

NHHR与糖尿病血管并发症风险的关联——基于循证医学思考

刘煜¹, 秦永章²

(1. 赣南医科大学第一临床医学院; 2. 赣南医科大学第一附属医院内分泌科, 江西 赣州 341000)

摘要: 糖尿病血管并发症(Diabetic vascular complications, DVC)是糖尿病患者致死致残的主要原因, 其风险预测亟待发掘超越传统血脂参数的新型生物标志物。非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, NHHR)作为一种整合了致动脉粥样硬化与保护性脂蛋白信息的复合指标, 近年来在评估DVC风险中展现出优越性。本文基于循证证据进行小结, 发现NHHR与DVC风险密切相关, 其预测效能优于传统指标, 并能识别出具有临床指导意义的风险阈值。进一步分析揭示, NHHR参与DVC发病的机制涉及内皮功能障碍、氧化应激与炎症激活等病理过程; 而以NHHR为靶点的治疗策略亦展现出临床转化潜力。综上, NHHR有望成为DVC的新型预测标志物及干预靶点, 但未来仍需前瞻性研究以明确其最佳切点及临床适用路径。

关键词: 糖尿病; 糖尿病血管病; 高密度脂蛋白胆固醇; 非高密度脂蛋白胆固醇; 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值

中图分类号: R587.2 文献标志码: A 文章编号: 2097-7174(2026)08-0705-07

DOI: 10.3969/j.issn.2097-7174.2026.08.003

Risk of NHHR and diabetic vascular complications: evidence-based medicine thinking

LIU Yu¹, QIN Yongzhang²

(1. The First Clinical Medical School of Gannan Medical University; 2. Endocrine Department,
The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi 341000)

Abstract: Diabetic vascular complications (DVC) are the leading cause of mortality and disability in diabetic patients. Its risk prediction needs new tools that go beyond traditional blood lipid indicators. Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), as a composite indicator that integrates information on atherosclerosis and protective lipoproteins, has demonstrated superiority in assessing the risk of DVC in recent years. This review, based on evidence-based literature, demonstrates that NHHR is closely associated with the risk of DVC, exhibiting superior predictive performance over traditional indicators, and identifies a clinically meaningful risk threshold. Further analysis reveals that the mechanisms by which NHHR participates in the pathogenesis of DVC involve endothelial dysfunction, oxidative stress, and inflammatory activation. Moreover, therapeutic strategies targeting NHHR also show promise for clinical translation. In summary, NHHR holds potential as a novel predictive biomarker and therapeutic target for DVC. However, future prospective studies are warranted to define its optimal cut-off value and establish feasible clinical application pathways.

Key words: Diabetes mellitus; Diabetic angiopathies; High-density lipoprotein cholesterol; Non-high-density lipoprotein cholesterol; Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio

糖尿病是一种全球高发的慢性代谢性疾病, 其中2型糖尿病(Type 2 diabetes mellitus, T2DM)占比超过90%^[1]。糖尿病血管并发症(Diabetic vascular

complications, DVC)是糖尿病患者致死致残的主要原因, 随着糖尿病患病率持续攀升, DVC的发病率也相应提高, 疾病负担日益严峻。DVC常由胰岛素

基金项目: 赣州市科技计划项目(2023LNS36720)

通信作者: 秦永章, 男, 博士, 副主任医师, 副教授, 硕士生导师, 研究方向: 糖尿病肾脏病发病机制。E-mail: sdiemd2008@126.com

缺乏和胰岛素抵抗(Insulin resistance, IR)伴持续性高血糖、血脂异常等代谢紊乱共同引起^[2],其中,血脂异常尤为关键。糖尿病患者的血脂异常具有复杂的代谢紊乱特征。因此,传统血脂指标在评估糖尿病患者血脂谱时存在局限性。非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, NHHR)作为新型复合脂质参数,因能更全面地反映脂质代谢平衡状态而被认为对DVC具有更有效的预测价值。本文旨在总结NHHR与DVC的流行病学关系、潜在机制、风险阈值及临床转化价值,为DVC防控提供理论依据。

1 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)

