles of mastication. This phenomenon can be verified both in clinical cases studies and kinetic experiments [31-33].

In cases of unilateral joint replacement, the restricted translational movements force 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 osteoarthrosis and internal derangements in the joint, leading to replacement of the natural joint as well [26]. In cases of bilateral replacement of the joints, translational movements of the whole mandible are restricted. This results in reduced anterior and mediolateral movements and decreased chewing function. Also, the incisal opening is reduced, mainly due to the lack of translational movement.

In TMJ replacement follow-up studies, Mercuri et al. obtained the measures of mandibular interincisal opening and lateral excursions from direct measurements by patients themselves. They noted a 24% and a 30% improvement in mouth opening after 2 years and 10 years, respectively. On the other hand, at 2 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 [34].

There are very few studies using mathematical computation approaches such as FEA to investigate TMJ implants in clinical patients. Kashi et al. used an FEA model to quantify the stress distribution in the Chistensen 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.

Table 1. Critical elements for TMJ tissue engineering.

Tissue-engineered TMJ						
Scaffolds		**Cells**		**Bioactive molecules**		
Natural materials	Synthetic materials	Differentiated chondrocytes	Stem cells	Growth factors	Other molecules	Gene therapy
Collagen	PLA	Autologous	MSC	TGF-1/3	PTHrP	
Chitosan	PGA	implantation	ESC	BMP-7	PRP	
Hyaluronan	PLGA		iPS	FGF-2		
Hydroxyapatite	Hydrogel			IGF-1		

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 use of poly-L/DL-lactide implant resulted in remarkable reduction in Von Mises stresses (approximately threefold) in the anterior, central, and medial regions of the mandibular condyle in comparison with slight to moderate stress reductions in the corresponding regions of the implant and glenoid fossa. The authors concluded that the use of bioresorbable laminate implants might prove an efficient technique to replace the articular disc and promote normal function of the temporomandibular joint.

Some works have 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. The direct measurements also indicate large discrepancies. Due to these reasons, there is currently no universally agreed upon value of TMJ loading. 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].

5. Stem cells and tissue engineering for TMJ

Approximately 6-12% of the adult population in the United States have TMDs [39]. Surgical replacement of the mandibular condyle remains the major and final option for those patients with advanced degenerative diseases. 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 and more promising to construct a bioengineered TMJ replacement that is bio-compatible and capable of withstanding the physiologic loads required of this joint. The TMJ, like other joints, is composed of different tissues including bone, cartilage, ligament, muscle and synovial membrane. It is a complicated and difficult task to engineer the joint with all needed cellular components in the right place. Future challenges will be 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 bioadhesives that promote tissue integration and prevent scaffold detachment during joint articulation. Tissue engineering is composed of three critical elements, including cells, scaffold and bioactive molecules. The important and well-investigated elements involved in the tissue engineering of TMJs are listed in Table 1 and discussed afterwards.

5.1 Cells

It is still unclear which cell type is optimal for articular cartilage tissue engineering. The chondrocyte is the predominant cell type, but has limited potential for intrinsic repair because it is well differentiated. There are a number of stem cell sources, of which embryonic stem cells and induced pluripotent stem cells have recently gained most attention. However, presently, it is the adult mesenchymal stem cell that is of most interest 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. Multipotent stem cells with chondrogenic differentiation potential have been identified and isolated not only in bone marrow [42], but also in other joint-related tissues such as synovial membrane [43], infrapatellar fat pad [44], periosteal tissue [45], skeletal muscle and umbilical cord matrix [46].

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 into 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. There are a number of studies that compared different cell sources in terms of their chondrogenic ability. It seems that stem cells from bone marrow and synovium are superior in cartilage regeneration when compared with other sources of mesenchymal stem cells [47]. 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.

Comparing to the mesenchymal stem cells, the embryonic stem cells or iPS can provide a more unlimited supply of precusor cells for articular cartilage tissue engineering and regenerative medicine applications. 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. It is not very possible for ESCs to represent a viable clinical option in articular cartilage repair with the degree of ethical problems surrounding them. On the other hand, induced pluripotent stem cells (iPS) represent a very exciting possibility once the tumorigenic potential is eradicated [49].

5.2 Scaffolds

There are several requirements for scaffolds. They must be biodegradable, with non-toxic byproducts, and exhibit favorable resorption kinetics to maintain initial stability; at the same time, they should not hinder further tissue regeneration. They had better be patient-specific and fix to the defect site, facilitate cell attachment and regulate cell differentiation. A crucial requirement for joint repair is that the scaffolding is attached at the cartilage lesions and integrates with the tissue; the attachment must balance temporary mechanical function with mass transport to aid biological delivery and tissue engineering.

