四川大学学报（医学版） 2023，54（6）：1074－1079
J Sichuan Univ（Med Sci）

在线全文

糖尿病肾脏疾病非经典临床类型与病理变化综述*

方晨茜，孙丽雅，刘 研，肖 力，孙 林△
中南大学湘雅二医院 肾内科（长沙 410011）

【摘要】 糖尿病肾脏疾病（diabetic kidney disease, DKD）是糖尿病的常见并发症，约1/3糖尿病患者可发展至DKD。典型DKD临床早期表现为微量蛋白尿，随着疾病进展可出现大量蛋白尿并伴随肾功能减退。一般认为DKD患者出现大量蛋白尿后病情逆转可能性降低，最终部分患者可发展为终末期肾病（end-stage renal disease, ESRD）。此外，DKD典型病理变化为肾小球基底膜增厚、系膜基质增多、K-W结节及晚期糖尿病肾小球硬化。然而，临床上某些DKD患者，特别是2型糖尿病（type 2 diabetes mellitus, T2DM）合并慢性肾脏病患者临床表现可呈多样性，疾病进展与转归不同，表现为非经典型DKD类型，如正常白蛋白尿型、蛋白尿缓解型、肾功能快速下降型。此外，肾活检还可见新月体形成这一特殊病理改变。但目前临床医师对此认识尚不足，故值得重视。本文结合国内外文献及本课题组既往研究结果，对非经典DKD临床表型与病理变化进行初步介绍，以期进一步加强临床医生对非经典DKD表型与病理变化的认识，提高我国DKD防治水平。

【关键词】 糖尿病肾病 蛋白尿缓解 肾功能快速下降 正常白蛋白尿 新月体 综述

Non-Classical Clinical Types and Pathological Changes of Diabetic Kidney Disease: A Review *FANG Chenxi*, *SUN Liya*, *LIU Yan*, *XIAO Li*, *SUN Lin*△. *Department of Nephrology*, *The Second Xiangya Hospital*, *Central South University*, Changsha 410011, China
△ Corresponding author, E-mail: sunlin@csu.edu.cn

【**Abstract**】 Diabetic kidney disease (DKD) is a common complication of diabetes mellitus and approximately 1/3 of diabetic patients may progress to DKD. A typical early clinical manifestation of DKD is microalbuminuria and patients may present with macroproteinuria accompanied by a decrease in renal function condition as the disease progresses. It is generally believed that the likelihood of a reversal of the disease is reduced after the development of macroproteinuria in patients with DKD, and that eventually some patients' condition may develop into end-stage renal disease (ESRD). Moreover, the thickening of the glomerular basement membrane, mesangial matrix expansion, Kimmelstiel-Wilson (K-W) nodules, and glomerulosclerosis in end-stage diabetes mellitus are typical pathologic changes of DKD. However, some DKD patients, especially those with type 2 diabetes mellitus (T2DM) combined with chronic kidney disease, may have diverse clinical manifestations, showing variations in disease progression and regression, and manifesting as non-classical types of DKD, such as normoalbuminuric DKD, proteinuria-reduced DKD, and DKD with rapid decline in renal function. In addition, the formation of crescents, a special pathological change, is observed in renal biopsy. However, this issue is currently under-recognized by clinicians and therefore deserves more attention. In order to improve clinicians' understanding of the presentations and pathological changes of non-classical DKD and the level of DKD prevention and treatment in China, we present a preliminary introduction to the clinical phenotypes and pathological changes of non-classical types of DKD in this paper by summarizing the findings of our prior studies as well as domestic and international literature.

【**Key words**】 Diabetic kidney disease Albuminuria remission Normoalbuminuria Rapid decline in renal function Crescent Review

中国成人糖尿病（diabetes mellitus, DM）患病率高达12.4%[1]。大约30%的1型糖尿病患者（type 1 diabetes mellitus, T1DM）和大约40%的2型糖尿病（type 2 diabetes mellitus, T2DM）患者会患上慢性肾脏病（chronic kidney disease, CKD），部分患者甚至可发展至终末期肾病（end stage renal disease, ESRD）[2]。随着DM发病率不断增加，糖尿病肾脏疾病（diabetic kidney disease, DKD）已成为引起ESRD的主要原因[3]。DKD发病机制十分复杂，可能与血流动力学变化、肾小球高滤过、糖脂代谢紊乱、异常炎症因子表达、氧化应激、蛋白激酶C激活、细胞自噬异常等相关[4-7]。目前DKD治疗措施仍然有限，患者常合并不良心血管事件、感染、贫血、营养不良等疾病，死亡风险显著升高[8]，应引起高度重视。

