

DOI:10.16781/j.0258-879x.2021.02.0203

· 综述 ·

慢性胰腺炎患者胰腺外分泌功能不全诊治现状

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[摘要] 慢性胰腺炎继发胰腺外分泌功能不全(PEI)严重影响患者的生活质量。PEI目前尚无单一的、可广泛应用的诊断方法,需根据患者的临床表现、胰腺外分泌功能、营养状态等多方面综合考虑做出诊断。PEI的主要治疗方法为胰酶替代治疗(PERT),此外还需配合营养状态改善和生活方式调整。PERT过程中应通过观察患者的临床表现、检测血清营养物质含量等监测疗效,对于PERT疗效欠佳者需仔细分析原因以制订合理的对策。

[关键词] 慢性胰腺炎; 胰腺外分泌功能不全; 胰酶; 酶替代治疗

[中图分类号] R 576.2 **[文献标志码]** A **[文章编号]** 0258-879X(2021)02-0203-06

Pancreatic exocrine insufficiency in chronic pancreatitis patients: diagnosis and treatment

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[Abstract] Pancreatic exocrine insufficiency (PEI) secondary to chronic pancreatitis seriously affects the quality of life of the patients. There is no single and widely used method for diagnosis of PEI. Diagnosis of PEI should be based on the clinical manifestations, pancreatic exocrine function tests, nutritional status and other aspects. Pancreatic enzyme replacement therapy (PERT) is the main treatment of PEI, which should be combined with improved nutritional status and lifestyle. Therapeutic effect should be monitored during PERT by observing the clinical manifestations, detecting the content of serum nutrients and so on. For the patients with poor prognosis after PERT, it is necessary to carefully analyze the causes to formulate a reasonable countermeasure.

[Key words] chronic pancreatitis; pancreatic exocrine insufficiency; pancreatin; enzyme replacement therapy

[Acad J Sec Mil Med Univ, 2021, 42(2): 203-208]

慢性胰腺炎是多种病因引起的胰腺组织进行性炎症性疾病,随着病程进展,会出现胰腺萎缩、胰管狭窄、胰管扩张、胰管结石、胰腺假性囊肿、胆总管狭窄等胰腺病理改变或相关并发症;同时由于胰腺组织的破坏,胰腺内、外分泌功能下降,继而出现胰腺内分泌功能不全和胰腺外分泌功能不全(pancreatic exocrine insufficiency, PEI)^[1]。研究报告42%~99%的慢性胰腺炎患者伴发PEI^[2]。PEI是指由于各种原因引起的胰酶分泌不足或胰酶

分泌不同步而导致患者出现消化不良等症,当胰腺外分泌功能下降至无法维持正常消化功能时,患者消化吸收能力下降,出现营养不良及营养相关并发症(如骨质疏松、骨软化症等),因此,PEI的发生严重影响患者的健康及生活质量^[3]。

PEI的临床表现不典型,轻中度PEI患者仅有腹胀、腹痛等症状,易被漏诊;重度患者会出现脂肪泻、体重下降等临床症状^[1,4],可依靠其症状进行诊断。此外,由于国内大部分地区目前无法开展

[收稿日期] 2019-04-09 **[接受日期]** 2019-08-28

[基金项目] 国家自然科学基金(81470883,81770635),上海市青年科技启明星计划(17QA1405500),上海青年拔尖人才开发计划(HZW2016FZ67),上海市卫生和计划生育委员会智慧医疗专项科研项目(2018ZHYL0229)。Supported by National Natural Science Foundation of China (81470883, 81770635), Shanghai Rising Star Program for Young Scientists (17QA1405500), Shanghai Top Talent Youth Development Program (HZW2016FZ67), and Special Research Project for Wise Information Technology of Medicine of Shanghai Health and Family Planning Commission (2018ZHYL0229)。

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PEI的实验室检查,因此PEI的诊断是临床一大难题。胰酶替代治疗(pancreatic enzyme replacement therapy, PERT)是PEI的主要治疗方法^[5],外源性胰酶的补充可以改善患者的消化功能,减少PEI相关并发症的发生。从各个角度了解PEI的诊治现状,对改善患者预后具有重要意义,现就慢性胰腺炎患者PEI的诊治研究进展进行综述。

