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终末期肾病患者合并胃食管反流病的临床研究进展*

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摘要:胃食管反流病(GERD)是最常见的食管疾病之一。多项研究表明,终末期肾病(ESRD)患者 GERD 的患病率高于普通人群。目前对于 ESRD 患者特别是血液透析患者 GERD 的症状特点及严重程度的研究较少。ESRD 患者常并发或伴发糖尿病、高血压等,而糖尿病神经病变可影响胃排空功能,钙拮抗剂和硝酸酯类药物可影响 LES 舒张功能。透析相关淀粉样变通过影响食管蠕动、食管下段括约肌张力和胃排空影响 GERD 的发生。ESRD 患者中,相当比例的患者全身状况不佳,行胃镜风险较高,常常应用标准化量表或质子泵抑制剂诊断试验评估患者症状性 GERD 患病情况。ESRD 及透析患者 GERD 的知晓率仍较低,部分患者自行服用碳酸氢钠等非一线药物控制症状。理论上对于 ESRD 及透析患者伴随的 GERD 进行早期诊断和治疗可能提高患者生活质量,并减少水钠摄入,改善血压及透析间期体重增加,降低心血管事件风险,具体的临床获益仍有待进一步研究证实。

关键词:终末期肾病;血液透析;胃食管反流病;患病率;诊断

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Clinical Research Progress of the Gastroesophageal Reflux Disease in End Stage Renal Disease Patients*

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ABSTRACT: Gastroesophageal reflux disease (GERD) is one of the most common esophageal diseases. Researches show that the prevalence rate of GERD in patients with end-stage renal disease (ESRD) is higher than in ordinary people. Currently there is not much study on the characteristics of symptoms or severity of GERD among patients with ESRD, especially among hemodialysis patients. ESRD patients usually have diabetes mellitus (DM) and hypertension as complications. Decreased gastric emptying was proved to be related to DM neuropathy. Lower esophageal sphincter relaxations were considered to be caused by administration of Ca-antagonists and nitrites. GI motility dysfunction and complications have been observed in patients with amyloidosis. Many GERD patients have severe concomitant disease, so endoscopy examination could not be operated easily. Structured questionnaires are often used instead of endoscopy, to diagnose symptomatic GERD. Awareness of GERD and administration of PPIs remains low in hemodialysis patients. Early diagnosis and routine proton pump inhibitors treatment would provide clinical benefits, reduce GERD symptoms and improve the quality of life of these patients. Furthermore, relieving chronic heartburn may reduce sodium bicarbonate consumption and interdialytic weight gain. Further studies are required to elucidate the mechanisms that increase the rate of GERD in ESRD patients, especially those on hemodialysis.

Key words: End stage renal disease(ESRD); Hemodialysis; Gastroesophageal reflux disease(GERD); Prevalence; Diagnosis

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前言

胃食管反流病(gastroesophageal reflux disease, GERD)是最常见的食管疾病之一,西方国家 GERD 患病率为 10%-30%,亚洲国家相对较低,为 5%左右^[1],而中国 GERD 的患病率约为 3.1%^[2]。GERD 的主要症状是烧心、反酸等^[3,4],患者中烧心症状每周发生一次的占 19.8%,而 58.7%有间歇性发作^[5]。GERD 可由酸性胃液反流入食管引起,其机制主要为食道下端括约肌括约肌一过性松弛^[6],食管蠕动障碍导致食管排空能力减低及反

流,胃排空能力下降引起残留物反流^[7],胃酸增加^[8]等。GERD 可通过 24 小时食管 pH 监测、胃镜检查及镜下活检诊断,对症状性胃食管反流病,可通过标准化问卷或诊断性治疗等形式形成临床诊断^[9]。西方国家通过内镜诊断的 GERD 患病率为 10%-20%^[10],日本的一项纳入 6010 例患者的前瞻性研究显示内镜下 GERD 的患病率为 16.3%^[11]。

全球范围内慢性肾病(CKD)的患病率约为 8%-16%^[12]。已有研究表明,终末期肾病(end-stage renal disease, ESRD),特别是血透患者上消化道症状的发生率^[13]及胃酸调节功能障碍发

