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Chapter 22

Current Advances in Mandibular Condyle Reconstruction

Tarek El-Bialy and Adel Alhadlaq

Additional information is available at the end of the chapter

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1. Introduction

The temporomandibular joint, like any other synovial joint, can be the subject of severe degenerative pathological conditions as well as fracture and ankylosis. Advanced conditions may require rib or hip grafts, allografts, or total joint replacement. All current approaches suffer from inherent shortcomings and the search continues for a new approach to reconstruct the mandibular condyle with minimal or no side effects. Stem cell-based tissue engineering approach to reconstruct the mandibular condyle has long been introduced; however its potential clinical application requires long and costly dedicated research programs. Other therapeutic physical approaches to enhance tissue regenerative capacity have also been proposed, however their potential application needs further attention and investigation.

2. Clinical indication

Articular joints have a poor innate ability to regenerate following either injury or disease. Among these diseases that affect articular joints is arthritis. In Canada, arthritis is the leading cause of work disability, with an economic cost of $4.4 billion in 1998 alone [1]. Statistics Canada reports estimated that 6 million Canadians will suffer from some form of arthritis by 2026, a significant increase from the current prevalence of four million Canadians [2]. The temporomandibular joint (TMJ) connects the mandible to the skull and is vital for speech, chewing, and swallowing.It is comprised of a mandibular condyle and an articular disk. TMJ is susceptible to arthritis, fractures, ankylosis, and dysfunctional syndromes that affect over 10 million individuals in North America [3-9]. To date, artificial joint replacement is considered the standard therapeutic procedure for degenerated TMJ, but this treatment approach has a

high cost and non-predictive outcome [10]. According to the Canadian Joint Replacement Registry, a total of 97,671 patients had different joint replacements between years 2007-2010 [11].It has been reported that about 10% showed foreign body response to TMJ metal replacement with allergic reaction to metal [12]. Consequently, developing effective methods to replace articular condyle are of paramount importance to current/modern society. This book chapter discusses in detail contemporary methods and future directions of mandibular condylar reconstruction.

3. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are increasingly being used in joint tissue engineering research [13-19]. Tissue engineering ofmandibular condyle as a whole has been proposed in the literature; however an in-vivo utilization of this technique is in need of further investigation based upon compelling evidence from pilot data [15-22]. Some limitations to MSCs based therapy include the extended time needed in the laboratory to expand them and differentiate them into chondrogenic and osteogenic lineages. An improved approach to enhance the expansion and differentiation of MSCs is highly demanded. Also, understanding MSCs differentiation process and their characterization must be achieved before they can be used safely and effectively in articular joint replacement.

The current approach used to tissue engineer articular constructs involves conditioning with some type of mechanical stress. Existing mechanical conditioning techniques to enhance engineered tissues are in the form of bioreactors, BioFlex mechanical modulation technologies (Flexercell), and Instron machines. However, these approaches are short of clinical application should the engineered tissue require more mechanical modulation after in-vivo implantation for functional use.

4. Low intensity pulsed ultrasound

Low intensity pulsed ultrasound (LIPUS) therapy stimulates stem cell growth and differentiation [20,23-24]. We have shown in a pilot study in rabbits that LIPUS may enhance tissue engineered mandibular condyles. This compelling preliminary data needs to be validated in a statistically determined study design. Moreover, there is increasing supporting data in the literature that the stimulatory effect of LIPUS on cell expansion and differentiation is dose dependent. The LIPUS is considered the preferred method of mechanical stimulation, also known as “preferred bioreactor” [25].

5. Articular condyle

An articular condyle consists of articular cartilage and subchondral bone (Fig. 1) [20]. Despite a common developmental origin from mesenchyme, the articular cartilage and subchondral

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bone have two distinct adult tissue phenotypes with few common morphological features. However, both tissues are structurally integrated and function in harmony to withstand mechanical loading up to several times the body's weight [26].

