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2型糖尿病患者致动脉粥样硬化性脂蛋白亚组分研究进展

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摘　要

2型糖尿病(Type 2 Diabetes Mellitus, T2DM)患者动脉粥样硬化性心血管疾病(Atherosclerotic Cardiovascular Disease, ASCVD)风险较非糖尿病人群提升2~4倍，其中血脂异常是其中关键的驱动因素之一。低密度脂蛋白胆固醇(Low-density lipoprotein cholesterol, LDL-C)虽为ASCVD风险评估的核心，但大量研究发现，部分T2DM患者即使LDL-C水平正常，仍存在较高的ASCVD残留风险。随着对脂蛋白研究的深入，小而密低密度脂蛋白胆固醇(small dense low density lipoprotein cholesterol, sdLDL-C)、脂蛋白残粒(remnant like particles, RLP)、高密度脂蛋白(high density lipoprotein, HDL)功能、脂蛋白(a) [lipoproteina, Lp(a)]等新型脂类标记物显示出独立于传统指标的动脉粥样硬化预测价值。本文主要就T2DM患者的致动脉粥样硬化性脂蛋白亚组分的研究进展作一综述。

关键词

2型糖尿病，动脉粥样硬化性心血管疾病，脂蛋白亚组分

Research Progress of Atherosclerotic Lipoprotein Subfractions in Patients with Type 2 Diabetes Mellitus

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Abstract

The risk of atherosclerotic cardiovascular disease (ASCVD) in patients with type 2 diabetes mellitus

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(T2DM) is 2~4 times higher than that in non-diabetic population, and dyslipidemia is one of the key driving factors. Although low-density lipoprotein cholesterol (LDL-C) is the core of ASCVD risk assessment, a large number of studies have found that some T2DM patients still have a high risk of ASCVD residual even if the LDL-C level is normal. With the deepening of the study of lipoprotein. New lipid markers such as small dense low density lipoprotein cholesterol (sdLDL-C), remnant like particles (RLP), high density lipoprotein (HDL) function, and lipoprotein(a) [lipoprotein a, Lp(a)] have shown predictive value for atherosclerosis independent of traditional indicators. This article mainly reviews the research progress of atherosclerotic lipoprotein subfractions in T2DM patients.

Keywords

Type 2 Diabetes Mellitus, Atherosclerotic Cardiovascular Disease, Lipoprotein Subfractions

1. 引言

ASCVD 是糖尿病最常见的并发症和死亡原因。脂代谢异常会增加 T2DM 患者发生 ASCVD 的风险，使临床预后不佳。随着研究者对脂蛋白亚组分研究的深入，脂蛋白亚组分在心血管残余风险中的重要性日益受到关注。《VAP 技术检测血脂与脂蛋白亚组分及其临床应用中国专家共识(2025 版)》的发布，意味着我国血脂亚组分检测已进入标准化阶段，为新型脂类标记物在 T2DM 人群中的临床应用提供了技术支撑，促进了脂质亚组分的精准迭代并有望进一步改善 ASCVD 患者的临床预后。本文就近年来有关 T2DM 患者的致动脉粥样硬化性血脂亚组分的研究进展进行综述。

2. 糖尿病合并血脂异常临床现状

糖尿病是一种严重危害人类健康的慢性代谢性疾病，2022 年至 2020 年期间，全球糖尿病患者的人数预计在 5.89 亿至 8.28 亿左右，其中 T2DM 占比在 90%至 95%之间[1] [2]。目前我国已成为世界上 T2DM 患病人数最多的国家，约占全球糖尿病总人数的 30%左右[3]。ASCVD 是糖尿病最常见的并发症和死亡原因，T2DM 人群发生 ASCVD 的风险是非糖尿病人群的 2~4 倍[4]。

T2DM 患者发生 ASCVD 的病理生理机制是多因素的，其中包括了肥胖、高血糖、胰岛素抵抗、血压升高、慢性低度炎症以及糖尿病性血脂异常等在内[5]。中国心血管代谢病系列登记(CCMR)-3B 研究提示 T2DM 患者中合并血脂异常的约占 42%左右。糖尿病患者的胰岛素抵抗状态使脂肪组织抗脂解效应减弱，从而引发典型的糖尿病血脂异常。脂代谢异常会导致动脉内脂质沉积与失调，推动动脉粥样硬化的发展并增加了大血管和微血管并发症风险，使 ASCVD 发病率升高[6] [7]。

