

MODULATORY ROLE OF GALECTIN-1 IN ULCERATIVE COLITIS WITH COMORBID METABOLIC SYNDROME

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Received: 25.05.2023.

Accepted: 17.07.2023.

ABSTRACT

Metabolic syndrome (MetS) and ulcerative colitis (UC) are widespread health conditions characterized by chronic, low-grade inflammation. Galectin-1 (Gal-1), an immunomodulatory peptide mainly secreted from adipose tissue, could potentially play a crucial role in mitigating these conditions. This cross-sectional study explores the involvement of Gal-1 in MetS and UC within a cohort of 75 patients, newly diagnosed with UC. The MetS subgroup displayed increased fecal Gal-1 levels compared to those without MetS. Furthermore, Gal-1 showed predominance over pro-inflammatory cytokines, including TNF- α , IL-6, and IL-17, in these subjects. These findings emphasize the potential involvement of Gal-1 in the pathophysiology of UC and MetS, presenting it as a promising diagnostic biomarker and therapeutic target for these conditions.

Keywords: Galectin-1, Ulcerative Colitis, Metabolic Syndrome, Inflammation.

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DOI: 10.2478/cabr-2023-0006

INTRODUCTION

Ulcerative Colitis and Metabolic Syndrome are two disparate medical conditions, both representing significant burdens on global health (1). UC, an inflammatory bowel disease, primarily affects the colon, leading to chronic inflammation and ulcers (2). MetS, on the other hand, is a cluster of conditions - increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol levels - that occur together, increasing the risk of heart disease, stroke, and type 2 diabetes (3).

Galectin-1 (Gal-1), a cell-surface binding lectin protein, is involved in numerous biological processes, including inflammation regulation, immune response modulation, cell-cell adhesion, and cell growth (4). This protein is notably abundant in inflamed tissues, and its secretion intensifies in activated macrophages within these areas (5). In patients with UC, characterized by mild colonic tissue inflammation, serum Gal-1 levels have been observed to significantly rise compared to those with severe inflammation (6). This discrepancy suggests a protective role for Gal-1 in preserving the intestinal epithelium.

Paralleling these observations in UC, MetS – a condition marked by chronic low-grade inflammation, insulin resistance, and obesity – also reveals intriguing connections with Gal-1 (7). This protein is implicated in managing inflammation within adipose tissue and moderating insulin resistance, both crucial elements in MetS pathophysiology (8). Increased systemic Gal-1 levels found in metabolic diseases underline its potential role in the genesis of these disturbances (9). Taken together, these findings highlight the potential pivotal role of Gal-1 in the pathophysiological mechanisms that underlie both UC and MetS. This suggests that Gal-1 could be a promising novel biomarker for these conditions.

The intersection between UC and MetS warrants further exploration. Patients diagnosed with UC are at a heightened risk of developing MetS, and reciprocally, those with MetS have a greater predisposition towards UC (10). Chronic inflammation, a shared trait in both conditions, might play a key role in the interrelation between UC and MetS. Given its function in managing inflammation and metabolic processes, Gal-1 could serve as a critical connector between these two pathologies.

Therefore, this study aims to delve into the relationship between systemic and local Gal-1 levels in individuals with UC and MetS. By doing so, we aim to contribute to a more profound understanding of the role of Gal-1 in inflammation and immune modulation in these conditions. Our findings may provide novel insights into potential therapeutic approaches for UC and MetS by targeting the inflammatory pathway via modulation of Gal-1.

