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文献综述 REVIEW

粪钙卫蛋白检测在肠道疾病诊断中的研究进展

蒋承志, 严喜章

蒋承志, 严喜章, 西安医学院第二附属医院消化科 陕西省西安市 710038
蒋承志, 在读硕士, 主要从事消化系统疾病诊断及其相关研究.
陕西省教育厅基金资助项目, No. 12JK0776
作者贡献分布: 本综述由蒋承志完成; 严喜章审校.
通讯作者: 严喜章, 主任医师, 710038, 西安市灞桥区纺东街167号, 西安医学院第二附属医院消化科. yxz82330916@163.com
电话: 029-86177596
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Fecal calprotectin for diagnosis of digestive system diseases

Cheng-Zhi Jiang, Xi-Zhang Yan

Cheng-Zhi Jiang, Xi-Zhang Yan, Department of Gastroenterology, the Second Affiliated Hospital of Xi'an Medical University, Xi'an 710038, Shaanxi Province, China
Supported by: Foundation of Shaanxi Educational Committee, No. 12JK0776
Correspondence to: Xi-Zhang Yan, Chief Physician, Department of Gastroenterology, the Second Affiliated Hospital of Xi'an Medical University, 167 Fangdong Street, Baqiao District, Xi'an 710038, Shaanxi Province, China. yxz82330916@163.com
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Abstract

Calprotectin is a 36 kDa calcium- and zinc-binding protein that belongs to the S100 family. Calprotectin shows an excellent stability in feces and appears to be superior to conventional fecal markers. Fecal calprotectin concentrations closely correlate with the fecal excretion of in-labelled leukocytes. In addition, fecal calprotectin has an overall high specificity. Therefore, it could be a useful marker for diagnosis of intestinal diseases. In this review we summarize the structure, physical and chemical characteristics of fecal calprotectin and analyze the relationship between calprotectin and intestinal diseases.

Key Words: Calprotectin; Digestive system diseases; Marker

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摘要

钙卫蛋白是S100蛋白家族的一种分子量为36 kDa的杂合性钙、锌结合蛋白. 其在粪便中及其稳定, 优于以往的粪便标志物. 此外, 其浓度与粪便中白细胞浓度密切相关, 且特异性较高, 可作为鉴别诊断肠道疾病的有用标志物. 本文就粪钙卫蛋白的结构、理化特征以及钙卫蛋白与肠道疾病的关系展开综述.

关键词: 钙卫蛋白; 消化系统疾病; 标志物

核心提示: 本文全面总结了炎症性肠病、肠易激综合征、大肠癌等常见的肠道疾病与粪钙卫蛋白相关性分析及其水平的最新研究进展, 以期通过无创、简便的检查方法为临床常见肠道疾病的早期诊断提供新的思路.

蒋承志, 严喜章. 粪钙卫蛋白检测在肠道疾病诊断中的研究

背景资料
结肠镜检查是许多肠道疾病的确诊检查手段, 但其具有侵袭性、花费高、程序复杂等缺点, 限制了其在临床上的广泛开展, 降低了疾病的早期检出率. 因此, 临床急需无创、简便的检查方法弥补结肠镜检查的不足, 当下有关粪钙卫蛋白(fecal calprotectin, FC)的研究为临床提供了新的思路.

同行评议者
黄缘, 教授, 南昌大学第二附属医院消化内科, 江西省分子医学重点实验室

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研发前沿
目前有关FC水平的研究主要仍集中在炎症性肠病和肠易激综合症, 对大肠癌等其他肠道疾病的FC水平研究较少, 目前建立更大的数据模型, 对常见肠道疾病的FC水平进行整体性分析非常必要.

0 引言

炎症性肠病(inflammatory bowel disease, IBD)、肠易激综合征(irritablebowelsyndrome, IBS)、大肠癌(carcinoma of large intestine)是常见的肠道疾病, 其确诊手段主要依靠结肠镜检查, 但是结肠镜检查具有侵袭性、花费高、程序复杂等缺点, 限制了其在临床上的广泛开展, 降低了疾病的早期检出率. 因而, 临床上寻求无创诊断肠道疾病十分迫切. 目前, 粪钙卫蛋白(fecal calprotectin, FC)这一无创、简便的检测手段的出现为肠道疾病的检出提供了新的思路.

