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糖尿病肾病致凝血异常的研究 *

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摘要: 糖尿病(DM)已成为世界性的常见病,其发病率高,并且随着生活水平的改善,其发病率必然还会进一步加剧。血管病变是DM的重要并发症之一,糖尿病肾病(DN)是糖尿病常见且严重的微血管并发症,与血栓形成密切相关。糖尿病肾病的进展伴随着体内凝血活性和抗凝活性的失调,同时激活自身免疫系统,发生炎症反应。炎症应答过程中释放的炎症因子损伤肾小球内皮细胞,导致抗凝活性减弱。DN患者体内血细胞激活,微粒形成增多会加强凝血活性。此外,纤溶酶抑制剂(PAI-1)与纤溶酶激活剂(tPA)的失衡会引起纤溶系统紊乱。这三个方面引起DN患者体内的高凝状态加重,并因此加速肾功能恶化,导致肾小球率过滤降低,系膜基质增多,最终引起肾小球硬化及终末期肾脏疾病。本文就糖尿病肾病致凝血异常的发生机制做一综述。

关键词: 糖尿病肾病;凝血功能异常;高凝状态

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Research on the Coagulopathy of Diabetic Nephropathy*

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ABSTRACT: Diabetes mellitus (DM) has become a common disease worldwide with a higher incidence of complications. Vascular disease is one of the most sever complication of DM. Diabetic nephropathy (DN) is a common complication which is closely related to the thrombus formation of microvascular system. The progression of diabetic nephropathy is accompanied with dysfunction of procoagulant and anticoagulant factors in vivo and simultaneously activated the immune system which could lead to the inflammation. Inflammatory cytokines will be released during the inflammatory response and damage the endothelial cell that decreased anticoagulant activity. Moreover, the increased procoagulant factor Xa and microparticles will enhance the clotting activity. The imbalance of plasminogen activator inhibitor (PAI-1) and tissue-type plasminogen activator (tPA) can cause disorders of fibrinolytic system. These three aspects caused a hypercoagulable state in patients with DN and promote the deterioration of renal function, finally, resulting in reduced glomerular filtration rate, mesangial matrix increase, and eventually the glomerulosclerosis and end-stage renal disease. In this study, we will make a review about the mechanism of coagulopathy in diabetic nephropathy.

Key words: Diabetic nephropathy; Coagulopathy; Hypercoagulable state

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前言

糖尿病肾病(DN)是糖尿病的微血管并发症,严重危害人类健康,是导致终末期肾病的主要原因。DN患者体内的固有免疫系统被激活,释放各种炎症因子,损伤肾小球内皮细胞,受损的细胞释放促炎蛋白,进一步加重炎症反应,此外,体内的抗凝活性也因此减弱。APC也由于内皮细胞受损导致膜上TM减少而抗凝活性下降。由此所引起的高凝状态进一步加重炎症反应,加速肾功能恶化。同样,研究证明DN患者体内的血细胞激活,微粒生成增多。其中,外翻的磷脂酰丝氨酸可以为凝血反应提供催化表面,加速凝血级联反应。同时,血小板的激活还可以进一步加剧炎症反应,与受损的内皮细胞功能相似,导致肾损伤。因子Xa,PAI-1等还与TGF-β功能相关,使肾小球系膜基质增多,导致肾小球硬化。由此可见,DN患者体内的凝血异常由多种因素构成。

1 凝血系统异常

1.1 凝血因子 Xa

凝血因子Xa在凝血级联瀑布反应中有重要的作用,它可以激活凝血酶原转变为凝血酶,进而增加纤维蛋白的生成,达到血液凝固的状态。糖尿病肾病患者的凝血因子Xa的表达和活性均有所提高[1]。凝血酶和凝血因子Xa通过激活肾小球系膜细胞表面的PAR蛋白家族[2,3],使肾小球细胞外基质增多和纤维蛋白沉积,引起肾小球硬化。此外,凝血酶刺激系膜TGF-β的生成增多,也会增加肾小球细胞外基质[4]。有研究表明:磺达肝癸钠,一种人工合成的戊糖类似物,可以选择性的抑制凝血因子Xa的活性,减少缺血再灌注期间肾损伤所致的炎症反应[5]。

1.2 磷脂酰丝氨酸

1.2.1 微粒 当人体内的细胞遭受凋亡,化学刺激,如凝血酶、内毒素等,或者在血流动力学改变的情况下,发生局部血管狭

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窄产生湍流和剪切力变化等物理刺激时,细胞便会释放出膜碎片,称之为微粒[6]。微粒表面表达含阴离子的磷脂酰丝氨酸(PS)及特异性母细胞抗体。糖尿病肾病患者体内,血小板源性(PMP)和内皮源性微粒(EMP)释放增多[7,8]。此外,单核细胞巨噬细胞,平滑肌细胞的等也可以释放微粒,DN 患者体内的病理环境同样会造成这些细胞的损伤,所以微粒也可能来源于此。微粒表面的 PS 为凝血酶原酶复合物的聚集提供一个催化表面,从而促进凝血反应的发生,导致血液的高凝状态利于血栓形成[9]。Brodsky 等[10]发现,微粒可以减少内皮细胞 NO 的产生,增加过氧化物的生成,进一步加重内皮细胞的损伤,减弱 DN 患者的抗凝活性。

