Advances in Clinical Medicine 临床医学进展, 2024, 14(8), 485-492
Published Online August 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.1482240

Hans汉斯

影响糖尿病认知功能相关因素的研究进展

曹惠荣[1,2]，甄艳凤[2*]

[1]华北理工大学研究生学院，河北 唐山
[2]唐山工人医院内分泌二科，河北 唐山

收稿日期：2024年7月12日；录用日期：2024年8月4日；发布日期：2024年8月14日

摘 要

糖尿病是一种严重威胁人类健康的疾病，其并发症的研究也越来越受到关注，其中糖尿病认知功能障碍(Diabetes cognitive impairment, DCI)是糖尿病非常重要的并发症之一。认知功能障碍的发病机制复杂，且尚未完全阐明，可能与胰岛素抵抗与缺乏、血糖控制不佳、血管疾病、炎症和心理因素等相关。这些因素可导致认知速度减慢、反应时间延长、神经退行性变、脑老化和痴呆等。

关键词

糖尿病，认知障碍，发病机制，综述

Research Progress on Factors Related to Cognitive Function in Diabetes

Huirong Cao[1,2], Yanfeng Zhen[2*]

[1]Graduate School of North China University of Science and Technology, Tangshan Hebei
[2]Endocrinology Department II, Tangshan Workers Hospital, Tangshan Hebei

Received: Jul. 12th, 2024; accepted: Aug. 4th, 2024; published: Aug. 14th, 2024

Abstract

Diabetes is a serious threat to human health, and the study of its complications is also getting more and more attention. Among them, diabetes cognitive impairment (DCI) is one of the most important complications of diabetes. The pathogenesis of cognitive impairment is complex and not fully understood, and may be related to insulin resistance and deficiency, poor blood sugar control, vascular diseases, inflammation, and psychological factors. These factors can lead to cognitive slowdown, prolonged reaction time, neurodegeneration, brain aging, and dementia.

*通讯作者。

文章引用: 曹惠荣, 甄艳凤. 影响糖尿病认知功能相关因素的研究进展[J]. 临床医学进展, 2024, 14(8): 485-492.
DOI: 10.12677/acm.2024.1482240

Keywords

Diabetes, Cognitive Impairment, Pathogenesis, Review

1. 糖尿病与认知障碍

1.1. 糖尿病认知功能障碍

轻度认知功能障碍(mild cognitive impairment, MCI)是介于正常衰老与痴呆之间的一种认知功能损害状态，轻度认知功能障碍可增加痴呆的发生率[1]，研究表明，它可能是阿尔茨海默病(Alzheimer's disease, AD)的极早期阶段，认知功能障碍患者中每年约有15%发展为AD [2]，是潜在的痴呆高危人群。目前有证据表明糖尿病是导致认知障碍以及痴呆的独立危险因素[3]。早在1966年，Reske Nielsen等就提出了“糖尿病脑病”[4]这一学说，通过尸检发现，糖尿病认知功能障碍患者脑组织退行性改变。Biessels等[5]研究表明，糖尿病增加了认知功能损害，并提高了痴呆风险。我国主要以2型糖尿病患者为主，占90%以上[6]。

DCI主要表现在学习、记忆、注意力、精神运动速度等方面异常[7]。记忆功能减弱和学习能力降低为其主要特点，严重者则进展为痴呆，生活自理困难。有研究表明[8]，糖尿病患者比未患糖尿病者发生认知功能障碍危险度增高6.485倍。

1.2. 认知功能评估

临床上认知功能的评估主要是应用量表来评定，量表一般分为测验和观察患者的行为活动两种方式。在国内常应用评估认知能力的量表有简易智力状态量表、蒙特利尔认知评估量表以及临床痴呆分级量表等。简易智力状态量表(MMSE)是最为广泛应用，可对认知功能障碍的直接诊断或筛查[9]，它是一个客观的、简单易用的评估工具。MMSE共19项，正常值 ≥26分。蒙特利尔认知评估(MoCA)是一个用来对轻度认知功能损伤进行快速筛查的评定工具。MoCA是Nasreddine等研究设计的[10]，它主要特点是为筛查轻度认知功能障碍(mild cognitive impairment, MCI)患者而设计的，评定了许多不同的认知领域，包括：计算和定向力，视结构技能，抽象思维，注意与集中，执行功能，记忆，语言等。本量表分为11个项目，总分30分，正常值为 ≥26分。临床痴呆评定量表(Clinical Dementia Rating，简称CDR)是一种用于评估痴呆症状严重程度的标准化工具[11]。CDR通过六个不同领域的子项评估认知功能，包括记忆、定向力、判断与问题解决能力、社交能力、家庭生活和兴趣爱好、自理能力。

