The diameter of the ileal J-pouch-anal anastomosis as an important risk factor of pouchitis – clinical observations

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Summary

Background: Patients’ quality of life after restorative proctocolectomy depends on the potential complications. Stricture of the ileal pouch-anal anastomosis is one of the complications following restorative proctocolectomy.

Material/Methods: We analyzed the correlation between the diameter of the anastomosis and clinical parameters, including pouchitis disease activity index (PDAI), the activity of fecal M2-pyruvate kinase and maximum tolerable volume of the pouch. The study group consisted of 31 patients in whom covering ileostomy had been closed 72±50 months before enrolment to the study. Restorative proctocolectomy for ulcerative colitis or familial adenomatous polyposis coli had been performed in this group.

Results: The study did not show any correlation between the diameter of the anastomosis and primary indication for surgery, the time elapsed after restoration of the bowel continuity, the activity of fecal M2-pyruvate kinase, or maximum tolerable volume. However, meaningful correlations between the stricture of the anastomosis and the presence and activity of pouchitis, together with the ileal villi atrophy, were detected.

Conclusions: Stricture of the anastomosis appears to be an important factor increasing the incidence of pouchitis, and is independent of the underlying condition and time after the operation. Dilation of the anastomosis and prevention of stricture should constitute a permanent element of postoperative follow-up.

key words: proctocolectomy • pouchitis • J-pouch • anastomotic stricture

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**Background**

Inflammation of the pouch mucosa is diagnosed in a considerable number of patients after restorative proctocolectomy. The reported incidence of pouchitis varies between 25% and 60% [1–4]. The etiology of pouchitis still remains unclear. The list of postulated contributing factors is long and includes autoimmune mechanisms, mucosal edema, bile acids, short chain fatty acids, and stasis of ileal contents with subsequent bacterial overgrowth. In some cases, backwash ileitis in the course of the ulcerative colitis can be a potential factor for pouchitis development [5]. In our previous studies on bacterial overgrowth in patients after restorative proctocolectomy, there was no difference between the group with pouchitis and the group without it [6]. However, the stasis of the ileal contents within the pouch may be an independent proinflammatory factor, and may be associated with anastomotic stricture. Narrowing of the anastomotic lumen occurs in the physiological process of healing, as a result of increased activity of the fibroblasts and intensified collagen production at the site of anastomosis. Stricture of the anastomosis is also an important complication of restorative proctocolectomy, which may affect as many as 15% of the patients operated on [7]. The absence of fecal flow through the diverted pouch is also postulated to stimulate anastomotic stricture, but the results of a meta-analysis of 17 studies on 1486 patients proved that the incidence of anastomotic stricture was higher in the patients operated on without temporary loop ileostomy. Therefore, faecal flow is a factor stimulating anastomotic stricture, probably by increasing inflammatory response [8]. It is difficult to clearly define adequate diameter of the ileo-rectal anastomosis. Commonly, the anastomosis is constructed with 28–35 mm diameter circular stapling instruments. Due to the aforementioned stricturizing processes, final diameter of the anastomosis should not be less than half of the initial one, which is a mean of 15 mm, with critical value, adopted after Dolinsky, of 8 mm [9]. Normal bowel transit is an important element influencing patient quality of life after restorative proctocolectomy. Any functional impairment may lead to severe disability and long-term complications. The aim of this study was to evaluate the influence of anastomotic stricture on the incidence of pouch mucosa inflammation. The severity of the inflammation has been rated with the pouchitis disease activity index (PDAI), which is widely recognized and applied. The index was introduced by Sandborn et al in 1994; it consists of clinical, endoscopic and histological sections, and allows for the diagnosis of pouchitis when total score equals 7 or higher [10]. However, some publications suggest the possibility of inflammation with scores below 7, which raised some criticism [11]; nevertheless, PDAI remains one of the most important and accepted tools for diagnosing pouchitis [12]. This scale is primarily based on subjective patient symptoms and subjective assessment by the examining physician. Although the PDAI scale is generally accepted, certain co-morbidities or disruptions within the pouch can lead to a false overvaluation of points, which can cause difficulties with final interpretation of the result.

Another relatively new method of determining the activity of pouchitis is evaluation of biochemical activity of fecal markers of inflammation. One of the first markers to be evaluated was pyruvate kinase, whose usefulness in diagnosing pouchitis was reported by Walkowiak et al. in 2005 [13], and confirmed in further studies [14]. Other fecal biochemical markers of pouch inflammation include lactoferrine and calprotectin [15].

Maximum tolerable volume is another parameter measured in anorectal manometry, and it correlates with severity of pouchitis. This parameter has not been used in clinical practice as a marker of inflammation; however, there are encouraging reports indicating low maximum tolerable volume is associated with pouchitis [16]. On the other hand, it is difficult to establish whether low compliance of a pouch may cause pouchitis, or if it is a direct result of inflammation.

