

骨赘在膝骨关节炎中的研究进展

马鹏飞¹, 刘宇轩², 刘宇宸²

¹承德医学院研究生院, 河北 承德

²河北医科大学研究生院, 河北 石家庄

收稿日期: 2025年11月16日; 录用日期: 2025年12月9日; 发布日期: 2025年12月18日

摘要

骨关节炎(osteoarthritis, OA)是一种慢性退行性关节疾病, 主要影响膝盖等负重关节。随着人口老龄化的日益加剧和肥胖率的上升, 全球骨关节炎的负担激增。骨赘形成是骨关节炎病理过程中的一个特征性表现, 其在OA病程中也具有重要影响和意义。本文旨在通过查阅国内外近年来关于膝骨关节炎(knee osteoarthritis, KOA)及骨赘的相关文献, 并进行总结分析。深入研究KOA骨赘的形成机制、临床意义、影像学检查及相关治疗等多方面特征, 并展望未来研究方向, 以期对OA的预防与治疗提供新的思路与方法。

关键词

骨关节炎, 膝关节, 骨赘, 综述

Research Progress of Osteophytes in Knee Osteoarthritis

Pengfei Ma¹, Yuxuan Liu², Yuchen Liu²

¹Graduate School of Chengde Medical University, Chengde Hebei

²Graduate School of Hebei Medical University, Shijiazhuang Hebei

Received: November 16, 2025; accepted: December 9, 2025; published: December 18, 2025

Abstract

Osteoarthritis (OA) is a chronic degenerative joint disease that mainly affects weight-bearing joints such as the knees. With the increasing aging of the population and the rising obesity rate, the global burden of osteoarthritis has surged. Osteophyte formation is a characteristic manifestation in the pathological process of osteoarthritis and also has significant influence and significance in the course of OA. This article aims to review and analyze the relevant domestic and foreign literature on knee osteoarthritis (KOA) and osteophytes in recent years. It delves into the formation mechanism,

clinical significance, imaging examination, and related treatment of KOA osteophytes, as well as looks forward to future research directions, with the aim of providing new ideas and methods for the prevention and treatment of OA.

Keywords

Osteoarthritis, Knee Joint, Osteophytes, Review

Copyright © 2025 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

骨关节炎(osteoarthritis, OA)是最常见的关节炎形式,是一种慢性退行性关节疾病,常见于中老年人群。OA的主要临床特征包括关节疼痛、肿胀和功能障碍,这会显著降低患者的生活质量并给个人和社会带来相当大的经济负担[1] [2]。近年来OA的患病率持续上升,已经成为全球70岁后第七大残疾原因,其主要影响膝关节[3]。

膝骨关节炎(knee osteoarthritis, KOA)被认为是一种全关节疾病,其结构改变涉及骨赘生成、关节软骨损伤、半月板撕裂、滑膜炎、前交叉韧带撕裂等[4]。其中,骨赘长期以来被视为KOA的标志性结构改变,也是诊断和评估KOA的主要指标[5]。骨赘的发生意味着OA的慢性、进行性和退行性过程[6]。但骨赘在KOA病程中的作用机制仍不明确,其与膝关节症状的相关性也存在较大争议[7]。本文就骨赘在OA中的研究进展作一总结。

2. 骨赘的定义和特征

骨赘是关节软骨表面生成的从骨皮质延伸的局灶性骨性赘生物,多位于关节边缘[8],被认为是关节不稳的适应性改变[9]。骨赘生成经历了软骨骨赘,骨-软骨骨赘到骨性骨赘的过程[10]。性别、年龄、BMI、机械应力和运动方式与骨赘形成密切相关[8] [11]。

从KOA患者手术中获得的骨赘染色发现,骨赘的长度近一半为软骨覆盖区[12]。Kazuha等人[13]利用显微计算机断层扫描(micro-CT)观察KOA患者膝内侧间室骨赘的三维微观结构特征发现,骨赘的小梁体积分数和小梁数显著低于松质骨、骨赘的小梁分离率始终显著较高。骨赘表现出杂乱无章的小梁方向、小梁穿孔及小梁断裂。这些发现表明骨赘在功能上是脆弱的,它们没有正常关节软骨的生物力学特征。三维微结构分析显示骨赘具有独特的矿化模式和空间分布特征,在内侧间室的表现尤为显著[14]。值得关注的是,目前骨赘微结构的进一步详细特征几乎没有得到研究。

3. 骨赘形成的机制

以往的研究将骨赘的生成分为五个连续的阶段:即骨膜或滑膜起源的间充质细胞(0期)、软骨源性细胞(I期)、纤维软骨(II期)、早期骨赘(III期)及成熟的骨赘(IV期)[15]。骨赘的生成是一个复杂的过程,尽管其潜在机制尚不完全清楚,但目前认为是由力学因素、生化因素及两者共同作用促进骨赘生成。

3.1. 生物力学因素

骨赘通常被认为是退行性关节过度机械负荷的内源性修复反应[16],试图稳定受累关节以更好地承

受异常力量[17]。在 OA 发病过程中,异常的机械负荷会导致软骨下骨过度骨破坏和骨吸收,进而引发快速的软骨下骨转换、囊肿形成、硬化和最终的关节软骨退化[18]。这种机械应力诱导的骨重塑过程被认为是骨赘形成的初始触发因素。

