·专题论坛 | 综述·

干预代谢危险因素对脑血管病影响的研究进展

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【摘要】　代谢危险因素是脑血管病的重要影响因素。随着代谢性脑血管病概念的提出，如何通过干预代谢危险因素改善此类患者的预后是未来重要的研究方向。代谢危险因素可相互影响并协同作用，降压、调脂、控制血糖等对传统代谢危险因素的干预可有效降低脑血管病的发病率和复发率；抗炎、补充维生素、调节肠道菌群等对残余代谢危险因素的干预同样是影响脑血管病发病及预后的重要措施。新型代谢药物“一专多能”的特点为代谢性脑血管病的治疗和管理提供了新的思路。本综述总结干预代谢危险因素对脑血管病影响的循证医学证据，旨在为代谢性脑血管病的管理提供更多理论支持。

【关键词】　代谢性脑血管病；代谢危险因素；胰高血糖素样肽-1受体激动剂
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Research Progress on the Influence of Intervening Metabolic Risk Factors on Cerebrovascular Disease

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【Abstract】　Metabolic risk factors play a significant role in the development of cerebrovascular diseases. With the concept of cerebro-metabolic disease proposed, how to improve the prognosis of patients with cerebro-metabolic disease by intervening metabolic risk factors is an important research direction in the future. Metabolic risk factors can interact and act synergistically. Intervention measures for traditional metabolic risk factors such as blood pressure lowering, lipid regulating, and blood glucose controlling can effectively reduce the incidence and recurrence rate of cerebrovascular diseases. Intervention measures for residual metabolic risk factors such as anti-inflammation, vitamin supplements, and regulation of intestinal flora are also key to affecting the incidence and prognosis of cerebrovascular diseases. The characteristics of new metabolic drugs with “one specialization and multiple capabilities” provide new ideas for the treatment and management of cerebro-metabolic disease. This review aims to provide more theoretical support for the management of cerebro-metabolic disease by summarizing evidence from evidence-based medicine on the influence of intervening metabolic risk factors on cerebrovascular diseases.

【Key Words】　Cerebro-metabolic disease; Metabolic risk factor; Glucagon-like peptide-1 receptor agonist

我国脑血管病患病率居全球首位，脑血管病致死率及致残率极高，给我国造成极大的经济负担[1]。《中国卒中报告（2020）（1）》数据显示，代谢性疾病在我国发病率居高不下，是脑血管病的重要危险因素[2]。基于代谢危险因素对脑血管病存在重要影响，代谢性脑血管病（cerebro-metabolic disease）的概念被明确提出：由传统代谢危险因素和残余代谢危险因素导致脑血管损害，以血管结构受损及功能障碍为主要病理生理学表现，以缺血性脑血管

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病、出血性脑血管病和脑小血管病等为主要结局，干预代谢危险因素可有效改善患者预后的一种临床综合征[3]。随着代谢性脑血管病概念的提出，如何对其进行管理需要更多的循证医学证据支持，本文对干预代谢危险因素对脑血管病影响的研究进展进行综述。

1 传统代谢危险因素及干预策略

传统代谢危险因素包括肥胖、高血糖、血脂异常以及高血压，是脑血管病的重要影响因素。代谢综合征以传统代谢危险因素各个组分为核心症状，是代谢上相互关联的危险因素的组合，也是动脉粥样硬化性脑血管病的主要病因[4]。

代谢综合征与卒中首次发病风险增加相关。一项孟德尔随机化研究显示，遗传相关的代谢综合征可增加卒中发病风险，其中遗传相关的高血压与缺血性卒中之间关联尤为显著[5]。此外，代谢综合征可导致颈动脉粥样硬化的患病率增加[6-7]。代谢综合征组分的数量与卒中的发病风险呈正相关，合并3个组分的患者卒中风险增加24%且代谢综合征组分数量与卒中发生率之间存在明显的剂量-反应关系[8-9]。

代谢综合征也可增加卒中的复发风险和卒中患者取栓后颅内出血风险[10-11]。一项meta分析显示，对于合并代谢综合征的卒中患者，HDL-C水平低和代谢综合征组分≥2个是卒中复发的预测因素，可使患者的全因死亡率增加27%[12]。

早期管理代谢综合征及其组分是降低卒中发病风险的有效策略。强化生活方式干预改善代谢综合征对脑血管病的一级预防长期有效[13]。限制进食时间等生活干预措施可改善代谢综合征患者的血压、体重及血脂水平[14]。除干预生活方式外，降脂、降糖和降压治疗均可有效降低代谢综合征患者首次卒中发病和复发的风险[15]。传统代谢危险因素是影响卒中发病及复发的关键，代谢综合征患者应积极进行生活方式干预和药物干预，这对改善其预后具有重要意义。

