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The Basic Science of Continuous Passive Motion in Promoting Knee Health: A Systematic Review of Studies in a Rabbit Model

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Abstract

Purpose—To determine whether the basic science evidence supports the use of continuous passive motion (CPM) after articular cartilage injury in the knee.

Methods—A systematic review was performed identifying and evaluating studies in animal models that focused on the basic science of CPM of the knee. Databases included in this review were PubMed, Biosis Previews, SPORTDiscus, PEDro, and EMBASE. All functional, gross anatomic, histologic, and histochemical outcomes were extracted and analyzed.

Results—Primary outcomes of CPM analyzed in rabbit animal models (19 studies) included histologic changes in articular cartilage (13 studies), biomechanical changes and nutrition of intra-articular tissue (3 studies), and anti-inflammatory biochemical changes (3 studies). Nine studies specifically examined osteochondral defects, 6 of which used autogenous periosteal grafts. Other pathologies included were antigen-induced arthritis, septic arthritis, medial collateral ligament reconstruction, hemarthrosis, and chymopapain-induced proteoglycan destruction. In comparison to immobilized knees, CPM therapy led to decreased joint stiffness and complications related to adhesions while promoting improved neochondrogenesis with formation and preservation of normal articular cartilage. CPM was also shown to create a strong anti-inflammatory environment by effectively clearing harmful, inflammatory particles from within the knee.

Conclusions—Current basic science evidence from rabbit studies has shown that CPM for the knee significantly improves motion and biological properties of articular cartilage. This may be translated to potentially improved outcomes in the management of articular cartilage pathology of the knee.

Clinical Relevance—If the rabbit model is relevant to humans, CPM may contribute to improved knee health by preventing joint stiffness, preserving normal articular tissue with better

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histologic and biologic properties, and improving range of motion as compared with joint immobilization and intermittent active motion.

Articular cartilage lesions are common in both symptomatic and asymptomatic knees.[1–6] After injury, the avascular, alymphatic nature of hyaline articular cartilage prevents superficial and partial-thickness chondral defects from effective healing. As a result, patients with symptomatic lesions may require operative treatment. Historically, postoperative management has included techniques aimed to immobilize, elevate, and rest the knee.[7–10] However, immobilization of the joint has been shown to cause decreased biosynthesis of cartilage matrix and essential cellular components, leading to cartilage thinning and softening.[11–21] Therefore early motion is a vital component to any joint rehabilitation if possible.

Compared with immobilization, motion produces mechanical signals that are perceived by mechano-sensitive chondrocytes in the cartilage that influence and stabilize the internal environment and tissue structure of cartilage. High, supraphysiological levels of mechanical signals are associated with cartilage damage and degeneration.[22,23] However, physiological levels of mechanical loading have been shown to inhibit expression of proinflammatory genes and inflammatory signaling cascades, stabilizing and repairing cartilage.[24–27] Cartilage tissue thus adapts best when under the influence of appropriate mechanical stimulation.[28]

By 1980, Dr. Robert B. Salter and colleagues[29] were able to verify from their study in rabbits that continuous motion was well tolerated and could improve cartilage healing and regeneration after an acute inflammatory injury. This idea, contradictory to traditional immobilizing practices, came to be known as continuous passive motion (CPM) and served as an effective adjunctive treatment for osteochondral pathologies afflicting the knee. Today, CPM is used after joint replacement, fixation of intra-articular fractures, release of arthrofibrosis/adhesive capsulitis, and cartilage repair and regenerative surgeries such as microfracture and autologous chondrocyte transplantation.

Despite CPM's use, no consensus exists endorsing it as a standard intervention to improve functional outcomes and cartilage health. Proponents of CPM therapy point to reduced levels of pain and stiffness, a decreased risk of unnecessary knee manipulation and risk of deep venous thrombosis, decreased hospital stays and costs, and improved range of motion.[13,30–37] Opponents of CPM therapy cite increased bleeding and wound drainage, as well as increased analgesic requirements, arguing that CPM offers no significant advantage in improving function, length of hospital stay, or range of motion.[38–40]

