Research Advances in the Development of Post-Traumatic Knee Osteoarthritis with Abnormal Mechanical Load, Inflammation, and Hemarthrosis

Changpeng Zhang[a], Weiwei Wang[b], Xiyong Li[c], Changsheng Liao[d], Pengfei Han[e], Yuan Li[f]*

Department of Orthopaedics, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, 046000, China
[a]*zhangcp265@163.com,* [b]*13595815865@163.com,* [c]*lxy160505@163.com,* [d]*15603441409@163.com,* [e]*18003551149@163.com*
*Corresponding author: liyuan10@sohu.com

Abstract: Knee injuries predominantly caused by anterior cruciate ligament (ACL) rupture and meniscal harm are most frequent among young people and sports activities enthusiasts. Post-traumatic osteoarthritis (PTOA) occurs in 25-50% of people with knee injuries. Previous researchers have thought that cartilage damage is caused by PTOA, but a growing body of research suggests that inflammation plays a key role in the development of PTOA. Hemarthrosis from knee injury may exacerbate inflammation of PTOA, and although mechanical symptoms such as joint instability and joint twisting can be relieved by surgical treatment, they are less effective in preventing PTOA progression. In order to explore more effective anti-inflammatory treatment plans to forestall PTOA progression, this article intends to review and summarize the results of the results on the pathophysiological mechanism of post-traumatic intra-articular inflammation, so as to identify potential targets and timing for future PTOA prevention and treatment, and provide theoretical guidance for clinical practice.

Keywords: Post-traumatic knee Osteoarthritis, inflammation, hemarthrosis, cartilage injury

In 25-50% of sufferers with knee injury, the persistence of harm is a recognised danger thing for the improvement of osteoarthritis (OA) and severe trauma [such as an anterior cruciate ligament (ACL) rupture] result in post-traumatic osteoarthritis (PTOA). However, patients with important osteoarthritis are commonly older, while younger people have a higher incidence of knee injuries and subsequently secondary PTOA[1]. Knee injuries lead to limited activity and bodily health, leading to reduced quality of life, most pronounced in patients with PTOA[1–3]. Most knee injuries are treated conservatively, but surgery is required for significant pain that cannot be recovered from conservative treatment. Although surgical treatment increases exercise levels, it does not reduce the incidence of PTOA[4]. 12% of patients with symptomatic OA are PTOA. In previous studies, the pathophysiology of PTOA used to be concept to be induced by means of mechanical stress and extraordinary joint loading, however a growing range of research in human and animal fashions provide sturdy proof that infection plays a key position in PTOA[5,6]. Knee injuries are often accompanied by hemarthrosis, and cartilage destruction due to repeated bleeding in the articular cavity in hemophilia patients has been studied[7,8]. However, literature describing the role of inflammation between hemophilia and non-hemophilia in the improvement of PTOA is lacking. PTOA is a disease that progresses for a longer period of time, and timely administration of treatment is concept to have the potential to slow or halt the progression of PTOA, which is essential to decrease the incidence of ailment and keep away from useless joint substitute surgery[9].

This article summarizes the existing literature and reviews the sickness development and common manifestations of knee PTOA, with a one of a kind focal point on irritation and hemarthrosis, in order to more accurately understand the disease progression about PTOA and the inflammatory function of hemarthrosis, which can help to implement appropriate treatment at the right target and timing.

