

# Lactose intolerance, lactose malabsorption and genetic predisposition to adult-type hypolactasia in patients after restorative proctocolectomy

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**This study provides up-to-date findings on lactose malabsorption, lactose intolerance and genetic predisposition to adult-type hypolactasia in 72 patients after restorative proctocolectomy (RPC). The lactose malabsorption was assessed by hydrogen-methane breath test. Genetic predisposition to adult-type hypolactasia was assessed by detecting –13910T/C polymorphism in the lactase gene. Lactose intolerance was more frequent in UC (ulcerative colitis) patients than FAP (familial adenomatous polyposis) patients (77.5% vs. 55.2%;  $p=0.01$ ). The C/C genotype of the lactase gene was observed in 39.1% subjects with no significant difference between UC and FAP patients. Lactose malabsorption occurred in 10.1% of subjects and almost only in patients with genetic predisposition, with the same frequency in UC and FAP patients.**

**Key words:** food tolerance, lactose, lactase, IPAA, pouch

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**Abbreviations:** BMI, body mass index; FAP, familial adenomatous polyposis; HMBT, hydrogen-methane breath test; RPC, restorative proctocolectomy; UC, ulcerative colitis

## INTRODUCTION

The general health and nutritional status after restorative proctocolectomy (RPC) remains good in most of the patients (Berndtsson *et al.*, 2011; Coffey *et al.*, 2002; Lerch *et al.*, 1989), however, some of them report food intolerance, including milk and dairy products intolerance (Schmidt *et al.*, 2008). Milk tolerance depends mostly on the presence of lactase in the apical surface of enterocytes in the brush border of the small intestine (Deng *et al.*, 2015). Most of the physicians (80%) recommend that the RPC patients should restrain from these types of products (Bernstein *et al.*, 1994).

To date, several diagnostic procedures are available to test milk tolerance. The gold standard involves the measurement of breath hydrogen, or preferably hydrogen and methane after lactose loading reflecting colonic fermentation of the nonabsorbed lactose (Lisowska *et al.*, 2008). A genetic predisposition towards adult-type hypolactasia can be excluded by analysis of the C/T<sub>-13910</sub> polymorphism (Enattah *et al.*, 2002). The T allele of that polymorphism is dominant and determines high activity

(lactase persistence) in the individual's life-span (Mądry *et al.*, 2011).

A previous study had suggested that around 60% of ulcerative colitis (UC) patients develop subjective milk intolerance in at least 10 years after operative treatment (Schmidt *et al.*, 2008). Self-reported dietary intolerances in the RPC patients with familial adenomatous polyposis (FAP) occur in 20–40% and diminish to 10% 10 years postoperatively (Schmidt *et al.*, 2008). The aim of this study was to multi-dimensionally assess the lactose intolerance, lactose malabsorption and genetic predisposition in UC and FAP patients who underwent RPC.

## METHODS

This study included 72 patients, aged 21–80 who had undergone RPC due to UC ( $n=43$ , 17 men, 26 women) and FAP ( $n=29$ , 14 men, 15 women) (Table 1). The operation procedure was performed in the years of 1979–2012 at The Department of General and Endocrine Surgery and Gastroenterological Oncology, as well as at the Chair of General and Colorectal Surgery of the Poznań University of Medical Sciences, Poland. The inclusion criteria were as follows: RPC, age  $\geq 18$ , time since ileal pouch-anal anastomosis  $\geq 1$  year. Exclusion criteria were: pouchitis, antibiotic therapy within the preceding month, other gastrointestinal conditions.