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 molding 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 byproducts and particulates can be released, causing inflammation, giant cell reaction and chondrocyte death owing to a reduction in pH [50].

Newly developed “solid free-form fabrication” methods, such as electrospinning and selective laser sintering, has been studied extensively for their potential use in osteochondral tissue engineering applications [51,52]. However, most of the techniques need further re-engineering for clinical application. For example, 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]. In order to be patient-specific, new techniques such as computational topology design or image-based design were developed to match defect site geometry [51,52]. Biphasic or multiphasic composite scaffold, such as combination of poly-epsilon-caprolactone and hydroxyapatite, is another future trend.

Considering cell behavior, 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 will require some degree of molecular modulation for successful application. This may be provided by the addition of growth factors or other bioactive molecules. The sophisticated scaffolding matrices can recruit existing cells from the surrounding tissue, and the cells further secrete enzyme to degrade the scaffold. Signaling molecules previously stored in the matrix will be released; these in turn stimulate the cells to more vigorous regeneration of new and normal tissue.

5.3 Bioactive molecules

Both chondrocytes and the mesenchymal stem cells are influenced by signaling molecules within the extracellular matrix which include hormones, cytokines and growth factors. An imbalance between the anabolic and catabolic signaling 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.

A number of different growth factors have been demonstrated to have an impact on articular cartilage repair. Transforming growth factor belongs to the TGF super-family, which also includes the bone morphogenetic proteins (BMPs). It is secreted in an inactive from, bound to a latency-associated peptide from which it dissociates before becoming active and binding to its target receptor [52]. *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 has been shown repeatedly 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]. More than 22 different members of the FGF family have been identified, of which basic FGF (FGF-2) is widely investigated in articular cartilage repair. FGF-2 is bound

to heparin sulphate proteolgycan and stored in the extracellular matrix. It 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].

Although good results have been found with many of these growth factors *in vitro*, translation *in vivo* and into clinical practice has not been as successful. A "cocktail" approach may be the next approach, but the timing and delivery of these factors remains an unsolved problem. It is difficult to determine what the best combination of growth factors is because of the contradictory evidence in the literature. Maybe one could summarize that FGF-2 is good for mesenchymal stem cell expansion, TGF-1 and -3 for chondrogenic differentiation of mesenchymal stem cell, and IGF-1 and BMP-7 for matrix production and chondrocyte phenotypic stability. More animal and clinical studies are called for to further clarify the problems.

5.4 Culturing methods

Bioreactors are the most frequently used method to perform the tissue engineering of hard tissues. It was reported that 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. Host animals to cultivate the xenogenic constructs are also extensively used. However, pathogen transmission and recipient rejection should be considered.

5.5 Future challenges

It has been reported that transplanted stem cells did not have a good stability. They 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 [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. It is important to establish a robust method for engineering anatomically shaped and fully viable bone grafts. 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].

6. Conclusion

The TMD affects more than 10% of population and exhibit a mixture of signs and symptoms. The etiology and pathogenesis of TMD are still largely mysterious. Biomechanical studies provide a niche to explore and understand the disease entity. Coupled with clinical researches and biochemical studies, we 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 OA, 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 geometrical mimic scaffold seem to hold the key to success 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.*, 8: 291-305, 1997.

[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.*, 8: 106-116, 1989.

[3] S. B. Milam, "Pathophysiology and epidemiology of TMJ," *J. Musculoskel. Neuron Interact.*, 3: 382-390, 2003.

[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, 211-226, 1995.

[5] M. Von Korff, S. F. Dworkin, L. LeResche and A. Kruger, "An epidemiologic comparison of pain complaints," *Pain*, 32: 173-183, 1988.

[6] S. F. Dworkin and L. LeResche, "Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique," *J. Craniomandib. Disord.*, 6: 301-355, 1992.

[7] K. Herb, S. Cho and M. A. Stiles, "Temporomandibular joint pain and dysfunction," *Curr. Pain Headache Rep.*, 10: 408-414, 2006.

[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.*, 68: 551-554, 1989.

[9] O. E. Ogle and M. B. Hertz, "Myofascial pain," *Oral Maxillofac. Surg. Clin. North. Am.*, 12: 217-231, 2000.