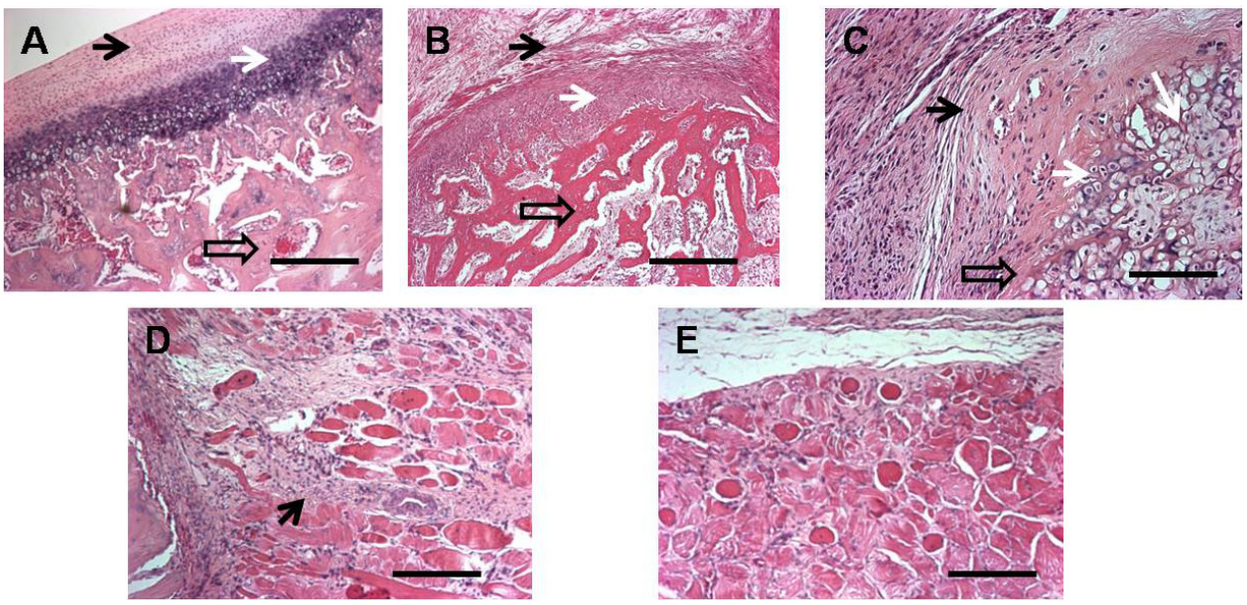

Figure 1. Photomicrographs of the histological examination of normal condyle showing fibrocartilage (black arrow) hypertrophic zone (white arrow) and subchondoral bone (hollow arrow) (Bar =100 µm)[20].

In osteochondral defects, bone regeneration can readily occur in the presence of an adequate blood supply up to a certain bony defect size. In contrast, articular cartilage has a poor capacity for self-regeneration. Furthermore, once articular cartilage is damaged, it undergoes degenerative events such as loss and/or destruction of key structural components, including type II collagen and proteoglycans. The poor capacity of cartilage for self-regeneration is likely attributed to the paucity of tissue-forming cells (i.e., chondrocytes) [27] and the lack of access to systemically available mesenchymal stem cells because the cartilage tissue is avascular. Thus, the self-regenerating capacity of articular cartilage is limited due to the sparsely available chondroprogenitor cells and/or the scant local mesenchymal stem cells that are habitual residents. Importantly, the articular cartilage is devoid of a nerve supply. Thus, articular cartilage injuries are often not accompanied by joint pain until the damage has progressed to involve the subchondral bone, which contains rich nerve supply [28]. In many of these disorders, structural damage of the TMJ necessitates surgical replacement.

6. TMJ replacement

The current TMJ replacement techniques utilize bone/cartilage grafts, muscles and artificial materials [9, 29-30]. Despite certain level of reported clinical success, autografts are associated with donor site morbidity such as discomfort in ambulation, sensorial loss over the donor

region, scars, and contour deformity when bone is harvested from the iliac bone. Also, predictability of clinical outcome of autografts is reported to be substandard with graft overgrowth in 10% of patients and undergrowth in 57% of patients, and a relatively high incidence of re-operation with 23% of patients requiring re-grafting [31-34].Alternatively, alloplastic and xenoplastic grafts are associated with potential transmission of pathogens and immunorejection [35-37].The failure rate of using alloplastic grafts to reconstruct the TMJ has been reported to reach 30% [38]. To date, there is no consistent clinically-effective and safe method to replace the TMJ or mandibular condyle.

7. Biological replacement of mandibular condyle

Biological replacement efforts for reconstruction of the mandibular/articular condyles have included using osteoblasts and chondroblasts/chondrogenic cells from different tissue/cell sources [15-22,38-41]. However, these efforts have been limited by several obstacles including: a) scarcity of stem cells with the capacity to differentiate into chondrogenic and osteogenic cells, b) different bone ingrowth patterns [37], c) different rates of the scaffold degradation compared to matrix production [15], and d) inferior mechanical properties of the regenerative tissue for clinical use [40]. Moreover, the integration of tissue engineered constructs for osteochondral repair requires an inordinate amount of time (3-6 months in rabbit femur heads [21],6-12 months in horses [41], and up to 9 months in sheep [19]). Regeneration of articular joints utilizing a cell-free scaffold by cell homing to the area shows some success [18]. However, this process did not provide full articular condyle replacement. In addition, this proof of principle lasted 9 weeks to obtain some articular joint regeneration in rabbits, which translates to 9 to 12 months in humans, given the difference in metabolism between the two species [42]. This lengthy time of manipulation can be complicated by tissue culture problems such as infection. Another attempt to tissue engineer mandibular condyle using porcine stem cells demonstrated bone formation in-vitro; however there was no attempt or success in translating this technique into in-vivo utilization [43]. A similar recent study demonstrated the possibility of tissue engineering a complete mandibular condyle in-vitro; however in-vivo utilization of this technique has yet to be studied[44]. Interestingly, this study highlighted the importance of bioreactor in stem cell expansion and differentiation [44]. It was first reported that tissue engineered osteochondral constructs from MSCs can be shaped into human-size mandibular condyles while maintaining the shape and size after extended period of in-vivo implantation [15,17,18]. Not only these constructs demonstrate MSCs-driven formation of osteochondral tissue-like histologically, but also both tissue types showed good histological integration attributed to the use of the same scaffolding material in both layers, and thus avoiding the potential fibrous tissue infiltration between the two layers usually observed in composite constructs [15,17,18].Our team was the first to report on the possibility of engineering condyles from stem cells [15,17,18] (Figure 2).