2021年《糖尿病肾脏疾病临床诊疗中国指南》中DKD诊断标准如下：①随机尿白蛋白和肌酐比（urinary albumin-to-creatinine ratio, UACR）≥30 mg/g，或尿白蛋白排泄率（urinary albumin excretion rate, UAER）≥30 mg/24 h，3至6个月内复检3次，有2次达到或大于临界值。②估算肾小球滤过率（estimated glomerular filtration

* 湖南省自然科学基金委员会重大揭榜项目（No. 2021JC0003）资助
△ 通信作者，E-mail: sunlin@csu.edu.cn
出版日期：2023-11-20

rate, eGFR)< 60 mL/(min·1.73 m^2) 3个月以上。③肾活检符合DKD病理改变。满足以上条件之一者, 即可诊断为DKD[9]。近年来, 改善全球肾脏病预后组织(KDIGO)与美国糖尿病协会(ADA)制定的DKD诊疗指南均以持续性蛋白尿和/或eGFR下降为临床诊断DKD指标[10-11]。一般认为DKD患者出现微量白蛋白尿可通过治疗逆转, 但一旦出现大量蛋白尿则不可逆转[12]。随着人们对DKD临床研究深入, 发现部分DKD患者表现不同于上述经典表型, 可表现为正常白蛋白尿型、蛋白尿缓解型、快速进展型这些非经典特殊类型。其次, DKD患者病理变化主要表现为肾小球基底膜增厚、系膜基质增多、K-W结节及晚期糖尿病肾小球硬化[13]。DKD也可出现肾小管间质及血管病变, 其损伤程度与肾脏不良预后相关[14]。此外, 在临床DKD患者病理结果中也发现非典型的病理改变, 如新月体[15]。本文对非经典DKD临床与病理表型进行初步介绍, 以加强临床医生对非经典DKD的认识, 提高我国对本病的防治水平。

1　DKD自然病程与病理变化

经典的DKD自然病程为5个阶段: ①高灌注高滤过期; ②间歇性微量白蛋白尿期; ③持续性微量白蛋白尿期(又称为早期DKD); ④临床蛋白尿期; ⑤肾功能衰竭期[16]。其中第1与第2阶段为临床前期, 其特征是患者肾脏形态有轻微变化, 但没有重要的肾脏损害迹象。第3阶段则出现持续性白蛋白尿, 即尿白蛋白> 30 mg/L, 肌酐稍增加、肾功能轻度减退, eGFR低于60 mL/(min·1.73 m^2)。第4和第5阶段也称为临床肾病期, 此期患者出现大量蛋白尿和进行性GFR下降。2010年国际肾脏病理学会提出了4类肾小球病变: Ⅰ类(基底膜增厚)、Ⅱ类(系膜基质增多)、Ⅲ类(结节性硬化症)和Ⅳ类(晚期糖尿病肾小球硬化), 并对肾小管损伤、肾间质与肾血管进行了描述与损伤分级[13]。目前发现, 肾小管与肾间质损伤也是DKD的病理特点, 且不完全继发于肾小球损伤[17-18]。FARIAS等[19]发现DKD早期肾小管损伤标志物(如β2微球蛋白)升高, 并出现小管间质病理损伤(如小管基底膜增厚, 间质细胞增多, 皮质肾小管-间质间隙面积增加), 但未出现肾小球病理损伤。既往研究也发现DKD患者小管间质纤维化与小管萎缩程度与eGFR下降和肾衰竭风险呈正相关[20-21]。提示DKD患者除常见的小球损伤外, 小管及间质病理变化也随着疾病进展而加重, 并与肾脏存活、患者预后密切相关。

2　DKD非经典临床类型

2.1　正常白蛋白尿型

白蛋白尿一直被认为是临床诊断DKD的关键指标, UACR≥30 mg/g或UAER≥30 mg/24 h为DKD临床诊断标准之一[22-23]。然而临床工作中常可发现部分DM患者UACR< 30 mg/g, 但其eGFR< 60 mL/(min·1.73 m^2)。国内外对此有不同命名, 如正常白蛋白尿型肾功能不全[24]、正常白蛋白尿糖尿病合并肾功能不全[25]等。最近中华医学会肾脏病专业委员会制定的《糖尿病肾脏疾病临床诊疗中国指南》将此特殊类型DKD正式命名为"正常白蛋白尿糖尿病肾脏疾病(normoalbuminuric diabetic kidney disease, NADKD)"[9], 其诊断要点包括: 6个月内至少两次尿液检查UACR< 30 mg/g, 但eGFR< 60 mL/(min·1.73 m^2), 或肾脏活检符合DKD病理改变。