MATERIALS AND METHODS

Characteristics of the Study Population

A total of 75 patients (42 males and 33 females), aged between 21 and 80 years, with newly diagnosed and histologically confirmed ulcerative colitis, were enrolled in an observational cross-sectional study. Recruited UC patients were divided in two groups, utilizing the Adult Treatment Panel III (ATP III) criteria for the diagnosis of MetS (11): Group without MetS (no MetS) and group with MetS. The criteria for diagnosing metabolic syndrome (MetS) according to the ATP III guidelines include the presence of three or more of the following components: 1) Central Obesity: Defined by waist circumference measurements. A waist circumference exceeding 40 inches (102 cm) in men and 35 inches (88 cm) in women is indicative of central obesity; 2) Hypertension: Characterized by blood pressure readings of 130/85 mmHg or higher, or active treatment for previously diagnosed hypertension; 3) Dysglycemia: Noted by a fasting plasma glucose level exceeding 5.5 mmol/L (99 mg/dL) and/or a 2-hour post-load plasma glucose level above 7.8 mmol/L (140 mg/dL), or active treatment for previously diagnosed dysglycemia; 4) Elevated Triglycerides: Triglyceride levels at or above 1.7 mmol/L (150 mg/dL) are considered high; 5) Low High-Density Lipoprotein (HDL) Cholesterol: Levels below 1.03 mmol/L (40 mg/dL) in men and 1.29 mmol/L (50 mg/dL) in women are deemed low, indicating potential metabolic imbalance.

All patients within the UC + MetS group meet all of the aforementioned criteria. Each patient received an exhaustive medical evaluation comprising a thorough medical history review, physical examination, routine laboratory tests, and diagnostic imaging procedures, including chest X-ray, abdominal ultrasound, abdominal computed tomography scan, and endoscopy. The research took place at two premier institutions - the Center for Gastroenterology, Clinical Center of Kragujevac, and the Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Serbia. Ethical approval was secured from the respective Ethic Committee of Clinical Center of Kragujevac. The study rigorously upheld the Principles of Good Clinical Practice and the Declaration of Helsinki. Informed consent was obtained from all patients before conducting blood and tissue analyses. Throughout the study, patients received continuous medical supervision at the Clinical Center Kragujevac, ensuring optimal care and safety.

The exclusion criteria for this study were as follows: Individuals under the age of 21 or over the age of 80, pregnant or breastfeeding women, patients with a history of other inflammatory bowel diseases such as Crohn's disease, individuals previously diagnosed with metabolic conditions other than Metabolic Syndrome, such as Type 1 diabetes or Cushing's syndrome. Additionally, those with a history of cancer, severe cardiovascular diseases, liver or renal insufficiency, or any autoimmune diseases were excluded. Patients who had undergone bowel resection surgery or had a stoma were also

excluded. Finally, individuals who had used immunosuppressants, systemic corticosteroids, or antibiotics within the past 3 months, or were participating in other clinical trials, were also excluded from the study.

The diagnosis and severity assessment of UC in each case were established based on histological and clinical scores. To ensure consistent evaluation of the mucosal condition, all endoscopic procedures were conducted by a skilled endoscopist. The severity of endoscopic lesions in UC was determined using the Mayo endoscopic sub-score (12). This scoring system assesses the extent and severity of inflammation observed during endoscopy. It includes various criteria such as vascular pattern, erythema, friability, and ulceration. The scoring ranges from 0 to 3, with 0 indicating no inflammation and 3 representing severe inflammation.

The clinical score for assessing the severity of UC was determined using two indices: the Truelove and Witts clinical activity index and the Mayo clinical index (13). The Truelove and Witts clinical activity index evaluates various clinical parameters such as the number of stools per day, presence of blood in the stool, temperature, pulse rate, and general well-being. Each parameter is assigned a score, and the cumulative score provides an overall assessment of disease activity. On the other hand, the Mayo clinical index incorporates additional factors such as physician's global assessment, patient-reported outcomes, and laboratory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. This index aims to provide a comprehensive evaluation of the patient's clinical status, considering both objective measures and subjective assessments.

The histological score in this study was determined using the Geboes grading system (14). Histological sections were analyzed in a blinded manner by two independent pathologists. This approach ensured unbiased evaluation of the histological features without knowledge of other clinical or endoscopic findings. The Geboes grading system provides a standardized framework for assessing histopathological changes in ulcerative colitis, including parameters such as inflammation, epithelial damage, crypt architecture, and presence of ulceration.

