

糖尿病肾病血液高凝状态的治疗策略综述

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摘要

糖尿病肾病(diabetic kidney disease, DKD)是糖尿病(diabetes mellitus, DM)的主要微血管并发症之一。由于长期代谢异常、血流动力学改变、内皮损伤、凝血抗凝血失衡、血小板活化、纤溶系统抑制、补体系统激活、表观遗传调控等方面, DKD常伴血液高凝状态, 不仅促进疾病进展, 且增加心脑血管事件及下肢血栓风险, 我们总结了当前DKD血液高凝的治疗策略以及发展前景, 为DKD高凝状态的进一步治疗提供理论依据。

关键词

糖尿病肾病, 血液高凝状态, 多靶点治疗

A Comprehensive Review of Therapeutic Strategies for Hypercoagulable State in Diabetic Kidney Disease

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Abstract

Diabetic kidney disease (DKD) is one of the major microvascular complications of diabetes mellitus (DM) and is often characterized by a hypercoagulable state in the blood due to long-term metabolic

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abnormalities, hemodynamic changes, endothelial damage, imbalances in coagulation and anticoagulation, platelet activation, inhibition of the fibrinolytic system, activation of the complement system, and epigenetic regulation. This hypercoagulable state not only accelerates disease progression but also increases the risk of cardiovascular and cerebrovascular events, as well as lower limb thrombosis. In this context, we have summarized the current treatment strategies for the hypercoagulable state in diabetic kidney disease (DKD) as well as its future development prospects, providing a theoretical basis for further treatment of this condition.

Keywords

Diabetic Kidney Disease, Hypercoagulable State, Multi-Target Therapy

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1. 引言

DKD 是 DM 的主要并发症之一, 其病理特征包括肾小球硬化、肾小管间质纤维化和微血管病变。国际糖尿病联合会(IDF)估计, 2024 年全球约有 5.89 亿成年人(20~79 岁)患有糖尿病。预计到 2050 年, 糖尿病患者的总人数将上升至 8.53 亿[1]。据估计, 40%的 DM 患者在其一生中会发生慢性肾脏疾病(Chronic kidney disease, CKD), 自 1990 年至 2017 年间, 全球因 2 型糖尿病(Type 2 diabetes mellitus, T2DM)导致的慢性肾脏病新增病例数量由 140 万增加到 2017 年的 240 万, 增幅约 74%, 其发病率从 11.31%上升至 37.05%, 2019 年, 全球报告了 260 万例 DKD 新发病例, 预计未来发病率将继续增加[2]。DKD 患者的高凝状态是由于促凝与抗凝过程中的异常, 导致血栓形成倾向增加, 这一状态是早期诊断血栓栓塞性疾病的重要组成部分。代谢异常、凝血与抗凝系统失衡、纤溶抑制、血小板活化、炎症及补体调节等因素共同导致了 DKD 患者机体高凝状态[3]-[6], 此状态在 DKD 患者肾动脉硬化以及伴发心脑血管等严重威胁生命的大血管疾病的过程中至关重要。由于 DKD 患者常见多种并发症, 建议实施综合护理和整体治疗, 以降低心血管疾病(cardiovascular disease, CVD)和肾脏疾病进展的风险[7]。近年来, 随着对高凝状态机制的深入研究, DKD 的治疗策略不断优化。本文旨在综述 DKD 血液高凝状态的治疗策略及其发展前景。

2. DKD 血液高凝状态及治疗策略

2.1. 血糖管理

严格控制血糖水平对于减轻 DKD 引起的血液高凝状态以及预防血栓栓塞的形成至关重要[8]。UKPDS [9]和 ADVANCE [10]等研究表明, 降糖治疗能有效降低糖尿病微血管并发症(包括 DKD)的风险。KDIGO 和美国糖尿病协会(ADA)推荐使用糖化血红蛋白(HbA1c)来监测长期血糖控制[7]。根据 ADA 2022 标准与 KDIGO 2022 指南, 二甲双胍和 SGLT2 抑制剂被推荐为 CKD 及 DM 患者的一线治疗方案[7]。对于 $eGFR \geq 30 \text{ mL/min/1.73 m}^2$ 的患者, 此联合用药是安全有效的[11]。SGLT2 抑制剂不仅能降糖, 还能降[1]在降低血糖和 HbA1c 方面表现优异, 并且低血糖风险较低[11] [13]。如果基础治疗未能达到目标血糖, 可考虑添加其他降糖药物[7] [11]。KDIGO 和 ADA 建议使用长效胰高血糖素样肽-1 受体激动剂(GLP-1RA)作为首选的附加治疗, 因其在改善血糖控制和促进体重减轻方面有效[11]。研究表明, GLP-1RA 在 HbA1c 为 7.0%且心血管风险高的糖尿病患者中可降低主要心血管不良事件的发生率[14]。Sattar 等人进行的随机试验荟萃分析表明, GLP-1RA 能降低包括严重蛋白尿、eGFR 下降和肾功能衰竭等在内的复合肾脏结局

