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糖尿病合并血液透析患者血糖管理的最新进展

苏俊杰[1*]，周厚地[2#]

[1]重庆医科大学第四临床学院，重庆
[2]重庆医科大学附属大学城医院内分泌科，重庆

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摘　要

目前，糖尿病合并血液透析患者的血糖管理主要参考普通糖尿病患者的指南，国内尚无专门针对糖尿病合并血液透析患者血糖管理的指南或专家共识，大多数临床医师以自身经验进行相关患者的血糖管理。本文就糖尿病合并血液透析患者血糖管理的特殊性、血糖监测手段、降糖药物选择、个体化治疗等方面进行了总结，并着重介绍了最新的血糖监测手段及降糖药物，以期提供更多优化当前糖尿病合并血液透析患者血糖管理的思路。

关键词

糖尿病，血液透析，血糖管理

Recent Advances in Blood Glucose Management for Diabetic Patients Undergoing Hemodialysis

Junjie Su[1*], Houdi Zhou[2#]

[1]The Fourth Clinical College, Chongqing Medical University, Chongqing
[2]Department of Endocrinology, University-Town Hospital of Chongqing Medical University, Chongqing

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Abstract

At present, the glycemic management of hemodialysis patients with diabetes mellitus mainly refers to the guidelines for general diabetes mellitus patients, and there is no guideline or expert consen-

*第一作者。
#通讯作者。

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sus in China specifically for glycemic management of hemodialysis patients with diabetes mellitus, and most clinicians carry out the glycemic management of the relevant patients with their own experience. This article summarizes the special features of glycemic management in hemodialysis patients with diabetes mellitus, means of glycemic monitoring, selection of hypoglycemic drugs, and individualized treatment. It highlights the newest means of glycemic monitoring and hypoglycemic drugs, in order to provide more ideas to optimize the current glycemic management in hemodialysis patients with diabetes mellitus.

Keywords

Diabetes, Hemodialysis, Glycemic Control

1. 简介

据估计，全世界约有 5 亿人患有 2 型糖尿病，预计到 2050 年将增加到 13 亿[1]。糖尿病(Diabetes Mellitus, DM)和慢性肾脏病(Chronic Kidney Disease, CKD)是两个非常常见且联系紧密的慢性疾病。糖尿病是全球终末期肾病(End Stage Renal Disease, ESRD)的主要原因，约占透析患者的 45% [2]。对于终末期肾病患者，血糖管理不仅仅是控制糖尿病本身的基本要求，更是影响其生存质量和预后的关键因素。

当 CKD 患者进展到终末期时，血液透析(以下简称透析)成为最常用的治疗方法。本文旨在探究糖尿病合并透析患者血糖管理的最新进展和挑战。在详细整理当前的糖尿病合并透析患者血糖管理策略、相关技术的更新以及药物治疗的最新进展的基础上为临床血糖管理提供切实的意见。此外，本文也将分析现今这一群体在血糖控制中遇到的困难，并探讨未来可能的研究方向。

2. 糖尿病合并透析患者血糖管理面临的挑战

糖尿病合并肾病的患者在进入透析阶段后，他们的血糖管理面临许多特殊情况和挑战。透析治疗虽然有助于去除体内积累的毒素、代谢废物和多余的水分，但也会显著影响血糖稳定、增加低血糖风险；同时，因为残余肾功能(Residual Renal Function, RRF)的逐渐降低，CKD 患者的尿液将逐渐减少，从而进一步加重体内代谢及内环境失衡，增加血糖管理难度。而良好的血糖控制可降低 CKD 相关死亡的风险[3]。

