Chapter

Nonsurgical Strategies for the Treatment of Temporomandibular Joint Disorders

Juan L. Cobo, Manuela Cabrera-Freitag, Teresa Cobo, Juan D. Muriel, Luis M. Junquera, Juan Cobo and José A. Vega

Abstract

Temporomandibular disorders are common maxillofacial disturbs of different etiologies (traumatic, inflammatory, degenerative, or congenital) that course with pain and dysfunctions of the temporomandibular joint. The treatment of these disorders includes systematically administered drugs (especially nonsteroid anti-inflammatory drugs and corticoids), physical therapies, and minimally invasive therapies that require intraarticular injections. These techniques are directed to clean or drain the articular cavity, to deliver intraarticularly drugs, biologically active compounds (as platelet-rich plasma), or to enhance lubrication (hyaluronic acid). Moreover, minimally invasive strategies are used in regenerative medicine for to deliver cells and stem cells, and nano- or micro-biomaterials. Surgery of temporomandibular disorders is only used in grave diseases that require arthrodesis or remotion of the temporomandibular joint. This review updates the nonsurgical therapeutic strategies to treat temporomandibular disorders, focusing the attention in the articular delivery or hyaluronic acid and platelet-rich plasma, two minimally invasive widely used at present.

Keywords: temporomandibular disorders, minimally invasive therapies, hyaluronic acid, platelet-rich plasma, regenerative medicine

1. Introduction: temporomandibular joint disorders

The temporomandibular joint (TMJ) is the only dynamic articulation of the head and present unique anatomical, structural, and biochemical characteristics. Up to 40–50% of the population suffers different pathologies of TMJ [1, 2] that requires therapeutic interventions by different medical and paramedical specialists and represents an increasing social and psychosocial impairment [3].

TMJ disorders (TMD) are a class of degenerative musculoskeletal conditions associated with morphological and functional deformities, which clinically result in pain and TMJ dysfunctions (impairment in mastication, speech, and facial expression) (see for a review [4]). Moreover, when TMD affect young subjects during growth, it can cause asymmetry of the facial skeleton [5]. In agreement with the above definition, TMD comprise a heterogeneous group of pathologies involving the TMJ, the associated jaw muscles, or both [6]. Up to 40–50% of the population suffers TMD [2], and up to 70% of them suffer TMD directly related to the articular disc [1].

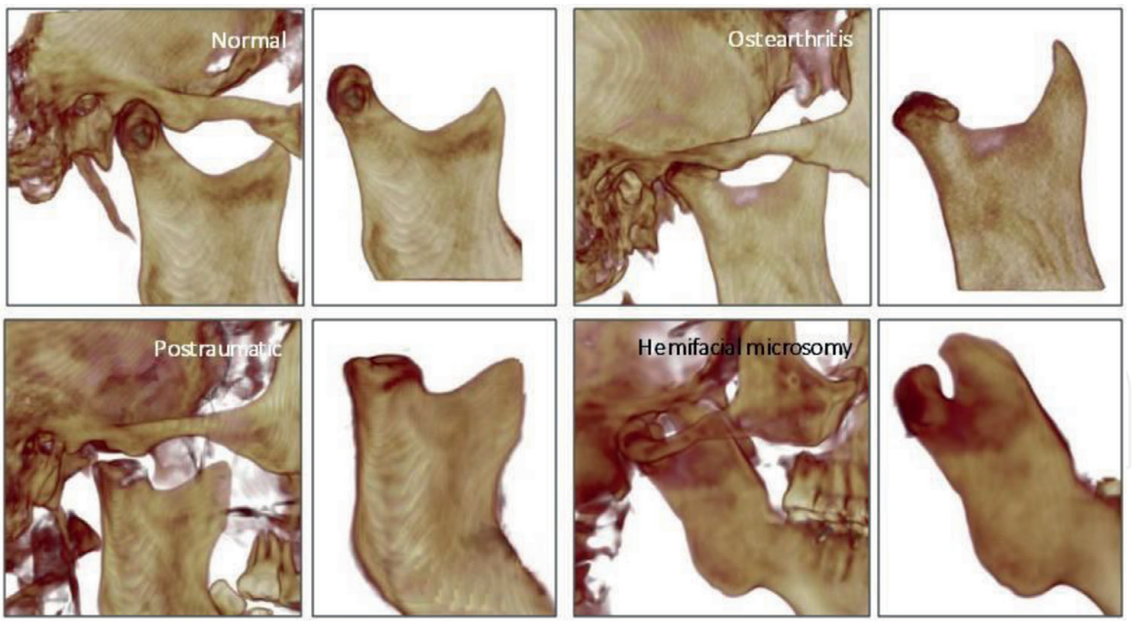

Figure 1.
Cone bean CT of the right adult TMJ in normal conditions, osteoarthritis, posttraumatic, and hemifacial microsomy. Images obtained from Instituto Asturiano de Odontolgía, Oviedo, Spain.

The etiology of TMD can be traumatic, inflammatory, and congenital [6]. However, the primary TMD are degenerative inflammatory or noninflammatory diseases, that is, osteoarthritis or arthrosis, respectively [6]. Typical osteoarthritic changes include alterations in shape and size of TMJ components (flattened fossa, reduced articular eminence, decreased condylar volume, and thickened disc), abrasion of articular cartilage, and thickening and remodeling of the subchondral bone that leads to morphological deformity and dysfunction (**Figure 1**) [4].

2. Brief summary of the anatomy and structure of the temporomandibular joint

TMJ is a bilateral diarthrodial joint formed by the condylar head of the mandible and the glenoid fossa (or mandibular fossa) of the temporal bone, surrounded by a fibrous capsule reinforced laterally (lateral temporomandibular ligament) and two extracapsular ligaments (sphenomandibular and stylomandibular). Interposed between the mandibular condyle and the temporal bone, there is an articular disc of fibrocartilage attached partially to the bones and the capsule that incompletely divides the TMJ into two chambers: upper or temporodisc chamber, and lower chamber or disc-condylar chamber [7].

One differential characteristic of TMJ is that the cartilage covering the articular surfaces is not hyaline cartilage, as in other diarthrosis, but a fibrocartilaginous tissue [8]. It can be regarded as a modified fibrous periosteum with an underlying proliferative zone that differentiates into fibrocartilage [9]. In TMJ articular cartilage, from the surface to the bone, two different zones are considered: the *fibrous zone* and the *fibrocartilage zone,* which can be subdivided into *proliferative* and *hypertrophic zones*. The fibrous zone contains fibroblasts, and the extracellular matrix (ECM) consists of type I collagen, type II collagen at residual levels, and versican-like chondroitin sulfate-based proteoglycan. The cells of the fibrocartilage zone are fibroblasts and chondrocytes, and the ECM is rich in type II collagen, but also contains type I and type X collagen, and aggrecan (**Figure 2** [10]).

