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Osteoarthritis of the Knee is a Multifaceted Disease. Do we Need Personalized Treatments

Francesco Onorato[1*], Massimiliano Rucci[2,3], Riccardo Ferracini[2,3]

[1]Department of Orthopedics and Traumatology, University of Turin, Turin, Italy
[2]Department of Surgical Sciences, University of Genoa, Genova, Italy
[3]Koelliker Hospital, Turin Italy

Editorial

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***For Correspondence:**
Riccardo Ferracini, Koelliker Hospital, Turin, Italy
E-mail:
riccardo.ferracini@osp-koelliker.it

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EDITORIAL NOTE

Osteoarthritis (OA) is a progressive pathology of the articular cartilage, causing pain, disability and joint deformity. This process has always been considered as irreversible, with a small role for disease modifying treatments.

According to recent estimates, OA affects approximately 15% of the population, with an increasing prevalence due to progressive aging and obesity [1,2]. The knee is the most affected joint by OA. Since the eighties, there has been a continuously growing demand for Total Knee Arthroplasty (TKA) in advanced stage degenerative knee OA. Although the success rate is around 80%, the continuous increase in first implant positioning is generating a subsequent surge in revision surgeries and overall complications. Despite the wide range of technological advancements, treatment options and surgical techniques, the management of implant failures is going to become a major healthcare burden in developed countries resulting in a dramatic increase in healthcare costs [3].

For these reasons, surgeons, clinicians and biologists are now approaching knee OA diagnosis and treatment from a different perspective. Emerging data on OA biomarkers and histologic differences are helping us to define OA “patho-clinical” subgroups. In addition, biomarkers may also enable the selection of personalized treatment combinations that, whenever a clinical indication exists, could lead to personalized disease modifying therapy for OA. This editorial aims at providing some updates in understanding the clinical phenotypes of knee OA and the related treatment options.

Osteoarthritis (OA) heterogeneity

OA is a complex disease, resulting from the interaction between a subset of cellular, mechanical and biochemical elements, determining its etiology. Historically, it has been classified as a non-inflammatory arthritis, due to the early evidence of poor leukocytes count in knee synovial fluid. On the other hand, past studies have demonstrated that synovial inflammation is present in patients with primary OA. Sohn, et al. showed a higher concentration of plasma proteins, complement components and cytokines in synovial fluid of patients with OA compared to healthy individuals [4]. In addition, Benito et al. found an overexpression of inflammatory mediators early in the disease compared to late stage OA, providing a potential window for therapeutic intervention [5].

New models have been designed to quantify inflammation and predict OA progression. However, patients' heterogeneity, low biomarker concentration and absence of relevant reference methods, still prevent a precise OA classification and consequently a personalized therapeutic approach [6,7].

Identification of the main pathogenic mechanisms, molecular pattern and clinical phenotypes is crucial for understanding knee OA progression and predicting therapeutic response [8,9].

Most of knee OA patients experience chronic pain. The alteration in pain neurophysiology and resulting psychological distress support a chronic pain phenotype with features beyond tissue-related OA pain. The continuous stimulation of the nociceptive receptors leads to sensitization of both peripheral and central neural pathways lowering pain threshold. In addition, consequent psychological pain negatively influences pain management outcomes [10].

Recent literature has revealed the existence of an OA inflammatory phenotype. This subgroup is characterized by the overexpression of inflammatory cytokines, an additional potential target of specific experimental therapies. Patients with the inflammatory phenotype complain of greater pain at baseline and experience a faster radiographic progression compared to patients with lower cytokine concentration. Synovitis is believed to contribute to the pathophysiology and symptoms of OA, increasing local production of pro-inflammatory mediators leading to joint tissue damage. As a result, synovial inflammation has been demonstrated to reduce the effectiveness of new immunomodulatory and cartilage renewal therapies [11].

Patients with metabolic syndrome represent an independent subgroup as far as inflammatory knee OA is concerned. Their phenotype results from a combination of factors such as obesity, diabetes, insulin resistance, hypertension, and dyslipidaemia, all of which have been linked to OA. Obesity, for instance, is not only a risk factor for OA due to excessive weight bearing, as even non-weight-bearing joints have an increased risk for OA development with obesity.