**Material and Methods**

The study group consisted of 31 patients (16 women and 15 men, mean age 40, 4 years (±) after restorative proctocolectomy performed because of ulcerative colitis or familial adenomatous polyposis coli. All the patients were operated on for elective indications. Restorative proctocolectomy was performed in 2 steps. First, total proctocolectomy and ileal J-pouch-rectal anastomosis were completed with diverting loop ileostomy. In the second step, the stoma was reversed. The patients were evaluated 72±30 months after ileostomy closure. Study procedures included history and physical examination, anorectal manometry and pouch endoscopy. Patients delivered 3 stool samples collected within the 48 hours before the visit, and stored in standard containers.

In history taking and physical examination, essential clinical data were evaluated, with special attention paid to the symptoms needed to assess the severity of pouchitis with the use of PDAI. Next, anorectal manometry was performed, avoiding any mechanical manipulations in the anorectal zone (eg, digital rectal examination, rectal enema) before this procedure. The manometry was performed using an 8-channel water-perfused catheter with a balloon. After the catheter was inserted into the rectum, the patient was allowed 5 minutes to adjust sphincters to the new settings, and then the procedure was started. The data were recorded by a multi-channel recording system (PC Polygram HR) for stationery upper and lower GI tract manometry. Anorectal manometry analysis was performed with Polygram software (Synectics Medical). Then, an enema with 250 ml solution of normal saline was performed to clean the pouch for endoscopy. A rigid rectosigmoidoscope was used. Rectoscopy was started with an 15mm diameter instrument. When insertion of the instrument of that calibre was feasible, the procedure was continued, and the diameter of the anastomosis was identified as “>15 mm” (Group 3). When the calibre of the instrument was too big for insertion, another instrument of 8.2 mm diameter was tried. If that was successful, the investigation was continued and the diameter of the anastomosis was identified as 8.2–15 mm (Group 2). If the insertion of a smaller instrument was not feasible, digital dilation of the anastomosis was performed and, according to the results of this manoeuvre, endoscopy was retried with either a rigid rectosigmoidoscope of 8.2 mm diameter or a 5.5 mm instrument (Group 1).

In order to perform complete evaluation of inflammation with PDAI, mucosal biopsies from the pouch were obtained in all patients. In every case, at least 2 samples were taken.
from the middle portion of the pouch and from the anastomosis. Biopsies were taken also from macroscopically apparent lesions of the pouch mucosa, anastomosis and anal canal. Changes found in the anal canal were not considered in the study. Pouchitis was diagnosed when patient PDAI score was at least 7 [10]. For the purpose of pouchitis evaluation, some additional descriptions were introduced. One of those was the pouchitis diseases activity index (PDAI), proposed by the Mayo Clinic group [10]. PDAI included clinical endoscopic and pathologic data. The pathologic data were based on the presence of polymorphonuclear leukocyte inflammation, which in pathologic meaning is equal to acute inflammatory infiltrate (acute inflammation). Additionally, some authors claim that biopsy taking and pathologic evaluation is unnecessary due to economic reasons. Moreover, to simplify classification, the proposed Japanese criteria of pouchitis does not contain any pathologic findings or scoring system [11]. However, even if the detailed description of acute inflammation was redundant for some [17], and not a good indicator of clinical outcome, Kohyama et al proved that patients with low PDAI had better response to antibiotic treatment [11]. The full PDAI remains an excellent research tool [17]. On that basis, it can be postulated that description of inflammation may be used for assessing of the clinical follow-up. Besides the aforementioned approaches to pouchitis description, we believe that the standard Moskowitz scale should be applied. The Moskowitz scale applies to morphologic changes seen in acute and chronic inflammation:

**Acute pouchitis rate:** a) acute inflammatory infiltration: insignificant 1; average + abscesses in crypts 2; significant + abscesses in crypts 3 b) ulceration: <25% of the examined area 1; 25–50% – 2; >50% – 3.

**Chronic pouchitis rate:** a) chronic inflammatory infiltration: insignificant 1; average 2; significant 3 b) colonic metaplasia: partial 1; almost complete 2; complete 3.

Histological evaluation was carried out every time by 2 pathologists, according to a routine protocol, 1 of them performed initial evaluation and the second confirmed the report after repeated assessment. In every case, histology included grading of inflammation with the Moskowitz classification and evaluation of ileal villous atrophy according to Laumonier’s score.

Fecal pyruvate kinase activity was measured for all patients. For that purpose, 3 samples of stools were collected from each patient and tested for dimeric M2 pyruvate kinase (M2 PK) activity (Schebo-Biotech, Giessen, Germany), using the double reaction of monoclonal antibodies binding with highly specific epitopes of an enzyme (ELISA) (Walkowiak 2005). For further analysis, mean value from 3 samples was calculated.

