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锌缺乏与糖尿病肾病的研究进展

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[摘 要] 锌是人体必需微量元素，在生物体中参与多种酶形成，可维持机体内环境稳态、加重氧化应激、促进间质纤维化、调控基因表达和介导细胞信号转导等。锌在体内缺乏可参与促进糖尿病肾病(diabetic nephropathy，DN)的发展，提示锌在DN发展中起重要作用。

[关键词] 锌缺乏；慢性肾病；糖尿病肾病

Research progress in zinc deficiency and diabetic nephropathy

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Abstract Zinc is an essential trace element and participates in numerous physiological processes. It can maintain the homeostasis of the body, aggravate oxidative stress, promote interstitial fibrosis, regulate gene expression, mediate cell signaling pathways and so on. The lack of zinc in the body can be involved in promoting the development of diabetic nephropathy, suggesting that zinc plays an important role in the development of diabetic nephropathy.

Keywords zinc deficiency; chronic kidney disease; diabetic nephropathy

我国糖尿病患病率从1980年的0.67%飙升至2013年的10.4%[1]，糖尿病已成为全世界面临的主要健康问题。糖尿病肾病(diabetic nephropathy，DN)是糖尿病常见的严重并发症，也是造成终末期肾病(end-stage renal disease，ESRD)的主要原因。慢性肾病(chronic kidney disease，CKD)常出现锌缺乏、电解质紊乱等不良作用，易被临床忽视[2]。糖尿病患者常发生锌缺乏[3]，其增加了内源性锌的丢失[4]。然而研究[5]表明：补锌治疗可以改善糖尿病小鼠肾病变结构，其细胞凋亡数目明显减少。因此，纠正锌缺乏对糖尿病及并发症具有重要意义。

1 锌的生物学功能

锌是人体必需微量元素，人体内约85%的锌存在肌肉和骨骼中，约11%存在皮肤和肾等其他组织中，少部分存在于血清中。在细胞中大部分锌与蛋白紧密结合，只有一部分以游离形式存在[6]。到目前为止，已发现300多种锌活化的金属蛋白酶和2 000多种锌依赖性转录因子。锌参与多种酶形成，维持机体内环境稳态、加重氧化应激、促进间质纤

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维化、调控基因表达和介导细胞信号转导等[7-8]。

2 锌稳态

人体内锌稳态对机体尤为重要，其维持主要依赖金属硫蛋白/硫蛋白缓冲体系、锌转运蛋白(Zn transporters family，ZnTs)和锌-铁转运体蛋白(zinc-iron-regulated transporter-like proteins，ZIPs)家族两大锌转运系统[9-10]。金属硫蛋白/硫蛋白缓冲体系重点参与锌的跨膜转运，而ZnTs和ZIPs家族主要参与锌的储存及运输[11]。锌稳态失衡在2型糖尿病和胰岛素代谢紊乱中具有潜在相关性[12-13]。锌稳态失衡可能取决于缓冲体系和锌的存储、转运蛋白的比例失调。金属硫蛋白是具有抗氧化特性的锌结合蛋白，可以保护细胞和组织免受氧化应激[14]，其表达可降低高血糖诱导的器官中的氧化应激、糖尿病并发症风险[15]。

3 锌缺乏与 DN

3.1 锌缺乏与氧化应激、炎症

DN的发生与氧化应激、炎症密切相关。高糖诱导活性氧类(reactive oxygen species，ROS)产生过多，促进了炎症因子等的基因表达，导致β细胞功能障碍和细胞凋亡，胰岛素信号转导障碍，导致糖尿病血管并发症的发生[16]。核因子网织红细胞2相关子(nuclear factor erythroid 2 related factor，Nrf2)为机体重要的抗氧化剂，锌是Nrf2的调节剂。研究[17]表明：补锌治疗小鼠组Nrf2激活后通过核移位可上调其下游的抗氧化因子，从而减轻肾小管上皮细胞及肾组织的氧化损伤。Hamdiken等[18]在链脲佐菌素诱导的糖尿病小鼠研究中发现：与对照组相比较，Ruta chalepensis抗氧化剂可以降低低锌饲养状态下小鼠肝肾组织的氧化应激标志物，其作用机制可能通过降低血糖起作用。Barman等[19]研究显示：补锌治疗可抑制NF-κB信号通路，从而使糖尿病鼠肾组织氧化损伤和炎性反应减轻，其确切机制有待进一步研究。

