Chapter

Nonsurgical Strategies for the Treatment of Temporomandibular Joint Disorders

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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].

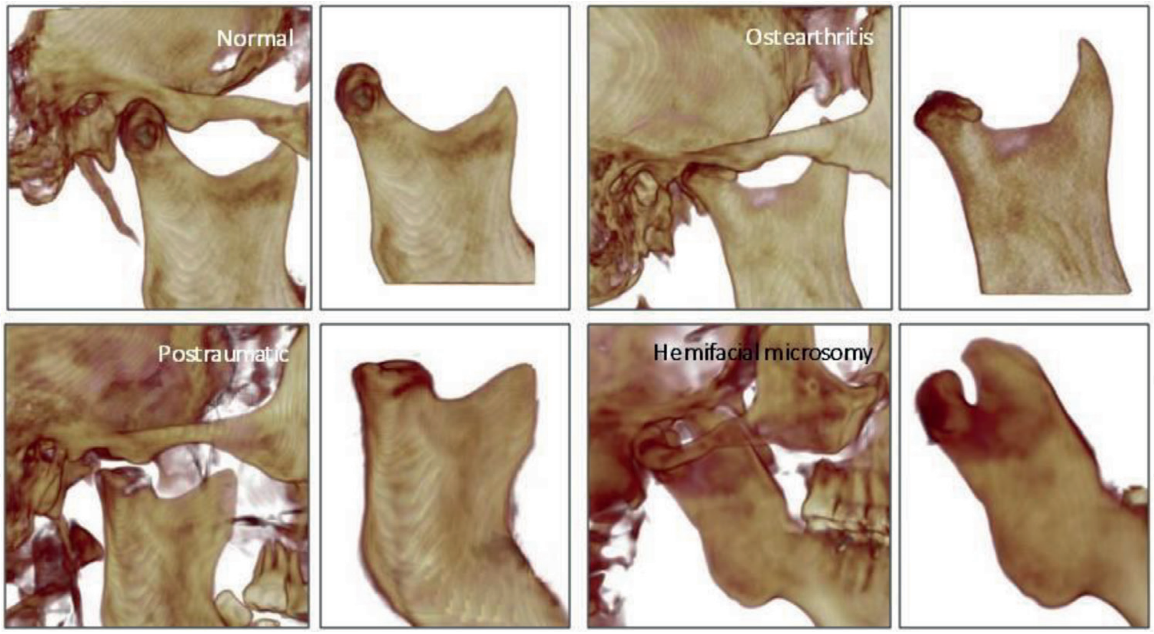


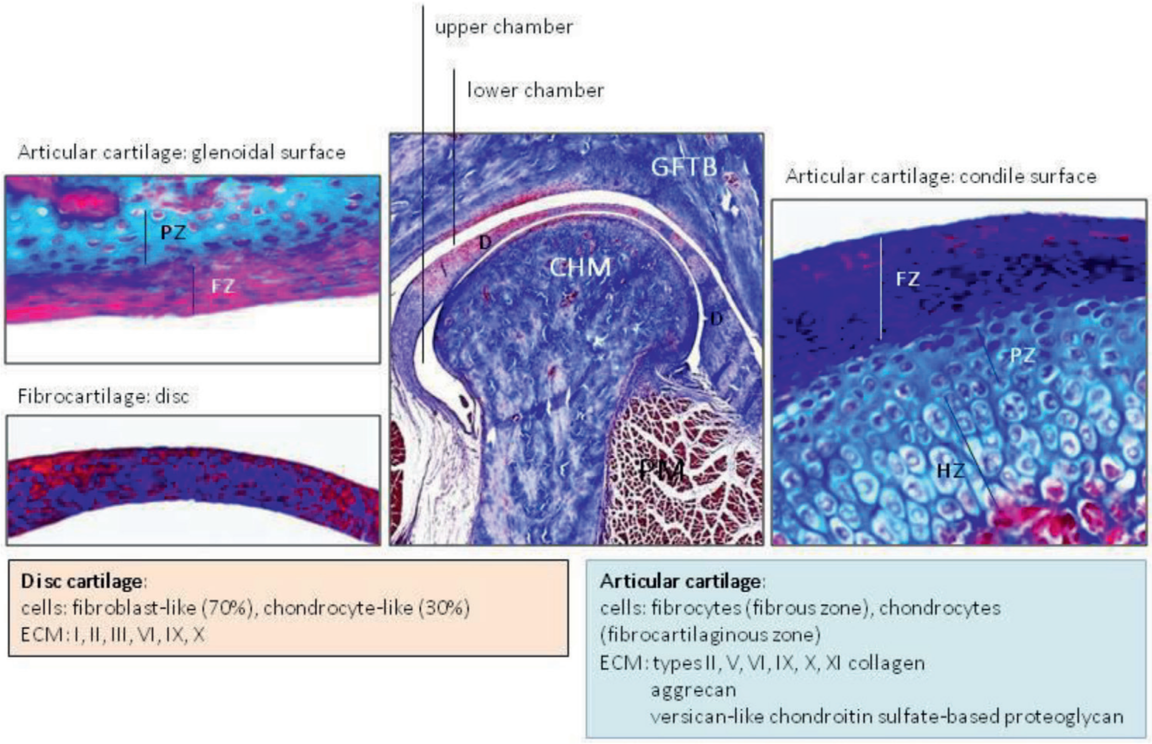
Figure 1.
Cone bean CT of the right adult TMJ in normal conditions, osteoarthritis, posttraumatic, and hemifacial microsomy. Images obtained from Instituto Asturiano de Odontolgía, Oviedo, Spain.

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]).



Disc cartilage:
cells: fibroblast-like (70%), chondrocyte-like (30%)
ECM: I, II, III, VI, IX, X

Articular cartilage:
cells: fibrocytes (fibrous zone), chondrocytes (fibrocartilaginous zone)
ECM: types II, V, VI, IX, X, XI collagen
aggrecan
versican-like chondroitin sulfate-based proteoglycan

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.

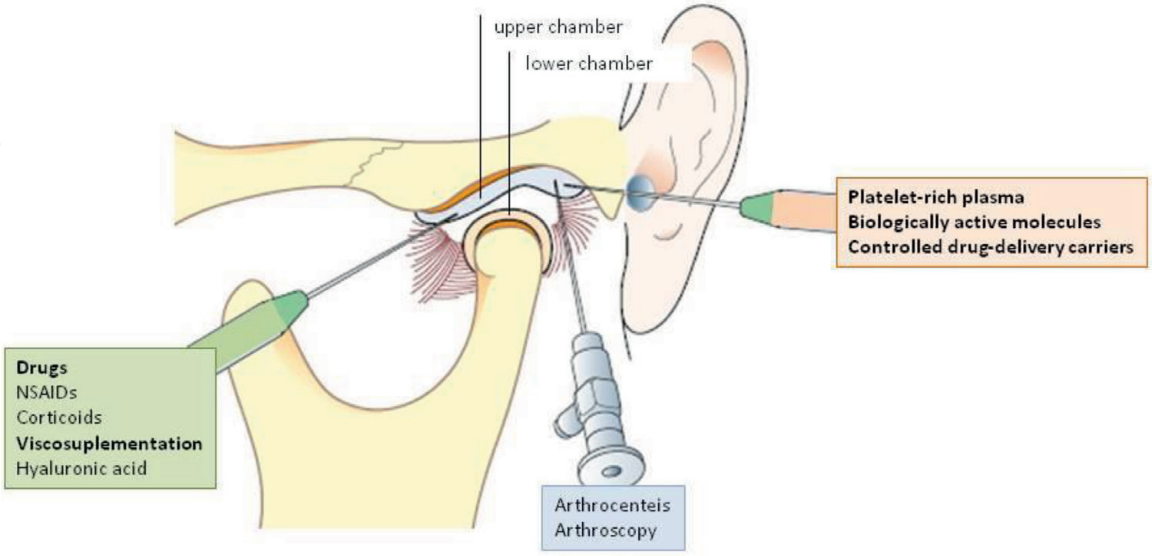


Figure 3.
Schematic representation of the minimally invasive methods and the compounds delivered in TMJ intraarticularly. Modified of https://pocketdentistry.com/33-temporomandibular-joint-surgery-including-arthroscopy/.

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 anti-apoptosis, 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.

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