1 钙卫蛋白的结构和理化特性及检测方法

钙卫蛋白(calprotectin)属于S100蛋白家族, 是一种分子量为36 kDa的杂合性钙、锌结合蛋白. 他属于中性粒细胞胞质部分, 主要存在于除溶菌酶外的细胞质中[1,2]. 钙卫蛋白在各种炎性疾病的细胞外液中高水平表达, 如类风湿性关节炎, 囊性纤维化和脓肿等. 中性粒细胞释放的钙卫蛋白对各种细胞包括肿瘤细胞和正常成纤维细胞具有生长抑制和诱导细胞凋亡活性, 表明钙卫蛋白在免疫调节中发挥重要作用[3]. 钙卫蛋白大约占细胞质总蛋白的60%, 他由两条14 kDa的重链和一条8 kDa的轻链共价相连的钙结合蛋白异二聚体构成, 每条链可结合两个钙离子. 此外, 钙卫蛋白通过竞争锌和抑制锌依赖性酶而抑制微生物的生长. 钙卫蛋白向胃肠道定向迁移, 然后随粪便排出, 称为FC. 其浓度与粪便中白细胞浓度密切相关. 因此, 他被认为是一种有用的肠道炎症标志物, 与其他全身炎症标志物如红细胞沉降率(erythrocyte sedimentation rate, ESR)和C反应蛋白(C-reactive protein, CRP)相比较, 钙卫蛋白水平不受肠道炎症以外的其他原因影响, 特异性较高[4].

钙卫蛋白在粪便中及其稳定, 在室温下可以存储7 d, 优于以往的粪便标志物[5]. 1992年, Røseth等[6]首先报道钙卫蛋白可以从小样本粪便(5 g)中提取, 再用标准ELISA方法测定. 2000年出现了改进测量钙卫蛋白的方法, 用含牛血清白蛋白的尿素/柠檬酸盐缓冲液, 仅需要微量粪便样本(0.1 g), 该方法操作更简便, 且准确性有所提高[7]. 粪便钙卫蛋白不易被蛋白酶水解; 收集单次粪便标本与收集24 h粪便混匀后取样, 检测结果同样可靠; 标本可室温储存1 wk, 适合于批量检测. 基于钙卫蛋白稳定性高、快速便捷、准确性高等优点, 最新研究热点集中在能否将FC作为鉴别诊断肠道疾病的标志物.

相关报道
FC对肠道炎症性疾病的临床意义已得到广泛的认可, 但对FC在整个消化系统疾病的意义仍缺少相关研究, 王少东等通过检测FC在不同消化系统疾病中的表达, 探讨了FC在全消化道系统疾病鉴别诊断中的意义, 为进一步的更大数据量的相关研究提供思路.

2 钙卫蛋白与肠道疾病的关系

2.1 与IBD关系 IBD是一组病因不十分明确的慢性肠道炎症性疾病, 主要包括溃疡性结肠炎(ulcerativecolitis, UC)和克罗恩病(Crohn's disease, CD). IBD的病情常常迁延不愈, 其预后不良[8]. 因此, 监测患者病情发展, 预测IBD的复发, 及时地调整治疗方案, 从而提高患者生活质量、减缓IBD的发生发展已成为一种治疗理念. 目前, 结肠镜检查仍然为诊断IBD的金标准, 但结肠镜检查患者常有不适感, 且操作具有侵袭性, 甚至有发生肠出血、肠穿孔等严重并发症的危险, 这些局限性限制了肠镜在临床上的广泛应用, 重复性低, 无法达到使用结肠镜监测患者病情的目的[9]. 因此, 最新的研究热点集中于应用无创技术检测IBD、鉴定疾病活动上. 有研究[10,11]报道, FC可作为一个非危险性、非侵袭性的客观而敏感的肠炎诊断方法. 研究[12]发现, IBD患者与健康个体和肠易激综合症患者相比, FC的浓度显著性升高. 值得特别指出的是: IBD患者的FC水平处于相对最高水平, 表明FC不仅是诊断IBD的生物标志物, 还能有效鉴别IBD与IBS. 此外, 密切监测FC能有效预测IBD的复发[13-15].

