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糖尿病对骨关节炎进展的影响

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摘　要

骨关节炎(Osteoarthritis, OA)是临床上老年患者中最常见的慢性退行性关节疾病，其病理过程会涉及关节软骨、软骨下骨、滑膜和周围神经等关节内各个结构。糖尿病(Diabetes Mellitus, DM)是老年人群中常见的慢性疾病之一，其存在会对全身各组织器官的功能产生不利影响。骨关节炎和糖尿病常共同存在。既往研究表明，二者之间存在着密切联系，糖尿病是骨关节炎的独立危险因素，糖尿病对骨关节炎的进展起着重要作用。本文对糖尿病在促进骨关节炎发展过程中对关节各结构的影响进行了综述。

关键词

骨关节炎，糖尿病，软骨，软骨下骨，滑膜

Effect of Diabetes Mellitus on the Progress of Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common chronic degenerative joint disease in clinic. Its pathological process involves cartilage, subchondral bone, synovium and peripheral nerve. Diabetes Melli-

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tus (DM) is one of the common chronic diseases among the elderly. The existence of DM will adversely affect the functions of various tissues and organs in the whole body. DM often coexists with OA. Previous studies have shown that there is a close relationship between them. DM is an independent risk factor for OA, and DM plays an important role in the progress of OA. This paper summarizes the influence of DM on joint structures in the process of promoting OA development.

Keywords

Osteoarthritis, Diabetes Mellitus, Cartilage, Subchondral Bone, Synovium

1. 引言

糖尿病(Diabetes Mellitus, DM)是一种常见的内分泌系统疾病，主要特征为血糖水平持续异常升高，是最为常见且患病率增长最快的疾病之一[1]，常由胰岛 β 细胞分泌功能异常导致体内胰岛素相对/绝对性不足和/或体内组织胰岛素抵抗而引起。DM 是一种慢性代谢性疾病，主要分为 I 型糖尿病(T1DM)和 II 型糖尿病(T2DM)两种类型，其中 T2DM 约占总数的 90% [2] [3]。T2DM 的长期存在会导致多种并发症的发生，常见的有心血管疾病[4] [5]、糖尿病肾病[6] [7]、糖尿病视网膜病变[8] [9]、神经病变[10] [11] [12]、糖尿病足[13] [14]和感染[15] [16] [17]。全球范围内的 2 型糖尿病(T2DM)患者人数在过去的 40 年里持续上升，并以亚洲、中东和北非的情况最为严重[18]。据统计，2021 年全球范围内 20~79 岁人群中 DM 的患病率约为 10.5% (5.366 亿人)；随着 DM 患者人数的持续增长，DM 的患病率预计将在 2045 年上升到约 12.2% (7.832 亿人) [19]。

骨关节炎(Osteoarthritis, OA)是一种与年龄相关的慢性退行性关节炎，其病程具有不可逆的特点，常带给老年患者以关节疼痛和关节活动受限，甚至导致残疾[20]，对患者的生活质量带来了巨大影响。导致 OA 发生的主要原因有年龄、性别、遗传、文化程度、职业、肥胖/代谢综合征和创伤等[21]。OA 的发病率有着明显的性别差异，女性患者更易患有症状性膝关节炎，尤其是老年女性[22]。据估计，60 岁以上的男性中 OA 患者约占 10%，而 60 岁以上的女性中 OA 患者约占 18% [23]。OA 的症状学与影像学也有着巨大的差异，影像学 OA 患者中没有骨关节炎相关症状的比例高达 50% [21]。OA 的发病率和患病率正随着社会人口老龄化的加剧、肥胖和关节损伤数量的增加而不断上升。目前，全球估计有 2.5 亿人患有症状性 OA [24]，而到 2030 年，这个数字将达到 4 亿[25]。

2. DM 与 OA 之间的关系

DM 和 OA 均为与年龄相关的常见疾病，且常与超重/肥胖等代谢综合征共同存在，二者之间存在着密切关系。在 Schett 等人进行的纵向队列研究中，T2DM 已被认为是膝关节 OA 的独立危险因素[26]。Eymard 等人对 559 名 50 岁以上的患者进行了为期 3 年的随访，发现了相同的结果，T2DM 患者的膝关节 OA 进展率明显高于非 T2DM 患者[27]。Louati 等人对收集到的 49 项研究结果进行 Meta 分析的结果也显示 DM 和 OA 之间具有显著的相关性：① 纳入研究的 5788 例 DM 患者中，平均 OA 的患病率为 29.5% ± 1.2%，DM 人群患 OA 的风险大于非 DM 人群(OR = 1.46 (1.08~1.96), p = 0.01)，② 纳入研究的 645,089 例 OA 患者中，平均 DM 的患病率为 14.4% ± 0.1%，OA 人群患 DM 的风险也高于非 OA 人群(OR = 1.41

(1.21~1.65), p < 0.00001) [28]。

关节软骨的严重退变是 OA 病程中的主要特征，因此，OA 常被认为是因为重力负荷增加和力学性能受损而引起的一种单纯的软骨磨损性疾病。软骨磨损引起的疼痛和炎症进一步导致了患者关节僵硬、肿胀和活动能力的丧失[29]。但是越来越多的研究表明 OA 的发展是一个整体的过程，关节内其他结构也受到了影响。软骨下骨内早期骨丢失、晚期骨硬化和组织病理学改变引起的骨赘是由软骨细胞、成骨细胞、破骨细胞、内皮细胞和软骨下骨微环境失衡引起的[30] [31]。此外，许多关节炎患者关节内还存在着严重的滑膜炎[32]；Sharma 等人研究发现，骨关节炎还可能是由原发性神经系统缺陷引起的[33]。而在 DM 患者膝关节 OA 的发展中，除了超重导致的关节重力负荷增加会加速其发展外，体内还普遍存在着由慢性高血糖引起的氧化应激(导致膝关节及周围组织中促炎因子和 AGEs 的浓度升高)和由胰岛素抵抗引起的局部/全身低度慢性炎症，也对 OA 的发生和发展起着重要作用[34]。本文从 DM 在 OA 发展过程中对关节内各结构的影响进行综述。

