Research Square

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Macroscopic and Microscopic Intestinal Evidences of Inflammation in Patients With Psoriasic Arthritis

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Research Article

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Abstract

Introduction: Psoriatic arthritis (PsA) is a chronic, inflammatory condition that primarily affects the skin and joints, with potential involvement of other organs, including intestinal inflammation.

Objectives: To assess the presence of both macroscopic and microscopic intestinal changes in patients with PsA and in a control group, in order to identify and characterize intestinal inflammation.

Methods: This study included 37 patients with PsA and 10 healthy participants. All underwent colonoscopy and biopsy of four intestinal segments (terminal ileum, ascending colon, sigmoid colon, and rectum) to evaluate both macroscopic and microscopic changes associated with intestinal inflammation.

The results. Patients with PsA presented a greater presence of macroscopic alterations of polyps ($p<0.00000$) and diverticula ($p<0.00000$), no significant presence of bowel inflammatory bowel (BID), and more microscopic intestinal abnormalities ($p<0.00000$) in all the intestinal segments investigated.

Conclusion. Patients with PsA exhibit minimal macroscopic evidence of microscopic intestinal alterations, with mild and limited involvement, indicative of non-acute, active chronic intestinal inflammation that requires constant control and monitoring.

INTRODUCTION

Conditions such as Reactive Arthritis (ReA), Psoriatic Arthritis (PsA), Spondyloarthritis (SpA), and Rheumatoid Arthritis (RA) are characterized by inflammatory lesions and systemic involvement. These disorders are multifactorial, with genetic predisposition, hereditary and environmental factors that contribute to a disordered immune response, leading to both localized and systemic manifestations[2,6,22].

Spondyloarthropathies are more strongly associated with intestinal involvement and exhibit characteristics of inflammatory bowel disease (IBD), resembling Crohn’s disease (CD), compared to other rheumatologic conditions. [9,22,4] The severity of intestinal involvement correlates with the intensity of the clinical manifestations. In Psoriatic Arthritis (PsA), both dermatologic and joint inflammatory symptoms often coexist with intestinal manifestations, which may evolve asymptomatically.[5,7] HLA-B27 antigen is present in 27.8% of patients.[3,21] The intestine is a complex and dynamic structure that participates in the body's balance and influences the etiopathogenesis and progression of various immunologically diseases.[15] This study aims to examine both macroscopic and microscopic intestinal inflammation in patients with PsA, comparing with those of participants. Tissue morphology and histological characteristics will be evaluated to assess bowel involvement and grade the extent of inflammatory changes.

METHOD

A prospective, case-control study was conducted from 2011 to 2013 involving outpatients diagnosed with Psoriatic Arthritis (PsA) by the Rheumatology and Gastroenterology departments at the Hospital Universitário, Universidade Federal do Rio de Janeiro.

Inclusion Criteria: Patients with a confirmed diagnosis of PsA, based on clinical data and defined according to the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria, who did not present with gastrointestinal manifestations.[27]
Exclusion Criteria: Patients with systemic or psychiatric disorders, as well as those with intestinal parasitosis.

Control Group: Healthy participants referred for periodic preventive colonoscopy to assess the possibility of intestinal malignancy.The study was approved by the Research Ethics Committee (Project 144/10, Opinion 171/11), on April 7, 2011.

Sample size. Epidemiological dataindicate that the frequency of psoriasis in the population is 3%, approximately 30% of affected individuals have AP. In a population of 2430 patients approximately 320 patients had spondyloarthropathies, 115 had APso, and the exclusion criterion utilized a sample size of 26.1 (95% CI 18. 6-34.6) patients for the study group, with a 95% confidence level, a statistical significance of 0.05, and a beta error of 20%.

Settings: Demographic and clinical data were collected at baseline, including patient age, sex, gender, ethnicity, and the year of Psoriatic Arthritis (PsA) diagnosis. Specific laboratory tests included the detection of HLA-B27, as well as parasitological fecal analysis using the Faust-Hoffman and Boerman methods.

Specific tests for intestinal investigation.

Colonoscopy: Colonoscopy was performed using an Olympus CV-180 Evia Exeria II video processor, coupled with an Olympus high-definition amplifier for enhanced visualization.

Biopsy: All participants, including both patients and controls (even those with macroscopically normal findings), underwent colonoscopy with biopsies taken from four designated segments typically investigated for inflammatory bowel diseases: the terminal ileum, right colon, sigmoid colon, and rectum.