风险, 并降低 T2DM 患者的全因死亡率。已知对 CVD 和 CKD 有益的 GLP-1RA 包括利拉鲁肽、司美格鲁肽、阿必鲁肽和杜拉糖肽[7]。当 eGFR 降至 15 mL/min/1.73 m² 时, GLP-1RA 仍可安全有效用于透析患者[7][11]。但在 eGFR < 60 mL/min/1.73 m² 的患者中, 其对心血管风险的益处较小[15]。对于晚期 CKD、eGFR < 30 mL/min/1.73 m² 或正在透析的患者, 很多药物的使用受到限制, 并且缺乏有关治疗策略的试验数据, 血糖控制可能具有挑战性。对于 1 型糖尿病(Type 1 diabetes mellitus, T1DM)患者而言, 唯一获批的治疗方式是胰岛素, 其剂量需根据 CKD 的进展进行调整[7]。在 T2DM 患者中, 晚期 CKD 增加了低血糖的风险, 因此应优先选择不易引发低血糖的降糖药物[7][16]。二肽基肽酶 4 抑制剂(如利格列汀和西格列汀)可用于 eGFR < 30 mL/min/1.73 m² 及透析患者, 作为无法使用 GLP-1RA 的替代方案。此外, 若其他药物存在禁忌、耐受性差或疗效不足, 通常需要使用胰岛素降糖[7]。

2.2. 血脂管理

血脂异常是 DKD 患者常见的合并症[17]。高水平的总胆固醇、低密度脂蛋白胆固醇和甘油三酯也是动脉粥样硬化性 CVD 和 DKD 发生进展的危险因素[18]。根据 2013 年 KDIGO 的指南, 大多数未透析的成年 DM 和 CKD 患者应接受他汀类药物治疗, 特别是 50 岁以上的 CKD 患者、eGFR ≥ 60 mL/min/1.73 m² 的患者以及 18~49 岁有 DM 或 CKD 的患者, 或有冠心病、既往缺血性卒中历史或 10 年内冠心病死亡风险 ≥ 10% 的患者[19]。ADA 推荐对 40~75 岁的成年 DM 患者、20~39 岁伴有动脉粥样硬化性 CVD 风险因素的成年人以及 75 岁以上的患者实施中等强度的他汀治疗[7]。接受血液透析的患者通常不在推荐范围内, 因为他汀对动脉粥样硬化性 CVD 的一级预防无效[20]。对于二级预防, ADA 建议使用高强度他汀治疗。如需加强治疗, 依据心血管疾病风险和低密度胆固醇水平, 可加用依折麦布或 PCSK-9 抑制剂[7]。英国临床糖尿病学家协会(ABCD)和英国肾脏协会(UKKA)在其 2024 年的指南中推荐在 DKD 的各阶段开始使用 20 mg 阿托伐他汀治疗, 对于未达到治疗目标的 G1-G3a 期肾病患者, 建议考虑更高剂量或与依折麦布联合治疗, 在肾病 G1-G3a 期出现他汀类药物不耐受的情况下, 若单用依折麦布不能达到治疗目标, 可联用苯甲多酸[21]。