3. DM 对 OA 进展的影响

3.1. DM 对关节软骨的影响

关节软骨是一种高度分化的组织，自愈能力十分有限，主要由细胞外基质和基质内散在的软骨细胞组成。软骨内不含血管和神经，因此软骨细胞的生存主要依赖滑膜液和软骨下骨内营养物质的扩散[35]。细胞外基质主要由 II 型胶原、蛋白多糖和非胶原蛋白等有机大分子物质组成。其中，由 II 型胶原纤维交织并由其他类型胶原和非胶原蛋白稳定而形成的三维网状结构，给予软骨抗拉能力；网孔内嵌入的聚合糖和其他蛋白多糖将水分吸入软骨，以提供抗压缩能力。关节软骨内由不同形态的软骨细胞组成水平层状结构，具有不同的分布和分泌特征，以此调节关节软骨的组成，维持软骨组织的良好性能，以应对机械和化学环境的不断变化[36] [37] [38]。

DM 患者体内长期高糖环境无疑会对软骨细胞的调控功能和软骨的成分和结构造成影响。Neumann 等人在为期 2 年内对 392 例 OA 患者(196 例 DM 患者，196 例非 DM 患者)进行膝关节核磁共振检查，并对软骨部分的 T2 值进行分析，发现 DM 患者软骨的 T2 值变化更快；除髌股关节处软骨外，DM 患者的胫骨内外侧和股骨内外侧间室软骨的退变相比于非 DM 患者都有显著差异；同时，DM 患者的膝关节较非 DM 患者具有更加严重的结构变形，关节内软骨的不均匀程度也更高，这表明 DM 患者的关节软骨发生了更严重和更迅速的退化[39]。许多科研人员使用 STZ 注射诱导的 I 型糖尿病模型和高脂肪饮食喂食诱导的 II 性糖尿病模型进行动物体内实验探索 DM 对 OA 的影响。Atayde 等人使用 STZ 注射诱导的 I 型糖尿病大鼠进行研究，结果发现尽管 DM 组大鼠体重较低，但却导致了关节软骨蛋白多糖的自发丢失[40]。ElKarib 等人进行的研究得到了相同的结果，在 STZ 诱导 8 周后，与非 DM 组大鼠相比，DM 组大鼠的关节软骨不仅出现了蛋白多糖的自发丢失，而且出现了显著的软骨损伤[41]。

3.1.1. 慢性高血糖对关节软骨的影响

既往研究发现，慢性高糖环境对关节软骨细胞会产生不利影响。关节软骨组织内无血管和神经支配，持续的低氧环境使软骨细胞主要依赖于糖酵解获得能量，所以，位于细胞膜表面的葡萄糖转运体(Glucose Transporters, GLUT)长期处于高表达状态，以加强细胞对糖的摄取。而当关节内处于高糖水平，例如 T2DM 时，则会导致潜在的葡萄糖毒性[42]。同时，高糖浓度下 DM 患者体内软骨组织的自噬作用[43]和血红素加氧酶-1 这两种抗氧化途径的表达减少，导致抗氧化特性的下降和氧化应激的增加，进而促进了前列腺素 E2 (PGE2)、IL-1β、IL-6、IL-10 和 TNF-α 等促炎介质的分泌[44]。持续的高糖暴露还会导致细胞内促进软骨变性退化的环氧化酶-2 (COX-2)和基质金属蛋白酶-13 (MMP-13)的表达增加，而 II 型胶原蛋白和

过氧化物酶体增殖物激活受体-γ (Peroxisome Proliferator-Activated Receptors-γ, PPAR-γ)的合成减少。其中，PPAR-γ 是一种细胞内受体，参与细胞内的糖脂代谢，并能够减少促炎因子和趋化因子的生成。Nielen 等人的研究发现，高糖浓度对软骨细胞表现出的促炎和促降解作用能够被 PPAR-γ 激动剂部分抑制[45]。此外，高浓度葡萄糖能够抑制间充质干细胞的成软骨分化，加速软骨损伤的同时减少软骨细胞形成，抑制软骨再生[46]。

3.1.2. 晚期糖基化产物对关节软骨的影响

晚期糖基化产物(Advanced Glycation End products, AGEs)也会对关节软骨产生不利影响。高浓度葡萄糖与体内蛋白质结合后形成的 AGEs 在细胞和组织中不断地进行积累，会导致人体衰老的加速和多种慢性退行性疾病的发生。既往进行的体外细胞实验发现，AGEs 可以通过 RAGE (AGE 受体)和 toll 样受体诱导软骨细胞表现出促炎和促分解代谢表型。这两种受体的激活进一步导致了 PPAR-γ 的合成减少以及 NF-κB 和 MAPK 通路的激活[47] [48] [49] [50]，最终导致细胞内 MMP-1、MMP-3、MMP-13、TNF-α 和其他促炎细胞因子的生成增加[51]，II 型胶原蛋白的合成减少[52]，软骨细胞凋亡、衰老[53]以及具有软骨保护作用的自噬减少[52]。与此同时，作为细胞内能够去除 AGE 前体的主要酶－乙二醛酶-1 的表达也被 OA 软骨细胞内氧化应激增加时分泌的 IL-1β 下调[54]。此外，PPAR-γ 激动剂已被证明可以缓解 STZ 诱导 DM 小鼠的 OA，并引起全身炎症(IL-6 和 AGEs)的减少[55]。

