Advances in Clinical Medicine 临床医学进展, 2022, 12(4), 2535-2540
Published Online April 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.124365

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糖尿病肾病患者TyG、SAA与动脉粥样硬化的相关性研究

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收稿日期：2022年3月6日；录用日期：2022年3月29日；发布日期：2022年4月11日

摘 要

糖尿病是我国发病率最高的慢性疾病之一，作为一种代谢性疾病，其会导致一系列机体病变造成严重的健康问题。糖尿病对患者的影响主要是由并发症导致。其中糖尿病肾病是糖尿病常见严重并发症中的一种，肾脏部位的微血管发生病变累及肾脏出现蛋白尿是导致糖尿病患者死亡的主要因素之一。研究发现在糖尿病肾病患者中动脉粥样硬化的发生几率也高于健康人群，然而其发生机理尚未有定论。近年来的研究显示，遗传因素、胰岛素抵抗、免疫功能和炎症反应都可能是导致并发动脉粥样硬化的原因，其中胰岛素抵抗、炎症反应在糖尿病肾病患者并发动脉粥样硬化的过程中可能起到最为关键的作用。因此，本综述拟探讨糖尿病肾病患者血清中炎症因子指标SAA水平与胰岛素抵抗并考察其预测糖尿病肾病患者并发动脉粥样硬化的效果。

关键词

糖尿病肾病，动脉粥样硬化，TyG，SAA

Study on the Correlation between TyG, SAA and Atherosclerosis in Diabetic Nephropathy Patients

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Received: Mar. 6th, 2022; accepted: Mar. 29th, 2022; published: Apr. 11th, 2022

文章引用: 朱文举, 左小芹. 糖尿病肾病患者 TyG、SAA 与动脉粥样硬化的相关性研究[J]. 临床医学进展, 2022, 12(4): 2535-2540. DOI: 10.12677/acm.2022.124365

Abstract

Diabetes is one of the chronic diseases with the highest incidence in China. As a metabolic disease, it will lead to a series of body lesions and cause serious health problems. The impact of diabetes on patients is mainly caused by complications. Among them, diabetic nephropathy is one of the common serious complications of diabetes. The microangiopathy in the kidney and proteinuria is one of the main factors leading to the death of diabetic patients. Studies have found that the incidence of atherosclerosis in diabetic nephropathy patients is also higher than that in healthy people, but the mechanism of its occurrence has not been determined. Recent studies have shown that genetic factors, insulin resistance, immune function and inflammatory response may be the causes of atherosclerosis, among which insulin resistance and inflammatory response may play the most critical role in the process of atherosclerosis in diabetic nephropathy patients. Therefore, this review aims to investigate the relationship between serum inflammatory factor SAA level and insulin resistance in diabetic nephropathy patients and its effect on predicting atherosclerosis in diabetic nephropathy patients.

