

口腔微生物与慢性肾病的研究进展*

刘子哈, 周学东, 张凌琳[△]

口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院 牙体牙髓病科(成都 610041)

【摘要】 慢性肾病(CKD)是临床上常见的泌尿系统疾病之一,其发病率近年来呈逐年升高趋势,已经成为全球重大公共卫生问题。CKD患者由于肾功能受损而导致病情反复,病程长达数年,最终导致不可逆转的肾功能衰竭,并伴有严重的系统性并发症,严重影响其生存质量。口腔微生物作为人类微生物群落的重要组成部分,在维持人类健康状况方面发挥重要作用,研究发现,口腔菌群失调与CKD存在着密切联系。因此,了解口腔微生物与CKD相关性具有重要的临床意义。本文对慢性肾病患者口腔菌群特征,口腔菌群参与CKD发生发展机制,以及口腔菌群失调与CKD研究的新进展进行综述,以期通过口腔微生物靶点为CKD的早期防控提供新思路。

【关键词】 口腔微生物 慢性肾病 终末期肾病 IgA肾病 口腔菌群失调

Research Progress in the Correlation Between Oral Microbiota and Chronic Kidney Disease LIU Zi-han, ZHOU Xue-dong, ZHANG Ling-lin[△]. State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department of Dental and Endodontic Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

[△] Corresponding author, E-mail: zhll_sc@163.com

【Abstract】 Chronic kidney disease (CKD), one of the common clinical urological diseases, is increasingly more prevalent in recent years and has emerged as a major concern of public health around the globe. The continuous recurrence of CKD caused by renal function impairment leads eventually to irreversible renal failure and severe systemic complications, which causes severe negative impact on the quality of life of the patient. As an essential component of human microbiome, oral microbiota plays a major role in maintaining health, and there has been research suggesting close association between oral dysbiosis and CKD. It is therefore of great clinical significance to understand the correlation between CKD and oral microbiota. Herein, we reviewed the characteristics of oral microbiota of CKD patients, the possible mechanisms of oral microbiota's involvement in the pathogenesis and development of CKD, and the latest research findings on oral dysbiosis and CKD, with a view to finding new approaches to early prevention and control of CKD through oral microbial targets.

【Key words】 Oral microbiota Chronic kidney disease End-stage renal disease IgA nephropathy Oral dysbiosis

慢性肾病(chronic kidney disease, CKD)是最主要的一类泌尿系统疾病,指肾功能在数月或若干年期间逐渐且难以逆转地衰退。目前的国际指南对其定义为:肾小球滤过率(GFR)低于60 mL/(min·1.73 m²)或提示肾功能下降的肾脏损害标志物增高,或两者兼而有之,至少持续3个月,而当GFR低于15 mL/(min·1.73 m²)时即进入了CKD的最后一个阶段,称为终末期肾病(ESRD)^[1]。世界范围内CKD的患病率在11%~13%之间,已构成全球性的健康负担^[2]。CKD及ESRD患者在肾功能衰竭的发展过程中以及持续的血液透析(HD)治疗过程中生活质量逐渐恶化,还可能增加心血管疾病甚至过早死亡的风险^[3]。高血压和糖尿病是引起CKD的主要病因,慢性肾小球肾炎次之^[4],其中免疫球蛋白A肾病(IgAN)是最常见的原发性慢性肾小球肾炎,其特征是肾小球系膜IgA沉积的表现,

导致肉眼血尿或连续镜下血尿和/或蛋白尿的频繁发作,并且血尿通常与扁桃体感染同时发生^[5-6]。由于IgA免疫复合物(IgA-ICs)的逐渐形成,多达40%的患者在诊断后约20年会发展为ESRD^[7]。

口腔微生物对人类微生物群落及人类的健康状况具有重要影响。各种口腔微生物的相互作用和平衡有助于人体抵御外界不良刺激的入侵,而口腔微生物稳态失调将导致口腔和全身系统性疾病^[8]。研究证实口腔微生物与消化系统疾病、心血管疾病、骨相关疾病、阿尔茨海默病等发生发展密切相关^[9-12]。随着临床研究对特定部位的口腔微生物与CKD相关标志物间关联的确认^[10],更多研究开始聚焦于口腔微生物与CKD发病机制之间的联系。