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病率^[14]均高于一般人群。根据检测方法不同,ESRD 患者及透析患者的 GERD 的患病率为 24%-78%。相对于进入透析前的 ESRD 患者,血液透析患者 GERD 患病率似乎更高^[15]。Kawaguchi 等通过胃镜检查发现血液透析(hematodialysis,HD)患者较透析前 ESRD 患者 GERD 的患病率显著升高,这也可能与 CKD 病程进展及肾功能恶化有关。因此,血液透析本身可能是 GERD 的危险因素。目前对于 ESRD 患者特别是血液透析患者 GERD 的症状特点及严重程度的研究较少。国内外已有多项研究旨在发现 HD 患者所特有的与 GERD 相关的危险因素。

1 ESRD 患者发生 GERD 的相关病理生理变化

GERD 由酸性为内容物反流如食管所致,主要与消化道损伤因素与保护机制失衡有关。GERD 的病理生理变化有多种因素参与,其中以胃酸生成增多与胃排空下降为主。但 ESRD 患者 GERD 患病率较高的原因仍不明确,国内外已有多项研究旨在发现 HD 患者所特有的与 GERD 相关的危险因素。当酸性胃内容物反流至食管,即发生烧心症状。正常人群中 6%-16% 的病理性烧心和反流症状^[1]。而 ESRD 及血液透析相关的多种病理生理变化可引起病理性反酸及相关症状。已有关于尿毒症患者胃炎或胃酸过多症的研究^[13]。

ESRD 患者常发生恶心呕吐,这与胃排空延迟有关。腹膜透析患者因腹透液物理压迫等因素,胃排空延迟程度更加严重^[16],食管的胃酸暴露更加严重^[17],腹膜透析(peritoneal dialysis,PD)患者相对于 HD 患者 GERD 的发生率相似^[18]或更高^[17],在合并低白蛋白血症的 ESRD 患者反酸往往更为严重^[19]。Abdulrahman 的研究发现血清肌酐升高是 GERD 的独立危险因素^[20]。已有研究证明血透前的肾衰竭患者及 HD 患者均存在胃排空延迟状况^[16,21],但也有部分研究未发现 HD 患者存在胃排空延迟^[22]。对于 ESRD 及 HD 患者的胃蠕动机律问题目前也存在争议,Ko 等的研究发现 ESRD 患者在 HD 前已经存在胃蠕动机律异常,且这种节律异常会在透析后加重^[23,24]。但也有研究认为 HD 患者并无胃蠕动机律异常或排空延迟^[22]。这种矛盾的结果可能与不同研究采用不同的抽样方法、不同的检测方式及不同的诊断标准有关,透析的方式、周期和充分性可能也对胃排空造成影响^[7]。Kawaguchi 等通过内镜检查发现 HD 患者 GERD 患病率高于尚未进入透析的 ESRD 患者,证实 GERD 患者无论有无症状,均存在胃排空延迟,并将其归因于病情进展和肾功能恶化^[24]。相当数量的 GERD 患者同时患有糖尿病,而糖尿病常可引起自主神经病变。而 ESRD 患者亦常并发或伴发糖尿病(DM)、高血压等(HT),糖尿病神经病变可影响胃排空功能,钙拮抗剂和硝酸酯类药物可影响 LES 舒张功能。DM 患者自主神经病变发生率升高。如果 ESRD 患者副交感神经和交感神经同时存在病变^[25],则可能出现胃排空延迟。近年来报道的 GERD 患病率逐渐升高,但 ESRD 患者,特别是血透患者的 GERD 患病情况及危险因素目前报道仍较少。目前关于尚无关于此类患者一过性 LES 松弛及食管清除率的研究。

有研究认为淀粉样变通过影响食管蠕动、食管下段括约肌张力^[26]和胃排空^[27]影响 GERD 的发生。Cekin 通过 24 小时 pH 监测研究发现消化道淀粉样变是 GERD 发生的独立危险因素

^[17]。ESRD 患者血清 $\beta 2$ 微球蛋白水平可较健康对照者升高 60 倍以上^[28],过量的血清 $\beta 2$ 微球蛋白负荷可在多种组织和器官形成淀粉样纤维沉积,引起透析相关淀粉样变。然而,在常规血液透析患者中,血清 $\beta 2$ 微球蛋白水平与组织淀粉样纤维沉积病变程度并未呈现很好的相关性,说明 $\beta 2$ 微球蛋白沉积的启动和进展还与其他因素有关,如年龄、肾衰竭年限、透析方式和剂量等^[29]。