Metabolic dysregulation is considered the major driver of persistent low-grade inflammation and high glucose levels increase oxidative stress on chondrocytes, possibly impairing their functions and turn-over [12].

Regarding the main joint tissue target of the disease, we can differentiate a chondral-driven OA and subchondral-driven OA. Cartilage degeneration is the result of chronic mechanical loading and chondrocytes senescence leading to an alteration in cartilage weight-bearing capacity and consequently to progressive tissue softening and erosion.

In contrast, subchondral bone changes, often in combination with overlying cartilage damage, are instead intrinsic alterations in the histology and mechanics of subchondral bone. Recent MRI evidence suggests that subchondral bone lesion and bone marrow edema play an even larger role in knee OA development than simple mechanical support [13].

In their review, Dell'Isola, et al. did not distinguish a traumatic or post-traumatic knee OA phenotype while Lambova classified previous injury within the mechanical phenotype [8,9]. However, when considering as an example the high percentage of tibial plateau fracture in patients who undergo knee replacement at young age, it is the authors' opinion that a history of traumatic knee injury should constitute a separate subgroup.

Lastly, literature reports a minimal joint disease phenotype characterized by mild imaging degeneration signs, modest clinical symptoms, and a slow progression rate.

Emerging data allow for the identification of several OA subgroups, which however, rarely exist as distinct clinical entities. An overlap between different subtypes is present most of the times. Nevertheless, the determination of the overlapping clinical phenotypes may provide clues for personalized and combined therapeutic strategies.

Current therapeutic strategies according to OA phenotypes

The choice of combined therapeutic strategies to restore joint homeostasis has always been fascinating. Nevertheless, the standard and universally accepted pharmacological treatment still consists of non-steroidal anti-inflammatory drugs, analgesics and chondroprotectors [14]. However, when considering the aforementioned knee OA entities, it is possible to hypothesize a target-specific treatment for any specific clinical phenotype.

Regarding patients with chronic pain, the alteration in pain perception leads to sleep disturbance, fatigue and psychological distress, which should be targeted when approaching this type of patients [10]. The latest OARSI guidelines suggest a central pharmacological management for chronic pain along with cognitive behavioural therapy through self-management programs. Moreover, for those patients with pain and psychological distress resulting in depression, the use of duloxetine could be considered appropriate when approved by patients [14].

Repetitive Intra-Articular (IA) hyaluronic acid injections are conditionally recommended for patients with chronic pain and depression, showing beneficial effects on pain beyond 12 weeks of treatment and a favourable long-term safety [14,15]. As an alternative IA injection of polyacrylamide hydrogel demonstrated good clinical effects at 12 weeks up to 52 weeks in patients with moderate to severe knee OA [16].

For the inflammatory driven phenotype, treatments should aim at reducing the pro-inflammatory joint milieu. IA corticosteroid injections have been widely used for decades, but they are a non-specific treatment that shows effectiveness up to 6 weeks without radiological evidence of joint cartilage preservation [17]. However, short-term treatment with corticosteroid injections is still recommended by all most recent guidelines [14,18].

Innovative immunomodulatory therapeutic alternatives such as Mesenchymal Stem Cells (MSCs) have been extensively studied for their plasticity. Among the multiple tissue sources, adipose derived MSCs injection demonstrated good outcomes in reducing pain and improving physical activity for up to 2 years. MRI has shown improvement in cartilage thickness, reported both using stromal vascular fraction and micro-fragmented adipose tissue extracts. However, evidence of synovial hypertrophy seems to hamper the response and the heterogeneity in product preparation prevents us from a clear understanding of MSCs treatment results [11,19].

Clinical and pre-clinical studies are attempting to demonstrate the effectiveness in targeting specific pro-inflammatory markers. However, a recent phase 2 trial of an anti-IL1α/β antibody in patients with knee OA and synovitis detected by MRI showed limited improvement in pain scores and no change in synovitis in the treated group compared to placebo [20].