此外,韧带损伤也是 OA 形成的一个危险因素。前交叉韧带损伤与骨赘形成之间存在复杂的双向关系。一方面,ACL 损伤后关节不稳定可加速骨赘形成[19];另一方面,已形成的骨赘又可进一步改变关节生物力学环境,增加 ACL 的机械负荷[20]。Hsia 等[21]通过非侵入方式断裂小鼠前十字韧带来构建外伤性 OA 模型,2 周后发现韧带损伤的关节内有软骨性骨赘形成,而在 8 周时有骨性骨赘形成。临床数据显示,约 50% 的 ACL 损伤患者在伤后 10 年内发展为骨关节炎,其中骨赘形成是重要的影像学标志[22]。值得注意的是,ACL 重建手术虽然能恢复关节稳定性,但并不能完全阻止骨赘形成和骨关节炎进展,这可能与手术时机、康复方案等多种因素有关[20] [23]。

3.2. 生物化学因素

骨赘的形成与软骨内成骨过程相似,受多个信号通路调控,其中 Wnt/ β -catenin 及 BMP 信号通路发挥主要调控作用[24] [25]。在 OA 中,软骨退变导致细胞因子表达失调,如骨形态发生蛋白(BMPs)和 Wnt 信号通路激活,促进间充质细胞向软骨细胞分化,并加速软骨内成骨过程,从而促进骨赘形成[26] [27]。同时,滑膜炎等炎症反应释放的炎症因子(如 TNF- α 、IL-1 β)进一步刺激骨赘形成[28]。

一系列研究表明,透明质酸(HA)在骨赘形成过程中扮演重要角色。HA 是脊椎动物组织细胞外基质的主要成分,为细胞提供机械支持,并作为调节组织稳态所必需的生化过程的介质[29]。在 OA 病理过程中,HA 含量的变化与疾病进展密切相关[29]。研究发现,HA 可通过其高分子量特性增加皮肤弹性并保护免受缺氧条件下的氧化应激[30],这种机制可能也参与关节组织的适应性改变。

此外,相关研究表明,血管内皮生长因子(VEGF)、降钙素基因相关肽(CGRP)、骨桥蛋白(OPN)、脂肪因子、转化生长因子- β (TGF- β)、胰岛素一号增长因子(IGF-1)等在 OA 骨赘的形成过程中发挥重要的作用[31]-[34]。但是,这些细胞因子在骨赘发生过程的各个阶段如何起作用,是否具有阶段特异性,目前尚不清楚。

4. 膝骨关节炎骨赘的临床意义

4.1. 骨赘在膝骨关节炎中的诊断地位

Kellgren-Lawrence (KL)分级系统是全球广泛接受的 OA 严重程度评估方法,该系统使用 0~4 级来分类 OA 严重程度[35] [36]。KL 分级为:0 级无 OA 表现;I 级轻微骨赘;II 级明显骨赘,但未累及关节间隙;III 级关节间隙中度狭窄;IV 级关节间隙明显狭窄,伴软骨下骨硬化。骨赘的存在和大小是 KL 分级的关键指标之一[35] [37]。值得注意的是,在早期 OA 诊断中(KLG 0 或 1 级),骨赘的出现可能预示着疾病进展的风险[38] [39],这进一步强调了骨赘在 OA 诊断和预后评估中的核心地位。

4.2. 骨关节炎骨赘形成具有双重作用

骨赘形成可能具有双重作用:一方面通过限制关节活动来适应改变的生物力学环境。迄今为止,几项研究支持这样一个假设,即骨赘是在过度的机械负荷下发育形成的,以试图减少 OA 关节上的应力,将力重新分配到更大的关节表面,为关节软骨提供保护[40] [41]。另一方面又成为疼痛和功能障碍的来源[37]。多项研究表明,骨赘的形成会限制关节活动范围,这种机械性限制作用与骨赘大小呈正相关关系。在膝关节骨关节炎患者中,较大的骨赘可显著降低关节活动度,特别是在屈曲和伸展运动中表现最为明显[37]。

4.3. 不同区域骨赘与临床症状的相关性

胫股关节骨赘(尤其是内侧间室)与膝关节骨性关节炎的严重程度显著相关。在 KL 分级 3 级和 4 级的膝关节中, 内侧间室的总骨赘体积显著大于外侧间室, 且内侧骨赘体积与股胫角(Femorotibial Angle, FTA)呈正相关, 提示骨赘可能加重下肢力线异常[42]。MRI 检测的胫股关节骨赘与膝关节症状进展(如总膝痛、负重痛、僵硬和功能障碍)显著相关, 尤其在合并骨髓病变(BMLs)或滑膜炎的患者中更为明显[7]。此外, 半月板撕裂是胫股关节骨赘发展的最强结构风险因素[5]。临床观察发现, 一些特殊部位骨赘如髁间窝骨赘患者更易出现关节绞锁症状, 而后内侧骨赘患者则更多表现为步行疼痛和活动受限[20][43](见表 1)。一项纵向研究发现, 内翻膝中存在大的胫骨内侧骨赘[44]。这会收紧内侧韧带结构, 增加内侧间室的不对称负荷。还有研究发现胫骨后外侧骨赘体积与 ALL 之间存在很强的相关性[45]。最近 Tzanetis P 等[46]进行了一项骨赘对 TKA 患者术前膝关节功能影响的数值研究发现, 严重的骨赘(对应 KL-4 级)膝关节严重拉伤了腓斜韧带(OPL)和后关节囊(PC), 表明 OA 膝关节中骨赘的存在诱导了韧带应变和运动学的临床相关变化。但这些变化是可变的, 且具有患者特异性。具体取决于骨赘体积和位置以及韧带与骨赘的相互作用。

髌股关节骨赘的发生率较高(51.7%), 但多为小型或可疑骨赘。与胫股关节骨赘导致的行走痛不同, 髌股关节骨赘更易导致上下楼梯痛[47]。髌股关节软骨损伤是髌股关节骨赘发展的主要风险因素, 可能通过局部生物力学因素(如髌骨轨迹异常)加重症状 3。

Table 1. The correlation between osteophytes in different regions and clinical symptoms
表 1. 不同区域骨赘与临床症状的相关性