2.3. 血压管理

高血压常见于 DKD 患者。高血压会使肾功能恶化, 促进血液高凝, 增加心血管疾病的风险, 因此, 控制血压对 DKD 患者至关重要[22]。低风险患者的目标为低于 140/90 mmHg, KDIGO 建议 CKD 患者的收缩压应低于 120 mmHg [7][23]。而 ADA 则建议 DKD、高血压、CVD 高风险患者的血压目标为低于 130/80 mmHg, 低风险患者的血压目标为低于 140/90 mmHg [7][24], 并可根据患者情况个性化调整。建议糖尿病、高血压和蛋白尿患者使用肾素-血管紧张素系统(RAS)抑制剂, 如 ACEI 或 ARB, 并以最高耐受剂量治疗[7]。一些临床试验发现, 与安慰剂或其他降压药物相比, RAS 抑制剂最有效地降低了 CKD 进展的风险[25][26]。因需多种药物联合以实现理想的血压控制, 常可将 RAS 抑制剂、钙通道阻滞剂及利尿剂联合使用。同时, 非甾体矿物皮质激素(ns-MRAs)如艾沙利酮和非奈利酮也被纳入治疗方案, 作为新疗法应用于临床[7]。虽然艾沙利酮已被证明可以降低血压和蛋白尿, 但评估其在 DKD 患者中的作用的长期研究仍缺乏[27]。当前唯一获批的能够减缓 CKD 进展并减少心血管事件的 ns-MRA 是非奈利酮[28]。

2.4. 抗血小板药物治疗

研究显示, 活化的血小板通过多种机制参与 DKD 的病理过程, 促进血液高凝。血小板不仅在止血和凝血中起关键作用, 还在炎症、纤维化等过程中发挥了重要作用。多项动物实验和临床研究表明, 抗血小板药物可以改善 DKD 患者的肾功能, 减少尿蛋白排泄, 并延缓血栓栓塞事件及疾病进展。例如, P2Y₁₂

受体抑制剂氯吡格雷被证明能显著减少纤维连接蛋白的积累, 改善 DM 诱导的肾纤维化[29]。磷酸二酯酶-3 (PDE-3)抑制剂西洛他唑被广泛用于治疗外周动脉疾病治疗, 并在 DKD 患者中显示出显著的疗效。一项随机对照试验表明, 西洛他唑显著降低了尿微量白蛋白水平, 改善了肾功能[30]。此外, PGI₂ 的类似物贝前列素钠也被证明能有效减少尿蛋白排泄, 改善肾功能[31], 并常用于外周动脉血栓栓塞性疾病。DKD 的治疗不应仅依赖单一药物, 而是需要综合考虑多种因素。结合抗血小板药物与其他治疗(如血管紧张素转换酶抑制剂、他汀类药物等)可以更有效地控制病情进展[32]。然而, 抗血小板药物在 DKD 患者中的应用仍存在局限性, 现有研究多为动物实验或小规模临床试验, 缺乏长期疗效和安全性的研究, 且未充分考虑个体差异和联合治疗的平衡。未来研究应深入探索抗血小板药物的作用机制, 优化联合治疗方案, 关注长期疗效和安全性, 并制定个体化治疗策略, 以更好地指导临床实践。

2.5. 抗凝药物治疗

为控制 DKD 患者血液高凝状态, 抗凝药物治疗是最直接的方法, 目前, 临床上常用的抗凝药物包括低分子肝素和口服抗凝药(OAC), 低分子肝素可以改善 DM 患者血液流变学和肾脏微循环, 延缓肾小球硬化, 降低肾内循环阻力。此外, 肝素具有一定的抗炎和抗氧化功能, 可以抑制炎症反应和肾细胞损伤[33]。对于合并 CKD 的 DM 患者, OAC 治疗的选择应基于 CHA₂DS₂-VASc 卒中风险评分, 低卒中风险患者(男性 0 分, 女性 1 分)不应接受 OAC 治疗; 而 CHA₂DS₂-VASc ≥ 1 的男性和 CHA₂DS₂-VASc ≥ 2 的女性患者则应考虑使用 OAC。所有其他患者均推荐使用 OAC, 并需评估出血风险, 可采用 HAS-BLED 评分[34]。在 OAC 的选择上, 优先考虑直接口服抗凝药(DOACs), 如 Xa 因子直接抑制剂利伐沙班、IIa 因子直接抑制剂达比加群, 相比维生素 K 拮抗剂(VKA)华法林, 其药代动力学特征更简单, 颅内出血风险更低[35]。DOACs 在 eGFR 大于 15 mL/min/1.73 m² 的患者中获批使用, 但达比加群要求 eGFR 超过 30 mL/min/1.73 m²。虽然华法林适用于 DKD 的所有阶段, 但对于 eGFR 低于 15 mL/min/1.73 m² 的患者, 其益处证据非常有限。此外, 现有研究表明, 与 DOACs 相比, VKA 的使用可能导致更快的肾功能下降, 这可能是由于患者血管钙化加重[36]。Olivia S. Costa 等人[37]的研究也显示, 与华法林相比, 利伐沙班能有效降低 T2DM 合并非瓣膜性房颤患者的肾脏和外周血管并发症的发生率及死亡率。因此, DKD 患者的 DOACs 给药应根据年龄、体重和肾功能进行个性化调整, 以确保治疗的安全性和有效性[34]。

