CPD |

Treatment option for cartilage, tendon and muscle disorders

Platelet-rich plasma in orthopedics: State of the Art

J. Enneper

Platelet-rich plasma (PRP) concentrates have become increasingly important in recent years in the treatment of disorders of the locomotor system. The great potential of PRP has also been demonstrated in impressive study results. This therapy is of particular benefit to sportsmen and women because it is a purely biological treatment which can support the regeneration of strained or damaged joints, tendons or muscles. The evidence available today indicates that intraarticular PRP injections have an anti-inflammatory and anabolic effect in both surgical and conservative treatment of osteoarthritis or cartilage damage.

Currently, various aspects of treatment with platelet-rich plasma are still under discussion, but the good clinical outcomes achieved with this therapy, given correct indication and a standardized application of the procedure, are encouraging and should stimulate further clinical research. A range of PRP preparations with different platelet (thrombocyte) concentrations are in use today.

A two-fold to three-fold PRP concentration is already sufficient to produce a significant effect on different types of tissues, according to Mazzocca et al. [27]. The critical difference between the various PRP preparations is whether PRP is produced with or without leukocytes. Moreover, platelet concentrations vary depending on the method of production used.

Platelets are the smallest blood cells **(Fig. 1)** circulating in the bloodstream. They are formed by fragmentation of megakaryocytes, have no nucleus and therefore cannot replicate themselves. They have a diameter of 2 to 4 µm and are composed of cytoplasm and vesicles. The platelets circulate for about ten days in the bloodstream and are broken down mainly in the spleen.

Platelets play a major and essential role in repairing tissues because they contain the largest reservoir of healing factors. The current literature shows that there are probably far more than 1,000 growth factors (GF) packed in the vesicles of the platelets [25] in an inactive form.

The key growth factors are:
— platelet-derived GF (PDGF)
— transforming GF Beta (TGF-ß)
— fibroblast GF (FGF)
— insulin-like-GF-1 (IGF-1)
— connective tissue GF (CTGF)
— epidermal GF (EGF)
— hepatocyte GF (HGF).

