doi: 10.3978/j.issn.1000-4432.2021.12.08
View this article at: https://dx.doi.org/10.3978/j.issn.1000-4432.2021.12.08

糖尿病性视网膜病变脂质代谢的研究进展

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[摘 要] 脂质代谢异常是糖尿病性视网膜病变可能的危险因素。糖尿病性视网膜病变被认为是致盲的主要原因。近年来研究认为总胆固醇、三酰甘油等血脂与糖尿病性视网膜病变及糖尿病黄斑水肿的进展有关，降脂药物的应用能够延缓糖尿病性视网膜病变进展。随着色谱分离和质谱分析等脂质组学分析方法的发展，除了常规的血清脂质标志物以外的各种脂质成分也被发现可能与糖尿病性视网膜病变进展有关。现总结脂质及其衍生物在糖尿病性视网膜病变发病机制中的作用，阐述糖尿病性视网膜病变脂质代谢治疗的潜在靶点和前景。

[关键词] 糖尿病性视网膜病变；脂质代谢；血脂；糖尿病

Emerging insights into lipid metabolism in diabetic retinopathy

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Abstract Abnormal lipid metabolism is a possible risk factor for diabetic retinopathy. Diabetic retinopathy is considered to be the main cause of blindness. In recent years, studies have shown that serum lipids, such as total cholesterol, triglycerides, are related to the progress of diabetic retinopathy and diabetic macular edema, and lipid-lowering drugs can delay the progress of diabetic retinopathy. With the development of lipidomics analysis methods such as chromatographic separation and mass spectrometry, lipid components other than conventional serum lipid markers have also been found to be related to the progression of diabetic retinopathy. The review summarizes the role of lipids and their derivatives in the pathogenesis of diabetic retinopathy, and highlights the potential targets and prospects of lipid metabolism treatment for diabetic retinopathy.

Keywords diabetic retinopathy; lipid metabolism; serum lipids; diabetes

收稿日期 (Date of reception)：2021–09–15
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糖尿病性视网膜病变(diabetic retinopathy，DR)是糖尿病的主要眼部并发症，是工作年龄段人口视力丧失的最主要原因之一[1]。据估计，到2030年，受DR影响的患者人数将增加到1.91亿[2]，这将给全球公共卫生和社会经济带来潜在的巨大负担。

DR在临床上可分为非增殖性糖尿病性视网膜病变(non-proliferative diabetic retinopathy，NPDR)和增殖性糖尿病性视网膜病变(proliferative diabetic retinopathy，PDR)2个阶段。它的发生机制包括晚期糖基化终产物的积累、氧化还原稳态受损、炎症因子和血管内皮生长因子(vascular endothelial growth factor，VEGF)的产生，以及神经退行性变、胶质细胞激活和肾素-血管紧张素系统的激活、内质网应激等[2-5]。高血糖和高血压被公认是DR发生和进展的危险因素。但是控制血糖和血压无法完全抑制DR和糖尿病黄斑水肿(diabetic macular edema，DME)的进展[6]，这证明DR的发病机制中仍然存在着其他需要探索的潜在危险因素。近年来多项研究[7-8]表明脂质代谢紊乱可能也是DR的发生发展的致病因素之一。在脂质中，低密度脂蛋白的升高和高密度脂蛋白的降低能够促进DR的进展[9]，而载脂蛋白AI(apolipoprotein AI，ApoAI)能够延缓DR的进展[10]。如贝特类和他汀类之类的降脂药物也被发现有益于减缓DR和DME的进展[11-13]。本文总结脂质代谢在DR中的发病机制的研究进展，探寻脂质代谢治疗的潜在靶点，展望脂质代谢的靶向调控前景，从而为DR的治疗提供新的方法与思路。

1 脂质代谢的研究现状

脂质是生物体的重要组成部分，在细胞中也发挥许多重要作用，包括细胞屏障、膜基质、信号和能量储存等[14]。根据LIPIDMAPS分类，脂质被分为八大类，包括脂肪酸、甘油脂、甘油磷脂、甾醇脂、戊烯醇脂、鞘脂、糖脂和聚酮化合物。目前已有超过40 000种脂质被记录在案[15]。由于脂质具有结构多样性、物理性质广泛以及化学异质性，其代谢反应和细胞过程的不同阶段的产物可能在不同的生物体中具有不同的功能，甚至在一个生物体的不同细胞中具有不同的功能，它们的新陈代谢通过许多途径和网络交织在一起，很难评估单个脂质类别在疾病中的作用，因此脂质代谢的研究具有挑战性[16-17]。