NADKD发病率报道不一, 横断面研究发现T1DM和T2DM患者NADKD的患病率分别为20%和40%[12]。糖尿病控制与并发症试验/糖尿病干预与并发症的流行病学(DCCT/EDIC)报道, eGFR< 60 mL/(min·1.73 m^2)的T1DM患者中, 22.47%患者表现为正常白蛋白尿[26]。最近一项荟萃分析的结果显示T2DM合并肾功能不全患者的NADKD总患病率为45.6%[27]; PICHAIWONG等[28]对一家医院中T2DM患者进行的回顾性研究显示, 45.4%的患者表现为NADKD。有报道提示: 526例肾功能损伤的T2DM患者中有16.7%表现为NADKD[29]。本课题组通过回顾性分析发现NADKD在DKD患者中发病率约为10%(未发表资料)。NADKD患病率报道不一可能与检测方法不一、研究人群不同以及肾素-血管紧张素系统阻滞剂(renin-angiotensin system inhibitors, RASi)、降糖、降压、降血脂及新型降糖药物钠-葡萄糖共转运蛋白2和胰高血糖素样肽-1激动剂应用后尿蛋白减轻有关[30-32]。

NADKD发生机制尚不清, 可能包括: ①大多数NADKD患者对RASi阻断反应良好, 通过RASi保护肾小球减少了蛋白尿[33]; ②年龄因素, NADKD常见老年人群, 随着年龄增长, 肾脏老化, eGFR也逐渐下降至60 mL/(min·1.73 m^2)以下。其原因可能是老年患者通常同时罹患其他疾病, 例如高血压、高血脂等, 这些都可导致动脉硬化从而引起肾脏缺血, 最终影响肾功能[33]。③遗传因素, 遗传基因的多态性与NADKD发生相关, 据报道, 蛋白激酶C-beta基因(protin kinase c-beta gene, *PRKCB*1)的多态与正常白蛋白尿的T2DM患者eGFR降低有关[34]。

有研究显示: NADKD患者年龄较大, 女性居多, 糖尿病病程较短, 血压较低, DM相关并发症如糖尿病视网膜病、神经病变、心血管疾病、肾衰竭等发生率较低[25, 27]; 但一项纳入了10 185例T2DM患者的研究发现, NADKD患者男性、老年比例较高, 三酰甘油水平较高, 高密度脂蛋白胆固醇水平较低[35]。此外, 患者eGFR下降速度更加

缓慢[36]。其次,NADKD肾脏病理变化类似于高血压肾硬化,除典型的DKD肾小球病变外,间质和血管病变更为常见[33, 37]。总之,NADKD是一种常见的非经典表型DKD,有其特殊的临床特征与病理改变,但其临床与病理、发病机制、防治策略仍有待进一步探讨。

2.2 蛋白尿缓解型

既往认为,DKD患者一旦出现大量蛋白尿则不可逆转,最终可发展至ESRD。然而,临床上某些患者蛋白尿由少量到大量的过程并不是单向的,大量蛋白尿通过有效治疗也可能会减轻,有学者将此称之为蛋白尿缓解型DKD。蛋白尿缓解型DKD定义为:DKD患者蛋白尿由3 500 mg/24 h以上,经积极治疗后减少至1 500 mg/24 h左右,并维持至少6个月,期间血清肌酐保持稳定[38]。2001年一项前瞻性观察性研究表明,在T1DM合并DKD患者中,40%患者表现为蛋白尿缓解型DKD,其中部分患者通过积极降压治疗获得长期缓解,其原因可能与RASi与其他抗高血压药物治疗有关[38-39]。我们在临床工作中也发现,部分大量尿蛋白的DKD患者,经积极综合治疗后,尿蛋白可明显减少。JONGS等[40]对达格列净开展的一项临床研究也提示有效控制血糖、血压在DKD治疗中尤为重要。