1 PEI的诊断

1.1 临床表现 轻中度PEI患者仅存在腹胀、腹痛等不典型症状,重度PEI患者可能出现脂肪泻、体重减轻和因消化不良导致的营养相关并发症^[1,4]。脂肪泻指胰脂肪酶的分泌量下降到正常分泌量的10%~15%时,食物中的脂肪无法被正常消化,导致脂类物质随粪便排出过多的现象。由于脂质消化吸收不良,患者可出现体重减轻和脂溶性维生素缺乏,后者会引起骨质疏松、骨软化症等营养相关并发症^[1]。由于PEI患者常会减少脂肪及难消化食物的摄入以避免脂肪泻的发生,故腹泻、腹胀症状的出现也是因人而异的,体重减轻出现也较晚^[4]。但当患者出现脂肪泻等临床表现时,须高度怀疑重度PEI的存在,建议进行进一步胰腺外分泌功能检测。

1.2 胰腺外分泌功能检测 胰腺外分泌功能检测结果有助于明确PEI的诊断。胰腺外分泌功能检测方法分为直接检测法和间接检测法。直接检测法即利用胃肠激素刺激胰腺分泌,通过测定胰液量及胰液成分判断胰腺的外分泌功能。间接检测法是基于胰腺功能降低、胰酶分泌减少,导致某些物质在肠道被胰酶分解减少,通过检测血液、尿液、粪便、呼出气中这些被水解物质的含量降低程度来评估胰腺外分泌功能。

传统的直接检测法包括胰泌素试验、胰泌素-雨蛙素试验、内镜下胰腺功能检测^[5]。其中,胰泌素试验和胰泌素-雨蛙素试验是诊断PEI的金标准,其灵敏度和特异度均高于90%,可用于确定PEI的严重程度^[6],但因其成本较高、具有侵入性等不足,尚未在临床普及。内镜下胰腺功能检测结果对判断PEI较为准确,但成本也较高,目前临床应用较少。随着影像学技术的进步,现已研发出无创的半定量直接检测法,包括胰泌素刺激下的磁共振胆胰管成像技术和胰泌素刺激下的磁共振弥散加

权成像技术^[6-7]。这2种方法是利用胰泌素刺激胰腺分泌后通过MRI技术判断胰液分泌量,其检测灵敏度有限,仅能进行半定量评估,但可观察胰管形态,因此目前更多用于慢性胰腺炎患者治疗后的随访。

间接检测法包括血清中胰蛋白酶测定、粪便脂肪定量、粪弹性蛋白酶1检测、糜蛋白酶检测、¹³C呼气试验、H₂呼气试验等^[8]。血清中胰蛋白酶的测定一定程度上可以帮助评估患者是否伴发PEI^[9]。粪便脂肪定量被很多专家认为是PEI间接检测法中的首选方法^[10-11],该检测需要至少连续5d高脂肪饮食(100g/d)并收集3d的粪便,通过Van de Kamer测定法或红外线光谱测定法检测粪便中的脂肪含量^[6,12]。这种检测方法精确度较高,但患者需住院治疗,并需专门的营养师负责膳食脂肪的记录,临床实际操作相对烦琐、耗时较长,所以并未广泛应用。粪弹性蛋白酶1检测和糜蛋白酶检测方法相似,可基于随机粪便样本检测。2种蛋白酶在经过肠道时都不会被降解,在粪便中容易被检测到,常用的ELISA即可测量,但这2种方法对诊断轻中度PEI的准确性不高^[6,13]。¹³C呼气试验需要让患者食用¹³C标记的标准餐,然后收集6h(每15min收集1次)患者的呼出气,检测呼出气中的¹³C恢复率^[5,14]。这种方法简单、无创,诊断PEI较为精确,但标准餐仅含420kcal(1758kJ)热量^[15],患者进食标准餐后需要在医院等待至少6h,这对健康人群而言尚且可以耐受,但42.8%~61%的慢性胰腺炎患者同时患有PEI和糖尿病^[2,16],慢性胰腺炎继发的糖尿病血糖较难控制、容易波动,故这部分患者接受¹³C呼气试验时容易发生低血糖,存在一定风险。