糖尿病患者的认知功能障碍仍表现在记忆力和注意力等方面的认知功能下降，主要是以记忆功能损害为核心的遗忘型轻度认知功能损害患者。糖尿病患者的血管危险因素及糖尿病本身是认知功能障碍的因素，研究表明因素有糖尿病病程、血糖水平、治疗的合理性、AGEs变化、胰岛素信号传导途径、氧化应激及炎症反应等[12]。

2. 糖尿病认知功能障碍患者脑部结构的改变

糖尿病会影响大脑的形态[13]。T1DM认知障碍患者颅脑磁共振成像(MRI)检查结果与无糖尿病者相比，额叶、中央后回以及边缘叶的灰质体积均缩小，其中额叶灰质体积缩小6%~19%，中央后回灰质体

积缩小 8%~13% [14]。其灰质体积缩小多开始于儿童期，儿童 T1DM 脑灰质体积缩小约 4% [15]。研究发现，1 型糖尿病患者大脑网络受到干扰且与认知功能减退有关[16]。

T2DM 相关脑形态改变主要表现为局部脑组织甚至是全脑的容积减少。对比单纯阿尔茨海默病患者，T2DM 合并阿尔茨海默病的脑皮质萎缩表现更明显[17]，其颅脑 MRI 检查结果为内侧颞叶、前扣带回以及内侧额叶灰质损失，还有额叶、颞叶白质的损失[18]。此外，研究表明，右侧大于左侧的不对称性海马萎缩与 T2DM 认知功能障碍相关[19]。

3. 糖尿病认知功能障碍相关因素

糖尿病是一种复杂的代谢紊乱，与多种微血管和大血管并发症有关，包括视网膜病变、肾脏病变、周围神经病变和心血管疾病。虽然糖尿病和这些并发症之间的机制已经明确，但糖尿病对大脑的影响，特别是对于认知能力下降的影响机制，尚不清楚。糖尿病与认知功能障碍之间关联的可能的机制如下：

3.1. 胰岛素抵抗与缺乏

胰岛素是由胰腺 β 细胞产生的，是一种多肽激素[20]。至今，胰岛素对神经元存活和脑功能有重要意义[21]，胰腺 β 细胞分泌的胰岛素，通过受体介导的机制穿越血脑屏障，胰岛素受体广泛分布于大脑，特别是与认知相关的区域，比如大脑皮层、嗅球、海马体和下丘脑部。有研究表明，大脑可能也能够合成胰岛素[22]，尤其是在特定的脑区。胰岛素受体在大脑中的分布为胰岛素在神经系统中的作用奠定了基础；大脑中的胰岛素受体与神经元的功能调节紧密相关，与认知功能、学习能力及记忆能力等过程密切相关。中枢神经系统中胰岛素信号的改变可能会使大脑衰老加快，影响其可塑性，且参与神经退行性变的过程，胰岛素抵抗可能导致血脑屏障的破坏，改变其通透性，从而可能导致毒性物质、炎性因子以及其他有害物质等进入脑部，进而引发神经炎症和神经退行性变。进一步影响神经元的功能和存活，这种损伤会导致脑血管功能障碍，导致突触可塑性，甚至认知功能的障碍[23]。

无论胰岛素抵抗或是胰岛素绝对缺乏都可导致糖尿病进展。胰岛素抵抗是指各种原因使胰岛素促进葡萄糖摄取和利用的效率下降，机体代偿性的分泌过多胰岛素产生高胰岛素血症，以维持血糖的稳定，易导致 2 型糖尿病。胰岛素绝对缺乏主要是指通过免疫介导胰腺 β 细胞的破坏而导致，易导致 1 型糖尿病。已有研究表明，胰岛素受体在在中枢神经系统(CNS)的下丘脑、海马、大脑皮层、嗅球、杏仁核和小脑中广泛表达。这足够证实了胰岛素在有调节糖尿病认知障碍的潜力。多项研究证实，系统性胰岛素缺乏通过下调内皮细胞胰岛素受体，降低血脑屏障对胰岛素的通透性而影响血脑屏障功能[24] [25]。因此，大脑中的胰岛素缺乏或抵抗可能导致胰岛素信号转导受损和认知功能障碍。那么全身胰岛素异常可能会影响中枢神经系统的胰岛素水平，大脑中胰岛素水平下降抑制了神经元和胶质细胞的活动。

