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Chapter 22

Current Advances in Mandibular Condyle Reconstruction

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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 reaction 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 of mandibular 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
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 subchondral 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).
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 [79, 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 project can 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].
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].

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 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 condylar cartilage 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. Histomorphometric 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])
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 αvβ3 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, α5β1 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 utilisations 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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References

[1] Health C. Health Canada; Economic Impact of Illness in Canada. Ottawa: Public Works and Government Services Canada. Catalogue # H21-136/1998E, 2002. 1998. Ref Type: Internet Communication

[2] Statistics C. Canadian Community Health Survey (CCHS). Public Health Agency of Canada http://www.phac-aspc.gc.ca/publicat/ac/ac_3e-eng.php, editors. 2000. Ref Type: Internet Communication.
[3] Ribeiro RF, Tallents RH, Katzberg RW, Murphy WC, Moss ME, Magalhaes AC, Tava‐
no O. The prevalence of disc displacement in symptomatic and asymptomatic volun‐
teers aged 6 to 25 years. J Orofac Pain 11:37-47, 1997.

[4] Ferrari R, Leonard MS. Whiplash and temporomandibular disorders: a critical re‐
view. J Am Dent Assoc 129:1739-1745,1998.

[5] Israel HA, Diamond B, Saed-Nejad F, Ratcliffe A. Osteoarthritis and synovitis as ma‐
jor pathoses of the temporomandibular joint: comparison of clinical diagnosis with
arthroscopic morphology. J Oral Maxillofac Surg 56:1023-1027, 1998.

[6] Sano T, Westesson PL, Larheim TA, Rubin SJ, Tallents RH. Osteoarthritis and abnor‐
mal bone marrow of the mandibular condyle. Oral Surg Oral Med Oral Pathol Oral
RadiolEndod 87:243-252, 1999.

[7] Stohler CS (1999) Muscle-related temporomandibular disorders. J Orofac Pain
13:273-284,1999. Goddard G, Karibe H. TMD prevalence in rural and urban Native
American populations. Cranio 20:125-128, 2002.

[8] Bell RB, Blakey GH, White RP, Hillebrand DG, Molina A. Staged reconstruction of
the severely atrophic mandible with autogenous bone graft and endosteal implants. J
Oral Maxillofac Surg 60:1135-1141, 2002.

[9] Henning TB, Ellis E 3rd, Carlson DS. Growth of the mandible following replacement
of the mandibular condyle with the sternal end of the clavicle: an experimental inves‐
tigation in Macacmulatta. J Oral Maxillofac Surg 50:1196-1206, 1992.

[10] Westermark A, Koppel D, Leiggener C.: Condylar replacement alone is not sufficient
for prosthetic reconstruction of the temporomandibular joint. Int J Oral Maxillofac
Surg. 2006 Jun;35(6):488-92.

[11] Data Quality Documentation for Users: Canadian Joint Replacement Registry, 2007–
2008 to 2009–2010 Data. http://secure.cihi.ca/cihiweb/products/
DQ_CJRR_2007-2010_e.pdf. Ref Type: Internet Communication

[12] Sidebottom AJ, Speculand B, Hensher R.: Foreign body response around total pros‐
thetic metal-on-metal replacements of the temporomandibular joint in the UK. Br J
Oral Maxillofac Surg. 2008 Jun;46(4):288-92.

[13] Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Ther.
2008;10:223-235.

[14] Goldring MB. Are bone morphogenetic proteins effective inducers of cartilage re‐
pair? Ex vivo transduction of muscle-derived stem cells.[comment]. Arthritis &
Rheumatism. 2006;54:387-389.

[15] Alhadlaq A, Mao JJ. Tissue-engineered Neogenesis of Human-shaped Mandibular
Condyle from Rat Mesenchymal Stem Cells. J Dent Res 82:951-6, 2003.
[16] Alhadlaq A, Mao JJ. Mesenchymal stem cells: isolation and therapeutics. Stem Cells Dev 13:436-48, 2004.

[17] Alhadlaq A, Elisseeff J, Hong L, Williams C, Caplan AI, Sharma B, Kopher RA, Tomkoria S, Lennon DP, Lopez A, Mao JJ. Adult stem cell driven genesis of human-shaped articular condyle. Ann Biomed Eng 32:911-923, 2004.