2.6. 抗炎治疗

DKD 患者的慢性炎症在血液高凝中起着重要作用, 抗炎治疗或许能间接改善血液的高凝, 一些现有药物如 RAS 抑制剂、ns-MRA 和 SGLT2 抑制剂具有抗炎特性。然而, 炎症的非特异性改善可能是其他有益作用的次要后果, 如肾小球高滤过和蛋白尿的减少。目前, 一些有效的抗炎药物仍在研究中。研究显示, 己酮可可碱的肾脏益处与其抗炎作用有关, DKD 患者在接受其治疗后蛋白尿减少与 TNF- α 水平下降直接相关[38]。PREDIAN 研究, 一项针对 DKD G3-G4 和残余蛋白尿的随机对照实验(RCT), 尽管 RAS 阻断, 己酮茶碱仍能减缓 CKD 进展, 减少尿白蛋白和尿 TNF- α 排泄, 并维持抗炎蛋白 klothos 的表达[39]。白藜芦醇具有抗氧化和抗炎作用, 早期一期试验结果显示白藜芦醇联合氯沙坦可减少 DKD 患者的蛋白尿[40]。甲基巴多洛酮通过激活 Nrf2 通路改善氧化应激, 在二期 RCT 中显示可提高 eGFR, 尽管存在安全性问题, 如体液超负荷、高血压、蛋白尿增加等, 但在某些特定人群中仍处于临床试验阶段[41]。针对炎症相关细胞因子的研究也在进行中, Ridker PM 等人发现[42]卡纳单抗作为 IL-1 β 的单克隆抗体能够降低伴或不伴糖尿病的 CKD 患者心血管事件发生率, 但未能改变肾功能。抗炎治疗在减轻 DKD 患者血液高凝方面有效, 但临床应用仍在探索中, 许多在动物模型中有效的药物在临床试验中未能取得相应

效果,可能是由于人类和小鼠免疫细胞表型的差异[43]。此外,针对单一炎症介质的药物多未成功,多靶点策略或许更具潜力。

2.7. 补体靶向治疗

补体的激活不仅加剧了肾脏的炎症反应,且与凝血系统交互作用,导致肾小管和肾小球的损伤。慢性的炎症状态还会进一步促进血液的高凝。针对补体系统的治疗策略受到越来越多的关注。依库珠单抗和依库丽珠单抗通过靶向 C5 被广泛用于治疗非典型溶血性尿毒症综合征,而 C5a 受体拮抗剂阿伐可泮已获批用于 ANKA 相关血管炎的治疗。Gefurulumab (ALXN1720)作为 C5 抑制剂,目前正在进行针对蛋白尿性肾病的 I 期临床试验,包括 DKD。此外,其他针对补体激活的干预措施,如补体抑制剂,可能通过减轻炎症改善 DKD 患者的血液高凝状态。最近的证据表明,C3a 和 C5a 介导 DKD 的代谢反应,促进炎症。不同的阻断补体的策略,如 SB290157 (C3aR 拮抗剂)、K-76 COONa (C5 和因子 I 抑制剂)和 NOX-D21 (L-RNA/DNA spiegelmer C5a 抑制剂)作为口服活性 C5aR1 抑制剂(PMX53),均显示出对 DKD 小鼠模型的保护效果[44]。未来的研究需要开发新型的补体靶向药物,以期改善 DKD 患者的血液高凝状态,延缓血栓形成,提高生活质量。