1. Anatomical basis of knee injury

Articular cartilage is a connective tissue that covers the surface of the joint without nerves, blood vessels and lymphatic vessels, which mainly provides a smooth surface for the joint and evenly distributes the forces to enlarge the load-bearing surface. Articular cartilage is different from other tissues in that its main component is the dense extracellular matrix (ECM). Chondrocytes are sparsely distributed in the ECM, and the metabolic mode is mainly anaerobic metabolism, and the regenerative capacity is weak. ACL and posterior cruciate ligament (PCL) have the effect of fixing the femur and tibia. The main components of the cruciate ligament are collagen bundles and a matrix composed of various proteins. The function of the cruciate ligament is to prevent anterior displacement of the tibia and posterior displacement of the tibia[10]. Cruciate ligament ruptures are often accompanied by branch damage to the middle knee artery, leading to intra-articular bleeding, known as hemarthrosis. Due to the anatomical characteristics of poor blood supply to ACLs, ACL healing ability after rupture is poor. The meniscus, made up of half-moon fibrocartilage, covers the natural contour of the tibial plateau and covers more than half of the articular surface. In addition to fibrochondrocytes, which synthesize ECM, the remaining components of the meniscus mainly include water, collagen, and a small number of GAGs[11]. The meniscus increases the tibial contact area of the knee joint by 50%, and the meniscus can cushion the shock and spread the knee load and prevent the anterior tibia displacement to a certain extent, all due to its unique shape and strong toughness. The meniscus releases joint fluid into the joint cavity when it is under load, lubricate the joint surface, and the diffuse joint fluid helps transport nutrients to the surface of the articular cartilage. The internal and external knee arteries supply nutrients to two-thirds of the perimeter of the meniscus, but the inner third of the meniscus has no blood supply. Therefore, it is difficult to recover after a meniscal injury. The synovium is a special connective tissue that covers the inner surface of the joint capsule and is rich in collagen, blood vessels, lymph and nerve fibers. Synovial cells include macrophages and fibroblasts. The main function of the synovial membrane is to produce lubricating agents and hyaluronic acid, which also provide nutrients to chondrocytes.

2. Incidence and risk factors for knee injury

The incidence of knee injuries tiers from 0.2% to 1.2%. The highest incidence of knee injuries ranges from 15 to 24 years[12]. Cruciate ligament rupture and meniscal injury are the most common factors leading to the development of PTOA and are also research hotspots. The incidence of ACL rupture in female athletes is approximately 3 times higher than in male athletes. According to statistics, the incidence of meniscal injury is similar in men and women, about 60-70 per 100,000 people, but the true incidence of meniscal injury may be underestimated due to multiple studies showing that many patients with meniscal tears are not clinically symptomatic[13]. Between one-third and two-thirds of patients with ACL tears have been reported with meniscal injury, and many studies have consistently shown that the longer the time between preliminary ACL damage and surgical treatment since functional defects in ACL rupture, the higher the incidence of meniscal and cartilage lesions[14]. Studies have noted a greater incidence of meniscal damage in men.

Physical activity is a very important factor in the development of knee injuries. Approximately 70-80% of ACL injuries are caused by non-contact shocks such as sudden acceleration, sudden deceleration, or rapid changes in trajectory. Several different risk factors have been pointed out to be directly related to non-contact ACL injury. These risk factors can be divided into different risk categories: external factors, such as temperature, exercise environment, intensity of exercise, and intrinsic factors, such as anatomical characteristics, neuromuscular coordination, biomechanics, psychological factors, and developmental status [15]. Obesity, exertion, poor exercise habits, and strength deficits are modifiable and controllable risk factors[16]. Age, sex, and anatomical features of women, such as narrower intercondylar notch width than in men, greater medial and lateral tibial slopes, and lax ligaments are immutable and controllable factors that greatly reduce the risk of ACL injury and recurrence if modifiable factors such as biomechanical and neuromuscular control at landing can be corrected[17]. Risk factors for meniscal injury are broadly divided into two categories: modifiable and non-modifiable. Modifiable risk factors include obesity (BMI >25), participation in highly confrontational physical activities such as basketball, rugby, or soccer, and work that requires prolonged kneeling, squatting, climbing stairs, and carrying weights. Risk factors for the immutability of meniscal tears include increasing age and physiologic deficits such as discoid meniscus, misalignment of the knee, biconcave tibial plateau, and knee laxity[18]. In addition, studies have shown that ACL injury beyond 12 months before undergoing reconstructive surgery significantly increases the

risk of medial meniscal tears[18].

3. Pathophysiology of PTOA

Progression from a knee injury to PTOA usually goes through three stages, starting with the immediate stage that occurs immediately after the knee injury. This is followed by an acute inflammatory phase within a few weeks of injury, which is often accompanied by hemarthrosis, fragmentation of the extracellular matrix (ECM), and cell death. If the trauma remains unrecovered within several months, the pain will persist and progress to stage three, where acute inflammation becomes chronic inflammation, eventually leading to PTOA progression. Below, we discuss the pathophysiology of the knee in terms of abnormal mechanical load, which induces an inflammatory response and increases the incidence of chronic synovitis, which in turn promotes the development of PTOA.