脂质组学利用分析化学的原理和技术对脂质进行研究，其通过量化单个脂质的类别、亚类和分子种类的变化来反映代谢的差异，为细胞新陈代谢的研究和脂质生物标志物的研发提供了强有力的技术支撑。而色谱分离和质谱分析等分析方法和计算机工作流程的发展使脂质的研究发展实现了新的跨越[18]。近年来，脂质代谢紊乱已被发现在多种疾病的发病机制中起推动作用，包括肥胖、心血管疾病、非酒精性脂肪肝和糖尿病等代谢性疾病[19]，在多种癌症中起促进肿瘤生长的作用，且在调节衰老过程中也起到重要的作用，是阿尔茨海默病和老年性白内障等年龄相关疾病的发病机制之一[20]。所以脂质代谢的靶向治疗研究受到了各个专业专家的关注，也是多种疾病的治疗新方向的热点之一。但是目前因为脂质合成、储存、利用和分解等生理机制仍然没有完全被了解，所以脂质的靶向治疗研究依然受到阻碍。

2 脂质代谢产物与糖尿病性视网膜病变

2.1 血脂

高脂血症被认为是糖尿病性视网膜病变发生发展的最强危险因素之一[9]。其相关机制可能是糖尿病患者的视网膜中异常的脂质清除导致非酶氧化和糖基化的增加[21]，激活炎症介质，导致血管高通透性和DME中血视网膜屏障的破坏。血清低密度脂蛋白(low density lipoprotein，LDL)被证明能够抑制体外内皮细胞的增殖、迁移[9]，且高浓度的低密度脂蛋白胆固醇(low density lipoprotein cholesterol，LDL-C)能够对血管内皮细胞产生细胞毒作用，增强血管床中的血管收缩，从而导致DR中非灌注区的病情进展[22]。

据报道[23-24]，1型和2型糖尿病患者的总胆固醇、三酰甘油、LDL-C水平的升高和高密度脂蛋白含量的降低与糖尿病黄斑水肿的发展呈正相关。LDL升高时，患有非显著糖尿病黄斑水肿的概率约是正常LDL水平患者的3倍；而对血清总胆固醇升高的患者，临床显著糖尿病黄斑水肿的患病率是正常水平患者的9倍[25]。从影像学证据上，研究[26-27]通过光学相干断层扫描(optical coherence tomography，OCT)发现三酰甘油的升高与中央视网膜厚度的增加呈正相关，较高的总胆固醇和LDL-C与高反射灶的数量呈正相关。且通过眼底

照相发现总胆固醇、LDL与硬渗出物的存在以及更大的硬渗出物面积呈正相关[28]。

2.2 脂蛋白和载脂蛋白

在血管疾病中，细胞的快速周转和膜的合成需要过量的脂质，脂质谱的改变和血管中脂质沉积的存在表明脂蛋白在受损血管生成的过程中具有明确作用。脂蛋白A[Lipoprotein A，Lp(A)]被认为是糖尿病微血管并发症的独立危险因素，且血清Lp(A)浓度与DR的严重程度显著相关[29]。Lp(A)与DR之间的病理机制可能包括以下3点：Lp(A)在血管壁上产生的活性氧破坏了微循环[10,29]，激活了典型的无翅型MMTV整合位点(wingless-type MMTV integration site，WNT)和激活炎症，从而导致更严重的DR[10,29-30]。

载脂蛋白是脂蛋白中的蛋白质部分，包括载脂蛋白A(apolipoprotein A，ApoA)和载脂蛋白B(apolipoprotein B，ApoB)等。研究[31]表明：ApoA和ApoB与糖尿病性视网膜病变的相关性比HDL和LDL更强。ApoAI是高密度脂蛋白的主要结构蛋白，在胆固醇从外周组织向肝脏的运输中起关键作用[10]。ApoA具有强大的抗血管生成活性，能直接抑制常规的血管生成信号通路，还可通过诱导内皮细胞凋亡、抑制内皮祖细胞的正常功能或通过载脂蛋白A氧化磷脂(apolipoprotein A-oxidized phospholipids，ApoA-oxPLs)联合上调内皮细胞中的核因子，从而间接发挥抗血管生成作用。相反地，ApoB是极低密度脂蛋白和LDL的主要结构蛋白，具有将胆固醇从肝和肠道转移到外周组织的作用。较高水平的ApoB可能通过释放脂蛋白相关毒素对视网膜血管细胞造成更大的损害，从而导致PDR[32]。队列研究[10]也证明ApoA与DR呈负相关，而Lp(A)和ApoB与糖尿病性视网膜病变呈正相关。

