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肥胖、高血压与骨关节炎相关研究进展

李超哲[1,2]，孙炳慧[1,2]

[1]内蒙古民族大学第二临床医学院，内蒙古 通辽
[2]内蒙古林业总医院骨科，内蒙古 牙克石

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摘　要

肥胖与高血压等疾病已被确认与骨关节炎(OA)的发病机制有着因果关系。最近的流行病学和临床研究结果证实，脂肪因子通过多种信号通路介导炎症、组织降解和OA发病机制。OA不再被认为只是一种“磨损性”疾病，OA发病机制中代谢相关成分的参与增加了疾病的复杂性。本论文旨在深入探讨肥胖及高血压在骨关节炎的发生与演进中的具体作用。

关键词

高血压，肥胖，骨关节炎

Research Progress of Obesity, Hypertension and Osteoarthritis

Chaozhe Li[1,2], Binghui Sun[1,2]

[1]The Second Clinical Medical College of Inner Mongolia University for Nationalities, Tongliao Inner Mongolia
[2]Orthopedics Department of Inner Mongolia Forestry General Hospital, Yakeshi Inner Mongolia

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Abstract

Obesity and hypertension have been confirmed to have a causal relationship with the pathogenesis of osteoarthritis (OA). Recent epidemiological and clinical research results have confirmed that adipokines mediate inflammation, tissue degradation, and the pathogenesis of OA through multiple signaling pathways. OA is no longer considered merely a “wear and tear” disease; the involvement of metabolism-related components in the pathogenesis of OA has increased the complexity of the disease. This paper aims to deeply explore the specific roles of obesity and hypertension in the occurrence and progression of osteoarthritis.

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Keywords

Hypertension, Obesity, Osteoarthritis

1. 引言

骨关节炎(OA)是最常见的关节炎类型，影响约 3.3%至 3.6%的世界人口。它是全球第 11 大使人衰弱的疾病，每年约有 4300 万人患有中度至重度残疾[1]。且不说这种疾病所带来的强烈的身体和情感后果，OA 还伴随着巨大的个人、社会和经济负担。OA 不仅仅是一种关节软骨疾病，而是一种复杂的多因素退行性疾病，涉及整个关节的各个组成部分[2]。关节软骨的恶化和破坏伴随着关节各种组织的各种结构和功能改变，包括软骨下骨重塑、骨赘形成、骨髓病变的发展、滑膜炎症、关节周围肌肉的减弱、韧带和半月板的改变都被认为是 OA 的标志[3]-[6]。OA 可发生于任何关节，但膝关节、髋部、手部、关节突关节和足部是最常见的受累部位，女性的患病率高于男性[7]。据估计，15 岁及以上人群中膝关节 OA 的全球患病率为 16%，40 岁及以上人群中患病率为 22.9% [8]。虽然最初认为 OA 是老年人的疾病，但已经确定了年龄以外的风险因素使个体易患 OA。OA 的患病率呈上升趋势，部分原因是 OA 风险因素的增加，包括肥胖、缺乏体育活动和关节创伤性损伤。尽管最初将骨关节炎视为一种老年性疾病，但研究已确定除了年龄之外还有其他风险因素可能导致个体易患 OA。随着肥胖、缺乏运动和关节创伤性损伤等这些风险因素的增加，OA 的发病概率呈现上升趋势。近期研究的有力证据表明，OA 可能是一种代谢性疾病，代谢综合征(MetS)的几个组成部分共同导致了疾病的发病和进展，代谢综合征增加了 OA 的风险[9]-[11]。本文的重点是讨论代谢综合征的肥胖及高血压部分对 OA 发病和进展的影响。

2. 肥胖和骨关节炎

骨关节炎(OA)是一种复杂疾病，具有多因素病理生理学，包括生物力学、代谢和炎症成分[12]。肥胖长期以来被确认为骨关节炎的主要且可能可避免的危险因素，对疾病的发生、进展和症状严重程度都具有多重影响。肥胖和超重在促进骨关节炎进展方面的作用可能是骨关节炎研究中最常被研究的话题。Coggon 等人[13]报告称，BMI 超过 30 kg/m^2 的受试者与正常体重的受试者相比，患膝关节骨关节炎的风险增加了 6.8 倍。过量的体重不仅会增加对承重关节的负担，还会导致关节错位和不利的关节力学，尤其是在膝盖上，从而增加机械应力和软骨降解，导致骨关节炎[14]。除了对软骨基质的直接有害影响外，机械负荷还能改变软骨细胞的炎症状态。对软骨细胞施加高强度的周期性拉伸应变可显著提高促炎介质的表达，如白细胞介素(IL)-1β、肿瘤坏死因子(TNF)-α、环氧化酶(COX)-2、基质金属蛋白酶(MMPs)-3、(MMPs)-13，这些介质通过 FAK、ERK、JNK、p38 和 NF-κB 信号通路介导[15]-[17]。在肥胖受试者中，膝关节的错位和过伸也会导致 OA。

肥胖引起的过度关节负荷是 OA 的一个重要风险因素。然而，生物力学的改变并不能充分解释为何肥胖者在非承重关节，如手和手腕，也面临更高的 OA 风险。这一现象表明，OA 的发病机制中存在系统性和非机械性的影响[18]。持续性炎症会引发软骨退化、骨赘生成及滑膜炎，这些病理变化是肥胖相关 OA 的主要发病机制[19]。在超重和肥胖的成年人中观察到较高水平的促炎细胞因子[20]。在高碳水化合物与高脂肪饮食实验中，肥胖大鼠模型的研究表明，促炎性巨噬细胞(M1)自发地浸润到关节组织的滑膜中，