[18] Alhadlaq A, Mao JJ.: Tissue-engineered osteochondral constructs in the shape of an articular condyle. J Bone Joint Surg Am 87:936-44, 2005.

[19] Pilliar RM, Kandel RA, Grynpas MD, Zalzal P, Hurtig M.: Osteochondral defect repair using a novel tissue engineering approach: sheep model study. Technol Health Care 15(1):47-56, 2007.

[20] El-Bialy, T., Uludag, H., Jomha, N., and Badylak, S.: In vivo ultrasound assisted tissue engineered mandibular condyle: a pilot study in rabbits. Tissue Eng Part C Methods (2010 Dec;16(6):1315-23).

[21] Lee, C.H., Cook, J.L., Mendelson, A., Moioli, E.K., Yao, H., Mao, J.J.: Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. Lancet 376: 440–48, 2010.

[22] Shao X, Goh JC, Hutmacher DW, Lee EH, Zigang G.: Repair of large articular osteochondral defects using hybrid scaffolds and bone marrow-derived mesenchymal stem cells in a rabbit model. Tissue Eng 12(6):1539-51, 2006.

[23] Ang, W.T.; Yu,C.; Chen, J.; El-Bialy, T.H.; Doschak, M.; Uludag, H. and Tsui, Y.: System-on-chip Ultrasound Transducer for Dental Tissue Formation and Stem Cell Growth and Differentiation, Proceeding of the IEEE, May, 2008.

[24] Aldosary, T.A.; Uludag, H.; Doschak, M.; Chen, J.; Tsui, Y. and EL-Bialy, T.: Effect of Ultrasound on Human Umbilical Cord Perivascular-Stem Cell Expansion. IADR, Toronto, July 2008, Abstract # 873.

[25] Marvel S, Okrasinski S, Bernacki SH, Loboa E, Dayton PA.: The development and validation of a LIPUS system with preliminary observations of ultrasonic effects on human adult stem cells. IEEE Trans UltrasonFerroelectrFreq Control. 2010 Sep;57(9): 1977-84.

[26] Martin, RB, Burr DB, and Sharkey NA. Skeletal Tissue Mechanics. New York: Springer-Verlag, 1998.

[27] Poole AR, Kojima T, Yasuda T, Mwale F, Kobayashi M, Laverty S.: Composition and structure of articular cartilage: a template for tissue repair. Clin Orthop Relat Res. 2001 Oct;(391 Suppl):S26-33.

[28] LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 8:291-305, 1997.
[29] MacIntosh RB. The use of autogenous tissues for temporomandibular joint reconstruction. J Oral Maxillofac Surg 58:63-69, 2000.

[30] Canter HI, Kayikcioglu A, Saglam-Aydinatay B, Kiratli PO, Benli K, Taner T, Erk Y.: Mandibular reconstruction in Goldenhar syndrome using temporalis muscle osteofascial flap. J Craniofac Surg. 2008 Jan;19(1):165-70.

[31] Dodson TB, Bays RA, Pfeffle RC, Barrow DL. Cranial bone graft to reconstruct the mandibular condyle in Macacamulatta. J Oral Maxillofac Surg 55:260-267, 1997.

[32] Wolford LM, Katras SC. Autologous fat transplantation around temporomandibular joint total joint prostheses: preliminary treatment outcomes. J Oral Maxillofac Surg 55:245-251, 1997.

[33] Wan DC, Taub PJ, Allam KA, Perry A, Tabit CJ, Kawamoto HK, Bradley JP. Distraction osteogenesis of costocartilaginous rib grafts and treatment algorithm for severely hypoplastic mandibles. Plast Reconstr Surg. 2011 May;127(5):2005-13.

[34] Mercuri LG. The use of alloplastic prostheses for temporomandibular joint reconstruction. J Oral Maxillofac Surg 58:70-75, 2000.

[35] Meyer RA. Costal cartilage for treatment of temporomandibular joint ankylosis. Plast Reconstr Surg 109:2168-2169, 2002.

[36] van Minnen B, Nauta JM, Vermey A, Bos RR, Roodenburg JL. Long-term functional outcome of mandibular reconstruction with stainless steel AO reconstruction plates. Br J Oral Maxillofac Surg 40:144-148, 2002.