Histopathologic Criteria: The following five criteria were used to assess and quantify the morphological and inflammatory characteristics:Villous Atrophy, Neutrophil Infiltration, Lymphoid Hyperplasia, Eosinophilia and edema. Each degree of inflammatory intensity was classified using a five-point grading system:**Grade 0 (Normal):**Abscence of histological criteria**. Grade I (Low):**Presence of edema and hyperemia, scoring 1 point.**Grade II (Mild):** Inflammatory infiltration of the lamina propria predominantly by lymphocytes and eosinophils, scoring 2 points.**Grade III (Moderate):** Moderate infiltration with a high predominance of neutrophils and inflammatory cells, scoring 3 points.**Grade IV (Intense):**Characterized by ulcers, fibrin and cellular debris, scoring 4 points.**Grade V (Severe):** Extensive

inflammatory response with marked edema, hyperemia, ulcers, fibrin deposition, and cellular debris, scoring 5 points. [10,13,14]

Statistical Analysis: To compare numerical data between independent samples, either Student's t-test or the non parametric Mann-Whitney U testas used, depending on the distribution of the data and the results of the homogeneity of variance test. The Chi-squaretest was applied to assess the proportions of categorical data, and Fisher's exact test was used for the 95% confidence interval for the evaluation of binomial proportions. A significance level of 95% ($p < 0.05$) was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics, version 20.0.

RESULTS

A total of 47 participants without intestinal parasitic infestations were included in the study, 37 (78.7%) in the PsA group and 10 (21.3%) in the healthy control group. (Figure 1,2,3) .

Demographic data and presence of HLA-B27 antigen, in patients with psoriatic arthritis (PsA) and controls.

The PsA group presented HLA-B27 in 21.6 % of the samples, whereas no HLA-B27 was detected in the control group (p=0.06). Figure 4

There were also more macroscopic and microscopic abnormalities: with 67.5% (95% CI 38.5- 67.1) of the patients in the colonoscopic group and 40% (p=0.009), OR 2.1 (95% CI 1.1- 3.7)in the control group 85.3 % of the biopsies from patients with PsA and 50% from the controls presented microscopic changes (p=0.000000), OR 5.6 (95% CI 2.8 -11.3). The controls presented significantly more normal results than the PsA patients did in all bowel segments.

In 53.1% the patients with PsA colonoscopies were abnormal, and the frequency was significantly greater than thosein the controls (p<0.000000) OR (CI 05% 11.8 (3.8-44). Macroscopic alterations were more evident in the PsA group than in the control group: intestinal polyps in 51.3% (p=0.01), OR (95% CI 35-68.7); diverticula in 21.2% of the patients in the APso group and 10% in the control group (p=0.01); and macroscopic inflammatory bowel disease in 4.2% the patients with APso (pancolitis/UC in 2.1%, ileitis/Crohn's disease in 2.1%), and absent in control group. Figure 5A,5B,5C,5D.

Patients with PsA showed more microscopic changes than controls p<0.00001 and OR 6.6 (95% CI 3.3 -13.5) and biopsies demonstrated inflammatory changes and microscopic involvement in all intestinal segments, with a significantly greater involvement in the PsA group with 83.7% (95% CI 77.1-89%) when compared to the control group 50% (IC 95% 34.7- 65.2), with a significant P value in all segments, showing the greatest difference in sigmoitis with OR 8 (95% CI 4.0 -15.3) followed by the right colon and rectum with OR 5.3 (95% CI 2.5-11.3) in both segments. Figure 6.

When analyzed as biopsies from both groups, we observed a significant difference and inflammatory involvement in all segments examined, being significantly higher in patients with PsA than in controls, however without evidence of severe inflammatory lesions, with an OR of 1.7 (95% CI 1.0 -3.0) for minimal lesions, OR 3.8 (95% CI 1.7-8.4) for mild lesions and OR 6.1 (95% CI 0.3 to 12.4) to moderately. Figure 7

A total of 51 biopsies were analyzed in the control group and 388 biopsies in the AP group, showing inflammatory involvement in all intestinal segments, being more frequent in patients with APS presenting P value < 0.001 and OR 3.3 (95% CI 1.8 – 6.1)characterized by significantly greater intensity of atrophy, tissue edema, lymphoid hyperplasia and eosinophilic activity, with no difference in relation to neutrophilic activity, and the same incidence of eosinophilia in all intestinal segments in both groups and terminal ileum with fewer histopathological changes. Figure 8,9,10,11.

DISCUSSION

Inflammatory rheumatic diseases exhibited intestinal inflammation of varying intensities, according to the underlying rheumatologic etiology and the sensitivity of the diagnostic method employed. Colonoscopy findings have demonstrated intestinal involvement rates of 13.5% in reactive arthritis (ReA), 26% in psoriatic arthritis (PsA), 14% in axial spondyloarthritis (axSpA), 11% in undifferentiated spondyloarthritis (USpA), and 11% in rheumatoid arthritis (RA).[12] Histochemical analysis of intestinal biopsy specimens increases the prevalence of detected intestinal inflammatory features to 51%, 45%, 48%, 39%, and 15%, respectively. Electron microscopy further raises the detection rates to 76%, 53%, 90%, 60%, and 50%, revealing the presence of underlying active intestinal inflammatory involvement [3,8,18,24,26]

In this study, forty-seven participants were assessed (Table 1), including thirty-seven patients in the PsA group and ten in the healthy control group. The groups were homogeneously matched for sex, age, ethnicity, and absence of intestinal parasites. The presence of HLAB27 was observed in 21.6% of the PsA group and was absent in the control group (p < 0.000006; OR 6.05, 95% CI 0.32–113). The extremely low p-value suggests an association between PsA and HLA-B27; however, the wide confidence interval indicates imprecision of the estimates due to the small sample size, although these results are supported by data in the literature [1].

