DOI: https://doi.org/10.25121/PNM.2017.30.11.596 Post N Med 2017; XXX(11): 596-600

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Can we predict mucosal inflammation in children with ulcerative colitis without colonoscopy? Own experience in assessing faecal calprotectin

Czy możemy przewidzieć aktywność zmian zapalnych w obrębie śluzówki u dzieci z wrzodziejącym zapaleniem jelita grubego? Własne doświadczenia w ocenie kalprotektyny w kale

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Keywords

calprotectin, children, ulcerative colitis

Słowa kluczowe

dzieci, kalprotektyna, wrzodziejące zapalenie jelita grubego

S u m m a r y

Introduction. Faecal calprotectin (FC) is a good marker in monitoring adults with ulcerative colitis (UC). Its concentrations in faeces is related to state of mucosa observed in endoscopy. There are a few studies concerning FC in mucosa status assessment in UC paediatric population.

Aim. Determination of cut-off points for FC levels in children with UC corresponding to the severity of inflammation in the colon.

Material and methods. 91 patients with UC (F 45, M 46, median 14.79 years) were involved to the study and had colonoscopy performed and FC level within a week before endoscopy measured. Mucosa status was assessed with Mayo score. We have identified three subgroups: those with mucosal healing and Mayo score 0 or 1, patients with moderate inflammation in gut mucosa defined as Mayo score 2 and those with sever colitis described as Mayo score 3. The ROC was used as a statistical method to establish cut-off points. The AUC assesses the differentiation quality of the study group. We also analysed other laboratory, clinical or demographic data to established their impact on state of mucosa.

Results. Strong significant positive correlation between Mayo score and PUCAI and FC was found, with $r = 0.61$; $r = 0.68$ respectively. AUC for FC in differentiation between mucosal healing and moderate disease was 0.90 whereas mild colitis and sever disease was 0.53. The optimal cut-off levels of FC of discrimination between subgroup with no or low disease activity and moderate activity in endoscopy findings was 300 μg/g with sensitivity 0.90 and specificity 0.82.

Conclusions. Only FC and PUCAI are strongly correlated with state of mucosa in children with UC. FC of 300 μg/g let us to distinguish children with no or low activity of the disease between those with moderate colitis. The differentiation between moderate and sever colitis is not possible in UC children with usage of model based only on FC.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

S t r e s z c z e n i e

Wstęp. Kalprotektyna w kale (FC) jest dobrym markerem w monitorowaniu dorosłych pacjentów z wrzodziejącym zapaleniem jelita grubego (UC). Jej stężenie jest związane ze stopniem aktywności zmian zapalnych uwidacznianych podczas badań endoskopowych. Nieliczne prace rozważają znaczenie kalprotektyny w ocenie stanu śluzówki w populacji pediatrycznej UC.

Cel pracy. Wyznaczenie punktów odcięcia dla stężenia FC odpowiadających nasileniu zmian zapalnych w jelicie u dzieci z UC.

Materiał i metody. Do badania włączono 91 dzieci z UC (K 45, M 46, mediana 14,79 roku), u których wykonano kolonoskopię oraz zmierzono poziom FC w przeciągu tygodnia przed badaniem endoskopowym. Nasilenie zmian zapalnych na śluzówce oceniano w skali Mayo. Pacjentów podzielono na trzy grupy: tych z wygojoną śluzówką jelita grubego ocenioną w skali Mayo na 0 lub 1, pacjentów ze średnio nasilonymi zmianami zapalnymi w obrębie śluzówki opisanymi jako Mayo 2 oraz tych z dużymi zmianami zapalnymi skalsyfikowanymi jako Mayo 3. W celu wyznaczenia punktów odcięcia jako metody

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statystycznej użyto krzywej ROC. AUC określa jakość FC jako klasyfikatora w rozróżnianiu grupy badanej. W pracy analizowano również wpływ innych badań laboratoryjnych, oceny klinicznej i danych demograficznych na stan śluzówki.

