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脂蛋白在2型糖尿病与冠心病患者动脉粥样硬化中的作用机制

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摘　要

2型糖尿病的发病率在世界范围内呈上升趋势。据估计，到2045年，全球糖尿病患者将达到7.832亿。虽然近年来2型糖尿病控制率得到很大程度的提高，但心血管疾病仍然是其死亡的一个重要原因，特别是冠状动脉粥样硬化性心脏病(简称冠心病)。冠心病是以动脉粥样硬化为病变基础，而糖尿病对动脉粥样硬化病变的发生和进展具有叠加作用，超过血脂异常本身，表明糖尿病诱导的脂代谢紊乱可能加速糖尿病相关的动脉粥样硬化。因此，本文就脂蛋白在2型糖尿病与冠心病患者动脉粥样硬化中的作用机制综述如下。

关键词

脂蛋白，2型糖尿病，动脉粥样硬化

The Mechanism of Lipoprotein in Atherosclerosis in Patients with Type 2 Diabetes and Coronary Heart Disease

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Abstract

The incidence rate of type 2 diabetes is on the rise worldwide. It is estimated that by 2045, the number of diabetes patients worldwide will reach 783.2 million. Although the control rate of type 2 diabetes has been greatly improved in recent years, cardiovascular disease is still an important

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cause of death, especially coronary atherosclerotic heart disease (CHD). Coronary heart disease is based on atherosclerosis, and diabetes has a superimposed effect on the occurrence and progress of atherosclerosis, exceeding the dyslipidemia itself , indicating that diabetes induced lipid metabolism disorder may accelerate diabetes related atherosclerosis. Therefore, this article reviews the mechanism of lipoproteins in atherosclerosis in patients with type 2 diabetes and coronary heart disease.

Keywords

Lipoprotein, Type 2 Diabetes, Atherosclerosis

1. 背景

2 型糖尿病患者的血脂异常主要表现为高密度脂蛋白胆固醇(HDL-C)水平降低、低密度脂蛋白胆固醇(LDL-C)水平升高、三酰甘油(TG)水平升高。研究已证实血清 HDL 水平与冠心病风险之间呈负相关[1] [2] [3] [4] [5]。其机制为 HDL 具有抗动脉粥样硬化作用，主要通过促进胆固醇从巨噬细胞流出、稳定动脉粥样硬化斑块、抑制 LDL 的氧化修饰、减少血管炎症、增强内皮修复及免疫调节控制[1] [2] [3] [4] [5]。最近研究指出载脂蛋白在糖脂的代谢中发挥重要作用。其中载脂蛋白 A1 (ApoA1)和载脂蛋白 B (ApoB)是两种主要研究的载脂蛋白。ApoA1 是与 HDL-C 相关的主要脂蛋白，可将胆固醇从机体组织运输到肝脏进行分解代谢，从而防止胆固醇在血管壁中的沉积。因此，ApoAl 具有抑制动脉粥样硬化斑块形成的作用。ApoB 是 LDL-C 的主要载脂蛋白，而 LDL-C 是动脉粥样硬化斑块的重要组成部分，是动脉粥样硬化的主要危险因素[6] [7]。因此，ApoB/ApoA-I 比值反映了致动脉粥样硬化和抗动脉粥样硬化的平衡，其水平越高，胆固醇沉积的趋势越高，患冠心病的风险越高。

