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2型糖尿病与骨质疏松症的研究进展

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摘　要

近年来，研究发现，与非糖尿病患者相比，2型糖尿病患者患骨质疏松症的风险增加，并且2型糖尿病人群中骨质疏松症的患病率正在逐年增高，2型糖尿病患者骨折风险显著增加，特别是髋部和腕部骨折。这可能与糖尿病使得骨折风险增加，骨折愈合延迟以及氧化应激、胰岛素抵抗等原因相关。本研究旨在探讨2型糖尿病与骨质疏松之间的关联，有助于更好地理解其病理机制，并为临床预防和治疗提供依据。

关键词

2型糖尿病，骨质疏松症，影响机制

Research Progress on Type 2 Diabetes Mellitus and Osteoporosis

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Abstract

In recent years, it has been found that people with type 2 diabetes have an increased risk of osteoporosis compared to non-diabetics, and that the prevalence of osteoporosis in the type 2 diabetic population is increasing every year, with people with type 2 diabetes being at a significantly increased risk of fracture, particularly hip and wrist fractures. This may be related to the fact that diabetes makes the risk of fracture increased, delayed fracture healing as well as oxidative stress,

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insulin resistance and other reasons. The aim of this study is to investigate the association between type 2 diabetes mellitus and osteoporosis, which will help to better understand its pathomechanisms and provide a basis for clinical prevention and treatment.

Keywords

Type 2 Diabetes Mellitus, Osteoporosis, Influence Mechanism

1. 引言

2 型糖尿病(Type 2 Diabetes Mellitus, T2DM)是一种慢性代谢性疾病，其特点是胰岛素抵抗和胰岛素分泌不足，导致血糖水平升高。我国糖尿病的知晓率、治疗率、控制率提升缓慢，未诊断的糖尿病比例仍较高。目前，随着我国城市化、人口老龄化、生活方式的改变，糖尿病(Diabetes, DM)的发病率越来越高，据统计，2018 至 2019 年，国家慢性病和非传染性疾病预防控制中心和中国疾病预防控制中心的调查结果显示，我国糖尿病患病率为 11.9%，按 ADA 2010 年标准患病率为 12.4% [1]。骨质疏松症(Osteoporosis, OP)是一种全身性骨骼疾病，其特点是低骨量和骨组织微结构破坏，导致骨脆性增加和骨折发生[2]。2 型糖尿病人群中骨质疏松症的患病率正在逐年增高，2 型糖尿病患者骨折风险显著增加，鉴于糖尿病及骨质疏松症对人体健康造成的危害，深入探究其发病机制将对有效诊断及及时治疗有着重要的意义。

2. 糖尿病与骨质疏松的关联

2.1. 骨密度降低，骨折风险增加

研究显示，2 型糖尿病患者的骨折风险比非糖尿病患者高 20%~50% [3]，尤其是髋部骨折和腕部骨折。这可能与糖尿病患者的跌倒风险增加和骨密度降低有关。双能 x 射线吸收仪(Hologic Horizon W, USA)检查发现，2 型糖尿病股骨颈(Femoral Neck, FN)、全髋(Total Hip, TH)相对于对照组人群有着较高水平的骨密度(Bone Mineral Density, BMD)，然而髋部和椎体(Lumbar Spine, LS)却有着较高的骨折风险[4] [5]。糖尿病病人体中的糖基化终末产物水平随着糖尿病病程的进展逐渐升高，并在骨基质中逐步地积聚，这对骨形成造成了明显不利的影响，同时糖基化终末产物还可以造成骨形成内环境紊乱，进一步导致糖尿病病人骨强度的下降以及骨折的风险增高[5] [6]。研究发现，胰岛素水平在一定程度上与 BMD 水平呈正相关，这可能是由于胰岛素样生长因子-1 (Insulin-Like Growth Factor 1, IGF-1)与胰岛素有相似的结构有关，胰岛素通过与成骨细胞中 IGF-1 受体相互作用，从而促进成骨细胞合成代谢[7]，从而促进成骨细胞胶原及骨钙素合成，加快骨矿化[7]。有学者发现，T2DM 患者使用胰岛素控制血糖有可能会增加非椎体性骨折发生风险，主要是由于胰岛素可以增加低血糖风险及跌倒会导致骨折风险增加，而低血糖发生风险较低的 T2DM 患者使用胰岛素时骨折风险是减少的[8]。在糖尿病的治疗过程中，口服降糖药对大部分人糖尿病患者来说是必不可少且伴随终身的，而目前有研究发现，一些口服降糖药物的使用会降低 BMD 并增加骨折风险，例如噻唑烷二酮类药物能够增加全身广泛的骨折风险，降低腰椎、全髋及前臂的 BMD [9]。关于口服降糖药物与 BMD 和骨折风险的关系还没有统一的研究定论，有学者认为二甲双胍可能导致腰椎及髋部 BMD 的降低[10]，但也有研究发现，二甲双胍对骨形成有促进作用[11]。因此，对于 T2DM 患

