Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

The Relationship between Maresin-1 Levels and Disease Activity in Patients with Crohn's Disease

Tuna Turan [1], Özlem Gül [2], Kemal Üreten [3], Üçler Kisa [4], Bilal Ergül [2]

[1] *Kirikkale High Specialization Hospital, Kirikkale, Türkiye*
[2] *Lokman Hekim University, Department of Gastroenterology, Ankara, Türkiye*
[3] *Kirikkale University, Department of Rheumatology, Kirikkale, Türkiye*
[4] *Kirikkale University, Department of Biochemistry, Kirikkale, Türkiye*

SUMMARY

Background: **Maresin-1 is considered to be a potential regulator of inflammatory disease through its anti-inflammatory and pro-resolving properties. However, no study to date has investigated Maresin-1 levels in Crohn's disease (CD). This study aimed to measure serum levels of Maresin-1 in patients with CD and to assess possible effects on disease activity.**
Methods: **Thirty patients with active CD, 30 patients with CD in remission, and 30 healthy individuals were included in the study. Clinical and demographic features of patients were obtained from the hospital database. Serum Maresin-1 levels were determined by enzyme-linked immunosorbent assay.**
Results: **Maresin-1 level was 215.74 (118.55 - 327.46) pg/mL in the active group, 413.29 (215.82 - 726.82) pg/mL in the remission group, and 753.4 (381.5 - 901.08) pg/mL in controls ($p < 0.05$). An inverse correlation was found between Maresin-1 and CRP in patients with active CD ($p = 0.039$). A Maresin-1 cutoff value of < 607.38 pg/mL showed 96.67% sensitivity and 80% specificity for the identification of CD patients in remission from controls (AUC = 0.919), while a < 327.46 pg/L cutoff yielded a sensitivity of 100% and a specificity of 100% to distinguish active CD from controls (AUC = 0.999), and finally, a < 296.28 pg/mL cutoff was also significant in identifying patients with active CD from those with remission (sensitivity: 96.67%, specificity: 80%, AUC = 0.946). According to multivariable logistic regression, CD patients with decreased Maresin-1 had increased likelihood of having active disease (OR: 0.942, 95% CI = 0.892 - 0.994, $p = 0.031$).**
Conclusions: **This was the first study to examine circulating levels of Maresin-1 in CD patients and showed that patients with active disease and those in remission had significantly lower values compared to controls. Our results suggest that Maresin-1 levels might be involved in the pathogenesis of CD. Serum Maresin-1 could be used as a diagnostic biomarker in predicting inflammation in CD and may emerge as a target for treatment.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250622)

Correspondence:
Assoc. Prof. Dr. Özlem Gül
Lokman Hekim University
Department of Gastroenterology
Polatli Caddesi, Andiçen Mh, İdil Sk. No. 44
06930, Sincan
Ankara
Turkey
Phone: + 90 5337385063
Email: ozlemgulx@yahoo.com

Manuscript accepted June 23, 2025

KEYWORDS

Crohn's disease, inflammation, resolution, Maresin-1

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by transmural inflammation that can affect various segments of the gastrointestinal tract from the mouth to the anus. The disease demonstrates periods of activation and remission [1]. The annual incidence of CD varies by geographic region, ranging from

3 to 20 cases per 100,000 individuals [2]. Although the etiology of CD has not been fully elucidated, it is thought that host factors (such as altered microbiota, intestinal epithelial cell barrier dysfunction, abnormal innate and adaptive immunity response) and various environmental factors (including smoking, diet and physical activity) interact to cause disease development and progression in patients with genetic predisposition [3]. The abnormal balance of pro- and anti-inflammatory molecules, including cytokines, chemokines, inflammasomes, miRNAs (micro-ribonucleic acids), and lipid mediators, in both innate and acquired immune functions, are key determinants of the development of CD [4].

Prior studies demonstrate that unresolved inflammation may be a primary culprit in various diseases, including atherosclerosis, rheumatoid arthritis, chronic obstructive pulmonary disease, IBD, obesity, asthma, cancer, and multiple sclerosis. Normally, inflammatory response is expected to be gradually suppressed and then resolved, with the affected cells ultimately returning to normal structure and functions [5]. Although it is known that the resolution of inflammation occurs as a result of activation of phagocytosis and apoptosis and suppression of pro-inflammatory gene expression, data regarding these pathways are currently limited, especially in specific pathologies. Nonetheless, it is well known that maresins, miRNAs, lipoxins, adenosine, resolvins, anti-inflammatory cytokines, and prostaglandins are locally-synthesized mediators contributing to the resolution of inflammation [6].