Keywords

Diabetic Nephropathy, Atherosclerosis, TyG, SAA

1. 引言

糖尿病肾病(DKD)在所有糖尿病患者中的发病率高达 30%~40%，是全球终末期肾衰竭(ESRD)的主要原因，占接受肾脏替代治疗的患者的近一半[1]。肾功能丧失与组织病理学变化相对应，包括肾小球和肾小管基底膜进行性增厚、系膜扩张、足细胞消失和丢失、肾小管间质纤维化和小动脉玻璃样变[2]。事实上，DKD 患者经常死于心血管疾病(CVD)，而糖尿病患者心血管死亡风险增加的大部分与 DKD 的存在有关[3]。通过对 1 型糖尿病患者发病和进展为 DKD 的研究[4]和 UKPDS [5]、ACCORD [6]、ADVANCE [7]、VADT [8]对 2 型糖尿病患者的研究，葡萄糖和血脂异常在内的一系列因素可能在诱导 DKD 的发生和进展中发挥相关作用。高脂血症是公认的 CVD 危险因素，在 T2DM 和 DKD 患者中也是如此[9]。尽管已有流行病学证据，但将致动脉粥样硬化性血脂异常与 DKD 联系起来的复杂病理生理关系尚未完全阐明。肾脏积极参与脂质代谢，肾功能不全通常与脂质的改变有关。因此，随着肾功能不全的进展，血浆脂质发生显着变化，LDL-C 和残余物增加，HDL-C 降低，TG 水平升高，尤其是在餐后[10] [11]。此外，有研究表明 CKD 患者的肝 TG 脂肪酶降低，导致机体处理血脂及血糖能力下降，虽然已经充分证明肾功能不全可能导致脂质代谢改变，值得注意的是，高血糖可能会加剧肾脏中的脂质积累和损伤，例如糖尿病。因此，已经证明高脂肪饮食加重糖尿病小鼠的蛋白尿和肾小球病变，表明脂质和葡萄糖水平对肾实质的有害协同作用[12] [13]。无论涉及何种机制，一旦脂质在肾脏中积聚，它们会通过增加胰岛素抵抗和炎症反应等导致一些有害后果，代谢紊乱聚集在一起，导致肾小球超滤和血管通透性增加、亚临床炎症和/或足细胞异常的机制[14] [15]，导致动脉硬化发生率增加，心脑血管死亡率增高。因此糖尿病肾病在发生动脉粥样硬化的过程中，血脂、血糖异常导致胰岛素抵抗及炎症反应是重要的病理生理基础，关系引起了

众多学者的重视。研究表明胰岛素抵抗状态常先于高血压、血脂紊乱、糖尿病等动脉粥样硬化的传统危险因素存在[16] [17] [18]。由于DKD本身引起的代谢紊乱使循环中IL-6、CRP、SAA等炎症介质增加，而微炎症状态与糖尿病血管并发症相关，本综述拟探讨糖尿病肾病患者血清中炎症因子指标SAA水平与胰岛素抵抗指数(TyG)并考察其预测糖尿病肾病患者并发动脉粥样硬化的效果。

2. 甘油三酯葡萄糖指数

甘油三酯葡萄糖指数(triglyceride glucose index, TyG指数)最早是由Simental-Mendia等提出的[18]，该指数对胰岛素抵抗(Insulin resistance, IR)的评价敏感度、特异度均较高[19]，它可作为评估IR的替代标志物，而且通过公式TyG = Ln [血清甘油三酯(mg/dL) × 空腹血糖(mg/dL)/2]简单的计算即可得出，适用于大型临床和流行病学研究[20]。微量蛋白尿患者往往存在更严重的IR，提示IR可能会加速DKD的进展[21]，既往的研究证实，2型DM患者伴随血脂异常及胰岛素抵抗，其表现主要为TG水平高及HDL水平低[22]，与正常肾脏相比，诊断为DKD的患者的肾脏活组织检查中可观察到大量脂质沉积和细胞内脂滴增加，脂质代谢异常可能在DKD的发病机制中起一定作用[23]，因此，DKD患者TG越高，TyG数值越大，IR越严重。此外IR使机体处于全身炎症环境状态，机体抗氧化能力下降，造成血管内皮功能异常，内皮功能异常是动脉粥样硬化的重要使动因素之一，内皮功能异常可导致动脉张力调节功能障碍[24]，渗透屏障作用下降，释放细胞因子促进血小板聚集等，从而引起冠状动脉粥样硬化，在胰岛素抵抗的状态下，脂肪组织代谢、分解增加，产生更多的游离脂肪酸(free fatty acids, FFA)，游离脂肪酸进入肝脏中，导致甘油三酯和低密度脂蛋白(low density lipoprotein, LDL)增加而高密度脂蛋白水平下降，加重了糖尿病患者的血脂异常，IR使各种炎症因子分泌异常，促使内皮细胞损伤，LDL进入动脉壁，单核细胞聚集，成纤维细胞增殖，伴随着高甘油三酯血症的并发症可促进低密度脂蛋白小颗粒的形成，TG和富含TG的脂蛋白是动脉粥样硬化心血管疾病的致病因素促进了动脉粥样硬化形成[25] [26]。且目前已经应用于冠状动脉钙化和亚临床动脉粥样硬化的预测因子。

