

Early Diagnosis and Biomarker Advances in Post-Traumatic Osteoarthritis after Knee Joint Injury

Yi Wu

Hwachong International School, Singapore, Singapore
wuyi1757199867@gmail.com

Abstract. Post-traumatic osteoarthritis (PTOA) is a common long-term consequence of knee joint injuries, particularly those involving the anterior cruciate ligament (ACL), meniscus and cartilage. It can develop in relatively young individuals and progressively impair joint function and quality of life. However, conventional imaging methods, particularly X-ray, have limited sensitivity to early biochemical and soft-tissue changes. This review examines current approaches to the early detection and treatment of PTOA, with particular emphasis on imaging techniques and biomarkers. X-ray and ultrasound can provide useful information about structural changes, but their ability to detect early disease is limited by their sensitivity, anatomical coverage and operator dependence. Biomarkers may provide earlier evidence of cartilage degradation, tissue remodelling and inflammation. Catabolic biomarkers such as C2C, CTX-II and COMP, anabolic biomarkers such as NTX-1, and inflammatory biomarkers including IL-6, IL-7, IL-8 and TNF have shown potential, although their clinical value remains inconsistent. Current treatments targeting inflammation and chondrocyte apoptosis may help slow disease progression, but limitations including side effects and poor drug retention remain. Future research should combine imaging with blood or synovial-fluid biomarkers, standardise diagnostic methods, establish clinically meaningful thresholds and validate multi-biomarker panels through large-scale longitudinal studies. Earlier identification of high-risk patients may allow intervention before irreversible joint damage occurs.

Keywords: Post-traumatic osteoarthritis, Knee joint injury, Early diagnosis, Biomarkers

1. Introduction

Post-traumatic osteoarthritis (PTOA) is a degenerative joint disease that occurs after a traumatic injury and is a common long-term consequence of knee injuries. It can affect young people at an earlier stage and is especially common in cases of injury to the anterior cruciate ligament (ACL), menisci and cartilage. PTOA will reduce people's joint function and quality of life to some extent, increasing the burden on both patients and the healthcare system.

Given that it is high-risk, we need to detect PTOA in an early stage. However, the traditional imaging methods cannot find the early signs of disease. Therefore, researchers have begun to focus more on biomarkers that can be used to detect joint degeneration early and help identify people who are likely to develop PTOA.

With the accumulation of scattered data on PTOA, this paper will review what is currently known about the distribution and early signs of the disease, as well as related tests, indicators and treatments [1].

2. Epidemiological characteristics of post-traumatic osteoarthritis

In the United States, approximately 27million adults aged 25 and above have been diagnosed Osteoarthritis(OA). Among them, about 12 per cent are patients with post-traumatic osteoarthritis (PTOA). In the United States, about 13 million people aged 60 and over have been diagnosed with osteoarthritis of the knee joint based on X-ray examination, and around 4 million of these individuals are experiencing symptoms of knee osteoarthritis. People who have been injured in the knee previously are about 4.2 times more likely to develop osteoarthritis than those who have never been injured in the knee.

Athletes and people in the military have jobs that are more likely to cause knee injuries and later develop PTOA. According to a meta-analysis of 3100 ex-athletes, the proportion of knee osteoarthritis among former athletes was 30%. The proportion of PTOA in the knees and hips of former top male athletes was considerably higher than that in age-matched non-athlete controls. Based on the above data, people with knee injuries are about 4.2 times more likely to develop PTOA and do so at a younger age. Most people who have acute ACL tears are under the age of 30. The reported incidence of posttraumatic osteoarthritis (PTOA) after ACL injury is 87%, which is relatively high compared with 19.2% in all adults over the age of 45.¹⁶ However, this figure will be different whether the meniscus was removed (87%) or left in situ (26%).¹⁷ Other less frequent injuries can also lead to PTOA and more serious functional problems for the injured individuals. However, the literature is scarce, and there has been less research on PTOA due to other traumas compared to ACL and meniscal injuries [2, 3].

3. Imaging diagnosis

3.1. X-ray

X-ray imaging is based on the principle that X-ray loses different amount of energy as they pass through different tissues. The extent of energy loss depends on the absorption behavior and thickness of the material. For example, X-rays undergo greater attenuation when passing through bone than through an equivalent thickness of soft tissue. This difference in attenuation allows X-ray imaging systems to measure the difference in energy lose and generate a contrast in image, enabling different anatomical structures to be distinguished. In radiographic images, bone therefore appears with greater radiopacity than surrounding soft tissues [4].