国外一项针对116例DKD患者的临床观察表明,与大量蛋白尿未缓解的DKD患者相比,缓解型DKD患者血清肌酐翻倍或发展至ESRD风险显著降低[41];但另一项纳入1 441例T1DM合并DKD患者研究数据提示,将微量白蛋白尿降低至正常似乎也不能改善预后[42]。此外,对456例临床疑诊为T2DM合并DKD患者随访研究发现:大量蛋白尿在1年和2年缓解至正常/微量蛋白尿与ESRD的发生率较低相关,然而它并不是ESRD的独立决定因素,还取决于初始eGFR和初始UACR[43]。其次,对此特殊类型的T2DM和早期DKD患者进行肾活检提示肾小球基底膜增厚程度较轻、肾小球硬化和系膜基质体积较少,但这些病理改变与GFR无关[44]。由于蛋白尿是肾脏病进展的独立危险因素,降低尿蛋白可延缓DKD进展,故以蛋白尿为切入点,将DKD大量蛋白尿减少作为一个特殊的临床表型有一定的临床价值,值得关注,但此型的病理生理机制、病理特点、临床与预后等一系列问题仍有较大的研究空间。

2.3 肾功能快速下降型

临床上DKD患者肾功能下降速率不同,分为“快速下降”和“无下降或缓慢下降”型[45]。2013年KDIGO指南提出,DKD患者eGFR年下降速率≥5 mL/(min·1.73 m^2)称为快速下降型[10]。随着时间推移,DKD患者肾脏功能呈线性丧失,预计每4例患者中有1例患者eGFR大幅下降,表现为“肾功能快速下降型DKD”,肾功能损害严重[46]。FURUICHI等[45]对377例经活检证实的DKD患者进行的多中心回顾性研究报告显示,61%的患者在6.9年的随访中eGFR出现过快速下降,其原因可能与高血压、蛋白尿和血糖控制不佳相关[47]。进一步研究表明除了蛋白尿等公认的预测因子外,循环游离脂肪酸、磷脂、组织蛋白酶D也可预测DKD患者早期快速肾功能下降[48-49]。

国外文献表明,与eGFR缓慢下降或者无下降的DKD患者相比,肾功能快速下降型DKD患者年龄更大,男性多见,收缩压更高,基线eGFR也更高[46]。DKD肾功能快速下降型患者微量或大量白蛋白尿、视网膜病变和心血管疾病的发生率也较高[46-47]。DKD患者eGFR快速下降有一定家族遗传性,FRODSHAM等[50]研究发现在15 612例DM患者中,2 127例(13.6%)患者表现为肾功能快速下降型,其中51个高危家系有过度聚集的快速肾功能下降。另外,有报道肾功能快速下降型DKD患者肾脏病理常见结节状病变和系膜溶解[45],而小动脉透明质化是GFR快速下降的危险因素[51]。一项大型临床观察对120万例肾脏疾病受试者和10万例死亡病例分析发现:先前的eGFR下降速率与死亡风险的增加有关,而与当前的eGFR无关,且eGFR年变化斜率与更高的全因死亡风险相关[52];eGFR下降速率与充血性心力衰竭、急性心肌梗死和卒中风险增加相关[53],提示eGFR下降速率越快,随后发生肾功能衰竭和心血管事件的风险就越高。

根据DKD患者肾功能变化情况,将其中GFR快速减退型的患者归为肾功能快速下降型这一特殊类型的DKD,可更加精准了解DKD临床特点与疾病转归,帮助判断预后。总之,目前对肾功能快速下降型DKD的认识才刚刚起步,机制尚不清,预防与干预措施有限,值得进一步深入研究。

3 非经典病理变化

新月体是肾小球囊壁层上皮细胞显著增生,堆积成层,在毛细血管丛周围形成的“新月形”小体,一般发生于免疫相关性肾小球肾炎。早在1975年,ELFENBEIN等[54]首次发现DKD患者存在新月体病理变化,之后有几项病例报告描述了DKD新月体这一特殊病理表现。2018年MOTTL等[55]首次进行了DKD新月体相关的临床回顾性研究,发现DKD患者新月体与ESRD进展相关。本课题组对155例病理诊断为DKD的患者进行回顾性队列研究,发现13%DKD患者病理特征中存在新月体,有新月体的DKD患者24 h蛋白尿和血清肌酐水平更高,且K-W结节、节段性硬化和系膜溶解更严重,同时,通过生存分析