2.1. 低血糖

近年来，透析中的低血糖被越来越多提及。对于透析患者来说，伴有低血糖的情况下住院率与死亡风险明显升高[4]。糖尿病合并透析患者因多个原因容易发生低血糖：1) 糖异生减少；2) 肾脏对胰岛素的清除功能受损；3) 红细胞对葡萄糖的摄取增加；4) 透析液对葡萄糖的滤过；5) 进食减少、营养不良；6) 降糖药物的影响；7) 自主神经病变导致对低血糖的自我反应性降低；8) 医务人员操作不当[5]-[7]。低血糖风险评估应该是对患者透析与非透析日血糖分析、用药情况、饮食习惯等情况的综合考虑。其中比较重要的是患者低血糖时间–事件分布情况、患者对于低血糖的感知与识别能力、降糖药物的选择等。一般认为，当肾小球滤过率(Glomerular Filtration Rate, GFR)低于 50 mL/(min × 1.73 m^2)时，总胰岛素需求量减少 25%，当 GFR 低于 10 mL/(min × 1.73 m^2)时，胰岛素总需求量进一步降低 50% [7]-[10]，故对于透析病人，一般建议透析前一次短效胰岛素减量甚至是减停，以降低低血糖风险。使用口服降糖药物的患者，

也应避免使用大部分由肾脏清除的药物(如格列本脲)，而由肝脏代谢和/或部分由肾脏排泄的药物(如二甲双胍)则可能需要减少剂量或停药[11]。其次，患者在透析前必须保证足量的进食，以减小透析过程中的低血糖风险。对于低血糖症状不明显的患者，需要予以更加频繁的血糖监测。在已经发生低血糖时，需立即予以处理，可选择经口或静脉补充葡萄糖来纠正低血糖。

2.2. 血糖波动

为了降低保存成本、减少病原体污染等原因，我国最常用的透析液为无糖透析液[12]。因此，透析对患者来说就像是一次降糖治疗，整个过程将从患者体内移除 15~30 g 葡萄糖，这种损失可导致临床上有症状或无症状的低血糖[5]，透析结束后，又往往出现反弹性高血糖[3]。此外，他们非透析日和透析日的血糖数据变化很大，尽管能量摄入相似，但透析日的平均血浆葡萄糖值明显低于非透析日[13] [14]。一个小样本的临床试验通过持续葡萄糖监测(Continuous Glucose Monitors, CGM)发现，血液透析前一天的平均葡萄糖为 128 (±20) mg/dL，血液透析当天为 93 (±8) mg/dL，后一天为 105 (±13) mg/dL [15]。此外，血糖的波动与糖尿病患者的心血管事件、微血管病变、中枢神经的改变、全因死亡风险升高相关[16]-[20]。所以，透析期间的血糖监测需更为频繁，以确保血糖水平保持在安全和理想的范围内。

糖尿病合并透析患者的血糖管理需要综合考虑多种因素，频繁的低血糖事件及剧烈的血糖波动都是预后不良的危险因素。对于此类患者，医护人员应综合考虑多种因素，更多地利用已有的循证医学证据来优化血糖管理策略。

3. 最新的相关血糖管理指南和建议

对于糖尿病合并透析患者来说，国际上尚无明确的血糖管理指南与共识。因为透析带来的代谢复杂性、各类合并症、降糖药物的药代动力学变化等情况，传统血糖监测指标似乎已经不能满足糖尿病合并透析患者的血糖监测需求，比如糖化血红蛋白(Hemoglobin A1C, HbA1c)。在长期接受血液透析的糖尿病患者中，约 1/3 的患者会出现 HbA1c 的下降或者改善[21]，这是由于存在红细胞寿命缩短、贫血、使用促红细胞生成素、血液透析期间红细胞溶解、频繁输血等情况[9] [22]；而血液高尿素、代谢性酸中毒等情况又会导致 HbA1c 的假性升高[23] [24]，但肾脏病预后质量倡议(K/DOQI)工作组仍建议使用 HbA1c 作为此类患者长期血糖控制程度的主要指标[22]，在一项针对日本人群的大型队列研究中，糖尿病合并透析患者的死亡率与 HbA1c 水平呈“U”形关系，HbA1c 水平为 6.0%至 7.0%的日本糖尿病合并透析患者的死亡风险最低，虽然这个范围在不同的国家地区中似乎存在差异[25]，但过高或过低的 HbA1c 水平始终与较高的死亡率相关[26]-[28]。虽然 HbA1c 仍有较强的指导意义，但是对于糖尿病合并透析患者，由于或多或少存在 HbA1c 的偏倚，现并未就其控制目标达成共识。最新的 KDIGO 指南中还提出了当患者低血糖风险较高时，使用 CGM 或自我血糖监测(Self-Monitoring of Blood Glucose, SMBG)可能有助于预防低血糖[22]。对于糖尿病合并透析患者，降糖药物推荐选用低血糖风险较低的药物。对于使用胰岛素治疗的患者来说，应建议减少胰岛素剂量以避免低血糖[7]。