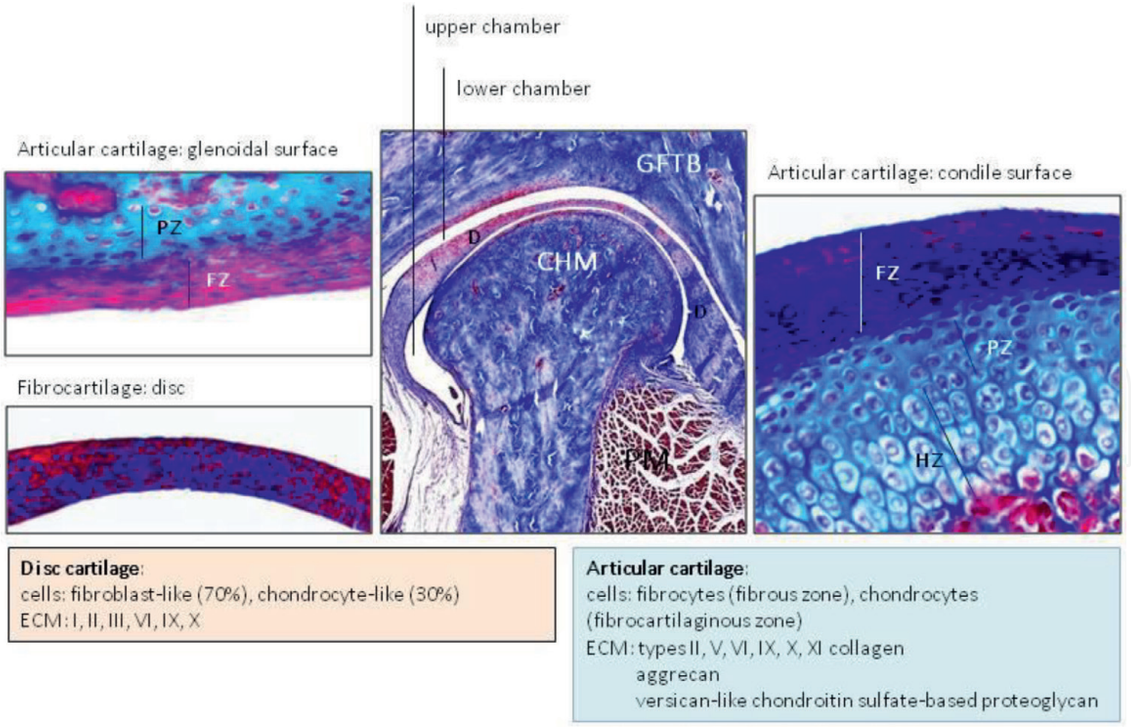

Figure 2.
Organization of the rat temporomandibular joint. CHM: condylar head of the mandible and GFTB: glenoidal fossa of temporal bone. FZ: fibrous zone, HZ: hypertrophic zone, and PZ: proliferative zone. The boxes contain the cells and the main biochemical characteristics of the articular cartilage and the articular disc.

The fibrocartilage forming the articular disc consists of several populations of cells: fibroblast-like and chondrocyte-like cells, 70 and 30%, respectively [11]. In ECM, type I collagen predominates but other collagens (types II, III, VI, IX, and XII) are present [12, 13], and also contains glycosaminoglycans (**Figure 2**) [14].

Along the articular temporal surface, each mandibular condyle has a wide motion range, consisting of both rotation and translation. TMJ movements are involved in facial expressions, talking, drinking, and eating [15, 16].

3. Treatment of TMD

The treatment of TMD varies according to the etiology and severity of the lesion and can be divided into noninvasive, minimally invasive, and invasive, all of them focused to alleviate the symptoms, and repair or replace the pathologic TMJ structures.

Invasive treatments that are always surgical are out of the scope of this chapter, and represent the unique option for patients suffering severe TMD like traumatisms, neoplasia, or developmental malformations. In most cases, it is necessary to perform an arthrotomy to restoring joint tissues or replace TMJ with autogenous or alloplastic material. In the TMD due to disc alterations, surgical repositioning, the removal (discectomy [17]), or replacement [14, 18] have been used with variable efficacy.

The noninvasive treatments include drugs, occlusal orthodontics, physical therapy, or acupuncture. The used drugs are analgesics, NSAIDs, anxiolytics, muscle relaxants, and opioids, all administered systematically [19–21]. The occlusal orthodontics and occlusal splint are widely used for the treatment of TMD, but their effectiveness remains questionable. At present, there is no evidence for a cause-effect relationship between orthodontic treatment and TMD, or that such treatment might improve or prevent them [22]. Furthermore, there is insufficient evidence either for or against the use of stabilization splint therapy for the treatment of the

pain of TMD [23]. The same applies for the oral appliances that might reduce pain and assist in maintaining stable function between jaw posture, muscle function, and temporomandibular joint stability [24] although TMD can result as a side effect from use those devices [25].

The physical therapies for TMD include different techniques like exercises, neuromuscular stabilization, electrotherapy and transcutaneous electrical nerve stimulation (TENS), low-intensity ultrasound, and low-level laser therapy. These methods are easily applicable and have demonstrated efficiency in some cases of TMD especially those of muscular origin.

Physiotherapy is commonly employed in the treatment of TMDs, but its relative efficacy is unclear, and most methods (short-wave diathermy, megapulse, ultrasound, and soft laser) have similar beneficial effects (range 70.4–77.7%) [25, 26]. In any case, a mixed approach of therapies has impact on reducing pain, increasing range of motion, but lacks a significant impact for functional improvement [27, 28]. The effect of low-level laser therapy in patients with TMD seems to relieve pain and improves functional outcomes [29] or dysfunctional TMJ [30]. And in comparing the effects of different methods, low intensity ultrasound and traditional exercise therapy were more effective that laser therapy reduced TMJ pain and trismus after oncologic surgery [31].

Finally, acupuncture has also demonstrated to reduce symptoms associated with TMD. Meta-analysis noted moderate evidence that acupuncture is effective to reduce symptoms associated with TMD, and trials with adequate sample sizes are necessary that address the long-term efficacy or effectiveness of acupuncture [32, 33].

As a whole, and despite limited evidence, physical therapy can be an effective treatment option for TMD, with jaw exercise (79%), ultrasound (52%), manual therapy (MT) (48%), acupuncture (41%), and laser therapy (15%) as the most effective modalities for managing TMD [34].