3.2 锌的类胰岛素样作用

胰岛β细胞是人体含锌量较高的组织细胞。锌抑制蛋白酪氨酸磷酸酶1B(protein tyrosine phosphatase 1B，PTP1B)对胰岛素/胰岛素样生长因子-1受体的去磷酸化作用，并维持受体下游信号转导处于活化状态[20]，具有类胰岛素样作用。葡萄糖转运蛋白4(glucose transporter4，GLUT4)是由胰岛素调节的重要葡萄糖转运体，可受磷脂酰肌醇-3-激酶(phosphoinositide-3-kinase，PI3K)和蛋白激酶B(Akt)信号通路介导。胰岛素调节的氨肽酶(insulin-regulated aminopeptidase，IRAP)是锌依赖性酶，可能是维持正常GLUT4水平以确保葡萄糖摄取进入组织细胞所必需的[21]。Coulston等[22]首先报道了锌促进大鼠附睾脂肪细胞的脂肪生成。锌参与小鼠3T3-L1脂肪细胞中转化生长因子β(transforming- growth factor-β，TGF-β)和Akt信号通路活化，调节葡萄糖转运，发挥胰岛素样作用，介导血糖代谢[23]。Luo等[24]研究发现：2型糖尿病并发肾病患者组血清锌水平明显低于无并发症组，且糖化血红蛋白较高，蛋白尿患者组血清锌水平显著降低，血清锌水平是DN的独立危险因素。说明锌能够缓解糖尿病高糖状态，可能与其增加胰岛素活性有关。

3.3 锌缺乏与肾小管间质纤维化

肾小管间质纤维化几乎是所有包括DN的慢性进行性肾病的最终共同途径[25]。肾间质纤维化涉及间质成纤维细胞的扩增，肌成纤维细胞活化和细胞外基质(extra-cellular matrix，ECM)积聚，导致正常肾功能丧失并最终导致肾功能衰竭[26]。ECM蛋白合成增加和/或ECM降低减少最终导致糖尿病相关肾小管间质纤维化的发生[27-28]。TGF-β是一种强促纤维化细胞因子，与DN中ECM积聚的发病机制有关[29]。Zhang等[30]研究发现：大鼠肾小管上皮细胞高糖诱导下，锌可通过调节TGF-β和PI3K参与上皮-间质转化。亦有研究[31]指出：DN小鼠给予补锌治疗可以抑制上皮间质转化，并通过下调缺氧诱导因子α减轻肾小管间质纤维化。Zhang等[8]研究还发现：锌缺乏可通过介导TGF-β/Smad2/3信号通路，进而加重糖尿病肾小管间质纤维化。Barman等[19]研究显示：与正常饮食组比较，补锌组大鼠肾中纤连蛋白和胶原蛋白表达水平明显降低，表明锌缺乏可加重糖尿病导致的肾间质纤维化。

3.4 锌缺乏与糖基化终末产物、自噬

长期高糖环境下，糖基化终末产物(advanced glycation end products，AGEs)会大量堆积。农伟虎等[32]研究显示：AGEs与其受体结合后导致肾的氧化应激增强，产生自由基，导致氧化损伤，促进DN的发生和发展。糖尿病患者高血糖及AGEs堆积可以活化NF-κB通路，导致ROS的增多，与血管内皮细胞的损伤、各种组织细胞的凋亡等多个病理生理过程相关[33]。补锌治疗可以抵抗

AGEs介导的血管内皮细胞功能障碍，增强内皮型一氧化氮合(endothelial nitric oxide synthase，eNOS)活性，并下调NF-κB的激活[34]。髓过氧化酶(myeloperoxidase，MPO)是一种过氧化物酶，其产生次氯酸导致羧基化物产生，从而导致AGEs生成。Sacan等[35]研究证实：锌可降低MPO水平及其诱导的ROS生成，从而减轻炎症和氧化应激反应。

在肾脏中，自噬存在于足细胞及近端肾小管细胞中，对于清除已损害或过度表达的蛋白、维持其内环境稳态具有重要作用。多种急性肾损伤动物模型中自噬对肾发挥保护作用[36]。在高糖环境下，自噬对足细胞溶酶体稳态具有重要作用，自噬受损可导致足细胞损伤，大量蛋白尿产生[37]。师朗等[38]研究发现：在足细胞受损过程中DN患者肾组织中自噬被激活。Vallon等[39]研究显示：在链脲佐菌素(Streptozocin，STZ)诱导的糖尿病小鼠中发现自噬-溶酶体降解途径中的底物p62/Sequestosome 1(SQSTM1)在肾中的累积。锌作为自噬的正调控因子，向培养基中添加锌发现大鼠嗜铬细胞-12 (pheochromocytoma- 12，PC-12)的自噬[40]。研究[41]显示：锌耗竭会诱导自噬，锌缺失可导致p62/SQSTM降解受损。降低p62/SQSTM1可以抑制NF-κB活化，减轻炎症反应[42]，但锌调节自噬的机制尚需进一步研究。

4 结语

锌缺乏可通过加重氧化应激、炎症，影响葡萄糖代谢，介导间质纤维化，调节AGEs生成及自噬等多种方式参与DN的发生与发展，其涉及多种信号通路。因此，尽管已经进行了大量研究，但DN的确切发病机制仍不十分清楚。此外，诸多外在因素如饮食、运动、肥胖及吸烟等均与DN的发生及发展密切相关。锌缺乏与DN的研究仍需进一步研究。

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