骨赘区域	胫股关节骨赘	髌股关节	股骨髁间窝骨赘
相关临床症状	行走痛、活动受限(后内侧)、下肢力线异常(内侧)	上下楼梯痛	关节绞索
主要风险因素	膝半月板撕裂	髌股关节软骨损伤	膝十字韧带损伤

5. 骨赘对膝关节置换术的影响

关节置换术通过切除受损关节并用人工关节替换来治疗 OA。当 OA 导致剧烈疼痛、残疾并严重损害生活质量, 以及保守治疗(如药物和物理治疗)未能缓解症状时, 通常会考虑进行人工关节置换术[48]。尽管骨赘通常不是人工关节置换术中外科医生关注的重点, 但它们通常可以预测手术的难度和时间。此外, 骨赘的大小和位置可能会对膝关节置换术产生一定影响。

近年来, 机器人技术开创了全膝关节置换术(total knee arthroplasty, TKA)的新时代。与传统手工对比, 机器人辅助全膝关节置换术(rTKA)具有多方面明显的优势[49]-[51]。rTKA 术前计划目前依赖于 OA 患者膝关节的术前计算机断层(CT)扫描, 通常包括骨赘特征。这使得外科医生在手术前预测骨赘的确切生物力学效应以及去除骨赘的后果变得复杂。

TKA 中, 外科医生通常会去除骨赘, 以实现更多生理性膝关节生物力学的恢复; 未能去除它们可能会导致屈伸间隙不等, 从而导致软组织失衡, 形成异常的关节运动学[47]。Mullaji A 进行了一项关于骨赘切除术对接受 rTKA 的内翻膝关节畸形矫正和软组织间隙平衡的研究, 发现 2/3 的膝关节可以通过仅释放交叉韧带和切除骨赘来实现对齐和平衡。骨赘切除是实现畸形矫正和间隙平衡的有用步骤, 而无需求助于内翻膝关节的软组织松解, 同时保持假体的经典冠状位和矢状位对齐[52]。Sriphirom P 等发现股骨后髁骨赘的存在导致使用计算机辅助系统测量的伸展和屈曲间隙增加[53]。但这两项研究都并未根据骨赘的大小以及位置分析去除骨赘带来的结果。Gustke 等[54]通过使用机器人辅助系统测量间隙, 证明了后骨赘大小和位置的影响。与以前的研究相比, 他们的结果是无论是否存在骨赘, 对于截骨前后冠状面

间隙平衡都没有观察到显著差异。然而,最新的一项关于 rTKA 术中去除股骨后内侧髁骨赘对内外侧屈伸间隙影响的研究发现,当骨赘的大小为 $<10\text{ mm}$ 时,观察到伸展和屈曲间隙的对称增加。相比之下,对于超过 10 mm 的骨赘,观察到内侧伸展间隙显著增加,导致不对称的内、外侧延伸间隙[55]。

综上所述,由于 OA 患者膝关节骨赘的存在使得在进行 rTKA 术前计划时变得困难,需根据患者骨赘大小及位置不同制定个性化手术方案;同时,在内翻膝 OA 患者术中由于股骨后髁较大骨赘的切除,导致内侧间隙比最初计划间隙略大。为了应对切除后内侧间隙的预期增加,在初始规划阶段,谨慎的做法是计划相对于外侧间隙稍微紧密的内侧间隙。该策略有助于确保截骨后更为平衡的屈曲和伸展间隙。此外,相关经验也可以为传统手工 TKA 给予一定指导意义。值得注意的是,目前关于膝关节骨赘对 TKA 的影响注意集中在后内侧髁上,而对胫骨平台后内侧骨赘的相关研究较少,作者认为较大的胫骨平台后内侧骨赘的去除对 TKA 术中间隙平衡的影响同样重要,此处需要进一步的实验研究。

6. 膝骨关节炎骨赘的放射学研究进展

不同影像学技术在骨赘评估中各具优势。X 线检查作为传统方法,具有操作简便、成本低的优点,但敏感性低于 CT 和超声[56]。CT 作为参考标准,在 SEKOIA 试验中显示出对膝部所有间室骨赘评估的最佳诊断性能[57]。MRI 的优势在于可同时评估多种关节结构异常,研究发现 MRI 检测的骨赘评分与膝关节症状进展相关[7]。在纵向研究中,MRI 可有效监测无放射学膝骨关节炎的中年受试者骨赘的发展过程[5]。重要的是,超声检查已被引入以检查膝关节的 OA 变化,据报道在检测膝骨赘[58]方面比 X 线更敏感。软骨在超声检查中表现为低回声区域[59],与传统 MRI 相比,超声检查低估了软骨厚度[60] [61]。然而,由于超声检查易于使用且成本比 MRI 低得多,因此可以通过超声检查频繁监测骨赘变化。

7. 膝骨关节炎骨赘的治疗

在治疗方面,目前的 OA 治疗主要是对症治疗,侧重于减轻疼痛和炎症,而并非解决潜在的疾病机制。药物治疗,如应用非甾体抗炎药,可提供短期缓解,但不会改变疾病的进展[62]。在临床实践中,当骨赘导致机械性撞击、显著限制关节活动或引发顽固性疼痛时,外科医生会考虑骨赘清除术。目前该手术的适应证仍存在争议,主要集中于对“保护性”与“破坏性”作用的权衡[37]。值得注意的是,髁间窝和后内侧等特殊部位的骨赘更易引发临床症状,这些区域的清除术可能获得更好的功能改善[7]。