3.2. 血糖异常

反复发作的低血糖可使 DM 患者发生痴呆的风险增加近 2 倍[26]；同时，低血糖的发作频率与认知水平存在负向关联，反复发作的严重低血糖可导致记忆力与处理速度的下降[27]。慢性高血糖一方面可以损伤血管内皮细胞，导致脑微血管病变，使脑组织易发生缺血缺氧性损害；另一方面还可以引起线粒体功能障碍，使神经细胞凋亡，进而损害患者的认知功能，甚至增加患者痴呆的发病风险[28] [29]。有研究表明，低血糖发作比没有低血糖发作的个体患痴呆的风险高 66%，高血糖发作的个体比无高血糖发作个体的痴呆风险增加超过了 2 倍，出现高血糖发作和低血糖发作的个体比无高血糖发作和低血糖发作患痴呆的风险高 6 倍，出现严重低血糖及高血糖事件与痴呆风险增加有关[30]。

大脑主要以葡萄糖为主要能量来源，因此 24 h 内血糖波动可能也会影响 DM 患者的认知功能[31]。相关研究也发现，血糖波动与认知水平下降独立相关，即血糖波动越大的患者认知功能越差[32]；与长期

血糖变异相比，短期血糖波动对认知功能的影响更为显著[31]。DM 控制和并发症试验提示了血糖变异性和微血管并发症之间的可能联系，高葡萄糖变异性与活性氧物质的产生增加有关，活性氧物质使血管系统暴露于氧化应激[33] [34]，从而使神经系统易受急性葡萄糖变异性的影响[35]。

3.3. 氧化应激和炎症

氧化应激是导致代谢异常(例如，葡萄糖和脂质代谢紊乱)以及脑变性、中枢神经系统损伤的主要病理因素，通常被定义为体内氧化剂(ROS 等)与抗氧化剂作用衡[36]。神经细胞氧化应激的主要途径：Sirt6→NRF2→HO1 和 Sirt6→p53→PGC1-α→TERT。这一途径可导致神经元凋亡、线粒体功能障碍、端粒不稳定[37]。在糖尿病患者中，慢性高血糖会使容易发生并发症的组织产生氧化应激，而大脑由于其高能量需求、高氧气消耗、高脂肪含量以及低水平的自由基清除，极容易受到氧化损伤[38]。作为 DM 患者氧化应激的产物活性氧被认为是神经毒物通过氧化蛋白质和破坏细胞膜的 DNA 和脂质，使神经元损伤或死亡，最终导致认知能力下降[39]。ROS 还可以诱导胰岛素抵抗[40]，上调炎症分子、加重炎症反应[41]，进而促进认知能力下降。

糖尿病的进展中一直离不开炎症因子的参与。临床上常用的炎症指标如：C 反应蛋白(C-reactive protein, CRP)、白介素 6 (Interleukin 6, IL-6)、肿瘤坏死因子 a (Tumornecrosis factor-a, TNF-a)。大量研究表明，IL 1B (Interleukin 1B，IL-1B)、TNF-a 和 IL-6 这些炎症因子在糖尿病小鼠海马中过度表达可能诱导 DCI。DCI 患者血液中 TNF-a 和 IL-6 水平显著升高。TNF-a 与海马活动密切相关，在 TNF-a 缺乏的小鼠中发现小鼠空间记忆能力增强，进一步研究发现 TNF-a 缺乏增加了神经生长因子的表达，从而影响海马的生长和功能[42]。海马是最敏感和最容易受累的结构，炎性损伤使海马神经元发生萎缩和变性，致使突触可塑性受损，进而引起认知功能障碍[43]。在 DCI 疾病过程中，高血糖能够诱导海马神经元中 NLRP3 炎症小体的激活，促进 IL-1B 的生成，诱导神经元损伤。高血糖诱导的 ROS 激增也可能通过调节 DCI 中硫氧还蛋白互作蛋白(TXNIP)介导 NLRP3 炎症小体的激活和 IL-1B 的分泌[44]-[47]。炎症因子在 DCI 的进展中有重义。未来的研究应集中于识别更多的血液和组织敏感的 DCI 炎症标志物。由于炎症和氧化应激是糖尿病与认知功能障碍相关的通路，这些路可能有利于改善 DM 患者的认知功能，未来可进一步进行深入探索。

3.4. 脑微血管功能

脑微血管功能障碍可能是 DM 认知功能障碍的相关机制之一[48]。从认知到调节心血管稳态是有大脑来执行的[49]。营养物质的输送、废物的清除、维持大脑间质环境以实现正常的胞能以及降低和稳定毛细管水平的脉动静水压任何步骤出现异常都可能导致脑微血管障碍[48] [50]。血脑屏障通透性增加，蛋白质和其他血浆成分渗入血管周围间，损害神经元，从而导致认知功能障碍[48]。脑微血管病变是糖尿病认 DM 知能力障碍最初的病理变化[51]。血脑屏障主要由脑微血管内皮细胞(BMVECs)、基底膜、周细胞、星形细胞终足以及它们之间的链接组成。在糖尿病状态下，高血糖可导致血管缺氧，基底膜增厚，血管通透性增加，足以导致大脑微血管功能障碍相关的 DCI。在糖尿病状态下，高血糖可导致缺氧血管生成，基底膜增厚，血管通透性增加，从而导致大脑微血管功能障碍相关的 DCI [52] [53]。