3.1.3. 胰岛素抵抗对关节软骨的影响

胰岛素抵抗对关节软骨也存在着不利影响。T2DM 主要由组织胰岛素抵抗引起，进而导致胰岛素分泌异常，高血糖出现的同时也引起了高胰岛素血症[56] [57]。既往多项研究表明，胰岛素能够发挥保护关节软骨的作用，例如，Tchetina 等人研究发现，胰岛素能够与细胞表面的胰岛素受体结合，发挥阻断致炎物质和保护关节组织的作用[58]。焦聚阳等人也发现胰岛素能够通过作用于软骨细胞表面的胰岛素受体激活蛋白酶 B 信号通路，促进软骨细胞合成 II 型胶原和蛋白聚糖[59]。Courties 等人研究也发现，胰岛素能够使人软骨细胞中的自噬标记蛋白 LC3-II 的表达下调，从而增加蛋白激酶 B 和核糖体蛋白 S6 的磷酸化，抑制软骨细胞的自噬[60]。此外，Hamada 等人进行的研究也证明，T2DM 患者通过体外注射胰岛素能够使血清中 MMP-1、MMP-13、TNF-α 和 IL-6 的表达下降，发挥保护软骨的作用[61]。但是当体内存在胰岛素抵抗时，胰岛素与受体的结合发生障碍，这会导致胰岛素阻断体内致炎物质产生和抑制软骨分解代谢的能力减弱，进而促进 OA 的发展[60]。因此，寻找有效的药物控制血糖的同时减缓软骨退变的速度，降低体内炎症因子的释放仍是骨关节炎治疗的一个重点。

3.2. DM 对软骨下骨的影响

软骨下骨位于关节软骨和骨组织之间，由软骨深处骨骺区的软骨下骨板和底层骨小梁构成。软骨与软骨下骨紧密结合构成一个保持动态平衡的承重架构，主要功能是吸收关节承受的重力负荷并将其转移分散至别处，还能通过调控代谢来维持关节内各结构间的动态平衡并对关节的形状进行调节[62]。既往的动物实验发现，在由关节不稳定诱导的早期 OA 模型(如前交叉韧带离断(ACLT))中，软骨下骨板变薄、软骨下骨囊肿和软骨的退变等现象的发生是由于破骨细胞和成骨细胞之间的平衡被打破导致的[63] [64]。骨吸收和骨形成之间的失衡导致软骨下骨的异常重建和结构受损，关节整体的力学性能产生改变，对关节表面软骨产生不利影响，促进了 OA 的进展[65] [66] [67]。

T2DM 常与全身骨骼系统异常的骨重塑和骨丢失相关。例如，T2DM 患者病理性骨折(如股骨颈、桡骨远端和胫骨骨折等)的风险增加是因为过多的骨质丢失导致骨微结构和强度不足而引起的[68] [69] [70] [71]。显而易见，T2DM 患者体内过度的骨质丢失是由骨吸收增加[72]和骨形成减少[73]造成的。因此，

在 OA 的多种发病机制中，T2DM 患者软骨下骨重塑的作用不容忽视。传统观点认为，与年龄相关的关节退行性变和超重引起机械负荷增加导致的软骨退变是 DM 患者 OA 进展的主要原因，如髋关节和膝关节等负重部位。但是 Reyes 等人研究发现 DM 患者在非负重关节处的 OA 亦更加明显，如手指关节[74]。来自广西医科大学附属第一医院骨关节外科的魏庆军等人的研究结果对这一现象做出了解释，T2DM 患者的膝关节 OA 具有软骨下骨异常重建、微结构和机械性受损的特点，这导致了关节内软骨退化的加剧；但是在软骨保持完整的区域，T2DM 患者的软骨下骨仍然存在异常骨重建现象，这表明软骨下骨异常骨重建的发生要比关节软骨的退行性变更早，是 T2DM 相关膝关节 OA 的起始环节[75]。T2DM 患者 OA 早期活跃的软骨下骨重塑(骨吸收的增加)使其发生硬化改变，导致位于其上方的关节软骨承受的应力异常而发生退变。此外，AGEs 在 T2DM 患者软骨下骨中的积累影响软骨下骨的机械阻力，并表现出促炎作用[76]。所以，针对软骨下骨代谢、抑制软骨下骨重塑速度进行新药物的开发，是改善 DM 患者合并 OA 时软骨下骨硬化，预防 OA 发生的重要手段，也是治疗 OA 的一个全新的突破点。

3.3. DM 对滑膜的影响

滑膜组织是生产关节内滑液的主要细胞，在软骨的代谢和物质交换中发挥着关键作用。滑膜衬里细胞产生两种重要物质，透明质酸有助于减少关节表面摩擦并保护和维持关节软骨的完整性[77]，润滑素则有助于减少关节表面蛋白质的病理沉积[78]。在发生关节损伤或 OA 后，透明质酸的浓度和平均分子量以及滑液中润滑剂的浓度发生改变，将对软骨完整性产生不利影响[79]。在 OA 的发展过程中，滑膜也会生成多种具有促炎和促分解代谢作用的物质，主要是金属蛋白酶和蛋白聚糖酶等，这些产物极大地促进了软骨基质的降解。因此，滑膜的改变可以导致软骨保护因子生成的减少，和软骨基质降解因子生成的增加[80]。