2 残余代谢危险因素及干预策略

残余代谢危险因素指在降低传统代谢危险因素后仍然存在，并对脑血管病产生负面影响的因素，包括炎症、高同型半胱氨酸血症、高尿酸血症及肠道菌群紊乱等。针对这些因素的干预措施可以进一步降低脑血管病发病风险，并改善患者预后。

2.1 炎症 传统代谢危险因素可引起慢性低水平炎症[16]。慢性低水平炎症常伴随与脑血管病发病率直接相关的代谢变化（如糖尿病、高血压和肥胖）[17]。炎症是导致动脉粥样硬化、血栓形成和脑小血管病的重要因素[18]。一项孟德尔随机化研究显示，*IL-6*基因多态性与缺血性卒中的个体易感性相关[19]。一项meta分析的结果显示，CRP水平每升高3倍，缺血性卒中的相对风险增加27%[20]。

研究发现，积极控制炎症有助于代谢相关疾病的管理，然而抗炎治疗在卒中患者中的有效性尚无确切结论[21]。目前针对心血管疾病的随机对照试验间接为抗炎药物预防卒中提供了参考。瑞舒伐他汀疗效评估干预试验（justification for the use of statins in prevention：an intervention trial evaluating rosuvastatin，JUPITER）结果证实瑞舒伐他汀具有降脂和抗炎双重作用，可使主要不良心血管事件（major adverse cardiovascular events，MACE）风险降低44%，首次卒中发病风险降低48%，LDL-C水平降低50%，hs-CRP水平降低37%[22]。卡那单抗抗炎治疗血栓形成结局研究（canakinumab anti-inflammatory thrombosis outcome study，CANTOS）及其后续分析结果显示，卡那单抗通过靶向结合IL-1β从而阻断IL-6通路，有效减少了复发性心血管事件的发生[23-24]。有观察性研究发现，秋水仙碱治疗与痛风或

家族性地中海热患者冠状动脉疾病的发病率降低相关，且能降低患者的hs-CRP、IL-1、IL-18和IL-6水平[25-26]。秋水仙碱心血管结局试验（colchicine cardiovascular outcomes trial，COLCOT）和低剂量秋水仙碱用于心血管疾病二级预防（low dose colchicine for secondary prevention of cardiovascular disease，LoDoCo2）研究相继证明了0.5 mg秋水仙碱能使稳定型冠心病患者显著获益：在COLCOT中，与安慰剂相比，秋水仙碱能使近期心肌梗死患者的心血管事件发生率降低23%[27]；在LoDoCo2研究中，与安慰剂相比，秋水仙碱使主要复合终点（心血管死亡、心肌梗死、缺血性卒中和缺血驱动的冠状动脉血运重建）的发生率降低31%[28]。

综上所述，抗炎治疗是心血管疾病治疗的新靶点，而随着脑血管病领域中抗炎药物临床研究的开展，抗炎治疗对脑血管病的有效性和安全性也将逐渐被揭示。

2.2 高同型半胱氨酸血症 高同型半胱氨酸血症可增加卒中发病、复发及全因死亡风险[29-30]，然而补充维生素降低Hcy水平与卒中发病风险的关系仍存在争议。早期研究结果显示维生素对心脑血管疾病的二级预防无积极作用[31-32]，这可能与氰钴胺对肾功能受损参与者的危害掩盖了对肾功能良好参与者的益处有关[33-34]。

中国卒中一级预防试验（China stroke primary prevention trial，CSPPT）结果显示叶酸（维生素B_9）可降低高血压患者的首次卒中风险[35]。CSPPT亚组分析结果显示B族维生素可降低卒中风险，且对高风险人群降低幅度更大；补充叶酸可使受试者缺血性卒中风险降低24%，在LDL-C≥2 mmol/L的受试者中，卒中风险可降低34%[36-38]。然而，过度补充维生素可能产生不良影响。荷兰发起的一项大型队列研究显示，老年人维生素B_{12}的血液浓度每增加1个标准差，全因死亡风险增加25%[39]。综合上述研究结果，适量补充B族维生素可有效降低卒中风险。

2.3 高尿酸血症 尿酸对于卒中的影响存在争议。早期研究指出，高尿酸血症可增加不稳定斑块形成和脑血管病发病的风险[40-41]。有研究显示，高尿酸血症与脑血管病发生及死亡风险增加相关[42]，血清尿酸水平每升高1 mg/dL，脑动脉狭窄风险增加21%[43]，脑血管病发病风险增加10%[44]。然而，近年来研究发现，高尿酸血症对脑血管可能具有保护作用。一项动物实验表明，高尿酸血症可减少脑梗死的面积[45]。尿酸联合静脉阿替普酶溶栓治疗急性缺血性卒中有效性研究（efficacy study of combined treatment with uric acid and r-tPA in acute ischemic stroke，URICO-ICTUS）的亚组分析结果同样提示尿酸治疗在减少卒中患者梗死面积及改善患者预后中具有积极作用[46]。未来仍需更多的基础实验及临床研究明确尿酸与卒中发病风险之间的机制与关联。