The purpose of this study was to systematically review the literature to identify the underlying mechanisms for the utility of CPM and determine what basic science evidence exists to support CPM use to improve cartilage and knee health. Specifically, we addressed the following questions: (1) Does CPM prevent or significantly reduce joint stiffness and adhesions? (2) Does CPM improve histologic, histochemical, biochemical, and biomechanical properties of articular cartilage? (3) Does CPM have significantly better motion and histologic and/or biological properties versus joint immobilization (IMM) and

intermittent active motion (IAM)? We hypothesized that when compared with IMM and IAM, CPM is a superior postoperative therapy. Specifically, CPM (1) effectively prevents stiffness and adhesions; (2) significantly improves chondrocyte health and recovery of normal articular tissue; and (3) has significantly better motion and histologic and biological properties versus IMM and IAM.

Methods

A systematic review was conducted to capture all basic science literature on CPM and knee articular cartilage injury. The following databases were searched: PubMed, Biosis Previews, SPORTDiscus, PEDro, and EMBASE. Each search included the following terms: continuous passive motion AND knee. The database search was performed on September 26, 2012.

The inclusion criteria were as follows: English language, animal subjects or tissue collected from animal subjects, Level I and Level II evidence, basic science evidence of CPM, or CPM of the knee joint or tissue from a knee source.

The exclusion criteria were as follows: non-English language; non–basic science evidence of CPM; human subjects; expert opinion or Level III, IV, or V evidence studies; focus on surgical technique or outcome other than that directly affected by CPM; or CPM on non-knee joint or non–knee-related tissue.

Search results of the databases yielded 481 citations. After application of the inclusion and exclusion criteria, 19 studies ultimately were included for further analysis within this review. Table 1 describes the topics evaluated by these 19 studies. Studies were grouped based on whether they addressed histologic, histochemical, biochemical, or biomechanical outcomes with CPM.

Parameters were individually examined and individual studies classified according to the primary outcome measured. Functional outcomes examined mobility data, incidence of flexion contracture formation, and gross findings (appearance, adhesions, erosions). Histologic results pertained to findings examining for fibrous tissue formation, predominant cartilage type, safranin O staining, neochondrogenesis, structural integrity, and incidence of abnormalities within cartilage. Histochemical markers included measurements of specific glycosaminoglycans and other components in cartilage (collagen, hexosamine). Inflammatory cytokine measurements were used to classify biochemical results, whereas biomechanical parameters focused on the flow of intra-articular solutes within the knee.

If available and possible between 2 or more studies, similar outcome measures were assimilated, weighted means (and measures of variance) calculated, and summary measures reported. However, if heterogeneity precluded meta-analysis, then individual statistical analyses were extracted and directly reported from individual studies ($P < .05$ or $P > .05$).

Results

Nineteen studies were identified for further investigation. All 19 studies were conducted in a rabbit model (Table 1). Of these studies, 6 addressed functional health under the influence of

CPM whereas 13 addressed histologic outcomes in cartilaginous tissue subjected to CPM. Histochemical, biochemical, and biomechanical results were described in 3 studies each. All studies compared CPM treatment with IMM, IAM, or both. CPM regimens spanned from 1 day to 4 weeks of therapy for as many as 24 hours per day, ranging from 40° to 130° of motion after creation of various chondral and osteochondral defects (Table 1).

Functional Health

CPM was found to significantly prevent joint stiffness and improve early motion (within the first 10 weeks after surgery) compared with IMM (Table 2) by preventing complications related to adhesions. No significant difference was found when CPM was compared with IAM 1 to 10 weeks after creation of the defect. At 52 weeks, there was no difference in flexion contracture, regardless of postoperative treatment strategy. Four studies showed a consistent trend in short-term results supporting CPM over IMM. In these studies IMM led to a flexion contracture in 40% to 100% of knees, whereas flexion contracture developed in only 0% to 13% of knees in the CPM groups.[29,41–43] In 5 studies IAM (defined as normal cage activity) was compared with CPM. The benefits of CPM over IAM were less consistent from 1 to 10 weeks, with IAM regimens preventing contracture formation[29,44] and erosion formation[42] and maintaining an intact articular surface[43,45] to a similar extent as CPM-treated knees. In addition, O'Driscoll et al.[46] showed that at 52 weeks, there was no flexion contracture in any group, regardless of whether IAM or CPM was used.

