



Calprotectin in Low anterior resection syndrome patients; a new insight into Etiology and Treatment.

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- Introduction

Low anterior resection syndrome (LARS) has been reported to occur in up to 80% of patients after low anterior resection (LAR). LARS specifically refers to the bowel dysfunction following rectal cancer resection.

Martellucci J. Low anterior resection syndrome: a treatment algorithm. *Dis Colon Rectum* 2016;59:79–82.

Keane C, Wells C, O'Grady G, Bissett IP. Defining low anterior resection syndrome: A systematic review of the literature. *Colorectal Dis* 2017;19:713–22.

- LARS includes Common symptoms of bowel dysfunction following rectal resection include urgency, clustering, difficulty in evacuation or incomplete emptying, and fecal incontinence.

- Over 40% of patients have been reported to become “toilet dependent,” which can have devastating consequences on patients’ physical, social, occupational, and psychological functioning, significantly decreasing their quality of life.

Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, et al. Low anterior resection syndrome and quality of life: An international multicenter study. *Dis Colon Rectum* 2014;57:585–91.

Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev* 2004: CD004323.

- Due to the absence of a consensus definition of LARS, functional outcomes after LAR have been measured using a wide variety of tools. Two tools, the Memorial Sloan Kettering Cancer Center Bowel Function Instrument and the LARS score , have been introduced to assess bowel function after LARS.

Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. *Dis Colon Rectum* 2005;48:1353–65.

Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg* 2012;255:922–8.

LARS-score - Scoring Instructions

Add the scores from each 5 answers to one final score.

Do you ever have occasions when you cannot control your flatus (wind)?

- | | |
|---|---|
| <input type="checkbox"/> No, never | 0 |
| <input type="checkbox"/> Yes, less than once per week | 4 |
| <input type="checkbox"/> Yes, at least once per week | 7 |

Do you ever have any accidental leakage of liquid stool?

- | | |
|---|---|
| <input type="checkbox"/> No, never | 0 |
| <input type="checkbox"/> Yes, less than once per week | 3 |
| <input type="checkbox"/> Yes, at least once per week | 3 |

How often do you open your bowels?

- | | |
|---|---|
| <input type="checkbox"/> More than 7 times per day (24 hours) | 4 |
| <input type="checkbox"/> 4-7 times per day (24 hours) | 2 |
| <input type="checkbox"/> 1-3 times per day (24 hours) | 0 |
| <input type="checkbox"/> Less than once per day (24 hours) | 5 |

Do you ever have to open your bowels again within one hour of the last bowel opening?

- | | |
|---|----|
| <input type="checkbox"/> No, never | 0 |
| <input type="checkbox"/> Yes, less than once per week | 9 |
| <input type="checkbox"/> Yes, at least once per week | 11 |

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

- | | |
|---|----|
| <input type="checkbox"/> No, never | 0 |
| <input type="checkbox"/> Yes, less than once per week | 11 |
| <input type="checkbox"/> Yes, at least once per week | 16 |

Total Score:

Interpretation:

- | | |
|---------------|-------------------|
| 0-20: | No LARS |
| 21-29: | Minor LARS |
| 30-42: | Major LARS |

Fig. 1. LARS score calculation and interpretation.

Dysbiosis?

- LARS is usually treated using high-fiber diets, constipating agents, and dietary Restrictions as well as Probiotics with some significant improvement in quality of life Assessments. “ as well as around 55% in our paper under evaluation for publication”

[Martellucci J. Low anterior resection syndrome, a treatment algorithm. Dis Colon Rectum 2016;59:79–82.](#)

Surgical Reconstruction Techniques to Reduce LAR Syndrome

The reduction in capacity and compliance following TME in patients with straight coloanal anastomosis (SCAA) has led to several surgical techniques to account for this change in the neorectum. Side-to-end coloanal anastomoses, colonic J-pouch-anal anastomoses (CJPAAAs), and transverse coloplasty pouch (TCP) have been performed and studied. This section will describe the technique for construction of these neorectal reservoirs and discuss the various benefits of each of these methods.

Low Anterior Resection Syndrome: Current Management and Future Directions

Timothy J. Ridolfi, MD¹ Nicholas Berger, MD¹ Kirk A. Ludwig, MD¹

¹Department of Surgery, Division of Colorectal Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin
Clin Colon Rectal Surg 2016;29:239-245.

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- Pathophysiology of LAR Syndrome

LAR syndrome is likely multifactorial. Many potential pathophysiologic mechanisms for LAR syndrome have been proposed:

1. internal anal sphincter (IAS) dysfunction,
2. decrease in anal canal sensation,
3. disappearance of the recto-anal inhibitory reflex (RAIR),
4. disruption in local reflexes between the anus and the Neorectum, and reduction in rectal reservoir capacity and compliance all have been described.