随着对骨关节炎病理机制认识的深入,针对骨赘形成的分子干预策略逐渐成为研究热点[63]。现有研究主要聚焦于调控骨代谢平衡的靶点,包括抑制过度破骨细胞活化和增强成骨细胞代谢活性的双重调节策略[64]。冲击波刺激等物理干预手段可促进局部药物控释,在骨质疏松模型中显示出恢复骨代谢平衡、提高骨密度的效果[65]。此外,针对羟基磷灰石的靶向递药系统也被开发用于骨赘的精准干预[66]。最近一项关于骨赘形成与骨密度和肌肉含量的研究发现,膝骨赘形成与股骨颈 T 评分和高血压有关,但与肌肉含量无关[67]。而 Zhu D 等人研究发现,饮食通过肠道微生物群和血清代谢物影响膝骨关节炎骨赘的形成。肠道中较高的布劳特氏菌属(*Blautia*)水平可能导致 KOA 骨赘的形成,血清代谢物 LTB4 和 PGD2 可能作为生物标志物[68]。

8. 未来研究方向

8.1. 骨赘分子分型与精准治疗路径

基于分子亚型分析在肿瘤学领域取得的突破性进展[69],膝骨关节炎骨赘的分子分型研究将成为未来重要方向。目前已有研究提出通过蛋白质组学方法建立明确的标志物组合[70],这将有助于开发针对不同骨赘亚型的精准治疗策略。实现个体化治疗方案的制定。

8.2. 动态影像评估技术的开发

随着人工智能驱动影像组学的发展[71], 动态影像评估技术将成为研究骨赘形成和进展的有力工具。目前 MRI 技术在骨关节炎诊断中已显示出重要价值[71], 但针对骨赘动态变化的定量评估方法仍有待开发。未来研究需要整合人工智能算法, 建立能够精确量化骨赘三维结构变化的技术平台。这种动态评估方法不仅能够提高早期诊断的准确性[71], 更重要的是可以监测治疗干预后骨赘的形态学改变, 为临床决策提供客观依据。

8.3. 智能机器人辅助的技术突破

基于深度学习的 ShapeMed-Knee 系统在骨赘定位和大小测量方面展现出 63% 的准确率, 显著优于传统影像分析方法[72]。这些技术进步为机器人辅助下的精准骨赘清除术奠定了基础, 特别是对于伴有前交叉韧带损伤的复杂病例[73]。未来智能机器人辅助系统将整合多模态影像数据和生物力学参数, 实现个性化手术方案的优化设计[72]。

参考文献

- [1] Perruccio, A.V., Young, J.J., Wilfong, J.M., Denise Power, J., Canizares, M. and Badley, E.M. (2024) Osteoarthritis Year in Review 2023: Epidemiology & Therapy. *Osteoarthritis and Cartilage*, **32**, 159-165. <https://doi.org/10.1016/j.joca.2023.11.012>
- [2] Yue, L. and Berman, J. (2022) What Is Osteoarthritis? *JAMA*, **327**, 1300. <https://doi.org/10.1001/jama.2022.1980>
- [3] Courties, A., Kouki, I., Soliman, N., Mathieu, S. and Sellam, J. (2024) Osteoarthritis Year in Review 2024: Epidemiology and Therapy. *Osteoarthritis and Cartilage*, **32**, 1397-1404. <https://doi.org/10.1016/j.joca.2024.07.014>
- [4] Eckstein, F., Wirth, W. and Culvenor, A.G. (2021) Osteoarthritis Year in Review 2020: Imaging. *Osteoarthritis and Cartilage*, **29**, 170-179. <https://doi.org/10.1016/j.joca.2020.12.019>
- [5] Snoeker, B.A.M., Ishijima, M., Kumm, J., Zhang, F., Turkiewicz, A.T. and Englund, M. (2021) Are Structural Abnormalities on Knee MRI Associated with Osteophyte Development? Data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*, **29**, 1701-1708. <https://doi.org/10.1016/j.joca.2021.06.012>
- [6] Xu, Z., Chen, T., Luo, J., Ding, S., Gao, S. and Zhang, J. (2017) Cartilaginous Metabolomic Study Reveals Potential Mechanisms of Osteophyte Formation in Osteoarthritis. *Journal of Proteome Research*, **16**, 1425-1435. <https://doi.org/10.1021/acs.jproteome.6b00676>
- [7] Fan, T., Ruan, G., Antony, B., Cao, P., Li, J., Han, W., et al. (2021) The Interactions between MRI-Detected Osteophytes and Bone Marrow Lesions or Effusion-Synovitis on Knee Symptom Progression: An Exploratory Study. *Osteoarthritis and Cartilage*, **29**, 1296-1305. <https://doi.org/10.1016/j.joca.2021.06.008>
- [8] Zhu, Z., Ding, C., Han, W., Zheng, S., Winzenberg, T., Cicuttini, F., et al. (2018) MRI-Detected Osteophytes of the Knee: Natural History and Structural Correlates of Change. *Arthritis Research & Therapy*, **20**, Article No. 237. <https://doi.org/10.1186/s13075-018-1734-5>
- [9] Zhu, Z., Laslett, L.L., Han, W., Antony, B., Pan, F., Cicuttini, F., et al. (2017) Associations between MRI-Detected Early Osteophytes and Knee Structure in Older Adults: A Population-Based Cohort Study. *Osteoarthritis and Cartilage*, **25**, 2055-2062. <https://doi.org/10.1016/j.joca.2017.09.005>
- [10] Junker, S., Krumbholz, G., Frommer, K.W., Rehart, S., Steinmeyer, J., Rickert, M., et al. (2016) Differentiation of Osteophyte Types in Osteoarthritis—Proposal of a Histological Classification. *Joint Bone Spine*, **83**, 63-67. <https://doi.org/10.1016/j.jbspin.2015.04.008>
- [11] Venne, G., Tse, M.Y., Pang, S.C. and Ellis, R.E. (2020) Mechanically-Induced Osteophyte in the Rat Knee. *Osteoarthritis and Cartilage*, **28**, 853-864. <https://doi.org/10.1016/j.joca.2020.02.834>
- [12] Hada, S., Ishijima, M., Kaneko, H., Kinoshita, M., Liu, L., Sadatsuki, R., et al. (2017) Association of Medial Meniscal Extrusion with Medial Tibial Osteophyte Distance Detected by T2 Mapping MRI in Patients with Early-Stage Knee Osteoarthritis. *Arthritis Research & Therapy*, **19**, Article No. 201. <https://doi.org/10.1186/s13075-017-1411-0>
- [13] Kizaki, K., Uchida, S., Yamashita, F., Tsukamoto, M. and Azuma, K. (2018) Microstructure of Osteophytes in Medial Knee Osteoarthritis. *Clinical Rheumatology*, **37**, 2893-2896. <https://doi.org/10.1007/s10067-018-4262-4>
- [14] Mi, C., Zhang, X., Yang, C., Wu, J., Chen, X., Ma, C., et al. (2023) Bone Disease Imaging through the Near-Infrared-II Window. *Nature Communications*, **14**, Article No. 6287. <https://doi.org/10.1038/s41467-023-42001-2>