The minimally invasive treatments include the therapies that require intraarticular injections, arthrocentesis, or arthroscopy. They are used to clean or drain the articular cavity, to deliver intraarticularly active substance like drugs (NSAIDs and corticosteroids [35–37], biologically-active compounds (for example platelet-rich plasma [38]), or enhance lubrication (hyaluronic acid (**Figure 3**) [35]). Current clinical therapies using intraarticular injections are effective in pain relief at an early stage of disease but fail to alleviate chronic pain.

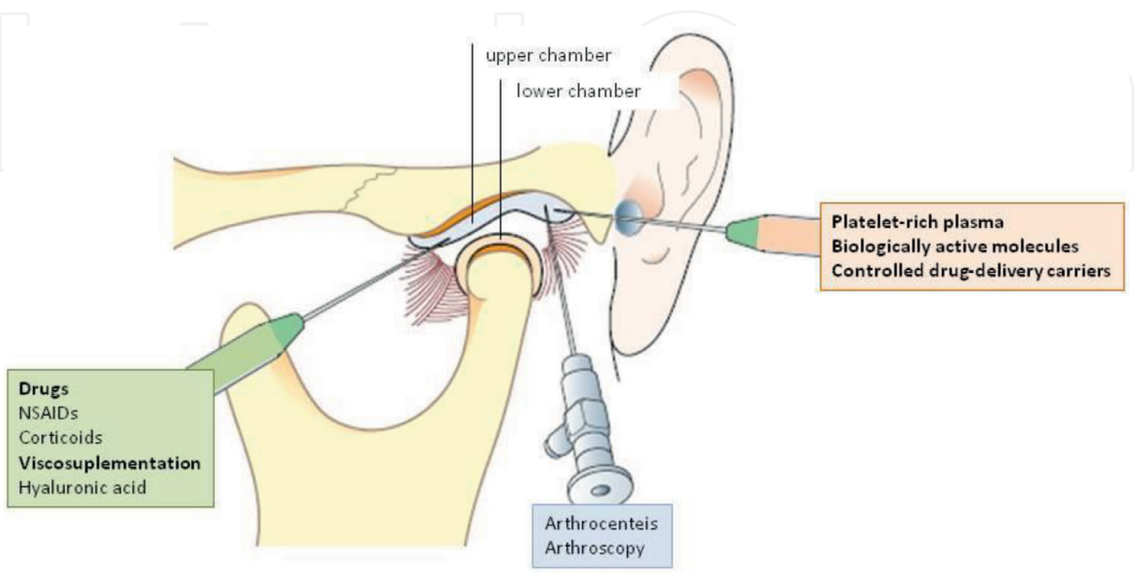

Figure 3.
Schematic representation of the minimally invasive methods and the compounds delivered in TMJ intraarticularly. Modified of https://pocketdentistry.com/33-temporomandibular-joint-surgery-including-arthroscopy/.

Furthermore, minimally invasive strategies are now used in regenerative medicine for treatment of TMD, to deliver cells and stem cells, nano- or micro-biomaterials, carriers of drugs with controlled release [39–41]. Actually, it is also of interest the delivery of therapeutic molecules through the use of nanoparticles- (NP-BDS) and microparticles- (MP-BDS) based delivery system that can release therapeutic molecules in a controlled or sustained manner and target specific cells (chondrocytes and synoviocytes). The nano- and microparticles interact with cells at the intra- and extracellular space depending on their size.

NP-BDS are solid or colloidal particles with sizes ranging from tens to hundreds of nanometers, which are endocyted and enter into the cytoplasm cells where they release small-sized biomolecules intracellularly [40, 41].

MP-BDS are synthetic or natural polymers spherically shaped with sizes ranging from ten to hundreds of micrometers and are suitable to deliver large drugs or biomolecules acting on the cell surface, thus extracellularly; they serve as vehicles for corticoids and NSAIDs. In addition, microparticles can also release biomolecules and deliver stem cells (see [41]).

4. Intraarticular delivery of hyaluronic acid

Hyaluronic acid or hyaluronan (HA) is a component of ECM and the body fluids, including the synovial fluid that organizes proteoglycans and other proteins on the cell membrane surface through noncovalent unions; in the fluids, it is responsible for their rheological properties. Structurally, HA is a glycosaminoglycan polymer formed by repeated sequence of D-glycuronic acid and N-acetyl-D-glycosamine linked by means of alternant β-1, β-1, 4, and 3 glycoside links. HA plays a key role in the physiology of diarthrosis especially in the articular cartilage as well as in the maintenance of synovial fluid viscosity, thus in viscoelasticity and lubrication. It is synthesized by the synoviocytes and has a molecular weight of about 6000–7000 kDa.

Most of the inflammatory and degenerative joint diseases course with increased local concentrations of pro-inflammatory molecules and proteases that degrade HA originating from small HA-fragments with a low-molecular weight. Consequently, in those diseases, there is a reduction in the viscosity and lubrication properties of the synovial fluid and a dramatic change in the biological receptor-mediated effects of HA. Moreover, the resulting small fragments acting through different membrane receptors can stimulate the inflammatory responses in the synovial membrane and the lesions in the articular cartilage [42, 43]. Therefore, one of the therapeutic strategies for the treatment of some joint diseases is to restore the rheological properties of the synovial fluid [44] and the joint homeostasis [45] throughout the intraarticular delivery of HA.

HA plays a key role in the pathogenesis of the degenerative and traumatic joint diseases acting as a pro-inflammatory or anti-inflammatory molecule, stimulating or inhibiting cellular migration, division, and differentiation [46]. The final effects depend both on the state of the tissue (expression of HA receptors, phase of the cell cycle, and signaling pathways) [47] and the characteristics of the HA (tridimensional structure and the size of the HA molecule) [48–50].

The intraarticular administration of exogenous HA is called "viscosupplementation," and it is focused to restore the rheological properties of the synovial fluid and to block the generative processes. Until now, the effectiveness of intraarticular administration of HA offers discordant results [51, 52]. Nevertheless, the meta-analysis of treatments that used intraarticular HA and the European Society for Clinical and Economic Aspects of Osteoarthritis recommends the use of intraarticular injections

of HA in absence of response to conventional anti-inflammatory drugs, since it improves the functionality of the joint and diminishes pain [53, 54].

The beneficial effects of viscosupplementation with HA in TMD have not been probed satisfactory and are not more effective that of corticosteroids and NSAIDs [35, 55, 56]. Also, although there was no significant difference between the effectiveness HA and corticoids intraarticular injections, there was some evidence that HA was better than placebo [57]. However, most studies report a decrease in pain levels independently by the TMD [58]. On the other hand, it seems that HA regulates various inflammatory mediators in osteoarthritis in the TMJ [59]. In any case, at present, there is insufficient, consistent evidence to either support or refute the use of HA for treating patients with TMD.