[10] C. H. Wilkes, "Internal derangement of the temporomandibular joint: pathological variations" *Arch Otolaryngol. Head Neck*

Surg., 115: 469-467, 1989.
[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.*, 53: 1240-1247, 1995.
[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.*, 35: 1301-1311, 2007.
[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.*, 26: 278-282, 1997.
[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, 933-947, 2004.
[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.*, 60: 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.*, 97: 472-479, 1990.
[17] D. C. Hatcher, "Development of mechanical and mathematical models to study temporomandibular joint loading," *J. Prosthet. Dent.*, 55: 377-384, 1986.
[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.*, 88: 69-96, 1992.
[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.*, 16: 316-322, 1994.
[20] J. Chen and L. Xu, "A finite element analysis of the human temporomandibular joint," *J. Biomech. Eng.*, 116: 401-407, 1994.
[21] J. Chen, U. Akyuz, L. Xu and R. M. V. Pdaparti, "Stress analysis of the human temporomandibular joint," *Med. Eng. Phys.*, 20: 565-572, 1998.
[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.*, 59: 775-778, 2001.
[23] E. Tanaka and J. Koolstra, "Biomechanics of the temporomandibular joint," *J. Dent. Res.*, 87: 989-991, 2008.
[24] D. W. Nitzan, "The process of lubrication impairment and its involvement in temporomandibular joint disc displacement: a theoretical concept," *J. Oral Maxillofac. Surg.*, 59: 36-45, 2001.
[25] A. P'erez del Palomarand and M. Doblare, "An accurate simulation of anteriorly displaced TMJ discs with and without reduction," *Med. Eng. Physics.*, 29: 216-226, 2007.
[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.*, 53: 984-996, 1995.
[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.*, 37: 103-110, 2008.
[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.*, 80: 273-278, 1995.
[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.*, 53: 106-115, 1995.
[30] P. D. Quinn, "Lorenz prosthesis," *Oral Maxillofac. Surg. Clin. North Am.*, 12: 93-104, 2000.
[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.*, 52: 2-8, 1994.
[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.*, 31: 13, 1998.
[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 foss-eminence partial joint replacement," *J. Oral Maxillofac. Surg.*, 65: 1569-1576, 2007.
[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.*, 60: 1440-1448, 2002.
[35] A. Kashi, A. R. Chowdhury and S. Saha, "Finite element analysis of a TMJ implant," *J. Dent. Res.*, 89: 241-245, 2010.
[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.*, 60: 1400-1411, 2002.
[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.*, 18: 782-788, 2007.
[38] S. Ingawale and T. Goswami, "Temporomandibular joint: disorders, treatments, and biomechanics," *Ann. Biomed. Eng.*, 37: 976-996, 2009.
[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.*, 124: 115-121, 1993.
[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.*, 60: 1389-1399, 2002.
[41] J. J. Jacobs, J. L. Gilbert and R. M. Urban, "Corrosion of metal orthopaedic implants," *J. Bone. Joint. Surg. Am.*, 80: 268-282, 1998.
[42] B. Sacchetti, A. Funari and S. Michienzi, "Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment," *Cell*, 131: 324-336, 2007.
[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*, 11: 790-800, 2003.
[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.*, 412: 196-212, 2003.
[45] H. Nakahara, V. M. Goldberg and A. I. Caplan, "Culture-expanded human periosteal-derived cells exhibit osteochondral potential *in vivo*," *J. Orthop. Res.*, 9: 465-476, 1991.
[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.*, 13: 2003-2010, 2007.
[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*, 17: 714-722, 2009.
[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.*, 60: 3686-3692, 2009.
[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*, 318: 1917-1920, 2007.
[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.*, 6: 777-792,

1988.
[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.*, 8: 313-319, 2005.
[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*, 26: 4817-4827, 2005.
[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.*, 120: 995-1002, 1993.
[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.*, 11: 1264-1273, 1996.
[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*, 6: 306-317, 1998.
[57] I. Sekiya, D. C. Colter and D. J. Prockop, "BMP-6 enhances chondrogenesis in a subpopulation of human marrow stromal cells," *Biochem. Biophys. Res. Commun.*, 284: 411-418, 2001.
[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.*, 85: 116-123, 2003.
[59] C. Gaissmaier, J. L. Koh and K. Weise, "Growth and differentiation factors for cartilage healing and repair," *Injury*, 39(Suppl. 1): 88-96, 2008.
[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.*, 59: 339-359, 2007.
[61] D. Davidson, A. Blanc and D. Filion, "Fibroblast growth factor (FGF) 18 signals through FGF receptor 3 to promote chondrogenesis," *J. Biol. Chem.*, 280: 20509-20515, 2005.
[62] H. Abukawa, "Reconstruction of mandibular defects with autologous tissue-engineered bone," *J. Oral Maxillofac. Surg.*, 62: 601-606, 2004.
[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*, 107: 3299-3304, 2010.
[64] A. 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.*, 219: 219-226, 2009.