- [15] Shio, K., Kobayashi, H., Asano, T., Saito, R., Iwadata, H., Watanabe, H., *et al.* (2010) Thrombin-cleaved Osteopontin Is Increased in Urine of Patients with Rheumatoid Arthritis. *The Journal of Rheumatology*, **37**, 704-710. <https://doi.org/10.3899/jrheum.090582>
- [16] Rockel, J.S. and Kapoor, M. (2018) The Metabolome and Osteoarthritis: Possible Contributions to Symptoms and Pathology. *Metabolites*, **8**, Article No. 92. <https://doi.org/10.3390/metabo8040092>
- [17] Cai, W., Li, H., Zhang, Y. and Han, G. (2020) Identification of Key Biomarkers and Immune Infiltration in the Synovial Tissue of Osteoarthritis by Bioinformatics Analysis. *PeerJ*, **8**, e8390. <https://doi.org/10.7717/peerj.8390>
- [18] Fang, C., Guo, J., Wang, Y., Li, X., Zhang, H., Cui, J., *et al.* (2021) Diterbutyl Phthalate Attenuates Osteoarthritis in ACLT Mice via Suppressing ERK/c-fos/NFATc1 Pathway, and Subsequently Inhibiting Subchondral Osteoclast Fusion. *Acta Pharmacologica Sinica*, **43**, 1299-1310. <https://doi.org/10.1038/s41401-021-00747-9>
- [19] Arakawa, K., Takahata, K., Enomoto, S., Oka, Y., Ozone, K., Nakagaki, S., *et al.* (2022) The Difference in Joint Instability Affects the Onset of Cartilage Degeneration or Subchondral Bone Changes. *Osteoarthritis and Cartilage*, **30**, 451-460. <https://doi.org/10.1016/j.joca.2021.12.002>
- [20] Daniel, A.V., Thompson, G.P., Levy, B.A. (2025) Editorial Commentary: Let's Finally Agree That Anterior Cruciate Ligament Reconstruction Lowers the Risk of Total Knee Arthroplasty When Compared with Nonoperative Treatment. *Arthroscopy*, **41**, 5265-5267.
- [21] Hsia, A.W., Anderson, M.J., Heffner, M.A., Lagmay, E.P., Zavodovskaya, R. and Christiansen, B.A. (2016) Osteophyte Formation after ACL Rupture in Mice Is Associated with Joint Restabilization and Loss of Range of Motion. *Journal of Orthopaedic Research*, **35**, 466-473. <https://doi.org/10.1002/jor.23252>
- [22] Putera, K.H., Kim, J., Baek, S.Y., Schlecht, S.H., Beaulieu, M.L., Haritos, V., *et al.* (2023) Fatigue-Driven Compliance Increase and Collagen Unravelling in Mechanically Tested Anterior Cruciate Ligament. *Communications Biology*, **6**, Article No. 564. <https://doi.org/10.1038/s42003-023-04948-2>
- [23] Filbay, S.R., Roemer, F.W., Lohmander, L.S., Turkiewicz, A., Roos, E.M., Frobell, R., *et al.* (2022) Evidence of ACL Healing on MRI Following ACL Rupture Treated with Rehabilitation Alone May Be Associated with Better Patient-Reported Outcomes: A Secondary Analysis from the KANON Trial. *British Journal of Sports Medicine*, **57**, 91-99. <https://doi.org/10.1136/bjsports-2022-105473>
- [24] Funck-Brentano, T., Bouaziz, W., Marty, C., Geoffroy, V., Hay, E. and Cohen-Solal, M. (2014) Dkk-1-Mediated Inhibition of Wnt Signaling in Bone Ameliorates Osteoarthritis in Mice. *Arthritis & Rheumatology*, **66**, 3028-3039. <https://doi.org/10.1002/art.38799>
- [25] Gelse, K., Ekici, A.B., Cipa, F., Swoboda, B., Carl, H.D., Olk, A., *et al.* (2012) Molecular Differentiation between Osteophytic and Articular Cartilage—Clues for a Transient and Permanent Chondrocyte Phenotype. *Osteoarthritis and Cartilage*, **20**, 162-171. <https://doi.org/10.1016/j.joca.2011.12.004>
- [26] Schett, G., Zwerina, J. and David, J. (2008) The Role of Wnt Proteins in Arthritis. *Nature Clinical Practice Rheumatology*, **4**, 473-480. <https://doi.org/10.1038/ncprheum0881>
- [27] Bouaziz, W., Funck-Brentano, T., Lin, H., Marty, C., Ea, H., Hay, E., *et al.* (2015) Loss of Sclerostin Promotes Osteoarthritis in Mice via β -Catenin-Dependent and -Independent Wnt Pathways. *Arthritis Research & Therapy*, **17**, Article No. 24. <https://doi.org/10.1186/s13075-015-0540-6>
- [28] Scanzello, C.R. and Goldring, S.R. (2012) The Role of Synovitis in Osteoarthritis Pathogenesis. *Bone*, **51**, 249-257. <https://doi.org/10.1016/j.bone.2012.02.012>
- [29] Gagneja, S., Capalash, N. and Sharma, P. (2024) Hyaluronic Acid as a Tumor Progression Agent and a Potential Chemotherapeutic Biomolecule against Cancer: A Review on Its Dual Role. *International Journal of Biological Macromolecules*, **275**, Article ID: 133744. <https://doi.org/10.1016/j.ijbiomac.2024.133744>
- [30] Zhao, Y., Zheng, Z., Zhang, Z., Xu, Y., Hillpot, E., Lin, Y.S., *et al.* (2023) Evolution of High-Molecular-Mass Hyaluronic Acid Is Associated with Subterranean Lifestyle. *Nature Communications*, **14**, Article No. 8054. <https://doi.org/10.1038/s41467-023-43623-2>
- [31] Jansen, H., Meffert, R.H., Birkenfeld, F., Petersen, W. and Pufe, T. (2012) Detection of Vascular Endothelial Growth Factor (VEGF) in Moderate Osteoarthritis in a Rabbit Model. *Annals of Anatomy-Anatomischer Anzeiger*, **194**, 452-456. <https://doi.org/10.1016/j.aanat.2012.01.006>
- [32] Kaneko, H., Ishijima, M., Futami, I., Tomikawa-Ichikawa, N., Kosaki, K., Sadatsuki, R., *et al.* (2013) Synovial Perlecan Is Required for Osteophyte Formation in Knee Osteoarthritis. *Matrix Biology*, **32**, 178-187. <https://doi.org/10.1016/j.matbio.2013.01.004>
- [33] Junker, S., Frommer, K.W., Krumbholz, G., Tsiklauri, L., Gerstberger, R., Rehart, S., *et al.* (2017) Expression of Adipokines in Osteoarthritis Osteophytes and Their Effect on Osteoblasts. *Matrix Biology*, **62**, 75-91. <https://doi.org/10.1016/j.matbio.2016.11.005>
- [34] Liu, F., Su, F., Zhang, T., Liu, R., Liu, N. and Dong, T. (2023) Relationship between Knee Osteophytes and Calcitonin