4. Anomalous mechanical load due to knee injury

Uninjured joints are able to repeatedly bear the load of all daily activities and osteoarthritis does not occur.However, articular cartilage regeneration is weak, and it is frequently difficult to repair trauma and cartilage wear due to joint instability[19]. Violent knee injuries are often accompanied by disruption of joint structures and biomechanical changes[20]. Death occurs when cells in the impact area at the time of injury are subjected to pressures greater than 10-20 MPa. When the knee joint is violently damaged, the cartilage will swell due to collagen rupture, and collagen will be overstretched, resulting in irreversible damage. The loss of glycosaminoglycans (GAGs) further promotes apoptosis due to the loss of cartilage ECM integrity. Since chondrocytes maintain the homeostasis of cartilage, the death of chondrocytes reduces cartilage's ability to regenerate and repair and therefore play a central role in the progression of PTOA. Post-traumatic vascular rupture and the accompanying mechanical load overload can lead to intra-articular hemorrhage. Some researchers believe that the blood in the joint dilutes the synovial fluid, which in turn reduces joint lubrication, causes synovitis, accelerates cartilage wear, and ultimately promotes the development of PTOA[20].

Many studies of biomechanical modifications following ACL rupture have shown that ACL defects alter the mechanics of knee motion[21]. Meniscal injuries typically occur shortly after an ACL rupture and often result in changes in knee kinematics that further reduce knee stability[22]. These biomechanical abnormalities led to changes in stress distribution on the tibial platform and spatial displacement of the bearing area, further contributing to the progression of PTOA[23].

The thickness of knee cartilage varies from region to region, and damage to cartilage on the joint surface can occur when pressure shifts from the weight-bearing area to the non-weight-bearing area. In addition to the destruction of cartilage by the initial trauma, changes in load can also lead to changes in chondrocyte metabolism that further damage cartilage[24]. Studies have proposed that cartilage damage can lead to collagen degeneration, resulting in increased tangential force and friction on the joint surface. This biomechanical alteration leads to cleavage of collagen fibers and stimulates chondrocytes to release matrix metalloproteinases (MMPs) and inflammatory cytokines, disrupting the structure and function of the ECM[25]. There is evidence that catabolic factors secreted by chondrocytes accelerate autoapoptosis, implying a positive feedback mechanism between ECM loss and chondrosis. Most patients with ACL injury will develop subchondral contusion of varying degrees depending on the mechanism of injury[26]. Bone contusions are thought to be a precursor to cartilage damage. The mechanism of subchondral bone contusion may include cartilage damage due to impact exceeding the cartilage's ability to bear. In addition, damaged subchondral bone heals into a hard callus with reduced deformation capacity, making cartilage more susceptible to wear out due to its inability to disperse load forces[27]. Long-term follow-up of changes in joint function after bone contusion will be of great significance in analyzing the relationship between bone contusion and the development of PTOA.

5. Hemarthrosis caused by knee joint injury

The incidence of acute traumatic hemarthrosis in the population was reported to be 4.7 per 10.000. Hemarthraxis is diagnosed by arthrocentesis at the time of presentation to the emergency department in 53% of patients with post-traumatic knee swelling. Patients with hemarthrosis have a 17% probability of lateral patellar dislocation, a 41% probability of meniscal tear, and a 52% probability of the most

common ACL rupture[28]. Many studies of hemophilia patients with traumatic haemothrrhax have found that joint cartilage damage tends to be more severe in these patients than in non-hemophilia patients[29]. Soon after knee injury, inflammatory markers in the synovial fluid of the knee are markedly elevated in patients with hemarthrosis[30]. Therefore, it is believed that hemodialysis accelerates the progression of PTOA. When red blood cells in the joint cavity break down, they release heme. The interaction of heme with hydrogen peroxide secreted by monocyte-macrophages produces hydroxyl radicals that are harmful to the human body, which in turn promote chondrosis[31]. The hemosiderin, produced by the breakdown of red blood cells, accumulates after being absorbed by synovial cells and macrophages and forms synovial hemosiderin deposits. It has been suggested that these deposited hemosiderosins promote synovial inflammation and induce the production of pro-inflammatory cytokines in synovial tissue[8]. In addition, an increase in MMPs activity and an irreversible decrease in proteoglycan synthesis can lead to adverse changes in the ECM even under blood exposure at low concentrations of articular cartilage. Other studies have shown that exposing healthy human cartilage to the bloodstream for more than 10 days releases the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6[32]. In summary, the persistence of hemarthrosis induces inflammation and promotes the development of PTOA[31].

