Elevated serum values of procollagen III peptide (PIIIP) in patients with ulcerative colitis who will develop pseudopolyps

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Abstract

AIM: To assess the impact of procollagen III peptide as a marker of collagenesis in the development of pseudopolyps in patients with ulcerative colitis.

METHODS: Development of pseudopolyps was monitored in 25 patients with ulcerative colitis classified according to Powell-Tuck index as mild (n=12) or moderate (n=13) form of disease. Patients with a mild form of disease were treated with oral mesalazine medication (2-4 g/day) and local mesalazine preparation (suppository). Patients with a moderate form of disease received oral mesalazine medication (2-4 g/day), local mesalazine preparation (suppository) and local methylprednisolone at an initial dose of 60 mg/day, followed by dose tapering. How many significant variables (previously determined by analysis of variance) were elevated in the groups with and without pseudopolyp development was observed. ROC analysis for calculation of new index was made.

RESULTS: Serum values of procollagen III peptide (PIIIP), C-reactive protein (CRP) and C4 complement component (C4) were statistically significantly lower in the group of patients free from pseudopolyp development than those who developed one or more pseudopolyps (0.45±0.12 vs 1.42±0.70; P<0.0027; 7.6±4.7 vs 17.8±9.17; P<0.035; and 0.46±0.11 vs 0.34±0.16; P<0.068, respectively) at endoscopic controls with pathohistologically samples during 13 months. There were no statistically significant differences in the values of C3, ceruloplasmin and IgM between the two groups (P>0.05). Discrimination function analysis yielded highest standardized cannon coefficients for PIIIP (0.876), CRP (0.104), C3 (-0.534) and C4 (0.184) (P<0.036). The elevation in two of three laboratory variables (PIIIP, CRP and C4) reached sensitivity of 93 % and specificity of 90 % in the development of pseudopolyps.

CONCLUSION: It is proposed that an increase in two of the three laboratory parameters (PIIIP, CRP and C4) could improve the accuracy of prediction of the development of pseudopolyps. When using PIIIP, CRP and C4 on decision making, the positive predictive value and accuracy were 90 % and 92 %, respectively.

INTRODUCTION

The role of procollagen and of its metabolites and enzymes involved in the synthesis and degradation of procollagen during the development of ulcerative colitis has already been investigated in a number of studies[1-6]. Higher levels of procollagen transcripts have been reported in patients with ulcerative colitis as compared with healthy subjects[7], pointing to an enhanced de novo synthesis of all types of collagen in patients with ulcerative colitis[1,3,4]. Also, the expression of collagenase has been demonstrated to be higher in patients with ulcerative colitis than in normal subjects[7]. These patients showed hyperexpression of procollagen III RNA transcripts. The elevated level of procollagen messenger RNA correlated with the rate of inflammatory infiltrations[1,3,4], represented by inflammatory polyps (pseudopolyps). In the process of healing inflammatory desctruced mucosa is changed with the reparatory process[1-7].

The development of pseudopolyps sometimes is seen in the stage of disease remission[7,8]. The presence of procollagen and other materials is necessary for polyp formation[1,9]. The measurement of procollagen may be helpful in the determination of the patient who will develop pseudopolyp formation. Insight to literature of the last 20 years, there were no studies into the predictive value of procollagen III peptide (PIIIP) for polyp development in patients with ulcerative colitis.

The aim of the study was to assess the role of PIIIP as a marker of collagen syntheses in the development of pseudopolyps in patients with ulcerative colitis.

MATERIALS AND METHODS

Patients

Twenty-five patients with ulcerative colitis[7,] 11 men with median age of 34 years (aged 30-45) and 14 women with median age 35 years (aged 29-47), were included in the study. Only newly detected patients were enrolled in the study, thus to exclude the effect of previous therapy on collagen formation[1-7]. Thus the patients were classified according to Powell-Tuck index[7] for disease severity into the groups with mild (n=12) and moderate (n=13) form of disease. Mild form of disease had no system symptoms, had less then 4 stools over 24 hours. This form of disease was without significant rectal bleeding, had no signs of anemia, had normal body temperature, normal pulse rate and had sedimantation rate under 30 mm per hour. Moderate form of disease had 4-6 diarrholic stools per day, crampy abdominal pain, elevated body...
temperature, increased pulse rate, tachycardia, anemia, elevated sedimantastion over 30 mm per hour and extraintestinal symptoms (arthritis). Severe form of disease with more than 6 diarrhea stools per day, more rectal bleeding and severe intestinal and extraintestinal complications, etc. were not included in the study, while the therapy for this form of disease can influence to the collagen formation[10-12].