Colonoscopy is widely recognized as an effective method for evaluating intestinal abnormalities. [17,21,28] In the present study, macroscopic alterations (Table 2) were observed in 83.7% of patients with psoriatic arthritis (PsA) and in 60% of the control group (p = 0.0001; OR = 3.5; 95% CI: 1.7–6.8), demonstrating a higher frequency than that reported in previous studies.[3,11] Among the macroscopic findings, polyps were the predominant lesion in both groups, detected in 51.3% of PsA patients and 40% of controls, without statistically significant difference between groups (p = 0.09; OR = 3.4; 95% CI: 0.7–16.1). Nevertheless, the frequency was higher than that described in epidemiological studies for the same age group, which report polyps in 13.5% of individuals aged 50 to 60 years. [16,23]

There were no significant differences between groups regarding the presence of uncomplicated colonic diverticular disease, which was identified in 27% of PsA patients and 20% of controls (p = 0.6; OR = 1.4; 95% CI: 0.2–8.1), in agreement with literature data reporting a 30% prevalence in individuals over 50 years of age. In this study, macroscopic inflammatory changes in the intestine were found in 5.4% of PsA patients—a result not statistically significant when compared to the control group (p = 0.4; OR 2.9; 95% CI 0.1–59). This finding aligns with previously described values, in which inflammatory bowel disease (IBD) affects approximately 3.3% of the general population.[23, 24, 29,30]

Inflammatory intestinal involvement in the biopsied segments was significantly more evident in 83.7% of patients with PsA compared to 50% in the control group (p < 0.00001; OR: 6.6; 95% CI: 3.3–13.5). A higher frequency of microscopic abnormalities was observed across all intestinal segments analyzed in the PsA group compared to the respective segments in controls. [19,25,27]

When analyzing the intensity of histopathological changes in all intestinal segments from patients with psoriatic arthritis (PsA) compared to controls, it was found that 16.2% of patients showed no evidence of inflammatory activity (p < 0.0001), while 54% displayed minimal involvement (p = 0.02), 29.7% showed mild involvement (p = 0.0004), and 2.2% exhibited moderate intensity (p = 0.1). No case presented severe involvement in any of the analyzed segments.

The results demonstrate that microscopic analysis was significantly more sensitive than macroscopic evaluation by colonoscopy for detecting inflammatory involvement, particularly in patients with PsA.

Inflammatory features identified in all intestinal segments were significantly more prevalent in PsA patients as compared to controls. Among the 388 biopsies evaluated from the PsA group, 52.4% exhibited inflammatory changes, whereas only 25.5% of biopsies from the control group (n = 51) did so (p < 0.001).

A review of the histological features and grades of inflammation in IBD, as described by Kellermann L and Riss LB, reveals that the histological diagnosis of IBD is based on four major features: (I) mucosal architectural distortion, (II) lamina propria and submucosal cellularity, (III) neutrophilic and granulocytic infiltration, and (IV) epithelial abnormalities. Therefore, understanding the normal histology of the gastrointestinal mucosa is essential for the optimal interpretation of biopsy samples.

Morphological changes in mucosal architecture observed in IBD are characterized by crypt distortion—including irregular arrangement, dilation, branching, and shortening of crypts. These alterations may indicate active inflammation or a regenerative tissue process. Abnormal cellularity of the lamina propria is characterized by increased cell numbers and altered distribution of cell types. Focal increases in lymphoid cells, closely associated with normal gut-associated lymphoid tissue (GALT), are also observed.

The abundance of eosinophilic granulocytes varies greatly among healthy individuals, whereas neutrophilic granulocyte infiltration is considered a marker of disease activity. Neutrophils may be

present in the lamina propria or invade the surface or crypt epithelium (cryptitis), and may accumulate in the crypt lumen to form crypt abscesses. Importantly, neutrophils are absent in normal intestinal mucosa.

Epithelial abnormalities in IBD include mucin depletion, metaplastic changes, and surface epithelial injury. Mucin depletion is marked by a reduction in the number of goblet cells or in intracellular mucin content. Metaplastic changes may present as pyloric gland metaplasia—a typical finding in chronic Crohn's disease involving the ileum—or as Paneth cell metaplasia. Surface epithelial injury, including focal cell loss, flattening, erosions, and ulcerations, reflects disease activity. However, none of these findings is specific to a single condition; they may be found in ulcerative colitis, Crohn's disease, or other forms of colitis.

