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Zhao, JG; Zhao, L; Jiang, XY (2015) “Platelet-Rich Plasma in Arthroscopic Rotator Cuff Repair: A Meta-analysis of Randomized Controlled Trials”, *Arthroscopy*. 2015 Jan;31(1):125-35. **Letter** *Currently No Access*

Adern, Clare L.; Taylor, Nicolas F.; Feller, Julian A.; Webster, Kate E. (2014) “Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors”, *Br J Sports Med* 48:1543-1552.

*Background* The aim of this study was to update our original systematic review of return to sport rates following anterior cruciate ligament (ACL) reconstruction surgery.

*Method* Electronic databases were searched from April 2010 to November 2013 for articles reporting the number of patients returning to sport following ACL reconstruction surgery. Return to sport rates, physical functioning and contextual data were extracted and combined using random-effects meta-analyses. Data from the original review (articles published up to April 2010) were combined with data from the updated search.

*Results* Sixty-nine articles, reporting on 7556 participants, were reviewed. On average, 81% of people returned to any sport, 65% returned to their preinjury level of sport and 55% returned to competitive level sport after surgery. Symmetrical hopping performance (d=0.3) and the contextual factors of younger age (d=−0.3), male gender (OR=1.4), playing elite sport (OR=2.5) and having a positive psychological response (d=0.3) favoured returning to the preinjury level sport. Receiving a hamstring tendon autograft favoured returning to competitive level sport (OR=2.4), whereas receiving a patellar tendon autograft favoured returning to the preinjury level sport (OR=1.2).

*Conclusions* Returning to sport varied according to different physical functioning and contextual factors, which could warrant additional emphasis in postoperative rehabilitation programmes to maximise participation.

Ajibade, David A.; Vance, Danica D.; Hare, Josua M. *et al.* (2014) “Emerging Applications of Stem Cell and Regenerative Medicine to Sports Injuries” *Orthopaedic Journal of Sports Medicine,* 2,2:1-7

*Background*: The treatment of sports-related musculoskeletal injuries with stem cells has become more publicized because of recent reports of high-profile athletes undergoing stem cell procedures. There has been increased interest in defining the parameters of safety and efficacy and the indications for potential use of stem cells in clinical practice.

*Purpose*: To review the role of regenerative medicine in the treatment of sports-related injuries.

*Method*: Relevant studies were identified through a PubMed search combining the terms stem cells and cartilage, ligament, tendon, muscle, and bone from January 2000 to August 2013. Studies and works cited in these studies were also reviewed.

*Results*: Treatment of sports-related injuries with stem cells shows potential for clinical efficacy from the data available from basic science and animal studies.

*Conclusion*: Cell-based therapies and regenerative medicine offer safe and potentially efficacious treatment for sports-related musculoskeletal injuries. Basic science and preclinical studies that support the possibility of enhanced recovery from sports injuries using cell-based therapies are accumulating; however, more clinical evidence is necessary to define the indications and parameters for their use. Accordingly, exposing patients to cell-based therapies could confer an unacceptable risk profile with minimal or no benefit. Continued clinical testing with animal models and clinical trials is necessary to determine the relative risks and benefits as well as the indications and methodology of treatment.

Atala, Anthony; Murphy, Sean (2015) “Regenerative Medicine” *JAMA,* 2015;313(14):1413-1414. doi:10.1001/jama.2015.1492 **Editorial**

The Culture of Organs, a book published in 1938 by Nobel Laureate Alexis Carrel and well-known aviator Charles Lindbergh, described how organs could be kept “alive” in culture for months, with the intent to reuse them. Decades later, regenerative medicine, a field of science that aims to restore or establish normal function by replacing or regenerating human cells, tissues, and organs affected by disease, is becoming a reality. The field is a progression of previous efforts to restore function, ranging from prosthetics to organ transplants. Advances in cell biology, biomaterial science, and biological molecule discovery have led to new options for cellular therapies, engineered tissues and organs, and new strategies to stimulate endogenous repair and regeneration.

Barrios, C *et al*. (2015) “Changes In Sports Injuries Incidence Over Time In World-Class Road Cyclists.” *Int J Sports Med,* 36(3):241-8. doi: 10.1055/s-0034-1389983. *Currently No Access*

This is a descriptive epidemiologic survey on all traumatic and overuse injuries which occurred in 2 groups of male elite road cyclists based on retrospective clinical interviews and physical examinations. The historical group consisted of 65 professional road cyclists surveyed from 1983 to 1995. The contemporary group included 65 elite racers still active and reporting injuries from 2003 to 2009. Injury/cyclist ratio was 1.32 in the historical group and 2.13 in those still active. Traumatic injuries increased from 39.5% (historical) to 53.9% (contemporary) (p<0.05). Severe traumatic lesions decreased from 49.9% in the historical group to 10.5% in the contemporary group (p<0.01). Patellofemoral pain decreased from 28.8% (historical) to 6.1% (contemporary) (p<0.01). Muscle injuries substantially increased from 13.4% to 44.9% (p<0.01). In the historical racers, the rates of risk for traumatic injury were 0.104 per year per cyclist, and 0.003 per 1 000 km of training and competition. These figures increased to 0.287 and 0.009 respectively in the contemporary group. In summary, contemporary professional road cyclists are exposed to double the risk of traumatic injuries than those competing in the 80s and early 90s. However, these lesions have less severity. Overuse injuries had a completely different clinical pattern, with the currently active cyclist exhibiting more muscle injuries and less tendinous lesions.

Bauer, Thomas (2016) “Stem Cell Therapy for Knee Pain—What Exactly Are We Injecting, and Why?” *Journal of Bone & Joint Surgery* – *American,*  98(18):1509–1510; doi: 0.2106/JBJS.16.00872 **Editorial** *No Abstract*

Bottini, M; Magrini, A; Fadeel, B and N Rosato (2016) “Tackling Chondrocyte Hypertrophy With Multifunctional Nanoparticles” *Gene Therapy* 23, 560–564; doi:10.1038/gt.2016.33; published online 14 April 2016 **Commentary** *No Abstract*

Brittberg, Mats (2014) “Autologous Chondrocyte Implantation For Cartilage Repair – Still Experimental?” *Aspetar,* 3:1

In October 1987, the first human autologous chondrocyte implantation in the world was performed. It is now 26 years since that first example of human musculoskeletal tissue engineering was done but still today, many patients who ask about such an operation are told by their doctors that these operations still are experimental. If this was the case, most of what we, as orthopaedic surgeons, do could be regarded as experimental surgery. Autologous chondrocyte implantation (ACI) has been performed in more than 30,000 patients worldwide since 1987. This paper aims to review the ACI technology.

Bruden, R.J., *et al.* “Is iron treatment beneficial in, iron-deficient but non-anaemic (IDNA) endurance athletes? A systematic review and meta-analysis*.” Br J Sports Med*. 2015 Nov;49(21):1389-97. doi: 10.1136/bjsports-2014-093624. Epub 2014 Oct 31 *Currently No Access*

*Purpose*: The aim of this study was to determine whether iron treatments improve the iron status and aerobic capacity of iron deficient non-anaemic endurance athletes.

*Method*: A meta-analysis of studies that investigated the effects of iron treatment on serum ferritin (sFer), serum iron (sFe), transferrin saturation (Tsat), haemoglobin concentration ([Hb]) and (VO(2max)). Seventeen eligible studies were identified from online databases.

*Results*: Analysis of pooled data indicated that iron treatments had a large effect on improving sFer (Hedges' g=1.088, 95% CI 0.914 to 1.263, p<0.001), sFe (Hedges' g=1.004, 95% CI 0.828 to 1.181, p<0.001) and Tsat (Hedges g=0.741, 95% CI 0.564 to 0.919, p<0.001) and a moderate effect on improving [Hb] (Hedges' g=0.695, 95% CI 0.533 to 0.836, p<0.001) and (VO(2max)) (Hedges' g=0.610, 95% CI 0.399 to 0.821, p<0.001). Regression analysis revealed a significant interaction between the effect of iron treatment on sFer and treatment duration, suggesting treatments that lasted beyond 80 days appear to have the least effect on sFer.

*Conclusions*: These results indicate iron treatments improve the iron status and aerobic capacity of iron deficient non-anaemic endurance athletes.

Carr, A (2015) “Arthroscopic surgery for degenerative knee: Overused, ineffective, and potentially harmful” *Br J Sports Med*;49:1223-1224. **Editorial** *Currently No Access*

Cassano, J.M.; Kennedy, J.G.; Ross, K.A. *et al.* (2016) “Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration” *Knee Surg Sports Traumatol Arthrosc*. doi:10.1007/s00167-016-3981-9

*Purpose* Bone marrow concentrate (BMC) and platelet-rich plasma (PRP) are used extensively in regenerative medicine. The aim of this study was to determine differences in the cellular composition and cytokine concentrations of BMC and PRP and to compare two commercial BMC systems in the same patient cohort.

*Methods* Patients (29) undergoing orthopaedic surgery were enrolled. Bone marrow aspirate (BMA) was processed to generate BMC from two commercial systems (BMC-A and BMC-B). Blood was obtained to make PRP utilizing the same system as BMC-A. Bone marrow-derived samples were cultured to measure colony-forming units, and flow cytometry was performed to assess mesenchymal stem cell (MSC) markers. Cellular concentrations were assessed for all samples. Catabolic cytokines and growth factors important for cartilage repair were measured using multiplex ELISA.

*Results* Colony-forming units were increased in both BMCs compared to BMA (p < 0.0001). Surface markers were consistent with MSCs. Platelet counts were not significantly different between BMC-A and PRP, but there were differences in leucocyte concentrations. TGF-β1 and PDGF were not different between BMC-A and PRP. IL-1ra concentrations were greater (p = 0.0018) in BMC-A samples (13,432 pg/mL) than in PRP (588 pg/mL). The IL-1ra/IL-1β ratio in all BMC samples was above the value reported to inhibit IL-1β.

*Conclusions* The bioactive factors examined in this study have differing clinical effects on musculoskeletal tissue. Differences in the cellular and cytokine composition between PRP and BMC and between BMC systems should be taken into consideration by the clinician when choosing a biologic for therapeutic application.

Caulfield, Timothy; McGuire, Amy (2012) “Athletes' Use of Unproven Stem Cell Therapies: Adding to Inappropriate Media Hype?”, *Molecular Therapy,* 20(9):1656-1658 **Editorial**

Few areas of research have received as much attention from the popular press as stem cells. And it is no wonder. Stem cell research is extraordinarily promising, with the potential to produce groundbreaking therapies for a range of ailments. In addition, it has generated an exceptional amount of public policy controversy, attracting attention from presidents, prime ministers, legislators, and religious leaders throughout the world. Combined, the representations of the promise and perils of this area of scientific inquiry have made stem cell research nothing short of a pop culture phenomenon. But many have speculated that this hype can be a less than constructive force,1 contributing to numerous science policy challenges—including the growing market for unproven stem cell therapies.

Cengiz, I.F.; Pitikakis, M.; Cesario, L. *et al*. (2016) “Building The Basis For Patient-Specific Meniscal Scaffolds: From Human Knee Mri To Fabrication Of 3d Printed Scaffolds” *Bioprinting,* 1-2:1-10, *Currently No Access*

The current strategies for the transplantation of meniscus should be strengthened to tackle the faced limitations of current methods in the clinics. One of the limitations is that current implants are not patient-specific. There is, therefore, a pressing need in the clinics to develop patient-specific implants. The aim of this study was to demonstrate a semi-automatic way of segmenting meniscus tissues from patients' volumetric knee magnetic resonance imaging (MRI) datasets in order to obtain patient-specific 3D models for 3D printing of patient-specific constructs. High-quality MRI volumetric images were acquired from five healthy male human subjects. The advanced segmentation software, RheumaSCORE, was used for semi-automatic MRI image segmentation of the meniscus tissues. Our methodology allows a full 3D segmentation of the menisci with only minimal interaction on 2D slices. The obtained 3D models were used for the fabrication of tissue engineering scaffolds from polycaprolactone with different internal architectures. The fabricated scaffolds were characterized by micro-computed tomography (µ-CT), scanning electron microscopy (SEM), and mechanical testing. This study demonstrated the 3D fabrication of patient-specific scaffolds with a 3D printer using the reconstructed 3D models obtained by an advanced segmentation method of menisci from knee MRI. This is a step towards a personalized tissue engineering therapy model for the knee meniscus.

Clark, Andrew W.; Alyas, Faisal; Morris, Tim *et al.* (2010) “Skin-Derived Tenocyte-like Cells for the Treatment of Patellar Tendinopathy” *The American Journal of Sports Medicine*, 39(3): 614 - 623

*Background*: Recent research of lateral elbow tendinopathy has led to the use of laboratory-amplified tenocyte-like cells.

*Hypothesis*: Ultrasound-guided injection of autologous skin-derived tendon-like cells are effective compared with other injectable therapies for the treatment of refractory patellar tendinosis.

*Study Design*: Randomized controlled trial; Level of evidence, 1.

*Methods*: From 60 patellar tendons in 46 patients with refractory patellar tendinopathy, a 4-mm skin biopsy was sampled to grow tenocyte-like collagen-producing cells. Patients were allocated into 2 groups: (1) injection with laboratory-prepared, amplified collagen-producing cells derived from dermal fibroblasts and suspended in autologous plasma from centrifuged autologous whole blood or (2) injection with autologous plasma alone. Injections were made into the sites of hypoechogenicity, intrasubstance tears, and fibrillar discontinuity within the patellar tendon. The Victorian Institute of Sport Assessment (VISA) score was used to assess pain, severity, and functional disability. Ultrasound was performed to assess structural and blood flow changes, evaluating 4 criteria: tendon thickness, hypoechogenicity, intrasubstance tears, and neovascularity.

*Results*: In the cell group, mean VISA scores improved from 44 ± 15 before treatment to 75 ± 17 at 6 months; in the plasma group, from 50 ± 18 to 70 ± 14. Estimated average difference between groups was 8.1, a significantly higher score in the cell group. Patients treated with collagen-producing cells also had significantly faster improvement and a highly significant effect of treatment, with the difference between groups estimated as 2.5 per unit increase in 1/time−−−−√1/time. One patient treated with cell therapy had a late rupture and progressed to surgery; histopathology showed normal tendon structure.

*Conclusion*: Ultrasound-guided injection of autologous skin-derived tendon-like cells can be safely used in the short term to treat patellar tendinopathy, with faster response of treatment and significantly greater improvement in pain and function than with plasma alone.

de Vos, Robert J. *et al* (2010) “Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy - A Randomized Controlled Trial”, *JAMA*. 2010;303(2):144-149. doi:10.1001/jama.2009.1986

Tendon disorders comprise 30% to 50% of all activity-related injuries; chronic degenerative tendon disorders (tendinopathy) occur frequently and are difficult to treat. Tendon regeneration might be improved by injecting platelet-rich plasma (PRP), an increasingly used treatment for releasing growth factors into the degenerative tendon.

de Vos RJ, Weir A, Tol JL, *et al.* (2011) “No Effects Of PRP On Ultrasonographic Tendon Structure And Neovascularisation In Chronic Midportion Achilles Tendinopathy” *British Journal of Sports Medicine* 45:387-392.