The optimal approach to metabolic dysregulation remains an intriguing question. The therapeutic strategies used for treating different components of metabolic syndrome may influence various manifestations including metabolic type knee OA [8]. Recent pre-clinical studies have explored the effects of targeting obesity-driven macrophage activation in metabolic OA. Interestingly, macrophage deletion strategies showed some degree of effectiveness in managing OA symptoms. However, the evidence of unaltered physiologic response of healthy macrophages, normally responsible for tissue regulation and healing, still needs to be demonstrated [12].

Lastly, mechanical knee OA has historically been treated by orthopedics surgeons addressing the primary biomechanical defect responsible for etiopathogenesis. High tibial or distal femoral osteotomies are performed for the surgical correction of varus or valgus metaphyseal deformities with excellent results up to medium term follow-up [21]. Diffused cartilage-driven OA in the absence of meniscal and ligamentous tear may benefit from IA visco supplementation, even if for short periods. Due to these reasons new therapeutic protocols aiming to treat both cartilage damage and subchondral lesions have been studied, showing valuable clinical and radiological improvement up to two years of follow-up [22].

Recent evidence suggests that OA is a multifaceted disease with multiple overlapping clinical phenotypes. A better understanding of the clinical subgroups and the underlying biomarkers can predict disease progression and facilitate personalized therapeutic strategies, with significant savings for the healthcare systems.

REFERENCES

1. Johnson VL, et al. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol. 2014;28:5-15.
2. Palazzo C, et al. Risk factors and burden of osteoarthritis. Ann Phys Rehabil Med. 2016;59:134-138.
3. Kurtz SM, et al. Are we winning or losing the battle with per prosthetic joint infection: trends in per prosthetic joint infection and mortality risk for the medicare population. J Arthroplasty. 2018;33:3238–45.
4. Sohn DH, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. Arthritis Res Ther. 2012;14:R7.
5. Benito MJ, et al. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis. 2005;64:1263–1267.
6. Bernotiene E, et al. Emerging technologies and platforms for the immunodetection of multiple biochemical markers in osteoarthritis research and therapy. Front Med (Lausanne). 2020;7:572-977.
7. De Francesco F, et al. Stem cells in autologous microfragmented adipose tissue: current perspectives in osteoarthritis disease. Int J Mol Sci. 2021;22:4-6.
8. Lambova SN. Knee osteoarthritis-how close are we to disease-modifying treatment: emphasis on metabolic type knee osteoarthritis. Life (Basel). 2023;13:22-28.

9. Dell'Isola A, et al. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord. 2016;17:425.
10. Egsgaard LL, et al. Identifying specific profiles in patients with different degrees of painful knee osteoarthritis based on serological biochemical and mechanistic pain biomarkers: a diagnostic approach based on cluster analysis. Pain. 2015;156:96-107.
11. Ferracini R, et al. Age and synovitis affect the results of the treatment of knee osteoarthritis with micro fragmented autologous fat tissue. Knee Surg Sports Traumatol Arthrosc. 2022;2:7-9.
12. Warmink K, et al. Macrophage-driven inflammation in metabolic osteoarthritis: implications for biomarker and therapy development. Int J Mol Sci. 2023;24:5-9.
13. Madry H, et al. The basic science of the subchondral bone. Knee Surg Sports Traumatol Arthrosc. 2010;18:419-433.
14. Bannuru RR, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil. 2019;27:1578–1589. [Crossref] [Google Scholar] [PubMed]
15. Bellamy N, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2005;2:CD005321.
16. Bliddal H, et al. Polyacrylamide hydrogel injection for knee osteoarthritis: results of a 52 week prospective study. Osteoarthr Cartil. 2021;29:S278.
17. Jüni P, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015;2015:CD005328.
18. Kolasinski SL, et al. 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip and knee. Arthritis Rheumatol. 2020;72:220-233.
19. Hurley ET, et al. Limited evidence for adipose-derived stem cell therapy on the treatment of osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2018;26:3499–507.
20. Fleischmann RM, et al. A phase ii trial of lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. Arthritis Rheumatol. 2019;71:1056–1069.
21. Kuwashima U. High tibial osteotomy: The past, present, and future. Journal of Joint Surgery and Research. 2023;1:103–107.
22. Kon E, et al. Combined subchondral and intra-articular injections of bone marrow aspirate concentrate provide stable results up to 24 months. Knee Surg Sports Traumatol Arthrosc. 2023;31:2511–2517.