Maresin-1, which is derived from docosahexaenoic acid (DHA), is a specialized mediator that resolves inflammation [7]. Maresin-1 is involved in the stimulation of apoptotic cells and macrophage phagocytosis, pro-inflammatory to anti-inflammatory macrophage switching, acceleration of tissue regeneration, elimination of inflammatory debris, prevention of neutrophil infiltration and migration, and regulation of pro-inflammatory cytokine synthesis (TNF-α, IL-1β, IL-6 and nuclear factor kappa B; NF-κB) [8,9]. Recently, *in vivo* and *in vitro* studies have reported that Maresin-1 levels decrease in metabolic and inflammatory conditions, including spinal cord injury, obesity, non-alcoholic fatty liver disease, asthma, sepsis, arthritis, infections and colitis [9, 10]. However, to date, there have been no studies examining clinically circulating levels in CD.

The aim of the present study was to investigate the serum levels of Maresin-1 in patients diagnosed with CD and to examine potential relationships with disease activity (patients with active CD and those in remission) by performing comparisons with other inflammatory parameters.

MATERIALS AND METHODS

Study design and ethics

This study was conducted between April 2021 and June 2021 in the Department of Gastroenterology of Kirikkale Medical School Training and Research Hospital, Kirikkale, Turkey. All research procedures were evaluated and accepted by the Research Ethics Committee of the Medical Faculty of Kırıkkale University (April 8 - April 15, 2021) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written and verbal informed consent was obtained from all participants prior to their participation in this study. In order to be able to assess relationships with disease activity, we planned to include patients with CD who were in the active and remission states of disease. Power analysis was used to determine the number of subjects necessary in each group (active CD, remission CD and controls). According to descriptive statistics obtained from the study by Fang et al., we determined an effect size of 0.312 for Maresin-1 levels. One-way analysis of variances power analysis showed that a sample size of 30 for each group (90 in total) achieved 80% power with a two-sided significance threshold of 0.05 [10].

Patients

Thirty patients with active CD, 30 CD patients in remission, and 30 healthy control participants were included in the study. The diagnosis of CD was made according to the criteria reported by the European Crohn´s and Colitis Organization (ECCO) guidelines, based on anamnesis, physical examination, radiological and endoscopic examination with histopathological evaluation [11]. Disease activity was measured by the CD Activity Index score (CDAI), and patients who scored greater than 150 at least 2 weeks before randomization were defined as patients with active CD, and patients with a score of less than 149 were defined to be in remission [12]. Participants with acute or chronic infections, malignancy, chronic inflammatory conditions, chronic kidney failure, diabetes mellitus, connective tissue diseases, those who are pregnant or within 1 year postpartum, subjects with a history of concomitant autoimmune diseases or colectomy were excluded from the study. Participants with a history of dietary omega 3 food supplement intake, non-steroidal anti-inflammatory drug use, or fish consumption during the prior week were also excluded from the study. The control group involved healthy individuals without known gastrointestinal diseases, autoimmune or chronic disorders, or drug use.

Clinical and demographic characteristics including age, gender, smoking, alcohol consumption, weight and height, CDAI scores, current medication(s), the site of gastrointestinal involvement, duration with CD, and type of CD were obtained from patients' files. Body mass index (BMI) was calculated as body weight (kg)/ height (m^2).

Sample acquisition and measurements

Blood samples were obtained from the antecubital vein after 12-hour fasting and were centrifuged at 3,000 rpm for 20 minutes to separate the serum. Within 1 hour, ali-

quots of these samples (for Maresin-1 measurement) were stored at -80ºC until the analyses were completed. Complete blood count, including white blood cell count (WBC), hemoglobin values and platelet counts were measured via a Mindray BC-6800 autoanalyzer (Mindray Electronics Co, Ltd, Shenzhen, China). Serum C-reactive protein (CRP) levels were measured with the immunoturbidimetric method using a Roche Cobas C501 biochemical autoanalyzer (Roche Diagnostic GmbH, Mannheim, Germany) and were expressed as mg/L. Erythrocyte sedimentation rate (ESR) was measured automatically with the Vacuplus ESR 120 analyzer (Len-Med Medical, Ankara, Turkey) at room temperature using Westergren's method and were expressed as mm/hour. All kit components were stored at 2 - 8ºC before using. After thawing frozen serum samples (within 3 months after storage), serum Maresin-1 was determined by an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (catalog number: SG-15235, SinoGeneclon Biotech, HangZhou, China). The intra-assay coefficient of variation of the kit was < 8%, while the inter-assay coefficient of variation was < 10%. Ten kits were used in calibration for validation of ELISA results.

