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甘油三酯－葡萄糖(TyG)指数在动脉粥样硬化性脑梗死中的研究进展

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摘　要

胰岛素抵抗促进动脉粥样硬化斑块形成及进展，在动脉粥样硬化性脑血管疾病的发病机制中发挥重要作用。甘油三酯－葡萄糖(TyG)指数已被证实为胰岛素抵抗的可靠替代指标，与动脉粥样硬化性脑梗死的发生发展关系密切，本综述旨在探讨甘油三酯－葡萄糖指数(TyG)与动脉粥样硬化性脑梗死之间的相关性。

关键词

甘油三酯－葡萄糖指数(TyG)，胰岛素抵抗，动脉粥样硬化性脑梗死

Research Progress of Triglyceride-Glucose (TyG) Index in Atherosclerotic Cerebral Infarction

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Abstract

Insulin resistance promotes the formation and progression of atherosclerotic plaque and plays an important role in the pathogenesis of atherosclerotic cerebrovascular diseases. The triglyceride-glucose (TyG) index has been proven to be a reliable proxy for insulin resistance and is

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closely related to the occurrence and development of atherosclerotic cerebral infarction. This review aims to explore the correlation between TyG and atherosclerotic cerebral infarction.

Keywords

Triglyceride-Glucose Index (TyG), Insulin Resistance, Atherosclerotic Cerebral Infarction

1. 引言

脑梗死又称缺血性脑卒中，是指各种脑血管病变所致脑部血流供应障碍，导致局部脑组织缺血、缺氧性坏死，而迅速出现相应神经功能缺损的一类临床综合征。每年全世界范围内发生超过 1370 万例脑梗死，550 万例死亡，其中老年人群居多，同时年轻人的发病率也逐年上升[1] [2]。脑卒中也是成人首要的致残疾病，约 2/3 的幸存者遗留有不同程度的残疾。全世界每 6 个人在一生中就有 1 个人患有脑卒中；每 6 秒钟就有 1 个人死于脑卒中；每 6 分钟就有 1 个人因脑卒而永久致残。根据 2019 年发表的 Ness-China 中国脑卒中流行病学调查研究，我国卒中发病率为 345.1/10 万人年，死亡率为 159.2/10 万人年。由于脑梗死的高致死率、高致残率和高复发率等特点，会降低患者及其家庭的生活质量，在世界范围内都会造成严重社会和家庭经济负担。尽管近些年对脑梗死患者的管理策略和技术不断提升，但复发的脑梗死患者仍占所有脑梗死患者约 30%，高复发率提示对于脑梗死二级预防的效果欠佳[3] [4]，他汀类药物是临床上预防脑梗死最常使用的降脂药物，但其降低 LDL-C 水平的效果存在局限性[5]。研究人员已经认识到，识别易患脑梗死的个体并单独针对他们进行预防脑梗死管理是减少脑梗死发病率的根本；迫切需要可靠的标志物早期识别易患脑梗死的个体，并制定适当的预防策略。然而，识别易患脑梗死的个体这一过程并非容易[3]。Frans Kauwa 证明，头颅磁共振成像(MRI)中多个缺血性改变和孤立的皮质病变可能成为脑梗死的预测因子，头部计算机断层扫描(CT)或超声对脑梗死无预测价值。然而过度使用头颅 MRI 来预测脑梗死费用高，耗时长，患者配合度欠佳[6]。因此我们再次从脑梗死的危险因素入手，脑梗死的危险因素除高血压、糖尿病、高脂血症、高凝状态、吸烟史、房颤(AF)和心室早搏外还有动脉粥样硬化[7]。动脉粥样硬化(Atherosclerosis, AS)是脑梗死最常见的病因。胰岛素抵抗(insulin resistance, IR)可以加速 AS 的发展，高胰岛素－正血糖钳夹(HIEC)被认为是目前确定 IR 的金标准[8]，TyG 指数已被验证为 IR 的简单替代标记。

2. 动脉粥样硬化机制

2.1. 血脂

动脉粥样硬化的病理变化是从动脉内中膜增厚，形成粥样斑块，斑块体积逐渐增大，血管狭窄，甚至闭塞。其中易损斑块即为“犯罪斑块”，其特点为斑块表面溃疡、破裂、血栓形成，斑块内出血，薄纤维帽，大脂质核，及严重血管狭窄等[9]。AS 形成的重要危险因素之一是血脂异常。中国 ＞18 岁成人居民血脂异常的患病率为 33.97%，且以 HTG (占 12.17%)和低高密度脂蛋白胆固醇(HDL-C)血症(占 15.31%)为主要类型[10]。内皮细胞功能被受到破坏，血管通透性增加，血液循环中的脂蛋白被困于内皮受损区域，其中天然低密度脂蛋白(LDL)就会被氧化成氧化性低密度脂蛋白(ox-LDL)；巨噬细胞表面的清

道夫受体不断吞噬并吸收 ox-LDL，从而产生泡沫细胞其内富含胆固醇酯，这是早期 AS 病变的特征[11]。

2.2. 炎症

炎症也会致 AS，高血压、低密度脂蛋白沉积等危险因素刺激内皮细胞产生细胞间黏附分子-1 (ICAM-1)、血管细胞黏附分子-1 (VCAM-1)、e-选择素等炎症因子，随后召集单核细胞进入内膜转化成巨噬细胞吞噬众多变性的低密度脂蛋白后再转化成泡沫细胞，进而形成早期的脂肪条纹。与此同时巨噬细胞也会诱导产生许多炎症因子，免疫细胞也会进入斑块加速斑块的进展[12]。氧化应激在 AS 的发生发展过程中有着不容忽视的作用，LDL 积聚在血管内皮上诱导炎症反应，产生大量活性氧(ROS)，其生成的超氧化物可以降解 NO 导致血管功能紊乱，高度氧化的 LDL 能够诱导巨噬细胞凋亡，巨噬细胞清理作用也被削弱[13]。简而言之，是通过抑制 ROS 生成，增加血管保护因子 NO 的生成抑制 AS 的病理过程。考虑到动脉粥样硬化的病理变化是一个长期的进展，迫切需要可靠的标志物早期识别患者，并制定适当的预防策略[14]。

3. 胰岛素抵抗与动脉粥样硬化

有研究发现，胰岛素抵抗(insulin resistance, IR)可以加速 AS 的发展，是除年龄、吸烟和高血压等传统危险因素外的动脉粥样硬化型脑梗死一个独立危险因素[15]。IR 是由于遗传与环境等因素导致的胰岛素促使葡萄糖摄取和利用率降低，机体对胰岛素生理作用的敏感性、反应性下降的一种病理状态，从而引起糖、脂代谢异常后导致糖尿病、冠心病、肥胖症、代谢综合征等多种代谢紊乱性疾病[16] [17]。胰岛素抵抗发病机制可总结为：在脂质代谢过程中，胰岛素抵抗导致游离脂肪酸通过未经充分的脂质代谢作用而过度释放到血液循环中[18]。游离脂肪酸含量的增加使肝脏中甘油三酯的合成和血浆中的释放增多，从而导致高甘油三酯血症和随后的代谢综合征，高血糖和脂质代谢异常均可影响胰岛素活性，加剧胰岛素抵抗[19]，还会使慢性全身炎症增强，降低胰岛素敏感性，增加泡沫细胞的形成，从而加速动脉粥样硬化和晚期斑块的形成。IR 还能抑制胰岛素样生长因子-1 (IGF-1)、胰岛素样生长因子-2 (IGF-2)、环鸟苷单磷酸(cGMP)和一氧化氮(NO)的代谢，从而在血小板粘附、活化和聚集中发挥重要作用[20] [21]。在全身葡萄糖稳态方面，葡萄糖转运体的表达和活性在多个组织中受到 IR 的调节，促进葡萄糖在循环中积累，形成高血糖[22]。此外，高血糖反过来可能损害胰岛素敏感性，导致向 IR 发展的恶性循环[23]。

IR 可能通过 Baylisefect (肌生成机制)、化学、神经元和代谢机制影响脑血管储备(CVR)，导致脑灌注血流动力学受损，这可能导致急性 IS 时脑灌注血流动力学紊乱。IS 的发病机制中，这一过程将会导致血管闭塞后致脑血流灌注不足而造成神经功能缺损。IR 被认为是 2 型糖尿病发病机制的关键要素，间接提高了急性缺血性脑梗死的风险。两项大型随机试验表明，吡格列酮，一种胰岛素增敏剂，可以降低诊断为 IS 或短暂性脑缺血发作(TIA)的糖尿病患者或非糖尿病 IR 患者的心血管风险[24] [25]。此外，Lundstrom 等人发现，在以氯吡格雷作为二级预防的轻度 IS 或 TIA 患者中，高水平的 IR 是治疗时血小板反应性高的先决条件，这可能会影响抗血小板治疗的疗效，导致预后不良[26]。从这个意义上说，IR 将成为 IS 或 TIA 患者卒中二级预防的新靶点[27]。

4. 胰岛素抵抗与甘油三酯－葡萄糖(TyG)指数

高胰岛素－正血糖钳夹(HIEC)被认为是目前确定 IR 的金标准；然而，HIEC 因其复杂和耗时的缺点，在大规模的临床实践中的应用较少。甘油三酯－葡萄糖(TyG)指数，是 IR 的生化标志物，可计算为 ln(空腹甘油三酯(mg/dl) × 空腹血糖(mg/dl)/2) [28] [29]。其弥补了 HIEC 的缺点，而逐渐被广泛认识并应用。墨西哥的一项研究表明，与金标准(HIEG 钳夹试验)相比，TyG 指数检测胰岛素抵抗的高灵敏度(96.5%)

和特异性(85.0%) [30]。一项纳入 9 个观察性研究、共 37,780 例研究对象的 meta 分析也发现，较高的 TyG 指数与 AS 相关，并可作为 AS 的独立预测因子[31]。对其在糖尿病中的应有了初步研究之后，许多研究人员通过不断研究，发表相关内容承认其在其他疾病中的效用。TyG 指数与动脉粥样硬化、心血管疾病(CVD)和代谢综合征(MetS) (一种以高血压、血脂异常、肥胖和血糖代谢失调为特征的代谢异常)的严重程度相关[14] [32] [33]。值得让人关注的是，Jiao 等人曾报道，在老年急性冠脉综合征患者中，高 TyG 指数的全因死亡率是正常 TyG 指数全因死亡率的 1.64 倍，主要不良心脏事件的 1.36 倍[34]。一项针对 54,098 名参与者的前瞻性研究表明，TyG 指数较高的患者患 IS 的风险增加了 1.30 倍[35]。Huang 等人报道，高血压患者 TyG 指数的长期处于较高值将会显著增加患脑梗死的风险，尤其是缺血性脑梗死[36]。此外，TyG 指标与 IS 患者预后研究的影响也受到了广泛关注。一项对来自中国国家卒中登记处的 16,310 名患者的研究发现，高 TyG 指数会使缺血性脑梗死患者的全因死亡率风险增加 1.25 倍和脑梗死复发风险增加 1.32 倍[37]。在接受静脉溶栓治疗的脑梗死患者中，具有相同的研究结果。基于这些价值性的研究[38]，考虑到这些因素，TyG 指数反映了胰岛素抵抗水平，可以间接用于预测 IS。这对 TyG 指数可能是动脉粥样硬化性缺血性脑梗死复发和临床表现的独立相关危险因素具有较大的意义。

5. 甘油三酯－葡萄糖(TyG)指数应用前景

已有证据表明，TyG 指数与动脉粥样硬化型缺血性脑梗死的危险因素(高血压、2 型糖尿病、高脂血症等)相关，TyG 指数计算简单、检测方便，价格低廉，对于 IS 具有较高的预测价值，可在临床上广泛应用，可作为急性动脉粥样硬化性脑梗死的初筛手段或辅助诊断的条件，协助临床医师诊断疾病，早期行相应的干预措施。TyG 指数在 IS 患者中的应用价值主要为以下几个方面：1) TyG 指数可作为 IR 的更简便的替代指标；2) TyG 与 IS 高危因素(2 型糖尿病、高血脂等)相关。3) 既往研究证实，TyG 指数的基本参数(TG 和 FPG)与动脉粥样硬化性血管疾病发生、发展相关[39] [40] [41]；4) 更重要的是，TyG 指数对 IS 的预测价值可能优于单一的 TG 或 FPG。正是 TyG 指数的独特优势，使其成为这些年研究的热点。对于 TyG 指数对于动脉粥样硬化性脑梗死有待更多的临床研究去探索。

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