4. 血糖监测技术的进展

传统的糖尿病瞬时血糖监测手段如指血糖、静脉血糖，长期血糖监测手段如 HbA1c、糖化白蛋白(Glycated Albumin, GA)、果糖胺等指标仍然被推荐使用于糖尿病合并透析患者。由于在接受透析治疗的患者中，HbA1c 测量的可靠性较低[22]，同时随着技术的进步，CGM 越来越多被应用于临床，在此基础上，利用 CGM 时推荐使用葡萄糖目标范围内时间(Time in Range, TIR)、葡萄糖高于目标范围时间(Time above Range, TAR)、葡萄糖低于目标范围时间(Time below Range)、葡萄糖变异性(GV)、葡萄糖管理指数(GMI，既往又被称作“eA1c”)等指标来衡量患者血糖控制情况[29]。

透析患者由于肾功能衰竭及透析过程本身的复杂性，使得他们的血糖控制更为困难[5]。而 CGM 设备的出现给透析患者的血糖监测带来了便利。相对于传统的血糖监测手段，CGM 并不需要患者反复忍受扎破手指的痛苦。CGM 设备都是微创的，通过将一根小细丝插入皮下组织以测量组织间液中的葡萄糖[30]。相比 HbA1c 可以代表患者一段时间内血糖整体控制情况，CGM 对于血糖的监测是实时的，可以根据需要对不同的时间段进行分析。当前 CGM 设备报告的平均偏差百分比范围为 8.1%至 12.3%，与血糖监测(Blood Glucose Monitor, BGM)设备的 5%~10%范围重叠，所以，CGM 现在可以独立于 BGM 设备单独使用[29] [31] [32]。GMI 有望成为 CKD 晚期患者 HbA1c 指标的替代指标[33]。使用时间范围也同样重要，有效和安全的血糖控制的主要目标是在降低 TBR 的同时增加 TIR [34]。而 GV 是糖尿病并发症的独立危险因素[19] [35]，GV 控制不佳似乎与严重低血糖发作的增加有关，从而导致不良心血管结局和全因死亡率的增加[36] [37]。

但是，CGM 在透析患者中的应用也面临一些挑战，首先是设备的准确性和可靠性问题。透析患者体内的代谢平衡常常发生不可预知的变化，可能会影响 CGM 设备的准确度。其次，其高昂的费用也是普及过程中需要解决的问题。

5. 药物治疗的最新进展

在透析患者中，肾功能的严重损害限制了许多降糖药物的使用，例如经典药物二甲双胍，使胰岛素成为大多数接受透析患者的主要降糖方案。一项基于 2012~2017 年美国肾脏数据系统的报道提示，糖尿病合并透析患者中胰岛素是最常用的降糖药，其次是磺酰脲类药物(SU)、DPP-4is 和噻唑烷二酮类药物[10]。