**Statistical analysis**

Statistical analysis was performed with Fisher’s exact test and ANOVA exact test for comparison of age, kinase activity, time of stoma closure, PDAI and maximum tolerable volume in the 3 groups of patients with different anastomosis diameters. The analysis was conducted with StatXact package software (Cytel Co.).

**RESULTS**

There were no statistically important associations between the diameter of the anastomosis and sex, age, maximum tolerable volume, the time of ileostomy closure or pyruvate kinase activity (Table 1). In 2 parameters, time of ileostomy closure and pyruvate kinase activity, standard deviation values were high. Additionally, there was no association between the diameter of the anastomosis and the reason for restorative proctocolectomy (ulcerative colitis vs familial polyposis coli) (Table 2).

The study revealed statistically important associations between the diameter of the anastomosis and the presence of inflammation (Table 3), between the diameter of the anastomosis and severity of the inflammation (Figure 1), and between the diameter of the anastomosis and villous atrophy in Laumonier’s score (Table 4). The tables below present the results. Patients with narrow anastomosis and grade IV villous atrophy constituted the majority (25.51%). This was statistically significant (p<0.05) in comparison to the groups with wider anastomosis and lower grades of villous atrophy. Patients with grade IV villous atrophy, and belonging to group 1 or 2 regarding the anastomosis diameter, constituted a 2-fold lower percent of the studied population.

The number of patients in this group did not significantly differ from the number of the patients with grade III villous atrophy and belonging to group 2 anastomosis diameter (9.68%). However, it was significantly higher than the number of patients with lower grades of villous atrophy and greater anastomosis diameter (Table 4).

**DISCUSSION**

Despite many publications on pouchitis, its etiology still remains unclear. Differentiation between causes of an inflammatory reaction, which can lead to narrowing of an anastomosis, and an inflammation that is the result of narrowing, is difficult and ambiguous. One of the common theories of pouch mucosa inflammation is that the stasis of ileal contents within the pouch results in alternated ileal bacterial flora, bacterial overgrowth, impaired vascular perfusion and direct proinflammatory reactions. Empirical proof of that theory is the clinical effectiveness of therapy with Metronidazole and Ciprofloxacin in many cases of pouchitis. However, lack of direct evidence of bacterial overgrowth has been reported in some patients with pouchitis [6], and in some patients antibiotics fail in pouchitis therapy. Therefore, it appears that many different factors may be involved in the etiology of pouch inflammation.

Stricture of the ileal pouch-anal anastomosis is one of the potential complications of restorative proctocolectomy. Among the factors that may increase the risk of stricture are the use of the 25mm circular stapling instrument, creation of a diverting ileostomy, anastomotic leak, and inflammation in the pelvis [18]. Opinions on the use of a temporary stoma are very divergent, and there are publications stating that strictures occurred more often in patients without ileostomy [19]. It is recommended that one-step restorative proctocolectomies without temporary stoma should be performed only in carefully selected patients.

In our study, a significant association between narrow lumens of the anastomosis and signs of pouchitis was found.
That association referred to pouchitis assessed with PDAI, and higher PDAI scores were seen in patients with narrower anastomosis. There were no statistically important differences in the diameter of the anastomosis between the patients operated on for ulcerative colitis and the patients operated on for familial adenomatous polyposis coli. In analyzed material, a relatively high percentage of patients operated on because of FAP had an inflammation. This could be due to social and economic situations of these patients – diagnosis of pouchitis, especially chronic, based mainly on symptoms reported by patients, could significantly simplify receiving of permanent social and financial benefits. Hence, it seems that anastomotic stricture is determined by factors other than the primary condition for which the patient has been operated on. That confirms our observation of largely similar postoperative courses in patients after restorative proctocolectomy for ulcerative colitis and familial polyposis coli [20]. In the results of our study, attention should be drawn also to the correlation between villous atrophy assessed with Laumonier’s score and the diameter of the anastomosis. It is assumed that villous atrophy is a response to a chronic inflammation. Although it facilitates adaptive changes of the mucosa, it also increases the risk of dysplasia. The above association confirms the fact that patients with narrow anastomoses are exposed to

| Table 1. Anastomotic diameter, sex, age and selected clinical parameters of study population. |
|---------------------------------|-------|-------|-------|--------|-----------------|
| Anastomotic diameter | Sex | Age (years) | Maximal tolerable volume | Time elapsed from ileostomy closure (months) | Pyruvate kinase activity |
| Female | Male | | | | |
| <8.2 mm | 5 (31.25%) | 4 (26.67%) | 39.4±11.1 | 152.8±55.2 | 78±65 | 193.1±165.4 |
| 8.2–15 mm | 3 (18.75%) | 5 (33.33%) | 40.6±9.9 | 188.1±64.6 | 87±40 | 127.2±99.4 |
| >15 mm | 8 (50.00%) | 6 (40.00%) | 40.9±11.7 | 171.4±55.2 | 60±44 | 69.8±93.4 |
| Total | 16 (100.00%) | 15 (100.00%) | 40.4±10.7 | 170.3±57.3 | 72±50 | 120.4±127.2 |