Histological findings in IBD differ according to the clinical phase of the disease and the degree of inflammatory activity. IBD can be classified as "chronic active," "chronic inactive," or "active" (without features of chronicity). Features of chronicity (regardless of activity) include crypt architectural distortion, crypt atrophy, diffuse and mixed lamina propria inflammation, basal plasmacytosis, lymphoid aggregates at the base of the mucosa, and Paneth cell metaplasia. Inflammatory activity is defined by the presence of neutrophils; neutrophilic cryptitis, crypt abscesses, hemorrhage, erosions, ulceration, and necrosis are characteristic of active inflammation.

The pathology report should describe both chronicity and activity features and, ideally, classify the degree of activity as mild, moderate, or severe. Classification should be based on the most affected biopsy sample and, where possible, separately reported for biopsies from different intestinal segments, as performed in the present study.

There is no gold standard for activity classification; however, the Nancy Index (2020), recommended by the ECCO (European Crohn's and Colitis Organisation), is utilized for daily clinical classification of ulcerative colitis (UC), establishing five grades (0–4).

Grade 0 corresponds to histological remission or a biopsy considered normal, characterized by absence of significant inflammatory infiltrate. Grade 1 refers to mild chronic inflammation, with only chronic inflammatory infiltrate present and no signs of active inflammation. Grade 2 represents moderate chronic inflammation with mild neutrophilic infiltrate, while grade 3 is defined by moderate chronic inflammation with moderate neutrophilic infiltrate. Lastly, grade 4 indicates severe chronic inflammation, with significant neutrophilic infiltrate and the presence of ulcerations.[20,22]

The results of this study indicate that patients with PsA exhibit systemic involvement with chronic subclinical intestinal inflammatory activity, and necessitate rigorous and ongoing clinical monitoring to evaluate associated and concomitant dermatological, articular, and intestinal manifestations.

CONCLUSION

Patients with PsA presented more intestinal abnormalities than controls, with microscopic inflammation of minimal to mild intensity observed in all investigated intestinal segments, thereby characterizing the presence of chronic, non-acute, and active intestinal inflammation, classified as indeterminate colitis.

Declarations

Ethical approval and consent to participate. The study was conducted following international and local ethical regulations, and the protocol was approved by the Ethics Committee of the participating institution. All participants signed the formed consent form previously approved by the local Ethics Committee.

Consent for publication. All authors permitted publication.

Data and materials. Available on upon request to the corresponding author. **Competing interests.** The authors declare that they have competing interests.

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Author's contributions. The authors contributed to the conception, design, acquisition, synthesis, and interpretation of the data. They wrote the manuscript and gave final approval to publish the version. The authors agree to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part are appropriately investigated and resolved.