血脂异常是糖尿病及DVC的关键危险因素,在NHHR提出之前,临床实践与研究主要依赖于低密度脂蛋白胆固醇(Low-density lipoprotein cholesterol, LDL-C)等单一脂质参数进行评估。然而,糖尿病患者的脂质代谢紊乱往往呈现复杂性与整体性^[3],因此单一脂质参数在风险评估中存在局限性。为更全面地评估血脂异常与疾病发生风险,研究者曾探索诸如总胆固醇(Total cholesterol, TC)/HDL-C、LDL-C/HDL-C等复合参数^[4],这些指标虽优于单一参数,但仍无法全面反映机体脂质代谢。在此背景下, NHHR作为新型复合脂质参数被提出^[5]。NHHR计算公式为: $NHHR = \text{non-HDL-C} / \text{HDL-C} = (\text{TC} - \text{HDL-C}) / \text{HDL-C}$, non-HDL-C包含了极低密度脂蛋白胆固醇(Very-low-density lipoprotein cholesterol, VLDL-C)、中间密度脂蛋白胆固醇(Intermediate-density lipoprotein cholesterol, IDL-C)、LDL-C、乳糜微粒残余物和脂蛋白等所有致动脉粥样硬化脂蛋白^[6]。NHHR升高意味着致动脉粥样硬化脂蛋白占主导,脂代谢平衡被打破。因此, NHHR被视为反映致动脉粥样硬化负荷与心血管保护能力之间平衡的综合指标^[7-8],在评估DVC发生风险时可能优于单一脂质参数。

现有研究多聚焦于与NHHR相关的脂质代谢异常在DVC中的分子与细胞生物学机制。主要涉及以下方面:(1)氧化应激与炎症方面, NHHR升高促进活性氧大量生成,激活内皮细胞NF- κ B等关键炎症信号通路,使炎症因子表达上调,驱动血管损伤^[9];(2)脂毒性方面,相关脂质异常诱导内质网应激、

线粒体功能障碍及铁死亡等,导致靶细胞损伤^[10]。此外,胆固醇代谢与逆向转运失衡至关重要,研究致力于阐明低HDL-C如何削弱胆固醇逆向转运能力,并损害抗炎、抗氧化及促血管舒张等功能^[11]。近年来,代谢通路间的交叉调控已成为近年来的研究热点。脂代谢紊乱可与高血糖、IR等因素产生协同致病作用,加剧DVC的病理过程^[12]。这些机制为后续临床转化提供了理论依据。

2 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与2型糖尿病(T2DM)

血脂异常与T2DM密切相关,常表现为高血糖和血脂异常共存,并与其他代谢紊乱共同作用导致IR和胰岛 β 细胞功能障碍^[3]。T2DM的血脂异常常表现为HDL水平降低、小而致密的LDL颗粒增多及甘油三酯(Triglyceride, TG)水平升高,即“脂质三联征”^[13]。研究发现, NHHR在预测IR和代谢综合征(Metabolic syndrome, MetS)等方面优于传统脂质参数^[14]。多项研究证实NHHR与糖尿病风险相关。一项前瞻性研究显示, NHHR升高显著增加T2DM发病风险^[15]。一项纵向队列研究提出, NHHR $\approx$ 2.74为风险阈值(HR=1), NHHR>2.74时糖尿病风险逐渐增加, ROC曲线分析显示NHHR预测效能优于HDL-C、non-HDL-C、TC等常规指标^[5]。Tan M Y等^[14]研究发现, NHHR>1.50时,其水平与T2DM发生风险呈显著正相关。尽管风险阈值可能因人群异质性而异,但NHHR指示的风险趋势明确, NHHR作为T2DM预测因子的价值得到初步证实。

3 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病血管并发症(DVC)

糖尿病合并血脂异常是DVC发生发展的重要因素^[3]。糖尿病患者由于“脂质三联征”导致血管损伤风险显著增加。non-HDL-C升高易导致脂质在血管壁沉积,促进内皮细胞炎症、氧化应激与内皮功能障碍。HDL-C水平降低则削弱其胆固醇逆向转运等血管保护作用^[11]。

3.1 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病微血管并发症

糖尿病微血管并发症包括糖尿病肾脏病(Diabetic kidney disease, DKD)、糖尿病视网膜病变(Diabetic retinopathy, DR)和糖尿病周围神经病变(Diabetic

peripheral neuropathy, DPN), 随着 T2DM 患病率的持续上升, 上述并发症的疾病负担也日益加重^[16]。然而, 其发病机制复杂, 涉及内皮功能障碍、晚期糖基化终末产物积累、氧化应激及细胞因子异常表达等多种致病因素的协同交互作用^[17]。