Histologic Health

CPM-treated knees were found to have significantly better histologic outcomes compared with both IMM and IAM treatment strategies (Table 2). A greater resemblance to normal articular cartilage was observed with improved contour of cartilage tissue, decreased secondary cartilaginous erosions, increased hyaline cartilage content, and decreased fibrous tissue. CPM was found to prevent the appearance of erosions by macroscopic visualization when compared with both IMM[41,42,46–49] and IAM,[41,44,46–48,50] being significantly superior ($P < .05$) in 3 cases.[41,48,50] In the only long-term study identified, CPM was found to be more effective than both IMM and IAM at preventing osteophyte formation ($P < .01$) and preserving the normal, smooth appearance of articular cartilage ($P < .05$) at 52 weeks.[46] Histologically, hyaline cartilage was identified as the predominant tissue in the healing defects in 70% to 100% of CPM-treated knees, 8% to 79% of IMM-treated knees, and 10% to 73% of IAM-treated knees.[41,42,46,48,50–52] In addition, neochondrogenesis was found to be superior in CPM-treated knees compared with IMM knees in 2 studies (83% *v* 46% and 100% *v* 69%).[51,52]

Histochemical Health

Histochemical analysis of cartilage showed that CPM-treated knees had greater amounts of type II collagen, keratin sulfate, chondroitin sulfate, and hexosamine (Table 2). Overall, 6 studies showed CPM-treated knees to possess a histochemical profile more similar to that of normal articular cartilage than knees treated with IMM, IAM, or both.[29,41,45–48]

Biochemical Health

Biochemically, application of CPM or cyclic tensile strain produced a strong anti-inflammatory effect in cartilage compared with IMM in 3 studies[53–55] (Table 3). By suppressing the expression of inflammatory cytokines (interleukin 1, interleukin 6, and tumor necrosis factor α), cyclic tensile strain allows for direct examination of the effects of the forces created by CPM on chondrocytes in vitro. Biochemical analyses of CPM are summarized in Table 3.

Biomechanical Support

Three studies described the mechanical effects of CPM on intra-articular fluid and solutes.[56–58] Overall, CPM does not seem to increase "nutrition" to intra-articular tissues, but it may play an important role in clearing substances from within the joint. CPM created sinusoidal changes in intra-articular pressure in the joint,[58] acting as a pump to clear radioactively labeled erythrocytes and low–molecular weight solutes, such as ^{35}S-sodium sulfate. Although diffusion is an important mechanism for nutrition and thus health of the menisci and articular cartilage, CPM does not effectively increase the uptake of low–molecular weight nutrients. Despite the presence of increased trans-synovial transport, overall uptake by the menisci did not seem to differ after the first hour of CPM treatment.

Discussion

The purpose of this review was to investigate the basic science literature regarding the use of CPM for the knee as compared with IMM and IAM. The main finding of this review was that CPM overall significantly improved cartilage and knee health, confirming nearly all of the hypotheses. Specifically, CPM significantly improved motion in comparison to IMM. However, no difference was observed in relation to IAM. CPM significantly improved histologic, histochemical, biochemical, and biomechanical properties of articular cartilage. This confirmed the second study hypothesis. Most, but not all, evidence showed significantly better outcomes in comparison to IMM and IAM.

The identified studies support multiple mechanisms by which CPM improves cartilage and knee health.[29,41–57] Grossly, CPM decreases adhesion[29,41,42,46,48,52] and erosion[41,42,44,46–49] formation while preserving the appearance of normal articular cartilage.[41,44,46,48,50–52] Histologically, CPM promotes greater neochondrogenesis with formation of healthier cartilage possessing increased hyaline cartilage content and safranin O staining.[29,41–52] Studies also confirmed the strong anti-inflammatory properties of CPM.[53–55] As such, CPM promotes the formation of healthier cartilage that more closely resembles native knee articular cartilage. Functionally, the production of healthier cartilage with limited exposure to inflammatory molecules may translate into better patient outcomes and decrease development of post-traumatic arthritic conditions.