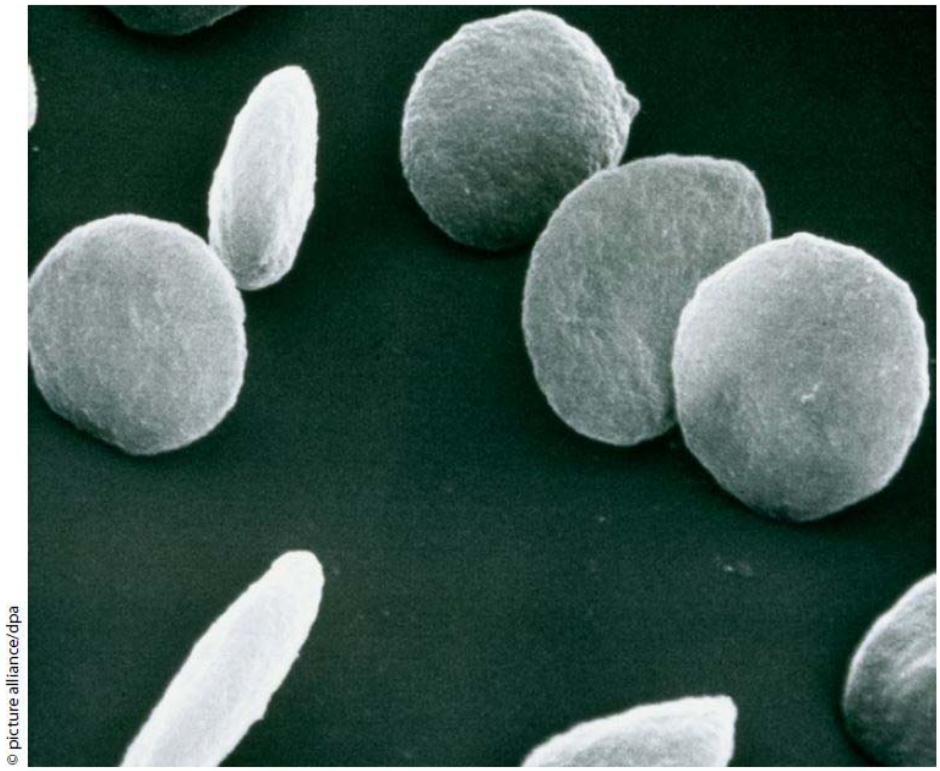

Fig. 1: Platelets under the SEM

Tab. 1: Trophic properties of PRP in cartilage lesions [25]	
1.	Interaction of the GFs: PDGF stimulates collagen synthesis; TGF-beta stimulates the matrix production of the chondrocytes, increases cell proliferation and inhibits catabolic interleukin (IL)-1); FGF stimulates different anabolic metabolic pathways.
2.	TGF-beta and FGF stimulate the chemotactic migration of mesenchymal stem cells (MSC) and subchondral progenitor cells.
3.	GFs generally promote the proliferation rate and differentiation of MSCs.
4.	Anti-inflammatory properties.
5.	IGF-1 may also inhibit or regulate cell apoptosis by means of a downregulation of the programmed cell death protein 5.

In addition, the vesicles contain micro-ribonucleic acids (RNA) which are involved in mesenchymal tissue regeneration. It is assumed that some of these RNAs, for example micro-RNA 23b, are involved in the differentiation of stem cells to chondrocytes. There are indications that micro-RNA 210 supports the healing of ligaments. In addition, activated platelets have anti-inflammatory properties, enabling tissue healing to be modulated and promoted [25]. This property could play a pivotal role in the treatment of joint lesions. It is widely known that an appropriate level of inflammation is essential for tissue regeneration. A reduction in synovial inflammation would therefore also lead to a reduction in the matrix metalloproteinases, which can otherwise attack and destroy the cartilage matrix. The trophic properties of PRP are summarized in **Tab. 1**.

Production of PRP

PRP products should contain a concentration of platelets at least two to three times greater than native blood. They can be produced in a number of different ways:

— Single spinning: A certain amount of whole blood (for example 15 ml) is centrifuged for five minutes at about 1,500 rpm. This produces a concentration of platelets three times the baseline. Moreover, the supernatant plasma is leukocyte-depleted.
— Double spinning: A PRP concentration of up to eight times the baseline can be produced, although with a high proportion of leukocytes.
— Blood filtration and plateletpheresis:
  This produces a high proportion of PDGF with few leukocytes, but the production costs are very high.

Normally, leukocyte-poor or leukocyte-rich PRP products are used in clinical practice.

— Pure PRP (P-PRP, leukocyte-poor) can be injected intraarticularly as a liquid solution or applied as a gel to a skin wound. The use of P-PRP ensures the desired effects of synovial modulation and, if required, the chondrocytic build-up of the cellular matrix.
— Leukocyte-rich PRP (L-PRP) is preferably used intraoperatively as a gel or injected in liquid form to treat cartilage damage or for cosmetic indications.

The use of leukocytes has aroused controversy because of the release of proinflammatory mediators, proteases and reactive oxygens, which can lead to a temporary inflammatory response. On the other hand, anabolic cytokines such as the IL-6 which have an anti-inflammatory effect are also released by peripheral monocytes. Generally speaking, a high proportion of leukocytes is associated with antibacterial activity. It has been demonstrated that L-PRP has a negative effect on the growth of staphylococci and Escherichia coli. In clinical use, however, more undesired side effects have been described after intra-articular injections. An antibacterial effect was also demonstrated for a leukocyte-poor PRP product [14].

The platelets can be activated by thrombin or $CaCl_2$, or simply mechanically by the injection process itself. Once activated, the platelets evacuate about 70% of all GFs in the first ten minutes: after an hour the evacuation is complete. Under certain circumstances, however, the release of GF may be delayed for up to seven or eight days. The PDGFs are first absorbed and then re-released from a fibrin mesh. The amount of GF released depends on the amount of fibrin in the area where the platelets act. The fibrin concentration and structure influence the release of GF from the vesicles of the platelets [25] via various enzymatic effects. This may explain the different mode of action of PRP at different locations in the locomotor system. All in all, the literature over the past ten years gives clear indications that PRP has a real effect on the repair of cartilage lesions and the treatment of osteoarthritis (OA) [25].