高糖浓度会通过氧化应激、PI3K、Akt、c-Jun 和 AP-1 信号通路来增加人滑膜成纤维细胞中血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)的表达[81]。新生血管对局部促炎细胞进行募集导致滑膜炎，这在 T2DM 患者的 OA 中更明显，通常表现为关节疼痛增加，且超声检查有明显的炎症迹象[26]。与此同时，滑膜炎症还会引起局部分解代谢酶的上调，从而导致软骨的降解[82]。文印宪团队的研究发现，DM 患者膝关节 OA 进展中滑膜的炎症反应更严重，内质网应激水平更高，AGEs 的水平也更高；大鼠模型中亦如此。在体外的共培养系统中，高糖刺激的大鼠成纤维细胞样滑膜细胞中 AGEs 的积累、内质网应激和炎症，导致软骨细胞变性。而且在 DM 患者的 OA 滑膜中，GLUT-1 及其调节因子缺氧诱导因子(HIF)-1α 的表达显著增加。HIF-1α、GLUT1 和 AGEs 受体抑制剂能够降低共培养系统中软骨细胞降解。因此，高血糖可通过 HIF-1α-GLUT-1 通路导致成纤维样滑膜细胞中 AGEs 的积累和炎症因子的释放增加，随后诱导关节软骨细胞降解，加速 OA 的进展[83]。Hamada 等人也发现，通过喂食高脂饮食诱导的 T2DM 小鼠产生了自发性 OA 的现象，这个结果的部分原因是肥胖糖尿病小鼠关节内滑膜中产生了过多的 TNF。此外，他们还发现，成纤维样滑膜细胞也表达胰岛素受体，能够结合胰岛素并部分抵消 TNF 的促炎和促降解作用。而 DM 患者由于胰岛素抵抗状态，FLSs 对胰岛素的反应减弱，TNF 的表达增加，加速了 OA 的发展[84]。因此，对早期滑膜炎症进行调控也能部分延缓 DM 患者 OA 的进展。

3.4. DM 对关节周围神经的影响

周围神经病变也是 DM 人群中的常见并发症之一，由于 DM 导致周围感觉神经末梢受到明显损伤，患者对疼痛等刺激的敏感度也大大降低，可能是 DM 患者 OA 进展较快的原因之一[85]。

糖尿病周围神经病变常表现为感觉异常、本体感觉丧失、麻木和周围感觉丧失[86]，通常累及四肢远端。痛觉和本体感觉的损害使得关节承受更多的超自然运动和异常负荷，导致关节退变，而损伤结构的

无疼痛可进一步加重这种退变[87]。段俊虎和朱延波二人的研究对此进行了验证，周围神经损害组患者的IL-6、TNF-α、OPN、CRP值均显著高于周围神经正常组，且关节损伤程度更高。这证明糖尿病周围神经病变能够诱导和/或加速OA的进展[88] [89]。因此，对DM患者血糖有效控制以及做好对周围神经损伤的预防能够有效减缓OA的进展。

4. 总结

总的来说，DM依然是OA的独立危险因素，DM带来的高糖浓度、AGEs和胰岛素抵抗能够对关节内的软骨、软骨下骨、滑膜和周围神经产生影响，导致关节内促炎和促分解代谢等不利因素的产生增加，抗炎和抗氧化等有利因素的产生减少，这些因素的共同作用导致OA的进展速度相对于非DM患者更快，关节的退变和治疗的预后更差。

随着人们生活水平的不断提高，DM患者的数量越来越多，DM合并OA的患者也会越来越多，给患者个人和社会带来了巨大的压力。随着DM和OA之间相关性的逐步探索，DM和OA之间的关系愈加明朗，更多人开始关注DM在OA进展中的作用。因此，除使用常规治疗手段延缓OA进展，缓解OA症状外，尽早对可能合并的DM进行诊断和治疗是预防和改善关节退变的重要手段。

参考文献

[1] Cho, N.H., Shaw, J., Karuranga, S., *et al*. (2018) IDF Diabetes Atlas: Global Estimates of Diabetes Prevalence for 2017 and Projections for 2045. *Diabetes Research and Clinical Practice*, **138**, 271-281. https://doi.org/10.1016/j.diabres.2018.02.023

[2] Bruno, G., Runzo, C., Cavallo-Perin, P., *et al*. (2005) Incidence of Type 1 and Type 2 Diabetes in Adults Aged 30-49 Years: The Population-Based Registry in the Province of Turin, Italy. *Diabetes Care*, **28**, 2613-2619. https://doi.org/10.2337/diacare.28.11.2613

[3] Holman, N., Young, B. and Gadsby, R. (2015) Current Prevalence of Type 1 and Type 2 Diabetes in Adults and Children in the UK. *Diabetic Medicine*, **9**, 1119-1120. https://doi.org/10.1111/dme.12791

[4] Group UPDS (1998) Tight Blood Pressure Control and Risk of Macrovascular and Microvascular Complications in Type 2 Diabetes: UKPDS 38. *BMJ*, **317**, 703-713. https://doi.org/10.1136/bmj.317.7160.703

[5] Schmidt, A.M. (2019) Diabetes Mellitus and Cardiovascular Disease: Emerging Therapeutic Approaches. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **39**, 558-568. https://doi.org/10.1161/ATVBAHA.119.310961

[6] Zelnick, L.R., Weiss, N.S., Kestenbaum, B.R., *et al*. (2017) Diabetes and CKD in the United States Population, 2009-2014. *Clinical Journal of the American Society of Nephrology*, **12**, 1984-1990. https://doi.org/10.2215/CJN.03700417

[7] Tuttle, K.R., Bakris, G.L., Bilous, R.W., *et al*. (2014) Diabetic Kidney Disease: A Report from an ADA Consensus Conference. *Diabetes Care*, **37**, 2864-2883. https://doi.org/10.2337/dc14-1296

[8] Yau, J.W., Rogers, S.L., Kawasaki, R., *et al*. (2012) Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care*, **35**, 556-564. https://doi.org/10.2337/dc11-1909

[9] Sabanayagam, C., Banu, R., Chee, M.L., *et al*. (2019) Incidence and Progression of Diabetic Retinopathy: A Systematic Review. *The Lancet Diabetes & Endocrinology*, **7**, 140-149. https://doi.org/10.1016/S2213-8587(18)30128-1