This review has highlighted the importance of CPM in limiting exposure of cartilage to inflammatory and destructive molecules by creating sinusoidal intra-articular pressure changes. Although CPM did not increase diffusion from the synovial fluid to the menisci as measured by ^{35}S-sodium sulfate incorporation in comparison to immobilized knees, trans-

synovial transport proved to be an important mechanism for the clearance of hemarthrosis in a rabbit model. By creating convective flow of intra-articular fluids to compartments external to the joint capsule, CPM may impart improved clinical outcomes through the expedited clearance of noxious stimuli, preventing cartilage degradation.

From the results of this review, it appears that on the basis of the superior histologic effects seen in treatment with CPM, CPM would prove beneficial as an adjuvant intervention to treatment strategies such as autologous chondrocyte implantation, osteochondral autograft or allograft, or marrow stimulation techniques such as microfracture. Given the importance of these procedures in the current treatment of chondral and osteochondral defects of the knee, further research in this area is warranted to elucidate the specific mechanisms by which these procedures benefit from the addition of CPM. In addition, the duration and intensity of CPM regimens have been examined without clear evidence as to what strategy may provide the optimal benefit to patients.[59,60] Studies showing the importance of timing in the initiation of CPM therapy clearly show that the optimal timing of initiation, duration, and intensity should continue to be a focus of future studies.[46,55]

This review supports the theory set forth by O'Driscoll and Giori[30] regarding the role of CPM in preventing the evolution of joint stiffness after trauma or surgery. O'Driscoll and Giori's 4 stages in the etiology of joint stiffness begin with bleeding into the joint, followed by edema formation under the influence of inflammatory mediators, resulting in granulation tissue formation, which over time matures into fibrotic scar tissue. CPM hinders the first stage by producing sinusoidal intra-articular pressure changes[61] that promote trans-synovial transport and clearance of blood. The continued effect of this transport of intra-articular fluid, combined with the strong anti-inflammatory environment, acts further to prevent edema formation, halting granulation and fibrotic tissue formation. This review has also shown that the mechanical signals delivered to chondrocytes by CPM create superior tissue histologically during the third stage of this process and also prevent the formation of fibrous tissue and subsequent adhesions. These results, combined with the potential to limit muscle atrophy[62] and decrease the sensation of pain,[63] provide a solid foundation for the use of CPM.

Limitations

Limitations were identified in this study based on the inherent weaknesses of the individual studies used. One weakness involved the heterogeneity of the 19 studies, which varied in the method of injury creation and defect location in the joint. Although there were many overlapping outcomes measured among studies, generalizing the benefits of CPM over other treatment regimens over all outcomes (functional, gross, histologic, histochemical, biochemical) is not feasible (improved generalizability and external validity of review at the expense of internal validity). Another source of selection bias is present in that histochemical outcomes in studies failed to report the content of other important articular cartilage components (type I, VI, and X collagen, percent/number chondrocytes or empty lacunae, percent/proportion of proteoglycans/glycosaminoglycans). In addition, the improved histologic results seen with the use of CPM and periosteal autografts further complicated the generalizability of CPM as being superior to other treatments because the

use of periosteal autograft is largely of historical interest only because it is no longer currently used internationally. This review also primarily focused on the short-term effects of CPM, with only 1 study examining time points beyond 12 weeks. Thus long-term analyses of the effects of CPM on knee articular cartilage health are warranted. In addition, the generalizability of our results to human patients is limited by the lack of studies examining the translation of basic science to clinical science or imaging studies. Finally, the impact of CPM was examined specifically in the knee, whereas other joints (shoulder, hips, talus) were not included in our search.

Conclusions

Current basic science evidence from rabbit studies has shown that CPM for the knee significantly improves motion and biological properties of articular cartilage. This may be translated to potentially improved outcomes in the management of articular cartilage pathology of the knee.