PRP injections for cartilage lesions

The anti-inflammatory and regenerative potential of PRP in the conservative treatment of degenerative cartilage damage and osteoarthritis in people has been the subject of many studies in the literature. There are discussions in the literature about promising results of in vitro and clinical studies with different levels of evidence. Some results were summarized by Khoshbin et al. [19] in 2013. Patel et al. [29] showed that PRP treatments are more effective than placebos.

Positive effects with a PRP treatment were achieved in various case studies and comparative studies using different protocols. These range from a reduction in pain to a complete remission of symptoms. The most frequent side effects reported were swelling and pain directly after an injection, which went away, however, after a few hours without diminishing the positive effect of the PRP [20, 21, 22, 25].

261 patients with OA of the knee **(Fig. 2)** were treated with P-PRP in a large study by Wang-Saegusa et al. [36]. The study participants were given three intraarticular injections at two-week intervals. The results after six months showed an improvement in all four scores used (visual analog scale [VAS], Western Ontario and McMaster Universities Arthritis Index [WOMAC], Health Physical Parameters, Leseque Algofunctional Index).

91 patients with chondropathy were treated by Kon et al. [20, 21]. They used L-PRP (three intraarticular injections administered at one-week intervals). In a follow-up after twelve months, 80% of the patients had improved scores on the International Knee Documentation Committee (IKDC) scale and on the VAS. This study illustrated for the first time two key aspects of PRP treatment: poorer results for older patients and a deterioration of results six months after treatment. In addition, the study showed poor results were achieved with female patients with a higher body mass index (BMI). Other authors described similar results. They showed that there was a drop in the evaluated scores 12 to 14 months after treatment with PRP, although a positive effect could still be observed. Various clinical parameters (for example VAS) were still improved up to 24 months after treatment compared with the baseline values. This observation suggests that PRP reduces synovial membrane hyperplasia in arthritic joints and modulates cytokines over the long term. From this it may be possible to deduce a long-term chondroregenerative and protective effect. Braun et al. [3] showed that L-PRP had a rather toxic effect on the synovial cells.

In 2013 Harpern et al. [13] observed pain reduction and a functional improvement (VAS and WOMAC) in 15 patients with low-grade gonarthrosis (osteoarthritis of the knee) 6 to 12 months after treatment with PRP. In addition, they established during MRI monitoring that no further cartilage degeneration occurred in 73% of the patients. Gobbi et al. [12] evaluated a group of patients over two years and recorded that a clear reduction of pain and improvement of functionality could be achieved if the treatment was repeated after one year.
In the case series, PRP seems to improve knee function and the quality of life in patients with chondropathy or OA **(Fig. 3)** [17]. This can be explained by the reduction in inflammation of the synovial membrane, and the modulation of the degeneration process associated with that, and possibly an improved gliding capacity of the joint partner [31].

To summarize [25], the optimal conditions to ensure the success of PRP are:

— Young patients
— Male
— A low BMI
— Low degree of cartilage degeneration
— Repeat of the treatment after about twelve months.

In various studies, the effect of PRP was compared with that of viscosupplementation (hyaluronic acid [HA]) or corticosteroid injections. One of the first comparative studies was carried out by Sanchez et al. in 2008 [32]. The effect of three P-PRP infiltrations with low molecular weight hyaluronic acid was investigated in these studies at a brief follow-up. There was an improvement in the WOMAC and the VAS score in the PRP group just five weeks after the third infiltration. There was only a slight improvement in scores in the control group.
L-PRP was then compared with low molecular (LMW) and high molecular (HMW) HA in complex multicenter studies [20, 21, 22]. No differences were ascertainable two months after treatment. The worst results were obtained with the HMW-HA. Six months after the end of treatment, the authors were able to describe a clearly positive effect in the PRP group. In this study too, younger patients with a lesser degree of cartilage damage benefited from the treatment, as shown by the results of the VAS and the IKDC scores. Patients with advanced osteoarthritis showed an average response to treatment with PRP.