已有研究证实 ESRD 患者的 GFR 下降,胃泌素清除减少和 G 细胞增多引起高胃泌素血症,进而引起壁细胞胃酸分泌增加^[30],而餐后血清胃泌素水平升高使食管下段括约肌压力下降并可造成一过性食管下段括约肌松弛。但当实际测定 ESRD 患者胃酸水平时,不同患者之间的差别很大,从胃酸过少到胃酸过多都有可能存在^[31]。尽管并非所有 ESRD 患者都存在胃酸增加,但已有研究证明 ESRD 患者高胃泌素血症的患病率升高,而高胃泌素血症却未必是 ESRD 发生 GERD 的独立危险因素^[17]。

幽门螺杆菌在 GERD 中的作用仍存在争议。2003 年的一项主要纳入亚洲研究的系统评价认为幽门螺杆菌感染与 GERD 无关^[32],但也有研究者认为幽门螺杆菌感染引起胃体部及胃窦部胃炎,可减少壁细胞数量造成低胃酸^[33]。Giovanni S 等的研究纳入 67 例 GERD 患者,通过内镜检查、食管测压及 24 小时 pH 监测对比发现相对于幽门螺杆菌阴性患者,幽门螺杆菌感染者即使在根除治疗后,发现胃酸返流引起的每日食管下段酸性环境(pH<4)总时间仍显著延长,食管上段则无显著差异,返流次数及返流持续时间也有显著增加,同时存在酸性胃内容物清除速度下降,而食管下段括约肌压力、食管上段及下段蠕动等无显著差异^[34]。有部分研究认为 HP 感染可能是 ESRD 患者避免发生 GERD 的保护因素^[17]。Cekin 研究中 ESRD 患者幽门螺杆菌感染率较非 ESRD 对照组低,推测可能与尿毒症的保护作用有关^[35]。

2 ESRD 患者 GERD 的诊断

GERD 的诊断方法很多,临床上常常仅根据烧心与反流的典型症状即建立临床诊断并开始药物治疗,但有时需要综合各种检查方式的敏感性、特异性、可行性、价格及对病变程度及并发症的评价能力选择相应检查。

内镜下诊断 GERD 具有较高的特异性^[30-35],但敏感性较低(50%)^[36],内镜检查常被应用于伴随预警症状的高危患者或评估 GERD 并发症(如食管狭窄、Barrett's 食管等)的存在与严重程度^[37]。已有多种分型方法用于评估病变严重程度,但国际上尚无一种分型方法得到广泛认可,目前应用最广泛的洛杉矶分型系统^[38],按照此分级系统,美国的初级中心 GERD 的患病率为 10~30%,而接受转诊的次级中心则高达 50%^[39]。日本对于 6010 例成人的前瞻性胃镜调查发现 16.3% 存在反流性食管炎^[41]。Margolis 的研究发现,ESRD 患者内镜下诊断的食管炎发生率与健康志愿者对照组无统计学差异^[40],而 Kawaguchi 的研究中 HD 患者内镜下 GERD 的检出率为 50%^[24],Abdulrahman 的研究中 ESRD 患者 GERD 的检出率为 78%,高于正常对照者^[20]。

24 小时食管 pH 监测诊断 GERD 的敏感性约 90%,而特异性 85~100%。对于临床怀疑的高危病例,内镜下发现食管正

常者可行 pH 测试,敏感性 60%,而特异性则为 85%-90%^[41]。食管 pH 监测的阳性结果虽可为 GERD 提供辅助检查证据,但阴性的结果仍不能排除 GERD^[42]。一项非对照研究通过 24 小时食管 pH 监测发现儿童 ESRD 患者 GERD 患病率为 73%。

食管钡餐诊断 GERD 比较廉价,而且相对无创,对于中重度食管炎诊断敏感性为 79%-100%,而对于轻度食管炎则常常漏诊^[43]。因通过蠕动障碍诊断病理性反流的特异性不佳,食管测压比较少用于诊断 GERD。对于这类患者,食管测压主要用于定位 pH 监测电极合适位置排除严重食管运动障碍(如失迟缓或蠕动障碍等)^[43]。食管失弛缓症及 GERD 患者均可同时发生烧心及反流症状,通过食管测压可做出鉴别诊断。而实时电阻抗与 pH 值变化曲线则可帮助鉴别 GERD 与反刍综合征^[44]。

病理诊断 GERD 的标准一般为每高倍镜视野下超过 15 个嗜酸性粒细胞,但这种方法敏感性及特异性均较低^[45],而且结论在不同观察者间可能存在较大差异,因此通常不直接用于 GERD 的诊断,而一般应用于与其他可能因素引起食管炎的鉴别。