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The Effect of Anastomotic Leakage on the Incidence and Severity of Low Anterior Resection Syndrome in Patients Undergoing Proctectomy: A Propensity Score Matching Analysis

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Results: Among the 179 patients included in this study, 37 were classified into the AL group. After propensity score matching, there were significant differences in the ratio of major LARS and MSKCC scores of the control group and AL group (ratio of major LARS: 11.1% and 37.8%, $P < 0.001$; MSKCC score: 67.29 ± 10.4 and 56.49 ± 7.2 , respectively, $P < 0.001$). Univariate and multivariate analyses revealed that AL was an independent factor for major LARS occurrence and MSKCC score.

Conclusion: This study showed that AL was a significant factor in the occurrence of major LARS and defecation symptoms after proctectomy.

However LARS can Happen in any Colonic Resection other than LAR !!!!

Low anterior resection syndrome after right- and left-sided resections for colonic cancer

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Results: Questionnaires were sent to 866 patients and complete responses were provided by 517 (59.7 per cent). After right-sided resection 20.6 per cent reported major LARS. After left-sided resection the proportion with major LARS was 15.6 per cent. The odds ratio (OR) for major LARS after right-sided resection was 1.45 (95 per cent c.i. 1.02 to 2.06; $P = 0.037$) compared with left-sided resection. After adjustment for age and sex, an increase in the risk of major LARS after right- *versus* left-sided resection remained (OR 1.48, 1.03 to 2.13; $P = 0.035$). Major LARS correlated with impaired quality of life.

Conclusion: Major LARS was more frequent after right-sided than following left-sided colonic resection. Major LARS reflected impaired quality of life.

Research Key Question.

Could it be due to Another associated Hidden “Modifiable”
Etiology???

- To me , the above mentioned symptoms associated with LARS resembled those of inflammatory bowel disease (IBD), which is how I got the idea of using fecal Calprotectin to diagnose the condition and the use of Mesalamine as an immune modulator for treatment of patients with high levels.

- Mesalamine (Mesalamine), a 5-aminosalicylic acid compound, is the treatment of choice for patients with mild-to moderate ulcerative colitis.

Ham M, Moss AC. Mesalamine in the treatment and maintenance of remission in Ulcerative Colitis. *Expert Rev Clin Pharmacol* 2012;5:113–23.



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Calprotectin in Low anterior resection syndrome patients; a new insight into diagnosis and management: A pilot study

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- The main objective of this study was to investigate the role of fecal Calprotectin in the diagnosis of LARS in patients who underwent LAR. We also aimed to investigate the role of Mesalamine (Pentasa) in controlling the symptoms.

Patients and methods

- Design, setting, and population of the study

This was a pilot study conducted on a group of patients that developed LARS after LAR, completed Neoadjuvant chemo-radiotherapy, and closure of the temporary stoma who presented to us from November 2019 to April 2021.

- Inclusion criteria:

Adult patients expressing LARS symptoms that persist for more than 20 days postoperatively and failed dietary manipulation for one month after low anterior resection of the rectum for rectal cancer.

- Exclusion criteria:

- 1- Evidence of local recurrence or distant metastasis during follow-up.

- 2- Comorbidities that may alter sensory and motor responses, such as collagen vascular and connective tissue disorders or neurologic disorders.

- 3- Diverticulitis, IBD, and major sphincter injury.

- 4- Improvement on nutritional management.

- Intervention:

All patients who met the inclusion criteria with persistent symptoms of LARS (as diagnosed via a LARS score of more than 20 days), were tested for the level of fecal Calprotectin postoperatively, and those with high levels were treated using Mesalamine tablets (500 mg, with a total of 3 g per day in divided doses) for one month, then 2 g per day for the subsequent five months alongside the prohibition of dairy products, spices, and heavy tomato sauce.

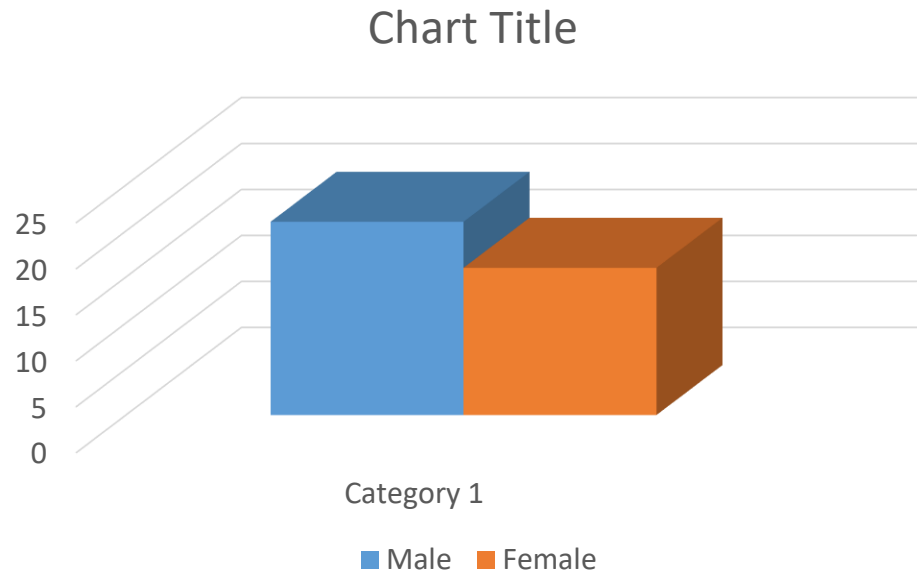
- Follow-up was done at the OPD via weekly visits to evaluate the symptoms, clinically only. Reevaluation via the LARS score and fecal Calprotectin levels was done after six months to assess the new strategy for diagnosis and treatment per the LARS management program