和Meta分析发现新月体是肾脏存活的独立危险因素[56]。对于DKD新月体的形成机制, ELFENBEIN等[54]提出新月体的形成可能与“渗出性病变”或“纤维蛋白帽”有关。透明帽可造成毛细血管壁的压力增加, 导致血管壁破裂, 血管内容外流, 形成新月体。透明帽通常出现在系膜溶解和毛细血管微动脉瘤形成部位[55]。本课题组的研究也发现新月体和系膜溶解之间呈显著正相关, 而与血管病变和毛细血管微动脉瘤无相关性[56]。2014年GAUT等[57]发现DKD新月体主要由肾小球壁上皮细胞和足细胞组成, 没有肾小球基底膜破裂, 且新月体中有一小部分细胞同时表达claudin 1(壁层上皮细胞标记物)和nephrin(肾小球足细胞标记物), 但在炎性新月体细胞中未见。这提示DKD新月体可能在受损肾小球壁层上皮细胞转分化为足细胞进行自我修复的过程中形成。NUNES等[58]通过高糖高脂饮食诱导Wistar大鼠糖尿病前期, 在大鼠的肾脏病理中观察到毛细血管外细胞增殖, 与肾小球Bowman囊腔内的新月体病变相似, 因此提出新月体可能是DKD的早期变化之一的观点。另外, 本课题组研究还观察到C3沉积与新月体之间存在显著的正相关[56], 提示补体系统异常可能也参与DKD新月体的形成。总之, DKD新月体是不可忽视的特殊病理改变, 其发生机制与临床表型的关系及其对预后的影响也需进一步探讨。

4　小结与展望

DKD临床诊断以蛋白尿增多、肾功能下降为主要依据。目前认为蛋白尿是临床诊断DKD的核心指标, 患者肾功能呈逐步减退趋势, 一旦出现大量蛋白尿则不可逆转, K-W结节是DKD典型病理变化。但于临床实际工作中, 我们发现DKD患者特别是T2DM合并DKD患者表现呈多样性、疾病进展与转归结果不一, 表现为非经典DKD类型。鉴于国内外同行对此认识尚不足, 有可能影响本病的正确诊断与治疗。为此, 本文参考了近年来国内外学者对非经典DKD研究进展, 结合本课题组既往研究的经验, 初步介绍了DKD三个非经典临床类型——正常白蛋白尿型、蛋白尿缓解型、肾功能快速下降型, 以及DKD新月体这一DKD特殊病理表现。虽然近年人们对NADKD认识有所加强, 但对蛋白尿缓解型DKD与肾功能快速下降型DKD的认识还有待提高, 特别是对DKD新月体的认识仍有更多的提升空间。故进一步开展大规模、多中心、前瞻性非经典DKD的临床研究, 并深入探讨其发病机制、临床与病理、预后与防治等, 有望进一步提高我们对非经典DKD的认知, 并为临床提出更加合理、精准、有效的防控措施。这些工作将有利于延缓DKD进展, 提高本病的整体防治水平。

*　　*　　*

作者贡献声明　方晨茜负责论文构思、调查研究、初稿写作和审读与编辑写作, 孙丽雅负责调查研究、初稿写作和审读与编辑写作, 刘研负责初稿写作和审读与编辑写作, 肖力负责论文构思和审读与编辑写作, 孙林负责论文构思、调查研究、监督指导、初稿写作和审读与编辑写作。所有作者已经同意将文章提交给本刊, 且对将要发表的版本进行最终定稿, 并同意对工作的所有方面负责。

利益冲突　所有作者均声明不存在利益冲突

参　考　文　献

[1] 马越, 孔祥婕, 彭雯, 等. 中国糖尿病疾病负担现状及趋势. 中国预防医学杂志, 2023, 24: 281–286. doi: 10.16506/j.1009-6639.2023.04.001.

[2] BONNER R, ALBAJRAMI O, HUDSPETH J, *et al*. Diabetic Kidney Disease. Prim Care, 2020, 47(4): 645–659. doi: 10.1016/j.pop.2020.08.004.

[3] ZOU Y, ZHAO L, ZHANG J, *et al*. Development and internal validation of machine learning algorithms for end-stage renal disease risk prediction model of people with type 2 diabetes mellitus and diabetic kidney disease. Ren Fail, 2022, 44(1): 562–570. doi: 10.1080/0886022x.2022.2056053.

[4] JIN Q, LIU T, QIAO Y, *et al*. Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. Front Immunol, 2023, 14: 1185317. doi: 10.3389/fimmu.2023.1185317.

[5] YU J, LIU Y, LI H, *et al*. Pathophysiology of diabetic kidney disease and autophagy: a review. Medicine (Baltimore), 2023, 102(30): e33965. doi: 10.1097/md.0000000000033965.

[6] RAYEGO-MATEOS S, RODRIGUES-DIEZ R R, FERNANDEZ-FERNANDEZ B, *et al*. Targeting inflammation to treat diabetic kidney disease: the road to 2030. Kidney Int, 2023, 103(2): 282–296. doi: 10.1016/j.kint.2022.10.030.