3.1.1 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病肾脏病(DKD) DKD 是 T2DM 最常见并发症, 也是终末期肾病的主要病因, 其发病机制涉及脂质代谢异常、肾血流动力学改变、氧化应激和免疫炎症反应等^[18]。目前认为, 在高血糖诱导的氧化应激条件下, 氧化型 LDL (ox-LDL) 浓度增加导致 ox-LDL 在肾小球沉积, 并诱导足细胞和系膜细胞凋亡通路激活, 是 DKD 主要分子机制之一^[19]。此外, HDL-C 对 DKD 的作用尚存争议, 尽管有分析显示 HDL-C 水平升高与 DKD 发生风险增加相关, 但更多研究提示 HDL-C 水平升高与 DKD 风险降低相关^[20-22]。

近年来, 随着肥胖相关 T2DM 发病率的增加, DKD 患病率也呈上升趋势^[23]。既往研究表明, NHHR 是慢性肾脏病的独立危险因素^[24]。一项对美国 41 225 例参与者的横断面分析显示, NHHR 升高与大量白蛋白尿发生风险增加相关^[25]。血脂异常和氧化应激引起细胞铁死亡等机制与 DKD 相关, 在此基础上, Zhang L 等^[26]对 8 329 例糖尿病患者的横断面研究发现, NHHR 与 DKD 患病率呈正相关。平滑曲线拟合显示二者呈 J 形关联。阈值为 1.75 时, 超过该值后, NHHR 每增加一个单位, DKD 风险增加 7%。然而该研究中患者年龄偏大, 具有一定局限性。另一横断面研究显示, NHHR 作为连续变量与 DKD 风险显著相关, 限制性立方样条分析 (Restricted cubic spline, RCS) 提示两者呈 J 形相关, NHHR=2.66 时风险最低^[19]。横断面研究显示, NHHR 与 DKD 风险剂量反应关系存在性别差异, 男性转折点为 3.09, 女性为 2.63, 低于该值时, DKD 风险随 NHHR 升高而增加, 高于该值后出现饱和效应^[27]。Cai D X 等^[28]对 3 243 例 T2DM 患者的加权 RCS 分析表明, NHHR 与 DKD 风险之间呈 L 形关联。NHHR≤2.82 时, NHHR 与 DKD 风险呈负相关, 而超过该点后无显著关联。目前研究结果不统一, 可能与实验设计、人群特征、DKD 定义及统计模型不同有关, 但多数研究支持 NHHR 与 DKD 存在非线性正相关, 提示 NHHR 可能是 DKD 风险的独立危险因素。

3.1.2 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病视网膜病变(DR)

血脂异常与 DR 的发生发展相关^[29]。血脂异常可通过上调循环细胞因子 (如 VEGF-A、VEGF-D 和 PlGF)、促进氧化应激和内质网应激等机制促进 DR 的发生与发展。血脂异常诱导的线粒体损伤也会加速视网膜神经元凋亡, 引起糖尿病患者微血管损伤与视网膜结构破坏^[30]。当前 NHHR 与 DR 的相关性研究结论不一, 部分研究提示 NHHR 升高与 DR 风险增加相关。一项多变量回归分析显示, 较高 NHHR 与 DR 发生风险增加密切相关 ($OR=1.19$)^[31]。研究表明, TC、TG 和 LDL-C 升高会增加视网膜硬性渗出物和黄斑水肿的风险^[32]。尽管多项研究表明 DR 与血脂异常存在关联, 但目前结果仍不一致。既往研究显示, TG、TC、HDL 和 non-HDL-C 水平与视网膜病变无一致的关联或无统计学显著性^[33]。一项前瞻性研究表明, HDL-C 与 DR 风险无关^[17]。一项涵盖 13 个国家、针对长病程 T2DM 患者的研究发现, 高 TG 和低 HDL-C 水平在单变量分析中与 DR 相关, 但调整混杂因素后关联不显著^[34]。Yang H 等^[27]对我国 T2DM 患者横断面研究发现, NHHR 等血脂参数与 DR 无显著关联。研究结果不一致可能源于 DR 发病的多因素性, 血脂作用相对次要或特定脂质成分影响更为显著。当前证据尚不足以支持将 NHHR 作为 DR 常规预测指标, 需进一步研究验证。

