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Articular Cartilage Injury and Potential Remedies

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Summary

Osteoarthritis affects millions of people worldwide, is associated with joint stiffness and pain, and often causes significant disability and loss of productivity. Osteoarthritis is believed to occur as a result of ordinary “wear and tear” on joints during the course of normal activities of daily living. Posttraumatic osteoarthritis is a particular subset of osteoarthritis that occurs after a joint injury. Developing clinically relevant animal models will allow investigators to delineate the causes of posttraumatic osteoarthritis and develop means to slow or prevent its development after joint injury. Chondroprotectant compounds, which attack the degenerative pathways at a variety of steps, are being developed in an effort to prevent posttraumatic osteoarthritis and offer great promise. Often times, cartilage degradation after joint injury occurs despite our best efforts. When this happens, there are several evolving techniques that offer at least short-term relief from the effects of posttraumatic osteoarthritis. Occasionally, these traumatic lesions are so large that dramatic steps must be taken in an attempt to restore articular congruity and joint stability. Fresh osteochondral allografts have been used in these settings and offer the possibility of joint preservation. For patients presenting with neglected displaced intra-articular fractures that have healed, intra-articular osteotomy techniques are being developed in an effort to restore joint congruity and function. This article reviews the results of a newly developed animal model of posttraumatic osteoarthritis, several promising chondroprotectant compounds, and also cartilage techniques that are used when degenerative cartilage lesions develop after joint injury.

Keywords

articular cartilage; posttraumatic osteoarthritis; model; chondroprotectant; microfracture; fresh osteo-articular allograft; intra-articular osteotomy

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INTRODUCTION

Despite billions of dollars spent over several decades worldwide by academic laboratories, biotech companies, and large pharmaceutical companies, we currently do not have a cure for osteoarthritis (OA). Perhaps, even more disappointing is that there are no cures in the developmental pipelines and that the commercial focus has shifted toward providing palliative care products until joint replacement becomes necessary. This review will outline our current understanding of OA and posttraumatic osteoarthritis (PTOA), current treatment capabilities, preventive measures being developed, and techniques to treat localized cartilage defects when all else has failed.

WHEN DOES OA BEGIN?

Because most OA is idiopathic (arising by itself without known cause), its inception is very difficult to determine. The current understanding of OA is that it is an organ-level or tissue-level pathologic process that ultimately ends with joint pain, stiffness, and loss of function. However, as imaging and arthroscopy capabilities improve, tissue degradation can be identified earlier. Yet, it seems likely that cellular and molecular changes begin to occur within the joint tissues even before any tissue-level changes can be visualized.

POSTTRAUMATIC OA

PTOA is a form of OA that is initiated by joint injury. Because the OA-initiating injury event is usually clearly defined, animal models of PTOA are a convenient way to study the early cellular and molecular changes caused by injury and how these affect the progression of PTOA. Approximately 12% of all OA is a result of an injury, and studies by Lohmander et al and others indicate that approximately 50% of patients who sustain a significant knee injury develop PTOA in 5–20 years. This percentage increases to 75% with more traumatic injuries that include intra-articular fracture.[1] As such, it is apparent that mitigating the effects of joint injury on articular cartilage would potentially decrease the development of PTOA.

EXAGGERATED RESPONSE TO INJURY

It is hypothesized that attenuating excessive cellular and molecular responses to injury might benefit the long-term health of the joint. This is based on the rationale that after joint injury, the body responds as though the wound was open and contaminated, initiating a significant inflammatory response to fight foreign pathogens. Other than increasing the odds of survival for the entire organism, this response probably does not directly benefit the long-term function of the injured joint. Because cartilage is an avascular, aneural, and alymphatic tissue, injury responses originating from the chondrocytes themselves are initially predominant. It is believed that attenuating these early cellular responses will benefit the joint long term by reducing the irreversible molecular degradation of the chondrocytes and the surrounding joint tissues, which occurs during this inflammatory response.