In general, when it comes to clearing the hemarthrosis, doctors prefer to allow it to be absorbed naturally. Conservative management is usually with cold compresses, compression dressings, and knee immobilization. Caluminocentesis does not occur unless there is significant swelling of the joint, or pain that is difficult to control, and infection is suspected because arthrocentesis is an invasive procedure, carries a risk of post-puncture infection, and most children require anesthesia[31,33]. However, aseptic procedures by experienced physicians may reduce the risk of iatrogenic infection[31]. Puncture and aspiration, after arthrosis, can relieve pain to a certain extent, and can also improve the sensitivity of physical examination. Studies have found that knee injuries with hemarthrosis have a greater range of motion than conservative treatment after two weeks of blood draw[34]. In addition, animal experiments have shown that complete absorption of hemarthrosis takes at least 4 days, so in most cases timely aspiration is considered a means of reducing potential cartilage damage [35].

6. Acute inflammation after knee injury

Damaged joint tissue releases damage associated molecular patterns (DAMPs) into the joint cavity. DAMPs are endogenous stimulants launched via ECM or dead cells. Pattern recognition receptors present on the surface of chondrocytes, immune cells, macrophages, osteoblasts, and fibroblasts include Toll-like receptors (TLRs), receptors for advanced glycation endproducts (RAGE), and NOD-like receptors (NLRs). These receptors are able to bind DAMPs and thus activate downstream signaling cascades, resulting in increased release of inflammatory cytokines by damaged synovial cells[9]. Synovial cells also produce other inflammatory factors such as chemokines, cathepsin, and complement cascades. These factors activate synovial cells and chondrocytes to produce the ADAMTS family and MMPs. Because these degrading enzymes promote the breakdown of cartilage, the broken cartilage in turn promotes synovial inflammation, creating a vicious cycle[36]. Furthermore, cytokines and mobilephone adhesion molecules set off leukocyte migration to synovial tissue and joint cavities. Some studies suggest that macrophages and T lymphocytes can aggregate and form multinucleated giant cells, the most dominant immune cells in the synovial membrane of OA[6]. The mechanism by which T cells promote OA progression is not fully understood. Once immune cells are immersed in synovial tissue, they release pro-inflammatory cytokines that promote the progression of PTOA[37].

7. Chronic inflammation and synovitis after knee joint injury

Joint stiffness, pain, and swelling are clinical symptoms of synovitis, common in primary arthritis[6]. The incidence of synovitis during surgery for end-stage osteoarthritis was 67%[38]. There is ample evidence that knee disorders such as ACL rupture or meniscal injury can lead to synovitis[39]. High levels of inflammatory factors can persist for years after knee injury also support this idea[9]. Microhistologic features of synovitis include stromal cell activation, degree of inflammatory infiltration, and synovial hyperplasia, and macroscopic features include angiogenesis, villi, fibrin deposition, and hyperplasia[39]. Synovitis occurs in the suprapatella, subpatella, lateral and medial parapatellar and subpopliteal fossa, and near the posterior cruciate ligament, and is patchy depending on location and severity[40].