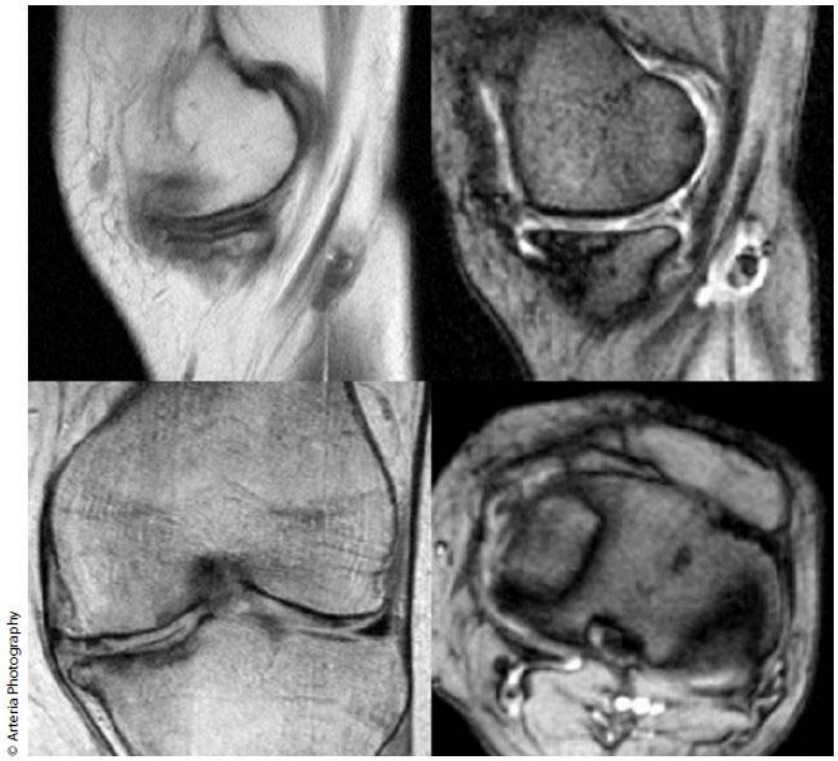

Fig. 2: MRI images of gonarthrosis

Fig. 3: The knee joints of footballers such as Sami Khedira have to withstand a great deal of stress and strain. This frequently results in long-term damage such as arthrosis.

On the other hand, the results in the LMW-HA group with advanced OA were substantially worse [5].

The results of these comparative studies confirm the results of studies that are already available. The length of treatment, the patient's age and the degree of arthrosis affect the results of the studies [8]. PRP is shown to be superior to HA [5]. To summarize, PRP offers the following benefits:

— PRP injections have a positive effect on patients with knee joint degeneration and OA.
— PRPs have a more pronounced and sustained effect than HA or a placebo in terms of reducing pain and improving function.
— The beneficial effect of PRP is still temporary. It can, however, be assumed that its positive effect will last on average for about twelve months, with the peak effect occurring about six months after the last infiltration.

With PRP it should always be borne in mind that a positive effect can only be achieved with correct indication and technically correct application.

A subject of ongoing discussion is the question whether PRP can be re-administered with the same effect one year after the end of the treatment, irrespective of the PRP infiltrations previously administered. Equally, the administration regime has not yet been precisely defined [25]. In the studies, three applications are administered in most cases. At clinical centers the patients are given 5-6 PRP infiltrations. A secondary cartilage protective effect is also currently under discussion. No anabolic effect of the cartilage tissue following administration of PRP has yet been demonstrated by MRI scans, although there are preclinical indications of cartilage matrix regeneration [16].

Good results with PRP treatments can be achieved with standardized procedures and technical support. In practice it is helpful to make preparations for treatment one day in advance. The materials should be assembled for each individual patient so that, as far as possible, all the materials are to hand on the day of treatment. Technical support in the form of ultrasound, for example, is available for the treatment of tendons. Radiologically assisted infiltrations are particularly effective in treating facet joints of the spinal column or the hip joint.

Effect of PRP on joint diseases

Shoulder

Both subacromial and intraarticular infiltration of the shoulder with PRP supports the healing process in various diseases of the shoulder. Repeated applications of PRP can have a positive effect on chronic bursitis, osteoarthritis of the shoulder as well as very therapy-resistant cases of idiopathic adhesive capsulitis (frozen shoulder). The intra- or post-operative results of PRP infiltrations following reconstruction of the rotator cuffs are so far rather heterogeneous. There are, however, slight indications of a lower re-rupture rate [15].

In a comparative study in 2015 (single dose of PRP versus cortisone infiltration), Von Wehren et al. [37] were able to show that, in the case of a rotator cuff rupture, the results in the PRP group were significantly better than those of the cortisone group twelve weeks after the injection. Cortisone only has a short term effect. PRP, on the other hand, alleviates pain for a more prolonged period.

Elbows

Disorders of the elbow can be caused by many factors. Detailed diagnostic investigations are essential in order to achieve good outcomes. Occasionally, disorders of the elbow are also combinations of clinical pictures of different origins (for example, radial epicondylitis with irritation of the radiohumeral joint). Differential diagnosis also indicates a neurogenic cause of pain as a possibility. With radial epicondylitis, as with all diseases of the tendons, attention should be paid to the structure of the tendon (partial rupture, tendinopathy, peritendinitis etc.). Ultrasound-assisted infiltration of the gliding tissue with PRP has proved its worth in treating peri-tendinopathies. If the tendon is already damaged, techniques using several needles can be helpful.

In 2014 Teschke et al. [34] compared the effect of three PRP injections with that of twelve laser applications in treating chronic lateral epicondylitis (tennis elbow). There was a significant improvement in symptoms in both groups. However, the application of PRP is a comparatively simple therapy option.

In a retrospective comparative study of PRP versus surgery in 2015, Ford et al. [10] found that both treatment methods produced comparable results in the treatment of lateral epicondylitis. PRP can be a good alternative to surgery in the treatment of epicondylitis involving considerably fewer risks.
In 2015 Lebiedzinski et al. [23] carried out a comparative study of injections with PRP versus betamethasone used to treat lateral epicondylitis. They described how betamethasone alleviated the symptoms more quickly but PRP alleviated them for a long period (twelve-month follow-up) and therefore had a substantially more sustained effect than cortisone.

Hip joint

Both coxarthrosis (osteoarthritis of the hip) in a young patient as well as different forms of impingement syndrome can be a good indication for a PRP treatment. A radiology- or ultrasound-assisted infiltration technique can have a positive effect on the treatment results because there is a greater degree of certainty that the needles have been correctly positioned.
In 2013 Battaglia et al. [2] carried out a comparative study with HA and PRP on 100 patients with symptomatic hip arthrosis. Each of the study participants received a total of three intraarticular injections at two-week intervals. Both HA and PRP had an analgesic effect. Rafols et al. [30] found that 57 patients (PRP versus control) experienced less pain and effusion than the control group six months after a PRP injection administered at the end of the hip arthroscopy procedure.

Knee

PRP treatment of the knee joint has already been described in detail. The latest results in the literature [25] also give reason to hope that PRP is a very good treatment option for a young patient with OA or moderate cartilage damage. In advanced arthrosis, PRP therapy alleviates the patients' symptoms considerably [5]. For example, Campbell et al. [4] in 2015 reported that PRP can alleviate symptoms for up to twelve months and that better outcomes are achieved in patients with slight degenerative changes. In a comparative study, Cerza et al. [5] found that PRP is superior to HA.

HA infiltration had no effect in grade-three gonarthrosis. According to this study, the effect of ACP is almost independent of the grade of arthrosis.

Patellar tip syndrome

The therapy of patellar tip syndrome can be a protracted process. In most cases a combination of balneophysical therapy and physiotherapy is recommended. In addition, a personal training regime and advice is necessary for sportsmen and women. The local application of PRP provides effective support to the healing of the bradytrophic tissue.

There are two good approaches for infiltration:

— transligamentous (direct, intralesional position of the needle, with support of the healing process by direct needling, if necessary).
— lateral infiltration (ultrasound-assisted for positional control of the needle. Caution must be exercised: hoffitis may develop!)

In 2013, Filarado et al. [9] reported good results in 43 patients after three ultrasound-controlled PRP injections directly into the defect site of the patellar tendon. There was an improvement in the activity score after 2, 4 and 6 months. 80% of the patients were satisfied and resumed their normal sporting activities. The outcomes were better in patients with fresh injuries than those with chronic lesions.

However, Charousset et al. [6] achieved significantly good outcomes in 2014 after one and three months in 28 patients with chronic patellar tendinopathy after administering three PRP injections at weekly intervals. There was a significant reduction in pain together with a significant improvement in function. After a brief period of rehabilitation, the patients were soon able to resume their sporting activities. MRI monitoring revealed regenerated tendon structures following treatment.

Achilles tendon

Injuries to the Achilles tendon are frequently observed in patients participating in sporting activities. Chronic stress syndromes can lead to inflammation of the paratenon (gliding tissue) or to remodeling processes in the tendon itself. Equally, ruptures of the Achilles tendon occur on sudden exposure to a high degree of force. The Achilles tendon is rather bradytrophic and regenerates slowly. Different therapy approaches can be helpful depending on the tendon lesion.

Peritendinous administration of PRP can support the healing process if the paratenon is inflamed. If the tendon is damaged, an intratendinous infiltration may also be necessary.

The results from studies are heterogeneous. This is possibly due to different therapy programs or infiltration techniques. For example, in a study conducted in 2012 with 26 patients with Achilles tendinopathy, Deans et al. [7] described a statistically significant improvement in terms of pain and other symptoms as well as sporting activities six months after a once-only PRP injection and an extensive training program.

In 2013, Mautner et al. [26] administered ultrasound-assisted injections of PRP to 180 patients with Achilles tendon disorders. 60% of the participants were given one, 30% two and 10% three or more PRP infiltrations. Six months after the end of treatment, 75% of the patients had less pain (VAS), 95% no pain at rest and 68% no pain during sporting activities. The clinical results are considerably better if the PRP infiltrations are administered with the assistance of ultrasound **(Fig. 4)**.

Fig. 4: Ultrasound-assisted PRP infiltration into the Achilles tendon.

Spinal column

Initial results of the treatment of the spinal column with PRP are promising. Degenerative diseases, in particular, are good indications for this treatment option. Treatment with PRP may also have a positive effect on radiculopathies. Radiology- or ultrasound-assisted infiltration techniques can improve treatment outcomes.

In a study carried out in 2015, Tuakli-Wosornu et al. [35] administered PRP infiltration (intradiskally versus contrast agent) to 47 patients with chronic pain in the lumbar spine. A significant improvement in function and a reduction in pain was achieved eight weeks up to a year after treatment.

Muscle injury

As a rule, muscle injuries heal very well. Rehabilitation measures vary depending on the degree of severity of the injury. Measures to assist the healing process are, however, frequently in demand in the field of sport. The infiltration of PRP to treat muscle injuries supports the healing process biologically. In practice 3 to 4 intralesional infiltrations have been found to be effective in supporting the muscle healing process. As a general rule, a local anesthetic should not be used. Presumably, the pH of the tissue would otherwise change, preventing the platelets from being activated. In 2015 Andia et al. [1] described a low level of evidence of improvement in muscle healing after PRP treatment. Kelc et al. [18] also achieved comparable results. In practice the symptoms can be alleviated during the acute phase of the injury and healing appears to be accelerated in the initial healing phases. Nevertheless, sportsmen and women must be closely monitored to ensure that the musculature does not re-rupture during a period of subjective wellbeing.

PRP and cartilage operations

The supporting effect of PRP in intra- and/or post-operative application in the course of cartilage operations has already been documented in in vitro and in preclinical studies. PRP has been used with the microfracture technique to promote cartilage regeneration. Milano et al. [28] demonstrated convincing results in sheep, while Lee et al. [24] have validated the results on humans in a randomized study. The effect of L-PRP on cartilage defects up to 4 mm was investigated in patients over the age of 40. L-PRP was injected into the areas of the microfractures after draining the arthroscopic fluid. The results were convincing and the authors propose the combination of L-PRP and microfracture as a standard procedure. Supporting scaffolds impregnated with PRP also support the healing process in the treatment of more major cartilage damage.

Giannini et al. [11] achieved promising results. They used a scaffold, made of bone marrow concentrate harvested from the iliac crest, in combination with a P-PRP gel to cover the cartilage defect.

Comparable applications by various authors demonstrated an improvement in the cartilage postoperatively and also by MRI scans. The bone marrow/P-PRP gel method is an interesting alternative in the treatment of larger osteochondral defects, and not on cost grounds alone.

The application of PRP can also be helpful in cruciate ligament surgery. In the treatment of a partial rupture of the anterior cruciate ligament, microfracture followed by intraoperative infiltration into the proximal cruciate ligament stump supports cicatrization. Good results are also achieved in the postoperative stability measurement with a KT-1000, given narrowly defined indication.

Conclusion

PRP therapy is a fascinating biological therapy option [25] in the field of regenerative medicine. Promising results are documented in the literature both in in vitro and in preclinical studies. However, further studies are necessary in order to strengthen general guidelines and recommendations. Both high-quality studies and the creation of registries will help to determine the optimum use of PRP in the surgical and non-surgical management of cartilage, tendon or muscle injuries. Modulations of PRP by other substances will be of value as a future option. Terada et al. [33] are researching the combination of PRP with losartan in order to improve muscle healing. The combination of VEGF antibodies and PRP appears to support cartilage regeneration noticeably. In this treatment, anti-VEGF is injected intravenously and PRP locally [25]. The systemic administration of G-CSF (supports stem cell mobilization) in combination with PRP may also be helpful for cartilage regeneration [25]. However, such methods require a very accurate preclinical and clinical evaluation.

Literature

www.springermedizin.de/orthopaedie-und-rheuma

Dr. med. Jens Enneper
Orthopädie und Sport
Kirchweg 2 a
50858 Cologne

Orthopädie und Rheumatologie, Springerverlag, 2015 18 (6)

Platelet-Rich-Plasma in der Orthopädie: „State of the Art"