MOUSE MODELS OF PTOA

To study the means of mitigating the effects of joint injury, a noninvasive model of PTOA in mice has been developed.[2] Using one of these models, PTOA consistently develops within 8 weeks of the injury and includes the hallmarks of OA at the tissue and cellular level. Although the time scale for progression to advanced PTOA is greatly accelerated in mice as compared to humans, the actual mechanisms are likely the same. With this noninvasive model of PTOA, one of the earliest in vivo injury responses identified was an increase in proteolytic activity as measured through proteolytic cleavage. After the injection of MMPSense probes (Perkin Elmer, Waltham, MA) into mice after injury, an increased matrix metalloproteinase (MMP) activity at the injured joint within 1–2 hours after injury was detected, and this MMP activity remained elevated for at least 8 weeks. Additional responses to injury were also observed in the days after joint injury, including temporary loss of subchondral trabecular bone. At this point, it is unclear as to which response is responsible for the loss of joint function. It is likely, however, that all observed and some still unidentified changes play a role in articular cartilage degeneration after joint injury. Microarray analysis was used to assess the injury response of healthy young (12 week) and old (54 week) mice. Baseline gene expression was found to be quite different between young and old mice. This suggests that baseline gene expression in addition to injury response genes may jointly affect the repair capacity after injury and the trajectory of PTOA progression.

In summary, based on the mice model for PTOA, there is a rapid biological response to joint injury that occurs before clinical PTOA symptoms occur.[3] Therefore, it seems practical that attenuating these early injury responses will protect the long-term health of the joint by preventing irreversible molecular damage to each of the joint tissues.

BIOLOGIC OPTIONS FOR THE TREATMENT OF ARTICULAR CARTILAGE INJURY

Biologic compounds are currently being investigated to mitigate the effects of cartilage and joint injuries. These compounds include chondroprotective agents, inhibitors of proinflammatory mediators, matrix protectants, and growth factors. Two chondroprotectant agents under investigation include p188 and rotenone.[4,5] P188 is best known as a cellular membrane stabilizer, but it has also been shown to inhibit or block stress-related p38 mitogen-activated protein kinase signaling, apoptosis-related glycogen synthase kinase-3 activation, and inflammation related to interleukin-6 (IL-6). The use of these types of compounds seems to be most effective when administered as close to the time of injury as possible.

Inhibitors of proinflammatory mediators have also been investigated in an effort to limit the long-term effects of inflammatory cytokines. Compounds such as IL-1 receptor antagonist (IL-1RA) and tumor necrosis factor–alpha (TNF-alpha) antagonist have been studied. IL-1RA has been studied as an injectable protein and as a gene in both in vitro and in vivo models. When injected as an adenoviral gene intra-articularly, it has been shown to decrease subchondral edema, joint fibrillation, and chondrocyte necrosis. IL-1RA has also been

shown to increase prostaglandin synthesis by the viable cells, but this effect is lost after the agent is removed.

TNF-alpha, a cytokine, has been associated with cartilage loss in OA and PTOA after joint injury. TNF-alpha receptor 1 is an antagonist of TNF-alpha and has been shown to downregulate MMP1, MMP3, and MMP13 expression and preserve cartilage by reducing the release of prostaglandins and increasing the release of lubricin in a rat model of PTOA.[6]

Although both IL-1RA and TNF-alpha receptor 1 hold promise as anti-inflammatory agents in the protection of cartilage after injury, they probably play a secondary role to the true chondroprotective agents.

AGENTS FOR MATRIX PROTECTION

MMPs, A disintegrin and metalloproteinases (ADAMs), A disintegrin and metalloproteinases with thrombospondin motif, and cathepsins are families of proteolytic enzymes, which cause degradation of cartilage matrix components after joint injury. Two potential pathways can be used to disrupt these mechanisms: direct inhibition of matrix-degrading proteinases and inhibition of factors responsible for their activation. Potential players in this arena are radical oxygen species scavengers, inhibitors of nitric oxide, inflammatory cytokines, and specific MMP inhibitors. L-N6-(1-iminoethyl) lysine has been shown to slow the progression of PTOA in canine experiments, suggesting that nitric oxide synthase could be a good target for matrix protection.[7] Unfortunately, MMP inhibitors are not widely available, and investigators have had to resort to transgenic modifications with only limited success.

A very promising approach to the prevention of PTOA after joint injury is the use of growth factors to stimulate the production of cartilage matrix and induce an anabolic response.[8] Transforming growth factor-B superfamily members, including bone morphogenetic proteins (BMPs), fibroblast growth factors 2 and 18, and insulin-like growth factor-1, have been widely studied.[8] Results thus far suggest that BMP-7 may be the best of these compounds in modifying the progression of OA and PTOA because of its proanabolic and anticatabolic properties.[9] In several different models of cartilage injury, BMP-7 was shown to stimulate regeneration of articular cartilage, increase repair tissue, and improve integrative repair between new cartilage and surrounding articular cartilage.[10] In PTOA-related studies, fibroblast growth factor 18 has been shown to induce anabolic effects on chondrocytes and chondroprogenitor cells and to stimulate cell proliferation and type II collagen production.[11] Although many biologically active compounds show promise, much work is still needed to ensure safety and to determine the most effective route of administration, dosage, and dosing regimens, and also the best timing relative to joint injury. Unfortunately, there are few biologic products commercially available that can positively influence injured cartilage.

SURGICAL TREATMENT OF CHONDRAL LESIONS: CHONDROPLASTY, MICROFRACTURE, AND CELLULAR OPTIONS

Articular cartilage is a highly organized complex tissue. Its viscoelastic properties allow it to withstand high levels of stress and repetitive loading over time. Unfortunately, articular cartilage injury is common, particularly involving the knee.[12] Partial thickness lesions have limited capacity to heal, whereas full-thickness lesions that penetrate the subchondral bone often "heal" with fibrocartilage. Numerous treatments for focal full-thickness chondral defects of the knee are available, but none have been proven to consistently restore normal hyaline cartilage and knee function.

Initial surgical intervention for the treatment of these lesions has included simple arthroscopic debridement (chondroplasty) with or without marrow stimulation (microfracture). More advanced treatment options, such as osteochondral autograft transfer (OATS/mosaicplasty), fresh osteochondral allograft transplantation, and chondrocyte transplantation (autologous chondrocyte implantation/ACI), are reserved for larger lesions or those that have failed previous treatment.

The goals of arthroscopic debridement/chondroplasty are to define the pathology, remove particulate debris, inflammatory mediators, and degradative enzymes, and create a smooth articular surface with stable borders. It is a single-stage procedure that requires no special instrumentation, allows easy access to the entire joint, is relatively inexpensive, and has a quick recovery time. Disadvantages include the possible removal of normal articular cartilage, difficulty in creating smooth surfaces with stable margins, and the lack of stimulating any significant healing response. In general, results are better for smaller, low-grade lesions, but these results tend to deteriorate over time.[13,14]

Microfracture is a popular treatment for full-thickness chondral defects of the knee. The technique involves using an arthroscopic awl to create multiple 3–4 mm deep holes, 3–4 mm apart, throughout the base of the lesion.[15] Penetration of the subchondral bone is essential and is believed to allow release of stem cells and growth factors from the bone marrow. It is best indicated for patients <55 years with full-thickness defects that are well contained and <2.5 cm^2. Unfortunately, fibrocartilage lacks the structure, composition, mechanical properties, and durability of normal articular cartilage. Consequently, clinical results tend to diminish over time.[16] Additional disadvantages of microfracture include postoperative restrictions, possible formation of subchondral cysts and osteophytes, and poor results in athletes.[15,17,18] Evidence-based analysis has shown microfracture to provide effective short-term functional improvement; however, there are insufficient data documenting long-term success.[16,19]

OATS/mosaicplasty involves the transfer of autogenous cylindrical osteochondral plugs from nonvital articular areas to the weight-bearing surfaces of the knee. This is a single-stage procedure that can be performed either arthroscopically or open, is cost effective, preserves hyaline cartilage viability, and allows for a relatively quick recovery. The main disadvantages include the limited number and size of the donor sites, potential donor site

morbidity, and the technical demands of the procedure required for precise fit and contouring of the plugs.[20–22]

ACI is a 2-stage procedure requiring an initial arthroscopy to harvest normal articular cartilage and a second open surgery to insert the culture expanded chondrocytes back into the defect.[23] Problems include difficulty with harvesting and suturing the periosteal patch, cell leakage, uneven distribution of cells, chondrocyte dedifferentiation in vivo, formation of “hyaline-like” cartilage or fibrocartilage, higher failure rates after microfracture, and high costs.[18] Reported complications include arthrofibrosis, and graft hypertrophy, delamination, or failure. In addition, prolonged rehabilitation is required to allow cartilage growth and maturation.[24] The literature is divided as to the optimal method when ACI is compared to microfracture and OATS.[25–28] Second-generation ACI was developed in an attempt to improve these results. In this procedure, an expanded population of chondrocytes that express a marker predictive of the capacity to form hyaline-like cartilage is selected for implantation (characterized chondrocyte implantation).[26] A third-generation procedure, known as matrix-assisted ACI, has now been developed. This technique involves seeding the culture-expanded cartilage cells onto a 3-dimensional scaffold, which is then inserted into the prepared defect. There are significant advantages to this procedure; however, at this time, matrix-assisted ACI is not Food and Drug Administration approved for use in the United States.

Evolving tissue engineering-based strategies have recently been developed, the goals of which are to create cartilage constructs that can be reimplanted in a single-stage procedure, and that result in the production of durable repair tissue. Necessary components include cells, scaffolds, and growth factors. Numerous scaffolds are under investigation, including protein-based platelet-rich plasma, carbohydrate-based, synthetics, and combination scaffolds. Additionally, several other means of using bone marrow aspirate and manipulated chondrocytes, including those from juveniles, are under developed to treat osteochondral defects.[29–34]

Overall, cartilage tissue engineering has advanced rapidly in the past decade. New products continue to be developed; however, engineered cartilage with properties that mimic native articular cartilage is currently unavailable, and multiple obstacles must still be overcome. Future scientific advances may ultimately be able to deliver the ideal construct with the optimal cell, ideal scaffold, and appropriate growth factors to provide a better solution for the treatment of focal chondral lesions.

OSTEOCHONDRAL ALLOGRAFTS IN THE TREATMENT OF LARGE FULL-THICKNESS OSTEOCHONDRAL DEFECTS

Large osteochondral defects can be quite a challenge to treat, as an appropriately sized and shaped osteochondral fragment(s) to fill the defect must be found, and cartilage and bone integration must be achieved. A potential solution is to use fresh osteochondral allografts.[35,36] These allografts contain viable chondrocytes but must be obtained and inserted in a timely fashion using techniques that preserve the viability of the chondrocytes and maximize the chance of bony integration. Allograft cell survival, cost, and availability make this option

only feasible in certain centers. In general, chondrocyte viability is believed to be 28 days on average with current storage techniques. New allograft preservation systems can now extend the survival of these allografts to 60 days with more viable chondrocytes (New Missouri Allograft Preservation System), increased glycosaminoglycan content, and maintenance of the biomechanical properties of the articular cartilage and collagen content.[37,38]

In general, one should maximize chondrocyte viability (ideally greater than 70%) and ensure bone and cartilage healing and incorporation of the grafts.

TREATMENT OF INTRA-ARTICULAR MALUNIONS

Although many treatment concepts exist for extra-articular deformities, there is limited information regarding the treatment of intra-articular deformities.[39] In this section, the current understanding of the surgical treatment of intra-articular malunions is described. The technique includes identification of the original articular fracture lines, thorough analysis of the overall deformity, and development of a comprehensive preoperative plan to ensure each mechanical and biologic issue is addressed, all of which has been developed over several years during the treatment of numerous patients with clinically significant intra-articular deformity.[40]

ASSESSMENT

Physical Examination

The limb and joint articulation of concern must be thoroughly examined to detect additional deformities, including shortening, malrotation, and angulation, and to determine the joint range of motion (ROM) and stability.

Imaging

Computed tomography (CT) with 2-dimensional and 3-dimensional reconstructions is an essential part of the assessment process. Articular steps and gaps must be fully appreciated and thoroughly analyzed, including their size and location. Additional analysis of length and torsional differences is crucial, and therefore the CT should generally include the contralateral uninjured limb. Long-standing radiographs are also needed for frontal plane alignment analysis under loading conditions. Magnetic resonance imaging is necessary for determining articular cartilage thickness and detailed surface structure, and also meniscal and ligamentous integrity.

Preoperative Planning

Essential for preoperative planning is radiographic analysis of the contralateral uninjured side. Virtual subtraction computerized techniques using the uninjured and injured sides enable the investigator to definitively assess the geometric deviations between the 2 and allow manipulation of the defective side to elucidate a means of correction.

Decision Making

Planning and decision making must take into account local factors such as intra-articular deformities, quality of the articular surfaces, extra-articular deformities, condition of the menisci and ligaments, joint stability, frontal plane alignment, ROM, and muscle strength. Additional factors include pain, presence of comorbidities, patient's age and activity level, and, perhaps most importantly, the patient's expectations.

Descriptive Case/Surgical Technique

A 24-year-old woman sustained a split-depression lateral tibia plateau fracture that was not reduced during her original surgery. Ten months postoperatively, she presented with severe knee pain, valgus deformity, and knee instability. Physical findings include 5° extension, 130° flexion, and lateral instability. Preoperative assessment included standing long radiographs (Fig. 1A), a CT (Fig. 1B), and magnetic resonance imaging. A preoperative plan was developed (Fig. 1C–G), and a meticulous operative correction and stabilization were performed (Fig. 1F').

The operative procedure included an intra-articular segment osteotomy, fragment elevation, reduction, and fixation (Fig. 1D). Because the cartilage was partially degenerative, a chondrocyte matrix with cultured chondrocytes was applied after the preparation of the articular surface (Fig. 1E–G). A high tibial osteotomy was performed to correct the frontal plane alignment (Fig. 1H). At 3 years, the patient had a good lateral joint space (Fig. 1I) and full knee ROM (Fig. 1J, J'), and her knee function and comfort had improved significantly.

CONCLUSIONS

PTOA is a worldwide problem for which there is no prevention or cure. Development of a clinically relevant animal model would support the identification and testing of chondroprotectant agents that could mitigate the effects of articular injury. However, at this time, depending on the size of the cartilage lesions, only techniques that either stimulate cartilage repair (fibrocartilage) or attempt to replace lost cartilage with chondrocytes or cartilage and bone fragments are available, with varying degrees of long-term success. Intra-articular osteotomies and mechanical realignment techniques are being explored for those patients with potentially repairable joints. Until a more complete understanding of the pathophysiological processes of PTOA is determined, it will be difficult to develop agents that prevent degeneration after joint injury. As such, chondrocyte and osteochondral transplantation, and occasionally intra-articular osteotomies, will be relied on to relieve pain and improve joint function in these degenerative joints.

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REFERENCES

1. Lohmander LS, Englund PM, Dahl LL, et al. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med. 2007;35:1756–1769. [PubMed: 17761605]

2. Christiansen BA, Guilak F, Lockwood KA, et al. Non-invasive mouse models of post-traumatic osteoarthritis. Osteoarthritis Cartilage. 2015; 23:1627–1638. [PubMed: 26003950]

3. Christiansen BA1, Anderson MJ, Lee CA, et al. Musculoskeletal changes following non-invasive knee injury using a novel mouse model of post-traumatic osteoarthritis. Osteoarthritis Cartilage. 2012; 20:773–782. [PubMed: 22531459]

4. Bajaj S, Shoemaker T, Hakimiyan AA, et al. Protective effect of P188 in the model of acute trauma to human ankle cartilage: the mechanism of action. J Orthop Trauma. 2010;24:571–576. [PubMed: 20736797]

5. Goodwin W, McCabe D, Sauter E, et al. Rotenone prevents impactinduced chondrocyte death. J Orthop Res. 2010;28:1057–1063. [PubMed: 20108345]

6. Elsaid KA1, Machan JT, Waller K, et al. The impact of anterior cruciate ligament injury on lubricin metabolism and the effect of inhibiting tumor necrosis factor alpha on chondroprotection in an animal model. Arthritis Rheum. 2009;60:2997–3006. [PubMed: 19790069]

7. More AS1, Kumari RR, Gupta G, et al. Tandan SK Effect of iNOS inhibitor S-methylisothiourea in monosodium iodoacetate-induced osteoarthritis pain: implication for osteoarthritis therapy. Pharmacol Biochem Behav. 2013;103:764–772. [PubMed: 23287799]

8. Fortier LA, Barker JU, Strauss EJ, et al. The role of growth factors in cartilage repair. Clin Ortho Rel Res. 2011;469:2706–2715.

9. Badlani N, Inoue A, Healey R, et al. The protective effect of OP-1 on articular cartilage in the development of osteoarthritis. Osteoarthritis Cartilage. 2008;16:600–606. [PubMed: 17977753]

10. Chubinskaya S1, Hurtig M, Rueger DC. OP-1/BMP-7 in cartilage repair. Int Orthop. 2007;31:773–781. [PubMed: 17687553]

11. Ellsworth JL1, Berry J, Bukowski T, et al. Fibroblast growth factor-18 is a trophic factor for mature chondrocytes and their progenitors. Osteoarthritis Cartilage. 2002;10:308–320. [PubMed: 11950254]

12. Curl WW, Krome J, Gordon ES, et al. Cartilage Injury: a review of 31,516 knee arthroscopies. Arthroscopy. 1997;13:456–460. [PubMed: 9276052]

13. Hunt SA, Jazrawi LM, Sherman OH. Arthroscopic management of osteoarthritis of the knee. JAAOS. 2002;10:356–363. [PubMed: 12374486]

14. Jackson RW. Arthroscopic surgery and a new classification system. Am J Knee Surg. 1998;11:51–54. [PubMed: 9533055]

15. Steadman JR, Briggs KK, Rodrigo JJ, et al. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy. 2003;19:477–484. [PubMed: 12724676]

16. Mithoefer K, McAdams T, Williams RJ, et al. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee. Am J Sports Med. 2009;37:2053–2063. [PubMed: 19251676]

17. Mithoefer K, Williams RJ, Warren RF, et al. High-impact athletes after knee articular cartilage repair: a prospective evaluation of the microfracture technique. Am J Sports Med. 2006;34:1413–1418. 17. [PubMed: 16735588]

18. Minas T, Andreas GH, Rosenberger R, et al. Increased failure rate of autologous chondrocyte implantation after Previous treatment with marrow stimulation techniques. Am J Sports Med. 2009;37:902–908. [PubMed: 19261905]

19. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different Compartments in the knee. Osteoarthritis and Cartilage. 2006;14:1119–1125. [PubMed: 16815714]

20. Ma HL, Hung SC, Wang ST, et al. Osteochondral autografts transfer for Post-Traumatic osteochondral defect of the knee – 2 to 5 Years Follow-up. Injury. 2004;35:1286–1292. [PubMed: 15561119]

21. Hangody L, Kish G, Karpati Z, et al. Mosaicplasty for the treatment of articular cartilage defects: Application in clinical Practice. Orthopedics. 1998;21:751–756. [PubMed: 9672912]

22. Hangody L, Vasarhelyi G, Hangody LR, et al. Autologous osteochondral Grafting-technique and long term results. Injury. 2008;39 Suppl:32–39.

23. Brittberg M, Lindahl A, Nillson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331:889–895. [PubMed: 8078550]

24. Niemeyer P, Pestka JM, Kreuz PC, et al. Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. Am J Sports Med. 2008;36:2091–2099. [PubMed: 18801942]
25. Knutsen G, Drogset JO, Engebretsen, et al. Randomized Trial comparing autologous chondrocyte implantation with microfracture: findings at Five Years. J Bone Joint Surg AM. 2007;89:2105–2112. [PubMed: 17908884]
26. Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better Structural repair when treating Symptomatic cartilage defects of the knee in a Randomized Controlled Trial versus microfracture. Am J Sports Med. 2008;36:235–246. [PubMed: 18202295]
27. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a Multicentered Randomized clinical Trial. Clin J Sport Med. 2005;15:220–226. [PubMed: 16003035]
28. Bekkers JE, Inklaar M, Saris DB. Treatment Selection in articular cartilage lesions of the knee: a systematic review. Am J Sports Med. 2008;37 (suppl 1):148–155.
29. Haleem AM, Chu CR. Advances in tissue engineering techniques for articular cartilage repair. Oper Tech Orthop. 2010;20:76–89. [PubMed: 29430164]
30. de Girolamo L, Bertolini G, Cervellin M, et al. Treatment of chondral defects of the knee with one step matrix-assisted technique Enhanced by autologous Concentrated bone Marrow: In vitro Characterization of Mesenchymal stem cells from Iliac Crest and subchondral bone. Injury. 2010;41:1172–1177. [PubMed: 20934693]
31. Abrams GD, Mall NA, Fortier LA, et al. Biocartilage: Background and operative technique. Op Tech Sports Med. 2013;21:116–124.
32. Gille J, Schuseil E, Wimmer J, et al. Mid-term results of autologous matrix-induced Chondrogenesis for treatment of focal cartilage defects in the knee. Knee Surg Sports Traumatol Arthrosc. 2010;18:1456–1464. [PubMed: 20127072]
33. Farr J, Tabet SK, Margerrison E, et al. Radiographic, and Histological Outcomes after cartilage repair with Particulated juvenile articular cartilage: a 2-Year prospective study. Am J Sports Med. 2014;42:1417–1425. [PubMed: 24718790]
34. Adkisson HD, Martin JA, Emendola RL. The potential of human Allogeneic juvenile chondrocytes for Restoration of articular cartilage. Am J Sports Med. 2010;38:1324–1333. [PubMed: 20423988]
35. De Caro F, Bisicchia S, Amendola A, et al. Large fresh osteochondral allografts of the knee: a systematic clinical and basic science review of the literature. Arthroscopy. 2015;31:757–765. [PubMed: 25660010]
36. Sherman SL, Garrity J, Bauer K, et al. Fresh osteochondral allograft transplantation for the knee: current concepts. J Am Acad Ortho Surg. 2014;22:121–133.
37. Cook JL, Stoker AM, Stannard JP, et al. A novel system improves preservation of osteochondral allografts. Clin Ortho Rel Res. 2014;472: 3404–3414.
38. Stoker A, Garrity JT, Hung CT, et al. Improved preservation of fresh osteochondral allografts for clinical use. J Knee Surg. 2012;25:117–125. [PubMed: 22928429]
39. Marti R, Kerkhoffs GMMJ. Malunions and Nonunions about the Knee. Skeletal Trauma. 4th ed.. Chapter 57. Elsevier; 2009.
40. Krettek C, Hawi N, Jagodzinski M. Intracondylar segment osteotomy: correction of intra-articular malalignment after fracture of the tibial plateau. Der Unfallchirurg. 2013;116:413–426. [PubMed: 23681487]