Lactose intolerance was defined as exhibition of specific clinical symptoms (such as nausea, abdominal distension, abdominal pain, cramps, flatulence, diarrhea or flatus). Lactose malabsorption was assessed by the gold standard hydrogen-methane breath test (HMBT) with the use of QuinTron MicroLyzer DP Plus (QuinTron Instrument Technology, USA). Patients were instructed to avoid ingesting products such as beans and similar vegetables, brans or high-fiber cereals the day before the test. Patients ingested 25 g of lactose dissolved in 250 ml of water. Hydrogen and methane concentrations in the exhaled breath were assessed at the baseline (at least 12-hour fasting) and at half an hour intervals for 3 hours. A positive result indicating lactose intolerance was assessed when the hydrogen level differed by  $\geq 20$  ppm from the baseline level and/or methane level differed by 12 ppm from the baseline.

Genetic predisposition to lactose intolerance was assessed by detecting the common –13910 T/C polymorphism in the promoter region of the lactase gene with the use of sequence-specific primer PCR and the Mu-

taGEL Lactase assay (Immundiagnostik AG, Bensheim, Germany).

Comparison between groups has been evaluated with  $\chi^2$  test and in case of values below 10, the  $\chi^2$  test with Yates correction. Statistical analysis was performed using STATISTICA 10.0 (StatSoft Inc., Tulsa, USA)

and MedCalc 14.8.1. The level of significance was set at  $p < 0.05$ .

### Ethical considerations

This study has been performed in accordance with the ethical standards of Helsinki Declaration and its later amendments. The protocol has been approved by the Bioethical Committee of Poznań University of Medical Sciences (decision 51/11). Three patients did not provide their consent to perform genetic testing.

### RESULTS

Self-reported lactose intolerance was more frequent in the UC patients than the FAP patients (77.5% vs. 55.2%,  $p=0.01$ ) (Table 1B). The C/C genotype of the lactase gene was observed in 39.1% of subjects, with no significant difference between the UC and FAP patients. Lactose malabsorption confirmed with objective HMBT occurred in 10.1% of the subjects, and almost exclusively in patients with a genetic predisposition, with the same frequency in the UC and FAP groups (Table 1B and 1C). No difference in time after ileostomy closure has been observed between the groups with and without lactose malabsorption, the difference between patients with lactose intolerance and lactose tolerance did not reach the level of significance (Table 2).

### DISCUSSION

Previous studies on lactose intolerance and malabsorption after RPC had either included a small sample sizes, had studied only clinical symptoms or mostly focused on patients operated due to UC. None of the studies conducted so far had analyzed the genetic predisposition to adult-type hypolactasia in the RPC patients. The study presented here is the first to provide an up-to-date status on lactose intolerance, lactose malabsorption and genetic predisposition to adult type hypolactasia among the RPC patients.

The main finding of the present study is that the lactose digestion and absorption disorders confirmed with HMBT occurred in 10.1% of subjects, and almost exclusively in patients with a genetic predisposition, with the same frequency in the UC and FAP groups. The C/C genotype of the lactase gene was observed in 39.1% of subjects. Our previous study had shown that the genetic predisposition for adult-type hypolactasia in a healthy population has a similar prevalence which accounted for 31.5% (Mađry *et al.*, 2010). Patients with the C/C genotype and lactose tolerance had seemingly longer postoperative courses, therefore we cannot exclude the effect of time on the presence of lactose intolerance.

Our study shows that the UC patients had reported lactose intolerance more frequently. This might be caused by the difference in pathophysiology of these two diseases. The disease course and general status in UC are dramatically different than FAP. A dysbiosis of the gut microbiota, as well as chronic inflammation, are more frequently present in UC than FAP. Also, the

Table 1. (A) Basic characteristics of the groups studied. (B) Genetic predisposition, result of the hydrogen-methane breath test (HMBT) and self-report. (C) Characteristics of the population studied in terms of the HMBT result and lactose intolerance depending on the 13919C/T genotype.