The course of disease was monitored clinically, endoscopically and histologically. The development of pseudopolyps was observed by using endoscopy[13-15]. The formation of intraluminal mucosal enlargement with one or more polyps in former or newly inflamed mucosa was observed. Histological criteria for inflammatory polyps (pseudopolyps) were: only the finding of a diffuse colitis with nonspecific inflammation, no granulomas, and involved rectum would be consistent with ulcerative colitis; however, even in cases that the patient might still have some other form of diffuse colitis and the diagnosis of ulcerative colitis is only established by exclusion of all other causes[13]. The criterias for the diagnosis of epithelial dysplasia and its distinction from the inflammatory and reparative[14,15] lesions and neoplasms[16] that regularly occur in these patients have been established.

Clinical and endoscopic controls were done once monthly during 12 months (12 times), and then once after six months again, what meant totally 13 controls[7].

Laboratory measurements and new index calculation
PIIP was measured by using RIA-gnost PIIP method (Berhingwerke). CRP, C3, C4, IgM and ceruloplasmin were measured by using Turbox Immunonephelometry method (Orion diagnostics).

The significant laboratory variables were determined by using analysis of variance. The contribution of each variable was determined by using the discriminant canonical function on Statistica 5.0 software.

The indexes from three most significant variables were calculated by using ROC analysis. How many significant variables were calculated above laboratory reference values for each patient in two groups (with and without pseudopolyps) was observed. ROC analysis was used to determine the sensitivity, specificity, accuracy and positive predictive value of our new index.

Therapy
The patients with a mild form of disease were treated with oral mesalazine medication (2-4 g/day) and local mesalazine preparation (suppository)[17]. The patients with a moderate form of disease received oral mesalazine medication (2-4 g/day), local mesalazine preparation (suppository) and oral methylprednisolone at an initial dose of 60 mg/day followed by methylprednisolone dose tapering[18]. Severe form of disease was excluded with Powell-Tuck index, while therapy for severe form of disease can influence on inflammatory polyps formation[19].

RESULTS
In the group of patients without pseudopolyp development (n=15), the levels of PIIP, C-reactive protein (CRP) and C4 complement component (C4) were statistically significantly lower than those in the group of patients developing pseudopolyps (0.45±0.12 vs 1.42±0.70, P<0.0027; 7.64±4.7 vs 17.8±4.9, P<0.035; and 0.46±0.11 vs 0.34±0.16, P<0.0068, respectively). Other parameters, i.e., C3 complement component (C3), ceruloplasmin and IgM, showed no statistically significant differences between the groups of patients with and without pseudopolyp development. Analysis of the discriminative cannon function yielded highest standardized cannon coefficients for PIIP (0.876), CRP (0.104), C3 (-0.534) and C4 (0.184) (P<0.036), which were then used for subsequent data analysis.

The use of PIIP, CRP and C4 levels showed that an increase in two of these three laboratory parameters improved the accuracy of prediction of pseudopolyp development. When using PIIP, CRP and C4 (ROC analysis) on decision making sensitivity was 93 % and specificity 90 %, the positive predictive value and accuracy were 90% and 92%, respectively.

DISCUSSION
In ulcerative colitis patients, inflammatory mucosal destruction is changed by regeneratory process (inflammatory polips (pseudopolyps)) in the formation of intraluminal mucosal enlargement with one or more polyps in former or newly inflamed mucosa was observed. Histological criteria for inflammatory polyps (pseudopolyps) were: only the finding of a diffuse colitis with nonspecific inflammation, no granulomas, and involved rectum would be consistent with ulcerative colitis; however, even in cases that the patient might still have some other form of diffuse colitis and the diagnosis of ulcerative colitis is only established by exclusion of all other causes[13]. The criterias for the diagnosis of epithelial dysplasia and its distinction from the inflammatory and reparative[14,15] lesions and neoplasms[16] that regularly occur in these patients have been established.

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assessment of intestinal resorption, however, in spite of previous belief, had no practical clinical relevance in the determination of disease activity[20,30]. The results of our study were consistent with these concepts. So, only the values of C4 complement component could be used for subsequent evaluation, and these only in combination with other parameters. Neither were the values of ceruloplasmin as an early inflammation reactant useful for further analysis.

According to Schmoud et al, age is an unfavorable prognostic factor for disease relapse in patients with inflammatory bowel disease (IBD) [21]. Therefore, the patients included in our study were matched by both sex and age, thus to minimize the impact of these factors on study results.

In the present study, we used the ever more popular method including a combination of factors, providing more accurate information on the real state than each of the factors alone. The role of procollagen should be investigated in a larger sample. Studies with tissue collagen determined before and after therapy may also be expected to yield interesting results. In addition, studies in more severe forms of the disease would be highly interesting, although it might be difficult to differentiate between the collagenase involved in the connective tissue formation in the intestinal wall and the collagenase formed by systemic stimulation of other tissues due to the disease severity [12,6,9].

In conclusion, based on the study results, it is proposed that elevation in two of the three laboratory parameters (PIIIP, CRP and C4) can improve the prediction of the development of pseudopolyps in patients with ulcerative colitis. When PIIIP, CRP and C4 are used in the assessment of pseudopoly development, the positive predictive value and accuracy were as high as 90 % and 93 %, respectively.

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