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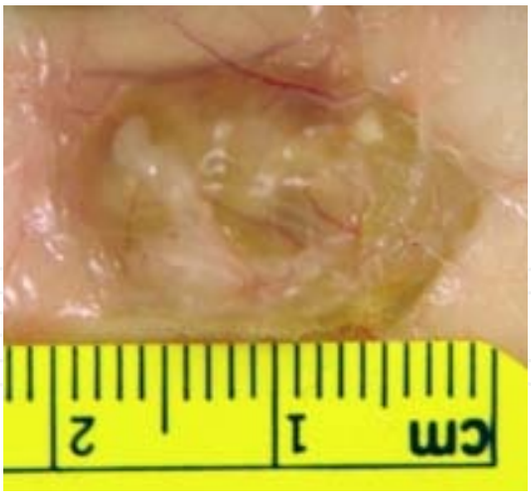

Figure 2. Appearance of a tissue engineered osteochondral construct holding the shape and dimensions of a human mandibular condyle during harvest after 12 weeks of subcutaneous implantation in the dorsum of immunodeficient mouse.

Although most of the recent studies, including ours, are focused on engineering scaffolds in the shape of mandibular or articular condyles [15,17,18,44], future research is needed to implement tissue engineered condyles into clinical application and to demonstrate functional integration. It is well known that inadequate mechanical strength is considered a major impediment to cartilage tissue engineering [45,46]. The material properties of tissue-engineered cartilage constructs are in the range of kilopascals [47], which are orders of magnitude lower than normal articular cartilage (in the range of megapascals) [48-53]. Different techniques have attempted to improve the quality of tissue-engineered articular joints. Pulsed electromagnetic fields (PEMF) have been shown to increase chondrocyte and osteoblast-like cell proliferation [54,55]. Bioreactors including LIPUS enhance the material properties of tissue-engineered cartilage constructs [25,56,57]. Cyclic compressive loading induces phenotypic changes in cartilaginous and osseous tissues in cell culture, scaffolds, and in-vivo [58-70]. Also, mechanical stimulation enhances the expression of vascular endothelial growth factor (VEGF) which is important for angiogenesis and bone formation in the mandibular condyles [71]. These important discoveries support the potential for clinical application of different forms of mechanical stimulation to enhance tissue-engineered joint tissues.

8. Low intensity pulsed ultrasound (LIPUS)

Low intensity pulsed ultrasound (LIPUS) is a form of mechanical stimulation that has been used to enhance healing of fractured bone and other tissues. Details about the current literature and the potential use of LIPUS for better autologous stem cell based mandibular condyle (ASCMC) will be discussed below. It is clear that there is a vital need for an approach to enhance stem cell expansion and differentiation for tissue engineering of articular condyles. LIPUS can be an effective tool to enhance tissue-engineering of mandibular condyles for many reasons.

Importantly, LIPUS is the preferred method of mechanical stimulation, also reported as "preferred bioreactor" [25] as it enhances angiogenesis [20, 72-76].This is especially relevant because vasculature is required to integrate the engineered tissue with the native surrounding tissues [77]. Recent studies showed that LIPUS enhances stem cell expansion and differentiation in tissue culture [78,79]. Also, LIPUS has been shown to enhance periosteal cell expansion [79] and stimulate bone marrow stem cells (BMSCs) expansion and differentiation into chondrogenic lineage [78,80-83].The matrix production and proliferation of the intervertebral disc cells in culture has been shown to be enhance by LIPUS [82]. In addition, LIPUS enhances osteoblast matrix formation [796,83] and minimizes apoptosis of human stem cells in-vitro [84]. The optimum LIPUS application time in bone fracture healing has been identified [85]; however, the optimum LIPUS treatment timing in articular condyle replacement is yet to be studied.Despite recent studies that have shown that the stimulatory effect of LIPUS in tissue culture is dose-dependent (treatment time) [23,24,75,78,86-88], the use of LIPUS has not resulted in any severe adverse events in tissue culture [88], human or animal models [89-92]. Our research has demonstrated that LIPUS can enhance stem cell expansion in monolayers [20-23-24] (Figure 3).There was an increase in cell number after LIPUS application for 20 minutes per day for 3 weeks. A future projectcan aim to optimize using LIPUS to enhance cell proliferation to a significant level that may justify its routine use in tissue engineering.