[10] Boulton, A.J., Malik, R.A., Arezzo, J.C., *et al*. (2004) Diabetic Somatic Neuropathies. *Diabetes Care*, **27**, 1458-1486. https://doi.org/10.2337/diacare.27.6.1458

[11] Ang, L., Jaiswal, M., Martin, C., *et al*. (2014) Glucose Control and Diabetic Neuropathy: Lessons from Recent Large Clinical Trials. *Current Diabetes Reports*, **14**, 1-15. https://doi.org/10.1007/s11892-014-0528-7

[12] Albers, J.W. and Pop-Busui, R. (2014) Diabetic Neuropathy: Mechanisms, Emerging Treatments, and Subtypes. *Current Neurology and Neuroscience Reports*, **14**, 1-11. https://doi.org/10.1007/s11910-014-0473-5

[13] Volmer-Thole, M. and Lobmann, R. (2016) Neuropathy and Diabetic Foot Syndrome. *International Journal of Molecular Sciences*, **17**, 917. https://doi.org/10.3390/ijms17060917

[14] Van Netten, J., Price, P.E., Lavery, L., *et al*. (2016) Prevention of Foot Ulcers in the At-Risk Patient with Diabetes: A Systematic Review. *Diabetes/Metabolism Research and Reviews*, **32**, 84-98. https://doi.org/10.1002/dmrr.2701

[15] Martin, E.T., Kaye, K.S., Knott, C., *et al*. (2016) Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-Analysis. *Infection Control & Hospital Epidemiology*, **37**, 88-99. https://doi.org/10.1017/ice.2015.249

[16] Luk, A.O., Wu, H., Lau, E.S., *et al*. (2021) Temporal Trends in Rates of Infection-Related Hospitalisations in Hong Kong People with and without Diabetes, 2001-2016: A Retrospective Study. *Diabetologia*, **64**, 109-118. https://doi.org/10.1007/s00125-020-05286-2

[17] Fang, M., Ishigami, J., Echouffo-Tcheugui, J.B., *et al*. (2021) Diabetes and the Risk of Hospitalisation for Infection: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetologia*, **64**, 2458-2465. https://doi.org/10.1007/s00125-021-05522-3

[18] Karter, A.J., Schillinger, D., Adams, A.S., *et al*. (2013) Elevated Rates of Diabetes in Pacific Islanders and Asian Subgroups: The Diabetes Study of Northern California (DISTANCE). *Diabetes Care*, **36**, 574-579. https://doi.org/10.2337/dc12-0722

[19] Sun, H., Saeedi, P., Karuranga, S., *et al*. (2022) IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Research and Clinical Practice*, **183**, Article ID: 109119. https://doi.org/10.1016/j.diabres.2021.109119

[20] Chen, D., Shen, J., Zhao, W., *et al*. (2017) Osteoarthritis: Toward a Comprehensive Understanding of Pathological Mechanism. *Bone Research*, **5**, 1-13. https://doi.org/10.1038/boneres.2016.44

[21] O'neill, T.W., Mccabe, P.S. and Mcbeth, J. (2018) Update on the Epidemiology, Risk Factors and Disease Outcomes of Osteoarthritis. *Best Practice & Research Clinical Rheumatology*, **32**, 312-326. https://doi.org/10.1016/j.berh.2018.10.007

[22] 黎丹东, 李琳琳, 苏峰, 等. 膝骨关节炎与性别和年龄的相关性研究[J]. 临床医学研究与实践, 2019, 4(31): 1-3+8. https://doi.org/10.19347/j.cnki.2096-1413.201931001

[23] Vina, E.R. and Kwoh, C.K. (2018) Epidemiology of Osteoarthritis: Literature Update. *Current Opinion in Rheumatology*, **30**, 160. https://doi.org/10.1097/BOR.0000000000000479

[24] Hunterdj, B. and Zeinstra, S. (1759) Osteoarthritis. *The Lancet*, **393**, 1745. https://doi.org/10.1016/S0140-6736(19)30417-9

[25] Zhang, Z., Huang, C., Jiang, Q., *et al*. (2020) Guidelines for the Diagnosis and Treatment of Osteoarthritis in China (2019 Edition). *Annals of Translational Medicine*, **8**, 1213.

[26] Schett, G., Kleyer, A., Perricone, C., *et al*. (2013) Diabetes Is an Independent Predictor for Severe Osteoarthritis: Results from a Longitudinal Cohort Study. *Diabetes Care*, **36**, 403-409. https://doi.org/10.2337/dc12-0924

[27] Eymard, F., Parsons, C., Edwards, M., *et al*. (2015) Diabetes Is a Risk Factor for Knee Osteoarthritis Progression. *Osteoarthritis and Cartilage*, **23**, 851-859. https://doi.org/10.1016/j.joca.2015.01.013

[28] Louati, K., Vidal, C., Berenbaum, F., *et al*. (2015) Association between Diabetes Mellitus and Osteoarthritis: Systematic Literature Review and Meta-Analysis. *RMD Open*, **1**, e000077. https://doi.org/10.1136/rmdopen-2015-000077

[29] Abramoff, B. and Caldera, F.E. (2020) Osteoarthritis: Pathology, Diagnosis, and Treatment Options. *Medical Clinics*, **104**, 293-311. https://doi.org/10.1016/j.mcna.2019.10.007

[30] Li, G., Yin, J., Gao, J., *et al*. (2013) Subchondral Bone in Osteoarthritis: Insight into Risk Factors and Microstructural Changes. *Arthritis Research & Therapy*, **15**, 1-12. https://doi.org/10.1186/ar4405

[31] Henrotin, Y., Pesesse, L. and Sanchez, C. (2012) Subchondral Bone and Osteoarthritis: Biological and Cellular Aspects. *Osteoporosis International*, **23**, 847-851. https://doi.org/10.1007/s00198-012-2162-z