[7] TONNEIJCK L, MUSKIET M H, SMITS M M, *et al*. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. J Am Soc Nephrol, 2017, 28(4): 1023–1039. doi: 10.1681/asn.2016060666.

[8] SELBY N M, TAAL M W. An updated overview of diabetic nephropathy: diagnosis, prognosis, treatment goals and latest guidelines. Diabetes Obes Metab, 2020, 22(Suppl 1): 3–15. doi: 10.1111/dom.14007.

[9] 中华医学会肾脏病学分会专家组. 糖尿病肾脏疾病临床诊疗中国指南. 中华肾脏病杂志, 2021, 37(3): 255–304. doi: 10.3760/cma.j.cn441217-20201125-00041.

[10] Chapter 2: Definition, identification, and prediction of CKD progression. Kidney Int Suppl (2011), 2013, 3(1): 63–72. doi: 10.1038/kisup.2012.65.

[11] American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: standards of medical care in diabetes-2022. Diabetes Care, 2022, 45(Suppl 1): S175–S184. doi: 10.2337/dc22-S011.

[12] OSHIMA M, SHIMIZU M, YAMANOUCHI M, *et al*. Trajectories of kidney function in diabetes: a clinicopathological update. Nat Rev

Nephrol, 2021, 17(11): 740–750. doi: 10.1038/s41581-021-00462-y.

[13] TERVAERT T W, MOOYAART A L, AMANN K, *et al*. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol, 2010, 21(4): 556–563. doi: 10.1681/asn.2010010010.

[14] EADON M T, SCHWANTES-AN T H, PHILLIPS C L, *et al*. Kidney histopathology and prediction of kidney failure: a retrospective cohort study. Am J Kidney Dis, 2020, 76(3): 350–360. doi: 10.1053/j.ajkd.2019.12.014.

[15] SCHROERS J E, GILBERT A M, MCKENZIE P R, *et al*. Rapidly progressive crescentic diabetic nephropathy: two case reports. Intern Med J, 2022, 52(3): 479–484. doi: 10.1111/imj.15702.

[16] MOGENSEN C E, CHRISTENSEN C K, VITTINGHUS E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. Diabetes, 1983, 32 Suppl 2: 64–78. doi: 10.2337/diab.32.2.s64.

[17] CHEN J, WANG X, HE Q, *et al*. YAP activation in renal proximal tubule cells drives diabetic renal interstitial fibrogenesis. Diabetes, 2020, 69(11): 2446–2457. doi: 10.2337/db20-0579.

[18] ZENI L, NORDEN A G W, CANCARINI G, *et al*. A more tubulocentric view of diabetic kidney disease. J Nephrol, 2017, 30(6): 701–717. doi: 10.1007/s40620-017-0423-9.

[19] FARIAS R S, SILVA-AGUIAR R P, TEIXEIRA D E, *et al*. Inhibition of SGLT2 co-transporter by dapagliflozin ameliorates tubular proteinuria and tubule-interstitial injury at the early stage of diabetic kidney disease. Eur J Pharmacol, 2023, 942: 175521. doi: 10.1016/j.ejphar.2023.175521.

[20] FURUICHI K, SHIMIZU M, OKADA H, *et al*. Clinico-pathological features of kidney disease in diabetic cases. Clin Exp Nephrol, 2018, 22(5): 1046–1051. doi: 10.1007/s10157-018-1556-4.

[21] SHIMIZU M, FURUICHI K, TOYAMA T, *et al*. Long-term outcomes of Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy. Diabetes Care, 2013, 36(11): 3655–3662. doi: 10.2337/dc13-0298.

[22] RODRIGUEZ F, LEE D J, GAD S S, *et al*. Real-world diagnosis and treatment of diabetic kidney disease. Adv Ther, 2021, 38(8): 4425–4441. doi: 10.1007/s12325-021-01777-9.

[23] MCGRATH K, EDI R. Diabetic kidney disease: diagnosis, treatment, and prevention. Am Fam Physician, 2019, 99(12): 751–759.

[24] LI A, YI B, LIU Y, *et al*. Urinary NGAL and RBP are biomarkers of normoalbuminuric renal insufficiency in type 2 diabetes mellitus. J Immunol Res, 2019, 2019: 5063089. doi: 10.1155/2019/5063089.

[25] DENG L, LI W, XU G. Update on pathogenesis and diagnosis flow of normoalbuminuric diabetes with renal insufficiency. Eur J Med Res, 2021, 26(1): 144. doi: 10.1186/s40001-021-00612-9.