载脂蛋白和脂蛋白可能能够用于作为早期检测DR和PDR的血清标志物[33]。最近的研究[10]对此提出了新的临界值，即ApoB/ApoAI低于0.58 g/L和ApoB低于77.5 g/L需要得到关注。相比于标准临界值的ApoB/ApoAI低于0.8 g/L和ApoB低于90 g/L，新的临界值敏感性更高。

鉴于载脂蛋白的上述机制以及抗血管生成治疗是眼科目前热门的治疗研究方向，已经有研究[34]尝试用毒性较低、抗血管生成的载脂蛋白(A)肽来抑制眼部新生血管。ApoA是由重复的Kringle结构域、单个Kringle-5样结构域(Kringle 5-like domain，KV)和1个非活性蛋白酶样结构域组成。源于人ApoA KV的11个氨基酸残基组成的多肽——KV11在体外小鼠模型中被证明是一种有效的视网膜病理性血管生成抑制剂[35]。ApoA KV衍生的另一种六氨基酸肽AU6在体内细胞和体外绒毛尿囊膜模型和角膜新生血管模型中减少了病理性新生血管[34]。这些肽具有视网膜穿透性，且对细胞或视网膜毒性很小，可能有希望成为抗VEGF治疗的替代疗法。

2.3 磷脂

甘油磷脂和鞘磷脂具有强大的促血管生成或抗血管生成作用[36-37]，被认为可能与DR的发生有关。其衍生物如溶血磷脂酰胆碱(lysophosphatidylcholine，LPC)、磷脂酰胆碱、磷脂酰乙醇胺和二酰甘油与糖尿病患病率增加有关，而鞘磷脂使糖尿病的患病风险降低[38]。

甘油磷脂在磷脂酶A(phospholipase A，PLA)作用下合成的溶血磷脂酸(lysophosphatidic acid，LPA)，在PDR患者的玻璃体内浓度显著升高[39]。通过诱导多种细胞因子的表达，促进VEGF、白细胞介素-8(interleukin-8，IL-8)、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1，MCP-1)和基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)的产生[40]。而LPC通过VEGF-R2影响视网膜血管内皮细胞，诱导血管通透性的增加[41]。

鞘磷脂是真核细胞膜脂双层的主要成分之一，是调节炎症、细胞活性和迁移的信号分子。有研究[42]指出：鞘磷脂在糖尿病患者和对照组的玻璃体液中差异性存在，它的变化在DR中具有特征性。它的衍生物1-磷酸鞘氨醇(sphingosine-1-phosphate，S1P)能够阻止缺氧诱导因子的降解，并且参与血管形成、分化和内皮细胞迁移，与$S1P_2$受体结合可促进VEGF和基质金属蛋白酶-2(matrix metalloproteinase-2，MMP-2)[43]的生成。

2.4 脂肪酸

脂肪酸是细胞脂类的组成部分。有研究[38]发现：碳原子数和双键数量与糖尿病风险有关，长链、不饱和脂肪酸能够降低DR的患病率，而短链、饱和脂肪酸则升高DR的患病风险。长链多不饱和脂肪酸(polyunsaturated fatty acids，PUFAs)是视网膜中富集的必需脂肪酸，对维持视网膜生理

功能和发育至关重要[5,44]。

脂肪酸中的多不饱和脂肪酸是PDR发病机制中的重要介质，即花生四烯酸(arachidonic acid，AA)及其衍生物[45]。花生四烯酸及衍生物被认为在DR炎症和血管生成中起到重要作用[46]。AA会通过环氧合酶(cyclooxygenase，COX)、脂肪氧化酶(lipoxygenase，LOX)和细胞色素P450(cytochrome P450 enzymes，CyP450)单加氧酶途径迅速代谢[47]。AA级联产生前列腺素(prostaglandin)、血栓素A2(thromboxane A2，TXA2)和一系列羟基二十碳四烯酸(hydroxy eicosatetraenoic acid，HETE)、白三烯和环氧二十碳三烯酸(epoxyeicosatrienoic acids，EETs)等炎症介质[18,48]。研究[45,48]显示：PDR玻璃体液中花生四烯酸的衍生物5-HETE、12-HETE、20-HETE水平显著高于无DR的对照组。

ω3-多不饱和脂肪酸(omega-3 polyunsaturated fatty acids，ω3-PUFA)可能存在潜在的治疗作用[49]。ω3-PUFA可抑制视网膜中肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)、白细胞介素-1β(interleukin-1β，IL-1β)、VEGF和细胞黏附分子的表达，以应对缺氧或血管生成因子，被认为能够保护视网膜血管疾病。所以膳食补充ω-3PUFA可能能够作为潜在治疗方法以阻止DR进展[50]。