Quantification of Fecal and Serum Cytokine Levels

The procedure for preparing fecal samples followed the method outlined earlier (15). To summarize, a 1g sample of feces was diluted, stirred, and homogenized in 5mL of a protease inhibitor cocktail (P8340, Sigma Aldrich, St. Louis, MO, USA). Blood samples were collected from both patients and control subjects at 8 am, with serum being separated, gathered, and preserved at -80 °C until required for testing. The serum and fecal supernatants from UC patients were assessed for levels of tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-17 (IL-17), and Gal-1. The quantification was carried out using ELISA tests commercially available, following the guidelines provided by the product manufacturer.

Statistical analysis

All statistical analyses in this study were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize participant demographics and clinical characteristics. Continuous variables were presented as mean $\pm$ standard error of mean (SE) based on their distribution, assessed by the Shapiro-Wilk test. Categorical variables were reported as frequencies and percentages. The Student's t-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data) were used to compare continuous variables between two groups. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant in all analyses.

RESULTS

Laboratory Parameter Differences between UC Patients with and without Metabolic Syndrome

A total of 75 patients were enrolled in the study, of which 61 had Ulcerative Colitis (UC) with Metabolic Syndrome (MetS) and 14 had UC without MetS. The study revealed significant differences in certain laboratory parameters between these two patient groups. Patients with UC and MetS demonstrated significantly elevated levels of creatinine ($82.21 \pm 2.89 \mu\text{mol/L}$ vs $66.75 \pm 3.54 \mu\text{mol/L}$, $p=0.014$) and urea ($6.17 \pm 0.42 \text{ mmol/L}$ vs $3.65 \pm 0.54 \text{ mmol/L}$, $p<0.05$) compared to UC patients without MetS. Furthermore, the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) also showed significantly higher values in UC patients with MetS (AST: $33.51 \pm 2.57 \text{ U/L}$ vs $22.74 \pm 2.27 \text{ U/L}$, $p=0.03$; ALT: $37.86 \pm 6.21 \text{ U/L}$ vs $22.69 \pm 3.39 \text{ U/L}$, $p=0.031$). Additionally, serum triglycerides ($1.72 \pm 0.21 \text{ mmol/L}$ vs $0.79 \pm 0.09 \text{ mmol/L}$, $p=0.003$) and cholesterol levels ($5.22 \pm 0.17 \text{ mmol/L}$ vs $3.63 \pm 0.25 \text{ mmol/L}$, $p=0.001$) were significantly higher in patients with both UC and MetS as compared to those with UC alone. In contrast, the leukocyte count was found to be significantly lower in UC and MetS patients ($8.09 \pm 0.25 \times 10^9/\text{L}$ vs $10.57 \pm 1.34 \times 10^9/\text{L}$). However, there were no significant differences between the two groups regarding the number of thrombocytes, hemoglobin levels, HDL, Low-Density Lipoprotein (LDL), Gamma-Glutamyl Transferase (gamma GT), albumin, and globulin levels (data not shown).

Severity of UC Manifestations in Patients with Metabolic Syndrome

Patients diagnosed with both Metabolic Syndrome (MetS) and Ulcerative Colitis (UC) displayed significantly milder manifestations, despite elevated metabolic markers. This was evidenced by a notably lower Mayo endoscopic subscore (3 ± 0 vs 2 ± 0.75 ; $p=0.038$) and Mayo clinical score (3 ± 0 vs 2 ± 1 ; $p=0.005$). Endoscopic examination typically showed minor mucosal abnormalities, in contrast to more severe findings in UC patients without MetS. Pathohistological scores, such as chronic inflammatory infiltration (2.20 ± 0.50