者，我们在使用药物控制血糖水平的同时也要注意兼顾患者的 BMD 变化，尽量选择对 BMD 影响较少的药物。

2.2. 骨折愈合延迟

骨骼具有罕见的无疤痕再生能力，能够完全恢复受伤的骨骼区域。骨愈合是一个动态的多步骤过程，需要协调多种细胞类型和信号网络，并经历不同的阶段，即炎症、修复和重塑阶段[12]。值得注意的是，有证据表明 2 型糖尿病、骨质降低和骨折愈合不良之间存在显着关联[13]。糖尿病是一种促炎性代谢疾病，会引起氧化应激、信号通路激活或抑制、炎症反应、脂肪生成/成骨转化失衡和骨髓中的微血管变化[14]，会加剧血肿形成并延长骨痂发育，导致骨折愈合整体延迟。愈伤组织形成和血管生成过程被炎症因子破坏，导致骨折部位形成的新骨质量差。研究表明，衰老细胞的积累也会加速骨骼老化并导致骨骼形成受损[15]。炎症紊乱也会导致骨愈合受损，特别是成骨细胞、脂肪细胞、骨髓干细胞和骨髓环境之间的相互作用[16]。在动物实验中发现，肿瘤细胞坏死因子-α (Tumor Necrosis Factor-α, TNF-α)可以作为糖尿病治疗靶点，来提高骨折愈合能力。低浓度 TNF-α 已被证明可以促进骨折愈合，而 TNF-α 受体缺陷小鼠与对照组相比，表现出明显的骨愈合障碍[17]。二甲双胍作为糖尿病治疗过程中的一线用药，它不仅有显著的降糖效果，还可以增加胰岛素敏感性，降低体重、血清甘油三酯及低密度脂蛋白水平。但是，二甲双胍对骨折愈合的影响存在激烈争议，以往有研究表明，在动物实验中，与对照组相比，二甲双胍治疗啮齿动物的皮质和小梁骨结构没有显着差异，虽然二甲双胍对骨吸收没有影响，但降低了小梁骨的骨形成率，结果表明，二甲双胍对体内骨量或啮齿动物骨折愈合没有影响[18]。但是。近期一项研究发现，二甲双胍可以促成骨细胞作用，对骨折愈合有潜在积极影响[19]。二甲双胍在缺氧下能够促进体外血管生成以及整个骨折愈合过程中 H 型血管(一种支持成骨的骨特异性血管亚型)的形成，从而促进骨折的愈合[20]。中性粒细胞在高糖微环境中形成的中性粒细胞胞外陷阱(Neutrophil Extracellular Traps, NETs)会影响组织的愈合，有学者发现二甲双胍可以在高糖环境中逆转 NETs 对成骨的抑制作用[21]。总之，糖尿病会导致骨折愈合延迟。而治疗糖尿病的药物(如二甲双胍)对骨折愈合的影响尚存在争论，我们需要更加深入的研究来探究其中的机制，为糖尿病患者造福，减轻患者及家庭的经济负担。