Statistical analyses

All analyses were performed on SPSS v23 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) and p-values of < 0.05 were accepted as statistically significant. Continuous variable normality was checked with the Shapiro-Wilk test, and descriptive values for continuous data were given accordingly (mean ± standard deviation or median [25% - 75% interquartile range]). Absolute (*n*) and relative frequencies (percentage) were given for categorical variables. Fisher's Exact Test or Pearson's chi-squared test was used to analyze categorical variable distributions in each of the groups. In 2-group comparisons, parametric continuous variables were analyzed with the independent samples *t*-test, while non-parametric variables were analyzed with the Mann-Whitney *U*-test. One-way ANOVA (Analysis of Variance) test was used for the comparison of the three groups with parametric characteristics, and the Tukey HSD (honestly significant difference) test was used as the post hoc test. The Kruskal Wallis test was used in the non-parametric comparison of the continuous variables of the groups and the Bonferroni correction as the post hoc test for significant cases. Diagnostic performances of the variables were evaluated by using Receiver Operating Characteristic (ROC) curve analysis, with calculation of the Youden index to determine optimal cutoff values for each parameter. Spearman's correlation test was performed to detect directional relationships between patient parameters. Multivariable logistic regression was performed to determine independent risk factors associated with active CD and remission status in patients, and the results are presented with odds ratio (OR) and 95% confidence intervals (CIs).

RESULTS

A total of 60 CD patients and 30 healthy participants were included in the study. Summary of the participants' characteristics were shown in Table 1. No significant differences were found between the groups in terms of age, gender, alcohol consumption, and BMI values. While 73.3% of patients with active CD were smokers, 10% of those in remission and 30% of the control group were smokers (p = 0.001). CDAI scores were found to be 207 (150 - 460) in active CD patients and 47.5 (10 - 147) in CD patients with remission (p = 0.001). The sites of gastrointestinal involvement were as follows: ileocolonic in 10 (33.3%) active patients and in 12 (40%) patients with remission, colonic in 4 (13.3%) active patients and in 2 (6.7%) patients with remission, perianal + ileocolonic in 5 (16.7%) active CD patients and in 1 (3.3%) patient with remission, ileal in 11 (36.7%) active patients and in 15 (50%) patients with remission (p = 0.303). While 23 patients presented with inflammatory CD, 5 patients had fistulizing CD and 2 patients had fibrostenosis formation in the active CD group. Twenty-eight (93.3%) patients had inflammatory CD in the remission group. No significant differences were found in terms of treatment(s) and duration of disease (p = 0.054 and 0.939, respectively).

The median serum levels of Maresin-1 were significantly lower in the active CD group (215.74 [118.55 - 327.46] pg/mL) compared to the remission group (413.29 [215.82 - 726.18] pg/mL) and the control group (753.4 [381.5 - 901.08] pg/mL) (p < 0.001). The median levels of serum CRP, ESR, WBC, and platelet were significantly higher in CD patients compared to controls and patients in remission (all, p < 0.05). The median hemoglobin values were similar between groups (p = 0.059).

Correlation analyses between participants' clinical and biochemical characteristics and Maresin-1 levels were shown in Table 2. An inverse correlation was found between Maresin-1 levels and CRP levels in active CD patients (r = -0.379, p = 0.039). No significant correlations were found between Maresin-1 levels and neither clinical characteristics (including CDAI) nor other biochemical markers (WBC, hemoglobin value, platelet value and ESR) in any of the groups (all, p > 0.05).

We performed ROC curve analyses to assess whether Maresin-1 levels could differentiate active CD from remission, active CD from controls, or remission from controls (Table 3, Figure 1). ROC curve analysis showed that < 607.38 pg/mL Maresin-1 was the ideal cutoff point for the determination of CD patients in remission from controls, with a sensitivity and specificity of 96.67% and 80%, respectively (area under the ROC curve [AUC]: 0.919). The optimum cutoff point of < 327.46 pg/L for Maresin-1 revealed a sensitivity of 100% and a specificity of 100% to distinguish active CD from controls with an AUC of 0.999. ROC curve analysis showed that a < 296.28 pg/mL cutoff for Maresin-1 could differentiate active CD from remission

Table 1. Summary of the participants' characteristics.