Extensive leukocyte infiltration is seen in synovial tissue in patients with traumatic OA, including proliferation of fibroblast-like synovial cells (FLS) and macrophage infiltration of lubricated membrane

folds. T cells, B cells, plasma cells, mast cells, and vascular endothelial cells can be found in the subsynovial layer[6,39]. Cartilage breakdown products released into synovial fluid are engulfed by synovial cells. When FLS is activated, it secretes MMPs, growth factors, cytokines, and tissue inhibitors of metalloproteinases (TIMPs), which will help activate macrophages and stimulate the catabolic pathway of chondrocytes. The inflammatory synovium also promotes osteophyte formation through the production of TGF-β and bone morphogenetic proteins (BMPs) by synovial cells and macrophages[6,39]. Cytokines such as TNF-α and IL-6 and immune cells such as synovial CD4+T cells increase the sensitivity of peripheral nociceptive neurons. This in turn leads to more intense pain[6]. Because synovitis is distributed in a patchy pattern across the knee joint, synovitis in different sites may present with varying degrees of pain[41]. Previous studies have shown that inflammatory biomarkers and imaging data in posttraumatic patients do not accurately predict prognosis and the development of PTOA[42]. However, these studies did not investigate in depth whether severe and recurrent inflammation and early post-traumatic hemarthrosis directly contribute to the development of PTOA. To better determine the role of inflammation in the progression of osteoarthritis after knee injury, more detailed analysis early in post-trauma and closer and longer follow-up after treatment are also needed.

8. Conclusion

PTOA is a common condition that causes decreased mobility. Current treatments do not prevent PTOA after a serious knee injury. Despite increasing research on the role of mechanical and inflammatory processes in the development of PTOA, the pathophysiological mechanisms leading to PTOA are not fully understood. Hemarthrosis plays an important role in the development of PTOA due to its role in inducing an inflammatory state after a knee injury. In the future, greater understanding of the post-injury inflammatory process and the role of hemarthrosis in promoting PTOA will be crucial for the early diagnosis and treatment of younger patients at risk of developing PTOA.

References

[1] Cy, L., Cm, T., Ca, E., and Jl, W. (2021) What Does the Future Hold? Health-Related Quality of Life 3-12 Years Following a Youth Sport-Related Knee Injury. International Journal of Environmental Research and Public Health. 18 (13)

[2] Lam, K.C. and Markbreiter, J.G. (2019) The Impact of Knee Injury History on Health-Related Quality of Life in Adolescent Athletes. Journal of Sport Rehabilitation. 28 (2), 115–119.

[3] Whittaker, J.L., Toomey, C.M., Nettel-Aguirre, A., Jaremko, J.L., Doyle-Baker, P.K., Woodhouse, L.J., et al. (2019) Health-related Outcomes after a Youth Sport-related Knee Injury. Medicine and Science in Sports and Exercise. 51 (2), 255–263.

[4] Chalmers, P.N., Mall, N.A., Moric, M., Sherman, S.L., Paletta, G.P., Cole, B.J., et al. (2014) Does ACL Reconstruction Alter Natural History? A Systematic Literature Review of Long-Term Outcomes. JBJS. 96 (4), 292.

[5] Boehme, K.A. and Rolauffs, B. (2018) Onset and Progression of Human Osteoarthritis—Can Growth Factors, Inflammatory Cytokines, or Differential miRNA Expression Concomitantly Induce Proliferation, ECM Degradation, and Inflammation in Articular Cartilage? International Journal of Molecular Sciences. 19 (8), 2282.

[6] Mathiessen, A. and Conaghan, P.G. (2017) Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Research & Therapy. 19 (1), 18.

[7] Gualtierotti, R., Solimeno, L.P., and Peyvandi, F. (2021) Hemophilic arthropathy: Current knowledge and future perspectives. Journal of Thrombosis and Haemostasis. 19 (9), 2112–2121.

[8] Zhu, H., Meng, Y., Tong, P., and Zhang, S. (2021) Pathological mechanism of joint destruction in haemophilic arthropathy. Molecular Biology Reports. 48 (1), 969–974.

[9] Khella, C.M., Asgarian, R., Horvath, J.M., Rolauffs, B., and Hart, M.L. (2021) An Evidence-Based Systematic Review of Human Knee Post-Traumatic Osteoarthritis (PTOA): Timeline of Clinical Presentation and Disease Markers, Comparison of Knee Joint PTOA Models and Early Disease Implications. International Journal of Molecular Sciences. 22 (4), 1996.

[10] Hassebrock, J.D., Gulbrandsen, M.T., Asprey, W.L., Makovicka, J.L., and Chhabra, A. (2020) Knee Ligament Anatomy and Biomechanics. Sports Medicine and Arthroscopy Review. 28 (3), 80–86.

