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维持性血液透析患者尿酸水平与死亡风险的研究进展

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摘　要

目的：了解维持性血液透析患者尿酸水平与死亡风险的关系。方法：分别以“尿酸”、“全因死亡”、“心血管死亡”为检索词检索Pubmed、中国知网(CNKI)数据库，获取并阅读相关文献，从炎症、营养、心血管死亡风险等方面进行综述。结果：在维持性血液透析患者中，基线血尿酸水平的降低与全因和心血管死亡的风险增加密切相关。结论：合理地管理尿酸水平在降低维持性血液透析患者死亡风险方面具有重要的临床意义。

关键词

尿酸，全因死亡，心血管死亡

Research Progress on Uric Acid Level and Risk of Death in Maintenance Hemodialysis Patients

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Abstract

Objective: To investigate the relationship between uric acid level and risk of death in maintenance

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hemodialysis patients. Methods: "Uric acid", "all-cause death" and "cardiovascular death" were used to search Pubmed and CNKI database. The related literatures were obtained and reviewed from the aspects of inflammation, nutrition and cardiovascular death risk. Results: In maintenance hemodialysis patients, the decrease of baseline serum uric acid levels was closely related to the increased risk of all-cause and cardiovascular death. Conclusion: Reasonable management of uric acid level has important clinical significance in reducing the risk of death in maintenance hemodialysis patients.

Keywords

Uric Acid, All-Cause Death, Cardiovascular Death

1. 前言

维持性血液透析(Maintenance hemodialysis, MHD)患者逐年增多，到 2017 年底，终末期肾脏病患者达 290 万人，其中 MHD 患者达 52 万人较 2011 年增长 2.23 倍，近几年平均增长率为 14.2% [1]。然而，对于尿酸(Uric acid, UA)高或低水平是否与慢性肾脏病(Chronic kidney disease, CKD)进展或死亡的风险有关，存在争议。因此，本文将针对 MHD 患者 UA 水平与死亡风险的关系进行综述。

2. UA 在人体中的主要功能

UA 根据生理环境具有不同的功能特性[2]。一方面，UA 是一种有效的自由基清除剂和抗氧化剂，可以降低人体内的氧化应激[3] [4] [5]。在这种情况下，UA 的特点是防止内皮酶的氧化失活，并在氧化应激期间保护内皮细胞介导血管扩张的能力[3] [4]。另一方面，特别是当血 UA 超过血液中的正常水平时，UA 可能会成为一种促氧化剂[2] [6]，实验和临床研究表明，细胞内 UA 具有促氧化作用：在内皮细胞内，UA 降低一氧化氮的生物利用度；在血管平滑肌细胞中，UA 促进细胞增殖；在脂肪细胞中，UA 刺激 NADPH 氧化酶依赖的活性氧的产生，并促进胰岛素抵抗[7]。

3. 血清 UA 与 ATP 结合盒转运蛋白亚家族 G 成员 2 (ABCG2)

ABCG2 主要表达于近曲小管的官腔膜侧，ABCG2 形成同型二聚体后即具备转运 UA 的活性，ABCG2 的功能异常变体是肾脏和肠道中的 UA 排出转运蛋白，其表达或功能障碍会导致 UA 排出减少，ABCG2 功能障碍可能会通过 UA 和尿毒症毒素的积累以及炎症的加速和自噬的抑制而影响临床结果[8]。而 ABCG2 是尿毒症毒素吲哚酚硫酸盐(IS)的主要转运蛋白[9]，吲哚硫酸盐通过减少一氧化氮的产生和增加氧化应激而导致内皮功能障碍[10] [11]。高浓度的 UA (0.5 mmol/L 相当于 8.4 mg/dL)可以减轻内皮功能障碍，抑制吲哚酚硫酸盐诱导的氧化应激和 UA 保护一氧化氮的产生[12]。通过基因变异估计的 ABCG2 功能障碍与血清 UA 水平呈显著正相关($r = 0.508$, $P < 0.05$) [8]。尿毒症患者高水平的 UA 可能是一种代偿机制，可以抵消吲哚酚硫酸盐等尿毒症毒素的氧化损伤和血管毒性[12]，从而减少因氧化应激所致的心血管死亡事件，降低病死率。