	Active CD Patients (n = 30)	CD Patients in Remission (n = 30)	Controls (n = 30)	p
Age (years)	43.8 ± 12.67	42.73 ± 10.69	43.77 ± 11.97	0.924
Gender				
Female	15 (50%)	15 (50%)	15 (50%)	0.999
Male	15 (50%)	15 (50%)	15 (50%)	
Smoking	22 (73.3%)	3 (10%)	9 (30%)	0.001
Alcohol	1 (3.3%)	1 (3.3%)	2 (6.7%)	0.770
BMI (kg/m2)	25.32 (20.89 - 29.29)	25.44 (19.6 - 27,010)	26.62 (20.57 - 29.4)	0.214
WBC (x 103/µL)	9.6 (2.8 - 15.8) a	7.4 (4.6 - 14.7) b	7.8 (4.5 - 10.9) b	0.002
Hemoglobin (g/dL)	13.17 ± 1.94	13.8 ± 1.92	14.32 ± 1.63	0.059
Platelet (x 103/µL)	338 (166 - 565) a	256 (177 - 442) b	271 (190 - 393) b	0.003
ESR (mm)	37 (8 - 69) a	15 (3 - 40) b	9.5 (2 - 30) c	< 0.001
CRP (mg/L)	18.81 (1.49 - 113.46) a	2.73 (0.39 - 23.4) b	2.7 (0.2 - 8.6) b	< 0.001
Maresin-1 (pg/mL)	215.74 (118.55 - 327.46) a	413.29 (215.82 - 726.18) b	753.4 (381.5 - 901.08) c	< 0.001
CDAI	207 (150 - 460)	47.5 (10 - 147)	-	0.001
Localization				
Perianal + Ileocolonic	5 (16.7%)	1 (3.3%)	-	0.303
Ileal	11 (36.7%)	15 (50%)	-	
Ileocolonic	10 (33.3%)	12 (40%)	-	
Colonic	4 (13.3%)	2 (6.7%)	-	
Type of disease				
Fistulization	5 (16.7%)	1 (3.3%)	-	0.175
Inflammatory	23 (76.7%)	28 (93.3%)	-	
Stenosis	2 (6.7%)	1 (3.3%)	-	
Treatment				
None	5 (16.7%)	0 (0%)	-	0.054
5-ASA	11 (36.7%)	8 (26.7%)	-	
5-ASA + Immsp	11 (36.7%)	19 (63.3%)	-	
5-ASA + Immsp + Anti-TNF	3 (10%)	3 (10%)	-	
Duration of disease	2 (0 - 10)	2 (1 - 10)	-	0.939

CD Crohn's disease, WBC white blood cell, ESR erythrocyte sedimentation rate, CRP C-reactive protein. Results were given as frequency (%) for categorical variables, and as mean ± SD or median (min - max) for continuous variables.

Table 2. Correlations with Maresin-1 and other variables.

	Active CD Patients (n = 30)		CD Patients in Remission (n = 30)		Controls (n = 30)	
	r	p	r	p	r	p
CDAI	-0.330	0.075	0.115	0.547	-	-
WBC	0.018	0.925	0.148	0.437	0.117	0.539
HGB	0.223	0.236	0.001	0.997	0.014	0.941
PLT	0.059	0.758	0.203	0.283	-0.327	0.078
ESR	0.118	0.535	0.180	0.340	0.056	0.768
CRP	-0.379	0.039	0.080	0.673	0.087	0.653

CD Crohn's disease, CDAI Crohn's Disease Activity Index, WBC white blood cell, HGB hemoglobin, PLT platelet, ESR erythrocyte sedimentation rate, CRP C-reactive protein.

Table 3. Measurement performance of Maresin-1 for the detection of group differences.

Group	AUC (95% CI)	p	Cutoff	Sensitivity	Specificity
Control-Remission	0.919 (0.819 - 0.974)	< 0.001	≤ 607.38	96.67%	80%
Control-Active	0.999 (0.940 - 0.999)	< 0.001	≤ 327.46	100%	100%
Active-Remission	0.946 (0.855 - 0.988)	< 0.001	≤ 296.28	96.67%	80%

AUC Area Under ROC Curve, CI confidence Intervals.

Table 4. Multivariate logistic regression analysis of biochemical variables.

Group	Variable	OR (95% CI)	Wald	p-value
Control-Remission * (Model 1)	ESR	1.084 (0.973 - 1.208)	2.124	0.145
	Maresin-1	0.987 (0.979 - 0.994)	12.896	< 0.001
Control-Active ** (Model 2)	WBC	1.002 (0.998 - 1.005)	2.574	0.109
	ESR	1.556 (1.001 - 2.418)	3.857	0.049
	CRP	2.978 (0.702 - 12.635)	2.191	0.139
Remission-Active ** (Model 3)	ESR	1.225 (1.015 - 1.477)	4.482	0.034
	Maresin-1	0.942 (0.892 - 0.994)	4.665	0.031

*** Controlled for age and gender, ** Controlled for age, gender and smoking. OR odds ratio, CI confidence of interval, ESR erythrocyte sedimentation rate, WBC white blood cell, CRP C-reactive protein.**

with a sensitivity of 96.67% and a specificity of 80% (AUC: 0.946).

Factors independently associated with active CD and remission status in patients were evaluated via multivariate logistic regression (Table 4). According to Model 1, which determined factors related to remission status by controlling age and sex, decreased Maresin-1 values in patients were found to be independently associated with remission status (OR: 0.987, 95% CI: 0.979 - 0.994; $p < 0.001$). According to Model 3 controlling for age, gender and smoking, CD patients with decreased Maresin-1 or increased ESR had increased likelihood for active disease rather than remission (OR: 0.942, 95% CI = 0.892 - 0.994; $p = 0.031$ for Maresin-1, and OR: 1.225, 95% CI = 1.015 - 1.477; $p = 0.034$ for ESR).