Wyniki. Znaleziono silną dodatnią korelację pomiędzy oceną nasilenia zmian zapalnych w skali Mayo oraz PUCAI i FC z odpowiednio r = 0,61 oraz r = 0,68. AUC dla FC w różnicowaniu pacjentów z wygojoną śluzówką jelita grubego od pacjentów ze średnio nasilonymi zmianami zapalnymi wyniosło 0,90, podczas gdy w dyskryminacji pomiędzy średnio zaawansowanym zapaleniem a dużym nasileniem w skali Mayo wniosło 0,53. Optymalny punkt odcięcia FC w rozróżnianiu pacjentów bez zmian zapalnych lub z nieznacznie przekrwioną śluzówką od tych ze średnim stopniem zaawansowania choroby wynosi 300 μg/g. Przy użyciu tego punktu odcięcia można zaklasyfikować pacjentów do podgrup z czułością 0,90 oraz specyficznością 0,82.

Wnioski. Tylko skala PUCAI oraz FC są silnie skorelowane z nasileniem zmian zapalnych w śluzówce jelita u dzieci z UC. FC poniżej 300 μg/g pozwala na odróżnienie pacjentów bez aktywnych zmian zapalnych od tych ze średniego stopnia stanem zapalnym w jelicie. Używając jedynie FC, nie można rozgraniczyć dzieci ze średnią aktywnością choroby od tych z intensywnymi zmianami zapalnymi.

INTRODUCTION

Ulcerative colitis (UC) is most common one of the inflammatory bowel diseases (IBD) (1). It is closely related to immunologic dysregulation. UC natural history consist of remissions and relapses. Due to relatively high rate of colectomy in childhood onset of UC the disease need to be under good monitoring (2, 3). The gold standard in defining the state of disease activity is colonoscopy. But this procedure is expensive and invasive, especially in young patients. Biomarkers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum albumin have low sensitivity and specificity so relaying on them is not recommended in assessing state of mucosa or in diagnosing a flare (4). On the other hand nowadays new non-invasive markers have been developed. Most popular, cheap and quick is faecal calprotectin (FC). Calprotectin is zinc and calcium binding protein found in cytosol of neutrophils, monocytes, macrophages (5). It is related extracellularly in times of cell stress or damage and can be found in faces. FC levels are stable in room temperature up to 3 days (6, 7). Like Szczepański et al. showed FC is closely related to state of mucosa in paediatric patients with IBD (8). Although FC has been available for some time its applications in monitoring inflammation of UC patients in clinical practice have not been standardized.

AIM

The aim of our study was to determine the relationship between FC and non-invasive markers and to establish cut-off points for FC levels in children with UC corresponding to the severity of inflammation in the colon.

MATERIAL AND METHODS

Patients

Into the study we involved 91 children with UC (45 females, 46 males, median age 14,79) administrated in our Institute between 2013 and 2015 year as an out- and inpatient admission. Each of them had elective colonoscopy performed and within a week before FC, ESR, CRP, haematocrit (HT), platelets (PLT), weight and height measured. They had also body mass index (BMI) and paediatric ulcerative colitis activity index (PUCAI) calculated. Disease activity was assessed during endoscopy by Mayo score. We divided our patients into subgroups based on Mayo score. Children with Mayo score 0 or 1 was defined as in remission, those with Mayo 2 as mild disease and with Mayo 3 as sever colitis. Table 1 contains patients characteristics.

Tab. 1. Patients characteristics

Parameter	Characteristic
Gender: male female	 46 (51%) 45 (49%)
Age in years (median)	14.79 (IQR 4.16)
Mayo: 0 1 2 3	 37 (40.7%) 28 (30.8%) 19 (20.9%) 7 (7.7%)
Disease duration in years (median)	1.82 (IQR 3.41)

Methods

The level of FC was assessed with Bühlmann Quantum Blue Calprotectin test. Quantum Blue Calprotectin is an immunologic test of double-binding which uses 2 types of mouse monoclonal antibodies (mAb) highly specific to human calprotectin. The test is a disposable cartridge which allows FC assessment within only about 45 minutes. After assessment, the outcome is registered with reader (9).