5.1. 传统降糖药物

5.1.1. 胰岛素

现在市面上使用的胰岛素类药物主要有人胰岛素制剂与胰岛素类似物，然而，由于前述原因，胰岛素诱导的低血糖很常见，故需要对患者的胰岛素剂量进行调整，但国际上对于具体的胰岛素调整方案并无统一指南或共识，不同的研究表明减量 50%、75%似乎都是不错的选择[24] [38]。对于基础胰岛素，最常见的建议是将其透析日的剂量减少 25% [39]。对于糖尿病合并透析患者来说，与人胰岛素相比，使用胰岛素类似物似乎是更好的选择，这些胰岛素制剂具有更稳定的作用时间曲线和更低的低血糖风险，使得它们更适合肾功能受损患者的使用。Thomas Ebert 等人的一项前瞻性观察性队列研究提示，胰岛素类似物与更低的全因死亡率、心血管不良事件(MACE)和住院治疗相关[40]。

5.1.2. 口服降糖药

磺酰脲类药物的作用为促进胰岛素分泌，主要不良反应为低血糖。研究表明，第二代磺酰脲类药物(如格列齐特)不仅可以安全地用于透析患者，也可能对于透析患者产生有益影响[41]-[43]。噻唑烷二酮类药物是一种胰岛素增敏剂(如吡格列酮)，它已被证明可以降低尿毒症相关的胰岛素抵抗[43] [44]，而且其低血糖风险较磺酰脲类药物低[45] [46]，所以对于胰岛素抵抗的糖尿病合并透析患者不失为一种优先的选择。但是在使用的时候要注意体重增加、水肿等不良反应[45] [46]。此外，吡格列酮可以改善接受透析治疗的非糖尿病患者的循环脂联素和 CRP 水平[47]，而脂联素和 CRP 的类似改变也可以见于肥胖、糖尿病或胰岛素抵抗的终末期肾功能衰竭患者[48]。

5.2. 新型降糖药物

5.2.1. 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 抑制剂(Sodium-Glucose Transport Protein 2 Inhibitors, SGLT-2is)作为最近

的“明星药物”，它可以促进葡萄糖通过尿液排出体外而降低血糖，已在非透析糖尿病患者中显示出良好的疗效。SGLT-2is 在透析患者中的临床经验有限，由于此类患者含有 SGLT-2 转运蛋白的肾小管数量减少，因此需要通过 SGLT-2 转运蛋白起作用的 SGLT-2is 的效果可能较差[49]。但 Fu-Shun Yen 等发现在 2 型糖尿病的 CKD5 期患者中，与不使用 SGLT-2is 相比，使用 SGLT-2is 与较低的透析、心血管事件、DKA 和 AKI 风险相关[50]。其对心血管和终末期肾脏血流动力学、纤维化和炎症具有有益作用[51]，这为糖尿病合并透析患者的治疗提供了应用可能。

5.2.2. 胰高血糖素样肽-1 受体激动剂

胰高血糖素样肽-1 受体激动剂(Glucagon-Like Peptide-1 Receptor Agonists, GLP-1 RAs)也是目前研究比较热门的药物。这类药物通过肠道激素的作用来实现血糖依赖的降糖作用[52]，由此可减少糖尿病合并透析患者因胰岛素而产生的低血糖风险。大部分 GLP-1RAs (如司美格鲁肽、度拉糖肽、利拉鲁肽)均可在 ESRD 患者中使用，而无需调整剂量[22] [53] [54]。Karly C Sourris 等人发现 GLP-1 RAs 在糖尿病肾病中的一种新的葡萄糖非依赖性肾保护作用，其中包括抑制关键肾细胞群中的非可控性炎症(Non-Resolving Nnflammation) [55]。与此同时，由于 GLP-1 RAs 抑制食欲、抑制胃排空等作用，伴有肥胖的糖尿病合并透析患者可能拥有更多获益。迄今为止积累的证据表明，GLP-1RAs 可以发挥适度的肾脏益处，KDIGO 指南推荐 GLP-1RAs 在糖尿病慢性肾脏病患者中作为二线药物[56] [57]。因为心血管疾病是终末期肾病患者死亡的主要原因[58]，而 GLP-1 RAs 不仅可以有效改善糖尿病合并透析患者的血糖，还具有促进心血管健康的额外益处[59] [60]，所以其在糖尿病合并透析患者中的心血管获益有待在更大规模的临床研究中进一步加以验证。