- Gene-Related Peptide Concentrations of Serum and Synovial Fluid in Knee of Osteoarthritis. *Medicine*, **102**, e34691. <https://doi.org/10.1097/md.00000000000034691>
- [35] Sohail, M., Azad, M.M. and Kim, H.S. (2025) Knee Osteoarthritis Severity Detection Using Deep Inception Transfer Learning. *Computers in Biology and Medicine*, **186**, Article ID: 109641. <https://doi.org/10.1016/j.compbiomed.2024.109641>
- [36] Wang, Y., Bi, Z., Xie, Y., Wu, T., Zeng, X., Chen, S., *et al.* (2022) Learning from Highly Confident Samples for Automatic Knee Osteoarthritis Severity Assessment: Data from the Osteoarthritis Initiative. *IEEE Journal of Biomedical and Health Informatics*, **26**, 1239-1250. <https://doi.org/10.1109/jbhi.2021.3102090>
- [37] Gui, T., Huan, S., Zhuang, T., Zhang, H., Yang, J., Li, B., *et al.* (2023) Hippo/Yap1 Inhibition by Verteporfin Attenuates Osteophyte Formation in a Mouse Surgical Osteoarthritis Model. *Biomaterials Advances*, **149**, Article ID: 213413. <https://doi.org/10.1016/j.bioadv.2023.213413>
- [38] Luo, P., Wang, Q., Cao, P., Chen, T., Li, S., Wang, X., *et al.* (2024) The Association between Anterior Cruciate Ligament Degeneration and Incident Knee Osteoarthritis: Data from the Osteoarthritis Initiative. *Journal of Orthopaedic Translation*, **44**, 1-8. <https://doi.org/10.1016/j.jot.2023.09.005>
- [39] Wu, Y., Liew, J.W., Boer, J.D., Westerland, M., LaValley, M., Voortman, T., *et al.* (2025) Chondrocalcinosis and Incident Knee Osteoarthritis: Findings from 2 Large Prospective Cohorts with 20 Years of Follow-Up. *Annals of the Rheumatic Diseases*, **84**, 1743-1751. <https://doi.org/10.1016/j.ard.2025.07.009>
- [40] Liu, L., Ishijima, M., Kaneko, H., Sadatsuki, R., Hada, S., Kinoshita, M., *et al.* (2016) The MRI-Detected Osteophyte Score Is a Predictor for Undergoing Joint Replacement in Patients with End-Stage Knee Osteoarthritis. *Modern Rheumatology*, **27**, 332-338. <https://doi.org/10.1080/14397595.2016.1206509>
- [41] Rabelo, G.D., vom Scheidt, A., Klebig, F., Hemmatian, H., Citak, M., Amling, M., *et al.* (2020) Multiscale Bone Quality Analysis in Osteoarthritic Knee Joints Reveal a Role of the Mechanosensory Osteocyte Network in Osteophytes. *Scientific Reports*, **10**, Article No. 673. <https://doi.org/10.1038/s41598-019-57303-z>
- [42] Omoumi, P., Schuler, A., Babel, H., Stoffel, C., Jolles, B.M. and Favre, J. (2021) Proximal Tibial Osteophyte Volumes Are Correlated Spatially and with Knee Alignment: A Quantitative Analysis Suggesting the Influence of Biochemical and Mechanical Factors in the Development of Osteophytes. *Osteoarthritis and Cartilage*, **29**, 1691-1700. <https://doi.org/10.1016/j.joca.2021.09.008>
- [43] Park, S.Y., Kim, M.J., Cho, J.H., Nam, H.S., Ho, J.P.Y. and Lee, Y.S. (2025) Osteoarthritis Progression Pattern Based on Patient Specific Characteristics Using Machine Learning. *NPJ Digital Medicine*, **8**, Article No. 464. <https://doi.org/10.1038/s41746-025-01878-7>
- [44] Holst, D.C. and Dennis, D.A. (2018) Pearls: Early Removal of Posterior Osteophytes in TKA. *Clinical Orthopaedics & Related Research*, **476**, 684-686. <https://doi.org/10.1007/s11999-0000000000000015>
- [45] Smeets, K., Slane, J., Scheyls, L., Claes, S. and Bellemans, J. (2017) Mechanical Analysis of Extra-Articular Knee Ligaments. Part One: Native Knee Ligaments. *The Knee*, **24**, 949-956. <https://doi.org/10.1016/j.knee.2017.07.013>
- [46] Tzanetis, P., de Souza, K., Robertson, S., Fluit, R., Koopman, B. and Verdonchot, N. (2024) Numerical Study of Osteophyte Effects on Preoperative Knee Functionality in Patients Undergoing Total Knee Arthroplasty. *Journal of Orthopaedic Research*, **42**, 1943-1954. <https://doi.org/10.1002/jor.25850>
- [47] Liew, J.W., Rabasa, G., LaValley, M., Collins, J., Stefanik, J., Roemer, F.W., *et al.* (2023) Development of a Magnetic Resonance Imaging-Based Definition of Knee Osteoarthritis: Data from the Multicenter Osteoarthritis Study. *Arthritis & Rheumatology*, **75**, 1132-1138. <https://doi.org/10.1002/art.42454>
- [48] Mazzei, D.R., Whittaker, J.L., Faris, P., Wasylak, T. and Marshall, D.A. (2025) Estimating Budget Impact and Joint Replacement Avoidance by Implementing a Standardized Education and Exercise Therapy Program for Hip and Knee Osteoarthritis in a Publicly Insured Health Care System. *Arthritis Care & Research*, **77**, 744-752. <https://doi.org/10.1002/acr.25492>
- [49] Hampp, E., Chughtai, M., Scholl, L., Sodhi, N., Bhowmik-Stoker, M., Jacofsky, D., *et al.* (2018) Robotic-arm Assisted Total Knee Arthroplasty Demonstrated Greater Accuracy and Precision to Plan Compared with Manual Techniques. *The Journal of Knee Surgery*, **32**, 239-250. <https://doi.org/10.1055/s-0038-1641729>
- [50] Li, C., Zhang, Z., Wang, G., Rong, C., Zhu, W., Lu, X., *et al.* (2022) Accuracies of Bone Resection, Implant Position, and Limb Alignment in Robotic-Arm-Assisted Total Knee Arthroplasty: A Prospective Single-Centre Study. *Journal of Orthopaedic Surgery and Research*, **17**, Article No. 61. <https://doi.org/10.1186/s13018-022-02957-1>
- [51] Parratte, S., Price, A.J., Jeys, L.M., Jackson, W.F. and Clarke, H.D. (2019) Accuracy of a New Robotically Assisted Technique for Total Knee Arthroplasty: A Cadaveric Study. *The Journal of Arthroplasty*, **34**, 2799-2803. <https://doi.org/10.1016/j.arth.2019.06.040>
- [52] Mullaji, A. (2020) Can Isolated Removal of Osteophytes Achieve Correction of Varus Deformity and Gap-Balance in Computer-Assisted Total Knee Arthroplasty? *The Bone & Joint Journal*, **102**, 49-58.