本文对CKD患者口腔菌群特征及口腔菌群在CKD发病过程中的可能作用机制进行综述,以期临床治疗及预防CKD提供新靶点。

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[△] 通信作者, E-mail: zhll_sc@163.com

1 CKD患者口腔菌群特点

1.1 非ESRD患者的口腔菌群特点

近年来,越来越多证据表明口腔菌群紊乱是导致CKD的重要原因之一,其中最常见的致病菌主要包括牙周致病菌。BASTOS等^[11]研究显示CKD患者龈下菌斑中牙龈卟啉单胞菌(*Porphyromonas gingivalis*)、福赛坦氏菌(*Tannerella forsythia*)、齿状密螺旋体(*Treponema denticola*)以及白色念珠菌(*Candida albicans*)含量增加。ISMAIL等^[12]在患有中度和重度牙周炎的CKD患者龈下菌斑中检测出齿状密螺旋体、福赛坦氏菌和微小消化链球菌(*Pepto streptococcus micros*)。龋病致病菌和牙周致病菌是IgA肾病患者常见的口腔微生物。有学者从IgAN患者口内及扁桃体样本中分离出 cnm 阳性的变异链球菌^[13-14],研究发现这类携带 cnm 基因的变异链球菌编码的胶原结合蛋白Cnm参与了IgAN的致病过程,由此推测 cnm 阳性的变异链球菌的出现与IgAN的病情严重程度相关^[15]。动物实验进一步证实了 cnm 阳性变异链球菌能诱发IgAN^[16]。NAGASAWA等^[17-18]在IgAN患者扁桃体内检测出密螺旋体、直肠弯曲杆菌(*Campylobacter rectus*)及牙龈卟啉单胞菌,并且通过动物实验证实了牙龈卟啉单胞菌具有IgAN致病性。

近年来,更多研究重点关注CKD患者口腔微生物在种属水平上的变化。HU等^[10]在属水平上检测到CKD患者口腔中奈瑟菌(*Neisseria*)的高丰度及链球菌(*Streptococcus*)的低丰度与eGFR较低相关。GUO等^[19]研究发现CKD患者的口腔微生物多样性高于健康组,其中链球菌属、放线菌属(*Actinomyces*)和细毛菌属(*Leptotrichia*)14个属增加,而普氏菌属(*Prevotella*)和嗜血杆菌属(*Haemophilus*)6个属减少,并且进一步利用随机森林模型确定了7个最佳OTU标记集,这些关键菌群可以区分CKD患者和健康人群,已进一步验证并具有较高的诊断潜力。LIU等^[20]发现CKD患者呈现出不同于健康组的唾液微生物群落和多样性,其中劳特罗普氏菌属(*Lautropia*)和假单胞菌属(*Pseudomonas*)含量增加,放线菌属、普氏菌属、普雷沃氏菌属7(*Prevotella*7)和束毛球菌属(*Trichococcus*)含量降低。HE等^[21]研究发现IgAN患者的唾液微生物多样性趋于降低,微生物谱有显著区分,包括二氧化碳嗜纤维菌(*Capnocytophaga*)、罗斯氏菌(*Rothia*)和嗜血杆菌(*Haemophilus*)等12个属的改变可以区分病例组和健康对照组。KHASHNOBISH等^[22]发现IgAN患者唾液微生物群的物种丰富度和多样性均低于健康组,但是IgAN组奈瑟菌属明显富集。而CAO等^[23]研

究发现IgAN患者龈下微生物多样性略高于健康对照组,其中密螺旋体和普氏菌较少,而伯氏菌(*Bergeyella*)、二氧化碳嗜纤维菌、放线菌、棒状杆菌(*Corynebacterium*)、丛毛单胞菌(*Comamonas*)、劳特罗普氏菌属和链球菌较多。

1.2 终末期肾病患者及接受血液透析患者的口腔菌群特点

大量研究结果提示慢性肾病患者口腔微生物的类型及分布较健康人有一定区别,其中ESRD患者尤其是接受血液透析治疗患者口腔微生物的改变受到学者更多的关注。研究表明HD患者相较于未进行透析的肾病患者牙周病原菌检出率较低,说明肾病患者的口腔环境可能会受到透析治疗的影响^[24]。DUAN等^[25]研究显示,HD患者表现出口腔微生物群结构、组成和功能的差异,并且随着血液透析时间的延长,口腔菌群也发生了变化,其中厚壁菌(*Firmicutes*)含量随透析时间延长而增加。CASTILLO等^[26]研究发现HD患者的牙周微生物数量高于对照组,但未显示出HD持续时间延长与牙周炎症破坏、特定微生物群或生物膜组成有统计学上的显著关系。ARAÚJO等^[27]的一项试验性研究表明ESRD和对照个体之间的龈下微生物组没有重大差异,但随透析时间延长,ESRD患者口腔微生物多样性降低,微生物群落也减少。