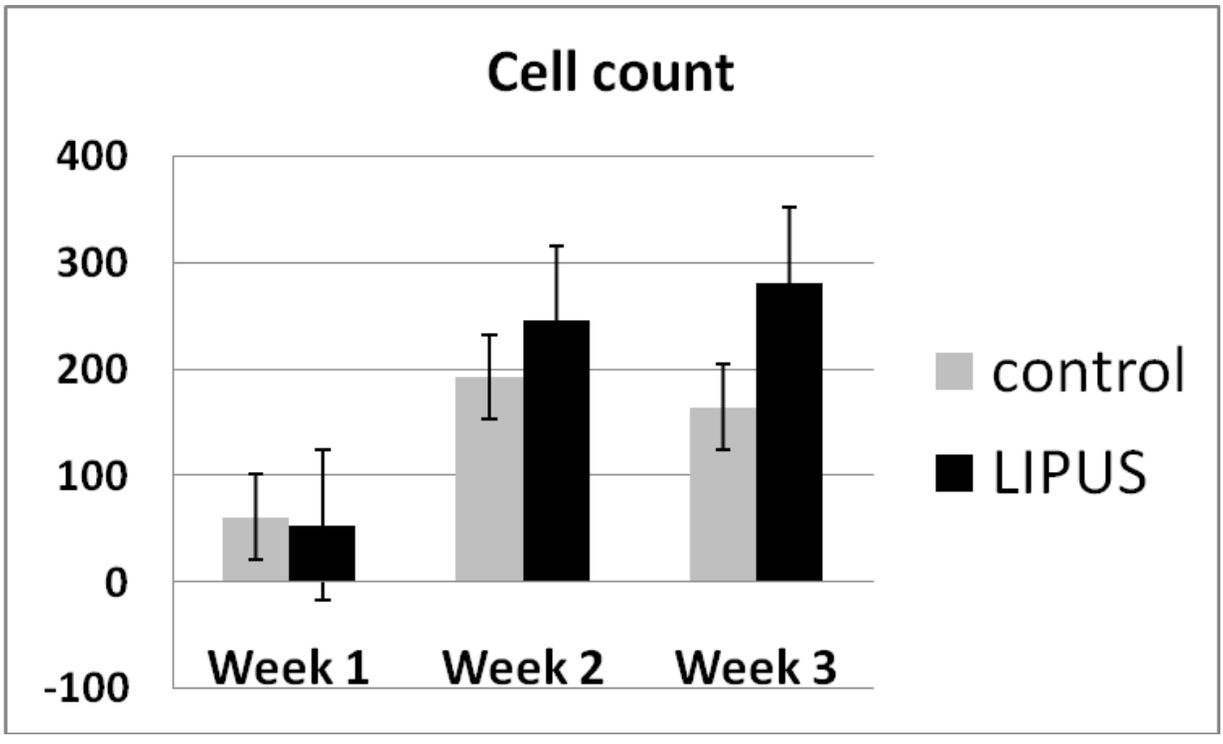

Figure 3. Rat BMSC count after treatment with 20 minutes per day for three weeks.It can be seen that LIPUS enhances cell count compared to untreated BMSCs by (20 minutes per day for three weeks). This reflects that LIPUS stimulates BMSC expansion and this stimulatory effect is treatment time-dependent. This experiment was performed three times and the presented data represents the average and standard error of nine samples [three trials in triplicate]. There is a significant difference in cell number at week 3 between the control and LIPUS treated BMSCs ($P<0.05$) [23].

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In addition, LIPUS enhances expression of bone morphogenetic proteins from pluripotent cells [88]. Moreover, we have shown that LIPUS application for 20 minutes per day for 4 weeks increased the expression of collagen II and osteopontin expression in osteogenic-induced differentiation of stem cells (P<0.05)[Figure 4 and Table A] [20].