2.8. 纤溶系统调节

DKD 患者胰岛素抵抗状态下常伴有纤溶酶原激活物抑制剂-1 (plasminogen activator inhibitor 1, PAI-1)水平升高,导致纤溶系统抑制,可能通过反馈机制刺激纤维蛋白原(fibrinogen, FIB)增加,从而促进血液高凝。Liu 等人发现 GLP-1RA 可以抑制人血管内皮细胞中 PAI-1 的产生,从而改善 T2DM 患者的内皮细胞功能和动脉粥样硬化[45]。同时,高血糖可以作用于两个 Sp1 位点促进 PAI-1 的产生,这表明血糖水平的改善有助于降低 PAI-1 水平[46]。PAI-1 在纤溶途径中发挥重要作用,还参与其他病理生理过程,包括癌症[47]、衰老[48]、心脏纤维化[49]和伤口愈合[50],使 PAI-1 成为一个非常有前景的治疗靶点。尽管大量的动物研究已经取得了较好的结果,但尚未有与 PAI-1 相关的药物获得临床批准。许多研究团队和制药公司正在开发 PAI-1 抑制剂,包括单克隆抗体、小分子物质和多肽[51] [52]。主要分为两类:直接抑制 PAI-1 的产生和干扰其生理作用。目前已开发出多种降低 PAI-1 mRNA 水平的药物(如 T686、T2639),其在动物模型实验中均有药理作用[53] [54],但缺少临床试验数据,其完全抑制及剂量调控仍面临挑战。基于 PAI-1 与纤溶-凝血系统的复杂作用,靶向其功能调控(如阻断活性位点或构象修饰)可能较单纯降低浓度更具临床潜力。例如,在兔颈静脉血栓形成模型中,小鼠单克隆抗人 PAI-1 抗体 CLB-2C8 可切割和灭活 PAI-1,并显著增强内源性血栓溶解和抑制血栓形成,但尚未在人体内进行进一步研究[55]。另一种抗体 MEDI-579 对 PAI-1 具有高亲和力和特异性,可调节其与 t-PA 和 u-PA 之间的相互作用[56]。在小分子药物中,经典的是 PAI-039 和替普沙汀,后续药物多基于提升其疗效。PAI-039 于 2004 年获得专利,并在各种动物模型中显示出有希望的结果[57]。然而,其不抑制与玻连蛋白结合的 PAI-1 [58],因此需要开发能够抵抗玻连蛋白结合的药物。尽管已经研发出多种能够作用于体外连接的 PAI-1 化合物,但尚未实现其完全抑制[59]。目前,针对 DKD 患者的 FIB 临床治疗仍然缺乏相关进展。不过,已有动物实验进行相关研究。Borna Sarker 等人[60]的研究表明,糖尿病视网膜病变小鼠模型显示视网膜小胶质细胞活化及 FIB 沉积,去纤剂恩克罗特治疗可减少上述病理改变及促炎因子水平。靶向 FIB 干预可能为 DKD 血管病变提供新策略,为开发更具选择性和认知的新疗法迈出了重要一步。调节纤溶系统以减轻 DKD 患者的高凝状态前景乐观。

2.9. 表观遗传调控

除了上述 DKD 高凝的机制外,正在进行的研究强调了表观遗传变化在调节与 DKD 高凝状态机制相

关的基因表达中的重要性。这些表观遗传修饰,包括 DNA 甲基化、组蛋白修饰、非编码 RNA 和 microRNA,可能是由于高血糖引起的,或作为 DKD 发展的独立因素。它们被认为是增加疾病进展复杂性的关键调控层面[61]。与这些表观遗传改变相关的一个关键概念是“代谢记忆”,即高血糖的长期不良影响在血糖控制恢复后仍然存在。表观遗传变化以及 AGEs 的积累被认为是代谢记忆的基本驱动因素。这种现象使 DKD 的病程复杂化,并对治疗提出了严峻挑战,因为尽管随后进行了干预,高血糖的持久影响仍然存在[62]。因此,通过表观遗传学靶向治疗来解决代谢记忆问题可能是改善糖尿病患者高凝引起的血栓栓塞的一个有希望的途径,即使在高血糖得到控制之后,也有可能缓解 DKD 的进展。

3. 总结与展望

DKD 的高凝状态机制复杂,涉及代谢异常、血小板活化、凝血-抗凝系统失调、纤溶抑制、补体级联激活及表观遗传调控等因素,常伴随多种并发症,并呈现显著个体化差异,目前尚未建立标准化诊疗方案。临床管理遵循多维度干预原则,在血糖、血压控制及调节脂代谢紊乱基础上,联合抗血小板、抗凝及抗炎治疗,并动态监测出血风险及肾功能变化。基于当前研究,我们建议未来的研究方向应包括多靶点联合治疗策略,借助基因组学、蛋白质组学、代谢组学及人工智能技术,精准解析肾脏局部凝血微环境的异质性,构建个体化诊疗体系,推动精准医学模式在 DKD 高凝状态中的应用,并为开发新型分子靶向治疗提供理论依据。

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