Statistics

All statistics test were performed by Statistica 12 (StatSoft, Tulusa, OK, United States) and StatsDirect (Copyright 1993-2004, Manchester).

Quantitative variables were tested for normality by Shapiro-Wilk test. Those with normal distribution were presented as means and standard deviations and others with medians and interquartile ranges (IQR). Binary and categorical variables were shown as numbers and

percentages. Correlation coefficient was conducted between Mayo score and other variables by Spearman's rank correlation. A *p* value of less than 0.05 was considered to be statistically significant. The receiver operating characteristic curve (ROC) was used as a statistical method to establish cut-off points.

RESULTS

Out of analysed variables only weight was considered as normally distributed. 65 children out of 91 presents mucosal remission during full endoscopy with terminal ileum intubation.

Demographic data

We did not found any significant correlation between age of diagnosis and Mayo score but the duration of the disease have small negative impact on endoscoping findings with r = 0.27.

Clinical and laboratory evaluation

Strong positive significant correlation was found between Mayo score and FC or PUCAI with r = 0.68 and r = 0.61 respectively and week positive correlation on ESR, PLT with r = 0.24 and r = 0.26. The moderate negative impact on Mayo score showed HT and BMI with r = 0.37 and 0.32 respectively. Also negative but week correlations was demonstrated by weight with r = 0.25. There were no significant correlation identified between Mayo and CRP or height. The clinical, laboratory and demographic characteristics of our patients subgroup are shown in tables 2-4.

Tab. 2. Patients with mucosal remission

n = 65	Mean	Median	IQR	SD
Age	14.36	15.16	3.77	3.22
Disease duration	3.15	2.22	3.25	2.73
PUCAI	5.27	0.00	7.50	10.44
FC	257.60	89.00	205.00	434.86
CRP	0.26	0.06	0.23	0.54
ESR	14.23	10.00	14.00	16.67
HT	39.18	38.90	4.70	4.23
PLT	289.89	283.00	112.00	91.58
Weight	54.72	54.50	20.90	17.46
Height	160.85	163.00	19.50	18.12
BMI	20.54	20.47	4.49	3.85

Tab. 3. Patient with mild disease

n = 19	Mean	Median	IQR	SD
Age	13.22	13.83	5.18	3.02
Disease duration	2.70	1.57	3.89	2.94
PUCAI	28.33	22.50	45.00	25.61
FC	1038.84	748.00	1482.00	697.36
CRP	0.38	0.11	0.50	0.67
ESR	15.37	11.00	16.00	11.30
HT	36.05	36.00	4.50	2.81
PLT	334.89	334.00	115.00	103.50
Weight	48.16	47.30	27.30	18.76
Height	160.41	164.50	36.50	16.40
BMI	18.02	18.36	4.98	4.08

Tab. 4. Patients with severe colitis

n = 7	Mean	Median	IQR	SD
Age	12.14	11.00	5.85	3.32
Disease duration	0.23	0.27	0.43	0.26
PUCAI	41.43	55.00	45.00	24.45
FC	1292.57	1800.00	1653.00	799.25
CRP	0.92	0.17	1.50	1.09
ESR	22.86	23.00	17.00	11.68
HT	30.74	31.70	15.30	6.98
PLT	488.00	366.00	505.00	230.32
Weight	40.89	39.10	21.00	14.81
Height	147.86	150.00	22.00	12.36
BMI	18.39	16.22	7.08	4.87

Predicting mucosal state with FC

The area under curve (AUC) for discrimination between subgroup of patients in remission vs moderate disease was 0.90 with cut-off level of FC = 300 μg/g and sensitivity 0.89, specificity 0.82. The figure 1 presents ROC curve distinguishing those two subgroups.

