

糖尿病慢性并发症与不良结局关联的研究进展

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摘要

近三十年来, 全球糖尿病患病率呈现显著上升趋势。根据世界卫生组织的数据, 糖尿病患者人数在不断增长, 这不仅对公共健康构成重大挑战, 也对社会经济造成巨大负担。糖尿病患者发病年龄提前, 病程延长, 若长期处于高血糖状态, 容易引发多种并发症。不仅会影响患者的生活质量, 还可能导致严重的健康问题, 甚至危及生命。因此, 在这篇综述中, 我们重点讨论糖尿病慢性并发症与不良结局之间关联的研究的新进展, 并总结如何对糖尿病并发症进行预防和控制。

关键词

糖尿病, 并发症, 不良结局

Research Progress on the Association between Chronic Diabetes Complications and Adverse Outcomes

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Abstract

Over the past three decades, the global prevalence of diabetes has shown a significant upward trend. According to data from the World Health Organization, the number of diabetes patients is constantly

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increasing, which not only poses a major challenge to public health but also imposes a huge burden on the social economy. The onset age of diabetes patients is earlier, and the disease duration is longer. If they remain in a state of high blood sugar for a long time, it is prone to trigger various complications. This not only affects the quality of life of patients but also may lead to serious health problems and even endanger life. Therefore, in this review, we focus on discussing the new progress in research on the association between chronic complications of diabetes and adverse outcomes, and summarize how to prevent and control diabetes complications.

Keywords

Diabetes, Complications, Adverse Outcomes

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1. 引言

糖尿病(Diabetes mellitus, DM)是一种由遗传与环境因素共同作用所导致的代谢性疾病,其核心特征为胰岛素分泌障碍或胰岛素作用受损,进而引发慢性高血糖状态[1]。根据国际糖尿病联盟(IDF)第10版全球糖尿病地图的预测,20至79岁成年人群的糖尿病患病率将持续显著上升,预计患病人数将从2021年的5.37亿增至2045年的7.83亿,将造成巨大的经济、社会和卫生负担[2]。与一般人群相比,糖尿病患者不仅有一系列代谢紊乱问题,而且患癌症和其他非传染性疾病的风险也较高[3]。糖尿病不仅是导致心血管疾病的重要影响因素,也是导致糖尿病患者死亡的首要原因[4]。随着中国社会经济发展和生活方式的逐步改变,国民饮食结构也产生变化,同时体力活动水平普遍下降。这一系列变化导致糖尿病患病率呈现显著且持续的上升趋势。值得注意的是,糖尿病不仅是一种独立的代谢性疾病,更是多种并发症的关键诱因。如急性并发症,包括糖尿病酮症酸中毒、高渗性非酮症糖尿病昏迷、乳酸性酸中毒及低血糖昏迷;慢性并发症,包括糖尿病肾病(Diabetic kidney disease)、糖尿病神经病变、糖尿病视网膜病变、冠心病、心肌梗死、心力衰竭及中风。此外,糖尿病是导致失明、肾衰竭、心脏病发作、中风和下肢截肢等疾病的主要原因。2019年,糖尿病及其引发的肾病导致的死亡人数约为200万[5]。全球12.2%的死亡与糖尿病及其并发症有关,同时其导致的医疗支出已高达9660亿美元,对社会经济与卫生体系构成了持续性压力[6]。因此,要想预防和控制糖尿病并发症,提升患者生存质量,必须要充分认识糖尿病并发症的流行状况、发病机制以及其与不良结局之间的关联。通过对现有文献的综合分析,我们期望为理解糖尿病慢性并发症对人体健康的影响提供更深入的见解,并为未来根据个体风险特征制定有针对性的预防策略提供更为科学的依据。

2. 糖尿病并发症流行状况

在中国,针对糖尿病并发症的大规模流行病学研究尚不充分。首次由中华医学会糖尿病学会对全国30个省市开展为期10年的调查显示,住院的糖尿病患者中,患糖尿病神经病变的人数比例高达60.3%;眼部并发症与肾脏并发症分别占34.3%与33.6%。在大血管并发症方面,心血管病变占15.9%,脑血管病变占12.2%,下肢血管病变占5.0% [7]。另外,在中国大庆进行长达30年的纵向研究发现49%的糖尿病患者死于心血管疾病[8]。