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Figures

Figure 1

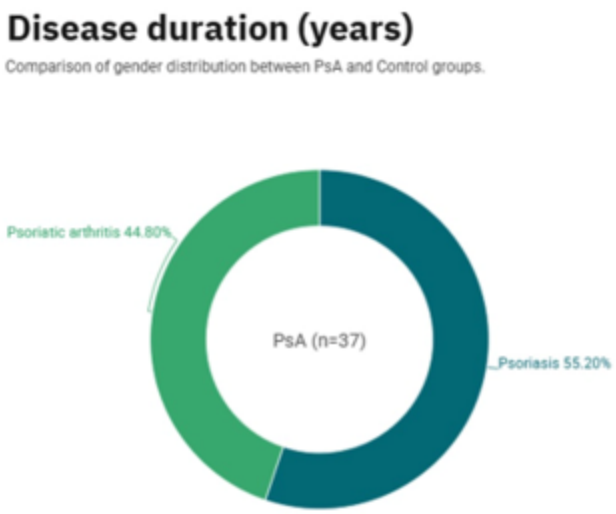


Figure 1

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Figure 2

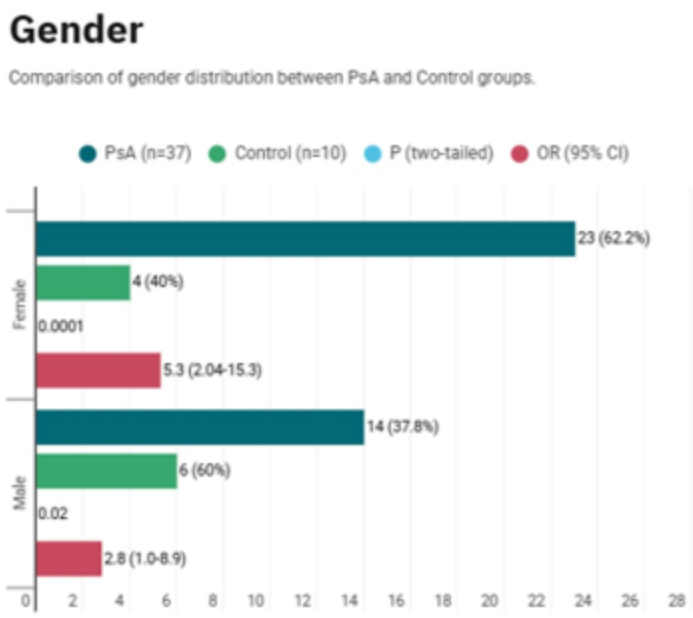


Figure 2

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Figure 3

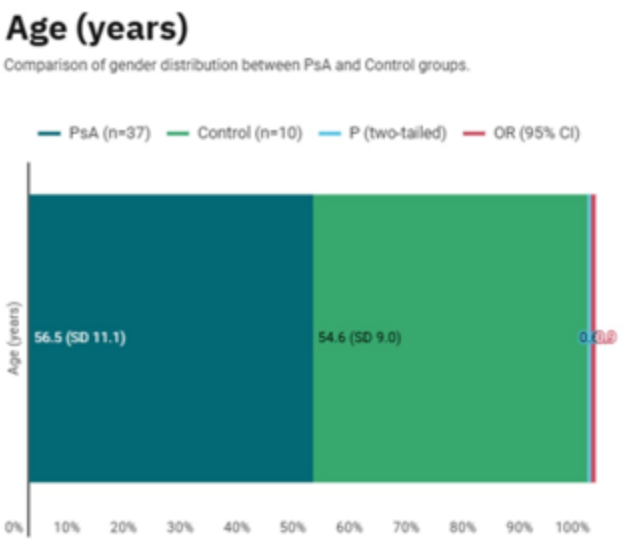


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Figure 4

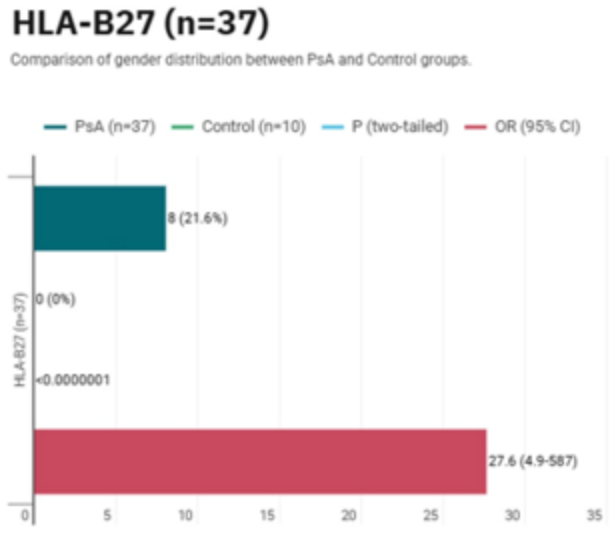


Figure 4

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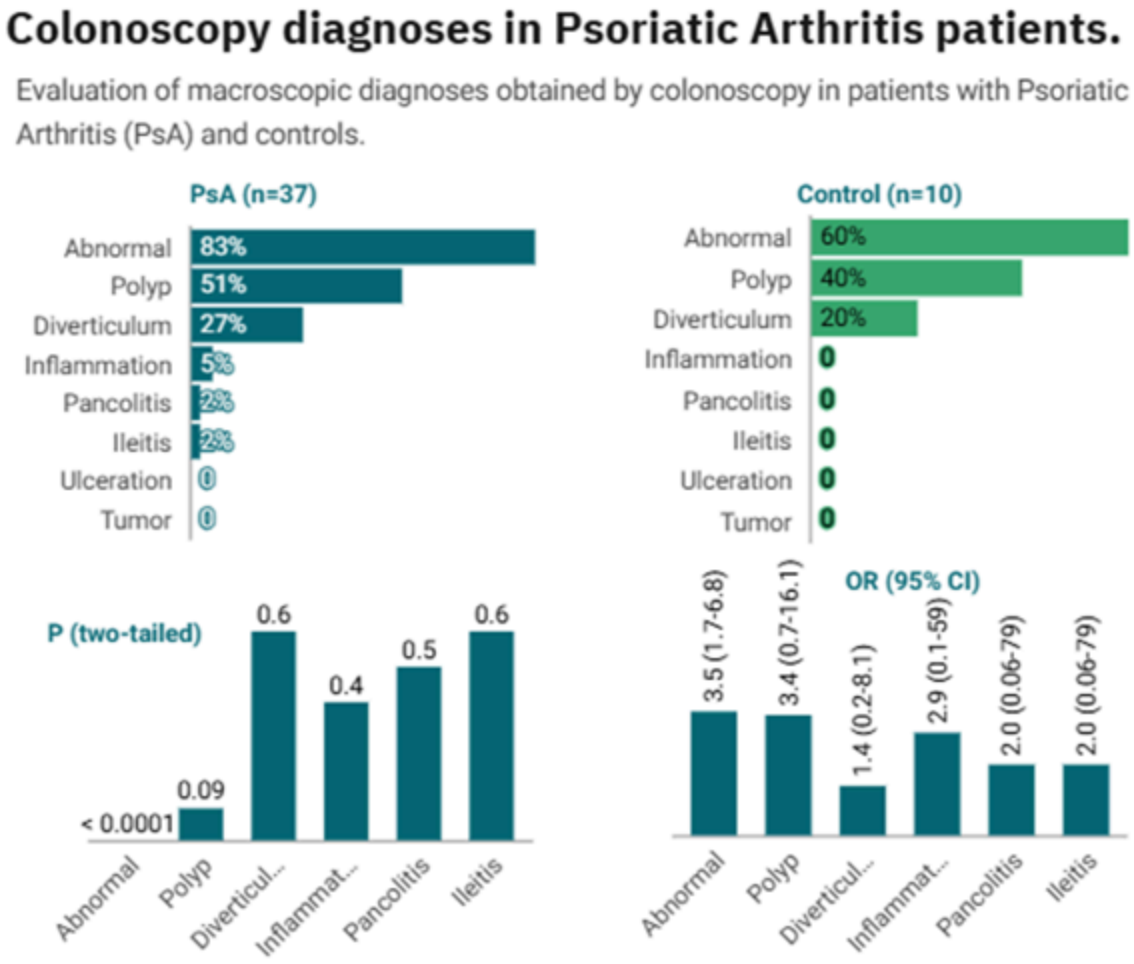