2. 载脂蛋白与 T2DM 的关系

2.1. 临床特点

目前关于 ApoA1、ApoB 及其比值与 T2DM 风险之间的关联尚不明确。多数研究表明 T2DM 患病率与 ApoA1 水平[8] [9] [10] [11]呈负相关，ApoB 以及 ApoB/A1 比值之间呈正相关[8] [11] [12] [13]。相反的是，Onat 等人在土耳其人群中发现血清 ApoA1 与糖尿病呈正相关[14]。而 Mellor 等人在 759 名女性希腊人群的前瞻性队列中发现血清 ApoA1 与糖尿病风险无关[15]。同时，对 9026 名美国人群进行的社区动脉粥样硬化风险研究中报道 ApoB 和 ApoB/A1 比值对糖尿病的无影响[16]。在 Aryan 等人研究中进一步发现 ApoB/A1 比值与 2 型糖尿病的微血管并发症之间无相关性[17]。Fatemeh Moosaie 等人在对 1057 例 T2DM 患者连续 5 年的随访后进行队列研究，结果显示 ApoB 及其比值与糖尿病并发症之间的相关性无统计学意义[18]。因此，ApoA1、ApoB 及其比值与 T2DM 及并发症间的关联有待进一步研究。

2.2. 载脂蛋白与 T2DM 动脉粥样硬化的潜在机制

2.2.1. 作用于胆固醇流出途径

目前研究指出 ApoA1 的具有直接抗动脉粥样硬化作用[19] [20]，而 ApoB 则使致动脉粥样硬化胆固

醇沉积在内皮内导致动脉壁损伤[13]。同时，在体外和动物研究进一步表明 ApoA1 和 ApoB 的抗或促糖尿病作用[21] [22] [23] [24]。据报告，T2DM 患者的胆固醇流出能力降低，在冠心病患者中进一步降低[25] [26]。因此，血清 ApoA1、ApoB、ApoB/A1 比值与 T2DM 的关联可通过作用于 RCT 途径发挥作用。首先，ApoA1 可以增加骨骼肌和脂肪组织的胰岛素敏感，降低脂质结合能力，改变蛋白结构，减弱巨噬细胞中胆固醇流出的能力。此外，ApoA1 能够通过腺苷单磷酸活化蛋白增加对骨骼肌和心脏的葡萄糖摄取来改善葡萄糖耐量[27]。第二，ApoB 通过作为从肝脏到外周脂肪的代谢途径来抑制脂肪细胞的脂解[28]。第三，载脂蛋白代谢失调可导致胰岛素抵抗[29]。一项研究表明 ApoB/AI 比值是美国非糖尿病受试者和中国肥胖受试者胰岛素抵抗的独立预测因子，且该研究中指出 ApoB/AI 比值与胰岛素抵抗之间的正相关，可能是由于 ApoB 和胰岛素抵抗与炎症状态有关[30]。

2.2.2. 抗炎、抗氧化和内皮修复作用

冠心病的发生发展与动脉粥样硬化密切相关，动脉粥样硬化是由体内多种炎症细胞因子参与多种因素而形成的。研究发现氧化应激和炎症在 T2DM 的病理生理学中发挥着重要作用，体内持续的慢性高血糖损害血管壁和内皮细胞，和各种炎症细胞因子的作用导致动脉粥样硬化斑块的形成，从而导致或加速冠心病的发生和发展和其他动脉粥样硬化病变[25] [26]。

先前研究指出 HDL 通过直接作用于血管内皮而抗血栓形成，其机制包括 HDL 诱导内皮细胞表达一氧化氮合酶(eNOS)，合成 NO 能力增加，减少内皮氧化应激，或抑制细胞组织因子、粘附分子的表达，促进内皮细胞迁移与修复。而 ApoA1 在 HDL 介导的氧化损伤保护中起着核心作用。首先，ApoA1 通过信号转到途径抑制炎症反应。其次，ApoA1 可刺激内皮产生一氧化氮和释放前列环素，表现出抗氧化和抗炎作用[1] [2] [3] [4] [5]。最近研究指出 ApoA1 通过清除促炎脂质、降低血浆丙二醛水平和肠道炎症发挥作用[31] [32]。

