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肥胖与糖尿病血管并发症的研究进展

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摘 要

随着生活方式的改变及人口老龄化的加速，2型糖尿病和肥胖的患病率呈快速上升趋势，已成为全球重大公共卫生问题。肥胖是2型糖尿病的重要致病因素，并加速糖尿病慢性并发症的产生。本文就肥胖与糖尿病血管并发症的相关性作一综述，主要包括糖尿病视网膜病变、糖尿病肾病与动脉粥样硬化性心血管疾病，重点关注临床数据、分子机制和治疗前景等方面，以期为糖尿病的早期干预及规范化诊疗提供依据。

关键词

肥胖，2型糖尿病，糖尿病视网膜病变，糖尿病肾病，动脉粥样硬化性心血管疾病

Advances in the Study of Obesity and Diabetic Vascular Complications

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Abstract

With the accelerated lifestyle changes and population aging, the prevalence of type 2 diabetes and obesity is rapidly increasing and has become a global public health problem. Obesity is an important causative factor of type 2 diabetes and accelerates the development of chronic complications of diabetes. In this paper, we review the correlation between obesity and diabetic vascular complications, including diabetic retinopathy, diabetic nephropathy and arteriosclerotic cardiovascu-

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lar disease, focusing on clinical data, molecular mechanisms and therapeutic prospects, with the aim of providing a basis for early intervention and standardized diagnosis and treatment of diabetes.

Keywords

Obesity, Type 2 Diabetes Mellitus, Diabetic Retinopathy, Diabetic Nephropathy, Atherosclerotic Cardiovascular Disease

1. 引言

近年来，糖尿病的全球患病率、发病率逐年增长，造成了巨大的社会及经济负担[1]。肥胖与糖耐量降低相关，并且是 2 型糖尿病(type 2 diabetes mellitus, T2DM)的独立危险因素[2]。肥胖导致脂质积累，并能够通过激活炎症和氧化应激造成脂毒性及代谢紊乱[3]。糖脂毒性的累加效应会引发糖尿病长期并发症，包括糖尿病视网膜病变(diabetic retinopathy, DR)、糖尿病肾病(diabetic nephropathy, DN)和动脉粥样硬化性心血管疾病(arteriosclerotic cardiovascular disease, ASCVD) [4]，此类血管并发症是糖尿病患者致残致死的主要原因。一项针对 4658 名中国糖尿病患者的研究显示，男性和女性的中国内脏肥胖指数(Chinese visceral obesity index, CVAI)与心血管疾病(cardiovascular disease, CVD)和 DN 的患病率呈显著正相关关系[5]。已有多项研究证实，减重代谢手术能够预防糖尿病微血管和大血管并发症[6] [7] [8] [9] [10]。本文探究肥胖在糖尿病血管并发症中的作用，将有助于理解疾病发生发展机制并指导临床实践。

2. 肥胖与 DR

微血管病变是糖尿病的特异性并发症，其典型改变是微循环障碍和微血管基底膜增厚。微血管病变可累及全身各组织器官，主要表现在视网膜、肾、神经和心肌组织，其中以 DR 和 DN 尤为重要。DR 是糖尿病最常见的微血管并发症，分为非增殖期视网膜病变(non-proliferative diabetic retinopathy, NPDR)和增殖期视网膜病变(proliferative diabetic retinopathy, PDR)。在中国，约 1/5 的糖尿病患者并发 DR [11]。DR 是造成糖尿病患者失明的主要原因[12]。尽管高血糖是主要诱因，全身和局部脂质代谢失调也在 DR 的发展中发挥关键作用[13] [14] [15]，多项前瞻性研究显示，肥胖与 DR 发病率正相关，且肥胖是 NPDR 的危险因素[16]。一项 2017~2020 年的前瞻性队列研究发现，中心型肥胖增加了 DR 发病的风险，表明中心型肥胖作为 DR 风险标志物具有临床代表性[17]。脂质蓄积产物(lipid accumulation product, LAP)和 CVAI 是新的肥胖评估指标[18]。一项研究证实，高 LAP 与 T2DM 患者的 DR 风险增加相关，与体质指数(body mass index, BMI)、腰围(waist circumference, WC)和 CVAI 相比，LAP 指数是 T2DM 患者 DR 患病风险和严重程度的良好预测指标[19]。