3.5. 心理因素

DM 不仅给患者带来沉重的躯体危害和经济负担，而且导致了很多严重的心理障碍，抑郁、焦虑和认知功能是受糖尿病影响和影响的主要心理特征，但以往的调查结果并不均匀。抑郁症在糖尿病患者中的患病率可能至少是糖尿病患者的两倍[54] [55]，而焦虑的数据则相互矛盾[56]，从 6% [57]到 32% [58]

不等，而一般人群的患病率估计为12%~21% [59]-[61]。

这些心理特征可能影响糖尿病控制和并发症的机制尚不清楚。抑郁症可能通过对自我护理的负面影响、对药物和饮食的不良依从性、生活质量的降低和医疗费用的增加来损害血糖控制[62]。焦虑可能与并发症、高血糖、生活质量下降和体重指数增加有关[63]。

3.6. 其他

钙稳态失衡会导致细胞内钙超载而诱导细胞凋亡。细胞死亡也与钙离子异常内流相关，激活磷脂酶、阻止线粒体电子传递、释放自由基，最终导致神经元功能障碍[64]。有实验表明，糖尿病小鼠认知功能相关能力明显下降，脑内钙通道的mRNA和蛋白质表达增加，说明突触钙摄取能力增强；钙通道抑制剂可以逆转这种异常表达，改善小鼠突触可塑性的钙依赖变化，从而改善认知功能[65]。综上，脑内钙稳态失衡可能是与DM认知障碍相关。

细胞凋亡是指细胞程序性死亡，内质网应激和自噬通路在神经元的存活和凋亡中发挥巨大作用。有研究发现，内质网应激通路可能参与了糖尿病介导的神经毒性，并加剧了认知功能障碍[66]。

亦有研究表明，雌激素受体被认为与神经退行性疾病有关，ERα和ERβ参与了T2DM的认知障碍[67]。雌激素受体激动剂的开发及应用是一种新的认知治疗方法。

4. 展望

DCI的表现取决于糖尿病发病年龄、病程、血糖水平、高血压以及微血管和大血管并发症的发生。现代研究证实，胰岛素抵抗、氧化应激及炎症、微血管功能障碍、心理因素等均可作为DCI的独立或共致病诱导因素。以上我们分析的所有数据表明，多靶点干预可能是DCI的最佳治疗方法。许多有害因素似乎共同作用，导致认知障碍。同时既往研究对象选取的多为中老年人、研究方法及对疾病的评价标准不一。因此DM认知功能障碍的相关危险因素还有待于进一步研究。但无论如何，这些危险因素都需要引起重视，这对DM患者延缓认知功能下降，预防痴呆，提升生活质量都有重要意义。

参考文献

[1] Bozoki, A., Giordani, B., Heidebrink, J.L., Berent, S. and Foster, N.L. (2001) Mild Cognitive Impairments Predict Dementia in Nondemented Elderly Patients with Memory Loss. *Archives of Neurology*, **58**, 411-416. https://doi.org/10.1001/archneur.58.3.411

[2] Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G. and Kokmen, E. (1999) Mild Cognitive Impairment. *Archives of Neurology*, **56**, 303-308. https://doi.org/10.1001/archneur.56.3.303

[3] Stewart, R. and Liolitsa, D. (1999) Type 2 Diabetes Mellitus, Cognitive Impairment and Dementia. *Diabetic Medicine*, **16**, 93-112. https://doi.org/10.1046/j.1464-5491.1999.00027.x

[4] Reske-Nielsen, E., Lundbæk, K. and Rafaelsen, O.J. (1966) Pathological Changes in the Central and Peripheral Nervous System of Young Long-Term Diabetics. *Diabetologia*, **1**, 233-241. https://doi.org/10.1007/bf01257917

[5] Biessels, G.J., Deary, I.J. and Ryan, C.M. (2008) Cognition and Diabetes: A Lifespan Perspective. The Lancet Neurology, **7**, 184-190. https://doi.org/10.1016/s1474-4422(08)70021-8

[6] 中华医学会糖尿病学分会. 中国2型糖尿病防治指南(2020年版) [J]. 中华内分泌代谢杂志, 2021, 37(4): 311-398.

[7] Kodl, C.T., Franc, D.T., Rao, J.P., Anderson, F.S., Thomas, W., Mueller, B.A., *et al*. (2008) Diffusion Tensor Imaging Identifies Deficits in White Matter Microstructure in Subjects with Type 1 Diabetes That Correlate with Reduced Neurocognitive Function. *Diabetes*, **57**, 3083-3089. https://doi.org/10.2337/db08-0724

[8] 李敏, 张丽. 老年2型糖尿病与轻度认知功能障碍的关系研究[J]. 中国全科医学, 2011, 14(5B): 1537-1539.