Parameter	Total (n=72)		FAP (n=29)		UC (n=43)	
	Mean $\pm$ S.D.	Median (1 <sup>st</sup> -3 <sup>rd</sup> quartile)	Mean $\pm$ S.D.	Median (1 <sup>st</sup> -3 <sup>rd</sup> quartile)	Mean $\pm$ S.D.	Median (1 <sup>st</sup> -3 <sup>rd</sup> quartile)
Age [years]	41.1 $\pm$ 12.8 39.0 (30.1-51.5)		37.9 $\pm$ 10.4 37.0 (30.0-43.0)		43.3 $\pm$ 13.9 43.0 (31.0-55.0)	
BMI (kg/m <sup>2</sup> )	23.1 $\pm$ 4.3 22.7 (20.1-25.2)		23.5 $\pm$ 3.3 23.8 (20.7-25.1)		22.9 $\pm$ 4.9 22.6 (19.4-25.4)	
Time after ileostomy closure [years]	8.5 $\pm$ 5.9 9.0 (2.0-13.0)		10.5 $\pm$ 5.7 11.0 (2.0-12.5)		7.1 $\pm$ 5.7 5.0 (2.0-13.0)	

  

Genotype	Positive HMBT		Lactose intolerance		Total (n=69)	
	CC	CT	CC	CT	CC	CT
FAP (n=29)	12 (41.4%)	7 (24.1%)	16 (55.2%)	7 (24.1%)	23 (77.5%)	12 (41.4%)
UC (n=40)	15 (37.5%)	5 (12.5%)	31 (77.5%)	5 (12.5%)	36 (90.0%)	12 (30.0%)
Total (n=69)	27 (39.1%)	12 (17.4%)	47 (68.1%)	12 (17.4%)	59 (85.5%)	24 (34.8%)

**Table 2. Time after ileostomy closure in patients with the C/C genotype with/without lactose malabsorption and with/without lactose intolerance.**

	C/C genotype		p value
	Positive HMBT n=6	Negative HMBT n=21	
Time after ileostomy closure [years]			
Mean ± S.D.	6.4±5.5	9.0±4.5	0.33
Median (1 <sup>st</sup> –3 <sup>rd</sup> quartile)	5 (2–10)	11 (4–12)	
	Lactose intolerance n=24	Lactose tolerance n=3	p value
Time after ileostomy closure [years]			
Mean ± S.D.	8.1±4.6	13±1.7	0.07
Median (1 <sup>st</sup> –3 <sup>rd</sup> quartile)	10.5 (3.5–12)	14 (11–14)	

incidence of pouchitis in the UC patients is considerably greater than in the FAP patients, and accounts for 30.1% vs. 5.5% (OR 6.44;  $p < 0.001$ ) (Lovegrove *et al.*, 2006). Furthermore patients with UC present the pouch failure, defined as excision of the ileoanal pouch with the need for permanent stoma construction or abdominoperineal reconstruction, more often (Shin *et al.*, 2008). These observations suggest that the underlying inflammatory pathogenesis associated with this systemic condition may predispose those individuals to more complications, including lactose intolerance.

In a previous report, Lerch *et al.* had found impairment in the intestine lactose absorption in 2 out of 12 RPC patients (Lerch *et al.*, 1989), whereas in the study of Croagh *et al.* lactose malabsorption was reported in 4 out of 8 UC patients identified as H<sub>2</sub>-producers with the lactulose breath test (Croagh *et al.*, 2007). In our study, we used the methane measurement in all patients during HMBT, which allowed us to reliably assess the malabsorption. Schmidt *et al.* evaluated subjective food intolerances in UC patients before and after proctocolectomy (Schmidt *et al.*, 2008). Milk and milk product intolerance occurred in 66.7% of patients before proctocolectomy and in 30.6% post proctocolectomy. The study included only 10 subjects with FAP whose preoperative dietary intolerance was negligible, whereas it occurred in 20–40% cases after operative treatment and diminished to 10% in 10 years post RPC (Schmidt *et al.*, 2008).

## CONCLUSION

In the study presented here, lactose intolerance was reported by the majority of RPC patients, including those without a genetic predisposition to adult-type hypolactasia. Lactose intolerance occurred more frequently in patients with RPC operated due to UC. Lactose malabsorption was less frequent and was present almost exclusively in patients with a genetic predisposition.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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