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残余胆固醇与血液透析患者血脂异常的现况

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摘　要

血液透析(HD)已成为大多数终末期肾病患者偏向选择的肾脏替代方式，心血管疾病(CVD)是其主要死亡原因。脂代谢紊乱是CVD和终末期肾病(ESRD)共同进展的机制。越来越多的证据表明，即使当低密度脂蛋白控制到最佳水平，残余胆固醇(RC)仍从流行病学及遗传学等方面被证明在预测ASCVD的发生中起着重要作用。现就HD患者血脂紊乱的特点及RC的定义、测量、机制、相关研究进展等进行总结。

关键词

残余胆固醇，终末期肾脏病，血液透析，心血管疾病，脂代谢紊乱

Remnant Cholesterol and Status of Dyslipidemia in Hemodialysis Patients

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Abstract

Hemodialysis (HD) has become the preferred renal replacement for most patients with end-stage renal disease, and cardiovascular disease (CVD) is the leading cause of death. Dyslipidemia is a mechanism for the co-progression of CVD and end-stage renal disease (ESRD). There is increasing evidence that even when low-density lipoprotein is controlled to optimal levels, remnant cholesterol (RC) is still proven to play an important role in predicting the occurrence of ASCVD from the aspects of pathogenic mechanism, epidemiology and genetics. This article summarizes the characteristics of dyslipidemia in HD patients and the definition, measurement, mechanism, and related research progress of RC.

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Keywords

Remnant Cholesterol, End-Stage Renal Disease, Hemodialysis, Atherosclerotic Cardiovascular Disease, Dyslipidemia

1. 引言

慢性肾脏病(chronic kidney disease, CKD)已逐渐发展为全球性卫生健康问题，而我国逐渐成为全球CKD患病率最高的国家[1]。当疾病进入终末期状态时，肾脏代替治疗包括肾移植、腹膜透析及血液透析(hemodialysis, HD)需纳入考虑，我国患者大多数选择了后者[2]。心血管疾病(cardiovascular diseases, CVD)是导致HD患者发病和死亡的一个重要原因，研究表明，HD患者CVD死亡率为普通人群的10~30倍[3]。众多导致CVD的因素中，脂代谢紊乱作为肾脏病和动脉粥样硬化性心血管病(atherosclerotic cardiovascular disease, ASCVD)的共同“通路”[4]，引发了近年来学者的广泛关注。

大量研究表明，在普通人群以及轻中度CKD患者中，应用HMG-CoA还原酶抑制剂(他汀类药物)预防心血管风险有良好的反应[5] [6] [7]。值得注意的是，CKD和终末期肾病(end-stage renal disease, ESRD)患者血脂异常的性质和机制以及CVD的特征与普通人群不同，尽管对低密度脂蛋白(low-density lipoprotein, LDL)进行了有效治疗，LDL的降低效果明显低于当前推荐的治疗目标，心血管事件复发率仍高于预期：SHARP试验和一项荟萃分析显示，经他汀治疗后CVD的风险仍随着CKD病情发展的晚期而增加[5] [8]。虽然他汀类药物对部分轻中度CKD患者有效，但不能降低ESRD人群的CVD发病率和死亡率[9] [10]。近年来，已有流行病学、遗传学和生物学等研究证明富含甘油三酯的脂蛋白(triglyceride-rich lipoprotein, TRL)升高是炎症、ASCVD和全因死亡率的因果风险因素[11] [12]，而其中最重要的成分或为残余胆固醇(remnant cholesterol, RC) [13] [14]。

目前国内外大量研究验证了RC与炎症以及缺血性心脏病、缺血性卒中和高血压的发展有关的相关性及因果关系[14]-[21]。也有研究表明RC浓度可预测糖尿病肾病和视网膜病变的发展及糖尿病患者的心血管风险[22] [23]。我国关于脂肪肝和非酒精性脂肪肝的研究中，RC和脂肪肝的发生率、严重程度呈强正相关，可能有助于进一步识别和预防脂肪肝[24] [25]。而在HD患者中，目前关于RC仍需进一步研究。本文将结合近年来的科研文献概述HD患者的血脂紊乱及治疗现况。

2. HD患者血脂紊乱特点及机制

HD人群中脂质异常主要表现有甘油三酯(TG)和TRL (包括极低密度脂蛋白(VLDL)、乳糜微粒(CM)及其胆固醇残余物)升高、高密度脂蛋白(HDL)和载脂蛋白A (apoA)降低及血浆总胆固醇(TC)和低密度脂蛋白(LDL)不变或降低为主[26]。其受多种因素如糖尿病、饮食、炎症、营养不良及与肾脏疾病无关的遗传疾病、脂质修饰药物(类固醇)和肾脏替代方式(即HD和腹膜透析)等的影响[27] [28]。