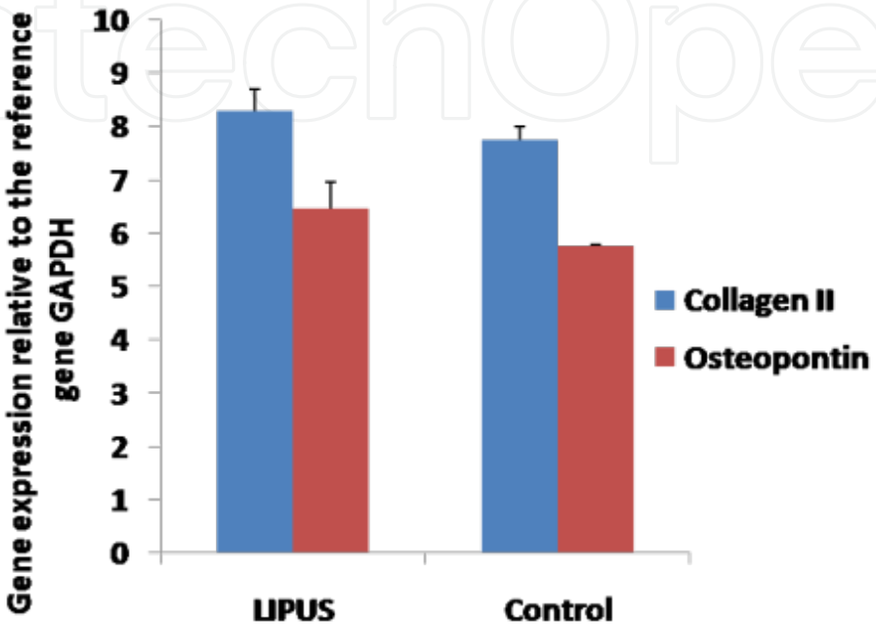

Figure 4. qPCR results of LIPUS treated (20 minutes/day) osteogenic differentiated BMSCs for four weeks and controls. LIPUS treated osteogenic cells expressed more osteopontin and collagen type II genes (normalized to GAPDH) which is indicative of enhancing osteogenic differentiation of BMSCs affected by LIPUS. Both graphs represent results of performing qPCR on nine samples (three trials in triplicate). This increase in Collagen II and Osteopontin by LIPUS is statistically significant (P< 0.005)[20].

Gene of interest	Average + Standard deviation		P
	LIPUS	Control	
Collagen II	8.3 + 0.4	6.4 + 0.5	0.009*
Osteopontin	7.7 + 0.02	5.7 + 0.3	0.004*

Table 1. Collagen II and osteopontin gene expression in vitro as evaluated by qPCR. Gene expression is presented as percentage to the reference gene GAPDH. Non parametric analysis (Mann-Whitney U) shows a statistical significant increase in Collagen II and Osteopontin gene expression by LIPUS when compared to non LIPUS treated samples [20].

Also, LIPUS application to gingival stem cells statistically increased the gene expression of alkaline phosphatase (ALP) in tissue culture (Figure 5) [88].

Figure 5.Alkaline phosphatase (ALP) gene expression was increased by daily treatment of GFs with 10 minutes LIPUS for 4 weeks as evaluated by qPCR. Data represents average of five replicates with the error bar representing standard deviation [885].

Our preliminary data indicated that LIPUS application enhanced osteogenic and chondrogenic differentiation of bone marrow stem cells in collagen sponges in-vitro (Figure 6) as determined by histochemical staining (safranin O for chondrogenic differentiation and von Kossa staining for osteogenic differentiation) [20].

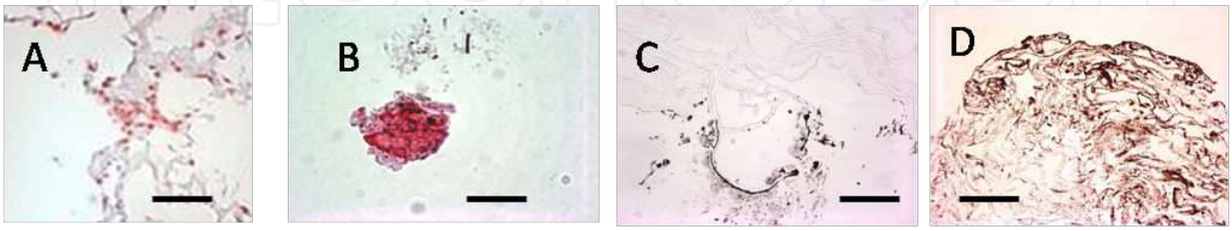

Figure 5. In-vitro chondrogenesis and osteogenesis of BMSCs in samples of collagen scaffolds. A: Positive reaction to safranin O (red staining) of BMSC-derived chondrogenic cell chondrogenic tissue formation in the control [no LIPUS] scaffolds following four-week treatment with chondrogenic medium, B: Increased (red staining) positive reaction to safranin O of the BMSC-derived chondrogenic cells treated with LIPUS and chondrogenic medium for four weeks. C: Positive but weak reaction to Von Kossa silver staining (black staining) of BMSC-derived osteogenic cells in the control [no LIPUS] scaffolds following four-week treatment with osteogenic medium. D: Increased positive reaction to Von Kossa silver staining (black staining) of the BMSC-derived chondrogenic cells treated with LIPUS treatment and osteogenic medium for four weeks. More mineralization nodules are observed with LIPUS treatment. Bar is 100 μm [20].

Finally, we have shown that LIPUS enhances tissue-engineered mandibular condyles in a pilot study invivo [20](Figures 7-13). This was confirmed qualitatively by MicroCT scanning, histological evaluations (safranin O and Von Kossa staining) (Figures 9-12) as well as quantitatively by histomorphometric analysis (Figure 13).