我国对糖尿病患者血脂异常的管理存在明显不足[6]。根据(CCMR)-3B 研究，T2DM 患者接受调脂治疗的比例仅有 55%，而总胆固醇(Total cholesterol, TC) < 4.5 mmol/L、甘油三酯(Triglyceride, TG) < 1.5 mmol/L、LDL-C < 2.6 mmol/L 和高密度脂蛋白胆固醇 > 1.04 mmol/L 同时达标的患者比例仅有 12%。大量临床研究指出，即使 TC、LDL-C 达标，部分 T2DM 患者仍有较高的心血管事件发生风险，因此 LDL-C 虽然是重要指标，但不应作为唯一的评估依据[8]-[10]。近年来，随着对脂蛋白研究的不断深入让 sdLDL-C、RLP、HDL 功能、Lp(a)等新型脂类标记物与 T2DM 及 ASCVD 的相关性获得了更多的关注，为糖尿病患者血脂管理的精准化发展提供了新的方向。

胰岛素抵抗作为T2DM的核心病理生理机制，是驱动上述脂蛋白谱系发生量与质异常的共同上游因素。在胰岛素抵抗状态下，脂肪组织脂解增强、LPL活性受抑及CETP介导的脂质交换加剧，共同塑造了T2DM患者特征性的致动脉粥样硬化性血脂谱——包括TRL及其残粒滞留、sdLDL生成增多、HDL功能受损等。下文将详述各脂蛋白亚组分在此背景下的具体变化及其临床意义。

3. 血脂与脂蛋白亚组分

血清中的TG、胆固醇、磷脂和游离脂肪酸等总称为血脂。胆固醇和TG极少游离存在，需与蛋白质、磷脂等结合形成脂蛋白，才能溶于血液并被运输至外周组织代谢。不同密度脂蛋白携带的TG和胆固醇含量不同，所含载脂蛋白的种类和数量也存在差异[11]。按密度大小，血浆脂蛋白可被分为乳糜微粒(chylomicrons, CM)、极低密度脂蛋白(very low density lipoprotein, VLDL)、中间密度脂蛋白(intermediate density lipoprotein, IDL)、低密度脂蛋白(low density lipoprotein, LDL)、Lp(a)、HDL。其中，CM、VLDL、IDL统称为富含甘油三酯脂蛋白(triglyceride rich lipoproteins, TRL) [12]。CM残粒和VLDL残粒是TRL的水解产物，又称RLP [12]。

3.1. 富含甘油三脂脂蛋白及其残粒

3.1.1. 乳糜微粒

CM是血液中颗粒最大且密度最小的脂蛋白，它的主要成分为TG。CM在十二指肠和空肠黏膜细胞内合成，分泌入肠淋巴液，经胸导管进入血液循环[11]。CM浓度升高所致的餐后高脂血症可能是冠心病发生的危险因素。巨噬细胞表面受体可以识别并摄取CM残粒，这可能与动脉粥样硬化有关。

3.1.2. 极低密度脂蛋白及其残粒

VLDL由肝细胞合成并分泌入血，富含TG和载脂蛋白B100，主要功能是将内源性脂肪酸输送至外周组织供能。VLDL分为VLDL1、VLDL2、VLDL3三个亚组分，其中VLDL3又细分为VLDL3a、VLDL3b等亚型。在正常生理条件下，胰岛素能够有效抑制TG降解从而减少游离脂肪酸的释放，然而在T2DM合并胰岛素抵抗的人群中，机体对胰岛素的敏感性明显下降，这种抑制作用减弱导致了TG被加速分解并且更多的游离脂肪酸被释放。游离脂肪酸作为合成VLDL的关键原料，其浓度的升高会直接促进肝细胞合成VLDL [13]。同时，胰岛素对VLDL颗粒合成与分泌的调控能力减弱，使得大量富含TG的VLDL释放进入血液，最终导致T2DM人群出现高TG血症。在血液循环的VLDL主要依赖脂蛋白脂肪酶(Lipoprotein Lipase, LPL)的作用水解。LPL锚定在毛细血管的内皮表面，经载脂蛋白C-II等辅因子激活后水解VLDL中所含的TG，释放出游离脂肪酸随后会被肌肉和脂肪组织摄取利用，使VLDL颗粒逐渐脱脂、体积缩小，形成VLDL残粒[14]。随着LPL持续作用，VLDL进一步失去TG和部分表面成分(如磷脂、载脂蛋白C)，同时获得载脂蛋白E，转变为IDL [12]。