Figure 5

PSA (n37) Figure 5B : Control (n=10) Figure 5C: P (two- tailed) Figure: 5D OR (95% IC)

Note: P values are based on chi-square test and Fisher´s exact test, as appropriate. OR (95% CI) represents odds ratio ith 95% cofidence interval. Significance level is 95% na= not apppicable.

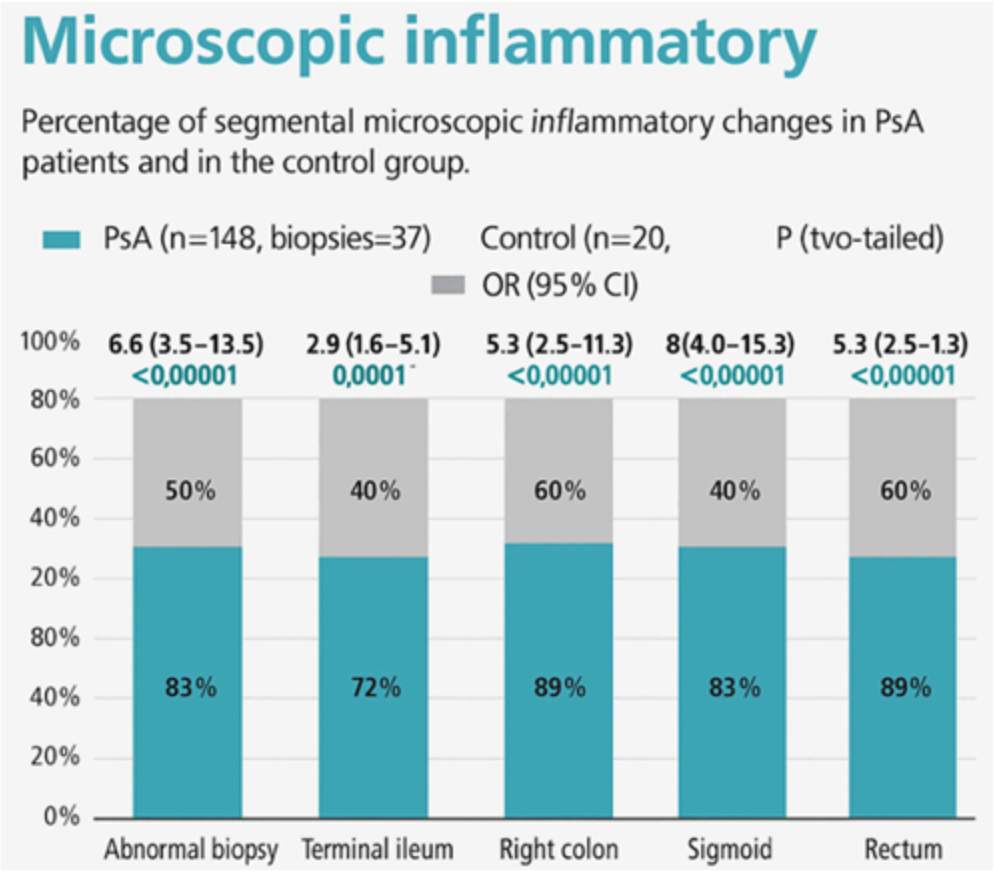


Figure 6

Note: P- values are based on chi-square test, as appropriate. OR (95% CI) represents odds Ratio With 95% confidence interval. Significance level is 95%