Mosli等[16]对2499个符合要求的病例进行了荟萃分析, 以结肠镜检查作为诊断IBD的金标准, 客观、系统的评价了CRP、FC诊断IBD的准确性, 结果表明, CRP的合并灵敏度、合并特异度分别为0.49(95%CI: 0.34-0.64)、0.92(95%CI: 0.72-0.96), FC的合并灵敏度、合并特异度分别为0.88(95%CI: 0.84-0.90)和0.73(95%CI: 0.66-0.79), 结果表明FC在诊断IBD方面, 灵敏度明显高于CRP, 在临床上应用FC开展筛查工作其漏诊率会较低. 有学者[9,17,18]发现, FC水平变化与患者疾病活动表现出良好的相关性, 患者炎症活动期FC浓度显著升高, 缓解

期FC水平趋于正常. 揭示FC还可以作为判断病情活动的生物标志物.

总而言之, FC诊断IBD的灵敏度和特异度均较高, 有较好的诊断价值, 且操作简便、没有创伤、可重复性高, 可以弥补内镜检查的不足, 具有广泛的临床推广价值[19,20].

2.2 与IBS的关系 IBS是一组持续或间歇发作, 以腹痛、腹胀、排便习惯和/或大便性状改变为临床表现, 而缺乏胃肠道结构和生化异常的肠道功能紊乱性疾病[21]. IBS虽不会造成永久器质性损害, 却会严重降低患者的生活质量[22-24]. 临床医师根据病史和临床特征作出初步诊断, 同时进行相应的辅助检查(结肠镜、钡剂灌肠等), 除外有症状的器质性肠病后才能得出IBS的诊断. IBS和IBD临床症状和体征相似, 常常不易鉴别[25]. 目前区分IBD和IBS的方法仍为结肠镜等侵入性检查. 但在年轻人群中, >60%的患者结肠镜检查均未见异常[26], 即带来了不必要的痛苦体验. FC检测的应用可能会为无创、简便诊断IBS开创新的思路[27-31].

Caviglia等[18]学者对66例肠病患者包括45例IBD患者, 21例IBS患者, 进行研究观察, 以结肠镜检查结果为诊断金标准. 研究发现, FC水平在IBD及IBS中, 中位数值分别为268 μg/g(95%CI: 151-343 μg/g)和49 μg/g(95%CI: 23-101 μg/g), P = 0.0001. 以100和150 μg/g的作为临界值时, FC区分IBD和IBS的受试者工作特征曲线下面积(area under the curve, AUC)分别为0.811(灵敏度 = 68.9%, 特异度 = 71.4%, 阳性预测值 = 83.8%, 阴性预测值 = 56.3%)和0.931(灵敏度 = 87.5%, 特异度 = 90.5%, 阳性预测值 = 91.3%, 阴性预测值 = 86.4%). AUC＞0.5表明有诊断价值, AUC越接近于1表明诊断价值越高. 在Caviglia等[18]的研究里, FC为150 μg/g时, 其鉴别IBD和IBS的AUC可高达0.931, 显示出了非常高的诊断效能, 可以为临床工作提供新的理论依据.

Chang等[32]学者对20名健康对照者、26例IBS患者和58例IBD患者进行研究. 发现IBS患者和IBD患者的FC水平较健康对照组显著升高, 同时IBD、IBS两者之间FC水平也存在显著性差异, 前者明显高于后者. D'Haens等[33]学者的研究结果与此一致. 这些结果均表明, FC可作为一种新的生物标志物有效的鉴别、诊断IBS和IBD[34,35].

2.3 与大肠癌的关系 大肠癌包括结肠癌(colon cancer)和直肠癌(rectal cancer), 故也称为结直肠癌(colorectal cancer, CRC), 是常见的肠道恶性肿瘤. 在亚洲, CRC的发病率和死亡率在逐年迅速增加, 是严重威胁人们健康、生命的重大疾病[36]. CRC的预后与早期诊断密切相关, 多数早期CRC可以治愈, 5年生存率可达90%, 而晚期患者生存率则不足10%[37], 但多数CRC患者就诊时已处于疾病的终末期, 错过了最佳治疗时间, 预后较差. 因此, 早期诊断对提高CRC患者治疗效果及患者生存率十分重要[38].