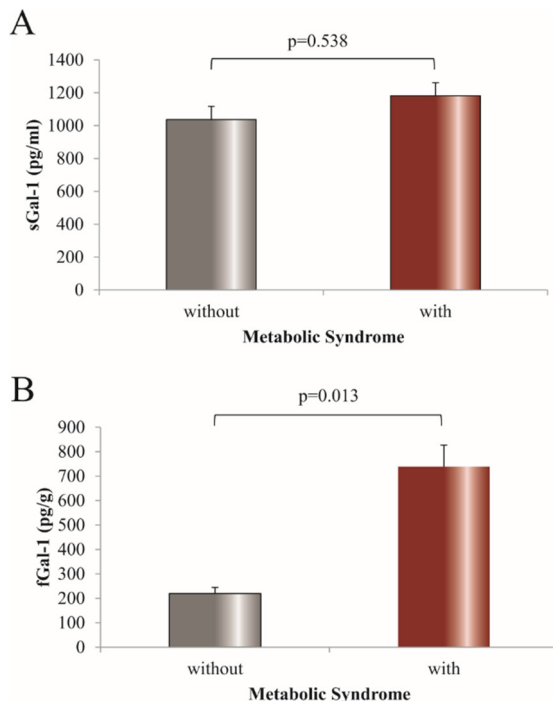
vs 1.75 ± 0.20 ; $p = 0.044$) and eosinophilic infiltration (2.10 ± 0.50 vs 1.50 ± 0.25 ; $p = 0.031$), further supported these observations, suggesting that MetS might attenuate UC severity.

Elevated Galectin-1 Levels and Its Ratio with Pro-Inflammatory Markers in Sera and Fecal Samples of UC Patients with Metabolic Syndrome

We evaluated the concentration of Gal-1 in both the sera and fecal liquid fraction across all UC patients. From previous research, it was demonstrated that patients with MetS displayed a significantly lower serum level of the pro-inflammatory cytokine IL-17 (16). Yet, in the same study, there were no significant differences in systemic concentrations of pro-inflammatory cytokines such as TNF- α and IL-6 between patients with or without MetS. Furthermore, fecal concentrations of these pro-inflammatory cytokines did not significantly differ between the two groups (16).

As illustrated in Figure 1A, no notable difference was observed in systemic concentration of Gal-1 between patients with and without MetS (181.4 ± 110.7 pg/ml vs 1037.0 ± 80.0 pg/ml; $p = 0.538$). Conversely, a significantly higher level of fecal Gal-1 was noted in MetS patients (738.78 ± 88.02 vs 219.07 ± 25.39 ; $p = 0.013$) (Figure 1B).

Figure 1. Galectin-3 (Gal-1) levels in patients with ulcerative colitis (UC) with and without metabolic syndrome (MetS).

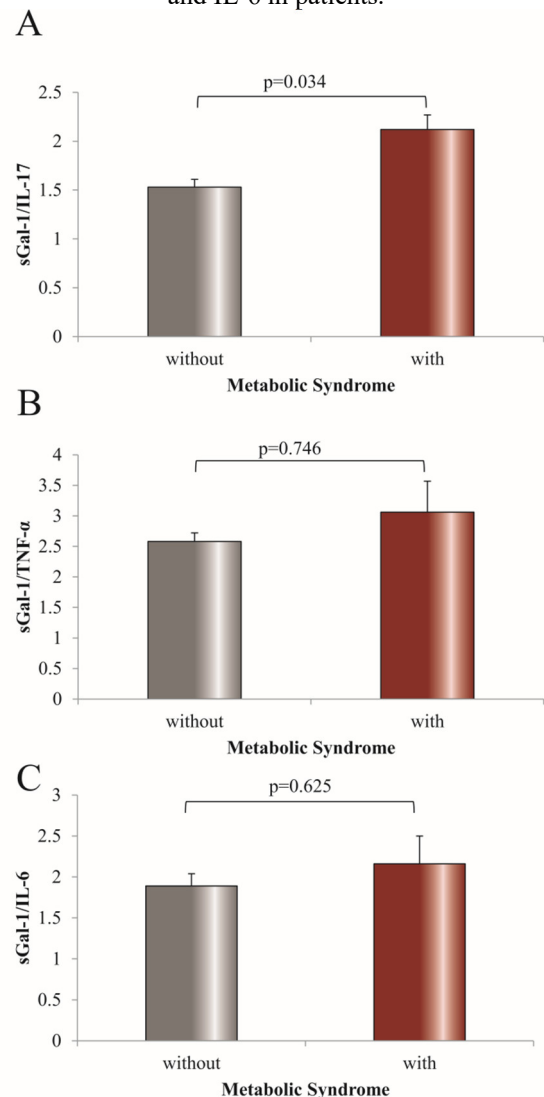


The figure displays serum (A) and fecal (B) Gal-1 values.