一项纳入南亚和东亚、北非、中东、南美和欧洲的多国研究报告,2型糖尿病(type 2 diabetes mellitus,

T2DM)患者微血管并发症患病率约为 50%，大血管并发症患病率约为 30% [9]。在糖尿病患者中，微血管并发症具有普遍性。研究数据显示，2008 年至 2018 年，美国退伍军人整体下肢截肢发生率上升 [10]。2006 年至 2015 年，韩国成年人中周围动脉疾病的发生率上升 [11]。

糖尿病大血管并发症主要累及心、脑及外周大血管系统，其病理基础为血管壁的炎症反应、斑块形成、钙化、血栓及恶性重塑等系列改变，最终导致管腔狭窄或闭塞，并引发心肌梗死、脑梗死及重症下肢缺血(如下肢坏疽、截肢)等严重临床事件。与非糖尿病人群相比，糖尿病患者的血管病变具有进展迅速、病情严重及病死率高等特征。一项涵盖 454.9 万 2 型糖尿病患者的系统评价进一步显示，大血管并发症的总体患病率为 32.2%，其中冠心病最为常见，占 21.2% [12]。另外，美国糖尿病监测系统(USDSS)的监测数据显示 2020 年因心血管疾病产生的住院率低于 2019 年，但在 2000 年至 2020 年间因心力衰竭、中风住院的人数呈先下降后上升的趋势 [13]。

3. 糖尿病并发症及其发病机制

3.1. 糖尿病微血管并发症

3.1.1. 糖尿病肾病

DKD 是 2 型糖尿病患者中最常见的微血管并发症之一。DKD 以微血管病变为特征，对人体健康构成的威胁极大，最终可能会发展为终末期肾病 [14]。胰岛素抵抗可通过改变肾小球血流动力学及破坏足细胞功能，进而增加 DKD 进展的风险。胰岛素直接作用于足细胞的胰岛素受体，参与细胞内 AKT/mTOR 或 GLUT-4 信号传导 [15]，具体机制包括：1) 胰岛素通过激活 NADPH 氧化酶来促进足细胞内的氧化应激 [16]；2) 通过刺激转化生长因子(Transforming growth factor, TGF) β -1 和胶原 IV 生成，促进肾小管间质纤维化；3) T2DM 患者的肾小管对钠的亲和力增强，导致水重吸收增多、血压升高及肾小球滤过率上升，最终增加白蛋白通透性 [17]。综上所述，糖尿病引起的胰岛素抵抗可导致胰岛素分泌异常、生长因子释放增加及氧化应激水平升高，进而引起肾小球滤过屏障功能失调与肾脏血流动力学改变，最终促进糖尿病相关肾小球疾病及肾损伤的发生发展 [18]。

3.1.2. 糖尿病神经病变

时立新 [19] 和邹大进 [20] 等人总结糖尿病神经病变是由多种因素共同作用的结果，其发病机制复杂，在高血糖状态下，多元醇通路、糖基化终末产物、氧化应激与细胞因子等因素可独立或相互协同作用，直接或间接地参与神经损伤的发生与发展。此外，脂质代谢途径在糖尿病神经病变的发生发展中的机制已受到越来越多的关注，如氧化低密度脂蛋白启动氧化应激和炎症反应，游离脂肪酸的增加参与胰岛素抵抗和 β 细胞功能障碍促进糖尿病神经病变的发生，脂质代谢中鞘脂代谢异常会产生神经毒性因子，从而造成神经损伤等 [21] [22]。

3.1.3. 糖尿病视网膜病变

DR 的发展基于高血糖所引发的一系列相互关联的病理生理机制。这些机制包括遗传和表观遗传因素、自由基产生增加、晚期糖基化终末产物积累、炎症因子和血管内皮生长因子(VEGF) [23]。Li 等人 [24] 的研究进一步强调了血管机制在其中的关键作用。同时，醛糖还原酶作为多元醇通路的初始酶，也可能在糖尿病并发症的发生发展中发挥重要调控作用。该途径涉及将葡萄糖转化为葡萄糖醇(山梨醇)。高葡萄糖水平会增加糖分子通过多元醇途径的通量，从而导致山梨醇在细胞中积累。山梨醇积累产生的渗透应激被认为是糖尿病微血管并发症发展的潜在机制 [25]。