DISCUSSION

This study was aimed at determining circulating levels of Maresin-1 and its relationships with disease activity in patients with CD. Maresin-1 level was found to be significantly lower in the active CD group compared to the remission and control groups. Maresin-1 was also observed to be lower in patients with remission compared to healthy controls. We found a negative correlation between Maresin-1 levels and CRP levels. We also showed that Maresin-1 levels demonstrate high sensitivity and specificity in distinguishing between patient groups and controls. Finally, CD patients with decreased Maresin-1 were found to have increased possibility of active disease according to multivariable logistic regression.

It is well-established that CD is associated with immune system-related defects that contribute to the impairments in mucosal homeostasis. Together, the uncontrolled activation of immune cells and unregulated secretion of multiple pro- and anti-inflammatory mediators result in a defective immune function [13]. In addition to clinical assessments, follow-up of gastrointestinal inflammatory response also plays an important role in the evaluation of the efficacy of CD treatment [14]. Although endoscopic-colonoscopic imaging and histopathological examination of biopsy preparations are beneficial in the evaluation of inflammation in CD, they are invasive and costly, and therefore, the research of possible markers associated with CD presence or severity are being researched. It has been reported that markers such as platelet value, CRP, and ESR might be used in CD, but none of them have been found to be specific for intestinal inflammation [15]. Therefore, there is a need for more sensitive and specific biomarkers that can be detected in the blood of patients in order to facilitate cost-effective and accurate assessment of intestinal inflammation and disease activity.

Research concerning pro-inflammatory mechanisms are focused on CD pathogenesis; however, the resolution stage of inflammation, which plays an important role in

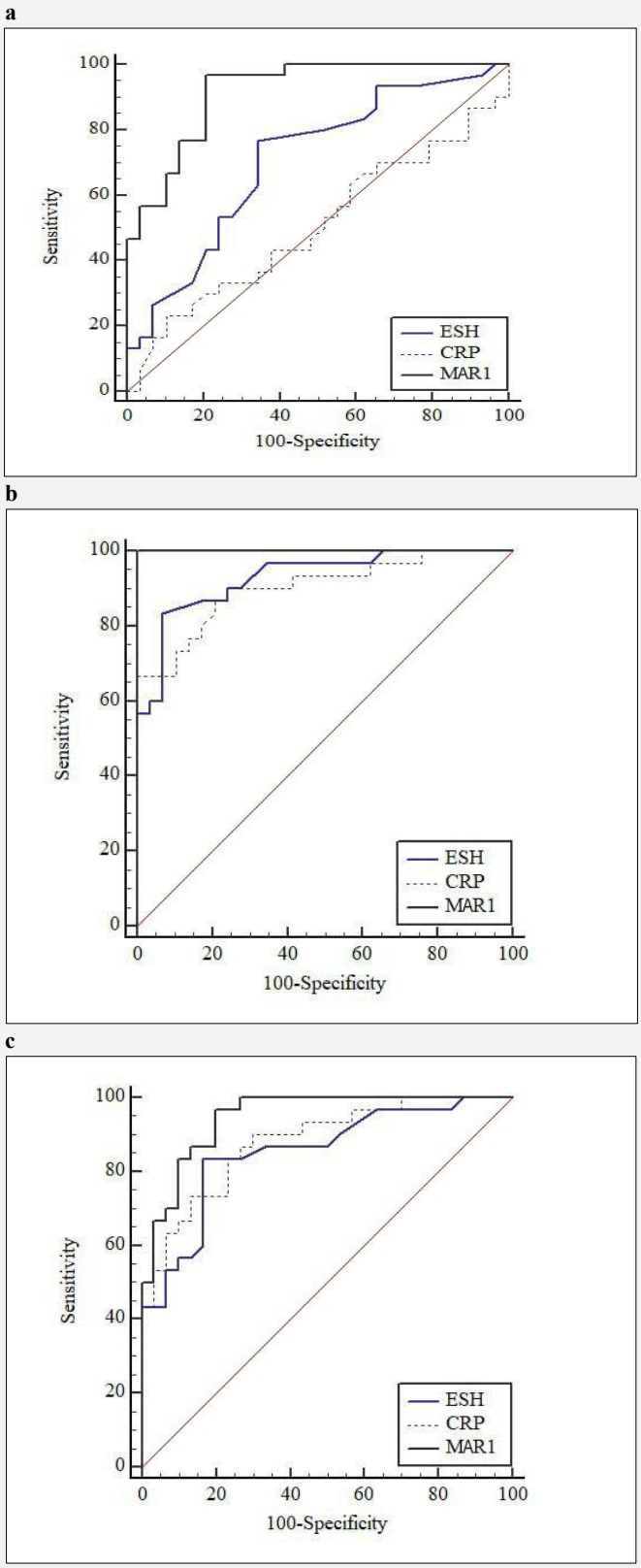

Figure 1. ROC curve for erythrocyte sedimentation (ESH), C-reactive protein (CRP), and Maresin-1, a) to differentiate patients in remission from controls, b) to differentiate active patients from controls, and c) to differentiate active patients from those in remission.