并且在巨噬细胞中激活 M1 表型，这一过程伴随着 OA 特征性的病理变化加剧[21]。最近，Liu 等人[22]报道，膝关节 OA 患者的滑液和外周血中 M1 与 M2 巨噬细胞的比例明显高于对照组，且与膝关节 OA 的 Kellgren-Lawrence 分级水平显著正相关，强烈提示巨噬细胞参与膝关节 OA 的发病机制。在肥胖中，脂肪组织被认为是最大的内分泌代谢器官，可分泌一系列促炎细胞因子、趋化因子和脂肪因子。脂肪因子由一系列多营养分子组成，包括由脂肪组织分泌的生物活性肽、免疫和炎症介质，并以自分泌/旁分泌和内分泌方式发挥作用[23]。髌下脂肪垫靠近滑膜，是膝关节关节液脂肪因子的主要来源。尽管脂肪因子主要由脂肪细胞分泌，但其他关节组织驻留细胞，包括软骨细胞、成骨细胞、滑膜细胞、基质细胞、巨噬细胞和免疫细胞也被证实产生一些脂肪因子[24]。脂肪因子受体在许多关节细胞类型中的存在表明了关节内脂肪因子信号传导的复杂调控网络。

瘦素是第一个被发现的主要由脂肪组织产生并由 Ob 受体介导执行其功能的脂肪因子[25]。由于瘦素受体在外周组织中广泛表达，并且瘦素参与胰岛素分泌、骨代谢和免疫反应等生理过程，因此被认为是肥胖和 OA 之间的潜在联系。与健康受试者相比，OA 患者的系统性瘦素水平较高。多项研究发现，OA 患者瘦素水平显著升高与疾病严重程度和疼痛呈正相关[26]-[28]。研究表明，瘦素可能通过诱导胰岛素样生长因子 1 (IGF-1)和 TGF-β 表达，对软骨细胞具有合成代谢作用[29]。然而，在晚期 OA 软骨和滑夜中，瘦素和瘦素受体(Ob-Rb)的表达水平显著升高。瘦素在软骨大代谢中发挥促炎和分解代谢功能，其固有的能力是单独或与其他促炎因子联合作用，以软骨细胞、滑膜细胞和成骨细胞为靶点，发挥 OA 发病机制的关键功能。脂肪因子脂联素，也被称为 AdipoQ，通过 AdipoR1 和 AdipoR2 受体介导发挥其作用。虽然临床和实验研究的证据表明脂联素在 OA 病理生理中起作用，但脂联素是否在 OA 中发挥保护作用尚不清楚。脂联素已被发现在关节滑膜细胞、IPFP、骨赘、软骨和骨组织中表达[30]。此外，最近的一项横断面研究表明，与滑膜瘦素相比，滑膜脂联素与女性膝关节 OA 的临床严重程度有更大的相关性[31]。脂肪因子抵抗素是一种富含半胱氨酸的多肽激素，主要由人类的巨噬细胞和脂肪细胞分泌。抵抗素已被确定与膝关节 OA 影像学相关。流行病学和临床研究表明，血清和滑液抵抗素水平与 OA 患者的严重程度、滑膜炎和结构异常呈正相关[32] [33]。由此可见，不同脂肪因子在 OA 中有着的不同作用。

3. 高血压和骨性关节炎

高血压是代谢综合征的重要组成部分，也是心脑血管疾病的独立危险因素。然而，流行病学研究现已证实，OA 在高血压患者中更为常见[34]，并且很可能是代谢综合征相关 OA 发病的关键因素。在最新的 Framing-ham 骨关节炎研究中，研究人员观察到，即使在调整 BMI 或体重后，高血压与 OA 的发生之间仍存在显著关联[35]。研究发现，高血压在 OA 病理进程中的作用机制，主要集中在由血管问题引起的软骨下缺血现象。高血压引起的血管收缩持续一段时间后，可减少通过软骨下骨小血管的血流量。此外，软骨下血管的静脉闭塞或微栓子形成可使血管腔变窄，导致阻塞和血流量减少，最终导致软骨下缺血[36]。软骨下缺血的有害影响有：1) 软骨和骨骼之间的营养和氧气交换减弱，引发软骨降解；2) 软骨下骨缺血区域的骨细胞凋亡，可能引发破骨细胞吸收，从而剥夺对上述结构的骨支持软骨[37]。关节载荷也会导致软骨下小梁丢失，从而引起软骨变形，导致软骨破裂。软骨下骨重塑在高血压介导的 OA 关节恶化中起重要作用。最近的流行病学证据也确定了高血压与膝关节 OA 放射学和症状性疾病以及疼痛严重程度之间的正相关，强调了高血压与 OA 之间的显著关系[37] [38]。

4. 结论与展望

随着临床和流行病学研究的进展产生了大量的新证据，人们对 OA 发病机制的认识发生了范式转变。不可否认的是，OA 并不像人们通常认为的那样仅仅是老年人的一种“磨损性”疾病。鉴于肥胖及其相关

代谢紊乱在全球范围内的上升速度令人担忧，在代谢性 OA 管理的整体方法中，解决代谢综合征及其可改变的风险因素的需求尤为突出。与肥胖相关的几种脂肪因子和促炎细胞因子介导的慢性低度炎症是代谢综合征相关 OA 发病机制的主要因素之一。大量证据表明，高血压与 OA 以及疼痛严重程度之间存在正相关。我们的综述强调了 OA 的多因素性质，其危险因素从高体重指数到特应性疾病。然而，OA 的发病机制具有多样性和复杂性，因此需要更大规模的研究来挖掘 OA 的发病机制。展望未来，随着各项研究的进展，OA 的发病机制逐渐更清晰、更明了，临床工作中应优先考虑综合风险评估，通过有针对性的干预，改变危险因素，从而预防 OA 的发生，以减轻日益增长的全球 OA 负担。

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