2.4 肠道菌群紊乱 肠道菌群对体重、脂质和炎症水平均有调节作用，使用益生菌已成为预防代谢综合征的有效方法之一[21]。肠道菌群作用广泛，在维持神经、代谢和免疫系统的稳定性中发挥重要作用。微生物-肠-脑轴的测定表明肠道微生物群与神经系统之间存在双向交流，肠道菌群紊乱可增加卒中发病风险[47-48]，而卒中也能引起肠道菌群紊乱，从而导致全身炎症水平升高，进一步影响卒中预后[49]。

近年来，肠道菌群及其代谢产物移植改善卒中患者预后的相关研究逐渐增多，此疗法改善患者预后的效果受移植肠道菌群种类、患者性别等多种因素影响[50-51]。有研究显示，多种肠道菌群代谢产物均可影响卒中患者的预后，在减少脑梗死体积、减轻脑水肿、降低血脂水平中发挥有效作用，该研究进一步指出，相较于其他肠道菌群代谢产物，移植丁酸的效果最好[52]。此外，还有研究提示，肠道菌群移植对卒中的治疗效果因性别而异，女性卒中患者改善肠道

菌群的获益更明显[53]。综上所述，肠道菌群有望成为脑血管病治疗的新靶点。

3 多效新型代谢药物的脑血管获益

目前针对代谢危险因素的干预和控制，多为“各个击破”，然而，代谢性脑血管病患者往往同时存在多个代谢危险因素，针对导致代谢失衡共同通路的干预将是未来代谢性脑血管病的重要研究方向。

司美格鲁肽作为胰高血糖素样肽-1（glucagon-like peptide-1，GLP-1）受体激动剂，在降低脑血管病发病风险中发挥稳定作用[54]。司美格鲁肽在2型糖尿病治疗中的心血管结局和其他长期结局评估试验（trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes，SUSTAIN™ 6）显示，与安慰剂相比，皮下注射司美格鲁肽可使MACE风险降低24%，非致死性卒中风险降低39%[55]。2型糖尿病患者口服司美格鲁肽的心血管安全性试验（a trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes，PIONEER 6）纳入了具有较高心血管风险的2型糖尿病患者，比较了口服司美格鲁肽和安慰剂两组患者的心血管结局差异。结果显示，司美格鲁肽组较安慰剂组的死亡率降低了约50%，心血管死亡事件发生率也较安慰剂组显著降低（0.9% *vs.* 1.9%）[56]。SUSTAIN™ 6和PIONEER 6的事后分析显示，与安慰剂相比，司美格鲁肽治疗使2型糖尿病患者发生MACE的风险降低24%，其中非致死性卒中的发生率降低35%[57]。另一项对SUSTAIN™ 6和PIONEER 6的事后分析结果显示司美格鲁肽能降低心血管高危2型糖尿病患者首次卒中的发生率，其中小动脉闭塞型卒中的发病风险降低尤为显著[58]。

司美格鲁肽除被证明能够降低糖尿病患者发生不良心血管事件的风险外，对非糖尿病患者，其同样可以降低与超重和肥胖相关的脑血管病风险。司美格鲁肽对超重/肥胖患者心血管结局的有效性（semaglutide effects on heart disease and stroke in patients with overweight or obesity，SELECT）研究表明，对于既往患有心血管疾病、超重或肥胖但无糖尿病的患者，应用司美格鲁肽治疗不仅能够有效减轻体重，且能使心血管疾病死亡或卒中的风险降低20%[59]。该研究显示，司美格鲁肽可改善多种代谢危险因素，其多重获益与代谢性脑血管病的治疗需求相契合[59]。新型代谢药物在糖尿病患者及非糖尿病患者中均展现出治疗心脑血管疾病的显著优势，值得进一步推广和应用。

4 总结和展望

传统代谢危险因素是脑血管病的重要影响因素，残余代谢危险因素在干预传统代谢危险因素后仍对脑血管病产生了负面影响，代谢危险因素的相互影响和共同作用导致了代谢性脑血管病的发生，综合管理代谢危险因素有望改善患者预后。司美格鲁肽作为一种新型、长效GLP-1受体激动剂，一方面能够有效纠正血糖异常、肥胖等传统代谢危险因素，另一方面也能纠正炎症等残余代谢危险因素，从而改善机体代谢紊乱的状态，实现对脑血管的保护。司美格鲁肽不仅在2型糖尿病患者中表现出稳定的降低脑血管病发病风险的作用，在非糖尿病患者中也展现出了改善多种代谢危险因素的效果。“一专多能”的新型代谢药物有助于对脑血管病的二级预防进行综合、多角度管理，并可能成为未来代谢性脑血管病药物研发的新风向。

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【点睛】综合管理传统及残余代谢危险因素是代谢性脑血管病治疗的重要方式。