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Table 1

Summary of Studies Included in Review

Study	Journal	Primary Focus	No. of Subjects	Defect	CPM Regimen
Salter et al.[29]	*J Bone Joint Surg Am* (1980)	Histology	147	Full-thickness OCD	40°–110° of flexion; 1 cycle/40 s; 1, 2, 3, or 4 wk
Salter et al.[47]	*Clin Orthop Relat Res* (1981)	Histology	60	*Staphylococcus aureus* septic arthritis	40°–110° of flexion; 1 cycle/40 s; 24 h/d × 2 wk
O'Driscoll and Salter[51]	*J Bone Joint Surg Am* (1984)	Histology	30	Free periosteal autograft (intercondylar notch)	40°–110° of flexion; 1 cycle/40 s
O'Driscoll et al.[41]	*J Bone Joint Surg Am* (1986)	Histology	143	Periosteal autograft in full-thickness OCD (trochlea)	40°–110° of flexion; 2 wk and 4 wk
O'Driscoll and Salter[42]	*Clin Orthop Relat Res* (1986)	Histology	55	Periosteal autograft in OCD (medial femoral condyle)	40°–110° of flexion; 1 cycle/40 s; 2 wk of CPM followed by 4 wk of IAM
O'Driscoll et al.[46]	*J Bone Joint Surg Am* (1988)	Histology	45	Periosteal autograft in full-thickness OCD (trochlea)	40°–110° of flexion; 2 wk of CPM followed by 50 wk of IAM
Delaney et al.[52]	*Clin Orthop Relat Res* (1989)	Histology	16	Free periosteal autograft (intercondylar notch)	Range of motion NR; 3 wk of CPM
Kim et al.[50]	*J Bone Joint Surg Am* (1991)	Histology	80	Abrasion of patella (40 subjects) and debridement of patella (40 subjects)	40°–110° of flexion; 1 cycle/40 s; 2 wk of CPM plus either 2 wk or 10 wk of IAM
Zarnett et al.[43]	*J Bone Joint Surg Br* (1991)	Histology	46	MCL reconstruction	40°–110° of flexion; 1 cycle/45 s; 3 wk of CPM
Moran et al.[48]	*J Bone Joint Surg Br* (1992)	Histology	55	Periosteal autograft (patella)	40°–110° of flexion; 1 cycle/45 s; 24 h/d × 2 wk
Williams et al.[45]	*Clin Orthop Relat Res* (1994)	Histology	48	Chymopapain-induced proteoglycan loss	40°–110° of flexion; 1 cycle/45 s; 2 d of IAM followed by 7 or 19 d
Kim et al.[49]	*J Rheumatol* (1995)	Histology	22	AIA	40°–110° of flexion; 1 cycle/45 s; 24 h/d × 2 wk
Chang et al.[44]	*Biomaterials* (2012)	Histology	38	Full-thickness OCD	60°–130° of flexion; 1 cycle/20 s; 15 min/d × 7 d
Gershuni et al.[56]	*Sports Med* (1988)	Nutrition	20	—	130° of flexion to 40° of extension; 7 cycles/min; 10, 30, 60, and 120 min
Danzig et al.[57]	*J Orthop Res* (1987)	Nutrition	13	—	130° of flexion to 40° of extension; 7 cycles/min; 1 h of CPM
O'Driscoll et al.[58]	*Clin Orthop Relat Res* (1983)	Trans-synovial transport	25	Hemarthrosis	40°–110° of flexion; 7 d of CPM
Ferretti et al.[53]	*J Orthop Res* (2005)	Biochemical	20	AIA	40°–110° of flexion; 1 cycle/45 s; 24 or 48 h of CPM
Gassner et al.[54]	*Int J Oral Maxillofac Surg* (2000)	Biochemical	In vitro chondrocyte	Inflammation	CTS
Xu et al.[55]	*J Immunol* (2000)	Biochemical	In vitro chondrocyte	Inflammation	CTS

AIA, antigen-induced arthritis; CTS, cyclic tensile strain; MCL, medial collateral ligament; NR, not reported; OCD, osteochondritis dissecans.