[37] Lindqvist C, Söderholm AL, Hallikainen D, Sjövall L.: Erosion and heterotopic bone formation after alloplastic temporomandibular joint reconstruction. J Oral Maxillofac Surg. 1992 Sep;50(9):942-9.

[38] Poshusta AK, Anseth KS. Photopolymerized biomaterials for application in the temporomandibular joint. Cells Tissues Organs 169:272-278, 2001.

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

[40] Chu TM, Orton DG, Hollister SJ, Feinberg SE, Halloran JW. Mechanical and in vivo performance of hydroxyapatite implants with controlled architectures. Biomaterials 23:1283-1293, 2002.

[41] Barnewitz D, Endres M, Krüger I, Becker A, Zimmermann J, Wilke I, Ringe J, Sitterer M, Kaps C.: Treatment of articular cartilage defects in horses with polymer-based cartilage tissue engineering grafts. Biomaterials 27(14):2882-9, 2006.

[42] Losken, A.; Mooney, M.P., and Siegel, M.I.: A comparative study of mandibular growth patterns in seven animal models. J. Oral Maxillofac. Surg., 50: 490-495; 1992.
[43] Abukawa H, Terai H, Hannouche D, Vacanti JP, Kaban LB, Troulis MJ.: Formation of a mandibular condyle in vitro by tissue engineering. J Oral Maxillofac Surg. 2003 Jan; 61(1):94-100.

[44] Grayson WL, Fröhlich M, Yeager K, Bhumiratana S, Chan ME, Cannizzaro C, Wan LQ, Liu XS, Guo XE, Vunjak-Novakovic G. Engineering anatomically shaped human bone grafts.: ProcNatlAcad Sci U S A. 2010 Feb 23;107(8):3299-304. Epub 2009 Oct 9.

[45] Mow VC, Wang CC.: Some bioengineering considerations for tissue engineering of articular cartilage. Clin Orthop Relat Res (367 Suppl):S204-23, 1999.

[46] Sikavitsas VI, Temenoff JS, Mikos AG. Biomaterials and bone mechanotransduction. Biomaterials 22:2581-2593, 2001.

[47] LeBaron RG, Athanasiou KA. Ex vivo synthesis of articular cartilage. Biomaterials 21:2575-2587, 2000.

[48] Patel RV, Mao JJ.: Microstructural and elastic properties of the extracellular matrices of the superficial zone of neonatal articular cartilage by atomic force microscopy. Front Biosci 8a:18-25, 2003.

[49] Cohen B, Chorney GS, Phillips DP, Dick HM, Buckwalter JA, Ratcliffe A, Mow VC. The microstructural tensile properties and biochemical composition of the bovine distal femoral growth plate. J Orthop Res 10:263-275, 1992.

[50] Hu K, Radhakrishnan P, Patel RV, Mao JJ. Regional structural and viscoelastic properties of fibrocartilage upon dynamic nanoindentation of the articular condyle. J Struct Biol 136:46-52, 2001.

[51] Narmoneva DA, Wang JY, Setton LA. Nonuniform swelling-induced residual strains in articular cartilage. J Biomech 32:401-8, 1999.

[52] Clark PA, Rodriguez T, Sumner DR, Clark AM, Mao JJ. Micromechanical analysis of bone-implant interface using atomic force microscopy. Proceedings of BMES-IEEE 16:304-305, 2002.

[53] Goldstein SA. Tissue engineering: functional assessment and clinical outcome. Ann N Y Acad Sci 961:183-192, 2002.

[54] De Mattei M, Caruso A, Pezzetti F, Pellati A, Stabellini G, Sollazzo V, Traina GC.: Effects of pulsed electromagnetic fields on human articular chondrocyte proliferation. Connect Tissue Res. 42:269-79, 2001.

[55] Hartig M, Joos U, Wiesmann HP.: Capacitively coupled electric fields accelerate proliferation of osteoblast-like primary cells and increase bone extracellular matrix formation in vitro. Eur Biophys J. 29:499-506, 2000

[56] Pei M, Solchaga LA, Seidel J, Zeng L, Vunjak-Novakovic G, Caplan AI, Freed LE. Bioreactors mediate the effectiveness of tissue engineering scaffolds. FASEB J 16:1691-1694, 2002.
[57] Gemmiti CV, Guldberg RE.: Fluid Flow Increases Type II Collagen Deposition and Tensile Mechanical Properties in Bioreactor-Grown Tissue-Engineered Cartilage. Tissue Eng. 12:469-79, 2006.