3.1.4. 糖尿病足

糖尿病足(Diabetes foot, DF)是指糖尿病患者因糖尿病所致的下肢远端神经病变和/或不同程度的血管

病变导致的足部溃疡和/或深层组织破坏, 伴或不伴感染[26]。糖尿病足是糖尿病常见且严重影响生活质量的并发症之一。其发病机制尚未完全明确, 目前临床认为主要与长期血糖控制不佳密切相关。长期处于高血糖状态将会导致足部周围神经病变及血管系统血流障碍, 引起神经缺血性损伤。患者常表现为足部肿胀、发凉、疼痛、麻木及反复感染等症状。若未能及时干预, 最终需要进行截肢处理治疗, 甚至会诱发死亡[27]。

3.2. 糖尿病大血管并发症

持续高血糖可通过多种途径作用于血管内皮细胞、平滑肌细胞及巨噬细胞等, 进而促进动脉粥样硬化与血管钙化等大血管病变的发生与发展。王中群[28]总结糖尿病大血管并发症的发病机制包括: 胰岛素抵抗与糖脂代谢紊乱, 糖尿病脂肪组织及 NGAL 影响, 高血糖诱导的生化途径改变, 内皮功能紊乱与炎症、氧化应激, 表观遗传学对糖尿病大血管并发症的影响。

4. 糖尿病并发症与不良结局的关联研究

4.1. 糖尿病并发症的住院率和死亡率

关于糖尿病相关并发症和死亡率国际趋势的数据很少。之前的一篇综述汇总了截至 2015 年发表的有关心血管、肾脏、眼科和急性并发症的数据, 并记录了数据的稀缺性, 描述了在少数可获得已发表数据的国家观察到的趋势[29]。来自韩国的一项研究显示[30], 在 2006 年至 2015 年期间, 主要心血管并发症(缺血性心脏病、缺血性中风和心肌梗死)引起的住院率均有所下降, 而心力衰竭和外周动脉疾病的住院率增加。一项为期 12 年的前瞻性研究中, 大约四分之三的肾病死亡发生在招募前被诊断为糖尿病的人群中[31]。与非糖尿病合并症者相比, 糖尿病患者年龄和性别调整后的死亡率风险比(hazard ratio, HR)为 1.6 (95% CI, 1.5~1.8), 中风患者为 2.1 (95% CI, 1.9~2.4), 心肌梗死患者为 2.1 (95% CI, 1.9~2.3), 糖尿病和心肌梗死患者为 4.3 (95% CI, 3.7~5.0), 糖尿病和中风患者为 3.9 (95% CI, 3.1~4.9)。中风和心肌梗死患者为 3.8 (95% CI, 2.9~4.9), 糖尿病、中风和心肌梗死患者为 6.0 (95% CI, 4.2~8.7) [32]。

4.2. 糖尿病并发症与认知功能、痴呆的关系

认知障碍和痴呆症影响着全世界数千万人, 给患者和护理人员带来巨大的痛苦, 给家庭和医疗保健系统带来经济负担。有研究表明痴呆患者总数几乎每 20 年翻一番, 到 2030 年达到 6570 万, 到 2050 年达到 1.154 亿[33]。因痴呆造成的成本也持续增加, 2023 国际阿尔茨海默病组织估计, 2030 年痴呆症相关的诊治费用也将增加一倍以上, 从 2019 年的每年 1.3 万亿美元增加到 2.8 万亿美元, 大大高于之前的估计[34][35]。老年人患认知障碍的风险更高, 在 ≥ 65 岁的成年人中约占 11% [36]。在糖尿病中, 认知障碍主要与高血糖和糖尿病相关的血管并发症有关, 包括心血管疾病和中风[37]-[40]。严重和反复的低血糖事件也与 T2DM 患者的初始认知障碍和加速下降有关[41]; 然而, 在 1 型糖尿病(Type 1 diabetes mellitus, T1DM)患者中未发现影响[42]。一项荟萃分析显示[43], DR 与糖尿病患者的认知障碍相关(HR: 1.34; 95% CI: 1.10~1.62), 并且 DR 的严重程度越高, 认知障碍的风险就越高。Chan 等人[44]还发现, DR 与痴呆之间也存在一定的关联。另外, Duan 等人[45]通过双向孟德尔随机化研究发现, 任何中风及其亚型都会导致认知障碍的风险升高。综上所述, 这些研究结果表明, 糖尿病并发症与认知障碍和痴呆的风险存在关联, 糖尿病并发症可能为认知障碍和(或)痴呆的危险因素。