the progression of acute inflammation to chronic inflammation, has not been comprehensively investigated. In addition to the demonstration of the role of various lipids and lipid mediators in the pathophysiology of various inflammation-related diseases [16-18], studies show that resolvin, maresin, lipoxin, and protectins are lipid mediators involved in the resolution of inflammation. The precursors of these mediators, EPA and DHA, are taken from the diet [19]. Chan et al. showed in an epidemiological study that high dietary DHA intake was protective against the development of CD and might in fact be a treatment option [20]. John et al. demonstrated in 25,639 healthy participants that ω-3 PUFA in diet was protective against the development of ulcerative colitis (UC) in healthy individuals [21]. Pearl et al. showed in 69 patients that, when compared to controls, ω-6 PUFA arachidonic acid level was higher and ω-3 PUFA EPA level was lower in the biopsy samples of patients with UC-induced intestinal mucosa inflammation [22]. Ungaro et al. found in biopsy samples taken from the colon of IBD patients that DHA-derived metabolites involved in the resolution of inflammation were found to be defective in the inflamed colonic mucosa in the active-disease group compared to the remission and healthy control groups [23]. In contrast to these intriguing results, in a study comprising 51 UC and 30 healthy controls, only a weak positive correlation was found between resolvin E1 and CRP levels in the UC group, and resolvin E1 levels were found to be unassociated with the disease or its status (active vs. remission) [24].

Clinical and animal studies have examined the mechanisms of DHA- and EPA-derived resolvins and maresins for their contribution to resolving inflammation in inflammatory diseases, and positive relationships have been found. Tejera et al. showed in 26 patients with ARDS (acute respiratory distress syndrome) that serum lipid mediators, including Maresin-1, lipoxin A4, thromboxane B2, and cysteinyl leukotrienes, were associated with prolonged intensive care unit stay and increased ventilator requirement, suggesting that low serum levels of inflammation-resolving lipid mediators may be associated with increased clinical severity and mortality of ARDS [25]. Francos-Quijorna et al. demonstrated that Maresin-1 therapy in mice with spinal cord injury (2 weeks after injury) caused decreased levels of pro-inflammatory cytokines and less macrophage accumulation at the site of injury. Furthermore, macrophages demonstrated a switch from a pro-inflammatory phenotype to an anti-inflammatory phenotype [26]. Gu et al. showed in a mouse sepsis model study (cecum ligation) that activation of ALX/cAMP/ROS (the lipoxin A4 receptor/cyclic adenosine monophosphate/reactive oxygen species) reduced mitochondrial dysfunction and pro-inflammatory cytokine release, thereby showing relative prevention of lung injury after Maresin-1 treatment [27]. Cho et al. demonstrated in a mouse model study with dextran sulfate sodium (DSS)-induced colitis that myeloperoxidase activity, colonic inflammation, IL-1B, and matrix metalloproteinase-3 levels decreased with the administration of DHA or sulfasalazine [28]. Arita et al. showed decreased levels of proinflammatory cytokines such as TNF-α, IL-12 (p40) and improved histological scores after treatment with resolvin E1 in a 2,4,6-TNBS (trinitrobenzene sulfonic acid)-induced colitis study [29]. Additionally, resolvin D1 treatment in mice with DSS-induced colitis was demonstrated to alleviate colon damage and weight loss, reduce disease activity, decrease polymorphonuclear leukocyte infiltration, and limit mRNA expression of NF-κB and cytokines (such as macrophage inflammatory protein-2, TNF-α, and IL-1B) [30]. Marcon et al. revealed in a mouse study with DSS- and 2,4,6-TNBS-induced colitis that Maresin-1 administration improved weight loss, colon injury, polymorphonuclear leukocyte count, and MPO activity in both types of colitis [31]. Wang et al. showed improved histological findings, reduced CD4+ T lymphocyte counts in the lamina propria, decreased levels of IL-17, IL-6, MPO, TNF-α, IFN-γ levels, suppression of hepcidin synthesis (liver) after Maresin-1 treatment in a colitis model [32]. These results show that these mediators contribute significantly to intestinal inflammation in various clinicopathological states, and therefore, regulation of their levels could be utilized as a therapeutic method in IBDs.