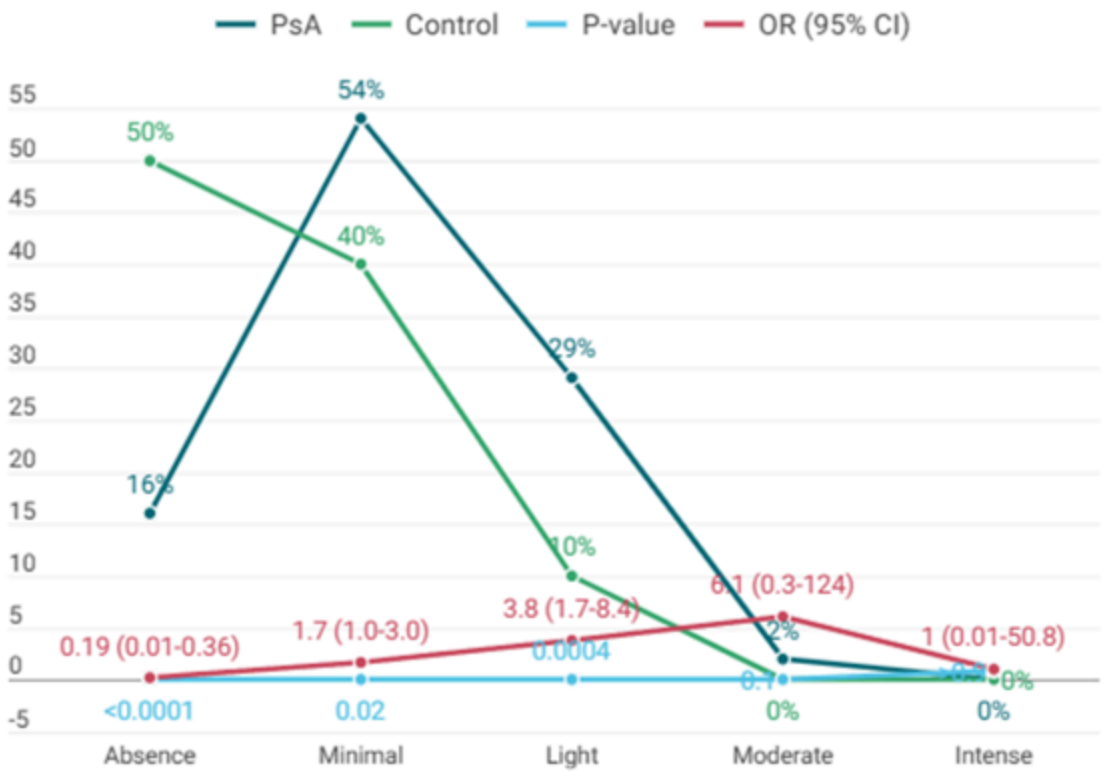


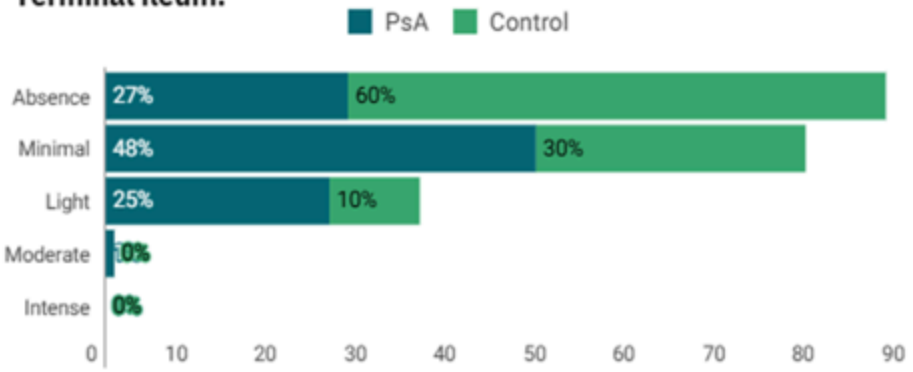
Figure 7

Inflammatory injury frequencies in intestines

Evaluation of the frequencies of inflammatory injury in intestinal segments between PSA patients (n =37, biopsies = 148) and Control group (n=10, biopsies =40)

Evaluation of the frequencies of inflammatory injury in intestinal segments between PsA patients (n=37, biopsies=148) and Control group (n=10, biopsies=40).

Terminal ileum:



Segment	P-value	OR (95% CI)
Absence	<0.0001	0.2 (0.1-0.4)
Minimal	0.03	1.8 (1.0-3.4)
Light	0.003	3.1 (1.4-6.9)
Moderate	0.5	2.6 (0.1-69.2)
Intense	>0.9	1 (0.02-50.8)

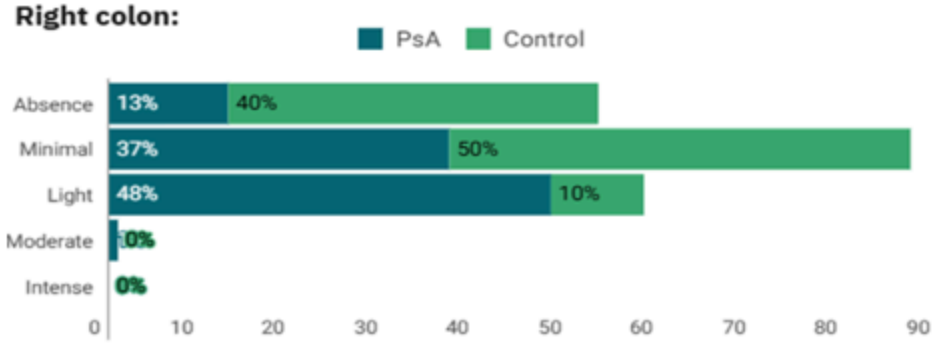
Note: Values are presented as n (%). PsA = Psoriatic Arthritis; OR = Odds Ratio; CI = Confidence Interval. P-values were calculated using chi-square test. Statistical significance was set at p<0.05.