*Objective* To assess whether a platelet-rich plasma (PRP) injection leads to an enhanced tendon structure and neovascularisation, measured with ultrasonographic techniques, in chronic midportion Achilles tendinopathy.

*Design* Double-blind, randomised, placebo-controlled clinical trial.

*Setting* Sports medical department of The Hague medical centre.

*Patients* 54 patients with chronic midportion Achilles tendinopathy were included.

*Interventions* Patients were randomised to eccentric exercise therapy with either a PRP injection PRP group) or a saline injection (placebo group).

*Main outcome measurements* Tendon structure was evaluated by ultrasonographic tissue characterisation, a novel technique which quantifies tendon structure into four echo-types: echo-types I+II represent organised tendon bundles, whereas echo-types III+IV represent a disorganised tendon structure. Colour Doppler ultrasonography was used to measure the degree of neovascularisation. Follow-up was at 6, 12 and 24 weeks.

*Results* A significant improvement in echo-types I+II was found after 24 weeks within both the PRP group (n=27) and the placebo group (n=27), but there was no significant between-group difference (95% CI −1.6 to 7.8, p=0.169). After 6 weeks, the neovascularisation score increased within the PRP group (p=0.001) and the placebo group (p=0.002), but there was no significant between-group difference in change in neovascularisation score at any point in time.

*Conclusion* Injecting PRP for the treatment of chronic midportion Achilles tendinopathy does not contribute to an increased tendon structure or alter the degree of neovascularisation, compared with placebo.

Dean, BJ; Franklin, SL; Murphy, RJ; Javaid, MK; Carr, AJ (2014) “Glucocorticoids induce specific ion-channel-mediated toxicity in human rotator cuff tendon: a mechanism underpinning the ultimately deleterious effect of steroid injection in tendinopathy?” *Br J Sports Med*. 2014 Dec;48(22):1620-6. doi: 10.1136/bjsports-2013-093178. Epub 2014 Mar 27. *Currently No Access*

*BACKGROUND*: Glucocorticoid injection (GCI) and surgical rotator cuff repair are two widely used treatments for rotator cuff tendinopathy. Little is known about the way in which medical and surgical treatments affect the human rotator cuff tendon in vivo. We assessed the histological and immunohistochemical effects of these common treatments on the rotator cuff tendon.

*STUDY DESIGN*: Controlled laboratory study.

*METHODS*: Supraspinatus tendon biopsies were taken before and after treatment from 12 patients undergoing GCI and 8 patients undergoing surgical rotator cuff repair. All patients were symptomatic and none of the patients undergoing local GCI had full thickness tears of the rotator cuff. The tendon tissue was then analysed using histological techniques and immunohistochemistry.

*RESULTS*: There was a significant increase in nuclei count and vascularity after rotator cuff repair and not after GCI (both p=0.008). Hypoxia inducible factor 1α (HIF-1α) and cell proliferation were only increased after rotator cuff repair (both p=0.03) and not GCI. The ionotropic N-methyl-d-aspartate receptor 1 (NMDAR1) glutamate receptor was only increased after GCI and not rotator cuff repair (p=0.016). An increase in glutamate was seen in both groups following treatment (both p=0.04), while an increase in the receptor metabotropic glutamate receptor 7 (mGluR7) was only seen after rotator cuff repair (p=0.016).

*CONCLUSIONS*: The increases in cell proliferation, vascularity and HIF-1α after surgical rotator cuff repair appear consistent with a proliferative healing response, and these features are not seen after GCI. The increase in the glutamate receptor NMDAR1 after GCI raises concerns about the potential excitotoxic tendon damage that may result from this common treatment.

Dijkstra, Paul; Pollock, Noel (2014) “The Role of the Specialist Sports Medicine Physician in Elite Sport” *Aspetar: Sports Medicine Journal*, 3:1 **Not peer reviewed?**

The role of the sports medicine physician has changed significantly over the last 2 decades. In some sporting organisations, the sports medicine physician served as a necessary, governance requirement – someone who could sign the scan request form, dispense analgesia and inject anaesthetic or other medication when required or desired. This approach was from an era when sports medicine doctors did not have the necessary skills, background or contractual relationship to critically evaluate or manage musculoskeletal health.

Sport and Exercise Medicine is now an official medical specialty in many countries. This has engaged governments and institutions to develop, publish and implement the criteria for the training of sports medicine physicians; it has improved the standards of care for participants in sport and exercise who have access to these specialists1. However, the role of the specialist sports medicine physician is not always well-understood by medical colleagues, team management or politicians.

Faulkner, Alex; McNamee, Michael; Coveney, Catherine, Gabe, Jonathan (2017) “Where Biomedicalisation And Magic Meet: Therapeutic Innovations Of Elite Sports Injury In British Professional Football And Cycling”, *Social Science & Medicine,* 178: 136-143

Injury is a conspicuous feature of the practice and public spectacle of contemporary elite sports. The paper argues that the ‘biomedicalisation’ thesis (medico-industrial nexus, techno-scientific drivers, medical optimisation, biologisation, the rise of evidence and health surveillance) goes some way to capturing the use in elite sports injury of some highly specialised mainstream therapies and some highly maverick biological therapies, which are described. Nevertheless, these main strands of biomedicalisation do not capture the full range of these phenomena in the contexts of sports medicine and athletes' practices in accessing innovative, controversial therapies. Drawing on multi-method qualitative research on top-level professional football and cycling in the UK, 2014–2016, we argue that concepts of ‘magic’ and faith-based healing, mediated by notions of networking behaviour and referral systems, furnish a fuller explanation. We touch on the concept of ‘medical pluralism’, concluding that this should be revised in order to take account of belief-based access to innovative bio-therapies amongst elite sportspeople and organisations.

Fernandez-Moure, Joseph S.; Van Eps, Jeffrey L.; Cabrera, Fernando J. *et al.* (2017) “Platelet-Rich Plasma: A Biomimetic Approach To Enhancement Of Surgical Wound Healing”, *Journal of Surgical Research*, 207: 33-44

Platelets are small anucleate cytoplasmic cell bodies released by megakaryocytes in response to various physiologic triggers. Traditionally thought to be solely involved in the mechanisms of hemostasis, platelets have gained much attention due to their involvement wound healing, immunomodulation, and antiseptic properties. As the field of surgery continues to evolve so does the need for therapies to aid in treating the increasingly complex patients seen. With over 14 million obstetric, musculoskeletal, and urological and gastrointestinal surgeries performed annually, the healing of surgical wounds continues to be of upmost importance to the surgeon and patient. Platelet-rich plasma, or platelet concentrate, has emerged as a possible adjuvant therapy to aid in the healing of surgical wounds and injuries. In this review, we will discuss the wound healing properties of platelet-rich plasma and various surgical applications.

Figueroa, David; Figueroa, Francisco; Calvo, Rafael (2015) “Platelet-Rich Plasma Use in Anterior Cruciate Ligament Surgery: Systematic Review of the Literature” *Arthroscopy,* 31(5): 981–988 *Currently No Access*

*Purpose* To systematically review the current literature for evidence that would substantiate the use of platelet-rich plasma (PRP) in the treatment of anterior cruciate ligament (ACL) ruptures.

*Methods* We performed a systematic search in PubMed and Embase of studies written in the English and Spanish languages that compared the use of PRP with a control group in patients with ACL injuries assessing graft-to-bone healing, graft maturation, and/or clinical outcomes and were randomized controlled trials or prospective cohort studies.

*Results* Eleven studies fulfilled the inclusion criteria, comprising 516 patients (266 ACL reconstructions using PRP and 250 ACL reconstructions without PRP). Six studies reported a statistically significant difference (4 studies) or tendency toward faster graft maturation in the platelet group (2 studies). One study found no differences. Regarding tunnel healing/widening, 1 study showed faster healing in the PRP group and 5 studies showed no differences between the 2 groups. Considering clinical outcomes, 1 study showed better clinical outcomes with PRP use and 5 studies showed no benefits with the use of PRP.

*Conclusions* Concerning ACL graft maturation, there is promising evidence that the addition of PRP could be a synergic factor in acquiring maturity more quickly than grafts with no PRP, with the clinical implication of this remaining unclear. Regarding tunnel healing, it appears that there is not an improvement with the addition of PRP. There is no proof that clinical outcomes of ACL surgery are enhanced by the use of PR.

Filardo, G., Kon, E., Roffi, A. *et al.* (2015) “Platelet-rich Plasma: Why Intra-Articular? A Systematic Review of Preclinical Studies and Clinical Evidence on PRP for Joint Degeneration” *Knee Surg Sports Traumatol Arthrosc* 23: 2459. doi:10.1007/s00167-013-2743-1

*Purpose* The aim of this review was to analyze the available evidence on the clinical application of this biological approach for the injective treatment of cartilage lesions and joint degeneration, together with preclinical studies to support the rationale for the use of platelet concentrates, to shed some light and give indications on what to treat and what to expect from intra-articular injections of platelet-rich plasma (PRP).

*Methods* All in vitro, in vivo preclinical and clinical studies on PRP injective treatment in the English language concerning the effect of PRP on cartilage, synovial tissue, menisci, and mesenchymal stem cells were considered. A systematic review on the PubMed database was performed using the following words: (platelet-rich plasma or PRP or platelet concentrate or platelet lysate or platelet supernatant) and (cartilage or chondrocytes or synoviocytes or menisci or mesenchymal stem cells).

*Results* Fifty-nine articles met the inclusion criteria: 26 were in vitro, 9 were in vivo, 2 were both in vivo and in vitro, and 22 were clinical studies. The analysis showed an increasing number of published studies over time. Preclinical evidence supports the use of PRP injections that might promote a favourable environment for joint tissues healing. Only a few high-quality clinical trials have been published, which showed a clinical improvement limited over time and mainly documented in younger patients not affected by advanced knee degeneration.

*Conclusions* Besides the limits and sometimes controversial findings, the preclinical literature shows an overall support toward this PRP application. An intra-articular injection does not just target cartilage; instead, PRP might influence the entire joint environment, leading to a short-term clinical improvement. Many biological variables might influence the clinical outcome and have to be studied to optimize PRP injective treatment of cartilage degeneration and osteoarthritis.

Filbay, Stephanie R. *et al.* (2013) “Health-Related Quality of Life After Anterior Cruciate Ligament Reconstruction - A Systematic Review”, *The American Journal of Sports Medicine,* 42(5): 1247-1255

Anterior cruciate ligament reconstructions (ACLRs) are frequently performed on young, active patients and can result in persistent knee symptoms and activity limitations that may affect health-related quality of life (HRQoL). To date, there has been no systematic review of HRQoL outcomes after ACLR.

This review found that patients assessed using a knee-specific measure (KOOS-QOL) were more likely to report poorer HRQoL values, compared with population norms, than those assessed using a generic HRQoL measure (SF-36). Revision surgeries, meniscal injuries, and severe radiographic osteoarthritis were associated with poorer HRQoL outcomes after ACLR. However, these relationships should be interpreted with caution, as they were only investigated in a small number of studies.

Flouzat-Lachaniette, CH.; Roubineau, F.; Heyberger, C. *et al.* (2016) “Multifocal Osteonecrosis Related To Corticosteroid: Ten Years Later, Risk Of Progression And Observation Of Subsequent New Osteonecrosis” *International Orthopaedics* (SICOT) (2016) 40: 669. doi:10.1007/s00264-015-3060-8

*Purpose* No study has reported the risk of other site osteonecroses after the diagnosis of multifocal osteonecrosis related to corticosteroids in patients who continue this corticosteroid treatment. An analysis of the time-course to other sites of osteonecrosis, as well as the effects of underlying corticosteroid risk factor on the evolution of asymptomatic lesions at the time of diagnosis, is presented.

*Methods* Two hundred patients were followed prospectively every year during a minimum ten years with a radiograph if a joint became symptomatic. In absence of evidence of osteonecrosis on radiographs of a symptomatic or non-symptomatic joint (hips, shoulders, knees, ankles), patients had an MRI performed at the most recent follow up. The average duration of follow-up after inclusion of the patient in the study was 15 years (range 10–20).

*Results* Of the 200 patients followed for an average of 15 years (minimum 10 years, maximum 20 years), 35 patients developed new osteonecrosis lesions during the period of study. Asymptomatic lesions became symptomatic and a high number of collapse was observed resulting in 258 arthroplasties (187 hips, 51 shoulders, 20 knees) at the most recent follow up.

*Conclusion* The continuation of peak doses (>200 mg) of corticosteroids predicted (p = 0.04) occurrence of new lesions and the continuation of corticosteroids without peak dose was a risk for quicker progression to collapse.

Freedman, Scott R.; Brody, Lori Thein; Rosenthal, Michael; Wise, Justin C. (2014) “Short-Term Effects of Patellar Kinesio Taping on Pain and Hop Function in Patients With Patellofemoral Pain Syndrome”, *Sports Health,* 6(4):294-300

*Background*: Patellofemoral pain syndrome (PFPS) is the most prevalent orthopaedic condition among physically active individuals, contributing to an estimated 30% to 40% of all sports medicine visits. Techniques using Kinesio Tape (KT) have become increasingly popular; however, there has been scant research supporting its use on patients with PFPS.

*Hypothesis*: The use of patellar KT to treat patients with PFPS will provide a statistically significant improvement in short-term pain and single-leg hop measures as compared with sham placement of KT.

*Study Design*: Nonrandomized controlled clinical trial with repeated-measures design.

Methods: Forty-nine subjects (41 females, 8 males) between the ages of 12 and 24 years with PFPS participated in this study. Each subject underwent patellar kinesio taping with both experimental and sham applications while completing 4 functional tasks and the single-leg triple jump test (STJT). The treatment outcome was analyzed using separate paired t tests to measure improvement on a numeric pain rating scale. A 2-way, 2 × 2 analysis of variance was used to analyze the relationship between taping condition (experimental vs sham) and side (involved vs uninvolved) for STJT scores.

*Results*: Separate paired t tests found step-up, step-down, and STJT pain improvement statistically significant between taping conditions. The 2-factor analysis of variance yielded a significant main effect for taping condition, but the main effect for side was not significant. The interaction between taping condition and side was significant. This showed there was little change in STJT distance between repeated measures performed on the untaped, noninvolved leg. However, subjects’ STJT distances were significantly greater for the experimental KT application than the sham application for the involved side.

*Conclusion*: Patellar kinesio taping provided an immediate and statistically significant improvement in pain and single-leg hop function in patients with PFPS when compared with a sham application. However, improvement in STJT scores did not surpass the minimally detectable change value, and therefore, the clinical effectiveness of KT for improving single-leg hop function was not established in the current study.

Görmeli, G.; Görmeli, C.A.; Ataoglu, B. *et al.* (2017) “Multiple PRP Injections Are More Effective Than Single Injections And Hyaluronic Acid In Knees With Early Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial” *Knee Surg Sports Traumatol Arthrosc* 25: 958. doi:10.1007/s00167-015-3705-6

*Purpose* To compare the effectiveness of intraarticular (IA) multiple and single platelet-rich plasma (PRP) injections as well as hyaluronic acid (HA) injections in different stages of osteoarthritis (OA) of the knee.

