

维持性血液透析患者高磷血症促动脉粥样硬化的机制及降磷治疗研究进展

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摘要

高磷血症是慢性肾脏病(CKD)尤其是晚期血液透析患者常见的并发症, 而高磷与动脉粥样硬化性心血管疾病(ASCVD)的发生发展密切相关。高磷血症可抑制内皮型一氧化氮合酶(eNOS)活性, 导致内皮功能障碍; 激活炎症小体, 释放促炎因子, 加剧血管炎症; 扰乱胆固醇稳态, 促进泡沫细胞形成。降磷治疗是改善CKD患者心血管预后的重要手段, 非含钙磷结合剂在降低血磷的同时, 部分研究表明, 还可显著减少心血管事件和全因死亡率。本文综述了高磷血症促进动脉粥样硬化的机制, 降磷药物的研究现状及减少CKD患者动脉粥样硬化发生率的机制, 为维持性血液透析高磷血症患者心血管疾病防治提供理论依据。

关键词

维持性血液透析, 高磷血症, 动脉粥样硬化, 降磷药物, 心血管死亡率

Mechanisms of Arteriosclerosis Induced by Hyperphosphatemia in Maintenance Hemodialysis Patients and Research Progress of Phosphorus-Lowering Therapy

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Abstract

Hyperphosphatemia is a common complication in patients with chronic kidney disease (CKD), especially those undergoing hemodialysis in advanced stages. It is closely associated with the occurrence and progression of atherosclerotic cardiovascular disease (ASCVD). Hyperphosphatemia can inhibit the activity of endothelial nitric oxide synthase (eNOS), leading to endothelial dysfunction; activate inflammasomes, release pro-inflammatory factors, and exacerbate vascular inflammation; disrupt cholesterol homeostasis and promote foam cell formation. Phosphorus-lowering therapy is an important approach to improve the cardiovascular prognosis of CKD patients. Non-calcium-based phosphate binders not only reduce serum phosphorus levels but also significantly decrease cardiovascular events and all-cause mortality. This article reviews the mechanisms by which hyperphosphatemia promotes atherosclerosis, the current research status of phosphorus-lowering drugs, and the mechanisms underlying the reduction of atherosclerosis incidence in CKD patients, providing a theoretical basis for the prevention and treatment of cardiovascular diseases in maintenance hemodialysis patients with hyperphosphatemia.

Keywords

Maintenance Hemodialysis, Hyperphosphatemia, Atherosclerosis, Phosphorus-Lowering Drugs, Cardiovascular Mortality

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1. 研究背景

慢性肾脏病(chronic kidney disease, CKD)已成为近年来我国愈发显著的公共卫生问题。在 1990 年至 2019 年期间, CKD 的患病率和死亡率从 6.7%显著增加到 10.6% [1]。研究发现, 慢性肾脏病(CKD)患者的心血管风险显著升高, 主要表现为冠心病、心力衰竭、心律失常及心源性猝死。其中, 动脉粥样硬化性心血管疾病(ASCVD)是心血管风险升高的重要原因之一[2]。流行病学调查显示, 维持性血液透析人群的 ASCVD 发病率较普通人群高 10~20 倍, 且构成其心血管死亡的 50%以上[3]。除了高血压、糖尿病、血脂异常及吸烟等传统因素外, 越来越多的证据表明, CKD 特有的非传统危险因素在心血管事件发病机制中起着关键作用, 这些因素包括肾性贫血, 缺铁, 慢性炎症, 氧化应激增加, 尿毒症毒素的潴留, 如硫酸吡啶酯、对甲酚硫酸盐和三甲基单胺-N-氧化物, 以及 CKD-矿物质和骨骼疾病(CKD-MBD) [4] [5]。在非传统危险因素中, CKD-MBD 已成为 CVD 发病机制的重要参与者[6] [7], 其中, 高磷血症是 CKD 的常见并发症, 越来越多的证据表明, 血清磷酸盐水平升高与 ASCVD 风险独立相关[8]-[10]。血清磷酸盐每升高 1 mg/dL, ASCVD 事件发生率增加 31% [10]。降磷药物如含钙/非含钙磷结合剂能有效降低 CKD 患者的血清磷酸盐水平, 有文献指出, 非含钙磷结合剂(如司维拉姆、碳酸镧)可显著改善炎症标志物, 减少非致命性心血管事件, 降低心血管死亡率[11]-[14]。