PEI的直接检测法费用相对较高,且为侵入性检查,但准确率高;而间接检测法操作相对烦琐,患者依从性较差。选择何种方式检测,应根据患者情况综合考虑。

1.3 营养状态评估 除胰腺外分泌功能检测外,还应对患者进行营养状态评估^[17],以明确PEI对机体的损害程度。常需检测的指标包括BMI、肌肉量、脂溶性维生素(维生素A、D等)、白蛋白、前白蛋白、血清微量元素(如血清镁、锌、铁)含量等^[7]。根据既往研究,PEI患者的BMI和肌肉量均低于健康人群^[18],53%的PEI患者存在维生素D

缺乏^[19]。一项回顾性研究发现,以低镁血症作为检测PEI的指标,其特异度为88%,灵敏度为66%^[20]。因此,营养状态评估也有助于PEI的诊断。

研究发现,慢性胰腺炎患者PEI的发生率随着患者年龄增长及病情进展而上升^[21-22]。对PEI的诊断,目前尚无一种可广泛应用的检测方法,因此对所有慢性胰腺炎患者应从临床表现、无创性胰腺外分泌功能检测、营养状态评估等方面综合考量,以早期对PEI做出诊断,并尽早干预。

2 PEI的治疗

2.1 PERT

2.1.1 治疗方法 PEI诊断明确后应立即规范治疗,PERT是PEI治疗中最首要也最重要的环节,可改善患者的消化功能、提高生活质量、延长生存期^[4]。PERT经历了很长的发展历史。1855年,Bernard^[23]首次报道犬胰管造瘘收集的胰液可以消化脂肪,并且结扎胰管、阻断胰液进入十二指肠会导致脂肪消化不良。1973年,DiMagno等^[24]研究发现,消化食物中的脂肪至少需要正常胰酶分泌量的5%~10%,当胰酶分泌量少于正常分泌量的2%时所有患者均会出现脂肪泻,胰酶分泌量为正常分泌量的2%~5%时一半患者会出现脂肪泻。因此,DiMagno等^[24-25]提出,补充正常胰液分泌量10%的胰酶,即90 000 USP U胰酶可消除脂肪泻。之后的研究发现,肠腔中胰酶的含量达到正常状态的5%~10%时也可消除脂肪泻^[26]。Seiler等^[27]研究发现,每餐75 000 IU胰酶可以显著改善慢性胰腺炎患者胰腺手术后的脂肪消化(粪脂肪吸收系数从56.9%增加到76.6%)和蛋白质消化。多部国内外指南推荐,一旦患者确诊PEI,应立即开始PERT,并且PERT应该从低剂量开始^[28-31]。各指南推荐的胰酶使用剂量略有不同。澳大利亚指南认为可以25 000~40 000 IU作为起始剂量^[32]。欧洲指南推荐每餐可补充40 000~50 000 IU胰酶,在进食小食时补充一半的剂量^[33],但重度PEI患者可能每餐需要补充90 000 IU胰酶^[10]。

2.1.2 疗效监测 PERT过程中应监测疗效,根据患者的临床反应调整用药。从PERT开始后患者消化不良相关症状即可缓解,如脂肪泻次数减少或消失、体重增加等^[6],故监测患者的临床表现及体重

等参数可在一定程度上反映PERT的治疗效果。但对PERT疗效的评估不应局限于临床症状和体征,因为某些患者可能没有明显的临床症状,但血清营养物质水平却低于正常^[34]。因此,对PERT疗效的评估还应监测血清营养物质含量,包括脂溶性维生素(维生素A、D等)、视黄醇结合蛋白、白蛋白、前白蛋白和微量元素(血清铁、镁、锌等)^[17,20]。

2.1.3 影响PERT疗效的因素 影响PERT疗效的因素包括很多方面。胰酶的稳定性受pH影响,传统胰酶制剂无肠衣包裹,在胃内强酸性环境中易被降解,影响疗效。目前大多数胰酶制剂均有耐酸的肠衣包裹,肠衣在pH为5.0以上的环境中才能溶解释放胰酶,故一般不会在胃内被降解,只有在到达十二指肠释放胰酶后才能发挥治疗效果。但部分重度PEI患者因碳酸氢盐分泌不足,使其肠腔为酸性环境,当胰酶被释放到十二指肠后,会在酸性环境中降解失活,影响疗效^[35-36]。

由于胰酶与食糜混合后才可发挥作用,故服用胰酶的机会会影响胰酶的疗效。一项研究比较了餐前、餐中、餐后服用胰酶的效果,发现餐中服用胰酶的患者脂肪正常消化的比例(63%)高于餐前(50%)和餐后(54%)服用的患者^[37]。

患者的饮食习惯也会影响胰酶的疗效。研究显示几乎一半的PEI患者会主动限制脂肪摄入^[38]。Boivin等^[39]研究发现低脂饮食与内源性胰液分泌减少相关,随着膳食脂肪含量减少,餐后及消化间期的淀粉酶、脂肪酶分泌量也减少。限制脂肪摄入还会掩盖PEI相关的临床症状,导致临床医师对其PERT指导出现偏差^[40]。此外,饮食中膳食纤维过多也会影响胰酶的疗效,Dutta和Hlasko^[41]研究发现补充75~80 g膳食纤维者的胰酶活性比正常饮食者更低,增加膳食纤维可导致胰酶活性下降,加重脂肪泻症状,增加粪脂肪含量。Duggan等^[42]也发现补充膳食纤维者粪脂肪含量明显增加,因此进食过多膳食纤维也会导致PERT疗效欠佳。

PEI患者常需长期服用胰酶,但我国很多地区无胰酶制剂销售,因此部分患者购买胰酶困难。另外,我国目前胰酶制剂种类较少,单片制剂胰酶含量低,最高胰酶含量仅每片(粒)10 000 IU,按照指南推荐,成人患者应从每餐3~4片(粒)作为起始剂量,对于重度PEI患者,甚至每餐需服用

8片(粒)胰酶制剂^[28]。因此,若患者服药依从性差,胰酶服用剂量不足,也可导致PERT疗效不满意。

2.1.4 PERT疗效不佳的应对措施 若患者接受PERT后消化不良相关症状未缓解,应注意检查患者胰酶服用方式是否正确、服用剂量是否合适及饮食结构是否合理^[43]。若患者胰酶服用方式不当,应加强宣教,推荐患者餐中服用胰酶,并且采用少食多餐的膳食模式,若需要服用1片以上的胰酶制剂,应将服用胰酶的时机在餐中均匀分配。若患者服用剂量不足,应加大剂量至2~3倍^[7]。若患者饮食结构不合理,应鼓励其尽量少食多餐,摄入正常量的脂肪^[17]。若患者服药依从性差,应加强宣教,告知PEI相关并发症的风险和PERT的必要性。若以上方法仍不能达到满意疗效,应加用抑酸药(如质子泵抑制剂)以改善胃肠道pH^[17]。若这些策略应用后患者症状仍未改善,则应该探讨是否存在其他引起消化不良的原因,如肠道细菌过度生长、脂肪酸吸收障碍、乳糜泻、炎症性肠病、乳酸不耐受等^[1,17,44]。

2.2 其他治疗 对于缺乏营养物质的PEI患者,通常无须口服营养制剂,应首先调整饮食来改善营养状态,一般推荐患者尽可能保持正常饮食,或少食多餐,进食高能量膳食,避免高纤维饮食^[5]。通过饮食调整,大部分患者营养状态均可改善,对于饮食干预效果不佳的患者可针对性地补充营养物质^[5]。另外,生活方式调整也是治疗PEI不可忽视的干预手段。既往研究报道,吸烟、饮酒是慢性胰腺炎患者病情加重的独立危险因素^[2,34],饮酒也是发生脂肪泻的独立危险因素^[2]。因此,应加强宣教,建议PEI患者戒烟、戒酒。

3 结 语

慢性胰腺炎继发PEI严重影响患者的生活质量,PEI目前尚无单一的、可广泛应用的诊断方法,需根据患者的临床表现、基础疾病、营养状态等进行综合评价,胰腺外分泌功能检测结果有助于明确诊断。PERT是PEI的主要治疗方法,营养状态改善和生活方式调整也是治疗PEI不可或缺的手段。PERT过程中应通过观察患者的临床表现、检测血清营养物质含量等监测疗效,对于PERT疗效欠佳

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