3. 血清淀粉蛋白A

血清淀粉样蛋白A (serum amyloid A, SAA)是由肝脏产生的急性期蛋白。作为炎性标志物，SAA水平升高比C反应蛋白(C-reaction protein, CRP)更早，灵敏度更高，部分情况下CRP数值在低于8 mg/L时不能被检测出，而SAA在急性感染中，12 h内可达到峰值，能够敏感地识别微弱炎症的刺激。在机体发生感染、创伤、炎症后血清SAA水平可在5~6 h升高1000倍[27]。随着SAA蛋白结构、生物学功能及分子调控机制研究的深入，其作为新的标记物在认知功能障碍、原发性肾病、DN、自身免疫性疾病中被广泛关注[28] [29] [30]。白伟等[31]的研究表明，T2DM肾病患者血清SAA水平显著高于单纯T2DM患者，且均显著高于健康人；当机体出现创伤或者出现急性炎症状态下，SAA水平会有大幅度的迅速升高，升高后的水平较其他急性时相反应蛋白明显更高[32]，SAA可刺激中性粒细胞加快炎性因子释放，炎性因子对肾脏产生更明显作用，加重肾脏炎性反应，从而会引起肾小球肥大、硬化，使糖尿病肾病病情进一步加重。在炎症激活后，SAA可诱导单核细胞和内皮细胞分泌组织因子，并通过诱导红细胞凝集、淋巴细胞、血小板活化和聚集，诱导内皮细胞表达促炎介质，导致内皮细胞功能障碍[33]。无脂SAA与HDL形成复合物，减少促炎作用的同时，使HDL无法有效转运胆固醇，导致胆固醇堆积并且使LDL在血管壁的滞留增加，破坏内皮细胞、加剧炎症反应、诱导血栓形成，加速血管动脉硬化形成。

4. 炎症因子与胰岛素抵抗

研究表明，机体慢性炎症参与了胰岛素抵抗的病理过程。当机体能量供应水平超过机体一般所需的

能量水平时，一些比较敏感的感知细胞受到刺激，分子机制信号转导通路很快被激活，而这些病理刺激通过干扰胰岛素信号胞内转导途径，最终导致慢性炎症及微炎症的产生。外周神经系统和中枢神经系统的一些慢性炎症反应均会不同程度地降低机体的胰岛素敏感性发生及糖耐量异常[34]。进一步导致胰岛素抵抗这一病理改变和糖脂代谢系统的功能障碍[35]，而且二者之间相互促进，相互联系，持续性恶化糖尿病肾病的病理进程，加速动脉硬化的发生，发展。

5. 总结

DKD 是糖尿病的严重并发症，是全球终末期肾病的主要原因之一[2]。近年来，一方面是科学、治疗和筛查的进步，另一方面是糖尿病人群的逐渐老龄化，深刻地改变了 DKD 的临床表现，多种机制促成了 DKD 的发展和进展，其中大部分机制需要进一步揭示。当然，遗传易感性与高血糖引起的代谢环境变化以及胰岛素抵抗对血流动力学平衡的影响是 DKD 发展的重要因素[23]。根据大量证据[36] [37] [38]支持承认微血管病和大血管病是疾病的连续统一体，糖尿病肾病的患病率随糖尿病增加随之上升，并发动脉硬化的风险也随之升高，由于其早期缺乏特征性临床表现，临床实施受到多种因素的影响。糖尿病早期肾脏损伤标志物的研究对于临床诊断糖尿病肾病合并动脉硬化意义重大，血清 SAA、TyG 单独或联合检测在早期 DKD 发生动脉粥样硬化的诊断中都具有一定应用价值，联合检测具有更高的灵敏度和特异度，可作为临床提供最佳诊断和早期预测评估标记物。

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