[9] 杨礼, 秦琴保. 老年高干人群轻度认知功能障碍调查及危险因素分析[J]. 中国神经精神疾病杂志, 2011, 37(8): 473-476.

[10] Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., *et al*. (2005) The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. *Journal of the American Geri-*

atrics Society, **53**, 695-699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

[11] 金肖青，许瑛. 失智症长期照护[M]. 北京：人民卫生出版社, 2019.

[12] 林露，刘礼斌. 低血糖对糖尿病患者认知功能障碍影响的研究新进展[J]. 中华内分泌代谢杂志, 2021, 37(5): 485, 488.

[13] Hirabayashi, N., Hata, J., Furuta, Y., Ohara, T., Shibata, M., Hirakawa, Y., *et al*. (2022) Association between Diabetes and Gray Matter Atrophy Patterns in a General Older Japanese Population: The Hisayama Study. *Diabetes Care*, **45**, 1364-1371. https://doi.org/10.2337/dc21-1911

[14] Hughes, T.M., Ryan, C.M., Aizenstein, H.J., Nunley, K., Gianaros, P.J., Miller, R., *et al*. (2013) Frontal Gray Matter Atrophy in Middle Aged Adults with Type 1 Diabetes Is Independent of Cardiovascular Risk Factors and Diabetes Complications. *Journal of Diabetes and its Complications*, **27**, 558-564. https://doi.org/10.1016/j.jdiacomp.2013.07.001

[15] Marzelli, M.J., Mazaika, P.K., Barnea-Goraly, N., Hershey, T., Tsalikian, E., Tamborlane, W., *et al*. (2013) Neuroanatomical Correlates of Dysglycemia in Young Children with Type 1 Diabetes. *Diabetes*, **63**, 343-353. https://doi.org/10.2337/db13-0179

[16] van Duinkerken, E., Schoonheim, M.M., Sanz-Arigita, E.J., IJzerman, R.G., Moll, A.C., Snoek, F.J., *et al*. (2012) Resting-State Brain Networks in Type 1 Diabetic Patients with and without Microangiopathy and Their Relation to Cognitive Functions and Disease Variables. *Diabetes*, **61**, 1814-1821. https://doi.org/10.2337/db11-1358

[17] Biessels, G.J. (2005) Increased Cortical Atrophy in Patients with Alzheimer's Disease and Type 2 Diabetes Mellitus. *Journal of Neurology, Neurosurgery & Psychiatry*, **77**, 304-307. https://doi.org/10.1136/jnnp.2005.069583

[18] Moran, C., Phan, T.G., Chen, J., Blizzard, L., Beare, R., Venn, A., *et al*. (2013) Brain Atrophy in Type 2 Diabetes. *Diabetes Care*, **36**, 4036-4042. https://doi.org/10.2337/dc13-0143

[19] Milne, N.T., Bucks, R.S., Davis, W.A., Davis, T.M.E., Pierson, R., Starkstein, S.E., *et al*. (2017) Hippocampal Atrophy, Asymmetry, and Cognition in Type 2 Diabetes Mellitus. *Brain and Behavior*, **8**, e00741. https://doi.org/10.1002/brb3.741

[20] Arnold, S.E., Arvanitakis, Z., Macauley-Rambach, S.L., Koenig, A.M., Wang, H., Ahima, R.S., *et al*. (2018) Brain Insulin Resistance in Type 2 Diabetes and Alzheimer Disease: Concepts and Conundrums. *Nature Reviews Neurology*, **14**, 168-181. https://doi.org/10.1038/nrneurol.2017.185

[21] Tumminia, A., Vinciguerra, F., Parisi, M. and Frittitta, L. (2018) Type 2 Diabetes Mellitus and Alzheimer's Disease: Role of Insulin Signalling and Therapeutic Implications. *International Journal of Molecular Sciences*, **19**, Article 3306. https://doi.org/10.3390/ijms19113306

[22] Gray, S.M. and Barrett, E.J. (2018) Insulin Transport into the Brain. *American Journal of Physiology-Cell Physiology*, **315**, C125-C136. https://doi.org/10.1152/ajpcell.00240.2017

[23] Werner, H. and LeRoith, D. (2014) Insulin and Insulin-Like Growth Factor Receptors in the Brain: Physiological and Pathological Aspects. *European Neuropsychopharmacology*, **24**, 1947-1953. https://doi.org/10.1016/j.euroneuro.2014.01.020

[24] de la Monte, S.M. (2012) Metabolic Derangements Mediate Cognitive Impairment and Alzheimer's Disease: Role of Peripheral Insulin Resistance Diseases. *Panminerva Medica*, **54**, 171-178.