Figure 8

Intestinal Segments:

Evaluation of the frequencies of inflammatory injury in intestinal segments between PsA patients (n=37, biopsies=148) and Control group (n=10, biopsies=40).

Right colon:



Segment	P-value	OR (95% CI)
Absence	<0.0001	0.2 (0.1-0.4)
Minimal	0.04	0.6 (0.3-10)
Light	<0.0001	8.6 (4-18.5)
Moderate	0.5	2.6 (0.1-69.2)
Intense	>0.9	1 (0.02-50.8)

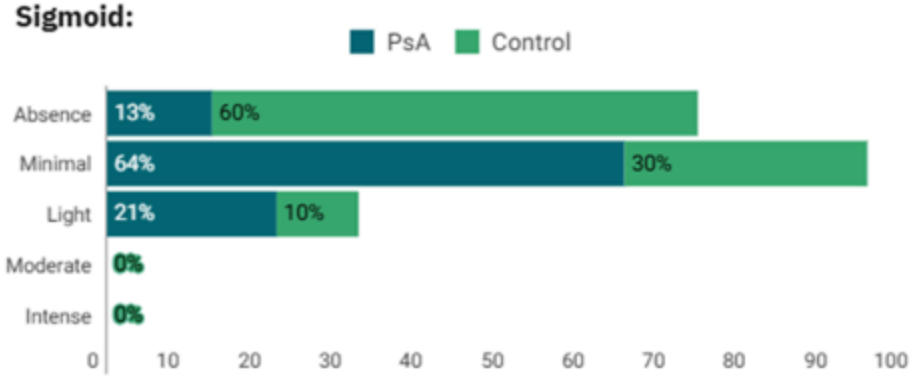
Note: Values are presented as n (%). PsA = Psoriatic Arthritis; OR = Odds Ratio; CI = Confidence Interval. P-values were calculated using chi-square test. Statistical significance was set at p<0.05.

Figure 9

Intestinal Segments:

Evaluation of the frequencies of inflammatory injury in intestinal segments between PsA patients (n=37, biopsies=148) and Control group (n=10, biopsies=40).

Sigmoid:



Segment	P-value	OR (95% CI)
Absence	<0.0001	0.09 (0.04-0.2)
Minimal	<0.0001	4.3 (2.3-7.8)
Light	0.02	2.5 (1.1-5.8)
Moderate	>0.9	1 (0.02-50.8)
Intense	>0.9	1 (0.02-50.8)

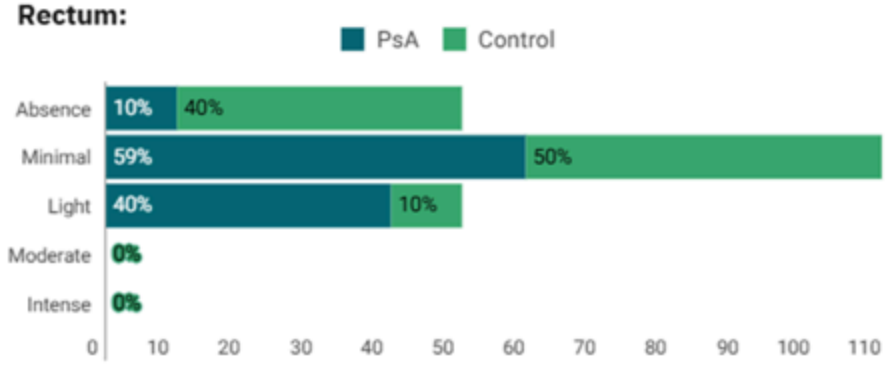
Note: Values are presented as n (%). PsA = Psoriatic Arthritis; OR = Odds Ratio; CI = Confidence Interval. P-values were calculated using chi-square test. Statistical significance was set at p<0.05.

Figure 10

Intestinal Segments:

Evaluation of the frequencies of inflammatory injury in intestinal segments between PsA patients (n=37, biopsies=148) and Control group (n=10, biopsies=40).

Rectum:



Segment	P-value	OR (95% CI)
Absence	<0.0001	0.1 (0.008-0.3)
Minimal	0.1	1.5 (0.8-2.6)
Light	<0.0001	6.2 (2.9-13.4)
Moderate	>0.9	1 (0.02-50.8)
Intense	>0.9	1 (0.02-50.8)

Note: Values are presented as n (%). PsA = Psoriatic Arthritis; OR = Odds Ratio; CI = Confidence Interval. P-values were calculated using chi-square test. Statistical significance was set at p<0.05.

Figure 11

Intestinal Segments: