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Biological treatment options in knee disorders

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Many options for the treatment of knee injuries have evolved during the last decades. Joint preservation through the activation of biology is the aim of current treatment strategies, with rising numbers of options. Varying preferences regarding the ideal method of treatment are seen. This article highlights the common treatment options of traumatic knee injuries, with emphasis on the anterior cruciate ligament, meniscus and cartilage.

KEY WORDS: Meniscus - Cartilage - Knee.

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Treatment options of knee disorders are being controversially discussed. This article summarizes current therapeutic strategies, highlighting the pros and contras of the various procedures, with focus on meniscal tears, cartilage defects and ACL ruptures. For ACL ruptures, reconstruction methods are present the gold-standard. Since many recent reports proved an excellent intrinsic healing capacity of the ACL, a reflection on clinical practice is being experienced and initial reports of successful results are starting to be published.

All the surgical treatment options aim at both initially restoring joint stability and function and reducing osteoarthritic risk in the long-term.

This article should provide an overview of current treatment options with an insight on future prospectives.

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Meniscal tears

Meniscal tears are common injuries resulting either primarily from degenerative changes or due to trauma.

Risk factors for degenerative meniscal tears are age (>60 years), gender (male), work-related kneeling and squatting, and climbing stairs (>30 flights).[1] In addition, chronic knee instability or malalignement can lead also to degenerative meniscal tears.

Risk factors for acute meniscal tears are sport activities such as soccer and rugby.[1] A study evaluating the incidence, risk, amount of time lost and effect on performance after isolated meniscal injury in athletes from the National Baketball Association (NBA) showed that the lateral meniscus is more often injured than the medial. In addition, the risk of tears was increased in players having a BMI >25.[2] Epidemiologically, medial meniscus posterior root tears (MMPRT) show an association with age, female gender, high BMI, greater varus mechanical axis angle and lower sports activity level compared

to individuals with other types of meniscal tears (Hwang *et al.*, 2012).

There are different lesion patterns in a symptomatic knee with meniscal injury. The clinically relevant patterns in a painful knee involving the meniscus are radial, vertical, complex or displaced meniscal tears and abnormalities of the collateral ligaments, pericapsular soft tissues and bone marrow.[3] Furthermore, meniscal injuries are often associated with anterior cruciate ligament (ACL) tears.[4]

The diagnosis is set clinically, as evidence has shown that with the radiological diagnostic tools (*e.g.*, MRI) it is not possible to have the absolute certainty of make a correct diagnosis in case of meniscal lesions.[5]

Conservative treatment

Meniscal tears are described by location and shape and are divided into the vascular and avascular zones (the red, red-white and the white zone). Zones are further divided into thirds both longitudinally and radially.[6]

The majority of meniscal tear patterns can be treated surgically. In some cases where no immobilization leads to pain relief with no signs of locking, conservative treatment involving physical therapy focusing on closed chain exercise of quadriceps and hamstrings could provide an option. There are no randomized trials comparing conservative therapy to surgical treatment of acute meniscal tears, however cohort studies showed considerable healing rates amongst patients treated conservatively.[7]

Resection

For many years total meniscectomy was a commonly performed procedure which was thought to have excellent results. In 1949 Fairbank described the potential damaging effects of total meniscectomy, this procedure is no longer performed nowadays.[8]

To avoid secondary damage after the total meniscectomy, partial meniscectomy is recommended when repair is not possible. Rosenberg *et al.* described general guidelines when a partial meniscectomy should be performed. All mobile sections that can be pulled past the inner margin of the meniscus into the center of the joint should be resected.[9]

A recently published study in the New England Journal of Medicine (NEJM) compared arthroscopic partial meniscectomy *versus* sham surgery for degenerative meniscal tears in a multicenter, randomized, double-blind, sham-controlled trial. The study showed that the outcomes after arthroscopic partial meniscectomy were no better than those after a sham surgical procedure in patients between 35 and 65 years of age without knee osteoarthritis; results that caused heavy debate in the orthopedic community.[10]

Repair and suture techniques

The indications to perform a meniscal repair include the following factors:[11]

— tear >1 cm and <4 cm in length;
— red-red zone tears;
— vertical tears;
— patient age <40 years;
— no mechanical axis malalignment;
— acute tears (*i.e.*, <6 wk);
— concurrent anterior cruciate ligament reconstruction.

The vascular supply plays a significant role in the outcome after a meniscal repair. Highest healing rates were reported in repaired tears within 2 mm of the meniscal vascular rim whereas tears lying >4 mm from the rim have a high failure rates following repair. Tears in the white zone are commonly resected, as it is not vascularized and healing is not possible. Repair techniques can be performed as inside-out, outside-in, all-inside or a combination of these techniques.

In the inside-out technique sutures are inserted into the meniscus arthroscopically, the needles with suture attached then are passed on either side of the tear through the meniscus, then out the knee through the capsule. An incision is made in the skin at the meniscus level, and the sutures are tied down to the capsule. The inside-out suturing was the first technique used for arthroscopic repair.

The outside-in techniques passes sutures through the meniscus from the outside, thus avoiding the more extensive incisions and retractions involved inside-out repairs. Outside-in repairs are largely limited to anterior portions of the medial and lateral menisci.

The inside-out or outside-in repair techniques are often used for tears within the intermedial portion or anterior horn of the meniscus. To perform this type of meniscal repair, an additional skin incision is needed with the occasional risk of creating neurovascular complications, usually involving the infrapatellar branch of the saphenic nerve, and postoperative stiffness.[12]

The gold-standard today, in the meniscus repair, represents the all-inside technique. This technique reduces surgery time and does not require an additional approach which eliminates the risk of iatrogenic neurovascular lesion.

The feasibility of the all-inside technique, especially in repairing the posterior horn of the lateral meniscus, have recently been confirmed using standard anteromedial and anterolateral portals.[13]

The all-inside-technique provides excellent results in the long-term.[14] No significant differences in meniscal healing between the all-inside comparing to the inside-out technique could have been demonstrated.[12]

Comparing meniscal repair with meniscectomy, it has been shown that meniscal repairs have a higher reoperation rate than partial meniscectomies, but the long-term outcome is better in patients treated with menical repair.[15]

Allograft

An alternative treatment option for a massive meniscal tears is meniscus allograft transplantation (MAT). The procedure is constantly gaining popularity and was shown to be effective, with success rates reaching 80% in young patients aged less than 45 according to Cole.[16, 17] The effectiveness of the procedure in older patients is currently questioned and further studies are necessary.[17]

In contrast, a study published in *The American Journal of Sports Medicine* finds a 32% reoperation rate for meniscal allograft transplantation (MAT) at mean 5-year follow-up (minimum 2 years). Simple arthroscopic debridement was the most common subsequent surgical treatment, performed. Overall, eight of the 172 patients (4.7%) eventually required either revision MAT or total knee arthroplasty. Patients who required secondary surgery within 2 years had an odds ratio of 8.4 for future arthroplasty or MAT revision.[18]

Another alternative option that has gained considerable attention is collagen or polyurethane graft implantation. Studies showed that biodegradable, polyurethane scaffolds could be utilized for the treatment of patients with painful irreparable partial meniscal defects successfully.[19] The acellular polyurethane scaffold showed consistent meniscus-like regeneration of tissue.[20]

A 10-year-follow up study by Zaffagnini *et al*. showed that pain, activity level and radiological outcomes with a collagen implant of the medial meniscus are significantly improved compared to partial meniscectomy, supporting meniscus-like matrix production and the integration of the implant.[21, 22] In addition, safety and effectiveness of the procedure has been confirmed;[23] the polyurethane graft implantation seems to become an established procedure.

Future aspect

Finally, PRP is becoming popular in acute or chronic soft tissue injury. Although the field is widely unexplored, current literature suggests that PRP as a biological boost can be applied on meniscal tears in the avascularized zone [24] even though tears in the avascularized zone are commonly resected due to non-healing.

Cartilage defects treatment options

Cartilage defects are a well known problem in the field of orthopedic medicine, causing variety of symptoms causing from

pain to joint stiffness and ultimately ending in osteoarthritis.

Several treatment options exist including: microfracturing, osteochondral autogenous transplantation system (OATS) autologous matrix induced chondrogenesis (AMIC) autologous chondrozyte transplantation (ACT) osteochondral).

Microfracturing – The gold standard?

The goal is to activate biology by inducing migration of potential repair cells into the chondral or osteochondral defect. This could allow for the generation of fibrocartilage in the defect region. This regenerated tissue is mostly composed of collagen type 1, compared to healthy cartilage tissue which is mostly [25] composed of collagen type 2. The difference in composition of fibrocartilage is reflected in its characteristics regarding stiffness, wear, and detoriation over time, which are known to be inferior to hyaline cartilage for the knee joint.[26]

An 11-year follow up by Steadman *et al.* showed that patients 45 years and younger who underwent the microfracture procedure for full-thickness chondral defects, without associated meniscus or ligament pathology, showed statistically significant improvement in function and indicated that they had less pain.[27]

This procedure provides the benefits of being simple, quick to perform and cheap; its effectiveness is, however, questioned for lesions larger than 3 cm^2 in size.[28]

The osteochondral autogenous transplantation system (OATS) is a further option based on harvesting cartilage tissue from the non-weight bearing posterior femoral condyle to fill the defect region. A 5.5 year follow-up case-series of young patients with large osteochondral defects on the weight bearing zones showed excellent improvement in the Lysholm score, daily-life-activity levels and return to recreational sports.[25]

The main problem encountered was described to be during the healing process where cartilage to graft transition zones showed non-healing and incongruency thereby presenting the main pitfall of the procedure.[29] To improve the approximation of the femoral cartilage curvature and joint congruence it is recommended to use only one osteochondral graft rather than many as in the case of mosaicplasty.[30]

The autologous matrix-induced chondrogenesis (AMIC) is the third alternative treatment option for cartilage. This procedure is an option for localized full-thickness cartilage defects combining microfracturing with a collagen I/III scaffold. The results of a two-year follow-up study published by Gille *et al.*, were very promising.[31]

Kusano *et al.* evaluated the clinical and radiological outcomes of patient with the AMIC procedure for full-thickness chondral and osteochondral defects of the femoral condyles and patella. Results showed that, especially osteochondral defects had a significant improvement in the clinical outcome scores (IKDC, Tegner, Lysholm and VAS pain score), whereas chondral defects showed an improvement too, but less than the osteochondral defects.[32]

Radiographically a moderate to complete filling with a normal to incidentally hyperintense signal in the MRI was seen in a 24- to 62-month follow-up observed by Gille *et al.*[33] in 27 patients with chondral lesions by a mean defect size of 4.2 cm^2.

However, further long-term results need to be awaited to determine structural integrity over time.

The last treatment option on cartilage defects mentioned in this review is autologous chondrocyte transplantation (ACT), where cartilaginous cells are arthroscopically harvested from the non-weight bearing regions of the knee, cultivated *in-vitro* for a duration of 4 to 6 weeks and reimplanted in an arthrotomy procedure in the regions of cartilaginous defects. Long-term results over 10 years proved the procedure to be effective in the treatment of localized, low impact cartilage lesions in young patients.[34] The success of the procedure is partially attributed to the quality of collagen type-2 rich hyaline-like cartilage produces in the defect lesions that is usually not achieved with the conventional treat-

ment methods; which produce collagen type-1 rich fibrocartilage.

Furthermore, patients with osteochondrosis dissecans (OCD) of the knee had statistically significant pain reduction and functional improvement 48 months after ACT, as shown by Cole et. al in a prospective study of 40 patients.[16]

The downsides of the procedure are the need for two operations, the extremely expensive costs, and the ongoing debates due to the lack of high level of evidence randomized trials proving the benefits over other methods.

Anterior cruciate ligament ruptures

One of the most frequently encountered injuries to the knee joint is tear or rupture of the ACL. ACL injury rates show an association with the persue of sports involving pivoting activities such as soccer, basketball or handball.[35] There is an inherent risk of ACL injury by the particular stress that the sport puts on the knee joint during turning, landing or falling. Cimino *et al*. summarized contributing impacts such as extrinsic (*e.g.*, level of competition, weather/ground conditions) and intrinsic risk factors (*e.g.*, leg axis, tight strength).[36]

It is well established that the decision to refer to an orthopaedic surgeon is largely dependent on the preferences and activity level of the patient. It is recommended that any patient who plans to continue activities involving rapid acceleration, deceleration and pivoting should be evaluated for surgery.[37]

Nowadays, arthroscopic reconstruction using a graft to replace the ligament is the gold standard among athletes with high sports activity level.[38] Graft choice for ACL reconstruction is influenced by individual patient factors such as age, activity level and associated injuries. The two most commonly used autografts in ACL reconstruction are the patellar bone-tendon-bone grafts (BTB) and the four-strand hamstring tendon graft (STG; consisting of the gracilis and semitendinosus tendons). To date, there have been a number of prospective and retrospective studies comparing BTB and STG. Overall, there are no significant clinical and functional differences between the two surgical techniques.[39, 40] The advantage of the STG is relatively low overall postoperative pain, especially anterior knee pain. Thus, it would be the preferred choice of graft in ACL reconstruction for patients with a history of knee pain or who require kneeling. The advantage of the BTB is that it takes relatively quick for the graft to be integrated since there is a "bone-to-bone" healing compared to STG. The other sources of autografts include the quadriceps tendons. Although there has been little research on quadriceps tendon grafts, several recent studies support their use in ACL reconstruction.[41]

Allografts are indicated in patients undergoing revision ACL. For primary ACL reconstruction, they are regularly used only in the United States. Allografts have advantages including decreased operative time and no donor-site morbidity. In a meta-analysis study and systematic review on the comparison of clinical outcomes of ACL reconstruction using autografts and allograft, there was no difference in the outcome scores, laxity, clinical failure rates, and return to sports.[42] However, especially in Europe autografts are still preferred because allografts carry the possibility of disease transmission.

Since the knee joint is mainly stabilized by ligaments and muscles, optimal structured rehabilitation programs following ACL reconstruction are needed. The goal is to reach the best functional level with a minimal risk of new injuries when returning to previous activity levels. Rehabilitation concepts must be mainly based on specific methods to challenge the stabilizing structures of the knee joint. There is growing knowledge on modifiable postsurgical risk factors such as biomechanical and neuromuscular impairments which can lead to second knee injury.[43] Therefore, the trend goes from conservative efforts of prolonged immobilization to current paradigms that advocate a progressive increase in training loads.[36] Standardized outcome measures for

evaluating individual patient progress in performance and knee function has been established.[44, 45]

The clinical results with tendon grafts are still under discussion. A recent meta-analysis revealed that only 40% of patients achieve full recovery independent of surgical technique. There are several well-known disadvantages when using autologous materials such as donor-site morbidity, loss of stability and persisting femoral muscle atrophy. High re-injury rates as well as early onset of osteoarthritis are reported as further consequences. One explanation could be that removal of the native ACL tissue containing sensory nerve fibres and mechanoreceptors causes the ligament to lose its function in "proprioceptive communication", followed by a decreased muscular stability of the knee joint.

Based on evidence from recent studies supporting the healing potential of the ruptured ACL,[46-48] dynamic intraligamentary stabilization (DIS: Ligamys, Mathys AG Bettlach, Switzerland) arised as a new surgical technique for the treatment of acute ACL ruptures.[49, 50] The DIS device combines an internal dynamic screw-spring mechanism with a thin polyethylene thread to provide continuous stability of the knee joint during the self-healing period. To enable biological healing, surgery involves micro fracturing of the femoral footprint according to Steadman *et al.*[51] and a leucocyte and platelet-rich fibrin (PRF) clot is attached to the rupture site.[52] Finally, a resorbable collagen patch is placed over the defect.[53, 54]

Compared to classical reconstruction techniques the DIS permits repair of the injured ACL exploiting physiological healing process. The major complications of the graft replacement techniques such as donor-site morbidity and weakening of secondary knee stabilizers can be avoid due to the preservation of the still vital cruciate ligament tissue. At the moment, further prospective studies of this new surgery approach are needed to evaluate mid- and long-term results regarding clinical outcomes as well as the safe return to sports performance.

Conclusions

Despite the wide variety of available treatment options of knee injuries and disorders, debate of which procedure to use is in the rise due to the lack of evidence from randomized trials. Nevertheless, joint preserving options are constantly gaining attention, and the indications are widening with improvement of surgical techniques and therapeutic strategies.

A glance at the future would allow for the prediction of less arthroplasty procedures and more biological therapeutic options, that would further reduce and delay the need for prosthetic implants.

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