*Methods* A total of 162 patients with different stages of knee OA were randomly divided into four groups receiving 3 IA doses of PRP, one dose of PRP, one dose of HA or a saline injection (control). Then, each group was subdivided into two groups: early OA (Kellgren–Lawrence grade 0 with cartilage degeneration or grade I–III) and advanced OA (Kellgren–Lawrence grade IV). The patients were evaluated before the injection and at the 6-month follow-ups using the EuroQol visual analogue scale (EQ-VAS) and International Knee Documentation Committee (IKDC) subjective scores. Adverse events and patient satisfaction were recorded.

*Results* There was a statistically significant improvement in the IKDC and EQ-VAS scores in all the treatment groups compared with the control group. The knee scores of patients treated with three PRP injections were significantly better than those patients of the other groups. There was no significant difference in the scores of patients injected with one dose of PRP or HA. In the early OA subgroups, significantly better clinical results were achieved in the patients treated with three PRP injections, but there was no significant difference in the clinical results of patients with advanced OA among the treatment groups.

*Conclusion* The clinical results of this study suggest IA PRP and HA treatment for all stages of knee OA. For patients with early OA, multiple (3) PRP injections are useful in achieving better clinical results. For patients with advanced OA, multiple injections do not significantly improve the results of patients in any group.

Grassi, Alberto; Zaffagnini, Stefano; Marcheggiani Muccioli, Giulio Maria *et al.* “After revision anterior cruciate ligament reconstruction, who returns to sport? A systematic review and meta-analysis”, *Br J Sports Med* Published Online First: 10 June 2015. doi: 10.1136/bjsports-2014-094089 **Review** *Currently No Access*

*Background* Return to sport and to pre-injury level represents an important outcome after both primary and revision anterior cruciate ligament (ACL) reconstructions.

*Purpose* The aim of the present meta-analysis was to determine the return to sport rate after revision ACL reconstruction.

*Material and methods* A systematic search was performed of the MEDLINE, Embase and the Cochrane Central Register of Controlled Trials Databases. All the studies that reported return to sport, return to pre-injury sport level and return to high level/competitive sport was considered for the meta-analysis. The overall pooled mean of post-operative knee laxity and pooled rate of positive pivot-shift and objective International Knee Documentation Committee (IKDC) categories was calculated as well.

*Results Overall*, 472 abstracts were identified and screened for inclusion and only 16 studies reported the rate of return to any level of sport activity at the final follow-up of 4.7 years (range 1.0–13.2 years), showing a pooled rate of 85.3% (CI 79.7 to 90.2). The return to pre-injury sport level was achieved in 53.4% (CI 37.8 to 68.7) of cases. Normal or quasi-normal objective IKDC, less than 5 mm of side-to-side difference at arthrometric evaluations and grade I-II pivot-shift test were reported in 84%, 88% and 93% patients, respectively.

*Conclusions* In spite of almost 8 patients out of 10 returning to sport after revision ACL reconstruction and showing good stability, only half of the patients returned to the same pre-injury sport level.

Hamilton, Bruce (2014) “Medical management of hamstring muscle injury: strained evidence for platelet rich plasma*” British Journal of Sports Medicine* 2014; 48 1335-1335 Published Online First: 20 Aug 2014. doi: 10.1136/bjsports-2014-094005 **Editorial** *Currently No Access*

Hauser, Ross A. & Hauser, Marion A. (2009) “A Retrospective Study on Dextrose Prolotherapy for Unresolved Knee Pain at an Outpatient Charity Clinic in Rural Illinois”, *Journal of Prolotherapy,* 1(1):11-21.

The optimal long-term, symptomatic therapy for unresolved knee pain has not been established. Accordingly, we investigated the outcomes of patients undergoing Hackett-Hemwall dextrose Prolotherapy treatment for unresolved knee pain at a charity clinic in rural Illinois. We studied a sample of 80 patients, representing a total of 119 knees, that were treated quarterly with Prolotherapy. On average, 15 months following their last Prolotherapy session, patients were contacted and asked numerous questions in regard to their levels of pain and a variety of physical and psychological symptoms, as well as activities of daily living, before and after their last Prolotherapy treatment. The results of this study showed that patients had a statistically significant decline in their level of pain, stiffness, crunching sensation, and improvement in their range of motion with Prolotherapy. More than 82% showed improvements in walking ability, medication usage, athletic ability, anxiety, depression, and overall disability with Prolotherapy. Ninety-six percent of patients felt Prolotherapy improved their life overall. Conclusion: In this study, patients with unresolved knee pain, treated with dextrose Prolotherapy, showed improvements in many clinically relevant parameters and overall quality of life.

Hauser, Ross A. (2009) “The Deterioration of Articular Cartilage in Osteoarthritis by Corticosteroid Injections”, *Journal of Prolotherapy.* 1(2):107-123.

The hallmark feature of osteoarthritis is the breakdown in the articular cartilage of joints such as the knee and hip. Both animal and human research has consistently shown that corticosteroid injections into normal and degenerated knees accelerate the arthritic process. A summary of the effects of the intraarticular corticosteroids on articular cartilage includes: a decrease of protein and matrix synthesis, matrix hyaline appearance becomes fibrotic, clumping of collagen, alteration in chondrocyte cell shape, chondrocyte cell proliferation inhibited, chondrocyte cytoxicity enhanced, loss of chondrocytes, surface deterioration including edema, pitting, shredding, ulceration and erosions, inhibition of articular cartilage metabolism, articular cartilage necrosis, thinning of articular cartilage, decrease in cartilage growth and repair, formation of articular cartilage cysts, and ultimately articular cartilage destruction.

When researchers microscopically and radiologically examine human joints after corticosteroid injections, the same results are found in humans as in animals. Intraarticular corticosteroid injections accelerate the osteoarthritic degenerative process. Because of this possibility, organizations such as the American College of Rheumatology acknowledge, “It is generally recommended, although not well supported by published data, that injection of corticosteroids in a given joint not be performed more than three to four times in a given year because of concern about the possible development of progressive cartilage damage through repeated injection in the weight-bearing joints.” It is this author’s opinion that there is no doubt that the rise of osteoarthritis, as well as the number of hip and knee replacements, is a direct result of the injection of corticosteroids into these joints.

Hauser, Ross A. *et al.* (2011) “Journal of Prolotherapy International Medical Editorial Board Consensus Statement on the Use of Prolotherapy for Musculoskeletal Pain” *Journal of Prolotherapy.* 3(4):744-764.

The purpose of this paper is to explicate the theory, scientific evidence, methods, and applications for the procedure of Prolotherapy in the treatment of musculoskeletal pain. The example of knee osteoarthritis is used as an example as to why Prolotherapy should be used compared to other invasive therapies.

Hernigou, Phillipe; Flouzat Lachaniette, C.H.; Delambre, J *et al.* (2014) “Biologic Augmentation Of Rotator Cuff Repair With Mesenchymal Stem Cells During Arthroscopy Improves Healing And Prevents Further Tears: A Case-Controlled Study.” *Int Orthop*., Sep;38(9):1811-8. doi: 10.1007/s00264-014-2391-1. Epub 2014 Jun 7.

*PURPOSE*: The purpose of this study was to evaluate the efficiency of biologic augmentation of rotator cuff repair with iliac crest bone marrow-derived mesenchymal stem cells (MSCs). The prevalence of healing and prevention of re-tears were correlated with the number of MSCs received at the tendon-to-bone interface.

*METHODS*: Forty-five patients in the study group received concentrated bone marrow-derived MSCs as an adjunct to single-row rotator cuff repair at the time of arthroscopy. The average number of MSCs returned to the patient was 51,000 ± 25,000. Outcomes of patients receiving MSCs during their repair were compared to those of a matched control group of 45 patients who did not receive MSCs. All patients underwent imaging studies of the shoulder with iterative ultrasound performed every month from the first postoperative month to the 24th month. The rotator cuff healing or re-tear was confirmed with MRI postoperatively at three and six months, one and two years and at the most recent follow up MRI (minimum ten-year follow-up).

*RESULTS*: Bone marrow-derived MSC injection as an adjunctive therapy during rotator cuff repair enhanced the healing rate and improved the quality of the repaired surface as determined by ultrasound and MRI. Forty-five (100 %) of the 45 repairs with MSC augmentation had healed by six months, versus 30 (67 %) of the 45 repairs without MSC treatment by six months. Bone marrow concentrate (BMC) injection also prevented further ruptures during the next ten years. At the most recent follow-up of ten years, intact rotator cuffs were found in 39 (87 %) of the 45 patients in the MSC-treated group, but just 20 (44 %) of the 45 patients in the control group. The number of transplanted MSCs was determined to be the most relevant to the outcome in the study group, since patients with a loss of tendon integrity at any time up to the ten-year follow-up milestone received fewer MSCs as compared with those who had maintained a successful repair during the same interval.

*CONCLUSION*: This study showed that significant improvement in healing outcomes could be achieved by the use of BMC containing MSC as an adjunct therapy in standard of care rotator cuff repair. Furthermore, our study showed a substantial improvement in the level of tendon integrity present at the ten-year milestone between the MSC-treated group and the control patients. These results support the use of bone marrow-derived MSC augmentation in rotator cuff repair, especially due to the enhanced rate of healing and the reduced number of re-tears observed over time in the MSC-treated patients.

Heuberger, Jules A.A.C.; Tervaert, Joost M. Cohen; Schepers, Femke M. L. *et al* (2013) “Erythropoietin doping in cycling: lack of evidence for efficacy and a negative risk–benefit”,  *British Journal of Clinical Pharmacology,* 75(6):1406-1421

Imagine a medicine that is expected to have very limited effects based upon knowledge of its pharmacology and (patho)physiology and that is studied in the wrong population, with low-quality studies that use a surrogate end-point that relates to the clinical end-point in a partial manner at most. Such a medicine would surely not be recommended. The use of recombinant human erythropoietin (rHuEPO) to enhance performance in cycling is very common. A qualitative systematic review of the available literature was performed to examine the evidence for the ergogenic properties of this drug, which is normally used to treat anaemia in chronic renal failure patients. The results of this literature search show that there is no scientific basis from which to conclude that rHuEPO has performance-enhancing properties in elite cyclists. The reported studies have many shortcomings regarding translation of the results to professional cycling endurance performance. Additionally, the possibly harmful side-effects have not been adequately researched for this population but appear to be worrying, at least. The use of rHuEPO in cycling is rife but scientifically unsupported by evidence, and its use in sports is medical malpractice. What its use would have been, if the involved team physicians had been trained in clinical pharmacology and had investigated this properly, remains a matter of speculation. A single well-controlled trial in athletes in real-life circumstances would give a better indication of the real advantages and risk factors of rHuEPO use, but it would be an oversimplification to suggest that this would eradicate its use.

Hogan, MaCalus, V; Walker, Garth N; Cui, Liang Richard; Fu, Freddie H; Huard, Johnny (2015) “The role of stem cells and tissue engineering in orthopaedic sports medicine: current evidence and future directions” *Arthroscopy: the Journal of Arthroscopic & Related Surgery* 2015, 31 (5): 1017-21 *Currently No Access*

The use of stem cell therapies for the treatment of orthopaedic injuries continues to advance. The purpose of this review was to provide an update of the current role and future directions of stem cell strategies in sports medicine. The application of cell-based treatments in the sports medicine arena has expanded in recent years. Promising preclinical results have led to translation of these novel therapies into the clinical setting. Early well-designed comparative clinical studies have also shown positive outcomes. Despite significant advances in this arena, there remains a need for additional high-powered and well-designed clinical trials to confirm the safety and efficacy of treatment.

Hunziker, Ernst B.; Lippuner, Kurt; Keel, Marius J.B.; and Shintani, Nahoko. (2015) “Age-Independent Cartilage Generation for Synovium-Based Autologous Chondrocyte Implantation “ *Tissue Engineering Part A.* June, 21(13-14): 2089-2098 *Currently No Access*

The articular cartilage layer of synovial joints is commonly lesioned by trauma or by a degenerative joint disease. Attempts to repair the damage frequently involve the performance of autologous chondrocyte implantation (ACI). Healthy cartilage must be first removed from the joint, and then, on a separate occasion, following the isolation of the chondrocytes and their expansion in vitro, implanted within the lesion. The disadvantages of this therapeutic approach include the destruction of healthy cartilage—which may predispose the joint to osteoarthritic degeneration—the necessarily restricted availability of healthy tissue, the limited proliferative capacity of the donor cells—which declines with age—and the need for two surgical interventions. We postulated that it should be possible to induce synovial stem cells, which are characterized by high, age-independent, proliferative and chondrogenic differentiation capacities, to lay down cartilage within the outer juxtasynovial space after the transcutaneous implantation of a carrier bearing BMP-2 in a slow-release system. The chondrocytes could be isolated on-site and immediately used for ACI. To test this hypothesis, Chinchilla rabbits were used as an experimental model. A collagenous patch bearing BMP-2 in a slow-delivery vehicle was sutured to the inner face of the synovial membrane. The neoformed tissue was excised 5, 8, 11 and 14 days postimplantation for histological and histomorphometric analyses. Neoformed tissue was observed within the outer juxtasynovial space already on the 5th postimplantation day. It contained connective and adipose tissues, and a central nugget of growing cartilage. Between days 5 and 14, the absolute volume of cartilage increased, attaining a value of 12 mm3 at the latter juncture. Bone was deposited in measurable quantities from the 11th day onwards, but owing to resorption, the net volume did not exceed 1.5 mm3 (14th day). The findings confirm our hypothesis. The quantity of neoformed cartilage that is deposited after only 1 week within the outer juxtasynovial space would yield sufficient cells for ACI. Since the BMP-2-bearing patches would be implanted transcutaneously in humans, only one surgical or arthroscopic intervention would be called for. Moreover, most importantly, sufficient numbers of cells could be generated in patients of all ages.

Hutchinson, Ian D.; Rodeo, Scott A.; Perrone, Gabriel S.; Murray, Martha M. (2015) “Can Platelet-Rich Plasma Enhance Anterior Cruciate Ligament and Meniscal Repair?”, *J Knee Surg* 28(01): 019-028; DOI: 10.1055/s-0034-1387166

The use of platelet-rich plasma (PRP) to improve clinical outcome following a soft tissue injury, regeneration, and repair has been the subject of intense investigation and discussion. This article endeavors to relate clinical and basic science strategies focused on biological augmentation of the healing response in anterior cruciate ligament (ACL) and meniscus repair and replacement using PRP. Therein, a translational feedback loop is created in the literature and targeted towards the entire multidisciplinary team. Ultimately, it is hoped that the theoretical benefits of PRP on soft-tissue interfacial healing will emerge clinically following a careful, focused characterization at the benchtop, and prospective randomized controlled clinical study.