3.1.3 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病周围神经病变(DPN)

NHHR 与 DPN 的相关性研究较为缺乏。T2DM 患者由于 MetS 的存在, 血糖控制仅略微影响 DPN 进展^[35]。研究发现血脂异常在 DPN 中起重要作用^[36]。临床前研究揭示多种病理生理机制, 包括细胞内葡萄糖水平升高、血清游离脂肪酸升高、氧化或糖化脂蛋白参与 DPN 的发生与进展。然而临床观察结果存在矛盾。有研究显示, 高 TG 血症与 DPN 风险增加相关, 尤其是小纤维神经病变^[37]。然而该研究中 DPN 定义不一致, 使用可变调查技术可能导致 DPN 患病率被高估。另一项对 1 111 例糖尿病患者的研究显示, 仅疼痛性 DPN 患者伴有高 TG 血症, 而无神经性疼痛患者的血浆 TC、TG 和 LDL-C 水平与 DPN 无相关性^[38]。相比之下, 一项基于 100 例 T2DM 患者进行的磁共振神经造影研究发现, 低血浆 TC 和 LDL-C 水平显著影响 DPN 的严重程度, 伴 DPN 者的基线和随访 TC 和 LDL-C 水平显著低于无 DPN 者^[39]。推测较低的胆固醇水平可能导致糖尿病神经性损伤后神经突触再生的胆固醇供应不足。上述研究因样本量和地域局限性可能存在较大

误差。一项涵盖39项随机对照试验的荟萃分析表明,与无DPN的糖尿病患者相比,伴DPN的糖尿病患者TG水平较高,HDL-C水平较低。但TC和LDL-C水平无显著差异^[40]。Chang K C等^[41]对成人T2DM患者的横断面研究显示,高脂血症和降脂药物都与DPN无显著关联。虽然基础研究提示血脂异常与DPN发病机制有关,但与现有临床研究的结果相互矛盾,其预测价值有待于未来高质量研究验证。

3.2 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与糖尿病大血管并发症 糖尿病大血管并发症包括冠心病(Coronary heart disease, CHD)、脑卒中和外周动脉疾病(Peripheral arterial disease, PAD)。NHHR因能综合反映致动脉粥样硬化脂蛋白和抗动脉粥样硬化脂蛋白的平衡状态,已被多项研究证实是大血管病变的有效预测指标。一项研究显示,NHHR与全因死亡率和心血管死亡率分别存在U型和L型关联,当NHHR超过2.72和2.83的拐点时,死亡率显著增加^[7]。ACCORD队列证据显示,将NHHR纳入常规模型后可提高对主要不良心血管事件预测效能^[8]。

3.2.1 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与冠心病(CHD) 糖尿病患者因多重代谢紊乱,引发血管内皮与平滑肌功能障碍及凝血异常,导致CHD发病风险显著升高^[42]。其病理过程的关键是non-HDL-C(尤其是LDL-C)在内皮下沉积,被氧化修饰成ox-LDL,诱导血管内皮表达黏附分子、促进泡沫细胞形成并激活NF- κ B等炎症信号通路,导致动脉粥样硬化斑块形成和血管内皮损伤等^[43]。Li Z等^[44]研究发现,T2DM患者NHHR与心血管疾病死亡率呈L形关联,拐点为1.68,低于该值时NHHR升高与心血管疾病死亡风险降低相关,高于该值后风险上升。You J等^[15]经多变量Logistic回归分析发现,较高NHHR与CHD发生风险增加显著相关,认为诊断CHD的最佳截断值为3.092。一项针对707例的研究显示,CHD风险随NHHR升高而非线性上升,ROC曲线分析表明模型AUC=0.922,预测效能良好^[45]。对930例接受冠状动脉造影的胸部不适患者的多变量Logistic回归分析显示,较高NHHR与CHD发生风险增加相关^[15]。鉴于上述部分研究样本量有限,其结论需谨慎解读。另一项对10 003例确诊冠状动脉疾病患者的前瞻性研究显示,NHHR与血管完全闭塞呈显著正线性关系^[46],但该研究中ApoB/apoA-1对完全闭塞的预测能力优于NHHR,因此NHHR的优越性有待进一步验证。