5. 糖尿病并发症的预防与治疗

糖尿病管理的主要目标是预防并发症, 糖尿病是并发症和死亡率的主要原因。从历史上看, 降低风

险的主要重点是降低血糖水平，直到 UKPDS 试验跟踪了新诊断的 T2DM 参与者，显示单独强化血糖控制对减少心血管并发症的结果并不理想。之后，治疗高血压和血脂异常的益处也在试验中得到证明，以及心血管和肾脏保护的特异性药物的出现，降低糖尿病风险的方法得到了广泛发展。现如今，减少糖尿病并发症的最有效策略是多因素方法，即血糖控制、心血管危险因素、心肾保护、体重管理四因素。

5.1. 生活方式干预

糖尿病患者普遍建议改变以均衡营养、体育锻炼和戒烟为重点的生活方式。Look AHEAD 试验检查了强化生活方式干预(包括饮食热量限制和增加身体活动)对 T2DM 患者心血管死亡率、非致命性心肌梗死、非致命性中风和心绞痛住院治疗的影响。尽管与标准护理相比，干预在体重、腰围、HbA1c、血压和大多数血脂方面产生了更大的改善，但在近 10 年的随访中，这些变化并未转化为心血管结局的显著减少，并且该试验根据无效分析提前终止[46]。另外，Steno-2 研究表明，除了控制血糖和血压外，对 T2DM 和白蛋白尿患者进行生活方式干预，导致心血管死亡、心肌梗死、中风、血运重建和下肢截肢的复合结局减少了 53% [47]。

目前的美国糖尿病协会(ADA)指南建议将饮食调整、身体活动和行为策略相结合，以实现和保持大多数 T2DM 超重或肥胖患者的体重至少减轻 5%，但减肥干预措施必须因人而异[48]。对于大多数患有 T2DM 的成年人，建议每周至少进行 150 分钟的中等强度有氧运动，每周至少 3 天[49]。

5.2. 血糖、血压、血脂的综合控制

强化血糖控制曾被认为是预防大血管并发症的基石，但近几十年来的数据相互矛盾。对 DCCT 和 UKPDS 试验的初步分析评估了强化治疗对 T1DM 患者的影响，结果表明微血管并发症有显著改善，但对大血管疾病仅无显著益处[50][51]。随后的 ADVANCE 试验和 VADT 同样发现，强化降糖治疗没有显著降低心血管风险[52][53]。而 ACCORD 试验发现强化血糖控制使全因死亡率增加了 22%，这主要是由心血管死亡率驱动的，导致试验提前终止[54]。

Zoungas 等人[55]在一项荟萃分析中证明，强化血糖控制可将复合肾脏结局的风险降低 20%，复合视网膜结局的风险降低 13%，但神经性事件的风险没有降低。一项针对心血管结局的 14 项随机临床试验的荟萃分析对 T2DM 患者的强化血糖控制与常规治疗进行了比较，结果表明，非致命性心肌梗死的相对风险降低 15%，对全因或心血管死亡风险没有显著影响，而严重低血糖的相对风险增加了 30% [56]。

抗高血压治疗对 T2DM 和高血压患者的心血管益处已得到充分证实[57][58]。在 UKPDS 队列中，通过使用卡托普利或阿替洛尔进行降压治疗，血压每降低 10 mmHg (达到<130 mmHg 的目标)，微血管终点的风险降低 10% [59]。

降脂疗法是降低心血管风险的另一个基石。一项荟萃分析显示，对 T2DM 患者使用他汀类药物后，全因死亡率降低了 9%，心血管死亡率、心肌梗死、冠状动脉血运重建和中风的发生率也显著降低[60]。