[11] Twomey-Kozak, J. and Jayasuriya, C.T. (2020) Meniscus Repair and Regeneration: A Systematic Review from a Basic and Translational Science Perspective. Clinics in Sports Medicine. 39 (1), 125–163.

[12] Schneider, O., Scharf, H.-P., Stein, T., Knapstein, S., Hermann, C., and Flechtenmacher, J. (2016)

[Incidence of knee injuries : Numbers for outpatient and inpatient care in Germany]. Der Orthopade. 45 (12), 1015–1026.

[13] Krych, A.J., Hevesi, M., Leland, D.P., and Stuart, M.J. (2020) Meniscal Root Injuries. The Journal of the American Academy of Orthopaedic Surgeons. 28 (12), 491–499.

[14] Adams, B.G., Houston, M.N., and Cameron, K.L. (2021) The Epidemiology of Meniscus Injury. Sports Medicine and Arthroscopy Review. 29 (3), e24–e33.

[15] Dauty, M., Crenn, V., Louguet, B., Grondin, J., Menu, P., and Fouasson-Chailloux, A. (2022) Anatomical and Neuromuscular Factors Associated to Non-Contact Anterior Cruciate Ligament Injury. Journal of Clinical Medicine. 11 (5), 1402.

[16] Uhorchak, J.M., Scoville, C.R., Williams, G.N., Arciero, R.A., St Pierre, P., and Taylor, D.C. (2003) Risk factors associated with noncontact injury of the anterior cruciate ligament: a prospective four-year evaluation of 859 West Point cadets. The American Journal of Sports Medicine. 31 (6), 831–842.

[17] Sepúlveda, F., Sánchez, L., Amy, E., and Micheo, W. (2017) Anterior Cruciate Ligament Injury: Return to Play, Function and Long-Term Considerations. Current Sports Medicine Reports. 16 (3), 172–178.

[18] Gee, S.M., Tennent, D.J., Cameron, K.L., and Posner, M.A. (2020) The Burden of Meniscus Injury in Young and Physically Active Populations. Clinics in Sports Medicine. 39 (1), 13–27.

[19] Heijink, A., Gomoll, A.H., Madry, H., Drobnič, M., Filardo, G., Espregueira-Mendes, J., et al. (2012) Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA. 20 (3), 423–435.

[20] L, P., P, G., R, L., M, F., R, R., F, O., et al. (2016) Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. RMD Open. 2 (2).

[21] Slater, L.V., Hart, J.M., Kelly, A.R., and Kuenze, C.M. (2017) Progressive Changes in Walking Kinematics and Kinetics After Anterior Cruciate Ligament Injury and Reconstruction: A Review and Meta-Analysis. Journal of Athletic Training. 52 (9), 847–860.

[22] Hoshino, Y., Miyaji, N., Nishida, K., Nishizawa, Y., Araki, D., Kanzaki, N., et al. (2019) The concomitant lateral meniscus injury increased the pivot shift in the anterior cruciate ligament-injured knee. Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA. 27 (2), 646–651.

[23] Agostinone, P., Di Paolo, S., Grassi, A., Pinelli, E., Bontempi, M., Bragonzoni, L., et al. (2021) ACL deficiency influences medio-lateral tibial alignment and knee varus-valgus during in vivo activities. Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA. 29 (2), 389–397.

[24] Lane Smith, R., Trindade, M.C., Ikenoue, T., Mohtai, M., Das, P., Carter, D.R., et al. (2000) Effects of shear stress on articular chondrocyte metabolism. Biorheology. 37 (1–2), 95–107.

[25] Andriacchi, T.P., Mündermann, A., Smith, R.L., Alexander, E.J., Dyrby, C.O., and Koo, S. (2004) A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of Biomedical Engineering. 32 (3), 447–457.

[26] Filardo, G., Andriolo, L., di Laura Frattura, G., Napoli, F., Zaffagnini, S., and Candrian, C. (2019) Bone bruise in anterior cruciate ligament rupture entails a more severe joint damage affecting joint degenerative progression. Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA. 27 (1), 44–59.

[27] Mandalia, V., Fogg, A.J.B., Chari, R., Murray, J., Beale, A., and Henson, J.H.L. (2005) Bone bruising of the knee. Clinical Radiology. 60 (6), 627–636.