[58] Vance J, Galley S, Liu DF, Donahue SW.: Mechanical stimulation of MC3T3 osteoblastic cells in a bone tissue-engineering bioreactor enhances prostaglandin E2 release. Tissue Eng. 11:1832-9, 2005.

[59] El Haj AJ, Wood MA, Thomas P, Yang Y.: Controlling cell biomechanics in orthopaedic tissue engineering and repair. Pathol Biol (Paris). 53:581-9, 2005.

[60] Janssen FW, Oostra J, Oorschot A, van Blitterswijk CA.: A perfusion bioreactor system capable of producing clinically relevant volumes of tissue-engineered bone: in vivo bone formation showing proof of concept. Biomaterials. 27:23-1, 2006.

[61] Stevens MM, Marini RP, Schaefer D, Aronson J, Langer R, Shastri VP.: In vivo engineering of organs: the bone bioreactor. Proc Natl Acad Sci U S A. 9:102:11450-5, 2005.

[62] Service RF.: Tissue engineering. Technique uses body as ‘bioreactor’ to grow new bone. Science. 309:683, 2005.

[63] Vunjak-Novakovic G, Meinl L, Altman G, Kaplan D.: Bioreactor cultivation of osteochondral grafts. Orthod Craniofac Res. 8:209-18, 2005.

[64] Haasper C, Colditz M, Kirsch L, Tschernig T, Viering J, Graubner G, Runtemund A, Zeichen J, Meller R, Glasmacher B, Windhagen H, Krettek C, Hurschler C, Jagodzinski M.: A system for engineering an osteochondral construct in the shape of an articular surface: Preliminary results. Ann Anat. 2008;190(4):351-9. Epub 2008 Mar 18.

[65] Davisson T, Kunig S, Chen A, Sah R, Ratcliffe F. Static and dynamic compression modulate matrix metabolism in tissue engineered cartilage. J Orthop Res 20:842-848, 2002.

[66] Mizuno S, Tateishi T, Ushida T, Glowacki J. Hydrostatic fluid pressure enhances matrix synthesis and accumulation by bovine chondrocytes in three-dimensional culture. J Cell Physiol 193:319-327, 2002.

[67] Elder SH, Goldstein SA, Kimura JH, Spengler DM. Chondrocyte differentiation is modulated by frequency and duration of cyclic compressive loading. Ann Biomed Eng 29:476-482, 2001.

[68] Huang CY, Hagar KL, Frost LE, Sun Y, Cheung HS.: Effects of cyclic compressive loading on chondrogenesis of rabbit bone-marrow derived mesenchymal stem cells. Stem Cells. 22:313-23, 2004.

[69] Butler DL, Juncosa-Melvin N, Boivin GP, Galloway MT, Shearn JT, Gooch C, Awad H. Functional tissue engineering for tendon repair: A multidisciplinary strategy using mesenchymal stem cells, bioscaffolds, and mechanical stimulation. J Orthop Res. 2008 Jan;26(1):1-9
[70] Kinneberg KR, Nirmalanandhan VS, Juncosa-Melvin N, Powell HM, Boyce ST, Shearn JT, Butler DL. Chondroitin-6-sulfate incorporation and mechanical stimulation increase MSC-collagen sponge construct stiffness. J Orthop Res. 2010 Aug;28(8): 1092-9.

[71] Rabie ABM, Shum L, Chayanupatkul A. VEGF and bone formation in the glenoid fossa during forward mandibular positioning. Am J Orthod Dentofacial Orthop. 2002;122:202–209.

[72] Young SR, Dyson M. The effect of therapeutic ultrasound on angiogenesis. Ultrasound Med Biol. 1990;16:261–269.

[73] El-Bialy T, El-Shamy I, Graber TM. Growth modification of the rabbit mandible using therapeutic ultrasound: is it possible to enhance functional appliance results?, Angle Orthod; 73:631-639, 2003.

[74] El-Bialy, T.H., Hassan, A., Albaghdadi, T., Fouad, H.A., and Maimani, A.R., Growth modification of the mandible using Ultrasound in baboons: A preliminary report, Am J Orthod Dentofacial Orthop, 130(4):435e7-14, 2006.