Hyllner, Johan; Mason, Chris; Wilmut, Ian (2015) “Cells: From Robert Hooke To Cell Therapy—A 350 Year Journey” *Phil. Trans. R. Soc. B* 2015 370 20150320; DOI: 10.1098/rstb.2015.0320. **Introduction** *No Abstract*

Jalowiec, Jagoda M.; D'Este, Matteo; Bara, Jennifer Jane *et al.* (2015) “An In Vitro Investigation of Platelet-Rich Plasma-Gel as a Cell and Growth Factor Delivery Vehicle for Tissue Engineering” *Tissue Engineering Part C: Methods*. November 2015, 22(1): 49-58. <https://doi.org/10.1089/ten.tec.2015.0223> *Currently No Access*

Platelet-rich plasma (PRP) has been used for different applications in human and veterinary medicine. Many studies have shown promising therapeutic effects of PRP; however, there are still many controversies regarding its composition, properties, and clinical efficacy. The aim of this study was to evaluate the influence of different platelet concentrations on the rheological properties and growth factor (GF) release profile of PRP-gels. In addition, the viability of incorporated bone marrow-derived human mesenchymal stem cells (MSCs) was investigated. PRP (containing 1000 × 103, 2000 × 103, and 10,000 × 103 platelets/μL) was prepared from human platelet concentrates. Platelet activation and gelification were achieved by addition of human thrombin. Viscoelastic properties of PRP-gels were evaluated by rheological studies. The release of GFs and inflammatory proteins was measured using a membrane-based protein array and enzyme-linked immunosorbent assay. MSC viability and proliferation in PRP-gels were assessed over 7 days by cell viability staining. Cell proliferation was examined using DNA quantification. Regardless of the platelet content, all tested PRP-gels showed effective cross-linking. A positive correlation between protein release and the platelet concentration was observed at all time points. Among the detected proteins, the chemokine CCL5 was the most abundant. The greatest release appeared within the first 4 h after gelification. MSCs could be successfully cultured in PRP-gels over 7 days, with the highest cell viability and DNA content found in PRP-gels with 1000 × 103 platelets/μL. The results of this study suggest that PRP-gels represent a suitable carrier for both cell and GF delivery for tissue engineering. Notably, a platelet concentration of 1000 × 103 platelets/μL appeared to provide the most favorable environment for MSCs. Thus, the platelet concentration is an important consideration for the clinical application of PRP-gels.

James, Steven L.; Ali, Kaline; Pocock, Chris; Robertson, Claire *et al.* (2007) “Ultrasound guided dry needling and autologous blood injection for patellar tendinosis”, *Br J Sports Med*. 2007 Aug; 41(8): 518–521.

*Objective* To evaluate the efficacy of ultrasound guided dry needling and autologous blood injection for the treatment of patellar tendinosis.

*Design* Prospective cohort study.

*Setting* Hospital/clinic based.

*Patients* 47 knees in 44 patients (40 men, 7 women, mean age 34.5 years, age range 17 to 54 years) with refractory tendinosis underwent sonographic examination of the patellar tendon following referral with a clinical diagnosis of patellar tendinosis (mean symptom duration 12.9 months).

*Interventions* Ultrasound guided dry needling and injection of autologous blood into the site of patellar tendinosis was performed on two occasions four weeks apart.

*Main outcome measures* Pre‐ and post‐procedure Victorian Institute of Sport Assessment scores (VISA) were collected to assess patient response to treatment. Follow up ultrasound examination was done in 21 patients (22 knees).

*Results* Therapeutic intervention led to a significant improvement in VISA score: mean pre‐procedure score = 39.8 (range 8 to 72) v mean post procedure score = 74.3 (range 29 to 100), p<0.001; mean follow up 14.8 months (range 6 to 22 months). Patients were able to return to their sporting interests. Follow up sonographic assessment showed a reduction in overall tendon thickness and in the size of the area of tendinosis (hypoechoic/anechoic areas within the proximal patellar tendon). A reduction was identified in interstitial tears within the tendon substance. Neovascularity did not reduce significantly or even increased.

*Conclusions* Dry needling and autologous blood injection under ultrasound guidance shows promise as a treatment for patients with patellar tendinosis.

Johnson, Jeffrey S.; Morscher, Melanie, A.; Jones, Kerwyn C. *et al.* (2015) “Gene Expression Differences Between Ruptured Anterior Cruciate Ligaments in Young Male and Female Subjects”, Journal of Bone & Joint Surgery - American Volume: 7 January 2015 - Volume 97 - Issue 1 - p 71–79 doi: 10.2106/JBJS.N.00246 *Currently No Access*

*Background*: The incidence of anterior cruciate ligament (ACL) injuries is two to eightfold greater in female compared with male athletes. Anatomic, hormonal, and neuromuscular factors have been associated with this disparity. This study compared gene expression and structural features in ruptured but otherwise normal ACL tissue from young female and male athletes.

*Methods*: A biopsy sample of ruptured ACL tissue (which would normally have been discarded) was obtained intraoperatively from seven female and seven male athletes (12.7 to 22.6 years old). Each sample was divided into portions for histological and gene expression analyses. Specimens for gene analysis were frozen and ground, and RNA was extracted and purified. Microarray analysis was performed on RNA isolated from four female and three male study participants (13.9 to 18.5 years old) who had a noncontact injury. Genes with an expression level that differed significantly between these female and male athletes were grouped into functionally associated networks with use of IPA software (Qiagen). Three genes of interest were chosen for further validation by RT-qPCR (reverse transcription-quantitative polymerase chain reaction) analysis of the samples from all fourteen patients. Several statistical methods were used to examine sex-related differences.

*Results*: Microarray analysis of the RNA isolated from the ruptured ACL tissue from the female and male athletes identified thirty-two genes with significant differential expression. Fourteen of these genes were not linked to the X or Y chromosome. IPA analysis grouped these genes into pathways involving development and function of skeletal muscle and growth, maintenance, and proliferation of cells. RT-qPCR confirmed significant differences in expression of three selected genes: ACAN (aggrecan) and FMOD (fibromodulin) were upregulated in female compared with male study participants, and WISP2 (WNT1 inducible signaling pathway protein 2) was downregulated. No morphological differences among the ruptured tissue from the various participants were apparent on histological examination.

*Conclusions*: The genes identified in this study as differing distinctly according to sex produce major molecules in the ACL extracellular matrix. Significant upregulation of ACAN and FMOD (which regulate the matrix) and downregulation of WISP2 (which is involved in collagen turnover and production) may account for the weaker ACLs in female compared with male individuals.

Kahn, Moin; Bedi, Asheesh (2015) “Cochrane in CORR®: Platelet-rich Therapies for Musculoskeletal Soft Tissue Injuries (Review)” *A. Clin Orthop Relat Res* (2015) 473: 2207. doi:10.1007/s11999-015-4207-z

This Cochrane systematic review and meta-analysis found no benefit attributable to PRP for short-, medium-, or long-term function. Short-term improvements in pain were identified but the effect sizes were small, and unlikely to be clinically important.

Kamenova, Kalina; Caulfield, Timothy (2015) “Stem cell hype: Media portrayal of therapy translation*” Science Translational Medicine* 11 Mar 2015: Vol. 7, Issue 278, pp. 278ps4 DOI: 10.1126/scitranslmed.3010496 **Editorial**

In this Perspective, we examine the portrayal of translational stem cell research in major daily newspapers in Canada, the United States, and the United Kingdom between 2010 and 2013, focusing on how timelines for stem cell therapies were represented before and after Geron terminated its pioneering stem cell program. Our content analysis reveals that press coverage has shifted from ethical, legal, and social issues to clinical translation issues, and highly optimistic timelines were provided with no substantial change in representation over time. Scientists were the dominant voice with respect to translation timelines. The findings raise questions about the degree to which the media’s overly optimistic slant fosters unrealistic expectations regarding the speed of clinical translation and highlight the ethical responsibility of stem cell researchers as public communicators.

Kieb, Matthias; Sander, Frank; Prinz, Cornelia *et al.* (2016) “Platelet-Rich Plasma Powder: A New Preparation Method for the Standardization of Growth Factor Concentrations”, *The American Journal of Sports Medicine,*  45(4): 954 – 960; First published date: November-30-2016; 10.1177/0363546516674475

*Background*: Platelet-rich plasma (PRP) is widely used in sports medicine. Available PRP preparations differ in white blood cell, platelet, and growth factor concentrations, making standardized research and clinical application challenging.

*Purpose*: To characterize a newly standardized procedure for pooled PRP that provides defined growth factor concentrations.

*Study Design*: Controlled laboratory study.

*Methods*: A standardized growth factor preparation (lyophilized PRP powder) was prepared using 12 pooled platelet concentrates (PCs) derived from different donors via apheresis. Blood samples and commercially available PRP (SmartPrep-2) served as controls (n = 5). Baseline blood counts were analyzed. Additionally, single PCs (n = 5) were produced by standard platelet apheresis. The concentrations of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor AB (PDGF-AB), transforming growth factor β1 (TGF-β1), insulin-like growth factor 1 (IGF-1), interleukin (IL)–1α, IL-1β, and IL-1 receptor agonist (IL-1RA) were analyzed by enzyme-linked immunosorbent assay, and statistical analyses were performed using descriptive statistics, mean differences, 95% CIs, and P values (analysis of variance).

Results: All growth factor preparation methods showed elevated concentrations of the growth factors VEGF, bFGF, PDGF-AB, and TGF-β1 compared with those of whole blood. Large interindividual differences were found in VEGF and bFGF concentrations. Respective values (mean ± SD in pg/mL) for whole blood, SmartPrep-2, PC, and PRP powder were as follows: VEGF (574 ± 147, 528 ± 233, 1087 ± 535, and 1722), bFGF (198 ± 164, 410 ± 259, 151 ± 99, and 542), PDGF-AB (2394 ± 451, 17,846 ± 3087, 18,461 ± 4455, and 23,023), and TGF-β1 (14,356 ± 4527, 77,533 ± 13,918, 68,582 ± 7388, and 87,495). IGF-1 was found in SmartPrep-2 (1539 ± 348 pg/mL). For PC (2266 ± 485 pg/mL), IGF-1 was measured at the same levels of whole blood (2317 ± 711 pg/mL) but was not detectable in PRP powder. IL-1α was detectable in whole blood (111 ± 35 pg/mL) and SmartPrep-2 (119 ± 44 pg/mL).

*Conclusion*: Problems with PRP such as absent standardization, lack of consistency among studies, and black box dosage could be solved by using characterized PRP powder made by pooling and lyophilizing multiple PCs. The new PRP powder opens up new possibilities for PRP research as well as for the treatment of patients.

*Clinical Relevance*: The preparation of pooled PRP by means of lyophilization may allow physicians to apply a defined amount of growth factors by using a defined amount of PRP powder. Moreover, PRP powder as a dry substance with no need for centrifugation could become ubiquitously available, thus saving time and staff resources in clinical practice. However, before transferring the results of this basic science study to clinical application, regulatory issues have to be cleared.

Krogh, Thøger P.; Ellingsen, Torkell; Christensen, Robin *et al.* (2016) “Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline - A Randomized, Blinded, Placebo-Controlled Trial”, *The American Journal of Sports Medicine* 44(8): 1990 – 1997

*Background*: Achilles tendinopathy (AT) is a common and difficult to treat musculoskeletal disorder.

*Purpose*: To examine whether 1 injection of platelet-rich plasma (PRP) would improve outcomes more effectively than placebo (saline) after 3 months in patients with AT.

*Study Design*: Randomized controlled trial; Level of evidence, 1.

*Methods*: A total of 24 patients with chronic AT (median disease duration, 33 months) were randomized (1:1) to receive either a blinded injection of PRP (n = 12) or saline (n = 12). The primary endpoint was improvement in Victorian Institute of Sports Assessment–Achilles (VISA-A) score at 3 months. Secondary outcomes were pain at rest, pain while walking, pain when tendon was squeezed, ultrasonographic changes in tendon thickness, and color Doppler activity. Patients were informed that they could drop out after 3 months if they were dissatisfied with the treatment.

*Results*: After 3 months, all 24 patients were reassessed (no dropouts). No difference between the PRP and the saline group could be observed with regard to the primary outcome (VISA-A score: mean difference [MD], –1.3; 95% CI, −17.8 to 15.2; P = .868). Secondary outcomes were pain at rest (MD, 1.6; 95% CI, −0.5 to 3.7; P = .137), pain while walking (MD, 0.8; 95% CI, −1.8 to 3.3; P = .544), pain when tendon was squeezed (MD, 0.3; 95% CI, −0.2 to 0.9; P = .208), color Doppler activity (MD, 0.3; 95% CI, −0.2 to 0.8; P = .260), and tendon thickness (MD, 0.8 mm; 95% CI, 0.1 to 1.6 mm; P = .030). After the 3-month follow-up, a large dropout was observed: 75% of patients in the PRP group and 33% in the saline group.

*Conclusion*: PRP injection did not result in an improved VISA-A score over a 3-month period in patients with chronic AT compared with placebo. The only secondary outcome demonstrating a statistically significant difference between the groups was change in tendon thickness; this difference indicates that a PRP injection could increase tendon thickness compared with saline injection. The conclusions are limited to the 3 months after treatment owing to the large dropout rate.

Liddle, Alexander D; Rodríguez-Merchán, E Carlos (2015) “Platelet-Rich Plasma in the Treatment of Patellar Tendinopathy: A Systematic Review” American Journal of Sports Medicine 2015, 43 (10): 2583-90

*BACKGROUND*: Patellar tendinopathy (PT) is a major cause of morbidity in both high-level and recreational athletes. While there is good evidence for the effectiveness of eccentric exercise regimens in its treatment, a large proportion of patients have disease that is refractory to such treatments. This has led to the development of novel techniques, including platelet-rich plasma (PRP) injection, which aims to stimulate a normal healing response within the abnormal patellar tendon. However, little evidence exists at present to support its use.

*PURPOSE*: To determine the safety and effectiveness of PRP in the treatment of PT and to quantify its effectiveness relative to other therapies for PT.

*STUDY DESIGN*: Systematic review.

*METHODS*: A systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A literature review was conducted of the Medline, EMBASE, and Cochrane databases as well as trial registries. Both single-arm and comparative studies were included. The outcomes of interest were pain (as measured by visual analog or other, comparable scoring systems), functional scores, and return to sport. Study quality and risk of bias were assessed using the methodological index for nonrandomized studies (MINORS) score and the Cochrane risk of bias tool.

*RESULTS*: Eleven studies fit the inclusion criteria. Of these, 2 were randomized, controlled trials (RCTs), and 1 was a prospective, nonrandomized cohort study. The remainder were single-arm case series. All noncomparative studies demonstrated a significant improvement in pain and function after PRP injection. Complications and adverse outcomes were rare. The results of the comparative studies were inconsistent, and superiority of PRP over control treatments could not be conclusively demonstrated.

*CONCLUSION*: Platelet-rich plasma is a safe and promising therapy in the treatment of recalcitrant PT. However, its superiority over other treatments such as physical therapy remains unproven. Further RCTs are required to determine the relative effectiveness of the many available treatments for PT and to determine the subgroups of patients who stand to gain the most from the use of these therapies.

Littlewood, Chris; May, Stephan, Walters, Stephan (2013) “A review of systematic reviews of the effectiveness of conservative interventions for rotator cuff tendinopathy”, *Shoulder & Elbow,* 5(3): 151-167

*Background* Rotator cuff tendinopathy is common and a wide range of conservative interventions are currently used to treat this problem. The purpose of this review is to systematically review the systematic reviews that evaluate the effectiveness of conservative interventions for rotator cuff tendinopathy.

*Methods* An electronic search of PEDro, MEDLINE and the Cochrane Library was undertaken and supplemented by hand and citation searching. The AMSTAR checklist was adopted for quality appraisal and a narrative synthesis was undertaken.

*Results* Twenty-six systematic reviews were retrieved. Methodological quality was variable. Exercise and multimodal physiotherapy appear to confer superior outcomes over no treatment or placebo, although the clinical significance of these results remains unclear. Surgery does not confer an additional benefit over exercise alone or multimodal physiotherapy. Combining manual therapy with exercise is not currently supported, neither is the use of corticosteroid injections or acupuncture. Other commonly prescribed interventions lack evidence of effectiveness.

*Conclusions* Exercise and multimodal physiotherapy might be effective interventions for rotator cuff tendinopathy, although the clinical significance of this effect is unclear. This interpretation is drawn from systematic reviews comprising mainly small randomized controlled trials that frequently measure outcome in a heterogeneous manner, limiting the strength of any conclusions.

Maffulli, Nicola (2013) “Autologous blood products in musculoskeletal medicine: Although they are trendy money spinners, best evidence shows little effectiveness”, *BMJ: British Medical Journal*, Vol. 346, No. 7908: 9 **Editorial** *No Abstract*

Malanga, Gerard; Nakamura, Reina (2014) “The Role of Regenerative Medicine in the Treatment of Sports Injuries”, *Phys Med Rehabil Clin N Am* 25: 881-895 **Editorial** *No Abstract , Currently No Access*

Mascarenhas, Randy; Erickson, Brandon J.; Sayegh, Eli T. *et al.* “Is There a Higher Failure Rate of Allografts Compared With Autografts in Anterior Cruciate Ligament Reconstruction: A Systematic Review of Overlapping Meta-analyses”, *Arthroscopy* 31(2):364-372 *Currently No Access*

*Purpose* Multiple meta-analyses of randomized controlled trials (RCTs), the highest available level of evidence, have been conducted to determine whether autograft or allograft tissue provides superior clinical outcomes and structural healing in anterior cruciate ligament reconstruction (ACLR); however, results are discordant. The purpose of this study was to conduct a systematic review of meta-analyses comparing ACLR with autografts and allografts to elucidate the cause of discordance and to determine which meta-analyses provide the current best available evidence.

*Methods* In this study we evaluated available scientific support for autograft versus allograft use in ACLR by systematically reviewing the literature for published meta-analyses. Data regarding patient outcomes and structural healing were extracted from these meta-analyses. Meta-analysis quality was assessed using the Oxman-Guyatt and Quality of Reporting of Meta-analyses (QUOROM) systems. The Jadad algorithm was then applied to determine which meta-analyses provided the highest level of evidence.

*Results* Eight meta-analyses containing a total of 15,819 patients met the eligibility criteria, 2 of which included Level II evidence and 6 of which included Level III/IV evidence. Four meta-analyses found no differences between autografts and allografts for patient outcomes, whereas 4 found autografts superior in one or more respects. Four meta-analyses reported higher graft rupture rates in the allograft group, and 2 found superior hop test performance in autograft-treated patients. Six meta-analyses had low Oxman-Guyatt scores (<4) indicative of major flaws.

*Conclusions* According to this systematic review of overlapping meta-analyses comparing autografts and allografts for ACLR, the current best available evidence suggests no differences in rupture rates and clinical outcomes. Lower quality meta-analyses indicate that autografts may provide a lower rerupture rate, better hop test performance, and better objective knee stability than do allografts.

Masci, Lorenzo (2015) “Is Tendinopathy Research at a Crossroads?” *British Journal of Sports Medicine* 2015; 49 1027-1027 Published Online First: 29 Jul 2015. doi: 10.1136/bjsports-2015-095213 **Editorial** *Currently No Access*

McCall, A; Carling, C; Davison, M *.* (2015) “Injury Risk Factors, Screening Tests And Preventative Strategies: A Systematic Review Of The Evidence That Underpins The Perceptions And Practices Of 44 Football (Soccer) Teams From Various Premier Leagues” *Br J Sports Med* 2015;49:583-589. *Currently No Access*

*Purpose* To systematically review the scientific level of evidence for the ‘Top 3’ risk factors, screening tests and preventative exercises identified by a previously published survey of 44 premier league football (soccer) teams. Also, to provide an overall scientific level of evidence and graded recommendation based on the current research literature.

*Methods* A systematic literature search (Pubmed [MEDLINE], SportDiscus, PEDRO and Cochrane databases). The quality of the articles was assessed and a level of evidence (1++ to 4) was assigned. Level 1++ corresponded to the highest level of evidence available and 4, the lowest. A graded recommendation (A: strong, B: moderate, C: weak, D: insufficient evidence to assign a specific recommendation) for use in the practical setting was given.

*Results* Fourteen studies were analysed. The overall level of evidence for the risk factors previous injury, fatigue and muscle imbalance were 2++, 4 and ‘inconclusive’, respectively. The graded recommendation for functional movement screen, psychological questionnaire and isokinetic muscle testing were all ‘D’. Hamstring eccentric had a weak graded ‘C’ recommendation, and eccentric exercise for other body parts was ‘D’. Balance/proprioception exercise to reduce ankle and knee sprain injury was assigned a graded recommendation ‘D’.

*Conclusions* The majority of perceptions and practices of premier league teams have a low level of evidence and low graded recommendation. This does not imply that these perceptions and practices are not important or not valid, as it may simply be that they are yet to be sufficiently validated or refuted by research.

McCarrell, T.M. *et al.* (2014) “Considerations For The Use Of Platelet-Rich Plasma In Orthopedics.”, *Sports Medicine*, 44(8):1025-36. doi: 10.1007/s40279-014-0195-5.

The use of platelet-rich plasma (PRP) is expanding to numerous medical fields, including orthopedic surgery and sports medicine. The popularity of this new treatment option has prompted a rapid increase in research endeavors; however, the differences in application technique and the composition of PRP have made it difficult to compare results or make any firm conclusions regarding efficacy. The purpose of this article is twofold. First, to recommend details that should be provided in basic science and clinical PRP studies to allow meaningful comparisons between studies which may lead to a better understanding of efficacy. Second, to provide an understanding of the different PRP preparations and their clinical relevance. There are biochemical rationales for the use of PRP because it addresses several aspects of the healing process, including cell proliferation and tissue matrix regeneration, inflammation, nociception, infection, and hemostasis, all of which will be addressed. Given the current understanding of the importance the composition of PRP plays in tissue regeneration, it is likely that our future understanding of PRP will dictate 'customizing' the PRP preparation to the specific pathology of interest. The potential complications following PRP use are minor, and thus it appears to be a safe treatment option with a variety of potentially beneficial effects to injured musculoskeletal tissues.

Müller, S.A., Todorov, A., Heisterbach, P.E. et al. (2015) “Tendon Healing: An Overview Of Physiology, Biology, And Pathology Of Tendon Healing And Systematic Review Of State Of The Art In Tendon Bioengineering” *Knee Surg Sports Traumatol Arthrosc* 23: 2097. doi:10.1007/s00167-013-2680-z

*Purpose* Tendon injuries vary from acute rupture to chronic tendinopathy. For an optimal treatment of either condition, a profound knowledge is essential. Therefore, this article shall give an overview of physiology, biology, and pathology of tendon healing and state of the art in tendon bioengineering.

*Methods* For a preferably comprehensive survey, the current literature listed in PubMed and published in English peer-reviewed journals (March 2013) was systematically reviewed for tendon healing and tendon bioengineering including cytokine modulation, autologous sources of growth factors, biomaterials, gene therapy, and cell-based therapy. No differentiation was made between clinical and preclinical in vitro investigations.

*Results* Tendon healing happens in certain stadiums of inflammation, formation, and remodelling. An additional process of “collagen recycling” close to the healing site has been described recently. With increasing comprehension of physiology and pathology of tendon healing, several promising approaches in tendon bioengineering using growth factors, biomaterials, gene therapy, or cell-based therapy are described. However, only some of these are already used routinely in clinics.

*Conclusion* Strong and resistant tendons are crucial for a healthy musculoskeletal system. The new approaches in tendon bioengineering are promising to aid physiological tendon healing and thus resulting in a stronger and more resistant tendon after injury. The growing knowledge in this field will need to be further taken into clinical studies so that especially those patients with prolonged courses, revision surgery, or chronic tendinopathy and high-demanding patients, i.e., professional athletes would benefit.

Mumme, Marcus; Barbero, Andrea *et al.* (2016) “Nasal Chondrocyte-Based Engineered Autologous Cartilage Tissue For Repair Of Articular Cartilage Defects: An Observational First-In-Human Trial”, *The Lancet,* 388(10055):1985-1994, http://dx.doi.org/10.1016/S0140-6736(16)31658-0

*Background* Articular cartilage injuries have poor repair capacity, leading to progressive joint damage, and cannot be restored predictably by either conventional treatments or advanced therapies based on implantation of articular chondrocytes. Compared with articular chondrocytes, chondrocytes derived from the nasal septum have superior and more reproducible capacity to generate hyaline-like cartilage tissues, with the plasticity to adapt to a joint environment. We aimed to assess whether engineered autologous nasal chondrocyte-based cartilage grafts allow safe and functional restoration of knee cartilage defects.

*Methods* In a first-in-human trial, ten patients with symptomatic, post-traumatic, full-thickness cartilage lesions (2–6 cm2) on the femoral condyle or trochlea were treated at University Hospital Basel in Switzerland. Chondrocytes isolated from a 6 mm nasal septum biopsy specimen were expanded and cultured onto collagen membranes to engineer cartilage grafts (30 × 40 × 2 mm). The engineered tissues were implanted into the femoral defects via mini-arthrotomy and assessed up to 24 months after surgery. Primary outcomes were feasibility and safety of the procedure. Secondary outcomes included self-assessed clinical scores and MRI-based estimation of morphological and compositional quality of the repair tissue. This study is registered with ClinicalTrials.gov, number NCT01605201. The study is ongoing, with an approved extension to 25 patients.

*Findings* For every patient, it was feasible to manufacture cartilaginous grafts with nasal chondrocytes embedded in an extracellular matrix rich in glycosaminoglycan and type II collagen. Engineered tissues were stable through handling with forceps and could be secured in the injured joints. No adverse reactions were recorded and self-assessed clinical scores for pain, knee function, and quality of life were improved significantly from before surgery to 24 months after surgery. Radiological assessments indicated variable degrees of defect filling and development of repair tissue approaching the composition of native cartilage.

*Interpretation* Hyaline-like cartilage tissues, engineered from autologous nasal chondrocytes, can be used clinically for repair of articular cartilage defects in the knee. Future studies are warranted to assess efficacy in large controlled trials and to investigate an extension of indications to early degenerative states or to other joints.

O’Sullivan, K. & O’Sullivan, P. (2015) “Stem cell therapy and other novel needle-based therapies for back pain: Disconnect between evidence and practice”, *British Sports Medicine Journal Blog,* URL: <http://blogs.bmj.com/bjsm/2015/01/19/stem-cell-therapy-and-other-novel-needle-based-therapies-for-back-pain-disconnect-between-evidence-and-practice/>, Accessed 01/07/17, **Blog**

The 14-time Grand Slam winner, Rafael Nadal’s recent struggles to participate at the highest level due to ongoing low back pain (LBP) once again brings the issue of novel therapies offering tantalizing cures to the fore; he is undergoing stem cell therapy (SCT). So it is timely to explore: i) what this therapy potentially offers, ii) the quality of the supporting evidence, iii) its comparison to other needle-based therapies, and iv) what the use of several novel needle-based therapies in the last decade (e.g. stem cell therapy, platelet-rich plasma, dry needling) reveal about attitudes to management of pain in sporting populations.

Oliver, Kristin S.; Bayes, Matthew; Crane, David, Pathikonda, Chakrapandi (2015) “Clinical Outcome of Bone Marrow Concentrate in Knee Osteoarthritis” *Journal of Prolotherapy,* 7:e937-e946

*Background*: Knee osteoarthritis is an increasing health concern in the adult population. Nonsurgical treatment options for pain reduction and function improvement are limited in number and provide only short-term relief. The potential of regenerative therapies to go beyond temporary symptom reduction and delay or negate the need for total knee joint arthroplasty is enticing to both patients and providers.

*Purpose*: This study evaluated the clinical efficacy of autologous intra-articular bone marrow concentrate with autologous lipoaspirate as a treatment option for osteoarthritis of the knee. Additionally, bone marrow concentrate samples from a patient population subset not necessarily enrolled in this study, but IRB approved, were sent for outside laboratory analysis.

*Study design:* This study is a prospective case series.

*Methods*: Treatment registry data for 70 patients diagnosed with Kellgren-Lawrence Stage 2–4 knee osteoarthritis were analyzed. Data regarding adverse events and Knee injury and Osteoarthritis Outcome Score metrics were obtained at baseline, 90 days, and 180 days. Samples of bone marrow concentrate from 11 patients were sent to an outside source for laboratory analysis.

*Results*: Adverse events were limited to transient pain and swelling of the treated joint. The mean reported KOOS changes from pre- procedure to 180 days post-procedure were as follows: Pain + 18.1, Activities of Daily Living +15.6, Symptoms +17.3, Quality of Life +20.3, and Sports/Recreation +18.1. Laboratory analysis of the samples demonstrated statistically significant increases in concentration of platelets, interleukin-1 receptor antagonist and IL-1β. The IL-1ra/IL-1β ratio was also statistically significant at 193.54 when processed with a 2% Hct setting, and 720.62 when processed with a 15% Hct.

*Conclusions*: This study of intra-articular injection of autologous bone marrow concentrate and lipoaspirate in patients diagnosed with knee osteoarthritis demonstrates encouraging results for positive outcomes without complication. Further study with randomized controlled trials is warranted to prove the potential of this intervention. With laboratory analysis of samples of bone marrow concentrate we were able to identify the presence of statistically significant increases in the concentration of platelets and IL-ra.

*What is known about the subject:* Bone marrow concentrate is known to contain a host of growth factors and stem cells and has been shown in animal studies to promote the regeneration of cartilage.22,46 There are two clinical studies published showing the efficacy of bone marrow concentrate in patients with knee osteoarthritis.12,32

*What this study adds to the existing knowledge:* This study supports the findings of the two published clinical studies of bone marrow concentrate on patients with knee osteoarthritis. This alternative treatment option provides positive patients outcomes with low risk.

Pa, HI; Reurink, G; Tol, JL; *et al.* (2015) “Efficacy of rehabilitation (lengthening) exercises, platelet-rich plasma injections, and other conservative interventions in acute hamstring injuries: an updated systematic review and meta-analysis” *Br J Sports Med*;49:1197-1205. *Currently No Access*

*Background* Our 2012 review on therapeutic interventions for acute hamstring injuries found a lack of high-quality studies. The publication of new studies warranted an update.

*Objectives* To update and reanalyse the efficacy of conservative treatments for hamstring injury.

*Data sources* PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and SPORTDiscus were searched till mid-February 2015.

*Study eligibility* criteria Randomised controlled trials (RCTs) on the effect of conservative interventions versus a control group or other intervention for hamstring injuries (HI) were included.

*Data analysis* The search results were screened independently by two authors. Risk of bias assessment was performed using a modified Downs and Black scale with a maximum score of 28. Meta-analysis was performed, where possible.

*Main results* 10 RCTs (526 participants), including 6 new RCTs, were identified. Two RCTs were of good/excellent quality, the rest were fair or poor (median Downs and Black score 16 (IQR 9)). Meta-analysis of two studies on rehabilitation (lengthening) exercises showed a significantly reduced time to return to play (HR 3.22 (95% CI 2.17 to 4.77), p<0.0001) but no difference in risk of re-injury. Meta-analysis of three studies investigating platelet-rich plasma (PRP) showed no effect when compared to control (HR 1.03 (95% CI 0.87 to 1.22), p=0.73). Limited evidence was found that progressive agility and trunk stability training may reduce re-injury rates.

*Conclusions* Meta-analysis showed superior efficacy for rehabilitation exercises. PRP injection had no effect on acute hamstring injury. Limited evidence was found that agility and trunk stabilisation may reduce re-injury rates. The limitations identified in the majority of RCTs should improve the design of new hamstring RCTs.

Phillips, Stuart M. (2014) “A Brief Review of Higher Dietary Protein Diets in Weight Loss: A Focus on Athletes” *Sports Medicine,* 44(2):149-153 **Editorial**

Thermodynamics dictates that for body weight (i.e. stored substrate) loss to occur a person must ingest less energy than they expend. Athletes, who owing to their oftentimes large daily energy expenditures, may have greater flexibility than non-athletes in this regard; however, they may also have different goals for weight loss. In particular, weight lost may be less important to an athlete than from which compartment the weight is lost: fat or lean. A critical question is thus, what balance of macronutrients might promote a greater fat loss, a relative retention of lean mass, and still allow athletic performance to remain uncompromised? It is the central thesis of this review that dietary protein should be a nutrient around which changes in macronutrient composition should be framed. The requirement for protein to sustain lean mass increases while in negative energy balance and protein, as macronutrient, may have advantages with respect to satiety during energy balance, and it may allow greater fat loss during a negative energy balance. However, athletes should be mindful of the fact that increasing dietary protein intake while in negative energy balance would come at the ‘expense’ of another macronutrient. Most recently there has been interest in lower carbohydrate diets, which may not allow performance to be sustained given the importance of dietary carbohydrate in high-intensity exercise. The relative merits of higher protein diets for athletes are discussed.

Pluim, B. M.; Loeffen, F. G. J.; Clarsen B. *et al.* (2015) “A One-Season Prospective Study of Injuries and Illness in Elite Junior Tennis” *Scandinavian Journal of Medicine & Science in Sports,* 26(5): 564–571

The objective of this study was to estimate the incidence and prevalence of injury and illness among elite junior tennis players. A cohort of 73 players (11–14 years) in the 2012–2013 Dutch national high-performance program was followed for 32 weeks; all participants completed the study. The OSTRC Questionnaire on Health Problems was used to record self-reported injuries and illnesses and to record training and match exposure. Main outcome measures were average prevalence of overuse injury and illness and incidence density of acute injury. On average, players practiced 9.1 h/week (SD 0.6; range 2.3–12.0) and had 2.2 h of match play (SD 0.6; range 2.3–12.0). During the course of the study, 67 players reported a total of 187 health problems. The average weekly prevalence of all health problems was 21.3% (95% CI: 19.2–22.9), of which 12.1% (95% CI: 10.9–13.3) constituted overuse injuries and 5.8% (95% CI: 4.6–6.9) illnesses. The incidence of acute injuries was 1.2/1000 h of tennis play (95% CI: 0.7–1.7). The high occurrence of overuse injuries among elite junior tennis players suggests that an early focus on preventative measures is warranted, with a particular focus on the monitoring and management of workload.

Pujol, N., Salle De Chou, E., Boisrenoult, P. et al. (2015) “Platelet-rich plasma for open meniscal repair in young patients: Any benefit?” *Knee Surg Sports Traumatol Arthrosc* 23: 51. doi:10.1007/s00167-014-3417-3

Purpose Many studies have demonstrated that injection of various growth factors including platelet-derived growth factor could increase meniscal cell activity and stimulate repair. The purpose of this study was to augment repair and promote meniscal healing by the use of platelet-rich plasma (PRP) within horizontal cleavage meniscal tears repaired via an open approach. The hypothesis was that the clinical outcomes and healing process would be improved using this meniscal healing augmentation technique.

*Methods* In this case–control study, 34 consecutive young patients underwent an open meniscal repair to treat symptomatic Grade 2 or Grade 3 horizontal meniscal tears [median age 28 years (13–40)]. The median time between the onset of symptoms and surgery was 11.5 months (6–50). In the first group (17 consecutive patients, Group 1), a standard open meniscal repair was performed. In the second group (17 consecutive patients, Group 2), the same surgical repair was performed, but platelet-rich plasma was introduced into the lesion at the end of the procedure. Clinical outcomes were evaluated using KOOS and IKDC 2000 scores. MRI was performed at 1 year after surgery for objective evaluation.

*Results* At a minimum of 24 months postoperatively (mean 32.2 months, 24–40), three patients underwent subsequent meniscectomy (two in Group 1, one in Group 2). The mean KOOS distribution (pain, symptoms, daily activities, sports, quality of life) was 78.4, 86.1, 93.8, 74.4, 74.6 in Group 1, and 93.3, 90.7, 97.1, 88.8, 78.3 in Group 2 (p < 0.05 for pain and sports parameters). MRI revealed five cases with the complete disappearance of any hypersignal within the repaired meniscus in Group 2, and none in Group 1 (p < 0.01).

*Conclusions* Open meniscal repair of horizontal tears extending into the avascular zone was effective at midterm follow-up in young patients. Clinical outcomes were slightly improved by the addition of PRP in this case–control study.

Rabago D, et al. (2015) “Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes”, *Complementary Therapies in Medicine*, 23(3):388-395

*Objective* Knee osteoarthritis (OA) is a common, debilitating chronic disease. Prolotherapy is an injection therapy for chronic musculoskeletal pain. Recent 52-week randomized controlled and open label studies have reported improvement of knee OA-specific outcomes compared to baseline status, and blinded saline control injections and at-home exercise therapy (p < 0.05). However, long term effects of prolotherapy for knee OA are unknown. We therefore assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with knee OA.

*Design* Post clinical-trial, open-label follow-up study.

*Setting* Outpatient; adults with mild-to-severe knee OA completing a 52-week prolotherapy study were enrolled.

*Intervention and outcome measures* Participants received 3–5 monthly interventions and were assessed using the validated Western Ontario McMaster University Osteoarthritis Index, (WOMAC, 0–100 points), at baseline, 12, 26, 52 weeks, and 2.5 years.

*Results* 65 participants (58 ± 7.4 years old, 38 female) received 4.6 ± 0.69 injection sessions in the initial 17-week treatment period. They reported progressive improvement in WOMAC scores at all time points in excess of minimal clinical important improvement benchmarks during the initial 52-week study period, from 13.8 ± 17.4 points (23.6%) at 12 weeks, to 20.9 ± 2.8 points, (p < 0.05; 35.8% improvement) at 2.5 ± 0.6 years (range 1.6–3.5 years) in the current follow-up analysis. Among assessed covariates, none were predictive of improvement in the WOMAC score.

*Conclusions* Prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with knee OA refractory to other conservative care.

Randelli, Pietro; Arrigoni, Paulo; Ragone, Vinbcenza; Cabitza, Paolo (2010) “Platelet Rich Plasma (PRP) in Arthroscopic Rotator Cuff Repair. A Prospective RCT Study, 2 Years Follow-up”, Presented at ICSES 2010, **Presentation**

Hypothesis: Local application of autologous PRP improves tendon healing in patients undergone arthroscopic rotator cuff repair. Study design: Prospective, randomized, controlled, double blind study; Level of evidence, 1. Considering an alpha level of 5%, a power of 80%, 22 patients for group are needed.

Materials and methods: Fifty-three patients who undergone a shoulder arthroscopy for the repair of complete rotator cuff tear, were randomly divided into two groups (block randomization procedure): a treatment group (N=26) who received an intra-operative application of PRP in combination with an autologous thrombin component and a control group (N=27). Patients were evaluated with Validated outcome score. An MRI was performed in all case at more than 1 year post-op. All patients had the same accelerated rehabilitation protocol.

Results: The two groups were omogeneous. Pain score in treatment group was lower than control group at 3, 7, 14 and 30 days after surgery (p<0,05). Strength in External Rotation (dynamometer), SST, UCLA and Constant scores in treatment group were significantly higher than control group at 3 months after surgery (SER: 31,6kg versus 2,11,3kg; SST: 8,92,2 versus 7,12,7; UCLA: 26,93 versus 24,24,9; Constant: 659 vs 57,912; p<0,05). There was no difference between the two groups after 6, 12 and 24 months.The MRI follow-up showed no significant difference in the healing rate. In the subgroup of stage 1 and 2 tears, with less retraction and more prone to the effect of a biological therapy, SER in PRP group were significant higher at 3, 6, 12 and 24 months post-op. (p<0,05).

Conclusions: The results of our study showed autologous PRP reduced pain in the first months post-op and promoted quicker healing. Long-term results of subgroups of stage 1 and 2 tears suggest PRP effectively affected cuff rotator healing.

Rees, JD, Stride, M; Scott, A (2004) “Tendons – Time to Revisit Inflammation” *Br J Sports Med* 2014;48:1553-1557.

It is currently widely accepted among clinicians that chronic tendinopathy is caused by a degenerative process devoid of inflammation. Current treatment strategies are focused on physical treatments, peritendinous or intratendinous injections of blood or blood products and interruption of painful stimuli. Results have been at best, moderately good and at worst a failure. The evidence for non-infammatory degenerative processes alone as the cause of tendinopathy is surprisingly weak. There is convincing evidence that the inflammatory response is a key component of chronic tendinopathy. Newer anti-inflammatory modalities may provide alternative potential opportunities in treating chronic tendinopathies and should be explored further.

Reurink, G; Goudswaard, GJ; Moen, MH *et al.*  (2014)“Platelet-Rich Plasma Injections in Acute Muscle Injury”, *N Engl J Med* 2014; 370:2546-2547 **Correspondence**

Platelet-rich plasma (PRP) injections are increasingly used in patients with sports-related injuries, but data from randomized trials to assess their efficacy are lacking. We performed a randomized trial to assess whether PRP was efficacious in hamstring strain, the most common acute muscle injury…

Although the 95% confidence interval still allows for a small chance that there was a clinically relevant between-group difference, our study demonstrated no benefit for intramuscular PRP injections, as compared with placebo injections, in patients with acute hamstring injuries.

Reurink, G; Goudswaard, GJ; Moen, MH *et al*. (2015) “Rationale, Secondary Outcome Scores and 1-Year Follow-Up of a Randomised Trial of Platelet-Rich Plasma Injections in Acute Hamstring Muscle Injury: the Dutch Hamstring Injection Therapy study” *Br J Sports Med* 2015;49:1206-1212. *Currently No Access*

*Background* Platelet-rich plasma (PRP) injections are an experimental treatment for acute muscle injuries. We examined whether PRP injections would accelerate return to play after hamstring injury. The methods and the primary outcome measure were published in the New England Journal of Medicine (NEJM) as ‘Platelet-rich plasma injections in acute muscle injury’ (2014). This article shares information not available in the NEJM letter or online supplement, especially the rationale behind the study and the secondary outcome measures including 1 year re-injury data.

*Methods* We performed a multicentre, randomised, double-blind, placebo-controlled trial in 80 competitive and recreational athletes with acute hamstring muscle injuries. Details can be found in the NEJM (http://www.nejm.org/doi/full/10.1056/NEJMc1402340). The primary outcome measure was the time needed to return to play during 6 months of follow-up. Not previously reported secondary outcome scores included re-injury at 1 year, alteration in clinical and MRI parameters, subjective patient satisfaction and the hamstring outcome score.

*Results* In the earlier NEJM publication, we reported that PRP did not accelerate return to play; nor did we find a difference in the 2-month re-injury rate. We report no significant between-group difference in the 1-year re-injury rate (HR=0.89; 95% CI, 0.38 to 2.13; p=0.80) or any other secondary outcome measure.

*Conclusions* At 1-year postinjection, we found no benefit of intramuscular PRP compared with placebo injections in patients with acute hamstring injuries in the time to return to play, re-injury rate and alterations of subjective, clinical or MRI measures.

Reurink, G; Whiteley, R; Tol, JL (2015) “Hamstring Injuries And Predicting Return To Play: ‘Bye-Bye MRI?’” *Br J Sports Med*;49:1162-1163. **Editorial** *Currently No Access*

Roelofs EJ, et al. (2015) “Muscle size, quality, and body composition: characteristics of division I cross-country runners.” *J Strength Cond Res*.,29(2):290-6 *Currently No Access*

The primary purpose of this study was to identify the relationship between muscle cross-sectional area (mCSA), echo intensity (EI), and body composition of Division I cross-country runners. The secondary purpose was to examine differences in these variables in athletes stratified based on stress-fracture (SFx) history. Thirty-six athletes were stratified based on sex and SFx history. A panoramic scan vastus lateralis was performed using a GE Logiq-e B-mode ultrasound. Echo intensity and mCSA were determined from the scan using a grayscale imaging software (ImageJ). Body composition measures were determined using dual-energy x-ray absorptiometry. For females, mCSA was significantly correlated with left leg lean mass (LM; R = 0.54) and EI (R = -0.57). Lean mass was significantly correlated with bone mineral density (BMD; R = 0.58) and bone mineral content (BMC; R = 0.56), whereas BMC was also correlated with leg LM (R = 0.72). For males, mCSA was significantly correlated with leg LM (R = 0.66), BMD (R = 0.50), and BMC (R = 0.54). Leg LM was significantly correlated with BMD (R = 0.53) and BMC (R = 0.77). Personal best times for males were significantly correlated with fat mass (R = 0.489) and %fat (R = 0.556) for the 10- and 5-km races, respectively. Female and male athletes with a history of SFx were not significantly different across any variables when compared with athletes with no history. These correlations suggest that more muscle mass may associate with higher BMD and BMC for stronger bone structure. Modifications in training strategies to include heavy resistance training and plyometrics may be advantageous for preventing risk factors associated with SFx reoccurrence.

Ronkainen, Noora J.; Tikkanen, Olli; Littlewood, Martin; Nesti, Mark S. (2014) “An Existential Perspective On Meaning, Spirituality And Authenticity In Athletic Careers” *Qualitative Research in Sport, Exercise and Health,* 2:253-270

This research examines athletes’ career paths and reflections of meaning in their sporting practices through an existential psychological lens. Through notions of spirituality and authenticity, we examined how competitive sport practices and bodily movement gain meaning, and often fundamentally shift meaning, in athletes’ lives. Reflective writings with a follow-up from 10 athletes were interpreted through an existential-narrative analysis. The results suggest that while the early years of sport practice are most often characterised as highly enjoyable experiences, for some, the later career development involves existential challenges such as value conflicts, losing a sense of authenticity, fear of failure and anxiety. The ways in which the participants related to their sport in mature years varied considerably from sustained love for competitive sport, to developing a personal philosophy built around learning and spirituality or disidentification from high-level performance sport. Based on the findings, we suggest several practical implications for future research and applied practice.

Rowden, A; Dominici, P; D'Orazio, J *et al.* (2015) “Double-blind, Randomized, Placebo-controlled Study Evaluating the Use of Platelet-rich Plasma Therapy (PRP) for Acute Ankle Sprains in the Emergency Department.”, *J Emerg Med.* Oct;49(4):546-51. doi: 10.1016/j.jemermed.2015.03.021. Epub 2015 Jun 3.

*BACKGROUND*: Over 23,000 people per day require treatment for ankle sprains. Platelet-rich plasma (PRP) is an autologous concentration of platelets that is thought to improve healing by promoting inflammation through growth factor and cytokine release. Studies to date have shown mixed results, with few randomized trials.

*OBJECTIVES*: To determine patient function among patients randomized to receive standard therapy plus PRP, compared to patients who receive standard therapy plus sham injection (placebo).

*METHODS*: Prospective, randomized, double-blinded, placebo-controlled trial. Patients with severe ankle sprains were randomized. Severity was graded on degree of swelling, ecchymosis, and ability to bear weight. PRP with lidocaine and bupivacaine was injected at the point of maximum tenderness by a blinded physician under ultrasound guidance. The control group was injected in a similar fashion with sterile 0.9% saline. Both groups had visual analog scale (VAS) pain scores and Lower Extremity Functional Scale (LEFS) on days 0, 3, and 8. LEFS and a numeric pain score were obtained via phone call on day 30. All participants were splinted, given crutches, and instructed to not bear weight for 3 days; at this time patients were reevaluated.

*RESULTS*: There were 1156 patients screened and 37 were enrolled. Four withdrew before PRP injection was complete; 18 were randomized to PRP and 15 to placebo. There was no statistically significant difference in VAS and LEFS scores between groups.

*CONCLUSION*: In this small study, PRP did not provide benefit in either pain control or function over placebo.

Samanta, Jo; Samanta, Ash (2014) “Quackery Or Quality: The Ethicolegal Basis For A Legislative Framework For Medical Innovation” *Journal of Medical Ethics* 2015;41:474-477

Innovative therapy is a matter of recent public interest, particularly following Lord Saatchi's Medical Innovation Bill. The purpose of the Bill is to encourage responsible innovation in medical treatment. We argue for the need to achieve a balance between the risks of medical innovation and patient safety considerations. We make the case for statutory regulation of medical innovation on the basis of responsible innovation, choice and patient-centred care. At the heart of regulation of medical innovation is care delivered by a process which is accountable, transparent and allows full consideration of all relevant matters. This paper proposes a two-stage test (to assess applicability of medical innovation as well as suitability for the choice of intervention to be undertaken). It is suggested that this model would provide safeguards for patients as well as define limits for doctors in the context of innovative therapy. Implementation and application of such therapy must be underpinned by due process and governance oversight, which could be provided through context-specific professional peer review. A combination of these ethicolegal principles would permit responsible medical innovation and maximise benefit in terms of therapy and patient-centred care.

Sampson, Steve; Smith, Jay; Vincent, Hunter *et al.* (2016) “Intra-Articular Bone Marrow Concentrate Injection Protocol: Short-Term Efficacy In Osteoarthritis” *Regenerative Medicine*  11(6), https://doi.org/10.2217/rme-2016-0081

*Aim*: Evaluate intra-articular injection of bone marrow concentrate (BMC), followed by platelet-rich plasma (PRP) injection at 8 weeks follow-up in moderate/severe osteoarthritis. Design: Single center, retrospective Case Series (n = 125).   
  
*Methods*: Bone marrow was aspirated/concentrated using a standardized technique. Patients received a single intra-articular injection of BMC, with follow-up injection of PRP at 8 weeks.   
  
*Results*: Median absolute pain reduction in all joints was five points (71.4%) on visual analog scale. Median patient satisfaction was 9.0/10, while 91.7% indicated that they would repeat the procedure and 94% said that they would recommend the procedure to a friend.   
*Conclusion*: Intra-articular injection of BMC, followed by a PRP injection, can provide short-term benefits in moderate-to-severe osteoarthritis.

Samra, DJ; Sman, AD; Rae, K *et al.* (2015) “Effectiveness of a single platelet-rich plasma injection to promote recovery in rugby players with ankle syndesmosis injury” *BMJ Open Sport & Exercise Medicine*;1:e000033. doi: 10.1136/bmjsem-2015-000033

*Aims* To determine whether a single ultrasound-guided platelet-rich plasma (PRP) injection into the anterior inferior tibiofibular ligament (AITFL) reduces the time for rugby athletes to return to function and match play following MRI confirmed ankle syndesmosis injury.

*Methods* Cohort controlled pilot study. 10 Rugby Union players were recruited during the 2014 season, and consented to receive a single autologous PRP injection into the AITFL within 14 days of MRI confirmed ankle syndesmosis injury. A historical control group included 11 comparable Rugby Union players between 2011 and 2013 who were treated conservatively with the same inclusion criteria and rehabilitation protocol as the intervention group. Participants followed a standardised rehabilitation protocol involving simple milestones for progression. Early functional tests were performed 2 weeks after the removal of the CAM (controlled ankle motion) boot. Time to return to play was recorded. Repeat functional testing occurred within 1 week of return to play.

*Results* Groups were comparable in anthropometrics, playing position and MRI injury severity. Time to return to play was significantly less in the intervention group (p=0.048). Following return to play, athletes in the intervention group showed higher agility (p=0.002) and vertical jump (p=0.001). There was a lower level of fear avoidance associated with rugby in the intervention group (p=0.014).

*Conclusions* This pilot study shows that, following ankle syndesmosis injury, a single autologous PRP injection may accelerate safe and successful return to Rugby Union, with improved functional capacity and reduced fear avoidance. It demonstrates the feasibility of a randomised controlled trial to further assess this therapy.

Sanderson, Lane M.; Bryant, Alan (2015) “Effectiveness And Safety Of Prolotherapy Injections For Management Of Lower Limb Tendinopathy And Fasciopathy: A Systematic Review”, *Journal of Foot and Ankle Research*, 8:57 DOI 10.1186/s13047-015-0114-5

*INTRODUCTION*: The aim of this review was to identify and evaluate existing research to determine the clinical effectiveness and safety of prolotherapy injections for treatment of lower limb tendinopathy and fasciopathy.

*REVIEW*: Nine databases were searched (Medline, Science Direct, AMED, Australian Medical Index, APAIS-Health, ATSIhealth, EMBASE, Web of Science, OneSearch) without language, publication or data restrictions for all relevant articles between January 1960 and September 2014. All prospective randomised and non-randomised trials, cohort studies, case-series, cross-sectional studies and controlled trials assessing the effectiveness of one or more prolotherapy injections for tendinopathy or fasciopathy at or below the superior aspect of the tibia/fibula were included. Methodological quality of studies was determined using a modified evaluation tool developed by the Cochrane Musculoskeletal Injuries Group. Data analysis was carried out to determine the mean change of outcome measure scores from baseline to final follow-up for trials with no comparative group, and for randomised controlled trials, standardised mean differences between intervention groups were calculated. Pooled SMD data were calculated where possible to determine the statistical heterogeneity and overall effect for short-, intermediate- and long-term data. Adverse events were also reported. Two hundred and three studies were identified, eight of which met the inclusion criteria. These were then grouped according to tendinopathy or fasciopathy being treated with prolotherapy injections: Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease. The methodological quality of the eight included studies was generally poor, particularly in regards to allocation concealment, intention to treat analysis and blinding procedures. Results of the analysis provide limited support for the hypothesis that prolotherapy is effective in both reducing pain and improving function for lower limb tendinopathy and fasciopathy, with no study reporting a mean negative or non-significant outcome following prolotherapy injection. The analysis also suggests prolotherapy injections provide equal or superior short-, intermediate- and long-term results to alternative treatment modalities, including eccentric loading exercises forAchilles tendinopathy, platelet-rich plasma for plantar fasciopathy and usual care or lignocaine injections for Osgood-Schlatter disease. No adverse events following prolotherapy injections were reported in any study in this review.

*CONCLUSIONS*: The conclusions of this review were derived from the best available scientific evidence. It is intended that the results of this study will assist clinical decision-making by practitioners. The results of this review found limited evidence that prolotherapy injections are a safe and effective treatment for Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease, however more robust research using large, methodologically-sound randomised controlled trials is required to substantiate these findings.

Scarpone, M; Rabago, D.; Snell, E. *et al*. (2013) “Effectiveness of Platelet-rich Plasma Injection for Rotator Cuff Tendinopathy: A Prospective Open-label Study.” *Glob Adv Health Med*. 2013 Mar; 2(2):26-31. doi: 10.7453/gahmj.2012.054. *Currently No Access*

*OBJECTIVE*: Assess platelet rich plasma (PRP) injection for rotator cuff tendinopathy (RCT).

*DESIGN*: Prospective open label study with 1-year follow-up.

*METHODS*: Participants recruited from an outpatient sports medicine clinic had clinically and magnetic resonance image (MRI)-demonstrated RCT refractory to physical therapy and corticosteroid injection. They received one ultrasound-guided injection of 3.0 mL of 1% xylocaine followed by 3.5 mL of PRP at the lesion and surrounding tendon.

*PRIMARY OUTCOME*: 0-10 visual analog scale (VAS; baseline, 8, 12, and 52 weeks).

*SECONDARY OUTCOMES*: functional shoulder tests assessing rotator cuff strength and endurance (at baseline and 8 and 12 weeks), MRI severity (1-5 points [at baseline and 4 and 8 weeks]), and patient satisfaction (52 weeks).

*RESULTS*: Eighteen participants with 19 assessed shoulders reported VAS pain score improvement from 7.5 ± 0.3 points to 0.5 ± 0.3 points by week 12 and 0.4 ± 0.2 (P = .0001) points at week 52. Functional outcomes significantly improved; the largest effect was seen in the external rotation test: 33.5 ± 5.7 seconds to 62.6 ± 7.2 seconds at week 12 (P = .0001). MRI appearance improved by 1 to 3 points in 16 of 18 assessed shoulders. Seventeen participants were "completely satisfied" (12) or "satisfied" (5). One participant was "unsatisfied."

*CONCLUSIONS*: A single ultrasound-guided, intralesional injection of PRP resulted in safe, significant, sustained improvement of pain, function, and MRI outcomes in participants with refractory RCT. Randomized multidisciplinary effectiveness trials that add ultrasound and validated clinical outcome measures are needed to further assess PRP for RCT.

Shapiro, E; Grande, D; Drakos M. (2015) “Biologics In Achilles Tendon Healing And Repair: A Review.” *Curr Rev Musculoskelet Med*. 2015 Mar;8(1):9-17. doi: 10.1007/s12178-015-9257-z.

Injuries of the Achilles tendon are relatively common with potentially devastating outcomes. Healing Achilles tendons form a fibrovascular scar resulting in a tendon which may be mechanically weaker than the native tendon. The resulting strength deficit causes a high risk for reinjury and other complications. Treatments using biologics aim to restore the normal properties of the native tendon and reduce the risk of rerupture and maximize tendon function. The purpose of this review was to summarize the current findings of various therapies using biologics in an attempt to improve the prognosis of Achilles tendon ruptures and tendinopathies. A PubMed search was performed using specific search terms. The search was open for original manuscripts and review papers limited to publication within the last 10 years. From these searches, papers were included in the review if they investigated the effects of biological augmentation on Achilles tendon repair or healing. Platelet-rich plasma may assist in the healing process of Achilles tendon ruptures, while the evidence to support its use in the treatment of chronic Achilles tendinopathies remains insufficient. The use of growth factors such as hepatocyte growth factor, recombinant human platelet-derived growth factor-BB, interleukin-6, and transforming growth factor beta as well as several bone morphogenetic proteins have shown promising results for Achilles tendon repair. In vitro and preclinical studies have indicated the potential effectiveness of bone marrow aspirate as well. Stem cells also have positive effects on Achilles tendon healing, particularly during the early phases. Polyhydroxyalkanoates (PHA), decellularized tendon tissue, and porcine small intestinal submucosa (SIS) are biomaterials which have shown promising results as scaffolds used in Achilles tendon repair. The application of biological augmentation techniques in Achilles tendon repair appears promising; however, several techniques require further investigation to evaluate their clinical application.

Singh, A.; Goel, S. C.; Gupta, K. K.; Kumar, M. *et al*. (2014) “The Role of Stem Cells in Osteoarthritis: An Experimental Study in Rabbits”, *Bone Joint Res* 2014;3:32–7.

Introduction Osteoarthritis (OA) is a progressively debilitating disease that affects mostly cartilage, with associated changes in the bone. The increasing incidence of OA and an ageing population, coupled with insufficient therapeutic choices, has led to focus on the potential of stem cells as a novel strategy for cartilage repair.

Methods In this study, we used scaffold-free mesenchymal stem cells (MSCs) obtained from bone marrow in an experimental animal model of OA by direct intra-articular injection. MSCs were isolated from 2.8 kg white New Zealand rabbits. There were ten in the study group and ten in the control group. OA was induced by unilateral transection of the anterior cruciate ligament of the knee joint. At 12 weeks post-operatively, a single dose of 1 million cells suspended in 1 ml of medium was delivered to the injured knee by direct intra-articular injection. The control group received 1 ml of medium without cells. The knees were examined at 16 and 20 weeks following surgery. Repair was investigated radiologically, grossly and histologically using haematoxylin and eosin, Safranin-O and toluidine blue staining.

Results Radiological assessment confirmed development of OA changes after 12 weeks. Rabbits receiving MSCs showed a lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis than the control group at 20 weeks post-operatively. The quality of cartilage was significantly better in the cell-treated group compared with the control group after 20 weeks.

Conclusions Bone marrow-derived MSCs could be promising cell sources for the treatment of OA. Neither stem cell culture nor scaffolds are absolutely necessary for a favourable outcome.

Singh, Ajit; Singh Gangwar, Devendra; Singh, Shekhar (2014) “Bone Marrow Injection: A Novel Treatment For Tennis Elbow” *J Nat Sc Biol Med* 2014;5:389-91

Objective: The objective of this prospective study was assessment of efficacy of bone marrow aspirate (BMA) (containing plasma rich in growth factors and mesenchymal stem cells) injection in treatment of tennis elbow. Materials and Methods: A total of 30 adult patients of previously untreated tennis elbow were administered single injection of BMA. This concentrate was made by centrifugation of iliac BMA at 2000 rpm for 20-30 min and only upper layer containing platelet rich plasma and mononuclear cells was injected. Assessment was performed at baseline, 2 weeks, 6 weeks and 12 weeks using Patient-rated Tennis Elbow Evaluation (PRTEE) score. Results: Baseline pre-injection mean PRTEE score was 72.8 ± 6.97 which decreased to a mean PRTEE score of 40.93 ± 5.94 after 2 weeks of injection which was highly significant (P < 0.0001). The mean PRTEE score at 6 week and 12 week follow-up was 24.46 ± 4.58 and 14.86 ± 3.48 respectively showing a highly significant decrease from baseline scores (P < 0.0001). Conclusion: Treatment of tennis elbow patients with single injection of BMA showed a significant improvement in short to medium term follow-up. In future, such growth factors and/or stem cells based injection therapy can be developed as an alternative conservative treatment for patients of tennis elbow, especially who have failed non-operative treatment before surgical intervention is taken.