[26] MOLITCH M E, STEFFES M, SUN W, *et al*. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care, 2010, 33(7): 1536–1543. doi: 10.2337/dc09-1098.

[27] SHI S, NI L, GAO L, *et al*. Comparison of nonalbuminuric and albuminuric diabetic kidney disease among patients with type 2 diabetes: a systematic review and meta-analysis. Front Endocrinol (Lausanne), 2022, 13: 871272. doi: 10.3389/fendo.2022.871272.

[28] PICHAIWONG W, HOMSUWAN W, LEELAHAVANICHKUL A. The prevalence of normoalbuminuria and renal impairment in type 2 diabetes mellitus. Clin Nephrol, 2019, 92(2): 73–80. doi: 10.5414/cn109606.

[29] YAMANOUCHI M, FURUICHI K, HOSHINO J, *et al*. Nonproteinuric versus proteinuric phenotypes in diabetic kidney disease: a propensity score-matched analysis of a nationwide, biopsy-based cohort study. Diabetes Care, 2019, 42(5): 891–902. doi: 10.2337/dc18-1320.

[30] ARAKI S, HANEDA M, SUGIMOTO T, *et al*. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes, 2005, 54(10): 2983–2987. doi: 10.2337/diabetes.54.10.2983.

[31] HEERSPINK H J L, STEFáNSSON B V, CORREA-ROTTER R, *et al*. Dapagliflozin in patients with chronic kidney disease. N Engl J Med, 2020, 383(15): 1436–1446. doi: 10.1056/NEJMoa2024816.

[32] MANN J F E, ØRSTED D D, BROWN-FRANDSEN K, *et al*. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med, 2017, 377(9): 839–848. doi: 10.1056/NEJMoa1616011.

[33] YAMANOUCHI M, FURUICHI K, HOSHINO J, *et al*. Nonproteinuric diabetic kidney disease. Clin Exp Nephrol, 2020, 24(7): 573–581. doi: 10.1007/s10157-020-01881-0.

[34] ARAKI S, HANEDA M, SUGIMOTO T, *et al*. Polymorphisms of the protein kinase C-beta gene (PRKCB1) accelerate kidney disease in type 2 diabetes without overt proteinuria. Diabetes Care, 2006, 29(4): 864–868. doi: 10.2337/diacare.29.04.06.dc05-1723.

[35] JIA X, ZANG L, PANG P, *et al*. A study on the status of normoalbuminuric renal insufficiency among type 2 diabetes mellitus patients: a multicenter study based on a Chinese population. J Diabetes, 2022, 14(1): 15–25. doi: 10.1111/1753-0407.13230.

[36] BUYADAA O, MAGLIANO D J, SALIM A, *et al*. Risk of rapid kidney function decline, all-cause mortality, and major cardiovascular events in nonalbuminuric chronic kidney disease in type 2 diabetes. Diabetes Care, 2020, 43(1): 122–129. doi: 10.2337/dc19-1438.

[37] CHANG D Y, LI M R, YU X J, *et al*. Clinical and pathological characteristics of patients with nonproteinuric diabetic nephropathy. Front Endocrinol (Lausanne), 2021, 12: 761386. doi: 10.3389/fendo.2021.761386.

[38] HOVIND P, ROSSING P, TARNOW L, *et al*. Remission of nephrotic-range albuminuria in type 1 diabetic patients. Diabetes Care, 2001, 24(11): 1972–1977. doi: 10.2337/diacare.24.11.1972.

[39] GEORGIANOS P I, DOUNOUSI E, LIAKOPOULOS V. Albuminuria and cardiorenal risk. Curr Opin Cardiol, 2023, 38(4): 331–336. doi: 10.1097/hco.0000000000001055.

[40] JONGS N, GREENE T, CHERTOW G M, *et al*. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol, 2021, 9(11): 755–766. doi: 10.1016/s2213-8587(21)00243-6.

[41] YOKOYAMA H, ARAKI S, HONJO J, *et al*. Association between remission of macroalbuminuria and preservation of renal function in patients with type 2 diabetes with overt proteinuria. Diabetes Care, 2013, 36(10): 3227–3233. doi: 10.2337/dc13-0281.

[42] De BOER I H, GAO X, CLEARY P A, *et al*. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC Study. Clin J Am Soc Nephrol, 2016, 11(11): 1969–1977. doi: 10.2215/cjn.02870316.