3.1.3. 中间密度脂蛋白

IDL分为IDL1、IDL2两个亚组，约50%被肝脏通过LDL受体或LDL受体相关蛋白快速摄取清除，剩余部分继续被肝脂肪酶(Hepatic Lipase, HL)水解为TG和磷脂，经过这一系列反应后最后转化为LDL [15]。胰岛素在T2DM患者的脂肪代谢过程中发挥着关键调节作用。胰岛素能够通过抑制脂肪组织中激素敏感性脂肪酶的活性来减少TG分解，从而促进脂肪储存；同时，胰岛素还会促进LPL活性提升并提高其基因表达，加快TRL的分解代谢，使得血浆里的TG水平能够有效降低。胰岛素抵抗是T2DM患者抑制LPL活性的核心机制[16]。LPL活性受抑使血浆TG及TRL水平显著升高，TRL不能被LPL充分水解，从而产生大量RLP。这些RLP颗粒虽体积较小，但富含胆固醇和载脂蛋白B，可直接沉积于动脉壁

并加剧心血管风险，其致动脉粥样硬化性被认为强于 LDL [17]。另有研究表明，餐后和空腹的 RLP-C 及 VLDL 亚组分变化可揭示其与冠心病相关的脂质代谢机制[18]。张晶梅等[19]发现，RLP-C 和 LDL P 可发现更多的常规血脂 TG 和 LDL C 检测“正常”的 ASCVD 高危人群。一项前瞻性队列研究显示，在 T2DM 患者群体里即使已经校正其他脂蛋白及降脂药物使用情况，RLP-C 水平的升高仍会显著增加他们发生脑卒中和心肌梗死的风险[20]。目前美国食品药品监督管理局已将 RLP-C 纳入了 ASCVD 危险性评估里，日本动脉粥样硬化学会也已将 RLP-C 当作一个危险因素纳入了常规的血脂筛查项目，并把它写入了 ASCVD 的预防指南当中[21]。针对 TRL 及其残粒升高的治疗，饮食调整被视为管理高甘油三酯血症的一线干预措施。研究显示，代谢饮食相较于低脂饮食，对特定基因型(如 rs7903146 TT 携带者)患者的 TRL 改善更显著[22]。此外，多种靶向 TRL 代谢通路的新型疗法正处于临床前及临床研究阶段，在降低高甘油三酯血症及 TRL 水平方面展现出有效性[23]-[25]。明确 TRL-C 及 RLP-C 的干预价值，有助于识别那些 LDL-C 达标但 TRL-C 及 RLP-C 仍高的高危 T2DM 患者，从而指导临床用药决策。

3.2. 低密度脂蛋白

LDL 分为五个亚组：LDL1、LDL2、LDL3、LDL4 和 sdLDL。LDL 颗粒在血浆中进一步修饰形成 sdLDL，该过程包括：胆固醇酯转移蛋白(Cholesterol Ester Transfer Protein, CETP)介导的 TG 富集；HL 水解富集 TG 的 LDL，使其体积减小，密度增加；随后的氧化、糖基化等翻译后修饰增强了其与动脉壁蛋白聚糖的结合能力及炎症潜能[26]。T2DM 患者普遍存在 TG 水平升高，促进 CETP 介导的 LDL 与 TRL 之间的脂质交换，使 LDL 颗粒中的胆固醇酯被 TG 取代，生成富含 TG 的 LDL 颗粒[27]；随后，HL 水解这些富含 TG 的 LDL，形成体积更小、密度更高的 sdLDL 颗粒。此外，T2DM 患者 VLDL 和 IDL 颗粒数量增加，而 LDL 和 HDL 颗粒减少，提示 IDL 向 LDL 的转化过程受阻，进一步促进了 sdLDL 的积累。