HD患者早在CKD早期就开始TG升高，这与脂蛋白脂酶(LPL)缺乏和功能障碍有关。正常情况下，LPL介导VLDL和CM中TG的水解，从而使得心肌细胞和脂肪细胞能够释放和吸收脂肪酸。ESRD导致各组织中LPL的表达降低[29]，糖基磷脂酰肌醇锚定结合蛋白1 (GPIHBP1)的缺失以及甲状旁腺激素血清浓度的增加也会导致LPL缺乏[30]。同时，载脂蛋白CIII (LPL抑制剂)/载脂蛋白CII(LPL激活剂)比率

增加、肝素介导的内皮结合 LPL 的释放和降解[30]、血管生成素样蛋白(ANGPTL) 3 和 4 的浓度增加都可以有效抑制 LPL 的活性[27]。此外，LDL 受体相关蛋白(LRP)和 VLDL 受体下调，这些蛋白在清除 VLDL、CM 和中低密度脂蛋白(IDL)颗粒中起关键作用[31]。上述异常不仅导致血清 TG 和 TRL 含量升高，损害能量传递和利用，也部分解释了 ESRD 中各种致动脉粥样硬化胆固醇残余物清除率降低的原因[31]。部分研究指出，与普通人群相比，HD 患者的血清 TG 和 TRL 水平升高与 HD 患者死亡率增加无关，一些研究则报告生存率提高[32]。

LDL 是导致 ASCVD 的主要危险因素之一[11]。虽然在 HD 患者中，LDL 水平往往并不升高甚至降低，但 LDL 代谢异常，极易被氧化为 oxLDL 并增加动脉粥样硬化的风险。具有这些特征的 LDL 的产生主要是由于 LPL 缺乏和活性降低，从而导致 TRL 和 LDL 的血清浓度升高。此外，在正常条件下，LDL 的胆固醇含量通过胆固醇酯转移蛋白(CETP)的作用而增加：CETP 促进胆固醇酯从 HDL 转移到 TRL，从而降低高密度脂蛋白胆固醇(HDL-C)的血清浓度。尽管在 ESRD 患者中，CETP 的血清活性可能正常或升高，但这些患者缺乏富含胆固醇的 HDL，从而导致 CETP 缺乏胆固醇底物，进一步增加小密度低胆固醇 LDL 的水平[33]。

HDL 浓度降低是 CKD 疾病进展的典型特征，二者之间的关联已在 HD 患者中得到证实[34]。HD 患者中 HDL 和 apoA 浓度降低，部分原因是肝合成 apoA 的能力减弱以及卵磷脂－胆固醇酰基转移酶(LCAT)浓度和活性缺陷导致血浆 HDL 重塑改变[34]。此外，HDL 的组成和功能的异常包括 HDL 介导的胆固醇逆向转运减少以及其抗氧化和抗炎特性降低[35]。目前还没有发现高浓度 HDL 与 HD 患者生存率的提高相关，在某些亚群中，高浓度 HDL 与更差的预后相关，此时此类 HDL 可能是促炎性的，通过积累对称性二甲基精氨酸(SDMA)促进内皮功能障碍[36]。同样，一项针对 170 万男性的研究发现，较低的肾小球滤过率(eGFR)会减弱 HDL 的任何有益作用[37]。因此，低 HDL 水平目前被认为是 ASCVD 风险的生物标志物，但不是治疗的目标，未来的研究将需要检查 HDL 的组成、抗氧化、抗炎和 HDL 内流/卸载能力，作为评估 ESRD 患者风险的临床工具[38]。

3. 残余胆固醇(RC)

3.1. 定义

残余胆固醇(RC)，一种与高浓度 TG 相关的新型脂蛋白指标，主要由 VLDL 和中等密度脂蛋白(IDL)、餐后状态时还包括 CM 等物质被 LPL 水解掉 TG、磷脂、apoA 和 C 等物质后剩余的胆固醇总称，占血浆 TC 的三分之一[39]。RC 的定量方法基本上包含两种：1) 据 Friedewald 方程计算，RC = TC − (LDL-C) − (HDL-C)，优点是无需额外成本，局限则表现为该方程假定 TG 与 VLDL-C 的比率固定，然而，实际的比率则不同情况下变化很大。目前可以通过使用 LDL-C 计算 RC 来部分缓解或通过直接分析 RC 含量来完全缓解[20] [40]。2) 获得 RC 还可通过医院实验室的循环酶法、免疫吸附法等测量，但由于血浆中代谢胆固醇残余物的浓度较低，且在不同时期大小和组成不均一，目前只能通过更费力的方法来如超速离心或核磁共振光谱法测量[11]。国内的一项研究显示，计算的与核磁共振直接测量的 RC 水平之间存在显著差异，而在某些 TG 水平内，二者测量方式所得几乎相等，意味着使用计算的 RC 是可行的[41]。所以，仍有必要开发一种更为准确且简便的临床方法来测量 RC 水平，或成为未来治疗的潜在靶点。