Values in brackets are expressed as a percentage of females/males groups. No statistically significant associations were found between sex and anastomotic diameter (p>0.05, Fishers’s exact test). Age and selected clinical parameters are expressed as means ±SD. No statistically significant difference was found between the groups of anastomotic diameter (p>0.05, ANOVA exact test).

| Table 2. The diameter of the anastomosis and initial diagnosis. |
|----------------|----------------|----------------|----------------|----------------|
| Indication | <8.2 mm | 8.2–15 mm | >15 mm | Total |
| CU | 6 (30.0%) | 4 (20.0%) | 10 (50.0%) | 20 (100.0%) |
| FAP | 3 (27.2%) | 4 (36.4%) | 4 (36.4%) | 11 (100.0%) |
| Total | 9 | 8 | 14 | 31 |

Values in brackets are expressed as a percentage of UC and FAP groups. No statistical association was found between the groups of anastomotic diameter and the indication for restorative proctolectomy p>0.05, Fisher’s exact test).

| Table 3. Association between the diameter of the anastomosis and pouchitis. |
|----------------|----------------|----------------|
| Anastomotic diameter | Pouchitis | p-value, Fishers’ exact test |
| No | Yes | |
| <8.2 mm | 1 (6.25%) | 8 (53.33%) | 0.0059 |
| 8.2–15 mm | 4 (25.00%) | 4 (26.67%) | >0.05 (ns) |
| >15 mm | 11 (68.75%) | 3 (20.00%) | 0.0113 |
| Total | 16 (100.00%) | 15 (100.00%) | |

Values in brackets are expressed as a percentage of pouchitis groups.

Figure 1. Association between the diameter of the anastomosis and PDAI (mean ±95% CI). Lower scores of PDAI were associated with increasing anastomotic diameter (statistically significant difference was found between patients with the low diameter <8.2 and high diameter >15 mm, p<0.01, ANOVA exact test).
higher risk of chronic inflammation, which induces the atrophy of ileal villi.

Our study failed to determine any association between pyruvate kinase activity and anastomosis diameter. The activity of fecal pyruvate kinase is a useful marker of pouchitis [13,14]. In our study population we recorded a high value of standard deviation; therefore, it is possible that anastomotic stricture and related fecal stasis may influence the activity of pyruvate kinase. No association between anastomotic stricture and maximum tolerable volume was detected. This may indicate that narrow anastomosis does not influence pouch volume; however, a high value of standard deviation was recorded for this parameter. This may be related to the highly variable time elapsed from stoma closure and the phenomenon of so-called “pouch aging”. The time after stoma closure had no influence on the diameter of the anastomosis, so the potential anastomotic stricture should be considered with the same probability at every step of follow-up, including the period before reversal of the stoma. Stricture of the anastomosis occurring at that time proves to be a factor significantly increasing the risk of pouchitis after stoma closure [1]. Some authors suggest prophylactic use of Ciprofloxacin and Metronidazole in patients with anastomotic stricture [1]. In our department a standard protocol for follow-up after pouch surgery was adopted – pouch enema with Metronidazole solution once a day for 5–7 days after ileal pouch-anal anastomosis, then repeated every 4–6 weeks until stoma closure and digital examination of the anastomosis with dilation in the case of a stricture every 4–6 weeks until the stoma is reversed.

Severe anastomotic stricture with apparent clinical manifestations calls for adequate therapeutic measures. The first recommended step is an endoscopic dilation, which is a safe and effective method [18] that increases the quality of life of patients with anastomosis stricture [21]. In case of failed endoscopic dilation, reoperation may be the only remedy. Remzi et al. recently reported that anastomotic stricture constituted 17.6% of all indications for reoperation, and that the results of repeated surgeries were very good [22].

Inflammation of the ileal pouch mucosa is a polymorphic clinical reaction for a number of endogenous and exogenous triggering actors. The mechanism of pouchitis is complex and difficult, if not impossible, to define. It appears that in order to reduce the incidence of pouchitis and refining the functional outcomes of pouch surgery, new clinically significant risk factors of pouchitis should be identified and eliminated. Anastomotic stricture is one of the causes of pouchitis, therefore early detection of a stricture and its dilation, together with adequate prophylaxis of stricture, is of utmost importance.

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