[32] Wenham, C.Y. and Conaghan, P.G. (2010) The Role of Synovitis in Osteoarthritis. *Therapeutic Advances in Musculoskeletal Disease*, **2**, 349-359. https://doi.org/10.1177/1759720X10378373

[33] Sharma, L., Pai, Y.C., Holtkamp, K., *et al*. (1997) Is Knee Joint Proprioception Worse in the Arthritic Knee versus the Unaffected Knee in Unilateral Knee Osteoarthritis? *Arthritis & Rheumatism*: *Official Journal of the American College of Rheumatology*, **40**, 1518-1525. https://doi.org/10.1002/art.1780400821

[34] Veronese, N., Cooper, C., Reginster, J.-Y., *et al*. (2019) Type 2 Diabetes Mellitus and Osteoarthritis. *Proceedings of the Seminars in Arthritis and Rheumatism*, **49**, 9-19. https://doi.org/10.1016/j.semarthrit.2019.01.005

[35] 王凯声, 亓建洪. 2 型糖尿病与软骨退变相关性的研究进展[J]. 实用骨科杂志, 2021, 27(11): 1015-1018.

[36] Buckwalter, J.A., Mankin, H.J. and Grodzinsky, A.J. (2005) Articular Cartilage and Osteoarthritis. *American Academy of Orthopaedic Surgeons Instructional Course Lectures*, **54**, 465-480.

[37] Glyn-Jones, S. and Palmer, A. (2015) Osteoarthritis. *The Lancet*, **386**, 376-387. https://doi.org/10.1016/S0140-6736(14)60802-3

[38] Li, Z., Huang, Z. and Bai, L. (2021) Cell Interplay in Osteoarthritis. *Frontiers in Cell and Developmental Biology*, **9**, Article ID: 720477. https://doi.org/10.3389/fcell.2021.720477

[39] Neumann, J., Hofmann, F.C., Heilmeier, U., *et al*. (2018) Type 2 Diabetes Patients Have Accelerated Cartilage Matrix Degeneration Compared to Diabetes Free Controls: Data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*,

26, 751-761. https://doi.org/10.1016/j.joca.2018.03.010

[40] Atayde, S.A., Yoshinari, N.H., Nascimento, D.P., *et al*. (2012) Experimental Diabetes Modulates Collagen Remodelling of Joints in Rats. *Histology and Histopathology*, **27**, 1471-1479.

[41] El Karib, A.O., Al-Ani, B., Al-Hashem, F., *et al*. (2016) Insulin and Vanadium Protect against Osteoarthritis Development Secondary to Diabetes Mellitus in Rats. *Archives of Physiology and Biochemistry*, **122**, 148-154. https://doi.org/10.3109/13813455.2016.1159698

[42] Rosa, S.C., Gonçalves, J., Judas, F., *et al*. (2009) Impaired Glucose Transporter-1 Degradation and Increased Glucose Transport and Oxidative Stress in Response to High Glucose in Chondrocytes from Osteoarthritic versus Normal Human Cartilage. *Arthritis Research & Therapy*, **11**, R80. https://doi.org/10.1186/ar2713

[43] Ribeiro, M., De Figueroa, P.L., Blanco, F., *et al*. (2016) Insulin Decreases Autophagy and Leads to Cartilage Degradation. *Osteoarthritis and Cartilage*, **24**, 731-739. https://doi.org/10.1016/j.joca.2015.10.017

[44] Vaamonde-Garcia, C., Courties, A., Pigenet, A., *et al*. (2017) The Nuclear Factor-Erythroid 2-Related Factor/Heme Oxygenase-1 Axis Is Critical for the Inflammatory Features of Type 2 Diabetes-Associated Osteoarthritis. *Journal of Biological Chemistry*, **292**, 14505-14515. https://doi.org/10.1074/jbc.M117.802157

[45] Nielen, J.T., De Vries, F., Dagnelie, P.C., *et al*. (2016) Use of Thiazolidinediones and the Risk of Elective Hip or Knee Replacement: A Population Based Case-Control Study. *British Journal of Clinical Pharmacology*, **81**, 370-378. https://doi.org/10.1111/bcp.12786

[46] 马丁, 师东良, 李姣, 等. 关节软骨损伤再生修复研究进展[J]. 生命科学, 2021, 33(11): 1353-1362.

[47] Rasheed, Z., Akhtar, N. and Haqqi, T.M. (2011) Advanced Glycation End Products Induce the Expression of Interleukin-6 and Interleukin-8 by Receptor for Advanced Glycation End Product-Mediated Activation of Mitogen-Activated Protein Kinases and Nuclear Factor-κB in Human Osteoarthritis Chondrocytes. *Rheumatology*, **50**, 838-851. https://doi.org/10.1093/rheumatology/keq380

[48] Rasheed, Z. and Haqqi, T.M. (2012) Endoplasmic Reticulum Stress Induces the Expression of COX-2 through Activation of eIF2α, p38-MAPK and NF-κB in Advanced Glycation End Products Stimulated Human Chondrocytes. *Biochimica et Biophysica Acta* (*BBA*)-*Molecular Cell Research*, **1823**, 2179-2189. https://doi.org/10.1016/j.bbamcr.2012.08.021

[49] Chen, Y.J., Sheu, M.L., Tsai, K.S., *et al*. (2013) Advanced Glycation End Products Induce Peroxisome Proliferator-Activated Receptor γ Down-Regulation-Related Inflammatory Signals in Human Chondrocytes via Toll-Like Receptor-4 and Receptor for Advanced Glycation End Products. *PLOS ONE*, **8**, e66611. https://doi.org/10.1371/journal.pone.0066611