3.2. 机制

根据已有研究结果，动脉粥样硬化由内膜的损伤和炎症触发，强有力的证据表明，高浓度的 RC 会导致 ASCVD [12] [42]。与 LDL 相比，RC 导致动脉粥样硬化的方式存在重大差异：TRL 经水解后的 RC 进入动脉壁，未经修饰即被巨噬细胞和平滑肌细胞吸收形成泡沫细胞，而 LDL 需要在吸收前进行氧化修饰

[43]。此外，一项巴西成人健康研究表明，空腹血糖受损的个体中 TRL 颗粒大小与肥胖、胰岛素抵抗和炎症高度相关[44]。TRL 颗粒比 LDL 大，携带胆固醇含量是其 40 倍，这可能使它们比 LDL 更容易导致动脉粥样硬化。Varbo A 等人的研究表明，RC 升高会导致低度炎症和缺血性心脏病，而 LDL-C 升高会导致缺血性心脏病而无炎症，进一步证明相对于 LDL，RC 会导致的动脉粥样硬化炎症反应更加明确[45]。

3.3. 部分研究进展

目前国内外大量研究验证了 RC 与 CVD、糖尿病、高血压、脂肪肝、深静脉血栓等各系统疾病的相关性，为 RC 的致动脉粥样硬化风险提供了有力支撑。肾脏病方面，FAVORIT 研究首次证明基线 RC 水平升高与心血管事件风险和肾移植受者全因死亡率之间存在因果关系[46]。一项横断面研究结果证明，在中国普通中老年人群中，较高的 RC 与 CKD 流行风险的增加独立相关，尤其是女性、超重/肥胖、非糖尿病前期、高血压、HDL-C 正常、适当和高 LDL-C 值以及无 CVD 事件的受试者[47]。一项队列研究证明，高浓度 RC 与传统血脂指标的升高相比，与肾损伤早期进展的关系更为密切[48]。Transplant Lines 生物库和队列研究的结果表示：基线 RC 水平与肾移植受者移植后新发糖尿病密切相关[49]。因此，通过生活方式和药物干预来监测和降低高危人群的 RC 值非常重要，从而在降低 CKD 风险和带来 CVD 相关方面益处。目前仍缺乏以 HD 患者为基础的心血管事件风险研究，仍需进一步的数据来支持帮助改善 HD 患者的预后。

4. 治疗

导致 ASCVD 残余风险的机制不仅表明了我们对动脉粥样硬化病变的不完全理解，且提出了新的治疗方法。已有的治疗中他汀类、贝特类、胆汁酸螯合剂和烟酸的潜力有限，促使人们寻找疗效和安全性更好的新药物分子，如 CETP 抑制剂，除了具有降低 LDL 的特性外，还具有提高 HDL 的潜力；微粒体甘油三酯转移蛋白(MTP)抑制剂和载脂蛋白 CIII 抑制剂已被批准用于家族性高胆固醇血症，但在非家族性环境中的经验非常有限；PCSK9 抑制剂有望在 LDL-C 控制中发挥作用；我国学者利用三项数据库对 CKD 患者的荟萃分析证明，补充辅酶 Q10 可能具有改善炎症水平、葡萄糖代谢、心脏结构和心脏生物标志物的潜力，此结果仍应在更大规模的高质量研究中得到证实[50] [51]；目前正在研究靶向针对脂蛋白(a)的新方法对心血管的益处[14]；欧洲药品管理局基于 REDUCE-IT 实验批准二十碳五烯乙酯(IPE)的使用，明显降低了 RC 的浓度，也可调节内皮功能、减轻斑块内炎症和氧化应激，以及减少巨噬细胞积累[52]。上述治疗方法仍有必要进行进一步的临床试验，RC 如何进一步降低及降低后的成果仍值得我们拭目以待。

5. 总结及讨论

血脂代谢异常及新近的指标 RC 已从致病机制、流行病学及遗传学等被证明是 CKD 和 ASCVD 的主要机制，在预测心血管风险的发生中起着重要作用。了解这些复杂和独特的脂蛋白变化特征不仅对现有临床数据结果的解释至关重要，而且对 ESRD 脂质紊乱治疗的个体化也至关重要。目前的降脂药物的使用有限，且针对 RC 治疗的研究较少，RC 的标准化检测尚存争议，未来需对该疾病的进一步了解以及使用可靠的技术进行更深入的研究，从而使我们在追求理想的抗血脂药物的道路上更进一步。

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