多项研究发现，在 LDL-C 水平处于正常范围的糖尿病患者群体中，低密度脂蛋白颗粒(low-densitylipoproteinparticle, LDL-P)往往会出现显著升高的现象[28]。这种颗粒浓度及其不同亚型的分布情况，能够更细致地反映出低密度脂蛋白内部结构的复杂差异。LDL-P 在预测心血管事件方面较 LDL-C 有更高的灵敏度和准确度[29]。Bourgonje AR 等发现[30]，T2DM 患者体内 LDL 总颗粒浓度的升高与微血管并发症风险的增加呈正相关。另外，Otvos 等人[31]的研究也证实了血浆中 LDL-P 水平对冠心病事件再次发生的预测价值。LDL-P 在 2015 年已被美国国家脂质协会纳入评估 ASCVD 风险的潜在指标[32]。2020 年 LDL-P 也被美国临床内分泌协会和美国内分泌学会发布的《糖尿病综合管理指南》作为糖尿病患者血脂管理中的重要干预靶点[33]。不过，当前针对 LDL-P 与糖尿病人群 ASCVD 风险之间关联的大规模、前瞻性队列研究仍然比较有限，因此 LDL-P 的临床应用价值仍需进一步验证。

sdLDL 颗粒较 LDL 更易发生氧化、糖基化修饰，更易沉积于血管壁，已被证实比 LDL 更具致动脉粥样硬化作用[34] [35]，且在糖尿病患者中较 LDL 升高更早[36]。在一项前瞻性研究中，对一组基线无 ASCVD 但在临床试验过程中出现 ASCVD 的患者进行测定 LDL-C、sdLDL、TG、富含甘油三酯的脂蛋白胆固醇以及脂蛋白残粒胆固醇，结果发现 sdLDL 是最易导致动脉粥样硬化的脂蛋白[37]。研究表明，sdLDL-C 水平能更精准地预测 ASCVD 风险，已被明确为独立于其他因素的心血管风险预测因子[34]。针对中国老年 T2DM 患者的研究也证实了，当体内 sdLDL 水平升高时会显著提升心脑血管事件风险[38]。sdLDL 已被美国胆固醇教育计划委员会正式纳入新型心血管病危险因素的范畴[39]-[41]。依据国外专家共识[17]，RLP、LDL-P 及小而密低密度脂蛋白颗粒浓度(sdLDL-P)等血脂亚组分指标对深入探索 ASCVD 的病因研究和预警诊断具有重要意义。LDL 颗粒性质改变和 sdLDL 水平升高是糖尿病患者血脂异常的共同特征，因此把 sdLDL-C 的水平控制在合理范围内，对糖尿病患者的心血管风险管理显得尤为关键。有研究显示，联合新型选择性过氧化物酶体增殖物激活受体 α 调节剂 pemafibrate 较加倍他汀剂量可更显著、

安全地降低致动脉粥样硬化性更强的 sdLDL-C [42]。前蛋白转化酶枯草溶菌素 9 抑制剂(PCSK9i)在显著降低低密度脂蛋白胆固醇(LDL-C)的同时，亦可有效降低小而密低密度脂蛋白胆固醇(sdLDL-C)水平及总 LDL 颗粒浓度(LDL-P) [43]。对于 LDL-C 已达标的 T2DM 患者，若 sdLDL-C 仍高，提示需联用非他汀类药物以优化 LDL 亚组分控制。

3.3. 高密度脂蛋白

HDL 的代谢路径与 VLDL、IDL、LDL 等相对独立，但存在交叉调控。HDL 由肝脏和小肠分泌，主要含载脂蛋白 A-Ⅰ和磷脂。HDL 分为 HLD2、HDL3 两个亚组分，按密度从小到大进一步分为 HDL2A、HDL2B、HDL2C、HDL3A、HDL3B、HDL3C 及 HDL3D。HDL 的核心功能是胆固醇逆向转运(RCT)：从巨噬细胞等外周组织摄取多余胆固醇，运输回肝脏代谢或排泄[44]。