[75] El-Bialy TH, Royston TJ, Magin RL, Evans CA, Zaki Ael-M, Frizzell LA, The effect of pulsed ultrasound on mandibular distraction. Ann Biomed Eng;30:1251-61, 2002.

[76] Peter J. Yang, Johnna S. Temenoff. Engineering Orthopedic Tissue Interfaces. Tissue Eng Part B Rev. 2009 June; 15(2): 127–141.

[77] Yoon JH, Roh EY, Shin S, Jung NH, Song EY, Lee DS, Han KS, Kim JS, Kim BJ, Jeon HW, Yoon KS.: Introducing pulsed low-intensity ultrasound to culturing human umbilical cord-derived mesenchymal stem cells. Biotechnol.Lett. 2009 Mar;31(3):329-335.

[78] Schumann D, Kujat R, Zellner J, Angele MK, Nerlich M, Mayr E, Angele P.: Treatment of human mesenchymal stem cells with pulsed low intensity ultrasound enhances the chondrogenic phenotype in vitro. Biorheology. 2006;43(3-4):431-43.

[79] Leung KS, Cheung WH, Zhang C, Lee KM, Lo HK.: Low intensity pulsed ultrasound stimulates osteogenic activity of human periosteal cells. Clin Orthop Relat Res.(418): 253-9, 2004.

[80] Ebisawa K, Hata K, Okada K, Kimata K, Ueda M, Torii S, Watanabe H.: Ultrasound enhances transforming growth factor beta-mediated chondrocyte differentiation of human mesenchymal stem cells. Tissue Eng. 10(5-6):921-9, 2004.

[81] Cui JH, Park K, Park SR, Min BH.: Effects of low-intensity ultrasound on chondrogenic differentiation of mesenchymal stem cells embedded in polyglycolic acid: an in vivo study. Tissue Eng. 12:75-82, 2006.

[82] Iwashina T, Mochida J, Miyazaki T, Watanabe T, Iwabuchi S, Ando K, Hotta T, Sakai D.: Low-intensity pulsed ultrasound stimulates cell proliferation and proteoglycan
production in rabbit intervertebral disc cells cultured in alginate. Biomaterials. 27:354-61, 2006.

[83] Naruse K, Miyauchi A, Itoman M, Mikuni-Takagaki Y.: Distinct anabolic response of osteoblast to low-intensity pulsed ultrasound. J Bone Miner Res 18:360-9, 2003.

[84] Lee, H.J. Choi, BH, Min, BH and Park, S.R. Low-Intensity Ultrasound Inhibits Apoptosis and Enhances Viability of Human Mesenchymal Stem Cells in Three-Dimensional Alginate Culture During Chondrogenic Differentiation: Tissue Engineering, 13: (5) 1049-1057, 2007.

[85] Tsai CL, Chang WH, Liu TK.: Preliminary studies of duration and intensity of ultrasonic treatments on fracture repair. Chin J Physiol. 1992;35(1):21-6. Erratum in: Chin J Physiol;35:168, 1992.

[86] El-Bialy, T., Hassan, A.H., Alyamani, A. and Albaghdadi, T.: Treatment of Hemifacial Microsomia by therapeutic ultrasound and hybrid functional appliance. A nonsurgical approach. Open Access Journal of Clinical Trials, 2, 29-30, 2010.

[87] Chan CW, Qin L, Lee KM, Cheung WH, Cheng JC, Leung KS.: Dose-dependent effect of low-intensity pulsed ultrasound on callus formation during rapid distraction osteogenesis. J Orthop Res. 2006 Nov;24(11):2072-9.

[88] Mostafa, N.Z.; Uludag, H.; Dederich, D.N.; Doschak, M.R.; El-Bialy, T.H.: Anabolic Effects of Low Intensity Pulsed Ultrasound on Gingival Fibroblasts, Archives of Oral Biology, 54 (8), 743 - 748, 2009.

[89] Hata T, Aoki S, Manabe A, Hata K, Miyazaki K. Three dimensional ultrasonography in the first trimester of human pregnancy. Hum Reprod 1997;12:1800-4.

[90] Blaas HG, Eik-Nes SH. Advances in the imaging of the embryonic brain. Croat Med J 1998;39:128-31.

[91] Turnbull DH, Foster FS. In vivo ultrasound biomicroscopy in developmental biology. Trends Biotechnol 2002;20:S29-33.