The advantages of X-rays are that they are relatively inexpensive and easy to obtain; thus, they are widely used in all levels of medical institutions for common diseases. They also have a relatively low radiation dose and can be repeated at different times to check for changes. Weight-bearing X-rays can also be used to observe the condition of the joint under normal weight and gain some information about changes in joint space and alignment.

There are still deficiencies in X-rays. For instance, the two-dimensional nature cannot show the three-dimensional shape of the knee, and some anatomical parts may be covered by others in a radiograph. X-rays are generally not very sensitive to early changes in the joint because they can only show the structure of the bones and cannot detect damage to the cartilage or other problems in soft tissues at an early stage. Therefore, pathological changes in PTOA may occur before they are

detectable by conventional X-rays, and thus, X-rays are unable to show early lesions and changes in the disease process of PTOA. Therefore, although radiography is still a general way to observe PTOA, its weak sensitivity to early changes and soft-tissue diseases will limit how fully we can detect the development of the disease.

3.2. Ultrasound

US uses high-frequency sound waves to image tissues with broad application in musculoskeletal medicine. It is estimated to be less expensive, better tolerated by patients, available for point of care applications, and able to function as a dynamic tool that can be tailored to the specific clinical situation. However, the diagnostic sensitivity in musculoskeletal medicine is highly user dependent. It is also unable to visualize deep structures obscured by bone or fluid layers.

Research has examined the diagnostic accuracy of ultrasound and X-ray in comparison with that of X-rays. Osteophytes and thinning of the femoral cartilage are present in about 95 per cent of cases and can be detected by ultrasound. Given that there are osteophytes and reduced thickness of the femoral cartilage, ultrasound also has a specificity of 94%. The amount of the sample in that study was small. Therefore, the diagnostic value of ultrasound for PTOA has not been verified.

US also have limitations. US has been estimated to image only about 66% of the medial femoral condyle (two-thirds) and 37% of the lateral femoral condyle cartilage (one-third). According to the US assessment of femoral cartilage pathology in the US, the decrease in thickness was underreported by 21-25 per cent. Another possible defect of using US for diagnosis is user variability, as has been pointed out in other applications of US. Research on primary knee arthritis has found that there is good intra- and inter-rater reliability in the assessment of arthritic changes, such as joint effusion, cartilage loss, damage to the medial meniscus, Baker's cysts and osteophyte formation. Finally, there is the problem of an undefined norm. The values for healthy athletes are likely different from those of sedentary people, and studies have shown that healthy athletes have thicker femoral cartilage ($p < .001$) [5].

4. Biomarkers

The old way of imaging is too insensitive to find early changes in PTOA; therefore, there will probably be little difference in X-ray images at this time. Therefore, biomarkers have begun to be used to find biochemical changes in the joint at an early stage. Biomarkers can be associated with all stages of the development of PTOA and are generally divided into three types: catabolic biomarkers, anabolic biomarkers and inflammatory biomarkers [6, 7].

4.1. Catabolic biomarkers

Catabolic biomarkers show that the cartilage and other tissues in the joint have been damaged. C2C is a marker of type II collagen breakdown, and it has been observed that it is relatively high in people with radiographic signs of PTOA. CTX-II is another marker for the breakdown of type II collagen that has shown an AUC greater than 0.70 in the detection of meniscal injury on MRI, so it can be used to find structural damage in joints. COMP has also been used as an index for the degeneration of cartilage and joint tissue, but it is not often associated with structural damage or other clinical signs. Therefore, the above results indicate that catabolic biomarkers can provide information on tissue degradation that is not easily obtained through other means.

4.2. Anabolic biomarkers

Anabolic biomarkers are associated with the synthesis, repair and remodelling of tissue after joint injury. Some anabolic indices have been found in the systematic review of structural changes in PTOA. For example, the lower the level of NTX-1, the more severe the radiographic changes in PTOA. There is little evidence to support the hypothesis of anabolism, and its relation to structural alteration has not been repeatedly observed in studies. Therefore, more research needs to be carried out to determine whether the biomarkers above can reliably reflect the repair and remodelling process of PTOA at different times.

4.3. Inflammatory biomarkers

Inflammation is a cause of the development and progression of PTOA after joint injury. Some of the pro-inflammatory factors measured are IL-6, IL-7, IL-8 and TNF. IL-7 is associated with radiographic osteoarthritis, IL-8 has been linked to effusion and synovitis, and both are related to a worse prognosis after traumatic joint injury. However, the relationship among inflammatory biomarkers and PTOA progression is not well known, and different studies have reported different results. Therefore, it is proposed that inflammation is associated with the breakdown and remodelling of cartilage tissue, rather than occurring independently.