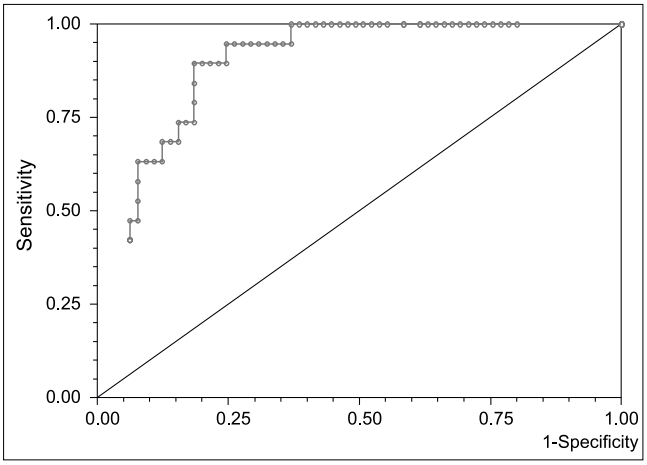

Fig. 1. ROC curve for discriminating patients with mucosal remission vs moderate activity lesions in mucosa

While the AUC for patients with moderate disease vs sever lesions was 0.53 with cut-off FC = 1592 μg/g and sensitivity 0.71, specificity 0.58. The ROC for those subgroups is showed below on figure 2.

DISCUSSION

The incidence of UC in paediatric population worldwide is increasing (10). There are several methods known in assessing disease activity from non-invasive like: PUCAI and laboratory tests to more complicate like endoscopic evaluation. Whereas the colonoscopy is a gold standard in assessing the disease activity it has its limitations in cost, invasiveness, or availability in a timely fashion. Therefore there is a great need in developing new monitoring tools in children with UC. One of them is FC which is closely correlated to mucosal status and can distinguished between disease

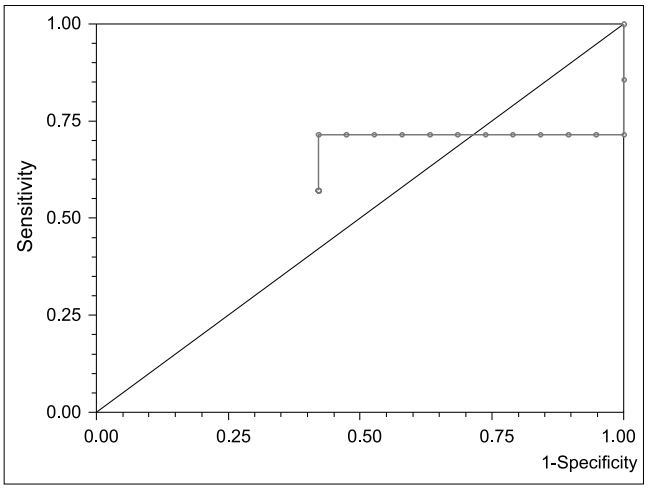

Fig. 2. ROC curve for discriminating patients with moderate colitis vs sever colitis

activity scores observed in colonoscopy like Lobaton Ortega et al. showed (11). In their work they observed 88 UC patients. They evaluated levels of FC that discriminate patients with Mayo 0/1 on 89.4 μg/g, Mayo 1/2 on 441.2 μg/g and Mayo 2/3 on 2004.1 μg/g. But the data from paediatric population with UC are limited. Canani et al. studied 58 children with IBD (23 Crohn's disease, 32 UC) to evaluate the correlation between FC, clinical scores, ESR, CRP, histology and endoscopy findings (12). They found high significant positive correlation between FC and histology or endoscopy grade of inflammation with r = 0.66 and r = 0.70 respectively. These observations are similar to ours but we are stepping forward and calculating the cut-off points of FC that determining the disease activity presented in Mayo score. We showed that FC below 300 μg/g can discriminate UC children with remission and moderate disease with high sensitivity and specificity whereas there is no reliable FC level that can differentiate patients with moderate from sever colitis. In this paper we have demonstrated that only PUCAI and FC are in strong correlation with endoscopy findings with r = 0.61 and r = 0.68 respectively. While there are many articles considering FC as a good surrogate marker in adults and children with UC and IBD (8, 11-13). The reports about PUCAI are contradictory. In Kerur et al. work is showed that Mayo score correlates well with PUCAI whereas in Dolinšek et al. paper were no significant correlation found (13, 14). Although we did not found any significant correlation between CRP and disease activity. This observation is in opposite to Turner's et al. article about concerning the role of CRP and ESR in assessing disease activity in paediatric population with UC (15). In the article they have demonstrated on the group of 451 UC children that CRP and ESR have significant positive correlation with endoscopy findings with r = 0.51 and r = 0.44, respectively. Moreover we also reports correlation between ESR and disease activity like in Turner's work, but relatively weaker; r = 0.24 vs r = 0.44.