[25] Heni, M., Schöpfer, P., Peter, A., Sartorius, T., Fritsche, A., Synofzik, M., *et al*. (2013) Evidence for Altered Transport of Insulin across the Blood-Brain Barrier in Insulin-Resistant Humans. *Acta Diabetologica*, **51**, 679-681. https://doi.org/10.1007/s00592-013-0546-y

[26] Yaffe, K. (2013) Association between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults with Diabetes Mellitus. *JAMA Internal Medicine*, **173**, 1300-1306. https://doi.org/10.1001/jamainternmed.2013.6176

[27] Chen, Y., Liu, Z., Yu, Y., Yao, E., Liu, X. and Liu, L. (2017) Effect of Recurrent Severe Hypoglycemia on Cognitive Performance in Adult Patients with Diabetes: A Meta-Analysis. *Current Medical Science*, **37**, 642-648. https://doi.org/10.1007/s11596-017-1784-y

[28] Freedman, B.I., Sink, K.M., Hugenschmidt, C.E., Hughes, T.M., Williamson, J.D., Whitlow, C.T., *et al*. (2017) Associations of Early Kidney Disease with Brain Magnetic Resonance Imaging and Cognitive Function in African Americans with Type 2 Diabetes Mellitus. *American Journal of Kidney Diseases*, **70**, 627-637. https://doi.org/10.1053/j.ajkd.2017.05.006

[29] Tahmi, M., Palta, P. and Luchsinger, J.A. (2021) Metabolic Syndrome and Cognitive Function. *Current Cardiology Reports*, **23**, Article No. 180. https://doi.org/10.1007/s11886-021-01615-y

[30] Whitmer, R.A., Gilsanz, P., Quesenberry, C.P., Karter, A.J. and Lacy, M.E. (2021) Association of Type 1 Diabetes and Hypoglycemic and Hyperglycemic Events and Risk of Dementia. *Neurology*, **97**, e275-e283. https://doi.org/10.1212/wnl.0000000000012243

[31] Rizzo, M.R., Marfella, R., Barbieri, M., Boccardi, V., Vestini, F., Lettieri, B., *et al*. (2010) Relationships between Daily Acute Glucose Fluctuations and Cognitive Performance among Aged Type 2 Diabetic Patients. *Diabetes Care*, **33**, 2169-2174. https://doi.org/10.2337/dc10-0389

[32] Zhong, Y., Zhang, X.Y., Miao, Y., *et al*. (2012) The Relationship between Glucose Excursion and Cognitive Function in Aged Type 2 Diabetes Patients. *Biomedical and Environmental Sciences*, **25**, 1-7. https://doi.org/10.3967/0895-3988.2012.01.001

[33] Quagliaro, L., Piconi, L., Assaloni, R., Martinelli, L., Motz, E. and Ceriello, A. (2003) Intermittent High Glucose Enhances Apoptosis Related to Oxidative Stress in Human Umbilical Vein Endothelial Cells. *Diabetes*, **52**, 2795-2804. https://doi.org/10.2337/diabetes.52.11.2795

[34] Ceriello, A., Esposito, K., Piconi, L., Ihnat, M.A., Thorpe, J.E., Testa, R., *et al*. (2008) Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress than Mean Glucose in Normal and Type 2 Diabetic Patients. *Diabetes*, **57**, 1349-1354. https://doi.org/10.2337/db08-0063

[35] Bragd, J., Adamson, U., Bäcklund, L.B., Lins, P.E., Moberg, E. and Oskarsson, P. (2008) Can Glycaemic Variability, as Calculated from Blood Glucose Self-Monitoring, Predict the Development of Complications in Type 1 Diabetes over a Decade? *Diabetes & Metabolism*, **34**, 612-616. https://doi.org/10.1016/j.diabet.2008.04.005

[36] Maciejczyk, M., Żebrowska, E. and Chabowski, A. (2019) Insulin Resistance and Oxidative Stress in the Brain: What's New? *International Journal of Molecular Sciences*, **20**, Article 874. https://doi.org/10.3390/ijms20040874

[37] Li, L., Zhang, H., Chen, B., Xia, B., Zhu, R., Liu, Y., *et al*. (2022) BaZiBuShen Alleviates Cognitive Deficits and Regulates Sirt6/NRF2/HO-1 and Sirt6/P53-PGC-1α-Tert Signaling Pathways in Aging Mice. *Journal of Ethnopharmacology*, **282**, Article 114653. https://doi.org/10.1016/j.jep.2021.114653

[38] Luo, A., Xie, Z., Wang, Y., Wang, X., Li, S., Yan, J., *et al*. (2022) Type 2 Diabetes Mellitus-Associated Cognitive Dysfunction: Advances in Potential Mechanisms and Therapies. *Neuroscience & Biobehavioral Reviews*, **137**, Article 104642. https://doi.org/10.1016/j.neubiorev.2022.104642

[39] Farbood, Y., Ghaderi, S., Rashno, M., Khoshnam, S.E., Khorsandi, L., Sarkaki, A., *et al*. (2019) Sesamin: A Promising Protective Agent against Diabetes-Associated Cognitive Decline in Rats. *Life Sciences*, **230**, 169-177. https://doi.org/10.1016/j.lfs.2019.05.071

[40] Yan, L. (2014) Pathogenesis of Chronic Hyperglycemia: From Reductive Stress to Oxidative Stress. *Journal of Diabetes Research*, **2014**, Article 137919. https://doi.org/10.1155/2014/137919

[41] Van Dyken, P. and Lacoste, B. (2018) Impact of Metabolic Syndrome on Neuroinflammation and the Blood-Brain Barrier. *Frontiers in Neuroscience*, **12**, Article 930. https://doi.org/10.3389/fnins.2018.00930

[42] Golan, H. (2004) Involvement of Tumor Necrosis Factor Alpha in Hippocampal Development and Function. *Cerebral Cortex*, **14**, 97-105. https://doi.org/10.1093/cercor/bhg108

[43] Vinuesa, A., Pomilio, C., Gregosa, A., Bentivegna, M., Presa, J., Bellotto, M., *et al*. (2021) Inflammation and Insulin Resistance as Risk Factors and Potential Therapeutic Targets for Alzheimer's Disease. *Frontiers in Neuroscience*, **15**, Article 653651. https://doi.org/10.3389/fnins.2021.653651

[44] Hui, S.T.Y., Andres, A.M., Miller, A.K., Spann, N.J., Potter, D.W., Post, N.M., *et al*. (2008) Txnip Balances Metabolic and Growth Signaling via PTEN Disulfide Reduction. *Proceedings of the National Academy of Sciences*, **105**, 3921-3926. https://doi.org/10.1073/pnas.0800293105

[45] Zhou, R., Tardivel, A., Thorens, B., Choi, I. and Tschopp, J. (2009) Thioredoxin-Interacting Protein Links Oxidative Stress to Inflammasome Activation. *Nature Immunology*, **11**, 136-140. https://doi.org/10.1038/ni.1831

[46] Zhang, J., Xia, L., Zhang, F., Zhu, D., Xin, C., Wang, H., *et al*. (2017) A Novel Mechanism of Diabetic Vascular Endothelial Dysfunction: Hypoadiponectinemia-Induced NLRP3 Inflammasome Activation. *Biochimica et Biophysica Acta* (*BBA*)-*Molecular Basis of Disease*, **1863**, 1556-1567. https://doi.org/10.1016/j.bbadis.2017.02.012

[47] Zhai, Y., Meng, X., Ye, T., Xie, W., Sun, G. and Sun, X. (2018) Inhibiting the NLRP3 Inflammasome Activation with MCC950 Ameliorates Diabetic Encephalopathy in db/db Mice. *Molecules*, **23**, Article 522. https://doi.org/10.3390/molecules23030522

[48] van Sloten, T.T., Sedaghat, S., Carnethon, M.R., Launer, L.J. and Stehouwer, C.D.A. (2020) Cerebral Microvascular Complications of Type 2 Diabetes: Stroke, Cognitive Dysfunction, and Depression. *The Lancet Diabetes & Endocrinology*, **8**, 325-336. https://doi.org/10.1016/s2213-8587(19)30405-x

[49] Phoenix, A., Chandran, R. and Ergul, A. (2022) Cerebral Microvascular Senescence and Inflammation in Diabetes. *Frontiers in Physiology*, **13**, Article 864758. https://doi.org/10.3389/fphys.2022.864758

[50] Stehouwer, C.D.A. (2018) Microvascular Dysfunction and Hyperglycemia: A Vicious Cycle with Widespread Consequences. *Diabetes*, **67**, 1729-1741. https://doi.org/10.2337/dbi17-0044

[51] Marseglia, A., Fratiglioni, L., Kalpouzos, G., Wang, R., Bäckman, L. and Xu, W. (2018) Prediabetes and Diabetes

Accelerate Cognitive Decline and Predict Microvascular Lesions: A Population-Based Cohort Study. *Alzheimer's & Dementia*, **15**, 25-33. https://doi.org/10.1016/j.jalz.2018.06.3060

[52] Orasanu, G. and Plutzky, J. (2009) The Pathologic Continuum of Diabetic Vascular Disease. *Journal of the American College of Cardiology*, **53**, S35-S42. https://doi.org/10.1016/j.jacc.2008.09.055