Although there are many functions of PTOA for early detection of PTOA, prognosis prediction and response assessment to treatment, its application in clinical practice has not yet been widespread. Most of the previous studies have focused on patients with ACL injuries who have had ACL reconstruction; thus, there is a lack of data on PTOA caused by other kinds of joint trauma in this group. In addition, there is considerable heterogeneity in the time since injury, sample types, biomarker assays, outcome measures and study methods; thus, direct comparison of these studies is difficult and no universal thresholds for abnormal biomarker concentrations have been established. To date, no single serum biomarker has been found that can be used alone to diagnose or predict the course of PTOA, and there is still no reliable individual biomarker or standardised biomarker panel for clinical application. Therefore, the next steps in research will be large-scale prospective studies, standardisation of test methods and construction of multi-marker panels for various diseases [8, 9].

5. Treatment

5.1. Anti-inflammatory treatment

Inflammation is one of the reasons why PTOA progresses, as well as other factors are that TNF- α and IL-6 are pro-inflammatory and damage cartilage. Dexamethasone and other corticosteroids are now used to reduce inflammation in people with PTOA. Dexamethasone can reduce the inflammation caused by TNF- α and IL-6, and also decrease glycosaminoglycan (GAG) loss and increase proteoglycan synthesis. Intranasal administration of dexamethasone in preclinical studies has shown that it can reduce cartilage damage and inflammation, and some protection against cartilage injury has been achieved.

Corticosteroids are not without flaws, either. After intra-articular injection, dexamethasone can quickly leave the joint and enter the bloodstream, so it is difficult to keep up with the blood levels and have a prolonged effect on chondrocytes. High doses of corticosteroids can also reduce the number of chondrocytes and synoviocytes and lower their metabolic activity. Glucocorticoids can also directly affect bone cells, and this is especially serious in PTOA because of subchondral bone

remodelling associated with the disease. Therefore, prolonged use of glucocorticoids may be harmful to the subchondral bone. Therefore, people have begun to explore low-dose and targeted delivery ways to reduce the side effects of corticosteroids and still achieve the desired therapeutic effect.

5.2. Anti-apoptotic treatment

Acute joint injury is likely to damage chondrocytes in the area of injury due to increased mechanical stress, and these chondrocytes will suffer from mitochondrial dysfunction and apoptosis. Chondrocyte death will increase the secretion of inflammatory factors, such as interleukin-6 (IL-6), and thus promote the release of matrix metalloproteinases (MMPs) by the remaining chondrocytes. Enzymes are present in the extracellular matrix of cartilage and cause its decay. At the same time, there is damage to the synovium and activation of resident macrophages, which results in the release of pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α , as well as other MMPs in the synovial fluid. Inflammatory factors will also activate osteoclasts in the subchondral bone and modify the structure of the bone. Changes in the subchondral bone and inflammation of the synovium will also produce inflammatory factors and MMPs that worsen the inflammation and damage to cartilage in a vicious cycle. Therefore, the interaction of chondrocyte death, synovial inflammation, cartilage damage and changes in subchondral bone is likely to promote the development of post-traumatic osteoarthritis (PTOA) [10].

Chondrocyte apoptosis is one of the first events after acute injury, so preventing excessive chondrocyte death may help to reduce the severity of PTOA. Mitochondrial dysfunction and the production of reactive oxygen species (ROS) in the injured area promote chondrocyte apoptosis. Therefore, the purpose of anti-apoptotic strategies is to protect chondrocytes from cell death by preventing mitochondrial dysfunction, oxidative stress, etc. Preventing the early death of chondrocytes will reduce the release of inflammatory factors that cause more damage to the cartilage and lead to further inflammation in the joint lining and under the bone. Therefore, inducing apoptosis in the early stage may break the link between acute cartilage injury and the development and progression of PTOA.

6. Conclusion

Post-traumatic osteoarthritis (PTOA) is a severe, prolonged disorder of the knee joint that frequently results from damage to the ACL, meniscus, etc. Given that PTOA occurs frequently after joint injuries, it is necessary to detect and treat it in an early stage, as the disease can affect young people's joints and quality of life progressively. Traditional imaging methods are relatively good at finding structural problems, but some changes in the body may have occurred earlier and are not yet visible in these pictures.

Therefore, researchers have begun to study biomarkers that can detect and monitor the early changes in the pathological conditions of PTOA, such as cartilage damage, tissue formation and inflammation. However, the current evidence is not uniform; there are various differences among patients, injury types, samples collected, analysis methods and clinical results. None of them have good clinical reliability for diagnosis or prognosis on their own. Therefore, the direction of the next research will be to carry out long-term controlled studies and to develop biomarker panels that incorporate many indices from all regions of the disease.