3. 糖尿病导致骨质疏松的机制

骨质疏松症的患病率越来越高，据估计，全球约有 2 亿人患有骨质疏松症，其中女性的发病率更高[22]，这已经成为公共卫生领域的主要关注点。骨质流失的过程是隐匿的，并不会直接诱发明显的症状，但骨质疏松症的并发症表明骨量减少是不可逆的。由于对骨质疏松症的认识浅薄，防范意识薄弱，在发生严重并发症时治疗，给患者及社会医疗资源带来了巨大负担。

3.1. 高血糖与氧化应激

糖尿病患者体内葡萄糖代谢紊乱和高血糖状态会导致机体高消耗状态、尿钙排泄增加、产生大量自由基，通过各种代谢途径诱导氧化应激反应[23] [24]。研究表明，氧化应激在骨质疏松症的发生和发展中起着重要作用。氧化应激会破坏线粒体功能并诱导胰岛素抵抗，形成了“胰岛素抵抗–高血糖–氧化应激”的恶性循环[25]。胰腺 β 细胞的正常分泌功能有利于维持骨量[26]，而糖尿病患者血清活性氧(Reactive Oxygen Species, ROS)水平升高，ROS 能够攻击胰腺 β 细胞使骨量难以维持平衡。一氧化氮(Nitric Oxide, NO)是糖尿病诱导的骨质疏松症中的主要 ROS，NO 导致内皮一氧化氮合酶(Endothelial Nitric Oxide Synthase, eNOS)减少和诱导型一氧化氮合酶(Inducible Nitric Oxide Synthase, iNOS)增加，eNOS 具有修复高糖诱导的成骨分化减少，iNOS 表达增加有助于高糖状态下破骨细胞生成，阻碍成骨细胞的分化和矿化[27]-[29]。众多体内

及体外实验研究表明，氧化应激会影响破骨细胞和成骨细胞活性[30] [31]，还会降低骨髓间充质基质细胞和成骨细胞前体的增殖[32]，对成骨细胞分化和活性以及矿化过程产生负面影响，这些作用引起骨重塑过程的变化，导致破骨细胞和成骨细胞活性之间的失衡，骨转换率增加，出现吸收超过形成的现象，导致骨质疏松症[33] [34]。

3.2. 胰岛素抵抗与胰岛素缺乏

糖尿病患者存在不同程度的胰岛素缺乏及胰岛素抵抗(Insulin Resistance, IR)。先前的研究表明，胰岛素在对骨量和骨小梁微结构的合成代谢作用中起重要作用，并且可能在这个过程中与 IGF-1 和甲状旁腺激素(Parathyroid Hormone, PTH)发挥协同作用[35] [36]。IGF-1 是骨骼发育和生长以及维持骨量最重要的生长因子之一，IGF-1 有效抑制细胞凋亡，增加成骨细胞的增殖和分化，增加了小梁骨的形成，并防止了小梁骨质流失。IGF-1 还可以在骨基质中产生和储存，通过自分泌或者旁分泌作用促进成骨细胞的增值与分化和抑制骨吸收来起到调节机体获得和维持骨量的作用[37]。在胰岛素缺乏动物模型中发现，骨形成减少，而胰岛素治疗可以逆转[36] [38]。这一点在 1 型糖尿病患者身上得到了支持。而 2 型糖尿病患者与健康人相比，虽然 BMD 更高，但骨折风险更高[39]。这表明 IR 可能会影响胰岛素血症对骨量的影响。一项横断面研究认为，空腹胰岛素水平与青少年 BMD 呈正相关[40]。IR 与绝经后妇女的皮质骨量和股骨颈 BMD 呈负相关[41]。因此，IR 可能会影响胰岛素血症与骨量之间的关联，并且对不同人群的调查可能会产生不一致的结果。