Garfinkle R, Loiselle CG, Park J, Fiore Jr JF, Bordeianou LG, Sender Liberman A, et al. Development and evaluation of a patient-centred program for low anterior resection syndrome: protocol for a randomized controlled trial. *BMJ Open* 2020;10.

- Results:

Thirty-six patients met the inclusion criteria and had high fecal Calprotectin levels (>50 mcg/g) and high LARS scores (all of them had major LARS scores of >30). All of them were treated using Mesalamine and re-evaluated after six months.

Male	Females
21	15



- Average Calprotectin = 379.5 units.
- Average LARS score = 36

	Calprotectin
1.	86
2.	206
3.	128
4.	320
5.	97
6.	730
7.	520
8.	444
9.	410
10.	220
11.	110
12.	136
13.	250
14.	330
15.	1440
16.	1020
17.	355
18.	260
19.	285
20.	456
21.	549
22.	680
23.	410
24.	433
25.	136
26.	178
27.	125
28.	99
29.	1230
30.	620
31.	274
32.	190
33.	163
34.	526
35.	145
36.	101

Table 1

Number and percentage of patients who showed major, minor, and no improvement.

	NumberTotal number (n = 36)	Percentage (%)
Marked improvement (LARS score 10–20 i.e., no LARS)	20	55.5%
Improved from major to minor LARS (score 20–30)	10	27.7%
No improvement regarding symptoms (high LARS score & high calprotectin levels)	6	16.6%

Table 1 below shows the numbers and percentages of patients who showed major, minor, and no improvement. Patients whose symptoms did not improve (high LARS scores) still had high levels of fecal Calprotectin while those whose symptoms did showed improvements in fecal Calprotectin levels (<50 mcg/g).

Discussion

- LARS had been described a long time after the introduction of Colonic resections and Low Anterior resection.
- The Incidence of LARS was not high in the early days of Ultra-Low AR, ISR and Neoadjuvant CRT.
- LARS incidence Peaked only in the second decade of the 21st century.
- The Symptoms of LARS specially pain, mucous, blood and tenismus are Mimicking the IBD with its associated frequency or ODS due to reflex anismus.

Discussion

- Fecal Calprotectin showed a high correlation ($r = 0.655$) with the histologic grade of mucosal inflammation, similar to that observed for endoscopy ($r = 0.699$), and it resulted in the most accurate tool (94% sensitivity, 64% specificity, 81% positive predictive value, and 87% negative predictive value) to detect the presence of active mucosal inflammation when compared to clinical scores and common serum markers.

Discussion

- The search for an new modifiable factor as a cause for LARS looked reasonable which may have a major impact on our Practice which had been ploughed by this annoying syndrome.



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- In this preliminary report, we studied patients with symptoms of LARS after rectal resection using Calprotectin and started treatment as IBD patients and followed them to determine the effect of this treatment on their LARS symptoms and score.

- Out of the 36 patients included in the study, 20 showed marked improvement from major to minor LARS with a significant drop in the fecal Calprotectin level, 10 improved from major to minor LARS, and six showed no improvement either in the LARS symptoms or the fecal Calprotectin levels.

- our study demonstrated the efficacy of immune modulators such Mesalamine (Pentasa), which was used in this report, in treating patients with LARS who were unresponsive to conventional dietary restrictions, as they mimic IBD patients.

- In conclusion, our study showed that fecal Calprotectin can be a useful tool in the diagnosis and treatment planning of patients with persistent LARS.

- Based on the results of this Pilot study, we recommend the use of fecal Calprotectin in predicting the patients that may experience LARS after colonic or rectal resection, which means this marker can be used Preoperatively in predicting LARS.

- “Prophylactic Dietary manipulation of Dysbiosis together with the use of Pentasa in patients with high Calprotectin as early as possible preoperatively is our new paper In the stage of Data Collection with preliminary results in prevention of LARS in around 90% of our patients”

- We suggest a Multicenter well-designed controlled multicenter study for the pharmacological treatment of patients with persistent LARS with increased fecal Calprotectin levels based on the results of our pilot study and the use of Mesalamine in treatment of patients with high levels.



• *Thank You*