This was the first clinical study to evaluate possible relationships between serum Maresin-1 level and CD activity in the literature. Increased prevalence of smoking in the active group compared to the remission group and control group was found to be similar to the literature [33]. Maresin-1 level was found to be significantly lower in the active CD group compared to the CD and control groups in remission. We found a negative correlation between Maresin-1 levels and CRP levels. We also showed that Maresin-1 level has high sensitivity and specificity in distinguishing between disease states, as well as differentiating between patients and controls. The fact that Maresin-1 was significantly lower in both the remission CD group and the active CD group compared to the control group indicates the importance of this marker in predicting subclinical inflammation. Our results are similar to the majority of experimental and clinical studies in the literature, which suggest that serum Maresin-1 level may be a marker in predicting inflammation or disease status in patients with CD.

The inability to measure Maresin-1 levels at the tissue level, the lack of measurements at different times during the course of the disease, and the completion of our study with a small sample size constitute the limitations of our study. The strengths of our study were the exclusion of patients receiving supplements containing ω-3 PUFA, those using NSAIDs, and subjects who consumed fish in the last week. Further studies with larger sample size must be performed and measurement of Maresin-1 level at tissue level in endoscopic/colonoscopic biopsy materials is critical. Comparison with other pro-inflammatory markers involved in pathogenesis, such as TNF-α, IFN-γ, IL-17, IL-6, or with more sensitive acute

phase reactants, including hs-CRP, may also yield more reliable results regarding the importance of this molecule as a biomarker.

In conclusion, this was the first clinical study in literature showing the relationship between serum Maresin-1 level and CD activity. Maresin-1 is decreased significantly in patients with CD and can also be used in distinguishing the active and remission periods of the disease. Further large-scale clinical studies, preferably performing tissue-level measurements together with serum measurements, are needed to confirm our results.

Declaration of Interest:

All authors meet ICMJE authorship criteria, and all authors declare that there are no conflicts of interest regarding the publication of this article.

References:

1. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon 2018 Feb;64(2):20-57. (PMID: 28826742)
2. Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. Nat Rev Dis Primers 2020;6(1):22. (PMID: 32242028)
3. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. Lancet 2017;389(10080):1741-55. (PMID: 27914655)
4. Park JH, Peyrin-Biroulet L, Eisenhut M, Shin JI. IBD immunopathogenesis: a comprehensive review of inflammatory molecules. Autoimmun Rev 2017;16(4):416-26. (PMID: 28212924)
5. Neurath MF. Resolution of inflammation: from basic concepts to clinical application. Semin Immunopathol 2019 Nov;41(6):627-31. (PMID: 31776733)
6. Conte MS, Desai TA, Wu B, Schaller M, Werlin E. Pro-resolving lipid mediators in vascular disease. J Clin Invest 2018 Aug 31; 128(9):3727-35. (PMID: 30168805)
7. Fattori V, Ferraz CR, Rasquel-Oliveira FS, et al. Resolving neuroinflammation and pain with maresin 1, a specialized pro-resolving lipid mediator. Treatments, Mechanisms, and Adverse Reactions of Anesthetics and Analgesics: Elsevier 2022. p. 431-41. https://doi.org/10.1016/B978-0-12-820237-1.00037-5
8. Tang S, Wan M, Huang W, Stanton RC, Xu Y. Maresins: Specialized Proresolving Lipid Mediators and Their Potential Role in Inflammatory-Related Diseases. Mediators Inflamm 2018 Feb 20; 2018:2380319. (PMID: 29674943)
9. Saito-Sasaki N, Sawada Y, Nakamura M. Maresin-1 and Inflammatory Disease. Int J Mol Sci 2022 Jan 25;23(3):1367. (PMID: 35163291)
10. Fang X, Wang H, Ye T, et al. Low serum Maresin-1 levels are associated with non-alcoholic fatty liver disease: a cross-sectional study. Lipids Health Dis 2021 Aug 30;20(1):96. (PMID: 34461919)
11. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis 2020;14(1):4-22. (PMID: 31711158)
12. Best WR, Becktel JM, Singleton JW, Kern Jr F. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439-44. (PMID: 1248701)
13. Atreya R, Neurath MF. Chemokines in inflammatory bowel diseases. Dig Dis 2010;28(3):386-94. (PMID: 20926862)
14. Petagna L, Antonelli A, Ganini C, et al. Pathophysiology of Crohn's disease inflammation and recurrence. Biol Direct 2020; 15(1):23. (PMID: 33160400)
15. Chen R, Li L, Chao K, et al. Platelet-to-lymphocyte percentage ratio index: a simple non-invasive index to monitor the endoscopic activity in Crohn's disease. Therap Adv Gastroenterol 2020;13: 1756284820979442. (PMID: 33425010)
16. Zhang C, Wang K, Yang L, et al. Lipid metabolism in inflammation-related diseases. Analyst 2018;143(19):4526-36. (PMID: 30128447)
17. Alhouayek M, Ameraoui H, Muccioli GG. Bioactive lipids in inflammatory bowel diseases - From pathophysiological alterations to therapeutic opportunities. Biochim Biophys Acta Mol Cell Biol Lipids 2021;1866(2):158854. (PMID: 33157277)
18. Samadi A, Sabuncuoglu S, Samadi M, et al. A Comprehensive Review on Oxysterols and Related Diseases. Curr Med Chem 2021;28(1):110-36. (PMID: 32175830)
19. Mozaffari H, Daneshzad E, Larijani B, Bellissimo N, Azadbakht L. Dietary intake of fish, n-3 polyunsaturated fatty acids, and risk of inflammatory bowel disease: a systematic review and meta-analysis of observational studies. Eur J Nutr 2020;59(1):1-17. (PMID: 30680455)
20. Chan S, Luben R, Olsen A, et al. Association between high dietary intake of the n-3 polyunsaturated fatty acid docosahexaenoic acid and reduced risk of Crohn's disease. Aliment Pharmacol Ther 2014;39(8):834-42. (PMID: 24611981)
21. John S, Luben R, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. Eur J Gastroenterol Hepatol 2010;22(5):602-6. (PMID: 20216220)
22. Pearl DS, Masoodi M, Eiden M, et al. Altered colonic mucosal availability of n-3 and n-6 polyunsaturated fatty acids in ulcerative colitis and the relationship to disease activity. J Crohns Colitis 2014;8(1):70-9. (PMID: 23619007)
23. Ungaro F, Rubbino F, Danese S, D'Alessio S. Actors and Factors in the Resolution of Intestinal Inflammation: Lipid Mediators As a New Approach to Therapy in Inflammatory Bowel Diseases. Front Immunol 2017;8:1331. (PMID: 29109724)
24. Günay S, Taşova F, Yılmaz HE, Paköz ZB, Çekiç C. Serum Resolvin E1 Levels and Its Relationship with Disease Activity in Ulcerative Colitis. Gastroenterol Res Pract 2019;2019:6258327. (PMID: 30906319)
25. Tejera P, Abdulnour R-EE, Zhu Z, Su L, Levy BD, Christiani DC. Plasma levels of proresolving and prophlogistic lipid mediators: association with severity of respiratory failure and mortality in acute respiratory distress syndrome. Crit Care Explor 2020; 2(10):e0241. (PMID: 33134939)
26. Francos-Quijorna I, Santos-Nogueira E, Gronert K, et al. Maresin 1 promotes inflammatory resolution, neuroprotection, and functional neurological recovery after spinal cord injury. J Neurosci 2017;37(48):11731-43. (PMID: 29109234)

27. Gu J, Luo L, Wang Q, et al. Maresin 1 attenuates mitochondrial dysfunction through the ALX/cAMP/ROS pathway in the cecal ligation and puncture mouse model and sepsis patients. Lab Invest 2018;98(6):715-33. (PMID: 29467458)

28. Cho JY, Chi SG, Chun HS. Oral administration of docosahexaenoic acid attenuates colitis induced by dextran sulfate sodium in mice. Mol Nutr Food Res 2011;55(2):239-46. (PMID: 20824662)

29. Arita M, Yoshida M, Hong S, et al. Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2, 4, 6-trinitrobenzene sulfonic acid-induced colitis. Proc Natl Acad Sci U S A 2005;102(21):7671-6. (PMID: 15890784)

30. Bento AF, Claudino RF, Dutra RC, Marcon R, Calixto JB. Omega-3 fatty acid-derived mediators 17 (R)-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. J Immunol 2011;187(4):1957-69. (PMID: 21724996)

31. Marcon R, Bento AF, Dutra RC, Bicca MA, Leite DF, Calixto JB. Maresin 1, a proresolving lipid mediator derived from omega-3 polyunsaturated fatty acids, exerts protective actions in murine models of colitis. J Immunol 2013;191(8):4288-98. (PMID: 24038091)

32. Wang H, Shi P, Huang C, Liu Q. Maresin 1 ameliorates iron-deficient anemia in IL-10-/-mice with spontaneous colitis by the inhibition of hepcidin expression though the IL-6/STAT3 pathway. Am J Transl Res 2016;8(6):2758-66. (PMID: 27398158)

33. van der Heide F, Wassenaar M, van der Linde K, Spoelstra P, Kleibeuker JH, Dijkstra G. Effects of active and passive smoking on Crohn's disease and ulcerative colitis in a cohort from a regional hospital. Eur J Gastroenterol Hepatol 2011;23(3):255-61. (PMID: 21191306)