[43] SHIMIZU M, FURUICHI K, TOYAMA T, *et al*. Decline in estimated glomerular filtration rate is associated with risk of end-stage renal disease in type 2 diabetes with macroalbuminuria: an observational study from JDNCS. Clin Exp Nephrol, 2018, 22(2): 377–387. doi: 10.1007/s10157-017-1467-9.

[44] LOOKER H C, MAUER M, SAULNIER P J, *et al*. Changes in albuminuria but not GFR are associated with early changes in kidney structure in type 2 diabetes. J Am Soc Nephrol, 2019, 30(6): 1049–1059. doi: 10.1681/asn.2018111166.

[45] FURUICHI K, SHIMIZU M, YAMANOUCHI M, *et al*. Clinicopathological features of fast eGFR decliners among patients with diabetic nephropathy. BMJ Open Diabetes Res Care, 2020, 8(1): e001157. doi: 10.1136/bmjdrc-2019-001157.

[46] ZOPPINI G, TROMBETTA M, PASTORE I, *et al*. Glomerular filtration rate decline in T2DM following diagnosis. The Verona newly diagnosed diabetes study-12. Diabetes Res Clin Pract, 2021, 175: 108778. doi: 10.1016/j.diabres.2021.108778.

[47] OFORI E, GYAN K F, GYABAAH S, *et al*. Predictors of rapid progression of estimated glomerular filtration rate among persons living with diabetes and/or hypertension in Ghana: findings from a multicentre study. J Clin Hypertens (Greenwich), 2022, 24(10): 1358–1369. doi: 10.1111/jch.14568.

[48] AFSHINNIA F, RAJENDIRAN T M, HE C, *et al*. Circulating free fatty acid and phospholipid signature predicts early rapid kidney function decline in patients with type 1 diabetes. Diabetes Care, 2021, 44(9): 2098–2106. doi: 10.2337/dc21-0737.

[49] LIMONTE C P, VALO E, DREL V, *et al*. Urinary proteomics identifies cathepsin D as a biomarker of rapid eGFR decline in type 1 diabetes. Diabetes Care, 2022, 45(6): 1416–1427. doi: 10.2337/dc21-2204.

[50] FRODSHAM S G, YU Z, LYONS A M, *et al*. The familiality of rapid renal decline in diabetes. Diabetes, 2019, 68(2): 420–429. doi: 10.2337/db18-0838.

[51] MORIYA T, YAMAGISHI T, YOSHIDA Y, *et al*. Arteriolar hyalinosis is related to rapid GFR decline and long-standing GFR changes observed on renal biopsies in normo-microalbuminuric type 2 diabetic patients. J Diabetes Complications, 2021, 35(4): 107847. doi: 10.1016/j.jdiacomp.2021.107847.

[52] NAIMARK D M, GRAMS M E, MATSUSHITA K, *et al*. Past decline versus current eGFR and subsequent mortality risk. J Am Soc Nephrol, 2016, 27(8): 2456–2466. doi: 10.1681/asn.2015060688.

[53] TURIN T C, JUN M, JAMES M T, *et al*. Magnitude of rate of change in kidney function and future risk of cardiovascular events. Int J Cardiol, 2016, 202: 657–665. doi: 10.1016/j.ijcard.2015.09.090.

[54] ELFENBEIN I B, REYES J W. Crescents in diabetic glomerulopathy. Incidence and clinical significance. Lab Invest, 1975, 33(6): 687–695.

[55] MOTTL A K, GASIM A, SCHOBER F P, *et al*. Segmental sclerosis and extracapillary hypercellularity predict diabetic ESRD. J Am Soc Nephrol, 2018, 29(2): 694–703. doi: 10.1681/asn.2017020192.

[56] SUN L, DUAN T, ZHAO Q, *et al*. Crescents, an independent risk factor for the progression of type 2 diabetic kidney disease. J Clin Endocrinol Metab, 2022, 107(10): 2758–2768. doi: 10.1210/clinem/dgac416.

[57] GAUT J P, HOSHI M, JAIN S, *et al*. Claudin 1 and nephrin label cellular crescents in diabetic glomerulosclerosis. Hum Pathol, 2014, 45(3): 628–635. doi: 10.1016/j.humpath.2013.10.030.

[58] NUNES S, ALVES A, PREGUIÇA I, *et al*. Crescent-like lesions as an early signature of nephropathy in a rat model of prediabetes induced by a hypercaloric diet. Nutrients, 2020, 12(4): 881. doi: 10.3390/nu12040881.

（2023 – 09 – 27收稿, 2023 – 10 – 28修回）

编辑　余　琳