T2DM 患者体内通常能观察到 HDL 水平的降低和 HDL 的功能障碍[45] [46]。血浆里的 TG 水平升高以后会促进 CETP 介导的 TRL 与 HDL 之间的脂质交换，使 TRL 中的 TG 转移到 HDL 中，而 HDL 中的胆固醇酯则被转移至 TRL 里[47]。这个交换过程让 HDL 富含 TG，而富含 TG 的 HDL 又成了 HL 的理想底物。胰岛素可提高 HL 活性[48]，HDL 在 HL 的催化下被分解为更小的颗粒并释放载脂蛋白 A-Ⅰ，这些脱离颗粒的载脂蛋白 A-Ⅰ会被肾脏清除，最终导致了 HDL-C 水平的下降[49]。英国前瞻性糖尿病研究数据显示，糖尿病患者的 TG 水平显著高于非糖尿病患者，而 HDL-C 水平却显著降低[50]。HDL 水平的降低不仅在 2 型糖尿病患者中普遍存在，还与糖尿病发病风险增加相关。遗传学证据表明，在两项大型研究中，低 HDL-C 水平可能与糖尿病风险增加存在因果关系[51] [52]。因此增加 HDL-C 浓度长期以来被认为是降低心血管风险的潜在目标。然而，多项临床试验表明，使用烟酸或 torcetrapib 等药物提高 HDL-C 水平对伴或不伴 T2DM 的个体心血管风险的有益影响有限[53]-[55]。这促使研究焦点从 HDL-C 的“量”转向其“质”即 HDL 功能。T2DM 患者体内长期存在的高血糖和炎症状态会让 HDL 经历氧化、糖化和氨甲酰化等翻译后修饰[56]-[58]，使 HDL 蛋白质组分发生结构上的变化，从而导致胆固醇逆向转运能力(cholesterol efflux capacity, CEC)下降，同时丧失了抗氧化、抗炎等血管保护功能[59] [60]。有研究指出，CEC 与 ASCVD 事件之间存在负相关关系，它对 ASCVD 风险的预测能力较 HDL-C 更强，且独立于 HDL-C [60] [61]。部分 HDL 颗粒甚至会被转变为促炎性的“功能障碍性 HDL”，反而推动了动脉粥样硬化进展[62]。目前，改善 HDL 功能仍缺乏有效的干预手段。

3.4. 脂蛋白(a)

Lp(a)由 1 分子 LDL 样颗粒和 1 分子载脂蛋白(a)组成，可分为 Lp(a)l、Lp(a)2、Lp(a)3、Lp(a)4、Lp(a)5 五个亚组。脂蛋白(a)作为一种由遗传因素主导决定的血脂成分，它的血液浓度在人的一生中基本保持稳定，儿童时期大约 5 岁就能检测到成年后的水平[63]。大量研究已经证实，高 Lp(a)水平是冠心病、冠状动脉钙化、缺血性脑卒中、外周血管病及钙化性主动脉瓣狭窄等疾病的独立危险因素之一。多项研究已证实 Lp(a)的致动脉粥样硬化作用，并认为这是心血管剩留风险的原因之一[64]-[66]。其水平不受常规降脂药物影响，主要与遗传因素相关[67] [68]。Sosnowska 等[69]发现，血清高 Lp(a)浓度与冠状动脉疾病患者的斑块加速进展相关，血清 Lp(a)浓度的测定可能更准确地评估 ASCVD 的风险。一项研究表明，Lp(a)每降低 10 mg/dL，冠心病发病风险会降低 5.8% [70]。总体而言，Lp(a)是 ASCVD 的重要独立危险因素。目前尚无专门靶向 Lp(a)且经心血管结局试验证实可降低事件风险的药物获批用于临床，以 RNA 干扰(如 Pelacarsen)与反义寡核苷酸(如 Olpasiran)为代表的新型 Lp(a)靶向疗法正处于临床研发阶段。Ⅱ期临床试验显示，在 Lp(a)超过 60 mg/dL 且合并 ASCVD 病史的患者中，使用 Pelacarsen 可使 Lp(a)水平降低高达 80% [71]。在 OCEAN(a)-Dose Phase 2 临床试验中，Olpasiran 在 Lp (a)水平超过 150 nmol/L 且有 ASCVD

病史的患者中可使 Lp(a)水平平均降低 70%至 100% [72]。

4. 总结

综上所述，目前关于 T2DM 患者血脂异常的研究已从脂质“量”的指标拓展到脂蛋白“质”的亚组分水平。除了 LDL-C、TG、HDL-C 等传统指标外，近年来作为心血管残留风险评估的 sdLDL、RLP-C、HDL 功能及 Lp(a)等新型血脂亚组分受到了广泛关注。一些横断面研究初步验证了这些指标与 T2DM 患者 ASCVD 风险的相关性，但目前仍缺乏以这些指标为干预靶点的大型随机对照试验。此外，规范检测方法的缺乏和有限的干预手段也制约了其临床转化。未来有必要在 T2DM 人群中开展大规模、规范化的前瞻性临床研究，明确脂蛋白亚组分指标能否独立指导治疗决策并改善心血管结局，真正实现从“血脂管理”到“血脂亚组分管理”的精准跨越。

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