由于以上研究纳入排除标准不一、样本量有限、取材部位不同、研究方法各异等因素,慢性肾病各阶段患者口腔菌群特征尚需进一步明晰。

2 口腔菌群失调与CKD的相关性

口腔菌群失调在龋病及牙周炎发生发展过程中起着重要作用,而许多研究表明龋病及牙周炎所引起的口腔卫生不佳与CKD有一定相关性,甚至危害全身健康。同时,CKD患者常患有许多全身性并发症,这些并发症可能导致代谢改变,免疫失衡和炎症性疾病,进而导致口腔健康状况不佳^[28]。

牙周炎与CKD的关系已经得到广泛研究。CKD与牙周病可相互影响,牙周炎症和由此诱导的全身炎症都可能影响肾功能,同时,骨代谢和肾功能下降的参与者患牙周炎的概率更高^[29]。血液透析患者口腔健康状况常常更差。PALMER等^[30]对欧洲各国血液透析肾病患者进行的研究结果表明受试者中20.6%患者无牙列,40.6%的患者有中度至重度牙周炎。GARNEATA等^[31]进行了一项横断面观察性研究,结果显示75%的HD患者牙周状况不佳,其中23%患有重度牙周炎且年龄较大、透析时间更长。IWASAKI等^[32]在日本老年CKD患者中开展了长达4年的队列研究,研究发现CKD与临床附着丧失增加的概率显

著升高有关。

有关CKD与龋病患病率之间的联系的研究结论往往互相矛盾,存在较高不确定性。部分研究表明CKD与血透患者龋病患病率呈正相关^[33-34]。ANDRADE等^[35]作了系统综述,弱支持儿童和成人CKD患者对龋病易感性更低。其他研究未发现龋齿患病率和CKD之间的显著关联^[36-37]。各组研究间存在较大异质性,需进行更大样本、多中心临床研究,同时在机制水平上探讨CKD患者龋病易感性。ANDRADE等^[38]为寻求有关CKD对龋齿影响的可靠依据而进行了更深入的研究调查,研究表明唾液中尿素含量升高可以增强对酸性物质的缓冲能力,因此尽管牙菌斑生物膜和牙结石沉积明显增多,但HD患者龋齿病例较少。另外,MISAKI等^[14]临床研究发现IgAN患者的龋病状态与肾功能下降有临床关联,但龋病与IgAN之间的流行病学联系仍需进一步实验验证。目前仍缺乏足够的临床试验来支持以上结论,因此CKD和龋病之间的关系仍值得深入探讨。

3 口腔菌群参与CKD发生发展的潜在机制

口腔菌群失调可能参与了CKD的发生发展,然而目前口腔微生物对CKD的致病机制的研究仍然较为局限,且缺乏系统性的理论解释,尤其是针对其具体的作用靶点和治疗策略等方面还有待进一步深入研究。随着分子生物学技术的不断发展,越来越多的研究者对CKD进展中口腔微生物致病机理进行了深入的研究,其中牙周病原菌在CKD发病过程中相关机制的报道比较丰富,可对口腔菌群紊乱导致CKD的潜在机制有一个较为全面的了解。

3.1 口腔微生物侵入

日常刷牙、咀嚼会促使口腔内细菌通过溃破牙周袋进入血液循环,诱发菌血症,而体循环内细菌引起的炎症负荷加重肾组织中原有炎症负担^[26]。老年人全身抵抗力下降会使炎症负荷加重。口腔微生物进入肾组织后,还会直接或间接损害肾内皮、肾小球毛细血管、肾基质系膜细胞和肾小球^[12]。已经定植于肾组织中的口腔病原体能逃避免疫细胞的清除,提高自身存活率以摄取更多养分,加剧组织损伤^[39]。