5. Intraarticular delivery of platelet-rich plasma

Platelet-rich plasma (PRP; blood plasma that has been enriched with platelets) therapies have emerged as a potential approach to enhance tissue repair and regeneration, and have demonstrated to be a safe, resourceful, and effective treatment. They are based on the delivery of growth factors and cytokines from anuclear platelets that can stimulate the healing of various tissues as a consequence of activation of migratory and local cells [60, 61]. Nevertheless, because PRP is autologous, the concentration of the PRP components differs according to the physiological conditions and clinical diseases of patients [62].

The biological effects of PRP are largely attributed to the platelet secretome and some plasma signaling proteins. In fact, the α-granules of platelets within PRP release numerous growth factors and cytokines (TGF-α, TGF-β, HGF, IL-6, EGF, FGF-2, IGF-1, VEGF, and interleukin β1). Moreover, PRP contains proteases, biologically active amines, and cell adhesion molecules such as fibrin, fibronectin, and vitronectin [60]. All those molecules are involved in repair and regeneration processes, including antiapoptosis, cell proliferation, differentiation, migration, angiogenesis, and the synthesis of ECM in both normal and pathological conditions [63]. Cells within the joint add to this milieu by secreting additional biologically active molecules in response to PRP.

PRP is currently used in patients with chronic joint pain caused by progressive cartilage degeneration of the synovial joints. The anti-inflammatory effects are carried out through its effects on nuclear factor κB signaling pathway (including synoviocytes, macrophages, and chondrocytes), but also by reducing TNF-α and IL-1β [64]. A systematic review and meta-analysis related to the clinical efficacy of intraarticular PRP injection in patients with osteoarthritis have shown significant clinical improvements [65, 66].

Recently, Kütük et al. [67] and Hegab et al. [68] reported that an intraarticular PRP injection is an effective treatment for TMJ osteoarthritis through the regeneration of fibrocartilage and cartilage, bone repair in the TMJ. Moreover, PRP has long-term analgesic effects in most patients with painful TMJ [69, 70]. Nevertheless, a randomized clinical trial in patients with TMJ osteoarthritis suggests that arthrocentesis plus PRP injections is not superior to arthrocentesis alone or combined with HA injection, and PRP does not add any significant improvement to clinical outcomes after surgery in patients with advanced internal derangement of the TMJ [71, 72]. Thus, PRP injection should not be considered as a first-line treatment for TMD, and arthrocentesis plus HA injection would appear to be more acceptable [73]. Nevertheless, other authors observed that PRP performed well than HA in the treatment of TMJ osteoarthritis in terms of pain reduction for the treatment of reducible disc displacement of the TMJ [68, 72, 74]. Future studies will focus on the synergistic actions of HA and PRP in the treatment of TMJ osteoarthritis as in other joints.

6. Tissue engineering

In recent past years, detailed and exhaustive reviews have been published covering all the relevant data about the experimental [75], technical aspects, and indications of tissue engineering in TMJ [76–81]. Therefore, this section only summarizes the most relevant aspects of tissue engineering of TMJ using minimally invasive techniques. In the last two decades, new studies have contributed to understand what are the appropriate scaffolds, cells and biological for TMJ diseases, and all these advancements are based on the perfectly known structures of the different joint constituents.

Traditionally, the principal elements of tissue engineering-based regenerative strategies are scaffolds, cells, and biological stimuli. Those used in TMJ are summarized in **Table 1**. Although through invasive methods all strategies are possible to regenerate TMJ components when minimally invasive techniques are used, two methods are possible in cartilage and bone engineering: *in situ* tissue engineering incorporating an acellular scaffold matrix that attract and fix local cells thus guiding the process of regeneration and *ex vivo* cell seeding on the scaffold that initiates and regulates the regenerative mechanisms [101]. On the other hand, to induce more rapid ECM synthesis, scaffolds can be embedded with growth factors. Also,

Tissue		**References**
Condylar cartilage		
Scaffolds	Hyaluronic acid hydrogels	[82]
	Agarose	[83]
	Poly-vinyl alcohol	[84]
	Poly-l-lactic-coglycolic acid	[85]
Cells	Chondrocytes	[86, 87]
	Synovial stem cells	[88, 89]
	Bone marrow mesenchymal stem cells	[88, 90]
	Adipose stem cells	[91]
	Tooth-derived stem cells	[92]
Articular disc		
Scaffolds	Polyglycerol sebacate	[93]
	Poly-glycolic acid	[94, 95]
	Poly-l-lactic acid	[77, 96]
	Poly(glycerol sebacate)	[93]
	Polycaprolactone	[97]
	Polytetrafluorethylene monofilaments + poly-l-lactic acid monofilaments + polyamide monofilaments + natural bone	[98]
	Chitosan	[99]
	Alginate hydrogels	[94]
	Decellularized ECM	[100]
Cells	Dermal fibroblasts	[95]
	Synovial stem cells	[88]

Table 1.
Scaffolds and cells used in TMJ tissue engineering.

intraarticular injection of cells or local delivery of biologically active molecules can be a strategy, but these cannot be regarded properly as tissue engineering.

Scaffolds serve as a supportive structure to the engineered tissues. As a rule, the used scaffolds must promote the differentiation of cells into chondrocytes and stimulate the synthesis of cartilaginous ECM. Both natural and synthetic scaffolds have been experimented for engineering the TMJ (**Table 1**). Nevertheless, the most suitable approach should be reconstructed for both full articulating surfaces by stabilizing scaffolds on the articular surfaces to be regenerated and autologous chondrocytes within the scaffold. But in the case of TMJ, the reconstruction of the disc is also important. Nevertheless, as the replacement of the articular disc does not seem to be feasible at the current state of tissue engineering, lining the articular fossa with resistant engineered cartilage tissue would be an alternative in patients after discectomy [78].

Diverse cells have been used in TMJ tissue engineering (see **Table 1**) within different scaffolds. The local delivery of mesenchymal stem cells (MSCs) within TMJ has proved to have beneficial effects on TMJ degenerative diseases [79]. Furthermore, another strategy would be stimulating the resident mesenchymal stem cells present in the synovial layer [102] and synovial fluid of TMJ [103]. MSCs are able to secrete bioactive molecules, such as growth factors, cytokines, and chemokines, which exert their biological role under injury conditions [104].