由于粪便潜血测试(fecal occult-blood test, FOBT)的简便性、非侵入性, 使他成为了CRC应用最广泛的初步筛选试验, 并且已经证实, 高危人群定期进行FOBT可以降低CRC的死亡率[39,40]. 但是, FOBT灵敏度欠佳, 同时, FOBT结果易受食物、药物等因素影响而出现较高的假阳性率[41,42], 这使FOBT的临床价值遭到质疑和争议. 同样作为简便、无创的检验方法, FC似乎要比FOBT具有相对更高的灵敏度. Khoshbaten等[43]学者在排除年龄等混杂因素后, 对50例CRC患者及50例良性胃肠病者进行对照研究, 发现CRC患者及良性胃肠病者平均FC水平分别为241.1 μg/g±205.2 μg/g(3.4-610.0 μg/g, 中位数为19.3 μg/g)和45.9 μg/g±55.1 μg/g(1.3-257.1 μg/g, 中位数为19.3 μg/g), 两组间存在显著性差异(P<0.001). 以FC浓度≥75.8 μg/g为最佳临界值鉴别CRC患者和良性胃肠病者的灵敏度和特异性分别为80%和84%. 研究[44,45]结果表明, FC是区分CRC和良性胃肠病十分有用的非侵入性生物标志物.

3 FC与结肠镜

结肠镜应用广泛, 通过镜子不但可以清楚地发现肠道病变, 还可对部分肠道病变进行治疗, 结肠镜检查技术是目前其他诊疗手段无法替代的主要手段. 但也存在了一些缺点: 前期准备麻烦、费用高、痛苦大, 部分患者因耐受性差导致半途而废, 而且有严重的心血管病患者不能做此项检查[46]. FC这种无创、简便的检查是否可以代替结肠镜检查, 或者作为结肠镜检查必要性的筛查性检查?

Hradsky等[47]学者对41例经过结肠镜检查并怀疑有肠道炎症的患者进行研究后发现, 在诊断肠道炎症方面, FC相比结肠镜检查具有

创新盘点

该文对常见的肠道疾病FC水平的差异进行了整体性的报道, 对临床肠道疾病的诊断具有较高的参考价值.

应用要点
通过无创、简便、可靠的检查方法, 对常见的肠道疾病进行早期的筛查、诊断, 为进一步临床诊治提供依据.

更高的敏感性(P = 0.000014). 将FC浓度为167 μg/g(AUC = 0.86, 95%CI: 0.81-0.92)作为最佳诊断界值, FC可以有效筛选哪些患者必须行结肠镜检查以确诊肠炎. 此外, FC相比结肠镜检查更易与组织学变化紧密联系, FC检查可以反应早期组织的变化, 在结肠镜检查还未见明显异常之前. FC可以为肠炎的早期诊断提供充足的依据[47-50].

目前, 结肠镜检查仍然是诊断CRC的最主要手段, 其次为影像学检查、肿瘤标志物、生化检查等[37], 但结肠镜检查昂贵、繁琐、有创, 使部分患者不愿接受, 降低了CRC的检出率. Mikhaĭlova等[38]学者通过研究表明, 通过联合应用FC和FOBT能够进一步有效提高早期CRC检出率, 该方法对于CRC的检测灵敏度高达97.2%, 特异性高达93.3%, 诊断准确性高达95.6%. 因此, 联合FC和FOBT筛查早期CRC患者, 可以提高诊断效率, 具有可观的应用前景.

4 结论

FC作为一种无创、简便的检查方法, 为肠道疾病早期的诊断提供新的思路, 对于疾病的鉴别诊断也提供了可靠的依据, 而对于病情的严重程度以及疾病的转归也有一定的临床价值. 当然, 国内外对FC的评价并不完全相同, 因此, 针对FC的研究仍需要深入研究, 建立更大的数据模型, 对常见肠道疾病的FC水平进行整体性分析, 开展多中心的前瞻性实验, 划分不同肠道疾病的FC水平区间, 将为FC在肠道疾病诊疗过程中的应用取得重大突破.

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名词解释

S100蛋白家族: 一种低分子质量(10-12 ku)的钙结合蛋白家庭, 包括20多名成员, 均有单独的基因编码, 至少16个蛋白基因位于1q21. S100蛋白主要存在于脊椎动物中, 与其他EF-手型(EF-hand)钙调蛋白具有同源性.

同行评价

FC在临床的应用是广大临床医生期待的事情, 特别是炎症性肠病的患者诊治有很多帮助. 该综述叙述全面, 条理清晰, 表达完整, 对FC水平与肠道疾病相关性的最新研究进展进行了报道.

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