5.2.3. GLP-1/GIP 双受体激动剂

与 GLP-1 RAs 相对应，GLP-1/GIP 双受体激动剂替尔泊肽(Tirzepatide)具有与之类似但某些方面更为突出的临床效应[61]。葡萄糖依赖性促胰岛素多肽(Glucose-Dependent Insulinotropic Polypeptide, GIP)可通过改善胰岛素敏感性、脂质稳态和全身能量代谢来提高治疗效果[62]。暂无研究证明替尔泊肽对于肾脏功能有直接损害作用，对于肾功能损害(包括 ESRD)的患者无需调整使用剂量[63]。替尔泊肽虽然对于糖尿病合并透析患者具有潜在的肾脏及心血管获益潜力，但其作为一种新型降糖药物，在糖尿病合并透析患者中使用及研究资料暂不足，需要继续在临床治疗与研究中收集相关的循证医学证据[64]。

5.2.4. 新型葡萄糖激酶激活剂

葡萄糖激酶(Glucokinase, GK)是己糖激酶家族中的重要一员，是葡萄糖代谢的第一个关键酶，在人体血糖稳态调控中发挥核心作用[65]，可以促进葡萄糖刺激的胰岛素分泌，并促进肝脏的葡萄糖摄取、糖原合成及储存[66]。多格列艾汀(Dorzagliatin)是我国研发的一种双重作用、口服生物可利用的新型葡萄糖激酶激活剂(Glucokinase Activator, GKA)，以葡萄糖依赖性方式增强葡萄糖激酶活性，改善葡萄糖刺激的胰岛素分泌[67]。多格列艾汀表现出了持续的降糖效果、较低的低血糖发生率，Jia Miao 等对非透析 ESRD 患者进行了多格列艾汀药效动力学相关研究，结果提示在 ESRD 患者中无需调整剂量[68]。此外，多格列艾汀也能通过改善 2 型糖尿病患者葡萄糖刺激的 GLP-1 释放来调节葡萄糖稳态[69]，从而发挥出 GLP-1 相关血糖及心脏益处。但与替尔泊肽相同，当前多格列艾汀于 ESRD 患者的研究并不充分，需获取更多证据以证实其临床安全性及其他获益。

糖尿病透析患者的降糖药物选择需在控制血糖的同时兼顾心肾保护、低血糖风险及药物代谢特点，综合最新研究进展，胰岛素类似物(如甘精胰岛素、德谷胰岛素)因稳定的药代动力学和较低的低血糖风险成为优选，透析日基础胰岛素剂量通常需减少 25%；口服降糖药中，第二代磺酰脲类(如格列齐特)及噻唑烷二酮类(如吡格列酮)可用于特定患者，但需警惕低血糖、水肿及心衰风险；新型药物中，SGLT-2 抑制

剂(如达格列净)虽在透析患者中降糖效果受限，但可能通过改善血流动力学和抗炎机制降低心血管事件及终末期肾病风险，GLP-1 受体激动剂(如司美格鲁肽)因血糖依赖性降糖机制和明确的心肾保护作用被推荐为二线药物，而 GLP-1/GIP 双受体激动剂(如替尔泊肽)及新型葡萄糖激酶激活剂(如多格列艾汀)虽具有潜在优势，仍需更多循证支持。总体需结合患者残余肾功能、心血管风险及个体化血糖目标调整方案，优先选择兼具代谢调节与器官保护作用的药物，并加强透析日血糖监测以平衡疗效与安全性。此外，其余新兴的药物研究也在探索更多靶向特定代谢途径的治疗方案，例如针对线粒体功能或炎症途径的药物[70] [71]、过氧化物酶体增殖物激活受体(PPAR)全激动剂(如西格列他钠)。这些治疗可能在未来为糖尿病合并透析患者提供更为个性化和精准的治疗选择。