At present, many new treatments are being developed to address the underlying causes of PTOA rather than only managing the symptoms. Anti-inflammatory agents reduce the amount of

inflammatory substances and cartilage damage, and at the same time, anti-apoptotic strategies can help protect the life of chondrocytes and block the first link in the chain of joint injury, inflammation and cartilage damage. However, there are still problems with the toxicity of the treatment, poor drug retention, and other harm to other joints. In short, by adding sensitive early biomarkers, better imaging technology and mechanism-based drugs, we can find people who are more likely to develop PTOA earlier and reduce the amount of harm to the tissue before it becomes irreversible.

The next problem to be addressed is how to detect PTOA early before serious damage occurs. MRI can be combined with other kinds of tests for blood and joint fluid markers to find early changes in the joint. Expand the previous longitudinal study, standardise the diagnosis method, and determine whether the promising biomarkers have clinical value and at what threshold. Based on the above information, identify high-risk patients early and take early measures to reduce the risk of PTOA.

References

- [1] Khella, C. M., Asgarian, R., Horvath, J. M., Rolaufts, B., & 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. <https://doi.org/10.3390/ijms22041996>
- [2] Castano Betancourt, M. C., Maia, C. R., Munhoz, M., Morais, C. L., & Machado, E. G. (2022b). A review of risk factors for post-traumatic hip and knee osteoarthritis following musculoskeletal injuries other than anterior cruciate ligament rupture. *Orthopedic Reviews*, 14(4). <https://doi.org/10.52965/001c.38747>
- [3] Thomas, A. C., Hubbard-Turner, T., Wikstrom, E. A., & Palmieri-Smith, R. M. (2017). Epidemiology of posttraumatic osteoarthritis. *Journal of Athletic Training*, 52(6), 491–496. <https://doi.org/10.4085/1062-6050-51.5.08>
- [4] Berger, M. (2018, August 3). X-ray imaging. *Medical Imaging Systems: An Introductory Guide [Internet]*. <https://www.ncbi.nlm.nih.gov/books/NBK546155/>
- [5] Fogarty, A. E., Chiang, M. C., Douglas, S., Yaeger, L. H., Ambrosio, F., Lattermann, C., Jacobs, C., Borg-Stein, J., & Tenforde, A. S. (2024a). Posttraumatic osteoarthritis after athletic knee injury: A narrative review of diagnostic imaging strategies. *PM&R*, 17(1), 96–106. <https://doi.org/10.1002/pmrj.13217>
- [6] O'Sullivan, O., Valdes, A. M., Watson, F., Kluzek, S., Bull, A. M., & Bennett, A. N. (2025). Insights into knee post-traumatic osteoarthritis pathophysiology from the relationship of serum biomarkers to radiographic features in the advance cohort. *Arthritis Research & Therapy*, 27(1). <https://doi.org/10.1186/s13075-025-03648-y>
- [7] Brophy, R. H., Cai, L., Duan, X., Zhang, Q., Townsend, R. R., Nunley, R. M., Guilak, F., & Rai, M. F. (2019). Proteomic analysis of synovial fluid identifies periostin as a biomarker for anterior cruciate ligament injury. *Osteoarthritis and Cartilage*, 27(12), 1778–1789. <https://doi.org/10.1016/j.joca.2019.08.002>
- [8] O'Sullivan, O., Ladlow, P., Steiner, K., Hillman, C., Stocks, J., Bennett, A. N., Valdes, A. M., & Kluzek, S. (2023). Current status of catabolic, anabolic and inflammatory biomarkers associated with structural and symptomatic changes in the chronic phase of post-traumatic knee osteoarthritis— a systematic review. *Osteoarthritis and Cartilage Open*, 5(4), 100412. <https://doi.org/10.1016/j.ocarto.2023.100412>
- [9] Dilley, J. E., Bello, M. A., Roman, N., McKinley, T., & Sankar, U. (2023). Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation. *Bone Reports*, 18, 101658. <https://doi.org/10.1016/j.bonr.2023.101658>
- [10] Zhang, L., Yang, M., Marks, P., White, L. M., Hurtig, M., Mi, Q.-S., Divine, G., & Gibson, G. (2012). Serum non-coding RNAs as biomarkers for osteoarthritis progression after ACL injury. *Osteoarthritis and Cartilage*, 20(12), 1631–1637. <https://doi.org/10.1016/j.joca.2012.08.016>