DR 的病因机制复杂，机体结构损伤和分子功能异常促进其发生发展[20]。实验表明，高糖高脂环境会增加毛细血管内皮细胞凋亡，促进 DR 进展[21]。据了解，表观遗传修饰，即可以在不影响 DNA 序列的情况下改变基因表达的修饰(如甲基化)，在糖尿病疾病进程中会发生改变[22] [23]。Rac1 是一种小分子量 G 蛋白，Rac1-Nox2-ROS 通路激活能够引起线粒体损伤[24]。研究显示，T2DM 肥胖大鼠有明显的视网膜病变，其线粒体拷贝数较低，mtDNA 和 Rac1 启动子 DNA 甲基化加剧，而肥胖/高脂血症进一步增

强了 mtDNA 的表观遗传修饰，加速了线粒体损伤和 DR 的发展，证明了肥胖/高血脂在 DR 疾病表观遗传修饰中的重要作用[25]。

调查研究显示，降脂治疗可减少 PDR 患者的激光治疗次数[26]。长期服用降脂药非诺贝特可减少 DR 病变进展[27]。综上所述，肥胖在 DR 疾病进程中发挥重要作用，降脂或减重治疗将是防止 DR 发生发展的有效措施。

3. 肥胖与 DN

DN 常见于糖尿病病史超 10 年的患者，是 T1DM 的主要死因，在 T2DM 其严重性仅次于心、脑血管疾病。DN 是全球慢性肾脏病变(chronic kidney disease, CKD)的主要原因，也是终末期肾衰竭的主要原因[28]。在 T2DM 人群中，肥胖将增加女性的 DN 风险[29]，同时，肥胖加速 T2DM 患者白蛋白尿和肾功能恶化的进程[30]。

肥胖所致的脂质和脂蛋白代谢异常导致肾损害，在 DN 的进展中起关键作用[31]。在高糖高脂环境中，DN 患者血浆中胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)和载脂蛋白 B (apolipoprotein B, Apo B)相关脂蛋白，如极低密度脂蛋白(very low density lipoprotein, VLDL)、低密度脂蛋白(low density lipoprotein, LDL)和脂蛋白 a (lipoprotein a, Lpa)水平升高，同时高密度脂蛋白(high density lipoprotein, HDL)水平下降，HDL 主要结构和功能蛋白载脂蛋白 A-I (apolipoprotein A-I, Apo A-I)水平也降低[32]，并且 Apo B100 (参与脂蛋白摄取)、Apo B48 (乳糜微粒主要成分)和 Apo CIII (脂蛋白脂酶抑制剂)等其他载脂蛋白亚型随之增加[33]。脂蛋白脂酶的减少破坏了胆固醇的逆向转运，并减少介导脂质摄取的受体数量[33]。随着这些不利血脂的定量升高，脂蛋白组成也逐渐发生定性变化，如 HDL 颗粒逐渐显示甘油三酯的富集和抗氧化剂的损失[33] [34]，血浆和肾实质中检测到氧化的 HDL 和 LDL 水平升高[35] [36] [37]。这些氧化脂蛋白具有肾细胞毒性并加速肾损害[38] [39]。例如，氧化脂蛋白增加 NADPH 氧化酶介导的活性氧(reactiveoxygenspecies, ROS)产生、募集循环单核细胞并分泌促炎细胞因子(IL-6、CCL2、CCL5 和 TNF-α)，进一步导致肾脏细胞凋亡和氧化应激[40] [41] [42]。总之，脂质代谢异常导致肾脏损伤并促进 DN 的进展。

脂肪组织的信号传递功能失调和脂质异位积聚与脂毒性密切相关[43]。在 DN 患者中，血脂异常同时促进了棕榈酸盐、神经酰胺和非酯化脂肪酸(nonestesterified fatty acid, NEFA)等脂质中间产物在肾脏及肾外组织(如肝脏、胰腺和心脏)积聚[44] [45]。肾实质中的这种脂质积聚导致局部炎症和氧化应激[46] [47]，对各种细胞(包括足细胞、近端小管上皮细胞和小管间质组织)造成损害，长期将对肾功能造成损害[48] [49] [50] [51] [52]。