Growth factors help tissue regeneration promoting the differentiation and proliferation of cells and supporting ECM synthesis and specialization. Thus, the incorporation of growth factors to the scaffolds, the direct intraarticular delivery of growth factors, or stimulating the exogenous or resident cells to secrete and release growth factor can result in an improvement of tissue regeneration. Various technologies for incorporation of growth factors into scaffolds are possible. At present, the three key growth factors for TMJ regeneration are bFGF, IGF-1, and TGF-β1 [105]. However, fibrochondrocytes from mandibular condyle are less responsive to IGF-1 than hyaline chondrocytes [86]. TGF-β1 stimlates cell proliferation, and on the production of ECM in TMJ disc implants [106], and TGF-β1 and IGF-1 acting together promote cellular proliferation and secretion of type I collagen and glycosaminoglycans [107]. In culture, bFGF increased the proliferation of fibrochondrocytes from mandibular condyle more than TGF-β1 and IGF-1 [108]. Finally, PDGF significantly increases the proliferation rate of the TMJ-disc-derived cells, collagen, and hyaluronic acid synthesis in engineered TMJ disc [109].

Another source of bioactive molecules to be delivered into TMJ is the MSC-conditioned medium collectively known as the MSC secretome. It contains trophic factors and various MSC-based clinical trials that have revealed that transplanted MSCs exert their biological functions through trophic modulations rather than differentiation potential [110]. Similar properties have the secretome of the periodontal ligament-derived MSCs [111]. Finally, exosomes, cell-secreted nano-sized vesicles covered by the bilipid membrane, containing a myriad of regulatory components including microRNAs (miRNAs), mRNAs, and proteins [112], could be in the future a reliable possibility to stimulate TMJ regeneration.

Author details

Juan L. Cobo[1,2], Manuela Cabrera-Freitag[1], Teresa Cobo[3,4], Juan D. Muriel[3], Luis M. Junquera[2,3], Juan Cobo[3,4] and José A. Vega[1,5*]

1 Departamento de Morfología y Biología Celular, Universidad de Oviedo, Spain

2 Servicio de Cirugía Máxilofacial, Hospital Universitario Central de Asturias, Oviedo, Spain

3 Departamento de Cirugía y Especialidades Médico-Quirúrgicas, Universidad de Oviedo, Spain

4 Instituto Asturiano de Odontología, Oviedo, Spain

5 Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Santiago de Chile, Chile

*Address all correspondence to: javega@uniovi.es

References

[1] Manfredini D, Guarda-Nardini L, Winocur E, Piccotti F, Ahlberg J, Lobbezoo F. Research diagnostic criteria for temporomandibular disorders: A systematic review of axis I epidemiologic findings. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2011;**112**:453-462

[2] Gopal SK, Shankar R, Vardhan BH. Prevalence of temporo-mandibular disorders in symptomatic and asymptomatic patients: A cross-sectional study. International Journal of Advanced Health Sciences. 2014;**1**:14-20

[3] De La Torre Canales G, Câmara-Souza MB, Muñoz Lora VRM, Guarda-Nardini L, Conti PCR, Rodrigues Garcia RM, et al. Prevalence of psychosocial impairment in temporomandibular disorder patients: A systematic review. Journal of Oral Rehabilitation. 2018;**45**:881-889

[4] Murphy MK, MacBarb RF, Wong ME, Athanasiou KA. Temporomandibular joint disorders: A review of etiology, clinical management, and tissue engineering strategies. The International Journal of Oral & Maxillofacial Implants. 2013;**28**:e393

[5] Roberts WE, Stocum DL. Part II: Temporomandibular joint (TMJ)-regeneration, degeneration, and adaptation. Current Osteoporosis Reports. 2018;**16**:369-379

[6] Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: Etiology, diagnosis, and treatment. Journal of Dental Research. 2008;**87**:296-307

[7] Alomar X, Medrano J, Cabratosa J, Clavero JA, Lorente M, Serra I, et al. Anatomy of the temporomandibular joint. Seminars in Ultrasound, CT, and MR. 2007;**28**:170-183

[8] Robinson PD. Articular cartilage of the temporomandibular joint: Can it regenerate? Annals of the Royal College of Surgeons of England. 1993;**75**:231-236

[9] Stocum DL, Roberts WE. Part I: Development and physiology of the temporomandibular joint. Current Osteoporosis Reports. 2018;**16**:360-368

[10] Kuroda S, Tanimoto K, Izawa T, Fujihara S, Koolstra JH, Tanaka E. Biomechanical and biochemical characteristics of the mandibular condylar cartilage. Osteoarthritis and Cartilage. 2009;**17**:1408-1415

[11] Detamore MS, Hegde JN, Wagle RR, Almarza AJ, Montufar-Solis D, Duke PJ, et al. Cell type and distribution in the porcine temporomandibular joint disc. Journal of Oral and Maxillofacial Surgery. 2006;**64**:243-248

[12] Minarelli AM, Del Santo Júnior M, Liberti EA. The structure of the human temporomandibular joint disc: A scanning electron microscopy study. Journal of Orofacial Pain. 1997;**11**:95-100

[13] Kalpakci KN, Willard VP, Wong ME, Athanasiou KA. An interspecies comparison of the temporomandibular joint disc. Journal of Dental Research. 2011;**90**:193-198

[14] Willard VP, Zhang L, Athanasiou KA. Tissue engineering of the temporomandibular joint. In: Ducheine P, editor. Comprehensive Biomaterials: Tissue and Organ Engineering. Vol. 5. Elsevier Science. 2011. pp. 221-235

[15] Naeije M, Hofman N. Biomechanics of the human temporomandibular

joint during chewing. Journal of Dental Research. 2003;**82**:528-531

[16] Tanaka E, Koolstra J. Biomechanics of the temporomandibular joint. Journal of Dental Research. 2008;**87**:989-991

[17] Miloro M, Henriksen B. Discectomy as the primary surgical option for internal derangement of the temporomandibular joint. Journal of Oral and Maxillofacial Surgery. 2010;**68**:782-789

[18] Gerbino G, Zavattero E, Bosco G, Berrone S, Ramieri G. Temporomandibular joint reconstruction with stock and custom-made devices: Indications and results of a 14-year experience. Journal of Cranio-Maxillo-Facial Surgery. 2017;**45**:1710-1715

[19] Liu F, Steinkeler A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. Dental Clinics of North America. 2013;**57**:465-479

[20] Heir GM. The efficacy of pharmacologic treatment of temporomandibular disorders. Oral and Maxillofacial Surgery Clinics of North America. 2018;**30**:279-285

[21] Ingawalé S, Goswami T. Temporomandibular joint: Disorders, treatments, and biomechanics. Annals of Biomedical Engineering. 2009;**37**:976-996

[22] Fernández-González FJ, Cañigral A, López-Caballo JL, Brizuela A, Moreno-Hay I, Del Río-Highsmith J, et al. Influence of orthodontic treatment on temporomandibular disorders. A systematic review. Journal of Clinical and Experimental Dentistry. 2015;7(2):e320-e327