3.3. 微量元素代谢异常

糖尿病不仅能够影响干扰器官的正常功能，还能通过破坏肠道、骨骼和肾脏等钙调节器官的功能来影响钙代谢过程[42]。钙水平受到三种经典钙调节激素的严格调节，即 PTH、1,25-二羟基维生素 D_3 (Calcitriol,1,25$(OH)_2D_3$)和降钙素(Calcitonin, CT)，以确保肠道钙的充分吸收、钙在骨骼中的适当储存以及通过肾脏排泄多余的钙。在糖尿病患者中，钙稳态是紊乱的。早期研究表明，口服和静脉注射葡萄糖均诱导高钙尿症[43]，糖尿病动物小鼠模型发现其尿钙和磷酸盐排泄均增加，与健康母鼠的后代相比，它们的后代表现出更少的骨化中心和更低的骨矿物质含量[44]。糖尿病患者体内的肾钙丢失可能是由促钙激素(如 PTH 和 1,25$(OH)_2D_3$)失调引起的。综上，糖尿病患者容易出现钙磷代谢紊乱及维生素 D 缺乏，从而影响骨矿化，削弱骨骼健康。

4. 影响骨质疏松的其他因素

骨骼健康在很大程度上依赖于机械负荷，即日常活动和运动对骨骼的刺激。当身体承受机械负荷时，骨骼会通过适应性反应增强其强度和密度。这种适应性反应是通过成骨细胞的活动增加和破骨细胞的活动减少来实现的。糖尿病患者可能由于以下原因可能导致运动量减少，从而影响骨骼健康：1) 周围神经病变：糖尿病患者常常出现周围神经病变，表现为手脚麻木、刺痛或疼痛。这些症状可能导致患者在运动时感到不适或疼痛，从而减少运动量[45]。2) 自主神经病变：自主神经病变可能导致心血管系统调节功能受损，使患者在运动时更容易出现心悸、头晕等症状，从而限制运动能力[46]。3) 视网膜病变：糖尿病视网膜病变可能导致视力下降，影响患者的运动安全，从而减少运动量[47]。4) 足部问题：糖尿病患者容易出现足部溃疡和感染，这些问题可能导致患者不得不减少步行或其他负重运动，从而影响骨骼健康[48]。除此之外，糖尿病患者可能因饮食限制(如低脂饮食)而减少摄入富含钙和维生素 D 的食物来影响骨骼健康。运动量减少会导致骨骼承受的机械负荷减少，从而降低骨密度和骨强度，增加骨质疏松和骨折的风险。

5. 骨质疏松的预防与治疗策略

糖尿病患者因运动量减少、神经病变导致活动受限以及低钙饮食和维生素 D 摄入不足，多重因素共同作用，显著增加骨质疏松和骨折的风险。我们可以通过以下措施预防和管理这一问题：1) 增加运动量：在医生指导下进行适量的负重运动和力量训练，以刺激骨骼健康。运动时应注重安全，避免因神经病变导致的跌倒风险。2) 改善饮食：增加富含钙和维生素 D 的食物摄入，如乳制品、鱼类和强化食品。必要时，可在医生指导下补充钙和维生素 D。3) 管理神经病变：积极控制血糖，延缓神经病变的进展。对于已出现神经病变的患者，应进行适当的康复训练，以改善运动能力和活动量。4) 定期监测骨密度：糖尿病患者应定期进行骨密度检测，早期发现骨质疏松并采取干预措施。通过综合管理，糖尿病患者可以有效降低骨质疏松和骨折的风险，改善整体健康状况。

综上所述，2 型糖尿病与骨质疏松之间存在复杂的相互作用，涉及高血糖、胰岛素抵抗、氧化应激反应、钙磷代谢异常等多个机制。了解这些机制有助于制定有效的预防和治疗策略。未来研究应进一步探索糖尿病与骨质疏松之间的具体分子机制，以及如何通过优化血糖控制和其他干预措施来预防骨质疏松的发生，使糖尿病患者可以更好地管理自己的健康，减少并发症的发生，提升生活质量。

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