[53] Soares, E., Prediger, R.D., Nunes, S., Castro, A.A., Viana, S.D., Lemos, C., *et al*. (2013) Spatial Memory Impairments in a Prediabetic Rat Model. *Neuroscience*, **250**, 565-577. https://doi.org/10.1016/j.neuroscience.2013.07.055

[54] Snoek, F.J., Bremmer, M.A. and Hermanns, N. (2015) Constructs of Depression and Distress in Diabetes: Time for an Appraisal. *The Lancet Diabetes & Endocrinology*, **3**, 450-460. https://doi.org/10.1016/s2213-8587(15)00135-7

[55] Semenkovich, K., Brown, M.E., Svrakic, D.M. and Lustman, P.J. (2015) Depression in Type 2 Diabetes Mellitus: Prevalence, Impact, and Treatment. *Drugs*, **75**, 577-587. https://doi.org/10.1007/s40265-015-0347-4

[56] Fisher, L., Skaff, M.M., Mullan, J.T., Arean, P., Glasgow, R. and Masharani, U. (2008) A Longitudinal Study of Affective and Anxiety Disorders, Depressive Affect and Diabetes Distress in Adults with Type 2 Diabetes. *Diabetic Medicine*, **25**, 1096-1101. https://doi.org/10.1111/j.1464-5491.2008.02533.x

[57] Roy, T. and Lloyd, C.E. (2012) Epidemiology of Depression and Diabetes: A Systematic Review. *Journal of Affective Disorders*, **142**, S8-S21. https://doi.org/10.1016/s0165-0327(12)70004-6

[58] Grigsby, A.B., Anderson, R.J., Freedland, K.E., Clouse, R.E. and Lustman, P.J. (2002) Prevalence of Anxiety in Adults with Diabetes. *Journal of Psychosomatic Research*, **53**, 1053-1060. https://doi.org/10.1016/s0022-3999(02)00417-8

[59] Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R. and Walters, E.E. (2005) Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, **62**, 593-602. https://doi.org/10.1001/archpsyc.62.6.593

[60] Leray, E., Camara, A., Drapier, D., Riou, F., Bougeant, N., Pelissolo, A., *et al*. (2011) Prevalence, Characteristics and Comorbidities of Anxiety Disorders in France: Results from the "Mental Health in General Population" Survey (MHGP). *European Psychiatry*, **26**, 339-345. https://doi.org/10.1016/j.eurpsy.2009.12.001

[61] Minelli, A., Pedrini, L., Magni, L.R. and Rotondo, A. (2009) Personality Traits in an Italian Sample: Relationship with Anxiety and Depression. *Clinical Practice & Epidemiology in Mental Health*, **5**, 26-30. https://doi.org/10.2174/1745017900905010026

[62] Egede, L. (2005) Effect of Depression on Self-Management Behaviors and Health Outcomes in Adults with Type 2 Diabetes. *Current Diabetes Reviews*, **1**, 235-243. https://doi.org/10.2174/157339905774574356

[63] Smith, K.J., Béland, M., Clyde, M., Gariépy, G., Pagé, V., Badawi, G., *et al*. (2013) Association of Diabetes with Anxiety: A Systematic Review and Meta-Analysis. *Journal of Psychosomatic Research*, **74**, 89-99. https://doi.org/10.1016/j.jpsychores.2012.11.013

[64] Xu, Y., Zhou, H. and Zhu, Q. (2017) The Impact of Microbiota-Gut-Brain Axis on Diabetic Cognition Impairment. *Frontiers in Aging Neuroscience*, **9**, Article 106. https://doi.org/10.3389/fnagi.2017.00106

[65] Singhal, K. and Sandhir, R. (2014) L-Type Calcium Channel Blocker Ameliorates Diabetic Encephalopathy by Modulating Dysregulated Calcium Homeostasis. *Journal of Neuroscience Research*, **93**, 296-308. https://doi.org/10.1002/jnr.23478

[66] Kong, F., Ma, L., Guo, J., Xu, L., Li, Y. and Qu, S. (2018) Endoplasmic Reticulum Stress/Autophagy Pathway Is Involved in Diabetes-Induced Neuronal Apoptosis and Cognitive Decline in Mice. *Clinical Science*, **132**, 111-125. https://doi.org/10.1042/cs20171432

[67] Tang, S., Ren, Y., Ren, X., Cao, J., Hong, H., Ji, H., *et al*. (2019) ERα and/or ERβ Activation Ameliorates Cognitive Impairment, Neurogenesis and Apoptosis in Type 2 Diabetes Mellitus Mice. *Experimental Neurology*, **311**, 33-43. https://doi.org/10.1016/j.expneurol.2018.09.002