The Student's t-test or the Mann-Whitney U test was utilized to assess statistically significant differences, as appropriate. Values are presented as mean $\pm$ standard error of the mean. Note that Gal-1 refers to Galectin-1 in this context.

It is hypothesized that the ratio of counter-regulatory cytokines may serve as a relevant disease indicator. Consequently, we analyzed the interrelationships of the examined biomarkers. Figure 2 presents the relationship between serum levels of Gal-1 and pro-inflammatory cytokines TNF- α , IL-6, and IL-17. There was a significant difference in the ratio of serum Gal-1 to IL-17 (2.12 ± 0.15 vs 1.53 ± 0.08 ; $p = 0.034$) (Figure 2A). The ratios of Gal-1/TNF- α (3.06 ± 0.51 vs 2.58 ± 0.14 ; $p = 0.746$) and Gal-1/IL-6 (2.16 ± 0.34 vs 1.89 ± 0.15 ; $p = 0.625$) were higher in the MetS patient group, albeit not statistically significant (Figures 2B and 2C).

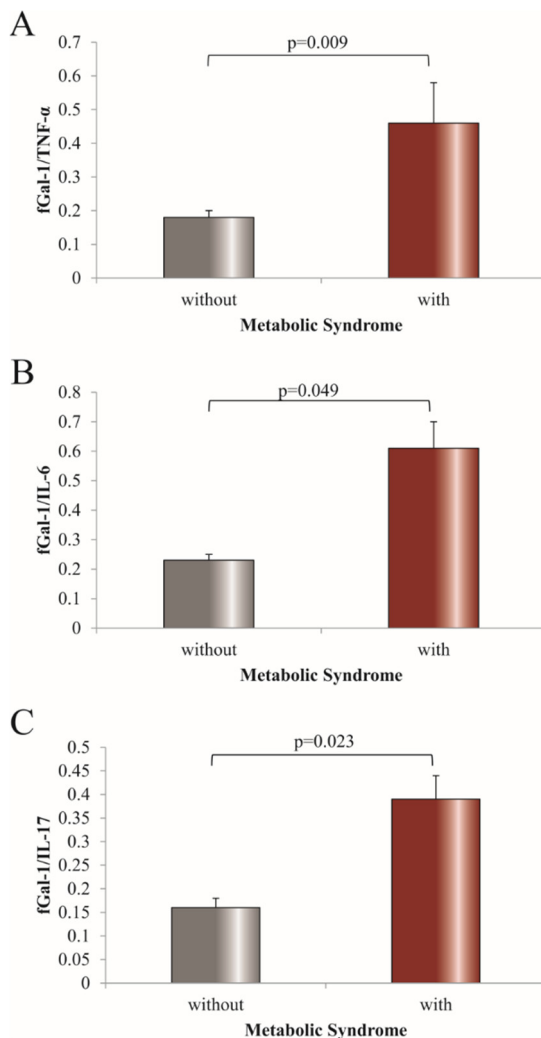
Figure 2. Relationships between serum Gal-1 and pro-inflammatory cytokines TNF- α , IL-17, and IL-6 in patients.



(A) Shows the ratio of serum Galectin-1 to IL-17 (sGal-1/IL-17). (B) Shows the ratio of serum Galectin-1 to TNF- α (sGal-1/TNF- α). (C) Shows the ratio of serum Galectin-1 to IL-6 (sGal-1/IL-6). Statistical significance was tested using the Mann-Whitney U test. Values are presented as mean $\pm$ standard error of the mean. Please note: Tumor necrosis factor α (TNF- α), Interleukin-17 (IL-17), Interleukin-6 (IL-6), and Galectin-1 (Gal-1) are the analytes involved.