多因素回归分析显示,NHHR在最佳临界值3.3时对冠状动脉慢血流(Coronary slow flow, CSF)具有高敏感性和特异性,ROC曲线分析表明NHHR(AUC=0.785)鉴别CSF的能力显著优于TG、TC、HDL-C和LDL-C等传统脂质参数^[47]。这提示NHHR是反映动脉粥样硬化有效且可靠的指标。一项荟萃分析表明,较高基线non-HDL-C水平与CHD风险增加相关^[48]。同时人群研究也显示,HDL-C水平与CHD风险呈负相关^[49]。这可能与HDL-C的血管保护效应有关,包括抑制内皮细胞NF- κ B通路、减少黏附分子和细胞因子表达、抑制泡沫细胞形成等^[11]。综上所述,目前研究总体支持NHHR异常是CHD发病的重要因素,NHHR有望成为临床评估CHD风险的工具。

3.2.2 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与脑卒中 颅内或颈动脉斑块及血栓栓塞导致脑部血液供应中断,引起脑组织损伤。T2DM患者因长期高血糖、血脂异常及慢性炎症加速动脉粥样硬化,脑卒中发生风险较非糖尿病患者增加2~4倍且恶化可能性更高^[50]。研究发现,NHHR与颈动脉斑块稳定性及脑卒中风险相关^[51]。在一项对10 183例中老年人前瞻性研究中,Cox比例风险回归显示NHHR与脑卒中之间存在非线性关系,拐点为2.685,低于该值时NHHR与脑卒中风险呈显著正相关,超过该值后出现饱和效应^[52]。此外,研究发现,高NHHR显著增加国内老年非致残性缺血性脑血管事件患者1年内脑卒中复发风险^[53]。一项基于NHANES的成人横断面研究显示,在整合糖尿病等因素后,NHHR与脑卒中呈正相关,且该模型的预测效能更优^[54]。现有研究初步表明,NHHR可能是脑卒中的有效预测指标。但现有研究多聚焦老年人,未来需在更广泛人群中验证NHHR的预测价值。

3.2.3 非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)与外周动脉疾病(PAD) 目前针对NHHR与PAD关系的研究较少。研究表明,在218例接受治疗的PAD患者中,高apoE组的TC、TG和non-HDL-C水平显著高于低apoE组。在中位随访3.6年间,13.8%的患者发展为不良肢体事件(Major adverse limb events, MALEs),高apoE组MALEs的累积发生率显著高于低apoE组^[55]。此外,一项对10 900例成年高血压患者的横断面研究发现,LDL-C/HDL-C、TC/HDL-C和non-HDL-C水平升高均与PAD风险显著正相关^[56]。上述研究提示脂质比值参数可能与PAD相关,据此推测NHHR也可能具有预测价值,但需直接研究予以证实。

4 基于非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR)的治疗策略及临床转化

基于NHHR的脂质调控为DVC防治提供了新思路。临床中可依据不同并发症的风险阈值进行分层与干预。目前治疗仍以降低non-HDL-C为核心策略。他汀类药物仍是基石,其可显著降低non-HDL-C(尤其是LDL-C)水平,并轻度升高HDL-C水平。他汀类药物疗效不足或不耐受患者,建议联合PCSK9抑制剂或依折麦布等药物协同降低致动脉粥样硬化脂蛋白负荷,优化NHHR。未来研究可探讨以NHHR降幅作为疗效评估指标,还可针对HDL功能(如ApoA-I模拟肽、CETP抑制剂)及Lp(a)靶向药物,通过提升HDL功能活性或特异性干预脂蛋白代谢来优化NHHR,从而为NHHR的调控提供新手段。但其临床获益需进一步证实。

5 小结与展望

NHHR作为一种新型脂质代谢指标,在DVC的预测上展现出显著潜力。然而,当前研究仍存在诸多争议和局限性。NHHR与不同DVC的关联阈值尚未统一,部分并发症关联性证据薄弱且矛盾,相关机制研究仍需深入,且缺乏前瞻性干预研究证明以NHHR为靶向治疗改善DVC终点的价值。未来需开展大规模研究以确立针对不同人群和并发症的NHHR最佳风险阈值,深入探究其分子机制,并通过随机对照试验验证以NHHR为治疗靶点的治疗策略。通过整合多指标构建预测模型,提高DVC风险预测精度。随着研究深入,NHHR有望成为糖尿病精细化管理与DVC防控的有力工具。

所有作者均声明不存在利益冲突关系。

参考文献:

- [1] GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021[J]. *Lancet*, 2023, 402(10397): 203–234.
- [2] Yu M G, Gordin D, Fu J, et al. Protective factors and the pathogenesis of complications in diabetes [J]. *Endocr Rev*, 2024, 45(2): 227–252.
- [3] Bardini G, Rotella C M, Giannini S. Dyslipidemia and diabetes: reciprocal impact of impaired lipid metabolism and Beta-cell dysfunction on micro- and macrovascular complications[J]. *Rev Diabet Stud*, 2012, 9(2/3): 82–93.
- [4] Yang W S, Li R, Shen Y Q, et al. Importance of lipid ratios for predicting intracranial atherosclerotic stenosis [J]. *Lipids Health Dis*, 2020, 19(1): 160.
- [5] Sheng G, Liu D, Kuang M, et al. Utility of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio in evaluating incident diabetes risk[J]. *Diabetes Metab Syndr Obes*, 2022, 15: 1677–1686.
- [6] Zachariah G. Management of triglycerides, non-high density lipoprotein cholesterol and high density lipoprotein cholesterol[J]. *Indian Heart J*, 2024, 76: S58–S64.
- [7] Yu B, Li M, Yu Z, et al. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) as a predictor of all-cause and cardiovascular mortality in US adults with diabetes or prediabetes: NHANES 1999–2018[J]. *BMC Med*, 2024, 22(1): 317.
- [8] Liu M, Pei J, Zeng C, et al. Association of non-high-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio with cardiovascular outcomes in patients with type 2 diabetes mellitus: Evidence from the ACCORD cohort[J]. *Diabetes Obes Metab*, 2025, 27(1): 300–311.
- [9] Borén J, Chapman M J, Krauss R M, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel[J]. *Eur Heart J*, 2020, 41(24): 2313–2330.
- [10] Lytrivi M, Castell A L, Poitout V, et al. Recent insights into mechanisms of β -cell lipo- and glucolipotoxicity in type 2 diabetes[J]. *J Mol Biol*, 2020, 432(5): 1514–1534.
- [11] Madaudo C, Bono G, Ortello A, et al. Dysfunctional high-density lipoprotein cholesterol and coronary artery disease: a narrative review [J]. *J Pers Med*, 2024, 14(9): 996.
- [12] Kane J P, Pullinger C R, Goldfine I D, et al. Dyslipidemia and diabetes mellitus: role of lipoprotein species and interrelated pathways of lipid metabolism in diabetes mellitus[J]. *Curr Opin Pharmacol*, 2021, 61: 21–27.
- [13] Bahiru E, Hsiao R, Phillipson D, et al. Mechanisms and treatment of dyslipidemia in diabetes [J]. *Curr Cardiol Rep*, 2021, 23(4): 26.
- [14] Tan M Y, Weng L, Yang Z H, et al. The association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio with type 2 diabetes mellitus: recent findings from NHANES 2007–2018[J]. *Lipids Health Dis*, 2024, 23(1): 151.
- [15] You J, Wang Z, Lu G, et al. Association between the non-high-density lipoprotein cholesterol to high-density