Table 2

Functional, Gross, Microscopic, and Histochemical Outcomes of CPM

Study	Functional Outcomes	Gross Outcomes	Microscopic Outcomes	Histochemical Outcomes
Salter et al.[29]	Mobility: IMM, stiffness at all time points; IAM, limited (1 wk), normal (2 wk); CPM, full ROM	Adhesions: IMM, 50% (3 wk), extensive (10 wk); IAM and CPM, none Articular cartilage tissue: IMM, 15%; IAM, 25%; CPM, 75%	Fibrous tissue (3 wk): IMM, 85%; IAM, 75%; CPM, 20%	Metachromasia (normal tissue, 3 wk): IMM, 10%; IAM, 12%; CPM, 60%
Salter et al.[47]	NR	Erosions (6 wk): IMM and IAM, 66%; CPM, none Erosions (10 wk): IMM, 75%; IAM, 50%; CPM, 20%	Indices of cartilage abnormalities: CPM superior to IMM and IAM at 10 wk ($P < .0001$)	At 10 wk: collagen, CPM > IMM, IAM ($P < .01$); KS, CPM > IMM, IAM ($P < .05$); CS, CPM > IMM, IAM ($P < .05$)
O'Driscoll and Salter[51]	NR	Appearance (14–17 d): grafts in CPM larger and smoother than IMM, IAM Appearance (14–21 d): grafts in CPM resemble articular cartilage; fibrous tissue in IMM, IAM	Neochondrogenesis: IMM, 46%; CPM, 83% Hyaline cartilage: IMM, 8%; CPM, 58.5%	NR
O'Driscoll et al.[41]	Flexion contracture: IMM, 42% (10°–30°); IAM, 5%; CPM, 10% (2 and 4 wk)	Adhesions: IMM, 68%; IAM, 20%; CPM, none (2 and 4 wk) Erosions: IMM, 58%; IAM, 35%; CPM (2 wk), 20%; CPM (4 wk), 5% Restoration of patellar curve ($P < .01$): IMM, 26%; IAM, 50%; CPM (2 wk), 75%; CPM (4 wk), 100%	Exclusively hyaline cartilage ($P < .001$): IMM, 37%; IAM, 20%; CPM (2 wk), 50%; CPM (4 wk), 70%*	HX,† CS,‡ KS, and collagen type II§ content: CPM (4 wk) > CPM (2 wk), IMM, IAM
O'Driscoll and Salter[42]	Flexion contracture: IMM, 40% (10°–30°); IAM and CPM, none	Adhesions: IMM, 30%; IAM, 10%; CPM, none Erosions: IMM, 30%; IAM and CPM, none	Hyaline cartilage ($P < .025$): IMM and IAM, 10%; CPM, 70% Fibrous tissue: IMM and IAM, 60%; CPM, 10% Smooth, intact surface: IMM, 30%; IAM, 20%; CPM, 90%	NR
O'Driscoll et al.[46]	Flexion contracture: no group at 52 wk	Adhesions ($P < .05$): IMM, 58%; IAM, 23%; CPM, 11% Erosions ($P > .25$): IMM, 58%; IAM, 53%; CPM, 23% Resembled smooth articular cartilage ($P < .05$): IMM, 43%; IAM, 45%; CPM, 77%	Hyaline cartilage ($P < .05$): IMM, 79%; IAM, 73%; CPM, 100% Safranin O staining ($P < .01$): CPM > IMM and IAM Safranin O staining *v* short-term study[4]: loss of staining in IMM and IAM groups ($P < .005$) but not in CPM Smooth, intact surface ($P < .005$): CPM > IMM and IAM Normal structural integrity ($P < .01$): CPM > IMM and IAM Thickness ($P < .01$): CPM > IMM and IAM Thickness *v* short-term study[4]: loss IMM and IAM but not in CPM Hypocellularity ($P < .005$): CPM > IMM and IAM	Type II collagen content: IMM, 76%; IAM, 87%; CPM, 84%