[92] Mende U, Zoller J, Dietz A, Wannenmacher M, Born IA, Maier, H. Ultrasound diagnosis in primary staging of head-neck tumors. Radiologe 1996;36:207-16.

[93] Ingber DE.: Mechanosensation through integrins: cells act locally but think globally. 1: ProcNatlAcad Sci U S A. 2003 Feb 18;100(4):1472-4. Epub 2003 Feb 10.

[94] Giancotti FG, Ruoslahti E.: Integrin signaling. Science. 1999 Aug 13;285(5430):1028-32.

[95] Aplin AE, Howe A, Alahari SK, Juliano RL.: Signal transduction and signal modulation by cell adhesion receptors: the role of integrins, cadherins, immunoglobulin-cell adhesion molecules, and selectins. Pharmacol Rev. 1998 Jun;50(2):197-263.
[96] Schlaepfer DD, Hunter T.: Integrin signalling and tyrosine phosphorylation: just the FAKs? Trends Cell Biol. 1998 Apr;8(4):151-7.

[97] Riveline D, Zamir E, Balaban NQ, Schwarz US, Ishizaki T, Narumiya S, Kam Z, Geiger B, Bershadsky AD.: Focal contacts as mechanosensors: externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and ROCK-independent mechanism. J Cell Biol. 2001 Jun 11;153(6):1175-86.

[98] Clark EA, King WG, Brugge JS, Symons M, Hynes RO.: Integrin-mediated signals regulated by members of the rho family of GTPases. J Cell Biol. 1998 Jul 27;142(2):573-86.

[99] Shyy JY, Chien S.: Role of integrins in cellular responses to mechanical stress and adhesion. CurrOpin Cell Biol. 1997 Oct;9(5):707-13.

[100] Kaibuchi K, Kuroda S, Amano M.: Regulation of the cytoskeleton and cell adhesion by the Rho family GTPases in mammalian cells. Annu Rev Biochem. 1999;68:459-86.

[101] Ridley AJ, Hall A.: The small GTP-binding protein rho regulates the assembly of focal adhesions and actin stress fibers in response to growth factors. Cell. 1992 Aug 7;70(3):389-99.

[102] Hotchin NA, Hall A. The assembly of integrin adhesion complexes requires both extracellular matrix and intracellular rho/racGTPases. J Cell Biol. 1995 Dec;131(6 Pt 2):1857-65.

[103] Lee DY, Yeh CR, Chang SF, Lee PL, Chien S, Cheng CK, Chiu JJ.: Integrin-mediated expression of bone formation-related genes in osteoblast-like cells in response to fluid shear stress: roles of extracellular matrix, Shc, and mitogen-activated protein kinase.J Bone Miner Res. 2008 Jul;23(7):1140-9.

[104] Takashi Nishida, Harumi Kawaki, Ruth M. Baxter, R. Andrea DeYoung, Masaharu-Takigawa, Karen M. Lyons.: N2 (Connective Tissue Growth Factor) is essential for extracellular matrix production and integrin signaling in chondrocytes. J Cell Commun Signal. 2007 June

[105] Zhou S, Schmelz A, Seufferlein T, Li Y, Zhao J, Bachem MG.: Molecular mechanisms of low intensity pulsed ultrasound in human skin fibroblasts.J Biol Chem. 2004 Dec 24;279(52):54463-9. Epub 2004 Oct 12.

[106] Takeuchi, R., Ryo,A., Komitsu, N., Mikuni-Takagaki, Y., Fukui, A., Takagi, Y., Shiraishi, T., Morishita, S., Yamazaki, Y., Kumagai, K., Aoki, I., Saito,T.: Low-intensity pulsed ultrasound activates the phosphatidylinositol 3 kinase/Akt pathway and stimulates the growth of chondrocytes in three-dimensional cultures: a basic science study. Arthritis Res Ther. 2008; 10(4): R77.

[107] ViniciusBuarque de Gusmão, C., Pauli, J.R., AbdallaSaad,M.J., Alves, J.M., Belangero, W.D.: Low-intensity Ultrasound Increases FAK, ERK-1/2, and IRS-1 Expression of In-
tact Rat Bones in a Noncumulative Manner. Clin Orthop Relat Res. 2010 April; 468(4): 1149–1156.