Our results proved that FC is better in assessing mucosal status then other clinical or laboratory variables. The differentiation based on Mayo score is only possible for remission to moderate disease using FC.

The main disability of our work is relatively small group of observations and retrospective character of the study. This may have impact on our results. The second lack is no follow-up period with clinical outcome, so we cannot evaluate any prognostic factors for relapse of UC in children.

CONCLUSIONS

Only FC and PUCAI are strongly correlated with state of mucosa in children with UC. FC of 300 μg/g let us to distinguish children with no or low activity of the disease between those with moderate colitis. The differentiation between moderate and sever colitis is not possible in UC children with usage of model based only on FC. Further affords are needed to elaborate novel models that better discriminate disease activity in paediatric UC patients.

BIBLIOGRAPHY

1. Castro M, Papadatou B, Baldassare M et al.: Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003). Inflamm Bowel Dis 2008; 14(9): 1246-1252.
2. Rinawi F, Assa A, Eliakim R et al.: Risk of colectomy in patients with pediatric-onset ulcerative colitis. J Pediatr Gastroenterol Nutr 2017; 65(4): 410-415.
3. Colombel JF, Rutgeerts P, Reinisch W et al.: Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011; 141(4): 1194-1201.
4. Brahmania M, Bernstein CN: Physician global assessments or blood tests do not predict mucosal disease activity in ulcerative colitis. Can J Gastroenterol Hepatol 2014; 28(6): 325-329.
5. Fagerhol M, Dale I, Andersson T: A radioimmunoassay for a granulocyte protein as a marker in studies on the turnover of such cells. Bull Eur Physiopathol Respir 1980; 16: 273-282.
6. Roseth A, Fagerhol M, Aadland E et al.: Assessment of the neutrophil dominating protein in feces. A methodologic study. Scand J Gastroenterol 1992; 27: 793-798.
7. Walsham NE, Sherwood RA: Fecal calprotectin in inflammatory bowel disease. Clin Exp Gastroenterol 2016; 9: 21-29.
8. Szczepański M, Dądalski M, Szymańska E et al.: Fecal calprotectin is a good biomarker of mucosal healing in monitoring of children with IBD. Post Nauk Med 2014; 27(3): 150-153.
9. Coorevits L, Baert FJ, Vanpoucke HJ: Faecal calprotectin: comparative study of the Quantum Blue rapid test and an established ELISA method. Clin Chem Lab Med 2013; 51(4): 825-831.
10. Benchimol EI, Fortinsky KJ, Gozdyra P et al.: Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011; 17: 423-439.
11. Lobaton Ortega T, Rodriguez-Moranta F, Guardiola J et al.: A new rapid test for fecal calprotectin (FC) predicts mucosal healing in ulcerative colitis (UC). European Crohn's and Colitis Organisation, Conference 2013.
12. Canani RB, Terrin G, Rapacciuolo L et al.: Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. Dig Liver Dis 2008; 40(7): 547-553.

13. Dolinšek J, Rižnik P, Sabath L et al.: Fecal calprotectin as a marker of the severity of mucosal inflammation in children with inflammatory bowel disease. Wien Klin Wochenschr 2016; 128(7-8): 253-259.
14. Kerur B, Litman HJ, Stern JB et al.: Correlation of endoscopic disease severity with pediatric ulcerative colitis activity index score in children and young adults with ulcerative colitis. World J Gastroenterol 2017; 23(18): 3322-3329.
15. Turner D, Mack DR, Hyams J et al.: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. J Crohns Colitis 2011; 5(5): 423-429.

received/otrzymano: 05.10.2017
accepted/zaakceptowano: 25.10.2017