Thibbotuwawa, Namal; Oloyede, Adekunle; Li, Tong *et al.* (2015) “Physical Mechanisms Underlying The Strain-Rate-Dependent Mechanical Behavior Of Kangaroo Shoulder Cartilage” *Appl. Phys. Lett.* 107, 103701; doi: <http://dx.doi.org/10.1063/1.4929498>

Due to anatomical and biomechanical similarities to human shoulder, kangaroo was chosen as a model to study shoulder cartilage. Comprehensive enzymatic degradation and indentation tests were applied on kangaroo shoulder cartilage to study mechanisms underlying its strain-rate-dependent mechanical behavior. We report that superficial collagen plays a more significant role than proteoglycans in facilitating strain-rate-dependent behavior of the kangaroo shoulder cartilage. By comparing the mechanical properties of degraded and normal cartilages, it was noted that proteoglycan and collagen degradation significantly compromised strain-rate-dependent mechanical behavior of the cartilage. Superficial collagen contributed equally to the tissue behavior at all strain-rates. This is different to the studies reported on knee cartilage and confirms the importance of superficial collagen on shoulder cartilage mechanical behavior. A porohyperelastic numerical model also indicated that collagen disruption would lead to faster damage of the shoulder cartilage than when proteoglycans are depleted.

Tiwari, Sashank S.; Raman, Sujatha (2014) “Governing stem cell therapy in India: regulatory vacuum or jurisdictional ambiguity?” *New Genetics and Society*, 33:4

Stem cell treatments are being offered in Indian clinics although preclinical evidence of their efficacy and safety is lacking. This is attributed to a governance vacuum created by the lack of legally binding research guidelines. By contrast, this paper highlights jurisdictional ambiguities arising from trying to regulate stem cell therapy under the auspices of research guidelines when treatments are offered in a private market disconnected from clinical trials. While statutory laws have been strengthened in 2014, prospects for their implementation remain weak, given embedded challenges of putting healthcare laws and professional codes into practice. Finally, attending to the capacities of consumer law and civil society activism to remedy the problem of unregulated treatments, the paper finds that the very definition of a governance vacuum needs to be reframed to clarify whose rights to health care are threatened by the proliferation of commercial treatments and individualized negligence-based remedies for grievances.

Vu, Thang Duc; Pal, Shripad N.; Ti, Lian-Kah *et al.* (2015) “An autologous platelet-rich plasma hydrogel compound restores left ventricular structure, function and ameliorates adverse remodeling in a minimally invasive large animal myocardial restoration model: A translational approach: Vu and Pal ‘Myocardial Repair: PRP, Hydrogel and Supplements’”, *Biomaterials* 45:27-35

*Aims* Cell-based myocardial restoration has not penetrated broad clinical practice yet due to poor cell retention and survival rates.

In this study, we attempt a translational, large-scale restorative but minimally invasive approach in the pig, aiming at both structurally stabilizing the left ventricular (LV) wall and enhancing function following ischemic injury.

*Methods and results* A myocardial infarction (MI) was created by permanent ligation of left circumflex coronary artery through a small lateral thoracotomy. Thirty-six Yorkshire pigs were randomized to receive transthoracic intramyocardial injection into both infarct and border zone areas with different compounds: 1) Hyaluronic acid-based hydrogel; 2) autologous platelet-rich plasma (PRP); 3) ascorbic acid-enriched hydrogel (50 mg/L), combined with IV ibuprofen (25 mg/kg) and allopurinol (25 mg/kg) (cocktail group); 4) PRP and cocktail (full-compound); or 5) saline (control). The latter two groups received daily oral ibuprofen (25 mg/kg) for 7 days and allopurinol (25 mg/kg) for 30 days, postoperatively. Hemodynamic and echocardiographic studies were carried out at baseline, immediately after infarction and at end-point. Eight weeks after MI, the full-compound group had better LV fractional area change, ejection fraction and smaller LV dimensions than the control group. Also, dp/dtmax was significantly higher in the full-compound group when the heart rate increased from 100 bpm to 160bpm in stress tests. Blood vessel density was higher in the full-compound group, compared to the other treatment groups.

*Conclusions* A combination of PRP, anti-oxidant and anti-inflammatory factors with intramyocardial injection of hydrogel has the potential to structurally and functionally improve the injured heart muscle while attenuating adverse cardiac remodeling after acute myocardial infarction.

Waters-Banker, C; Dupont-Versteegden, EE; Kitzman, PH; Butterfield, TA (2014) “Investigating the mechanisms of massage efficacy: the role of mechanical immunomodulation.” *J Athl Train.* 2014 Mar-Apr;49(2):266-73. doi: 10.4085/1062-6050-49.2.25. Epub 2014 Mar 18.

Massage has the potential to attenuate the inflammatory process, facilitate early recovery, and provide pain relief from muscular injuries. In this hypothesis-driven paper, we integrate the concept of mechanotransduction with the application of massage to explore beneficial mechanisms. By altering signaling pathways involved with the inflammatory process, massage may decrease secondary injury, nerve sensitization, and collateral sprouting, resulting in increased recovery from damage and reduction or prevention of pain. Our goal is to provide a framework that describes our current understanding of the mechanisms whereby massage therapy activates potentially beneficial immunomodulatory pathways.

Weimin Guo, Shuyun Liu, Yun Zhu, *et al.,* (2015 ) “Advances and Prospects in Tissue-Engineered Meniscal Scaffolds for Meniscus Regeneration” *Stem Cells International*, Article ID 517520, 13 pages, 2015. doi:10.1155/2015/517520

The meniscus plays a crucial role in maintaining knee joint homoeostasis. Meniscal lesions are relatively common in the knee joint and are typically categorized into various types. However, it is difficult for inner avascular meniscal lesions to self-heal. Untreated meniscal lesions lead to meniscal extrusions in the long-term and gradually trigger the development of knee osteoarthritis (OA). The relationship between meniscal lesions and knee OA is complex. Partial meniscectomy, which is the primary method to treat a meniscal injury, only relieves short-term pain; however, it does not prevent the development of knee OA. Similarly, other current therapeutic strategies have intrinsic limitations in clinical practice. Tissue engineering technology will probably address this challenge by reconstructing a meniscus possessing an integrated configuration with competent biomechanical capacity. This review describes normal structure and biomechanical characteristics of the meniscus, discusses the relationship between meniscal lesions and knee OA, and summarizes the classifications and corresponding treatment strategies for meniscal lesions to understand meniscal regeneration from physiological and pathological perspectives. Last, we present current advances in meniscal scaffolds and provide a number of prospects that will potentially benefit the development of meniscal regeneration methods.

Windt, Tommy S. de; Vonk, Lucienne A.; Slaper-Cortenbach, Ineke C. M. *et al.* (2016) Allogeneic Mesenchymal Stem Cells Stimulate Cartilage Regeneration and Are Safe for Single-Stage Cartilage Repair in Humans upon Mixture with Recycled Autologous Chondrons” *Stem Cells* 35(1): 256–264

Traditionally, mesenchymal stem cells (MSCs) isolated from adult bone marrow were described as being capable of differentiating to various lineages including cartilage. Despite increasing interest in these MSCs, concerns regarding their safety, in vivo behavior and clinical effectiveness have restrained their clinical application. We hypothesized that MSCs have trophic effects that stimulate recycled chondrons (chondrocytes with their native pericellular matrix) to regenerate cartilage. Searching for a proof of principle, this phase I (first-in-man) clinical trial applied allogeneic MSCs mixed with either 10% or 20% recycled autologous cartilage-derived cells (chondrons) for treatment of cartilage defects in the knee in symptomatic cartilage defect patients. This unique first in man series demonstrated no treatment-related adverse events up to one year postoperatively. At 12 months, all patients showed statistically significant improvement in clinical outcome compared to baseline. Magnetic resonance imaging and second-look arthroscopies showed completely filled defects with regenerative cartilage tissue. Histological analysis on biopsies of the grafts indicated hyaline-like regeneration with a high concentration of proteoglycans and type II collagen. Short tandem repeat analysis showed the regenerative tissue only contained patient-own DNA. These findings support the novel insight that the use of allogeneic MSCs is safe and opens opportunities for other applications. Stem cell-induced paracrine mechanisms may play an important role in the chondrogenesis and successful tissue regeneration found.

Woo, Savio L.-Y.; Abramowitch, Steven, D.; Kilger, Robert; Liang, Rui (2006) “Biomechanics of knee ligaments: injury, healing, and repair.” *Journal of Biomechanics*, 39:1-20

Knee ligament injuries are common, particularly in sports and sports related activities. Rupture of these ligaments upsets the balance between knee mobility and stability, resulting in abnormal knee kinematics and damage to other tissues in and around the joint that lead to morbidity and pain. During the past three decades, significant advances have been made in characterizing the biomechanical and biochemical properties of knee ligaments as an individual component as well as their contribution to joint function. Further, significant knowledge on the healing process and replacement of ligaments after rupture have helped to evaluate the effectiveness of various treatment procedures. This review paper provides an overview of the current biological and biomechanical knowledge on normal knee ligaments, as well as ligament healing and reconstruction following injury. Further, it deals with new and exciting functional tissue engineering approaches (ex. growth factors, gene transfer and gene therapy, cell therapy, mechanical factors, and the use of scaffolding materials) aimed at improving the healing of ligaments as well as the interface between a replacement graft and bone. In addition, it explores the anatomical, biological and functional perspectives of current reconstruction procedures. Through the utilization of robotics technology and computational modeling, there is a better understanding of the kinematics of the knee and the in situ forces in knee ligaments and replacement grafts. The research summarized here is multidisciplinary and cutting edge that will ultimately help improve the treatment of ligament injuries. The material presented should serve as an inspiration to future investigators.

Yamasaki, Shinya; Mera, Hisashi; Itokazu, Maki *et al.* (2014) “Cartilage Repair With Autologous Bone Marrow Mesenchymal Stem Cell Transplantation”, *Review of Preclinical and Clinical Studies,* 5,4

Clinical trials of various procedures, including bone marrow stimulation, mosaicplasty, and autologous chondrocyte implantation, have been explored to treat articular cartilage defects. However, all of them have some demerits. We focused on autologous culture-expanded bone marrow mesenchymal stem cells (BMSC), which can proliferate without losing their capacity for differentiation. First, we transplanted BMSC into the defective articular cartilage of rabbit and succeeded in regenerating osteochondral tissue. We then applied this transplantation in humans. Our previous reports showed that treatment with BMSC relieves the clinical symptoms of chondral defects in the knee and elbow joint. We investigated the efficacy of BMSC for osteoarthritic knee treated with high tibial osteotomy, by comparing 12 BMSC-transplanted patients with 12 cell-free patients. At 16-month follow-up, although the difference in clinical improvement between both groups was not significant, the arthroscopic and histological grading score was better in the cell-transplanted group. At the over 10-year follow-up, Hospital for Special Surgery knee scores improved to 76 and 73 in the BMSC-transplanted and cell-free groups, respectively, which were better than preoperative scores. Additionally, neither tumors nor infections were observed in all patients, and in the clinical study, we have never observed hypertrophy of repaired tissue, thereby guaranteeing the clinical safety of this therapy. Although we have never observed calcification above the tidemark in rabbit model and human histologically, the repair cartilage was not completely hyaline cartilage. To elucidate the optimum conditions for cell therapy, other stem cells, culture conditions, growth factors, and gene transfection methods should be explored.

Yong, Sang Kim; Oh, Ryong Kwon; Yun, Jin Choi *et al.* (2015) “Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis “ *The American Journal of Sports Medicine*, 43(11):2738 – 2746 *Currently No Access*

*Background*: The mesenchymal stem cell (MSC)–based tissue engineering approach has been developed to address the problem of articular cartilage repair in knee osteoarthritis (OA). However, the most effective method of MSC application has not yet been established.

*Purpose*: To compare the injection and implantation of MSCs in patients with knee OA in terms of clinical and second-look arthroscopic outcomes.

*Study Design:* Cohort study; Level of evidence, 3.

*Methods*: Among 182 patients treated with arthroscopic surgery using MSCs for knee OA from October 2010 to August 2012, patients treated with an injection of MSCs in combination with platelet-rich plasma (injection group; n = 20) were pair-matched with patients who underwent MSC implantation on a fibrin glue scaffold (implantation group; n = 20) based on sex, age, and lesion size. Clinical outcomes were evaluated using the International Knee Documentation Committee (IKDC) score and Tegner activity scale, and cartilage repair was assessed arthroscopically with the International Cartilage Repair Society (ICRS) grading system.

*Results*: The mean (±SD) IKDC and Tegner activity scores significantly improved from 38.5 ± 9.2 to 55.2 ± 15.0 and from 2.5 ± 1.2 to 3.5 ± 1.2, respectively, in the injection group and from 36.6 ± 4.9 to 62.7 ± 14.1 and from 2.3 ± 0.9 to 3.6 ± 1.1, respectively, in the implantation group at the time of second-look arthroscopic surgery (mean, 12.6 months postoperatively) (P < .001 in all cases). At final follow-up (mean, 28.6 months postoperatively), the mean IKDC and Tegner activity scores in the implantation group had improved further to 64.8 ± 13.4 and 3.9 ± 1.0, respectively (P < .001 and P = .035, respectively), while no significant improvements were found in the injection group (P = .130 and P = .655, respectively). At final follow-up, there was a significant difference in the mean IKDC score between groups (P = .049). Significant correlations between the number of administered MSCs and the postoperative clinical outcomes were found only in the injection group. Significant correlations between the clinical outcomes and the ICRS grades were found in both groups. The ICRS grades were significantly better in the implantation group (P = .041). In the injection group, 2 of the 20 lesions (10%) were grade I (normal), 5 (25%) were grade II (near normal), 8 (40%) were grade III (abnormal), and 5 (25%) were grade IV (severely abnormal). In the implantation group, 6 of the 20 lesions (30%) were grade I, 7 (35%) were grade II, 4 (20%) were grade III, and 3 (15%) were grade IV.

*Conclusion*: Utilizing the described method, MSC implantation for knee OA resulted in better clinical and second-look arthroscopic outcomes than an MSC injection.

Zhao, JG; Zhao, L; Jiang, XY (2015) “Platelet-Rich Plasma in Arthroscopic Rotator Cuff Repair: A Meta-analysis of Randomized Controlled Trials”, *Arthroscopy*. 2015 Jan;31(1):125-35. **Letter** *Currently No Access*