- <https://doi.org/10.1302/0301-620x.102b6.bjj-2019-1597.r1>
- [53] Sriphrom, P., Siramanakul, C., Chanopas, B. and Boonruksa, S. (2018) Effects of Posterior Condylar Osteophytes on Gap Balancing in Computer-Assisted Total Knee Arthroplasty with Posterior Cruciate Ligament Sacrifice. *European Journal of Orthopaedic Surgery & Traumatology*, **28**, 677-681. <https://doi.org/10.1007/s00590-017-2118-2>
 - [54] Gustke, K.A., Cherian, J.J., Simon, P. and Morrison, T.A. (2022) Effect of Posterior Osteophytes on Total Knee Arthroplasty Coronal Soft Tissue Balance: Do They Matter? *The Journal of Arthroplasty*, **37**, S226-S230. <https://doi.org/10.1016/j.arth.2022.01.034>
 - [55] Lee, J.H., Jung, H.J., Lee, J.K., Hwang, J.H. and Kim, J.I. (2023) Large Osteophytes over 10 mm at Posterior Medial Femoral Condyle Can Lead to Asymmetric Extension Gap Following Bony Resection in Robotic Arm-Assisted Total Knee Arthroplasty with Pre-Resection Gap Balancing. *Journal of Clinical Medicine*, **12**, Article No. 5980. <https://doi.org/10.3390/jcm12185980>
 - [56] Ebrahimzadeh, S., Islam, N., Dawit, H., et al. (2022) Thoracic Imaging Tests for the Diagnosis of COVID-19. *The Cochrane Database of Systematic Reviews*, **5**, CD013639.
 - [57] Roemer, F.W., Engelke, K., Li, L., Laredo, J.-. and Guermazi, A. (2023) MRI Underestimates Presence and Size of Knee Osteophytes Using CT as a Reference Standard. *Osteoarthritis and Cartilage*, **31**, 656-668. <https://doi.org/10.1016/j.joca.2023.01.575>
 - [58] Koski, J., Kamel, A., Waris, P., Waris, V., Tarkiainen, I., Karvanen, E., et al. (2015) Atlas-Based Knee Osteophyte Assessment with Ultrasonography and Radiography: Relationship to Arthroscopic Degeneration of Articular Cartilage. *Scandinavian Journal of Rheumatology*, **45**, 158-164. <https://doi.org/10.3109/03009742.2015.1055797>
 - [59] Saarakkala, S., Waris, P., Waris, V., Tarkiainen, I., Karvanen, E., Aarnio, J., et al. (2012) Diagnostic Performance of Knee Ultrasonography for Detecting Degenerative Changes of Articular Cartilage. *Osteoarthritis and Cartilage*, **20**, 376-381. <https://doi.org/10.1016/j.joca.2012.01.016>
 - [60] Schmitz, R.J., Wang, H., Polprasert, D.R., Kraft, R.A. and Pietrosimone, B.G. (2017) Evaluation of Knee Cartilage Thickness: A Comparison between Ultrasound and Magnetic Resonance Imaging Methods. *The Knee*, **24**, 217-223. <https://doi.org/10.1016/j.knee.2016.10.004>
 - [61] Keshava, S.N., Gibikote, S.V., Mohanta, A., Poonnoose, P., Rayner, T., Hilliard, P., et al. (2015) Ultrasound and Magnetic Resonance Imaging of Healthy Paediatric Ankles and Knees: A Baseline for Comparison with Haemophilic Joints. *Haemophilia*, **21**, e210-e222. <https://doi.org/10.1111/hae.12614>
 - [62] Buttgeriet, F., Burmester, G. and Bijlsma, J.W.J. (2015) Non-Surgical Management of Knee Osteoarthritis: Where Are We Now and Where Do We Need to Go? *RMD Open*, **1**, e000027. <https://doi.org/10.1136/rmdopen-2014-000027>