抑酸药物诊断性治疗实验是诊断 GERD 及评价其症状与胃酸关系的最简单方法之一。在质子泵抑制剂(PPI)类药物广泛用于临床之后,诊断性治疗实验广泛用于评价伴有或不伴典型症状的疑似 GERD 病例。如果服药 1~2 周后症状缓解,停药后症状再次出现,则确立诊断。一项纳入 15 项研究的系统评价认为,以 24 小时食管 pH 监测为金标准,应用 1~4 周 PPI 类药物的诊断性治疗实验敏感性为 78%(95% CI: 66~86%) 而特异性为 54%(95% CI: 44~65%)^[46]。

尿毒症及血液透析患者中,相当比例的患者全身状况不佳,行胃镜风险较高,而且胃镜也不能完全替代对患者症状的评估,因此常常应用标准化量表或 PPI 诊断试验代替食管 pH 监测及胃镜检查评估患者症状性 GERD 患病情况^[47]。目前,已有多项单维或多维问卷评分系统进入临床应用,特别是过去十几年中出现了大量的问卷评分系统,但多数敏感性较低。问卷主要通过 GERD 的典型症状对 GERD 形成诊断,如烧心及反流症状对 GERD 诊断的特异性为 89%-95%,敏感性为 6%-38%^[48]。而部分 GERD 患者可只出现如上腹胀痛、恶心、呕吐、声嘶、胸痛、喘息等不典型症状干扰诊断。此外,问卷调查不可避免存在一些回忆偏倚,因此需要回顾的时间窗一般不超过一月^[49]。本土化的 GERDQ 量表通过对近 1 周的症状评分,建立 GERD 诊断,并评价严重程度及对生活的影响^[50]。具有较高的敏感性和特异性,已经被用于 GERD 的流行病学研究。但我们仍要注意通过量表与内镜下诊断 GERD 的结果并不完全一致。

3 ESRD 患者 GERD 的治疗

GERD 的治疗包括生活方式改变、药物治疗、内镜下治疗及外科手术治疗等,其中生活方式的改变常被忽略,控制体脂,低脂饮食及增加膳食纤维摄入被认为可减轻 GERD 风险^[51]。终末期肾病患者多合并脂代谢紊乱及代谢性酸中毒,可从此类生活方式调整中获益^[52]。国内 ESRD 及透析患者对 GERD 的知晓率较低,常自行服用非处方口服药物控制反酸烧心等症状,除了 PPI、H₂ 受体拮抗药(H₂RAs)、硫糖铝等药物外,相当数量的 ESRD 及透析患者通过自行增加碳酸氢钠用量缓解烧心反酸

症状,而过量的碳酸氢钠摄入增加体内钠负荷及透析间期体重增加,进而增加血压波动及心血管疾病风险^[53]。

GERD 的口服药物治疗中,PPI 治疗的治愈率高于 H₂ 受体阻滞剂及安慰剂^[54]。Sifrim D 的研究中 PPI 对 GERD 的治愈率为(84%±11%),高于 H₂RAs(52%±17%)、硫糖铝(39%±22%)及安慰剂(28%±16%)^[55]。一项荟萃分析认为 GERD 患者的 PPI 治疗中(如烧心反流),19%-44%的患者为不完全缓解或无缓解^[56]。Hoogendoorn 等的一项纳入 4929 例 GERD 患者的调查性研究中,70%的患者常规服用 PPI。我中心的数据表明,仅 23%的 GERD 患者常规服用 PPI 治疗,其中 81%的患者过量使用碳酸氢钠的情况有所改善。

4 小结

综上所述,尽管现有临床证据及理论研究倾向于认为 ESRD 患者尤其是 HD 患者的 GERD 患病率更高,但现有研究并未得到一致的结论,仍需更多研究进一步评价。虽然有多项研究发现 ESRD 及透析患者 GERD 的危险因素,这些危险因素的控制及针对性治疗仍有待进一步探索。ESRD 及透析患者 GERD 的知晓率仍较低,部分患者自行服用碳酸氢钠等非一线药物控制症状。理论上对于 ESRD 及透析患者伴随的 GERD 进行早期诊断和治疗可能提高患者生活质量,并减少水钠摄入,改善血压及透析间期体重增加,降低心血管事件风险,具体的临床获益仍有待进一步研究证实。

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