- lipoprotein cholesterol ratio and the risk of coronary artery disease[J]. *BioMed Res Int*, 2020, 2020: 7146028.
- [16] Ali M K, Pearson-Stuttard J, Selvin E, et al. Interpreting global trends in type 2 diabetes complications and mortality[J]. *Diabetologia*, 2022, 65(1): 3–13.
- [17] Morton J, Zoungas S, Li Q, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study [J]. *Diabetes Care*, 2012, 35(11): 2201–2206.
- [18] Kanwar Y S, Sun L, Xie P, et al. A glimpse of various pathogenetic mechanisms of diabetic nephropathy [J]. *Annu Rev Pathol*, 2011, 6: 395–423.
- [19] Pan J, Li C, Zhang J, et al. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and diabetic kidney disease in patients with diabetes in the United States: a cross-sectional study [J]. *Lipids Health Dis*, 2024, 23(1): 317.
- [20] Jiang W, Wang J, Shen X, et al. Establishment and validation of a risk prediction model for early diabetic kidney disease based on a systematic review and meta-analysis of 20 cohorts[J]. *Diabetes Care*, 2020, 43(4): 925–933.
- [21] Guo J, Liu C, Wang Y, et al. Dose-response association of diabetic kidney disease with routine clinical parameters in patients with type 2 diabetes mellitus: a systematic review and meta-analysis[J]. *EClinicalMedicine*, 2024, 69: 102482.
- [22] Russo G T, de Cosmo S, Viazzi F, et al. Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: the AMD annals initiative[J]. *Diabetes Care*, 2016, 39(12): 2278–2287.
- [23] Guo W, Song Y, Sun Y, et al. Systemic immune-inflammation index is associated with diabetic kidney disease in Type 2 diabetes mellitus patients: Evidence from NHANES 2011–2018 [J]. *Front Endocrinol*, 2022, 13: 1071465.
- [24] Zuo P Y, Chen X L, Liu Y W, et al. Non-HDL-cholesterol to HDL-cholesterol ratio as an independent risk factor for the development of chronic kidney disease[J]. *Nutr Metab Cardiovasc Dis*, 2015, 25(6): 582–587.
- [25] Huang D, He Y. Association between non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio and macroalbuminuria: evidence from NHANES 1999–2018 [J]. *Front Endocrinol*, 2025, 16: 1503780.
- [26] Zhang L, Fan D, Zhu T, et al. The ratio of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol is associated with diabetic kidney disease: a cross-sectional study [J]. *PLoS One*, 2024, 19(11): e0311620.
- [27] Yang H, Young D, Gao J, et al. Are blood lipids associated with microvascular complications among type 2 diabetes mellitus patients? A cross-sectional study in Shanghai, China[J]. *Lipids Health Dis*, 2019, 18(1): 18.
- [28] Cai D X, Huang Y H, Lin N N, et al. The nonlinear relationship between the ratio of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol and the risk of diabetic kidney disease in patients with type 2 diabetes mellitus[J]. *Front Med*, 2025, 12: 1492483.
- [29] Perais J, Agarwal R, Evans J R, et al. Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy[J]. *Cochrane Database Syst Rev*, 2023, 2(2): CD013775.
- [30] Li Z, Yuan Y, Qi Q, et al. Relationship between dyslipidemia and diabetic retinopathy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis [J]. *Syst Rev*, 2023, 12(1): 148.
- [31] Zhang Z, Liu C, Zhao L, et al. Non-high-density lipoprotein-to-high-density lipoprotein cholesterol ratio as a predictive biomarker for diabetic retinopathy risk: a population-based analysis of US adults [J]. *Ophthalmic Res*, 2025, 68(1): 301–309.
- [32] Seo H, Park S J, Song M. Diabetic retinopathy (DR): mechanisms, current therapies, and emerging strategies [J]. *Cells*, 2025, 14(5): 376.
- [33] Van Leiden H A, Dekker J M, Moll A C, et al. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study [J]. *Arch Ophthalmol*, 2003, 121(2): 245–251.
- [34] Sacks F M, Hermans M P, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries [J]. *Circulation*, 2014, 129(9): 999–1008.
- [35] Elafros M A, Andersen H, Bennett D L, et al. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments [J]. *Lancet Neurol*, 2022, 21(10): 922–936.
- [36] Eid S A, Rumora A E, Beirowski B, et al. New perspectives in diabetic neuropathy [J]. *Neuron*, 2023, 111(17): 2623–2641.
- [37] Smith A G, Singleton J R. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy [J]. *J Diabetes Complications*, 2013, 27(5): 436–442.
- [38] van Acker K, Bouhassira D, De Bacquer D, et al. Prevalence and impact on quality of life of peripheral neuropathy