5.3. 心肾保护的药物治疗策略革新与循证证据

5.3.1. 钠 - 葡萄糖协同转运蛋白 2 抑制剂

钠 - 葡萄糖协同转运蛋白 2 (Sodium-glucose cotransporter-2, SGLT-2)抑制剂是通过抑制近端小管中 Na⁺葡萄糖偶联运输来降低血浆葡萄糖浓度的药物[61]。SGLT2 抑制剂能够保护患有或未患有 T2DM 患者的肾脏和心脏，同时也能防止肾功能正常或受损的患者出现肾衰竭的情况[62]。SGLT-2 抑制剂与心力衰竭住院率的显著降低以及心血管疾病死亡和因心力衰竭住院的风险降低之间存在关联。Wiviott 研究发现，达格列净能使心血管死亡率或心力衰竭住院率降低[63]。在 Perkovic 等人的试验中[64]，卡格列净不

仅能降低心血管死亡、心肌梗死或中风的风险(HR, 0.80, 95% CI, 0.67~0.95), 还能降低终末期肾病的风险(HR, 0.68, 95% CI, 0.54~0.86)。此外, 因心力衰竭住院的风险也显著降低(HR, 0.61, 95% CI, 0.47~0.80)。多项研究显示, 恩格列净与因心力衰竭后住院和死亡率的风险降低相关[65][66]。值得注意的是, 临床应用 SGLT-2 抑制剂治疗 T2DM 患者时应遵循个体化原则。对于心血管事件风险显著增高的患者, 可优先考虑卡格列净; 恩格列净在现有证据中显示出良好的总体安全性特征; 而达格列净在具有反复尿路感染病史或高风险因素的患者中需谨慎使用[67]。

5.3.2. 胰高血糖素样肽-1 受体激动剂

胰高血糖素样肽-1 (Glucagon-like peptide-1, GLP-1)受体激动剂具有外周和中枢双重作用, 包括促进胰岛素分泌和抑制胰高血糖素分泌和胃排空, 以及抑制食物摄入。除了降低血糖和体重, GLP-1 受体激动剂还能降低 T2DM 患者慢性肾病、心肌梗死、中风和心血管死亡的发生率[68]-[70]。虽然 GLP-1 受体激动剂已被广泛确立用于治疗 T2DM 和肥胖, 但对于减少炎症或阿尔茨海默病等神经退行性疾病等疾病的剂量-反应关系仍不明确[71]。

5.3.3. 非甾体盐皮质激素受体拮抗剂

盐皮质激素受体拮抗剂(Mineralocorticoid receptor antagonists, MRA)是一类通过阻断盐皮质激素受体发挥作用的药物, 主要用于治疗高血压、心力衰竭、肾脏疾病等。目前可用的甾体 MRA 在降低发病率和死亡率方面有较好效果。由于高钾血症和激素副作用的风险, 一类新的非甾体 MRA 被开发出来, 其益处风险关系有所改善。与甾体 MRA 类似, 它们在肾脏、心血管中都具有抗炎、抗重塑和抗纤维化的作用[72]。在 FIDELIO-DKD 和 FIGARO-DKD 中, 非奈利酮显著降低了肾病进展, 心血管死亡、非致死性心肌梗死、非致死性卒中或心衰住院的复合风险[73]-[75]。

此外, 早期发现并发症也可以提前对并发症进行预防。应对可能出现的并发症进行筛查, 并迅速进行治疗和/或管理。患者应每年对视网膜病变、畸形史、神经病变、缺血进行检查, 应用 10 g 单丝或 128 Hz 音叉检查四肢感染情况, 用血管检查评估神经病变, 以及每年检测尿白蛋白血清肌酐, 以评估糖尿病肾病。患者应筛查大血管并发症全面的病史, 包括心绞痛和跛行症状的评估[76][77]。

6. 总结与展望

综上所述, 随着研究的深入, 糖尿病慢性并发症与多种不良结局之间的关联性日益显著, 包括但不限于心血管疾病、心脏代谢疾病、肾脏疾病、癌症、神经退行性疾病等。这些发现不仅揭示了糖尿病并发症对人体健康的不良影响, 还为疾病的早期诊断、风险评估和治疗策略提供了新的视角。未来的研究应进一步探索不同糖尿病并发症及其联合效应与多种不良结局之间的联系, 以期为临床实践提供更有有效的工具和策略。

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