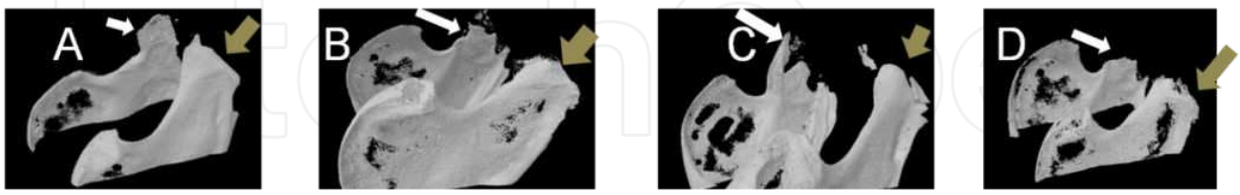

Figure 6. MicroCT scanning of: (A) Group 1 (TEMC + LIPUS); (B) Group 2 (TEMC no LIPUS) (C) Group 3 (scaffold with no cells + LIPUS) and (D) scaffold with no cells and with no LIPUS. In each rabbit, the yellow arrow refers to normal condyle and the white arrow refers to the experimental site (either TEMC or empty scaffold). It can be seen that LIPUS enhanced TEMC as indicated by close morphology of the LIPUS-assisted TEMC compared to the normal condyle (A). The condylar healing was not as pronounced when there were cells present in the scaffold but no LIPUS was applied (B). LIPUS did enhance some healing of the amputated condyle site even without a scaffold (C). The negative control (empty scaffold and no LIPUS) showed no signs of healing (D). Note: TEMC consisted of a scaffold and chondrogenic and osteogenic cells [20].

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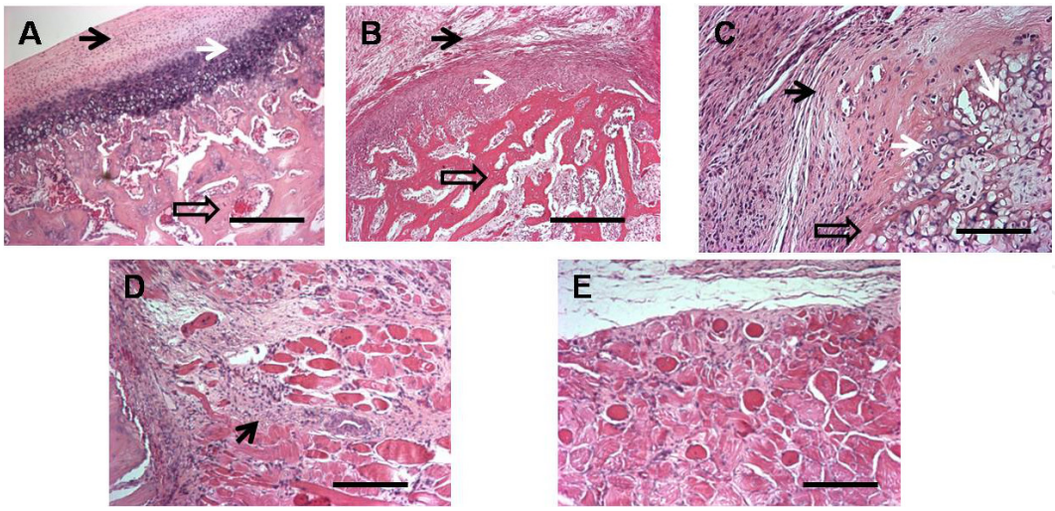

Figure 7. Photomicrographs of the histological examination of (A) normal condyle; (B) LIPUS-assisted TEMC in group 1; (C) TEMC with no LIPUS; (D) empty scaffold with LIPUS; and (E) empty scaffold without LIPUS. The LIPUS-enhanced TEMC (B) has comparable histological features to the normal condyle (A), and TEMC without LIPUS (C) shows some structural integration between the chondrogenic and osteogenic parts of the TEMCs. The empty scaffolds (D, E) show inflammatory cell invasion without bone or cartilage formation. Black arrows refer to fibrocartilage area, white arrows refer to condylarcartilage or new cartilage formed by TEMC areas, and empty arrows refer to condylar bone or new bone formed by the TEMC. Scale bar: 100 mm [20].

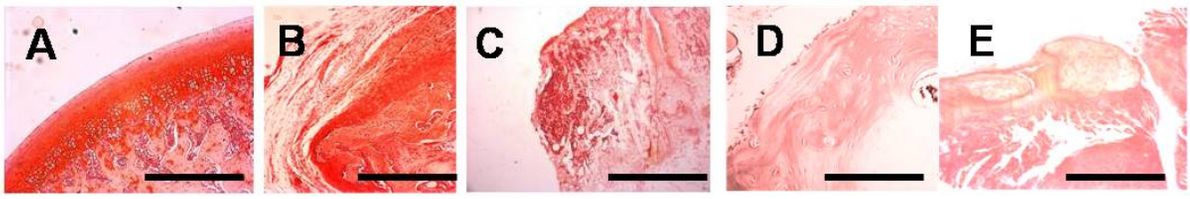

Figure 8. Photomicrographs of safranin O stained histological slides of (A) normal condyle; (B) LIPUS assisted TEMC; (C) TEMC with no LIPUS; (D) Empty scaffold with LIPUS; and (E) empty scaffold without LIPUS. It can be seen that the cartilaginous part of the normal condyle and TEMC have comparable safranin O staining that indicates improved chondrogenesis with LIPUS compared to either empty scaffolds (D and E). TEMC with no LIPUS still shows some reaction to safranin O staining but not like TEMC and LIPUS (Magnification = 16 X) [20].