 - [63] Cho, Y., Jeong, S., Kim, H., Kang, D., Lee, J., Kang, S., et al. (2021) Disease-Modifying Therapeutic Strategies in Osteoarthritis: Current Status and Future Directions. *Experimental & Molecular Medicine*, **53**, 1689-1696. <https://doi.org/10.1038/s12276-021-00710-y>
 - [64] Li, H., Hu, F., Pan, X., Wang, Q., Liang, H., Lv, L., et al. (2025) Multidimensional Regulation of Bone Marrow Niche Using Extracorporeal Shock Wave Responsive Nanocomposites for Osteoporosis Therapy. *Small*, **21**, e05863. <https://doi.org/10.1002/sml.202505863>
 - [65] Kim, S., Lee, H., Hong, J., Kim, S.H.L., Kwon, E., Park, T.H., et al. (2023) Bone-Targeted Delivery of Cell-Penetrating-RUNX2 Fusion Protein in Osteoporosis Model. *Advanced Science*, **10**, e2301570. <https://doi.org/10.1002/adv.202301570>
 - [66] Zeng, L., Deng, Y., He, Q., Yang, K., Li, J., Xiang, W., et al. (2022) Safety and Efficacy of Probiotic Supplementation in 8 Types of Inflammatory Arthritis: A Systematic Review and Meta-Analysis of 34 Randomized Controlled Trials. *Frontiers in Immunology*, **13**, Article ID: 961325. <https://doi.org/10.3389/fimmu.2022.961325>
 - [67] Wu, K.T., Wang, Y.W., Wu, R.W., Huang, C.C. and Chen, Y.C. (2022) Association of a Femoral Neck T Score with Knee Joint Osteophyte Formation but Not with Skeletal Muscle Mass. *Clinical Rheumatology*, **42**, 917-922. <https://doi.org/10.1007/s10067-022-06410-w>
 - [68] Zhu, D., Wang, X., Xi, Z., Chen, K., Feng, Y., Zi, C., et al. (2024) Diet Influences Knee Osteoarthritis Osteophyte Formation via Gut Microbiota and Serum Metabolites. *iScience*, **27**, 110111. <https://doi.org/10.1016/j.isci.2024.110111>
 - [69] Xi, Y., Zheng, K., Deng, F., Liu, Y., Sun, H., Zheng, Y., et al. (2024) Themis: Advancing Precision Oncology through Comprehensive Molecular Subtyping and Optimization. *Briefings in Bioinformatics*, **25**, bbae261. <https://doi.org/10.1093/bib/bbae261>
 - [70] Thakur, R. and Singh, P.K. (2021) Molecular Subtypes of Pancreatic Cancer: A Proteomics Approach. *Clinical Cancer Research*, **27**, 3272-3274. <https://doi.org/10.1158/1078-0432.ccr-21-0640>
 - [71] He, J., Liu, N. and Zhao, L. (2025) New Progress in Imaging Diagnosis and Immunotherapy of Breast Cancer. *Frontiers in Immunology*, **16**, Article ID: 1560257. <https://doi.org/10.3389/fimmu.2025.1560257>

-
- [72] Hambright, W.S., Duke, V.R., Goff, A.D., Goff, A.W., Minas, L.T., Kloser, H., *et al.* (2024) Clinical Validation of C12FDG as a Marker Associated with Senescence and Osteoarthritic Phenotypes. *Aging Cell*, **23**, e14113.
<https://doi.org/10.1111/acer.14113>
- [73] Gatti, A.A., Blankemeier, L., Veen, D.V., *et al.* (2024) ShapeMed-Knee: A Dataset and Neural Shape Model Benchmark for Modeling 3D Femurs.