[23] Al-Ani MZ, Davies SJ, Gray RJ, Sloan P, Glenny AM. Stabilisation splint therapy for temporomandibular pain dysfunction syndrome. Cochrane Database of Systematic Reviews. 2004;(1):CD002778. DOI: 10.1002/14651858.CD002778.pub2

[24] Greene CS, Menchel HF. The use of oral appliances in the management of temporomandibular disorders. Oral and Maxillofacial Surgery Clinics of North America. 2018;**30**:265-277

[25] Gray RJ, Quayle AA, Hall CA, Schofield MA. Physiotherapy in the treatment of temporomandibular joint disorders: A comparative study of four treatment methods. British Dental Journal. 1994;**176**:257-261

[26] McNeely ML, Armijo Olivo S, Magee DJ. A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders. Physical Therapy. 2006;**86**:710-725

[27] Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of manual therapy and therapeutic exercise for temporomandibular disorders: Systematic review and meta-analysis. Physical Therapy. 2016;**96**:9-25

[28] Dickerson SM, Weaver JM, Boyson AN, Thacker JA, Junak AA, Ritzline PD, et al. The effectiveness of exercise therapy for temporomandibular dysfunction: A systematic review and meta-analysis. Clinical Rehabilitation. 2017;**31**:1039-1048

[29] Xu GZ, Jia J, Jin L, Li JH, Wang ZY, Cao DY. Low-level laser therapy for temporomandibular disorders: A systematic review with meta-analysis. Pain Research & Management. 2018;**2018**:4230583

[30] Alan H, Yolcu U, Koparal M, Ozgur C, Ozturk SA, Malkoc S. Evaluation of the effects of the low-level laser therapy

on swelling, pain, and trismus after removal of impacted lower third molar. Head & Face Medicine. 2016;**12**:25

[31] Elgohary HM, Eladl HM, Soliman AH, Soliman ES. Effects of ultrasound, laser and exercises on temporomandibular joint pain and trismus following head and neck cancer. Annals of Rehabilitation Medicine. 2018;**42**:846-853

[32] Cho SH, Whang WW. Acupuncture for temporomandibular disorders: A systematic review. Journal of Orofacial Pain. 2010;**24**:152-162

[33] Jung A, Shin BC, Lee MS, Sim H, Ernst E. Acupuncture for treating temporomandibular joint disorders: A systematic review and meta-analysis of randomized, sham-controlled trials. Journal of Dentistry. 2011;**39**:341-350

[34] Rashid A, Matthews NS, Cowgill H. Physiotherapy in the management of disorders of the temporomandibular joint; perceived effectiveness and access to services: A national United Kingdom survey. The British Journal of Oral & Maxillofacial Surgery. 2013;**51**:52-57

[35] Machado E, Bonotto D, Cunali PA. Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: A systematic review. Dental Press Journal of Orthodontics. 2013;**18**:128-133

[36] Dym H, Bowler D, Zeidan J. Pharmacologic treatment for temporomandibular disorders. Dental Clinics of North America. 2016;**60**:367-379

[37] Gopalakrishnan V, Nagori SA, Roy Chowdhury SK, Saxena V. The use of intra-articular analgesics to improve outcomes after temporomandibular joint arthrocentesis: A review. Oral and Maxillofacial Surgery. 2018;**22**:357-364

[38] Zotti F, Albanese M, Rodella LF, Nocini PF. Platelet-rich plasma in treatment of temporomandibular joint dysfunctions: Narrative review. International Journal of Molecular Sciences. 2019;**20**:pii: E277

[39] Huang G, Zhang Z. Micro- and nano-carrier mediated intra-articular drug delivery systems for the treatment of osteoarthritis. Journal of Nanotechnology. 2012;**2012**:748909

[40] Mountziaris PM, Sing DC, Mikos AG, Kramer PR. Intra-articular microparticles for drug delivery to the TMJ. Journal of Dental Research. 2010;**89**:1039-1044

[41] Dashnyam K, Lee JH, Mandakhbayar N, Jin GZ, Lee HH, Kim HW. Intra-articular biomaterials-assisted delivery to treat temporomandibular joint disorders. Journal of Tissue Engineering. 2018;**9**:2041731418776514

[42] Campo GM, Avenoso A, D'Ascola A, Prestipino V, Scuruchi M, Nastasi G, et al. Inhibition of hyaluronan synthesis reduced inflammatory response in mouse synovial fibroblasts subjected to collagen-induced arthritis. Archives of Biochemistry and Biophysics. 2012;**518**:42-52

[43] Campo GM, Avenoso A, D'Ascola A, Scuruchi M, Nastasi G, Micali A, et al. The SOD mimic MnTM-2-PyP(5+) reduces hyaluronan degradation-induced inflammation in mouse articular chondrocytes stimulated with Fe (II) plus ascorbate. The International Journal of Biochemistry & Cell Biology. 2013;**45**:1610-1619

[44] Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: Evidence for disease-modifying activity. Osteoarthritis and Cartilage. 2005;**13**:216-224

[45] Rani N, Sabbioni G, Mazzotta A, Rocchi M, Stagni C, Filanti M, et al. Infiltrative therapy as conservative treatment in hip osteoarthritis: A literature review. Hip International. 2016;**26**(Suppl 1):8-13

[46] Dicker KT, Gurski LA, Pradhan-Bhatt S, Witt RL, Farach-Carson MC, Jia X. Hyaluronan: A simple polysaccharide with diverse biological functions. Acta Biomaterialia. 2014;**10**:1558-1570

[47] Petrey AC, de la Motte CA. Hyaluronan, a crucial regulator of inflammation. Frontiers in Immunology. 2014;**5**:101

[48] Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiological Reviews. 2011;**91**:221-264

[49] Stern R, Asari AA, Sugahara KN. Hyaluronan fragments: An information-rich system. European Journal of Cell Biology. 2006;**85**:699-715

[50] Maytin EV. Hyaluronan: More than just a wrinkle filler. Glycobiology. 2016;**26**:553-559

[51] Health Quality Ontario. Intra-articular viscosupplementation with hylan g-f 20 to treat osteoarthritis of the knee: An evidence-based analysis. Ontario Health Technology Assessment Series. 2005;**5**:1-66

[52] Newberry SJ, Fitzgerald JD, Maglione MA, O'Hanlon CE, Booth M, Motala A, et al. Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee. Rockville, MD: Agency for Healthcare Research and Quality (US); AHRQ Technology Assessments; 2015. Available from: https://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=101&bc=AAAQAAAAAAAAAA%3D%3D&

[53] Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: A systematic review and network meta-analysis. Osteoarthritis and Cartilage. 2016;**24**:2022-2041

[54] Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Seminars in Arthritis and Rheumatism. 2016;**45**(4 Suppl):S28-S33

[55] Goiato MC, da Silva EV, de Medeiros RA, Túrcio KH, Dos Santos DM. Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. International Journal of Oral and Maxillofacial Surgery. 2016;**45**:1531-1537

[56] Ferreira N, Masterson D, Lopes de Lima R, de Souza Moura B, Oliveira AT, Kelly da Silva Fidalgo T, et al. Efficacy of viscosupplementation with hyaluronic acid in temporomandibular disorders: A systematic review. Journal of Cranio-Maxillo-Facial Surgery. 2018;**46**:1943-1952

[57] Moldez MA, Camones VR, Ramos GE, Padilla M, Enciso R. Effectiveness of intra-articular injections of sodium hyaluronate or corticosteroids for intracapsular temporomandibular disorders: A systematic review and meta-analysis. Journal of Oral & Facial Pain and Headache. 2018;**32**:53-66

[58] Manfredini D, Piccotti F, Guarda-Nardini L. Hyaluronic acid in the treatment of TMJ isorders: A systematic review of the literature. Cranio. 2010;**28**:166-176

[59] Iturriaga V, Bornhardt T, Manterola C, Brebi P. Effect of hyaluronic acid on the regulation of inflammatory

mediators in osteoarthritis of the temporomandibular joint: A systematic review. International Journal of Oral and Maxillofacial Surgery. 2017;**46**:590-595

[60] Andia I, Abate M. Platelet-rich plasma: Underlying biology and clinical correlates. Regenerative Medicine. 2013;**8**:645-658

[61] Andia I, Abate M. Platelet-rich plasma: Combinational treatment modalities for musculoskeletal conditions. Frontiers of Medicine. 2018;**12**:139-152

[62] Andia I, Maffulli N. A contemporary view of platelet-rich plasma therapies: Moving toward refined clinical protocols and precise indications. Regenerative Medicine. 2018;**13**:717-728

[63] Andia I, Maffulli N. Muscle and tendon injuries: The role of biological interventions to promote and assist healing and recovery. Arthroscopy. 2015;**31**:999-1015

[64] Tohidnezhad M, Bayer A, Rasuo B, Hock JVP, Kweider N, Fragoulis A, et al. Platelet-released growth factors modulate the secretion of cytokines in synoviocytes under inflammatory joint disease. Mediators of Inflammation. 2017;**2017**:1046438

[65] Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: A systematic review and meta-analysis. Archives of Physical Medicine and Rehabilitation. 2014;**95**:562-575

[66] Zubair U, Salam O, Zubair Z. Role of intra-articular platelet rich plasma in the management of osteoarthritis: A review. Cureus. 2018;**10**(9):e3359

[67] Kütük N, Baş B, Soylu E, Gönen ZB, Yilmaz C, Balcioğlu E, et al. Effect of platelet-rich plasma on fibrocartilage, cartilage, and bone repair in temporomandibular joint. Journal of Oral and Maxillofacial Surgery. 2014;**72**:277-284

[68] Hegab AF, Ali HE, Elmasry M, Khallaf MG. Platelet-rich plasma injection as an effective treatment for temporomandibular joint osteoarthritis. Journal of Oral and Maxillofacial Surgery. 2015;**73**:1706-1713

[69] Bousnaki M, Bakopoulou A, Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: A systematic review. International Journal of Oral and Maxillofacial Surgery. 2018;**47**:188-198

[70] Chung PY, Lin MT, Chang HP. Effectiveness of platelet-rich plasma injection in patients with temporomandibular joint osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology. 2018;**pii**:S2212-4403(18)31187-8

[71] Fernández Sanromán J, Fernández Ferro M, Costas López A, Arenaz Bua J, López A. Does injection of plasma rich in growth factors after temporomandibular joint arthroscopy improve outcomes in patients with Wilkes stage IV internal derangement? A randomized prospective clinical study. International Journal of Oral and Maxillofacial Surgery. 2016;**45**:828-835

[72] Fernández-Ferro M, Fernández-Sanromán J, Blanco-Carrión A, Costas-López A, López-Betancourt A, Arenaz-Bua J, et al. Comparison of intra-articular injection of plasma rich in growth factors versus hyaluronic acid following arthroscopy in the treatment of temporomandibular dysfunction: A randomised prospective study. Journal of Cranio-Maxillo-Facial Surgery. 2017;**45**:449-454

[73] Cömert Kiliç S, Güngörmüş M. Is arthrocentesis plus platelet-rich plasma superior to arthrocentesis plus hyaluronic acid for the treatment of temporomandibular joint osteoarthritis: A randomized clinical trial. International Journal of Oral and Maxillofacial Surgery. 2016;**45**:1538-1544

[74] Hancı M, Karamese M, Tosun Z, Aktan TM, Duman S, Savaci N. Intra-articular platelet-rich plasma injection for the treatment of temporomandibular disorders and a comparison with arthrocentesis. Journal of Cranio-Maxillo-Facial Surgery. 2015;**43**:162-166

[75] Almarza AJ, Brown BN, Arzi B, Ângelo DF, Chung W, Badylak SF, et al. Preclinical animal models for temporomandibular joint tissue engineering. Tissue Engineering. Part B, Reviews. 2018;**24**:171-178

[76] Shu W, Liu L, Bao G, Kang H. Tissue engineering of the temporomandibular joint disc: Current status and future trends. The International Journal of Artificial Organs. 2015;**38**:55-68

[77] Aryaei A, Vapniarsky N, JC1 H, Athanasiou KA. Recent tissue engineering advances for the treatment of temporomandibular joint disorders. Current Osteoporosis Reports. 2016;**14**:269-279

[78] Salash JR, Hossameldin RH, Almarza AJ. Potential indications for tissue engineering in temporomandibular joint surgery. Journal of Oral and Maxillofacial Surgery. 2016;(4):705-711

[79] Cui D, Li H, Xu X, Ye L, Zhou X, Zheng L, et al. Mesenchymal stem cells for cartilage regeneration of TMJ osteoarthritis. Stem Cells International. 2017;**2017**:5979741

[80] Acri TM, Shin K, Seol D, Laird NZ, Song I, Geary SM, et al. Tissue engineering for the temporomandibular joint. Advanced Healthcare Materials. 2018;**17**:e1801236

[81] Van Bellinghen X, Idoux-Gillet Y, Pugliano M, Strub M, Bornert F, Clauss F, et al. Temporomandibular joint regenerative medicine. International Journal of Molecular Sciences. 2018;**19**(2):pii: E446

[82] Kim IL, Mauck RL, Burdick JA. Hydrogel design for cartilage tissue engineering: A case study with hyaluronic acid. Biomaterials. 2011;**32**:8771-8782

[83] Willerth SM, Sakiyama-Elbert SE. Combining stem cells and biomaterial scaffolds for constructing tissues and cell delivery. In: StemBook, editor. The Stem Cell Research Community. Cambridge, MA, USA: Harvard Stem Cell Institute; 2008

[84] Bodugoz-Senturk H, Macias CE, Kung JH, Muratoglu OK. Poly(vinyl alcohol)-acrylamide hydrogels as load-bearing cartilage substitute. Biomaterials. 2009;**30**:589-596

[85] Uematsu K, Hattori K, Ishimoto Y, Yamauchi J, Habata T, Takakura Y, et al. Cartilage regeneration using mesenchymal stem cells and a three-dimensional poly-lactic-glycolic acid (PLGA) scaffold. Biomaterials. 2005;**26**:4273-4279

[86] Wang L, Lazebnik M, Detamore MS. Hyaline cartilage cells outperform mandibular condylar cartilage cells in a TMJ fibrocartilage tissue engineering application. Osteoarthritis and Cartilage. 2009;**17**:346-353

[87] Anderson DE, Athanasiou KA. A comparison of primary and passaged chondrocytes for use in engineering the temporomandibular joint. Archives of Oral Biology. 2009;**54**:138-145

[88] Wu Y, Gong Z, Li J, Meng Q, Fang W, Long X. The pilot study of fibrin

with temporomandibular joint derived synovial stem cells in repairing TMJ disc perforation. BioMed Research International. 2014;**2014**:454021

[89] Koyama N, Okubo Y, Nakao K, Osawa K, Fujimura K, Bessho K. Pluripotency of mesenchymal cells derived from synovial fluid in patients with temporomandibular joint disorder. Life Sciences. 2011;**89**:741-747

[90] Sunil P, Manikandhan R, Muthu M, Abraham S. Stem cell therapy in oral and maxillofacial region: An overview. Journal of Oral and Maxillofacial Pathology. 2012;**16**:58-63

[91] Mäenpää K, Ellä V, Mauno J, Kellomäki M, Suuronen R, Ylikomi T, et al. Use of adipose stem cells and polylactide discs for tissue engineering of the temporomandibular joint disc. Journal of the Royal Society Interface. 2010;**7**:177-188

[92] Guo L, Li J, Qiao X, Yu M, Tang W, Wang H, et al. Comparison of odontogenic differentiation of human dental follicle cells and human dental papilla cells. PLoS One. 2013;**8**:e62332

[93] Hagandora CK, Gao J, Wang Y, Almarza AJ. Poly(glycerol sebacate): A novel scaffold material for temporomandibular joint disc engineering. Tissue Engineering Part A. 2013;**19**:729-737

[94] Almarza AJ, Athanasiou KA. Seeding techniques and scaffolding choice for tissue engineering of the temporomandibular joint disk. Tissue Engineering. 2004;**10**:1787-1795

[95] Almarza AJ, Athanasiou KA. Effects of initial cell seeding density for the tissue engineering of the temporomandibular joint disc. Annals of Biomedical Engineering. 2005;**33**:943-950

[96] Allen KD, Athanasiou KA. Scaffold and growth factor selection in temporomandibular joint disc engineering. Journal of Dental Research. 2008;**87**:180-185

[97] Legemate K, Tarafder S, Jun Y, Lee CH. Engineering human TMJ discs with protein-releasing 3D-printed scaffolds. Journal of Dental Research. 2016;**95**:800-807

[98] Springer IN, Fleiner B, Jepsen S, Açil Y. Culture of cells gained from temporomandibular joint cartilage on non-absorbable scaffolds. Biomaterials. 2001;**22**:2569-2577

[99] Suh JK, Matthew HW. Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: A review. Biomaterials. 2000;**21**:2589-2598

[100] Brown BN, Chung WL, Almarza AJ, Pavlick MD, Reppas SN, Ochs MW, et al. Inductive, scaffold-based, regenerative medicine approach to reconstruction of the temporomandibular joint disk. Journal of Oral and Maxillofacial Surgery. 2012;**70**:2656-2668

[101] Kinoshita Y, Maeda H. Recent developments of functional scaffolds for craniomaxillofacial bone tissue engineering applications. Scientific World Journal. 2013;**2013**:863157

[102] Zhang S, Yap AU, Toh WS. Stem cells for temporomandibular joint repair and regeneration. Stem Cell Reviews. 2015;**11**:728-742

[103] Sun YP, Zheng YH, Liu WJ, Zheng YL, Zhang ZG. Synovium fragment-derived cells exhibit characteristics similar to those of dissociated multipotent cells in synovial fluid of the temporomandibular joint. PLoS One. 2014;**9**:e101896

[104] Meirelles S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine & Growth Factor Reviews. 2009;**20**:419-427

[105] Almarza AJ, Athanasiou KA. Evaluation of three growth factors in combinations of two for temporomandibular joint disc tissue engineering. Archives of Oral Biology. 2006;**51**:215-221

[106] Kalpakci KN, Kim EJ, Athanasiou KA. Assessment of growth factor treatment on fibrochondrocyte and chondrocyte co-cultures for TMJ fibrocartilage engineering. Acta Biomaterialia. 2011;**7**:1710-1718

[107] Kang H, Bi YD, Li ZQ, Qi MY, Peng EM. Effect of transforming growth factor β(1) and insulin-like growth factor-I on extracelluar matrix synthesis of self-assembled constructs of goat temporomandibular joint disc. Zhonghua Kou Qiang Yi Xue Za Zhi. 2011;**46**:541-546

[108] Jiao Y, Wang D, Han WL. Effects of various growth factors on human mandibular condylar cartilage cell proliferation. Zhonghua Kou Qiang Yi Xue Za Zhi. 2000;**35**:346-349

[109] Hanaoka K, Tanaka E, Takata T, Miyauchi M, Aoyama J, Kawai N, et al. Platelet-derived growth factor enhances proliferation and matrix synthesis of temporomandibular joint disc-derived cells. The Angle Orthodontist. 2006;**76**:486-492

[110] Ankrum J, Karp JM. Mesenchymal stem cell therapy: Two steps forward, one step back. Trends in Molecular Medicine. 2010;**16**:203-209

[111] Zhang J, Guo F, Mi J, Zhang Z. Periodontal ligament mesenchymal stromal cells increase proliferation and glycosaminoglycans formation of temporomandibular joint derived fibrochondrocytes. BioMed Research International. 2014;**2014**:410167

[112] Lai RC, Tan SS, Teh BJ, Sze SK, Arslan F, de Kleijn DP, et al. Proteolytic potential of the MSC exosome proteome: Implications for an exosome-mediated delivery of therapeutic proteasome. International Journal of Proteomics. 2012;**2012**:971907