3.2 口腔微生物关联免疫紊乱和炎症反应

已有证据显示炎症及代谢紊乱与CKD患者口腔微生物组改变可能相关,从而引起唾液尿素浓度升高、患者唾液pH及流速改变,加重口腔疾病^[40]。KSHIRSAGAR等^[41]研究了口腔病原微生物血清抗体与肾功能的相关性,发现牙龈卟啉单胞菌、齿状密螺旋体和伴放线放线杆菌

(*Actinobacillus actinomycetemcomitans*)等牙周病原菌IgG升高与肾功能损害密切相关,表明免疫反应在CKD的致病机制中的重要性。MOUTSOPOULOS等^[42]发现牙龈卟啉单胞菌的外膜蛋白上调白介素(IL)-17 mRNA表达并诱导IL-17对Th17的应答,进而导致肾循环中Th17相关细胞因子(IL-6、IL-1b、IL-23)产生。MIKAMI等^[43]研究发现循环TNF受体水平和血液透析牙周炎患者唾液牙龈卟啉单胞菌浓度呈正相关,提示牙周炎可能对HD患者产生不良影响。牙周病原体在IgA肾病的发生发展中也起重要作用。HE等^[21]研究亚表型关联分析表明二氧化碳嗜纤维菌和嗜血菌属分别与蛋白尿和血清IgA水平呈正相关,而罗氏菌属计数与hs-CRP水平呈负相关。另有研究显示罗氏菌属计数降低及与hs-CRP的负相关关系可能是机体炎症状态的一种表现,这与IgA的产生有一定联系^[44]。

牙周病原菌及副产物可激活多种受体及信号通路,诱导多种促炎细胞因子,趋化因子及前列腺素的释放进入肾循环,肾小球系膜及肾上皮细胞内^[39]。SAWA等^[45]和KAJIWARA等^[46]调查了牙龈卟啉单胞菌脂多糖(Pg-LPS)同时也是TLR4的配体在糖尿病肾病中的作用,研究发现Pg-LPS能诱导肾小球内皮产生有助于肾小球硬化的细胞因子,而TLR4阻滞剂能抑制Pg-LPS诱导的糖尿病肾病。除了Toll样受体信号转导途径之外,牙龈卟啉单胞菌还能通过刺激中性粒细胞释放可溶性触发受体TREM-1(STREM-1),激活髓系细胞上表达的触发受体(TREM-1)/配体肽聚糖识别蛋白1(PGLYRP1)轴放大炎症反应,增加MMP-8和IL-1b的释放^[47]。CKD发生发展过程中牙周病原体介导的其他促炎信号通路仍有待发掘及深入探讨。

3.3 牙周病原菌的氧化应激途径

牙周病原菌除直接入侵组织器官并引起炎症反应外,还可通过氧化应激反应驱动肾内脂质过氧化物生成,尿液及肾小管细胞内脂滴聚集,并伴有肾小管刷状缘破坏、肾脂肪堆积、系膜膨胀、足细胞受损、谷胱甘肽(GSH)含量下降及丙二醛(MDA)浓度增高,导致肾内皮细胞表型明显改变、细胞因子生成增加、表面粘附分子的表达发生变化以及血管重构等一系列组织学改变,最终造成肾损伤^[48-49]。未来仍需更多实验深入研究牙周病原体如何通过氧化应激途径参与肾损伤发生机制。

4 展望

口腔菌群失调引起的口腔疾病是慢性肾病发生发展的重要危险因素,口腔微生物与慢性肾病之间存在重要且紧密的联系。相比健康群体而言,CKD患者的多样性、物种丰富度和特定微生物群组成有较大差异。口腔

微生物经血流入肾循环、肾小球系膜和肾上皮细胞, 扰乱免疫系统并诱发局部和全身炎症反应, 通过氧化应激反应导致肾内脂质过氧化物的产生, 从而引起肾损伤。

目前大多数研究存在样本量小, 研究指标单一, 研究方法、疾病诊断标准及检测方法不统一等问题, 研究结果存在矛盾。随着CKD和IgA肾病发病机制研究的深入, 下一步将研究口腔微生物与肾脏疾病的双向联系, 探讨口腔菌群失调如何引发系统性疾病, 从而为通过微生物靶点对慢性肾病等系统性疾病进行治疗铺平道路。

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利益冲突 所有作者均声明不存在利益冲突

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