2. 高磷血症促动脉粥样硬化的分子机制

2.1. 高磷血症促进血管内皮损伤

动脉粥样硬化是一种发生于弹性动脉和肌性弹性动脉的慢性炎症性疾病, 其特征是动脉粥样硬化斑

块(含胆固醇)的形成, 这些斑块可导致血管狭窄[15]。高磷血症通过多种分子机制促进动脉粥样硬化的发生发展, 其中内皮功能障碍是导致心血管疾病的动脉粥样硬化的主要原因。高磷酸盐经Ⅲ型钠-磷酸盐协同转运蛋白(PiT-1 和 PiT-2)进入血管内皮细胞后, 激活传统蛋白激酶 C(PKC), 诱导 eNOS 的 Thr⁴⁹⁷ 位点磷酸化, 抑制其活性, 减少 NO 生成; 同时刺激内皮细胞产生过量活性氧(ROS), ROS 与 NO 结合生成过氧亚硝酸盐(ONOO⁻), 进一步消耗 NO, 双重作用导致血管舒张功能受损, 促进动脉粥样硬化发生[16]-[18]。

2.2. 高磷血症促进血管炎症

高磷血症通过Ⅲ型钠-磷酸盐协同转运蛋白(PiT-1 和 PiT-2)促进细胞内磷酸盐蓄积, 直接激活核因子 κ B(NF- κ B)信号通路[19]。NF- κ B 是调控炎症反应的核心转录因子, 能诱导炎症因子(如 IL-6、IL-1 β)和急性时相蛋白(如 Saa1)的表达, 引发全身性炎症[19][20]。还有实验显示, FGFR4 基因敲除(Fgfr4^{-/-})小鼠在高磷饮食或腺嘌呤诱导的慢性肾病(CKD)中, 仍出现与野生型小鼠相似的炎症因子(IL-6、IL-1 β)升高, 表明高磷血症可直接引发炎症[21]。

此外, 高磷酸盐经 PiT-1/PiT-2 进入内皮细胞后, 还可以通过激活 NAD(P)H 氧化酶(主)和黄嘌呤氧化酶(次)产生超氧阴离子(O₂⁻)等 ROS, 引发氧化应激。ROS 氧化 LDL 形成 ox-LDL(动脉粥样硬化斑块关键诱因), 并加剧内皮损伤和炎症[17]。ROS 积累激活 NF- κ B 等通路, 促使内皮细胞分泌 IL、TNF 等炎症因子, 招募单核细胞黏附并分化为巨噬细胞, 参与泡沫细胞形成; 同时刺激内皮表达 VCAM-1、ICAM-1, 促进白细胞浸润, 加速斑块进展[22][23]。

2.3. 高磷血症促进脂质沉积

研究表明, 高磷血症可能通过扰乱胆固醇稳态参与 CKD 患者的动脉粥样硬化形成[24][25], 过量的磷酸盐会激活高尔基体中的 α -甘露糖苷酶 II, 该酶可催化固醇调节元件结合蛋白裂解激活蛋白(SCAP)的 N-糖基化修饰, 将其糖链从简单的高甘露糖型转化为多分支的复杂型。这种修饰改变会延缓 SCAP 的降解过程(正常情况下 SCAP 通过泛素-蛋白酶体系统代谢), 导致 SCAP 在细胞内异常蓄积。蓄积的 SCAP 会与内质网中的锚定蛋白 INSIG1 分离, 进而携带固醇调节元件结合蛋白 2(SREBP2)形成复合体, 从内质网转运至高尔基体。在高尔基体中, SREBP2 被酶切后释放活性片段 SREBP2-N, 该片段进入细胞核, 激活 3-羟基-3-甲基戊二酰辅酶 A 还原酶(HMGCR)和低密度脂蛋白受体(LDLR)的基因转录。HMGCR 的上调促进胆固醇从头合成, LDLR 的增加则增强低密度脂蛋白摄取, 最终导致血管平滑肌细胞等动脉壁细胞内胆固醇过度蓄积, 形成泡沫细胞, 加速动脉粥样硬化斑块的形成与进展[26]。

2.4. CKD-MBD 相关动脉粥样硬化

矿物质骨病(MBD)是慢性肾脏病(CKD)的常见并发症, 表现为体内正常矿物质稳态被破坏, 是钙、磷酸盐、镁、甲状旁腺激素(PTH)、维生素 D 和成纤维细胞生长因子 23 (FGF-23)之间复杂相互作用的结果。在合并 CKD-MBD 的患者中, 动脉粥样硬化相关心血管事件(如心力衰竭、猝死)发生率是单纯传统风险因素患者高 2~3 倍[27][28]。在慢性肾病(CKD)患者中, 随着肾功能逐步减退, 磷酸盐代谢失衡引发高磷血症, 进而导致循环中甲状旁腺激素(PTH)和成纤维细胞生长因子 23 (FGF23)水平代偿性升高, 驱动钙化蛋白颗粒(CPPs)形成, 同时, 血清 α -klotho 蛋白、骨化三醇(calcitriol)及骨化二醇(calcidiol)等保护性因子浓度降低。这些 CKD-MBD 的特征性病理改变, 会诱发血管钙化、激活炎症反应及破坏血管壁稳态等, 直接加速动脉粥样硬化进程, 最终显著增加患者的心血管事件风险及死亡风险[27]。