[50] Wang, J., Wang, G. and Sun, G. (2016) Role of PPARα in Down-Regulating AGE-Induced TGF-β and MMP-9 Expressions in Chondrocytes. *Genetics and Molecular Research*, **15**, gmr7963. https://doi.org/10.4238/gmr.15027963

[51] Nah, S.-S., Choi, I.-Y., Yoo, B., *et al*. (2007) Advanced Glycation End Products Increases Matrix Metalloproteinase-1, -3, and -13, and TNF-α in Human Osteoarthritic Chondrocytes. *FEBS Letters*, **581**, 1928-1932. https://doi.org/10.1016/j.febslet.2007.03.090

[52] Huang, C.-Y., Lai, K.-Y., Hung, L.-F., *et al*. (2011) Advanced Glycation End Products Cause Collagen II Reduction by Activating Janus Kinase/Signal Transducer and Activator of Transcription 3 Pathway in Porcine Chondrocytes. *Rheumatology*, **50**, 1379-1389. https://doi.org/10.1093/rheumatology/ker134

[53] Cecil, D.L., Johnson, K., Rediske, J., *et al*. (2005) Inflammation-Induced Chondrocyte Hypertrophy Is Driven by Receptor for Advanced Glycation End Products. *The Journal of Immunology*, **175**, 8296-8302. https://doi.org/10.4049/jimmunol.175.12.8296

[54] Trellu, S., Courties, A., Jaisson, S., *et al*. (2019) Impairment of Glyoxalase-1, an Advanced Glycation End-Product Detoxifying Enzyme, Induced by Inflammation in Age-Related Osteoarthritis. *Arthritis Research & Therapy*, **21**, 1-12. https://doi.org/10.1186/s13075-018-1801-y

[55] Chen, Y.J., Chan, D.C., Lan, K.C., *et al*. (2015) PPARγ Is Involved in the Hyperglycemia-Induced Inflammatory Responses and Collagen Degradation in Human Chondrocytes and Diabetic Mouse Cartilages. *Journal of Orthopaedic Research*, **33**, 373-381. https://doi.org/10.1002/jor.22770

[56] 中国 2 型糖尿病防治指南(2020 年版)(下) [J]. 中国实用内科杂志, 2021, 41(9): 757-784.

[57] 中国 2 型糖尿病防治指南(2020 年版)(上) [J]. 中国实用内科杂志, 2021, 41(8): 668-695.

[58] Tchetina, E.V., Markova, G.A. and Sharapova, E.P. (2020) Insulin Resistance in Osteoarthritis: Similar Mechanisms to Type 2 Diabetes Mellitus. *Journal of Nutrition and Metabolism*, **2020**, Article ID: 4143802. https://doi.org/10.1155/2020/4143802

[59] 焦聚阳, 石晶晟, 夏军, 等. 糖尿病性骨关节炎发病机制研究进展[J]. 国际骨科学杂志, 2016, 37(6): 368-372.

[60] Courties, A. and Sellam, J. (2016) Osteoarthritis and Type 2 Diabetes Mellitus: What Are the Links? *Diabetes Re-*

search and Clinical Practice, **122**, 198-206. https://doi.org/10.1016/j.diabres.2016.10.021

[61] Hamada, D., Maynard, R., Schott, E., *et al*. (2016) Suppressive Effects of Insulin on Tumor Necrosis Factor-Dependent Early Osteoarthritic Changes Associated with Obesity and Type 2 Diabetes Mellitus. *Arthritis & Rheumatology*, **68**, 1392-1402. https://doi.org/10.1002/art.39561

[62] Sharma, A.R., Jagga, S., Lee, S.-S., *et al*. (2013) Interplay between Cartilage and Subchondral Bone Contributing to Pathogenesis of Osteoarthritis. *International Journal of Molecular Sciences*, **14**, 19805-19830. https://doi.org/10.3390/ijms141019805

[63] Suri, S., Walsh, D.A. (2012) Osteochondral Alterations in Osteoarthritis. *Bone*, **51**, 204-211. https://doi.org/10.1016/j.bone.2011.10.010

[64] Siebelt, M., Waarsing, J., Groen, H., *et al*. (2014) Inhibited Osteoclastic Bone Resorption through Alendronate Treatment in Rats Reduces Severe Osteoarthritis Progression. *Bone*, **66**, 163-170. https://doi.org/10.1016/j.bone.2014.06.009

[65] Kazakia, G.J., Kuo, D., Schooler, J., *et al*. (2013) Bone and Cartilage Demonstrate Changes Localized to Bone Marrow Edema-Like Lesions within Osteoarthritic Knees. *Osteoarthritis and Cartilage*, **21**, 94-101. https://doi.org/10.1016/j.joca.2012.09.008

[66] Zhen, G., Wen, C., Jia, X., *et al*. (2013) Inhibition of TGF-β Signaling in Mesenchymal Stem Cells of Subchondral Bone Attenuates Osteoarthritis. *Nature Medicine*, **19**, 704-712. https://doi.org/10.1038/nm.3143

[67] Chen, Y., Wang, T., Guan, M., *et al*. (2015) Bone Turnover and Articular Cartilage Differences Localized to Subchondral Cysts in Knees with Advanced Osteoarthritis. *Osteoarthritis and Cartilage*, **23**, 2174-2183. https://doi.org/10.1016/j.joca.2015.07.012

[68] Patsch, J.M., Burghardt, A.J., Yap, S.P., *et al*. (2013) Increased Cortical Porosity in Type 2 Diabetic Postmenopausal Women with Fragility Fractures. *Journal of Bone and Mineral Research*, **28**, 313-324. https://doi.org/10.1002/jbmr.1763