J. Enneper

Literatur

1. Andia L et al.: Expert OpinBiolTher. 2015 Jul;15(7):987-99. doi: 10.1517/14712598.2015.1038234. Epub 2015 Apr 20.
2. Battaglia M et al.: Orthopedics. 2013 Dec;36(12):e1501-8.
3. Braun J. et al.: Am J Sports Med published online March 14, 2014. doi: 10.1177/0363546514525593
4. Campbell KA et al.: Arthroscopy. 2015 May 29. pii: S0749-8063(15)00353-9. doi: 10.1016/j.arthro.2015.03.041.
5. Cerza F et al.: Am J Sports Med. 2012 Dec;40(12):2822-7. doi: 10.1177/0363546512461902. Epub 2012 Oct 25.
6. Charousset C et al.: Am J Sports Med. 2014 Apr;42(4):906-11. doi: 10.1177/0363546513519964. Epub 2014 Feb 11.
7. Deans VM et al.:J Foot Ankle Surg. 2012 Nov-Dec;51(6):706-10. doi: 10.1053/j.jfas.2012.06.009. Epub 2012 Jul 21.
8. Filardo G et al.: BMC MusculoskeletDisord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229.
9. Filardo G et al.: Int Orthop. 2013 Aug;37(8):1583-9. doi: 10.1007/s00264-013-1972-8. Epub 2013 Jun 23.
10. Ford RD et al.: Hand (N Y).2015 Jun;10(2):285-91. doi: 10.1007/s11552-014-9717-8.
11. Giannini S et al.: Am J Sports Med. 2013 Mar;41(3):511-8. doi: 10.1177/0363546512467622. Epub 2012 Dec 5.
12. Gobbi A et al.: Knee Surg Sports TraumatolArthrosc. 2015 Aug;23(8):2170-7. doi: 10.1007/s00167-014-2987-4. Epub 2014 Apr 20.
13. Halpern B et al.: Clin J Sport Med. 2013 May;23(3):238-9. doi: 10.1097/JSM.0b013e31827c3846.
14. Intravia J. et al.: Muscles, Ligaments and Tendons Journal 2014; 4 (1): 79-84
15. Jo CH et al. Am J Sports Med. 2013 Oct;41(10):2240-8. doi: 10.1177/0363546513497925. Epub 2013 Aug 6.
16. Ji Liu et al.: MD PLOS one 2014
17. Kanchanatawan W. et al.: Knee Surg Sports Traumatol Arthrose doi 10.1007/s00167-015-3784-4
18. Kelc R et al.: Injury. 2015 Feb;46(2):428. doi: 10.1016/j.injury.2014.12.010. Epub 2014 Dec 16.
19. Khoshbin A et al.: Arthroscopy. 2013 Dec;29(12):2037-48. doi: 10.1016/j.arthro.2013.09.006.
20. Kon E et al.: Arthroscopy.2011 Nov;27(11):1490-501. doi: 10.1016/j.arthro.2011.05.011. Epub 2011 Aug 10.
21. Kon E et al.: Knee Surg Sports TraumatolArthrosc. 2011 Apr;19(4):516-27. doi: 10.1007/s00167-010-1306-y. Epub 2010 Nov 17.

22. Kon E et al.: Open Orthop J. 2013 May 3;7:120-8. doi: 10.2174/1874325001307010120. Print 2013.
23. Lebiedziński Ret al.: IntOrthop. 2015 Jul 30.
24. Lee GW et al.: Eur J OrthopSurgTraumatol. 2013 Jul;23(5):581-7. doi: 10.1007/s00590-012-1038-4. Epub 2012 Jul 5.
25. Marmotti A et al.: Biomed Res Int. 2015;2015:542502. doi: 10.1155/2015/542502. Epub 2015 May 5.
26. Mautner K et al.: 2013 Mar;5(3):169-75. doi: 10.1016/j.pmrj.2012.12.010. Epub 2013 Feb 9.
27. Mazzocca AD et al.: Am J Sports Med. 2012 Aug;40(8):1742-9. doi: 10.1177/0363546512452713. Epub 2012 Jul 16.
28. Milano G et al.: Osteoarthritis Cartilage. 2010 Jul;18(7):971-80. doi: 10.1016/j.joca.2010.03.013. Epub 2010 Apr 28.
29. Patel S et al.: Am J Sports Med. 2013 Feb;41(2):356-64. doi: 10.1177/0363546512471299. Epub 2013 Jan 8.
30. Rafols C et al.: Arthroscopy. 2015 Oct; 31(10):1886-92. doi: 10.1016/j.arthro.2015.03.025. Epub 2015 May 15.
31. Sakata R. et al.: AJSM PreView, published on March 26, 2015 as doi: 10.1177/0363546515575023
32. Sánchez M et al.: ClinExpRheumatol. 2008 Sep-Oct;26(5):910-3.
33. Terada S et al.: J Bone Joint Surg Am. 2013 Jun 5;95(11):980-8. doi: 10.2106/JBJS.L.00266.
34. Tetschke E et al.: Am J PhysMedRehabil. 2015 Sep;94(9):696-706. doi: 10.1097/PHM.0000000000000234.
35. Tuakli-Wosornu YA et al.: PM R.2015 Aug 24. pii: S1934-1482(15)00971-5. doi: 10.1016/j.pmrj.2015.08.010.
36. Wang-Saegusa A et al.: Arch Orthop Trauma Surg. 2011 Mar;131(3):311-7. doi: 10.1007/s00402-010-1167-3. Epub 2010 Aug 17.
37. Wehren von L et al.: Knee Surg Sports Traumatol Arthrosc. 2015 May 28.