6. 个性化管理

现今，接受透析治疗的肾衰竭患者的糖尿病管理对我们来说仍具有挑战性[72]。糖尿病合并透析患者的个体情况各不相同，对于透析患者，药物代谢和清除率常因肾功能减退而改变，这要求对常规治疗糖尿病药物的使用进行仔细调整。个性化药物治疗应基于患者的残余肾功能、透析效率以及患者并发症等情况。与此同时，医生应该根据患者的体重、活动水平和营养状况调整饮食，透析日和非透析日的饮食可能需要不同，尤其是在碳水化合物的摄入上进行调整，并反复、积极地进行宣教，以避免透析过程中出现剧烈血糖波动。与此同时，也需考虑到食物的磷、钾和蛋白质含量，以维持内环境的稳定及正常脏器功能。适量地增加植物性膳食可能与更低的炎症生物标志物、更轻的尿毒症症状、心肌肥大和动脉粥样硬化以及更低的心血管事件和死亡风险有关[73] [74]。透析患者的血糖监测频率可能需要比常规糖尿病患者更频繁，尤其是在透析日。CGM 可以为患者提供更详细的血糖波动数据[75]，除开昂贵的价格，将会是一个不错的血糖监测手段。此外，糖尿病合并透析患者的心理健康也尤为重要，透析本身就是一个主观和客观上的负担，这可能影响患者是否遵医嘱治疗。透析疗程长、频繁、耗费人力与财力，常常让患者感到疲惫和压力，一项前瞻性研究表明，述情障碍是血液透析患者全因死亡的强独立危险因素[76]，这些情绪与心理因素都可能直接或间接影响患者的血糖控制[77]。所以，糖尿病合并透析患者血糖的个性化管理涵盖了药物、饮食、血糖监测、心理健康等多个方面，需要患者与医生之间的积极配合与共同努力。

7. 总结

糖尿病合并血液透析患者的血糖管理是一项复杂的临床挑战，需要综合考虑代谢紊乱、药代动力学变化和透析治疗的效果。在这些患者中，肾功能衰竭会导致胰岛素清除率降低、糖异生能力降低和透析过程中葡萄糖损失，从而显著增加低血糖风险。透析后反弹性高血糖进一步加剧了血糖波动，从而增加了心血管事件的风险和死亡率。对于葡萄糖监测，由于红细胞寿命缩短和贫血等原因，传统的 HbA1c 测量变得不那么可靠，因此需要整合糖化白蛋白、果糖胺等其他生化指标和连续葡萄糖监测技术等新型生物标志物。葡萄糖范围内时间和血糖变异性等动态指标对于优化管理的重要性进一步提高。对于此类患者，药物治疗必须平衡疗效和安全性：胰岛素仍然是主要治疗方法，在透析日减少 25%~50%的剂量以预防低血糖，而胰岛素类似物因其药代动力学稳定性和较低的风险成为更优的选择。尽管 SGLT-2 抑制剂在透析患者中的降糖效果有限，但它们的心肾保护作用使其成为潜在的治疗选择。GLP-1 受体激动剂利用葡萄糖依赖性降血糖机制和经过验证的器官保护，被推荐作为二线治疗方案。个体化治疗策略应纳入多维因素，包括根据年龄、合并症和预期寿命设定 HbA1c 目标，以及在透析日调整碳水化合物摄入量以稳定血糖水平。此外，心理干预和营养管理，如控制磷和钾的摄入量，同时增加植物性蛋白质，在改善预后方面发挥着关键作用。

综上所述，糖尿病合并透析患者的血糖管理仍旧是一个任重而道远的命题。它涉及多个学科、多种系统，有着新兴的技术与药物手段，同时也面临着更高效、更精细化的管理要求。除此之外，人工智能的出现(AI)或将进一步改变糖尿病合并透析患者的血糖管理格局。随着医学研究的深入和医疗技术的进步，糖尿病合并透析患者的血糖管理正在逐步优化，以更好地满足这一特殊群体的需求。

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