1.2.2 **血小板** DM 患者微血管并发症的机制之一即是血小板的活化。激活的血小板分泌促炎蛋白和生长因子,并且膜内侧的磷脂酰丝氨酸外翻,增加疾病发生炎症反应和血栓栓塞的倾向性[11],活化的血小板表面表达的 P 选择蛋白可以吸引中性粒细胞核单核细胞的聚集,加剧凝血和炎症反应[12]。糖尿病肾病患者体内血小板活性及平均血小板体积均增加[13],不仅增加 DN 患者的凝血活性,而且是蛋白尿和心血管疾病的高危因素[14]。值得注意的是,有研究表明,当肾脏疾病发展到晚期时,血小板膜糖蛋白 GPIIb/IIIa 受损,ADP 的释放发生变化,花生四烯酸和前列环素的代谢异常,尿毒素增加,这些均会影响血小板的粘附和聚集,导致患者的出血倾向[15]。

1.3 **组织因子**

TF 是凝血级联反应的主要激活物,通过转录因子 NF-KB 信号通路转导[16],可以被体内的的 NO 抑制,游离脂肪酸激活。DN 患者体内缺乏 eNOS,导致 NO 生成减少,对 TF 生成的抑制减弱,导致体内 TF 增多。增多的 TF 使 FVIIa, FXa 以及凝血酶生成增多,使凝血活性增强。同时,这些激活的蛋白酶可以激活 PAR,可能与 DN 的进展相关[17]。此外,TF 可以介导炎症反应,NO 的缺乏会使 DN 患者炎症基因表达增多,炎症反过来又会使单核细胞,巨噬细胞聚集,进一步增加 TF 的表达,提高促凝活性,使 DN 肾损伤加剧[18]。

2 抗凝系统异常

2.1 **活化蛋白** C (APC)

蛋白 C 是由肝脏合成的维生素 K 依赖因子。过去的研究表明 APC 可以灭活凝血因子Ⅴa 和Ⅷa,从而减少凝血酶的生成[19]。最近研究显示,APC 还具有抗炎,抗凋亡和促纤维蛋白溶解等作用。APC 通过和肾小球内皮细胞上的凝血酶—血栓调节蛋白(TM)复合体结合,使肾小球内皮细胞受到保护,避免凋亡[20]。DN 患者肾小球内皮细胞受损,细胞膜上的 TM 大量释放到血浆中,从而使留在内皮细胞膜表面的 TM 减少,最终导致 APC 生成减少[21]。糖尿病肾病患者体内 APC 含量和功能的降低会影响肾小球毛细血管的通透性,增加肾小球内皮细胞和足细胞的凋亡几率,增加 DN 患者的凝血活性[22]。

2.2 **内皮细胞**

在正常情况下,内皮细胞表面表达各种抗凝成分如血栓调节蛋白、内皮蛋白 C 受体、蛋白 S 和组织因子途径抑制物等[23]。因此,在生理状态下,血管内皮具有防止血栓形成的功能。糖尿病肾病的患者,由于胰岛素抵抗等各种因素,内皮细胞功能紊乱,内皮型一氧化氮合酶减少(eNOS),从而使 NO 的生成减少,NO 的功能与抗氧化和抗血栓形成有关。相反,活性氧物质的产量增多[24]。eNOS 的减少与 ROS 的增多会上调炎症介质和炎症分子的表达,从而进一步损伤内皮细胞。此外,血管内皮生长因子(VEGF)在生理情况下对血管起保护作用,但是在内皮细胞受损、eNOS 减少的情况下,人体 VEGF 就会表现出一种毒性作用,它会促进血管的增长[25],导致肾小球基膜增厚和基质增生。同时,内皮细胞的损伤会伴随血浆 vWF 的表达增加,从而增加血液的促凝活性[26]。肾小球内皮细胞上表达的硫酸乙酰肝素具有抗血栓的功能,DN 患者内皮细胞受损,影响该物质的新陈代谢,使胞膜上该物质分布减少,抗凝活性降低[21]。受损的内皮细胞表现出的促凝活性还与内皮细胞上 PGI2 表达降低,血栓素表达增加有关,因为这使血小板聚集增多,从而在微循环中易形成微血栓。

3 纤溶系统异常

3.1 **纤溶酶抑制剂**(PAI-1)

PAI-1 是组织型纤溶酶激活剂(tPA)和纤溶酶原激活剂(uPA)的对抗剂,可以抑制蛋白酶的水解,对细胞粘附和增殖起到重要的作用。糖尿病肾病患者的炎症和免疫系统的激活增加促炎因子 THF-α,IL-6 等的释放,这些因子激活 PAI-1 等蛋白的释放[27]。DN 患者体内增加的 PAI-1 不仅会抑制肾小球内纤维蛋白的溶解,增加高凝状态,还会引起 TGF-β 增多,使肾小球细胞外基质积聚,纤维化,最终导致肾小球硬化[28]。实验证明 PAI-1 抑制剂的使用,会缓解 DN 肾小球的纤维化,溶解血栓,但至今为止对于 PAI-1 的研究并不深入,它在临床应用中的价值还未确定[29]。

3.2 **纤溶酶源激活剂**(tPA)

凝血过程中,tPA 的快速释放在调节血栓形成中起到重要的作用。DN 患者的 tPA 释放减少[30],会影响血栓的及时溶解,从而造成高纤维化及高凝状态。此外,患者体内纤维蛋白的增多会增加血浆粘度,导致动脉粥样硬化,加速血小板聚集[31]。

4 小结

综上所述,DN 患者的凝血异常是多方面因素决定的,包括凝血系统紊乱,抗凝系统紊乱,以及纤溶系统平衡紊乱。各个因素又是相辅相成,互相促进的,如炎症增加凝血活性,高凝状态又加速炎症因子的释放。此外,DN 的高凝状态与动脉粥样硬化,心衰以及终末肾脏疾病密切相关。因此,DN 凝血紊乱的治疗有着重要意义,应该引起广泛的关注和深入研究。

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