[28] Olsson, O., Isacsson, A., Englund, M., and Frobell, R.B. (2016) Epidemiology of intra- and peri-articular structural injuries in traumatic knee joint hemarthrosis - data from 1145 consecutive knees with subacute MRI. Osteoarthritis and Cartilage. 24 (11), 1890–1897.

[29] Vanderhave, K.L., Caird, M.S., Hake, M., Hensinger, R.N., Urquhart, A.G., Silva, S., et al. (2012) Musculoskeletal care of the hemophiliac patient. The Journal of the American Academy of Orthopaedic Surgeons. 20 (9), 553–563.

[30] Swärd, P., Frobell, R., Englund, M., Roos, H., and Struglics, A. (2012) Cartilage and bone markers and inflammatory cytokines are increased in synovial fluid in the acute phase of knee injury (hemarthrosis) – a cross-sectional analysis. Osteoarthritis and Cartilage. 20 (11), 1302–1308.

[31] Potpally, N., Rodeo, S., So, P., Mautner, K., Baria, M., and Malanga, G.A. (2021) A Review of Current Management of Knee Hemarthrosis in the Non-Hemophilic Population. Cartilage. 13 (1_suppl), 116S-121S.

[32] van Vulpen, L.F.D., Popov-Celeketic, J., van Meegeren, M.E.R., Coeleveld, K., van Laar, J.M., Hack, C.E., et al. (2017) A fusion protein of interleukin-4 and interleukin-10 protects against blood-induced cartilage damage in vitro and in vivo. Journal of Thrombosis and Haemostasis: JTH. 15

(9), 1788–1798.

[33] Hanley, J., McKernan, A., Creagh, M.D., Classey, S., McLaughlin, P., Goddard, N., et al. (2017) Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline. Haemophilia: The Official Journal of the World Federation of Hemophilia. 23 (4), 511–520.

[34] Wang, J.H., Lee, J.H., Cho, Y., Shin, J.M., and Lee, B.H. (2016) Efficacy of knee joint aspiration in patients with acute ACL injury in the emergency department. Injury. 47 (8), 1744–1749.

[35] Jansen, N.W.D., Roosendaal, G., Bijlsma, J.W.J., Degroot, J., and Lafeber, F.P.J.G. (2007) Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: an in vitro study. Arthritis and Rheumatism. 56 (1), 199–207.

[36] Lambert, C., Zappia, J., Sanchez, C., Florin, A., Dubuc, J.-E., and Henrotin, Y. (2020) The Damage-Associated Molecular Patterns (DAMPs) as Potential Targets to Treat Osteoarthritis: Perspectives From a Review of the Literature. Frontiers in Medicine. 7 607186.

[37] Woodell-May, J.E. and Sommerfeld, S.D. (2020) Role of Inflammation and the Immune System in the Progression of Osteoarthritis. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 38 (2), 253–257.

[38] Wyatt, L.A., Moreton, B.J., Mapp, P.I., Wilson, D., Hill, R., Ferguson, E., et al. (2017) Histopathological subgroups in knee osteoarthritis. Osteoarthritis and Cartilage. 25 (1), 14–22.

[39] E, S.-L., R, C., A, T., Ne, L., and M, G. (2022) Synovial inflammation in osteoarthritis progression. Nature Reviews. Rheumatology. 18 (5),.

[40] Mussawy, H., Zustin, J., Luebke, A.M., Strahl, A., Krenn, V., Rüther, W., et al. (2022) The histopathological synovitis score is influenced by biopsy location in patients with knee osteoarthritis. Archives of Orthopaedic and Trauma Surgery. 142 (11), 2991–2997.

[41] (n.d.) Association of Pain in Knee Osteoarthritis With Distinct Patterns of Synovitis.

[42] Roemer, F.W., Englund, M., Turkiewicz, A., Struglics, A., Guermazi, A., Lohmander, L.S., et al. (2019) Molecular and Structural Biomarkers of Inflammation at Two Years After Acute Anterior Cruciate Ligament Injury Do Not Predict Structural Knee Osteoarthritis at Five Years. Arthritis & Rheumatology (Hoboken, N.J.). 71 (2), 238–243.