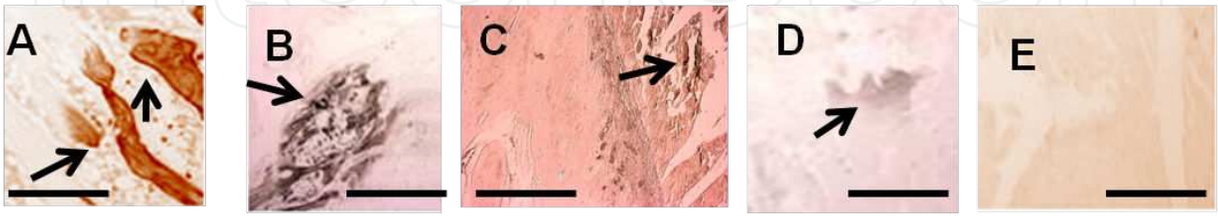

Figure 9. Photomicrographs of Von Kossa stained histological slides of (A) Normal condyle; (B) LIPUS assisted TEMC; (C) TEMC with no LIPUS; (D) Empty scaffold with LIPUS and (E) Empty scaffold without LIPUS.LIPUS assisted TEMC and normal condyle show comparable Von Kossa silver staining of the bone underlying the cartilage/chondrogenic part of the condyle/TEMC. In empty scaffold implanted condyles, minimum or no mineralization nodules can be seen by Von Kossa silver staining. Bar is 100 μm [20].

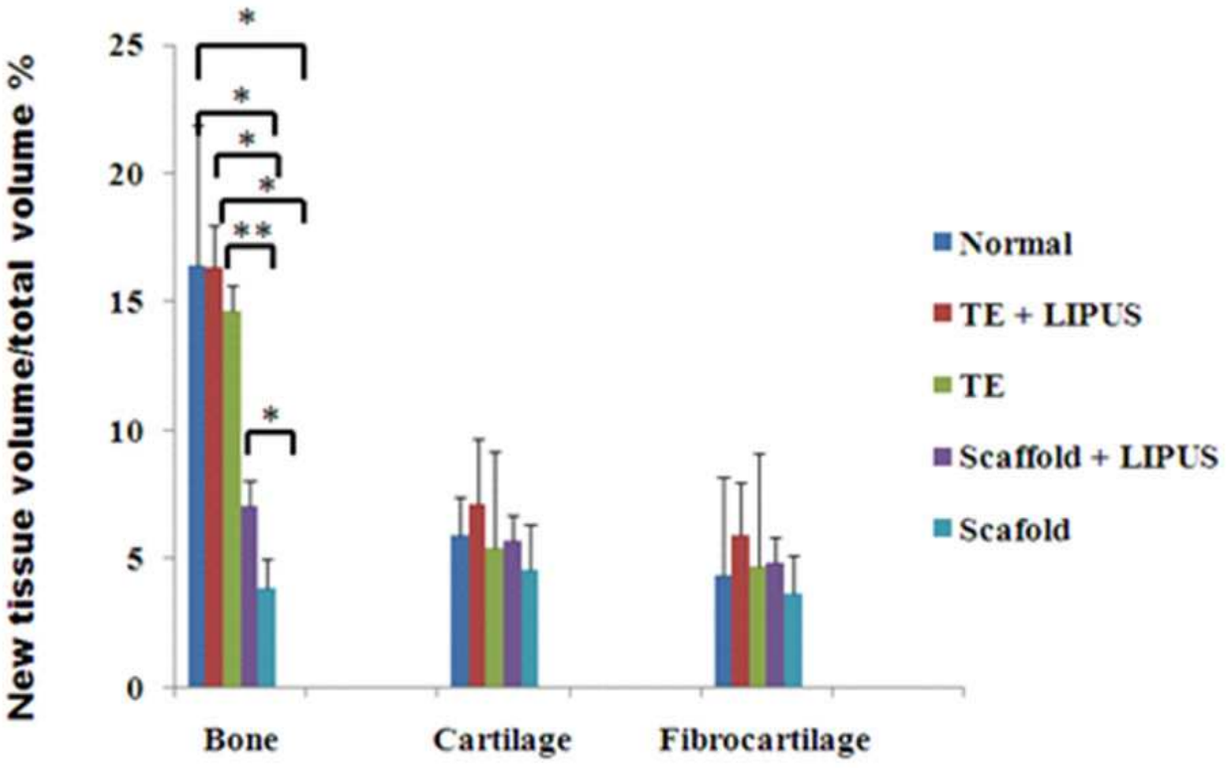

Figure 10. Histomorphomteric Analysis of the TEMC + LIPUS or empty scaffolds + LIPUS [20].

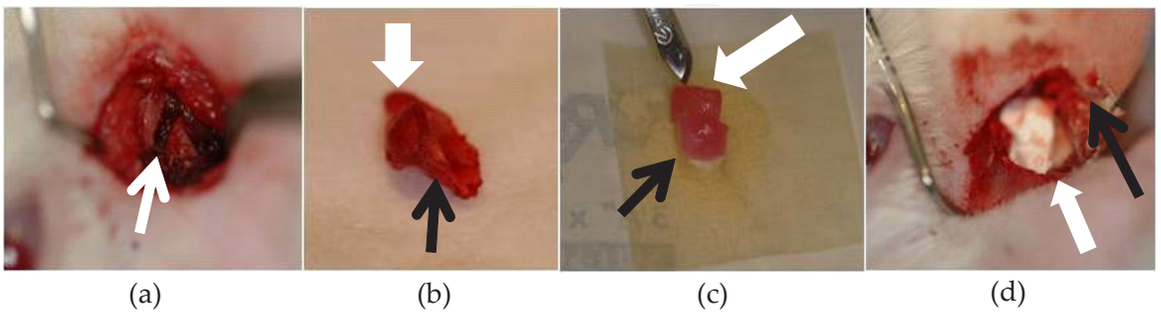

Figure 11. A: Rabbits after condylectomy [white arrow indicates condylectomy site]. B: Condyle after dissection [white arrow refers to the cartilage part and black arrow refers to the bony part of the condyle], C: Collagen sponge containing chondrogenic [white arrow] and osteogenic [black arrow] cells; D: TEMC [black arrow] fixed in place with white bone cement [white arrow]. (Photos from pilot study [20])

Figure 12. LIPUS: application to the rabbit while it is restrained [20].

8.1. Mechanical stress and intracellular signaling

There is growing evidence in the literature that integrins are promising candidates for sensing extracellular matrix-derived mechanical stimuli and converting them into biochemical signals [93-96]. Integrin-associated signaling pathways include an increase in tyrosine phosphorylation of several signaling proteins, activation of serine/threonine kinases, and alterations in cellular phospholipid and calcium levels [97-98]. These events are associated with the formation of focal adhesions, which contain structural proteins such as Src, and Shc. Focal adhesions act as a bridge to link integrin cytoplasmic domain to the cytoskeleton and activate integrin-associated signaling pathways, such as the mitogen-activated protein kinase (MAPK) pathway [99] and the Rho pathway [100-101]. Rho and its downstream target Rho kinase/Rho-associated coiled-coil-containing protein kinase (ROCK) [102] are involved in the reorganization of cytoskeletal components [99], [102-103]. It has been recently reported that β1 integrin plays predominant roles for shear-induced signaling and gene expression in osteoblast-like MG63 cells on FN, COL1, and Laminin (LM) and that $\alpha v\beta 3$ also plays significant roles for such responses in cells on fibronectin (FN). The β1 integrin-Shc association leads to the activation of ERK, which is critical for shear induction of bone formation-related genes in osteoblast-like cells [103]. Moreover, $\alpha 5\beta 1$ integrin is expressed by chondrocytes [104] and it plays an important role in mechanically enhanced cartilage tissue engineering. Furthermore, integrins were found to be responsible for ultrasound-induced cell proliferation. It has been suggested that integrins act as mechanotransducers to transmit acoustic pulsed energy into intracellular biochemical signals inducing cell proliferation [105]. It has been reported recently that LIPUS activates the phosphatidylinositol 3 kinase/Akt pathway and stimulates the growth of chondrocytes [106] as well as increases FAK, ERK-1/2, and IRS-1 expression of intact rat bone cells [107]. This has yet to be investigated in MSC derived chondrocytes and in osteoblasts-like cells.

9. Conclusion

The literature supports that mechanical stress, for example LIPUS have a stimulatory effect on stem cell expansion and differentiation as well as enhancing stem cell matrix production in-

vitro and in a pilot study in-vivo in rabbits. However, these results need to be validated in a large scale in-vivo.We are now poised to prove these effects in a large scale study. Although the optimum mechanical stimulation, for example LIPUS treatment time, for bone fracture healing is well documented, the corollary for enhancing autologous stem cell based replacement of mandibular condyles has not been investigated. This represents a major gap of knowledge in the field of tissue engineering considering the numerous positive utilizations of mechanical stimulation as well as LIPUS reported in the literature. Overall, the current literature and knowledge developed through our and others' research has the potential to increase our understanding of the details of LIPUS induced chondrogenesis and osteogenesis and how to utilize LIPUS to enhance articular joint replacement using MSCs. Furthermore, this knowledge could give rise to a novel cell-based therapy for replacement of mandibular condyles as well as other tissue types.

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