除此，ApoB 可以通过与烯醇化酶-1 结合，释放更多的炎症细胞因子(如肿瘤坏死因子-α、IL-1β 和 IL-6)来加重炎症反应导致动脉粥样硬化形成[33]。

2.2.3. ApoA1 结构完整性在 T2DM 动脉粥样硬化的作用

现有研究表明 ApoA1 的结构与功能完整性对其发挥抗动脉粥样硬化是必需的，而在 T2DM 患者中发现 ApoA1 的结构与功能改变，这可能诱发糖尿病患者动脉粥样硬化发生，使发生冠心病风险增加。

有证据指出糖化的 ApoA1 诱导促动脉粥样硬化效应和血管结构的改变[34]。ApoA1 可在 T2DM 患者体内糖化，这种非酶糖基化损害了其促进胆固醇外排和保护内皮细胞的能力，同时可能部分削弱其对内皮细胞的抗炎作用[35] [36] [37]。有研究进一步发现其糖基化水平与巨噬细胞中 ApoA1 抗炎能力呈负相关，机制为 ApoA1 通过 7 个赖氨酸残基的糖基化改变了自身构象，从而导致其对巨噬细胞的亲和力降低，抑制巨噬细胞中细胞因子的释放；以及 ApoA1 也可以直接结合 LPS，使糖化 ApoA1 与 LPS 的结合减少[38]。此外，在 T2DM 中 ApoA1 还可以通过氧化、硝化和氯化等作用进行修饰[39] [40]。

2.2.4. LP(a)的作用

Lp(a)是在载脂蛋白(a)和 ApoB-100 之间形成共价键时形成的[41]。目前关于 LP(a)在冠心病中的生理功能和确切机制尚不清楚，而 LP(a)在糖尿病中的作用更是知之甚少。在大多数研究中，Lp(a)浓度的增加与冠心病的高风险有关[42]。同时，在糖尿病患者中 LP(a)浓度的增加与冠心病的高风险相关[43] [44] [45]。然而，在一些研究中指出 Lp(a)与 2 型糖尿病并发症无关[18]。且尚不清楚 LP(a)浓度是否与 2 型糖尿病或胰岛素抵抗的风险有关。有人认为高胰岛素血症降低 Lp(a)浓度[46] [47]。其中一些研究发现 2 型糖尿病患者的 LP(a)浓度没有变化[48]，而另一些研究发现 LP(a)浓度升高或降低[49] [50]。在一项针对墨

西哥裔美国人的小型病例对照研究中，发现糖尿病患者的 LP(a)浓度低于对照组，结果表明 LP(a)与 2 型糖尿病风险呈反向相关，低 LP(a)浓度可能是胰岛素抵抗的标志[50]。因此 LP(a)在胰岛素抵抗和糖代谢中的作用值得进一步研究，以阐明其机制。

2.3. 其他机制

除此，冠状动脉疾病与 2 型糖尿病患者中部分蛋白质成分也参与病变形成。研究表明在糖尿病患者的动脉粥样硬化中可表达生长分化因子 15 (GDF15)、肾素、脂联素、丝氨酸蛋白酶 1 (HTRA1)、软骨中间层蛋白 1 等物质。GDF15 可反映炎症、氧化应激和缺氧，且在巨噬细胞、血管平滑肌细胞、脂肪细胞中广泛表达[51]。脂联素具有抗氧化、抗炎、抗动脉粥样硬化和胰岛素增敏作用，被认为是血管稳态、葡萄糖代谢和脂质氧化的关键保护性调节因子[52] [53]。HTRA1 在血管异常和血管生成中起作用，参与抑制转化生长因子-b 信号传导、程序性细胞死亡和调节 EGFR/Akt 通路[54] [55]。软骨中间层蛋白 1 可能在心肌细胞外基质重塑和胰岛素抵抗中发挥作用[56] [57]。因此，也有可能通过上述物质反映糖尿病患者的动脉粥样硬化程度。

3. 小结

综上所述，2 型糖尿病患者通过多个环节影响脂代谢途径，进而诱发动脉粥样硬化所致的心血管疾病。因此血脂异常的干预和治疗在提高 2 型糖尿病患者的生存率中至关重要。

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