- with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics [J]. *Diabetes Metab*, 2009, 35(3):206-213.
- [39] Jende J M E, Groener J B, Rother C, et al. Association of serum cholesterol levels with peripheral nerve damage in patients with type 2 diabetes [J]. *JAMA Netw Open*, 2019, 2(5):e194798.
- [40] Kang E Y, Chen T H, Garg S J, et al. Association of statin therapy with prevention of vision-threatening diabetic retinopathy [J]. *JAMA Ophthalmol*, 2019, 137(4):363-371.
- [41] Chang K C, Pai Y W, Lin C H, et al. The association between hyperlipidemia, lipid-lowering drugs and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus [J]. *PLoS One*, 2023, 18(6):e0287373.
- [42] Damaskos C, Garmpis N, Kollia P, et al. Assessing cardiovascular risk in patients with diabetes: an update [J]. *Curr Cardiol Rev*, 2020, 16(4):266-274.
- [43] Mortensen M B, Dzaye O, Bøtker H E, et al. Low-density lipoprotein cholesterol is predominantly associated with atherosclerotic cardiovascular disease events in patients with evidence of coronary atherosclerosis: the western Denmark heart registry [J]. *Circulation*, 2023, 147(14):1053-1063.
- [44] Li Z, Xu H. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and cardiovascular disease mortality in patients with type 2 diabetes mellitus and diabetic kidney disease [J]. *Front Endocrinol*, 2025, 16:1509752.
- [45] Ding W, Li T, Fang C, et al. Association of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio with coronary heart disease: establishment and validation of a clinical nomogram model [J]. *Medicine*, 2025, 104(11):e41896.
- [46] Li T, Yuan D, Wang P, et al. Associations of lipid measures with total occlusion in patients with established coronary artery disease: a cross-sectional study [J]. *Lipids Health Dis*, 2022, 21(1):118.
- [47] Toprak K, Karataş M, Kaplangoray M, et al. Comparison of the effect of non-HDL-C/HDL-C ratio on coronary slow flow with other non-traditional lipid markers [J]. *Acta Cardiol Sin*, 2024, 40(4):388-401.
- [48] Liu H, Deng X, Peng Y, et al. Meta-analysis of serum non-high-density lipoprotein cholesterol and risk of coronary heart disease in the general population [J]. *Clin Chim Acta*, 2017, 471:23-28.
- [49] Natarajan P, Ray K K, Cannon C P. High-density lipoprotein and coronary heart disease current and future therapies [J]. *J Am Coll Cardiol*, 2010, 55(13):1283-1299.
- [50] Zhao M, Dong Y, Chen L, et al. Influencing factors of stroke in patients with type 2 diabetes: a systematic review and meta-analysis [J]. *PLoS One*, 2024, 19(6):e0305954.
- [51] Wang A, Li Y, Zhou L, et al. Non-HDL-C/HDL-C ratio is associated with carotid plaque stability in general population: a cross-sectional study [J]. *Front Neurol*, 2022, 13:875134.
- [52] Wang L, Han Y, Cao C, et al. The non-linear link between non-high-density lipoprotein to high-density lipoprotein ratio and the risk of stroke in middle-aged and older adults in Chinese: a prospective cohort study from the China health and retirement longitudinal study [J]. *Front Endocrinol*, 2023, 14:1303336.
- [53] Liu Z, Lin X, Zeng L, et al. Elevated non-HDL-C/HDL-C ratio increases the 1-year risk of recurrent stroke in older patients with non-disabling ischemic cerebrovascular events: results from the Xi'an Stroke Registry Study of China [J]. *BMC Geriatr*, 2023, 23(1):410.
- [54] Ma H X, Chen H Q, Wang P C. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and stroke among adults in the USA: a cross-sectional NHANES study [J]. *Biomed Environ Sci*, 2025, 38(1):37-46.
- [55] Fukase T, Dohi T, Kato Y, et al. High apolipoprotein E levels predict adverse limb events in patients with peripheral artery disease due to peripheral artery disease undergoing endovascular treatment and on-statin treatment [J]. *Int Heart J*, 2021, 62(4):872-878.
- [56] Ding C, Chen Y, Shi Y, et al. Association between nontraditional lipid profiles and peripheral arterial disease in Chinese adults with hypertension [J]. *Lipids Health Dis*, 2020, 19(1):231.
- (收稿:2025-09-11)(修回:2026-02-08)
(责任编辑:李萍)