Study	Functional Outcomes	Gross Outcomes	Microscopic Outcomes	Histochemical Outcomes
			Hypocellularity *v* short-term study: decrease in IMM ($P < .001$) and IAM ($P < .001$) groups but not in CPM Freedom from degenerative change in adjacent cartilage: IMM, 57%; IAM, 55%; CPM, 100% ($P < .05$) Total indices of healing ($P < .0005$): CPM > IMM and IAM	
Delaney et al.[52]	NR	Adhesions ($P < .025$): IMM, 16 of 16; CPM, 12 of 16 Smooth articular cartilage ($P < .005$): IMM, 3 of 16; CPM, 11 of 16	Neochondrogenesis: IMM, 69%; CPM, 100% Hyaline cartilage ($P < .025$): IMM, 69%; CPM, 100% Predominate tissue: IMM, bone (69%); CPM, hyaline cartilage (63%)	NR
Kim et al.[50]	NR	Complete defect filling (4 wk): IMM, 7 of 9; CPM, 10 of 10 Complete defect filling (10 wk): IMM, 8 of 10; CPM, 10 of 10	Thickness of repair tissue in defect (4 wk) ($P < .05$): IAM, 5 of 9; CPM, 10 of 10 Mature hyaline-like cartilage predominates (12 wk) ($P < .05$): IAM, 60%; CPM, 100%	NR
Zarnett et al.[43]	Range of motion: greater ROM in CPM group *v* IMM and IAM ($P < .01$)	Intra-articular cartilage lesions: IMM, 3 of 10; IAM, 0 of 11; CPM, 0 of 11	Bone–fibrous tissue ratio: CPM > IMM and IAM groups	NR
Moran et al.[48]	Flexion contracture ($P < .05$): IAM, none; CPM, 13% (mean, 10°)	Adhesions ($P < .05$): IAM, 13%; CPM, none Restoration of articular surface: IAM, 73%; CPM, 86% Erosions ($P < .01$): IAM, 20%; CPM, 87%	Histologic and histochemical scoring system: CPM score > IAM score in the following: **1** Mean cellular morphology score **2** Mean safranin O score **3** Mean structural integrity score **4** Mean thickness score **5** Mean bonding score **6** Mean chondrocyte clustering	Anti–type II collagen staining: CPM > IAM ($P < .05$)
Williams et al.[45]	NR	Articular surface (9 d): IAM and CPM, 8 of 8 intact in low (n = 4) and high (n = 4) dose Articular surface (21 d): IAM and CPM, 8 of 8 intact in low (n = 4) and high (n = 4) dose	NR	KS content (9 d): IAM > CPM at low and high dose KS content (21 d): CPM > IAM at low and high dose
Kim et al.[49]	NR	Erosions: IMM, 5 of 12; CPM, 0 of 12	Safranin O staining: acute, CPM > IMM ($P = .008$); chronic, IMM > CPM	NR
Chang et al.[44]	Mobility: IMM, stiffness all times;	Appearance: IMM, abrasions and joint degeneration; IAM	Appearance: IMM and IAM, mild inflammation; CPM, normal cartilage	NR

Study	Functional Outcomes	Gross Outcomes	Microscopic Outcomes	Histochemical Outcomes
	IAM and CPM, normal activity (7 d)	and CPM, no contractures or inflammation Quantitative scoring (4 and 12 wk): empty defects and PLGA implants, CPM > IMM, IAM	Histologic modified scale score (4 wk and 12 wk): empty defects, IMM > CPM > IAM; PLGA implants, IAM > IMM > CPM	

CS, chondroitin sulfate; HX, hexosamine; KS, keratin sulfate; NR, not reported; PLGA, poly(lactic-co-glycolic acid).

*No significant difference ($P > .05$) between 2- and 4-wk CPM.

†CPM (4 wk) greater than all other treatment groups ($P < .01$).

‡CPM (4 wk) greater than all other treatment groups ($P < .05$).

§CPM (4 wk) greater percent type II collagen than all other treatment groups ($P < .005$).