3 降脂药物与 DR

大多数降血脂药物似乎都能改善血糖稳态。自从威斯康星州的糖尿病性视网膜病变流行病学研究[51]发现：血清胆固醇和糖尿病性视网膜病变的视网膜渗出之间存在相关性以来，降脂药在调节血脂水平和糖尿病性视网膜病变进展中的作用受到广泛关注。并且大部分的研究都认为降脂药物的应用对DR有益。

非诺贝特(Fenofibrate)被研究[12-13]证实能够减少糖尿病性视网膜病变的激光治疗需求，并且能够减缓轻到中度非增殖性糖尿病性视网膜病变的进展。另有研究指出[52]：非诺贝特与VEGF抑制剂联合使用治疗DME比单独使用VEGF抑制剂有更大的改善。一项32 253例患者参与的大型研究[53]证明了长期服用非诺贝特可以降低2型糖尿病患者视网膜病变的发生率，并且这种效果是剂量依赖性的。其中的机制可能在于非诺贝特增加DR的保护因素载脂蛋白A-I[54]，但是它延缓DR进展的确切机制尚不完全清楚[55]。此外非诺贝特是过氧化物酶体增殖物激活受体α(peroxisome proliferators-activated receptorα，PPARα)的激动剂，而PPARα是调节新陈代谢、炎症和氧化应激的关键转录因子，所以可能非诺贝特可能还能以不依赖于脂质的方式调节DR[53]。在一些基础研究[56]中，非诺贝特被证明增加了血清成纤维细胞生长因子-21(fibroblast growth factor-21，FGF-21)，局部诱导视网膜和肾脏中氧化应激反应基因，并且可能通过抑制腺苷酸活化蛋白激酶 (AMP-activated protein kinase，AMPK)的能力阻止IL-1β对视网膜色素上皮的破坏[53]。据报道[57]，新的PPARα激动剂药物培马贝特(Pemafibrate)比非诺贝特具有更强的降低三酰甘油浓度和升高高密度脂蛋白胆固醇(high density lipoprotein cholesterol，HDL-C)浓度的能力，同样通过增加血浆和肝中FGF-21的水平来减少视网膜中的病理性新生血管。

与贝特类不同，使用他汀类药物作为预防DR的策略仍然存在争议，但是近年来的文献都支持他汀类药物对DR的有效性。Chung等[27]的研究证明：使用他汀类药物进行降脂治疗可预防2型糖尿病患者发生DME和DR的概率。队列研究[58]发现：他汀类药物依从性越高，糖尿病性视网膜病变的累积风险越低。他汀类药物治疗还可以延缓DR进展，并减少以后的视网膜激光治疗、玻璃体腔注射和玻璃体切除术的次数。且在重度DR病例中，强化使用他汀类药物治疗比标准治疗更能改善DR的预后[22]。一项荟萃分析[59]对2019年以前所有他汀类药物和DR的关系进行总结，更加证明了他汀类药物与DR及其亚型的风险降低相关。他汀类药物还能降低高胆固醇血症合并糖尿病性视网膜病变患者心血管事件的风险[60-61]。其机制可能是他汀能够改善内皮功能、抑制炎症[62]和纤维化增殖[4]，并且通过氧化应激减少VEGF的表达，减少脂质渗漏，改善眼睛中的脂质清除[22]。此外，贝特类和他汀类联合使用，和与安慰剂联合使用相比更能减缓DR的发生与进展[11]。

4 结语

众多研究证实了脂质是糖尿病性视网膜病变的危险因素之一，降脂药物也被证明可以延缓糖尿病性视网膜病变的进展。随着脂质组学与质谱分析的进展，除了血脂以外的脂质谱在糖尿病性视网膜病变中的发生机制中的影响应该得到重

视。糖尿病性视网膜病变中脂质代谢的变化的研究为其治疗拓展了可能的新的途径和思路。

开放获取声明

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本文引用：邵哲怡，李建桥. 糖尿病性视网膜病变脂质代谢的研究进展[J]. 眼科学报, 2022, 37(2): 93-99. doi: 10.3978/j.issn.1000-4432.2021.12.08

Cite this article as: SHAO Zheyi, LI Jianqiao. Emerging insights into lipid metabolism in diabetic retinopathy[J]. Yan Ke Xue Bao, 2022, 37(2): 93-99. doi: 10.3978/j.issn.1000-4432.2021.12.08