透射电子显微镜或磁共振成像发现，肥胖和糖尿病患者肾细胞中存在脂滴[53]，这种脂滴的积累导致了炎症激活、ROS 产生、线粒体功能紊乱、自噬功能失调和细胞凋亡[3] [45] [54]，而脂滴形成的机制涉及到脂质有毒代谢物的积累，如二酰基甘油、脂肪酰基-CoA、神经酰胺和鞘脂，它们参与了蛋白激酶 C (protein kinase C, PKC)的激活、甘油酯的合成和线粒体功能障碍[55] [56]。因此，利用血脂代谢产物寻找肥胖与 DN 之间新的关联是研究疾病的新思路。最近，一项综合脂质组学分析已确定脂质介质(不饱和 NEFA、磷脂酰乙醇胺和长链酰基肉碱等)是肾功能保留(GFR ≥ 90 mL/min)的美国印第安人 DN 进展的预测因素[57]。Tofte 等人发现，鞘磷脂和磷脂酰胆碱种类与 T1DM 患者肾损害进展及死亡率相关[58]。基于血脂代谢异常与 DN 的相关性，一系列观察性研究陆续展开，已证实某些抗脂毒性药物能降低 DN 的肾毒性，如非诺贝特[59]、利拉鲁肽[60]、异槲皮素[61]以及白藜芦醇[62]等。

总之，在糖尿病进程中，肥胖所致的脂毒性靶向肾脏，这主要与脂质和脂蛋白代谢异常、异位脂质聚集和有害脂质代谢产物增加有关。在某种程度上讲，脂质标记物可以作为 DN 的预测因子。新型药物靶向肾脏脂肪毒性，可能是对抗 DN 的一种选择。减轻体重、改善肥胖将有利于延缓肾功能衰退进程。

4. 肥胖与 ASCVD

肥胖增加糖尿病大血管并发症风险，尤其是 ASCVD。一项关于日本 T2DM 人群调查显示，BMI 升高与颈动脉内膜中层增厚显著相关，这提示肥胖可能是日本 T2DM 患者发生大血管病变的重要危险因素[63]。ASCVD 的病理事件主要包括血栓形成、内皮细胞功能障碍、脂质浸润、氧化应激和血管炎症，炎症促进斑块的形成和发展，最终导致斑块破裂引发急性心脑血管事件[64] [65] [66]。肥胖人群一氧化氮(NO)生物利用度降低，会导致内皮依赖性血管舒张功能受损[67]，从而导致内皮一氧化氮合酶(eNOS)的改变，造成内皮细胞功能障碍。同时，高脂环境促进血管炎症，增加动脉粥样硬化负担[68]。因此，高脂血症、胰岛素抵抗和慢性炎症与 ASCVD 之间相互作用，增加疾病相关死亡风险[69]。

脂肪细胞分泌的脂肪因子在糖脂代谢方面发挥重要作用。脂肪组织可依据机体自身的生理环境分泌多种不同的脂肪因子。常见的脂肪因子包括脂联素(adiponectin, APN)、瘦素(leptin, LEP)、血管生成素样蛋白 4 (angiopoietin-like protein 4, ANGPTL4)、趋化素等[70]。新型脂肪因子包括 chemerin、apelin、vaspin 等[71]。脂肪因子可通过血液循环直接作用于血管内皮细胞，或通过影响交感神经系统活性、胰岛素敏感性等方式间接影响血管内皮细胞功能，同时作为炎性介质直接影响动脉粥样硬化的发生，是糖尿病血管病变的高危要素之一。例如，脂肪因子 chemerin 能增加人微血管内皮细胞(human microvascular endothelial cells, HMECs) ROS 的产生，并且抑制 PI3K/Akt 信号通路，进而抑制胰岛素诱导的 eNOS 磷酸化以及 NO 生成，而 CMKLR1 (chemerin 受体)拮抗剂能减少 ROS 生成并且改善血管舒张功能和胰岛素信号通路的活性[72]。另有研究指出，2 型糖尿病患者肾脏中脂肪因子 apelin 的水平增加，进一步的研究发现，apelin 可以通过上调 VEGFR2 以及 Tie2 诱导糖尿病肾小球中异常的血管生成，并且增加肾小球内皮细胞的通透性，进而加速 DN 的进展[73]。脂肪组织过度增生，加之糖尿病相关的代谢紊乱导致脂肪因子谱发生变动，加速糖尿病血管病变发生。总之，作为糖脂代谢及动脉粥样硬化过程中的关键环节，许多脂肪因子直接参与到糖尿病血管病变进程中，未来仍需进一步深入研究，为防治糖尿病及其并发症开辟出新的领域。

5. 总结与展望

糖尿病病因及发病机制复杂，肥胖加剧 T2DM 患者血管并发症的发生。T2DM 合并肥胖的疾病管理形势非常严峻，新的肥胖指标的建立可帮助及时调整治疗方案。针对 T2DM 合并肥胖患者，在降糖的同时加强体重管理，是糖尿病综合管理的重要内容，对于预防糖尿病血管并发症、提高患者生活质量具有重要意义。

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