3. 降磷药物能否降低 MHD 患者动脉粥样硬化风险

3.1. 降磷药物的现有研究

现有降磷药物主要分为含钙磷结合剂、非含钙磷结合剂和新型药物三大类, 目前, 临床降磷的一线药物主要是含钙磷结合剂, 代表性药物主要包括醋酸钙和碳酸镧, 在降磷的同时易致钙负荷过高, 增加血管钙化风险, 2017 年 KDIGO 指南已建议限制其用量[29]; 不含钙磷结合剂司维拉姆、碳酸镧, 降低血磷水平的同时还能降低低密度脂蛋白胆固醇及 C 反应蛋白水平, 减少血管钙化进展。一项 Meta 分析表明, 与含钙磷结合剂相比, 可减少慢性肾脏病患者的全因死亡率及血管钙化评分, 但其胃肠道不良反应(如便秘、恶心)发生率较高[30]。部分研究显示, 碳酸镧能延缓冠状动脉钙化、改善心脏结构与收缩功能, 对骨转换的抑制作用较弱, 但长期使用可能导致胃肠道黏膜镧沉积[29] [31] [32]。新型降磷药物以替那帕诺(tenapanor)为代表, 能抑制肠道钠氢交换体 3 (NHE3)减少磷的细胞旁吸收, 从而降低血磷, 最常见不良反应为腹泻, 目前尚未获批用于 CKD 患者高磷血症治疗[33]。

3.2. 降磷药物对心血管结局的临床影响

高磷血症是 CKD 患者动脉粥样硬化性疾病的危险因素[34], 提示降磷治疗可能对心血管具有保护作用。对于 CKD 3b-4 期且血磷正常患者, 碳酸镧虽显著降低尿磷排泄分数, 但未改善肱动脉血流介导的舒张功能(FMDBA)和颈动脉-股动脉脉搏波速度(cfPWV), 也未降低内皮或循环中氧化应激与炎症标志物, 对血管内皮功能和动脉僵硬度无明显影响[35]。在终末期肾病(ESRD)高磷血症患者中, 使用钙基磷结合剂(CBPBs)比不使用磷结合剂的患者具有更长的总生存期(OS)和无 CVD 时间。先使用 CBPBs 再转为非钙基磷结合剂(NCBPBs)的患者 OS 和无 CVD 时间最长, 但差异无统计学意义[36]。使用钙基磷结合剂可能增加高钙血症风险, 而非钙基磷结合剂如司维拉姆, 可降低血清钙水平, 还能降低总胆固醇、低密度脂蛋白胆固醇等, 对心血管可能有一定保护作用[37]。

3.3. 降磷药物减少动脉粥样硬化的分子机制

在慢性肾脏病(CKD)中, 能够促进血管平滑肌细胞和巨噬细胞中从头胆固醇合成[38]。通过有效降磷, 理论上可以逆转或减轻这种促合成效应, 从而减少脂质在血管壁的积累。慢性炎症和氧化应激是 CKD 患者动脉粥样硬化的核心驱动因素。一些磷结合剂, 特别是司维拉姆, 被认为具有超越降磷作用的多效性效应, 包括抗炎和抗氧化作用。司维拉姆作为一种聚合物, 除了结合磷酸盐外, 还能结合尿酸、内毒素和一些尿毒症毒素, 从而可能减轻全身炎症反应[39]。此外, 通过降低血磷, 可以减少钙蛋白颗粒(CPPs)的形成, 而 CPPs 本身就是重要的促炎因子, 能够激活炎症通路并导致细胞损伤。因此, 降磷治疗通过减少 CPPs 的生成, 可能间接抑制血管炎症[39]。

4. 结论与展望

高磷血症作为慢性肾脏病(CKD)患者常见的代谢紊乱, 是动脉粥样硬化性心血管疾病(ASCVD)发生发展的重要危险因素。其通过多种机制参与动脉粥样硬化进程: 一方面, 高磷可直接损伤血管内皮功能, 通过氧化应激、NO 生物利用度降低及 NF- κ B 通路激活破坏血管屏障; 另一方面, 通过诱导钙磷蛋白颗粒形成、促进促炎因子释放及细胞表型转化, 加剧血管局部炎症反应; 还可以通过调控 SCAP/SREBP2 通路扰乱胆固醇稳态, 导致泡沫细胞形成及脂质沉积, 协同 CKD-MBD 相关因子放大血管损伤效应, 促使 CKD 患者发生动脉粥样硬化的风险增加。降磷药物对 CKD 患者具有心血管保护作用。临床证据显示, 非含钙磷结合剂在有效降低血磷的同时, 更能延缓血管钙化进展, 显著降低心血管事件风险及全因死亡率, 其优势可能与改善内皮功能、抑制炎症级联及调控脂质代谢相关。因此, 高磷血症是 CKD 患者 ASCVD

防治的重要靶点, 对于高风险患者, 优先选用非含钙磷结合剂有助于减轻动脉粥样硬化负担, 改善长期心血管预后。

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