[69] Farr, J.N., Drake, M.T., Amin, S., *et al*. (2014) *In Vivo* Assessment of Bone Quality in Postmenopausal Women with Type 2 Diabetes. *Journal of Bone and Mineral Research*, **29**, 787-795. https://doi.org/10.1002/jbmr.2106

[70] Napoli, N., Strotmeyer, E.S., Ensrud, K.E., *et al*. (2014) Fracture Risk in Diabetic Elderly Men: The MrOS Study. *Diabetologia*, **57**, 2057-2065. https://doi.org/10.1007/s00125-014-3289-6

[71] Schwartz, A.V. (2016) Epidemiology of Fractures in Type 2 Diabetes. *Bone*, **82**, 2-8. https://doi.org/10.1016/j.bone.2015.05.032

[72] Jiajue, R., Jiang, Y., Wang, O., *et al*. (2014) Suppressed Bone Turnover Was Associated with Increased Osteoporotic Fracture Risks in Non-Obese Postmenopausal Chinese Women with Type 2 Diabetes Mellitus. *Osteoporosis International*, **25**, 1999-2005. https://doi.org/10.1007/s00198-014-2714-5

[73] Li, J., He, W., Liao, B., *et al*. (2015) FFA-ROS-P53-Mediated Mitochondrial Apoptosis Contributes to Reduction of Osteoblastogenesis and Bone Mass in Type 2 Diabetes Mellitus. *Scientific Reports*, **5**, Article No. 12724. https://doi.org/10.1038/srep12724

[74] Reyes, C., Leyland, K.M., Peat, G., *et al*. (2016) Association between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. *Arthritis & Rheumatology*, **68**, 1869-1875. https://doi.org/10.1002/art.39707

[75] Chen, Y., Huang, Y.-C., Yan, C.H., *et al*. (2017) Abnormal Subchondral Bone Remodeling and Its Association with Articular Cartilage Degradation in Knees of Type 2 Diabetes Patients. *Bone Research*, **5**, 1-12. https://doi.org/10.1038/boneres.2017.34

[76] Franke, S., Rüster, C., Pester, J., *et al*. (2011) Advanced Glycation End Products Affect Growth and Function of Osteoblasts. *Clinical and Experimental Rheumatology-Incl Supplements*, **29**, 650.

[77] Hui, A.Y., Mccarty, W.J., Masuda, K., *et al*. (2012) A Systems Biology Approach to Synovial Joint Lubrication in Health, Injury, and Disease. *Wiley Interdisciplinary Reviews*: *Systems Biology and Medicine*, **4**, 15-37. https://doi.org/10.1002/wsbm.157

[78] Rhee, D.K., Marcelino, J., Baker, M., *et al*. (2005) The Secreted Glycoprotein Lubricin Protects Cartilage Surfaces and Inhibits Synovial Cell Overgrowth. *The Journal of Clinical Investigation*, **115**, 622-631. https://doi.org/10.1172/JCI200522263

[79] Dahl, L., Dahl, I., Engström-Laurent, A., *et al*. (1985) Concentration and Molecular Weight of Sodium Hyaluronate in Synovial Fluid from Patients with Rheumatoid Arthritis and Other Arthropathies. *Annals of the Rheumatic Diseases*, **44**, 817-822. https://doi.org/10.1136/ard.44.12.817

[80] 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

[81] Tsai, C.-H., Chiang, Y.-C., Chen, H.-T., *et al*. (2013) High Glucose Induces Vascular Endothelial Growth Factor Production in Human Synovial Fibroblasts through Reactive Oxygen Species Generation. *Biochimica et Biophysica Acta* (*BBA*)-*General Subjects*, **1830**, 2649-2658. https://doi.org/10.1016/j.bbagen.2012.12.017

[82] Pessler, F., Dai, L., Diaz-Torne, C., *et al*. (2008) The Synovitis of "Non-Inflammatory" Orthopaedic Arthropathies: A Quantitative Histological and Immunohistochemical Analysis. *Annals of the Rheumatic Diseases*, **67**, 1184-1187. https://doi.org/10.1136/ard.2008.087775

[83] Li, Q., Wen, Y., Wang, L., *et al*. (2021) Hyperglycemia-Induced Accumulation of Advanced Glycosylation End Products in Fibroblast-Like Synoviocytes Promotes Knee Osteoarthritis. *Experimental & Molecular Medicine*, **53**, 1735-1747. https://doi.org/10.1038/s12276-021-00697-6

[84] Hamada, D., Maynard, R., Schott, E., *et al*. (2016) Insulin Suppresses TNF-Dependent Early Osteoarthritic Changes Associated with Obesity and Type 2 Diabetes. *Arthritis & Rheumatology* (*Hoboken, NJ*), **68**, 1392. https://doi.org/10.1002/art.39561

[85] 叶文春, 方向明, 王玉容, 等. 鼠神经生长因子联合硫辛酸治疗糖尿病周围神经病变的疗效观察[J]. 四川医学, 2013, 33(12): 2098-2100.

[86] Zochodne, D.W. (2007) Diabetes Mellitus and the Peripheral Nervous System: Manifestations and Mechanisms. *Muscle & Nerve*: *Official Journal of the American Association of Electrodiagnostic Medicine*, **36**, 144-166. https://doi.org/10.1002/mus.20785

[87] Leaverton, P.E., Peregoy, J., Fahlman, L., *et al*. (2012) Does Diabetes Hide Osteoarthritis Pain? *Medical Hypotheses*, **78**, 471-474. https://doi.org/10.1016/j.mehy.2012.01.008

[88] 段俊虎. 2 型糖尿病周围神经损害与膝关节骨关节炎严重程度的关系研究[J]. 中国医药导刊, 2015, 17(5): 462-464.

[89] 朱延波. 2 型糖尿病周围神经损害对膝关节骨关节炎严重程度的影响[J]. 实用妇科内分泌电子杂志, 2016, 3(5): 133.