Table 3

Biochemical Outcomes for CPM

Study	Biochemical Outcomes
Ferretti et al.[53]	COX-2 (mean No. of positive cells): • IMM at 24 h: 83 ± 11 • CPM at 24 h: 22 ± 6 ($P < .05$) • IMM at 48 h: 86 ± 19 • CPM at 48 h: 21 ± 9 ($P < .05$) MMP-1 (mean No. of positive cells): • IMM at 24 h: 79 ± 17 • CPM at 24 h: 26 ± 11 ($P < .05$) • IMM at 48 h: 84 ± 22 • CPM at 48 h: 24 ± 16 ($P < .05$) IL-1β (mean No. of positive cells): • IMM at 24 h: 103 ± 23 • CPM at 24 h: 18 ± 9 ($P < .05$) • IMM at 48 h: 121 ± 31 • CPM at 48 h: 13 ± 6 ($P < .05$) IL-10 (mean No. of positive cells): • IMM at 24 h: 39 ± 18 • CPM at 24 h: 111 ± 24 ($P < .05$) • IMM at 48 h: 51 ± 22 • CPM at 48 h: 122 ± 27 ($P < .05$) Loss of glycosaminoglycans (mean No. of positive cells): • IMM at 24 h: 48% in zone A, 26% in zone B • CPM at 24 h: 12% in zone A, 6% in zone B • IMM at 48 h: +37% in zone A, +26% in zone B • CPM at 48 h: +8% in zone A, +3% in zone B
Gassner et al.[54]	Nitric oxide production: • Resting culture (control): 1.24 ± 0.38 μm • Resting + CTS: 1.05 ± 0.31 μm • Resting + IL-1 (inflamed): 35.3 ± 7.75 μm • Resting + IL-1 + LMA: 4.26 ± 1.18 μm • CTS + IL-1: 21.8 ± 3.78 μm • CTS + IL-1 + LMA: 3.5 ± 1.01 μm Proteoglycan synthesis: • Resting culture (control): 100% • CTS: 102.3% ± 13.5% • Resting + IL-1 (inflamed): 62.4% ± 11% • Resting + IL-1 + LMA: 70.3% ± 11.35% • CTS + IL-1: 75.43% ± 13% ($P = .001$) • CTS + IL-1 + LMA: 85.7% ± 12.3% ($P = .047$) TGF-β: • Resting culture (control): 9 pmol/L • CTS: 36 pmol/L • Resting + IL-1 (inflamed): 16 pmol/L • CTS + IL-1: 40 pmol/L
Xu et al.[55]	• Induction of iNOS: IL-1β increased expression of iNOS mRNA; presence of CTS suppressed iNOS mRNA expression ($P \leq .05$) • COX-2: CTS consistently suppressed COX-2 mRNA expression at 4 and 24 h by 86% and 92%, respectively ($P < .01$) • PGE_2: CTS inhibited PGE_2 formation at 4 h, 24 h (82%), and 48 h (81%) ($P < .05$)

Study	Biochemical Outcomes
	• MMP-1: CTS suppressed MMP-1 mRNA expression at 4 and 24 h by 98% and 83%, respectively; CTS inhibited MMP-1 synthesis at 8 and 24 h by 92% and 87%, respectively ($P < .05$)
	• TIMP: consistent inhibition of TIMP-II mRNA expression with IL-1β alone; addition of CTS resulted in hyperinduction of TIMP-II mRNA at 4 h (4 ± 0.62–fold) and 24 h (7.4 ± 1.1–fold) ($P < .05$)
	• Collagen type II: CTS suppressed IL-1β– mediated induction of collagen type II mRNA at 24 h, 48 h, and 72 h ($P \leq .05$); no induction of collagen type II mRNA with CTS alone
	• Proteoglycan mRNA expression: IL-1β consistently inhibited aggrecan mRNA expression at 4 and 24 h (12%–14% reduction); CTS + IL-1β caused hyperinduction of aggrecan mRNA expression (increase by 2.6-, 4.1-, and 5.8-fold at 4, 24, and 48 h, respectively)
	• Proteoglycan synthesis (at 24, 48, and 72 h): IL-1β alone—decreased synthesis by 62% ± 5%, 67% ± 4%, and 61%†; CTS alone—decreased synthesis by 15% ± 3%, 18% ± 3%, and 14% ± 3%; CTS + IL-1β—no significant difference compared with control at any time period† (i.e., 100% synthesis)
	• Timing of CTS and IL-1β: inhibition of iNOS mRNA expression greatest when CTS was initiated simultaneously with IL-1β application (82% ± 3.5%); only 40% of inhibition noted when CTS was begun 1 hour after IL-1β application; CTS was ineffective when begun 2 h after IL-1β application

COX, cyclooxygenase; CTS, cyclic tensile strain; IL, interleukin; iNOS, inducible nitric oxide synthase; LMA, L-N-monomethyl arginine; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; PGE_2, prostaglandin E_2; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase.

†Significant decrease in proteoglycan synthesis in alone versus CTS + IL-1β ($P \leq .05$).