4. 血清 UA 与营养

研究发现 30%~50%的血液透析患者有不同程度的营养不良，患者的营养状态与住院事件和死亡事件

高度相关[13]。长时间随访发现 UA 的动态变化与营养状态变化一致，血 UA 水平的增加伴随着营养状况的改善，可降低患者死亡率[14]。低 UA 水平往往与蛋白能量消耗、糖尿病、高龄等伴随存在[13]。糖尿病本身就是代谢消耗性疾病，其并发症多，导致蛋白质代谢紊乱，加重蛋白质、热量及嘌呤或核苷酸等必须营养物质摄入相对不足引起营养不良[15]和 UA 水平的降低[16]。蛋白质能量消耗(protein-energy wasting, PEW)是指 CKD 患者存在的多种营养和代谢异常[17]，与白蛋白、前白蛋白、转铁蛋白、肌酐、胆固醇和碳酸氢盐的血浆浓度有关，低 UA 往往伴随着低体重指数、低白蛋白水平、低磷，意味着营养不良，而营养不良往往是透析患者死亡的独立危险因素。

5. 血清 UA 与炎症

越来越多的证据表明 UA 是一种炎症因子[18] [19] [20]。UA 单钠晶体刺激痛风炎症也是公认的[21] [22]。研究表明，UA 可以激活近端肾小管上皮细胞中的 NF-kB 信号[23] [24]，NF-kB 信号作为一个关键的转录因子，通过调节细胞因子和趋化因子的表达来介导炎症[25]。UA 通过激活 NF-kB 信号通路诱导肾组织炎症细胞浸润和炎症介质的小管表达[26]。另一方面，UA 是一种强大的氧自由基清除剂，具有抗氧化和抗炎作用[27] [28]，总抗氧化能力与较高的血 UA 水平相关[29]。高水平的 UA 可以阻断尿毒症的毒素作用，增加一氧化氮水平，减少线粒体中活性氧的产生，从而改善内皮细胞功能[30]。低水平的 UA 患者白蛋白水平较低，hs-CRP 水平较高，营养不良可以减少心肌细胞体积和肌原纤维含量，引起纤维蛋白原增加，诱导氧化应激和血管炎症，促进动脉粥样硬化[31]。低 UA 血症与 MIA 综合征(营养不良－炎症－动脉粥样硬化)密切相关[32] [33]。MIA 综合征与 HD 患者的高死亡率密切相关[34] [35]。综上两方面，低 UA 血症促进血液透析患者 MIA 进展，从而引发高死亡率。

6. UA 与全因和心血管死亡风险

尽管在一般人群中，高 UA 水平与全因和心血管相关死亡风险之间的联系是一致的，但探索 UA 在终末期肾脏病患者高死亡风险和心血管疾病背景下的作用的研究没有定论[2]。台湾肾病学会透析登记处针对 27,229 名血液透析患者的研究发现，血 UA 水平越低全因和心血管相关死亡率的风险越高[30]，一项来自亚洲的有 1738 名患者的大型队列研究中，发现 UA 和全因死亡率之间存在 U 型关联[36]，而更小规模的研究则发现了 J 型关联[37] [38]。高 UA 会引起氧化应激、内皮功能障碍以及冠状动脉血流缓慢[39]，有研究表明透析患者中，当 UA 大于 6 mg/dL 时，UA 水平越高则患者的血管钙化及心血管不良事件越高[40]，其机制包括：UA 增高会形成结晶沉积在动脉壁上，引起动脉内膜受损；可促进低密度脂蛋白的氧化和脂质过氧化，并与增加的氧自由基参与炎症反应;可促进血小板聚集，介导多种氧化物损伤血管内皮[41]。白蛋白是常用的营养学指标，亦被认为是尿毒症患者的一种迟发负性炎症蛋白[42]，透析患者的血 UA 升高及白蛋白下降会加重自身的氧化应激和微炎症状态，从而增加 MIA 综合征，进一步引起心血管事件[43]。

7. 结论

综上所述，在 MHD 患者中，一方面高浓度的 UA 水平减轻内皮功能障碍，抑制基因功能障碍诱发氧化应激反应和 UA 保护一氧化氮的产生，抵消炎性反应造成的氧化损伤和血管毒性，从而对 MHD 患者起到保护作用；另一方面，UA 水平的动态变化与营养状态一致，低 UA 水平往往伴随着多种营养和代谢异常，患者基础状况越差，死亡风险越高。高炎低代谢状态，加重心血管负担，增加 MIA 综合征(营养不良－炎症－动脉粥样硬化)，增加 MHD 患者死亡风险。然而，由于各种族、各地域针对当地患者个体差异的不同，采用的透析模式不同，尿酸水平对 MHD 患者全因死亡影响有负相关、J 型关联及 U 型关

联三种不同结论，因此需进一步的多中心前瞻性试验来证实这些结论的准确性，此外还需要进一步的基础研究来澄清这些发现背后的确切机制。

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