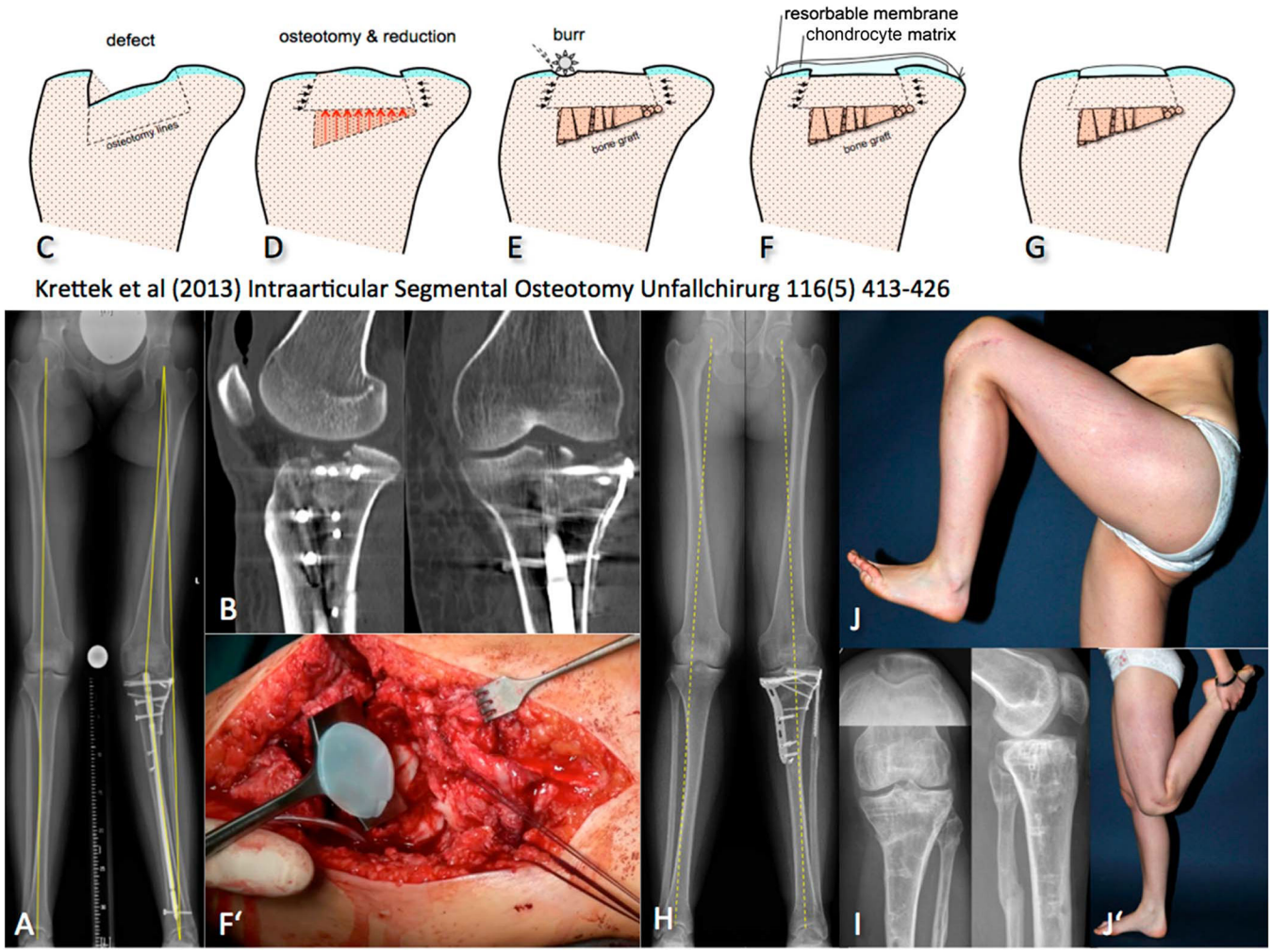

FIGURE 1.

Pre-operative images of intra-articular defect of the left lateral tibial plateau (A, B), pre-operative plan for correction of defect (C–G), intra-operative photograph of articular correction (F') and post-operative radiographic outcome (H, I) and knee range of motion (J, J'). Reprinted from Krettek et al[40] with permission of the publisher. Copyright @ 2013, Springer.