As demonstrated in Figure 1B, the concentration of Gal-1 was significantly higher in the feces of individuals with UC and MetS. Subsequently, we determined the ratio of Gal-1 to pro-inflammatory cytokines TNF- α , IL-6, and IL-17 in patient feces. Figure 3A shows that the ratios of Gal-1 to TNF- α were significantly higher in the patient group with MetS (0.46 ± 0.12 vs 0.18 ± 0.02 ; $p=0.009$). Examination of Gal-1/IL-6 in feces (Figure 2B) also revealed significantly higher ratio values ($0.61 \pm 0.09/0.36$ vs $0.23 \pm 0.02/0.20$; $p=0.049$) in patients with MetS. Similar to the Gal-1/IL-17 ratio in serum, this ratio was also statistically higher in UC patients' feces (0.39 ± 0.05 vs 0.39 ± 0.05 ; $p=0.023$). These results indicate a dominance of Gal-1 over pro-inflammatory cytokines in both serum and feces of patients with ulcerative colitis and metabolic syndrome.

Figure 3. Association between fecal Galectin-1 (Gal-1) and pro-inflammatory cytokines TNF- α , IL-17, and IL-6 in patients.



Each patient was evaluated separately. (A) Illustrates the ratio of fecal Galectin-1 to Tumor Necrosis Factor α (fGal-1/TNF- α). (B) Shows the ratio of fecal Galectin-1 to Interleukin-6 (fGal-1/IL-6). (C) Depicts the ratio of fecal Galectin-1 to Interleukin-17 (fGal-1/IL-17).

Statistical significance was determined using the Mann-Whitney U test. Results are presented as the mean $\pm$ standard error of the mean. Please note: Tumor necrosis factor α (TNF- α), Interleukin-17 (IL-17), Interleukin-6 (IL-6), and Galectin-1 (Gal-1) are the analytes involved.

DISCUSSION

In this study, we sought to explore the intersection of Ulcerative Colitis (UC), Metabolic Syndrome (MetS), and their relationship to galectin-1 (Gal-1), a biomarker with proposed immunomodulatory properties. The results of our investigation have revealed several compelling findings that significantly contribute to the existing body of research.

Our study noted elevated levels of creatinine, urea, AST, ALT, triglycerides, and cholesterol in UC patients with MetS compared to those with UC alone, aligning with previous literature and indicating metabolic dysregulation in MetS patients (3, 16). Interestingly, despite these heightened metabolic markers and chronic inflammation typically associated with MetS, the severity of UC was lesser in MetS patients. This is in line with our previous study (16), suggesting a potential interaction between systemic metabolic factors and local gut inflammation that merits further exploration.

Galectin-1, a recently identified peptide primarily released from adipose tissue, has been shown to have anti-inflammatory effects, although its specific function is not precisely defined (17). The aim of our study was to compare the relationship between serum and fecal levels of Gal-1 in relation to metabolic syndrome. Though we found no significant difference in serum concentrations of Gal-1 between UC patients with and without MetS, we observed that patients with MetS had a significantly higher fecal concentration of Gal-1. The reason behind this discrepancy remains unclear, but it might be due to local changes in the gut environment.

Previous studies have reported elevated systemic levels of Gal-1 in metabolic disorders (9). For instance, Acar et al. found significantly higher serum levels of Gal-1 in obese children compared to those of normal weight (18). The level of Gal-1 was significantly increased in the subcutaneous dialysate of patients with type 2 diabetes compared to healthy controls (19). Moreover, the expression of messenger RNA for Gal-1 was found to be increased in the adipocytes of patients with type 2 diabetes (20). In line with these findings, serum Gal-1 was 4.8 times higher in diabetic samples compared to controls (20). These results point to a potential role of Gal-1 in the genesis of metabolic disorders and identify Gal-1 as a new diagnostic marker for these diseases.

In our investigation, we found higher local levels of Gal-1 (Figure 2), and a predominance of Gal-1 over pro-inflammatory cytokines TNF- α , IL-6, and IL-17 (Figures 3 and 4) in patients with metabolic syndrome. Galectin-1 can function both intracellularly and extracellularly following secretion (21). Soluble Gal-1 interacts with fibronectin, integrin, laminin, and Vascular Endothelial Growth Factor Receptor 2

(VEGFR2) receptors, consequently triggering proliferation, adhesion, migration, or angiogenesis (22, 23). The role of Gal-1 in the onset, progression, and resolution of inflammation is well-defined (24). Earlier studies have revealed that Gal-1 inhibits cell growth and induces apoptosis of activated leukocytes (25). Previous work has also shown that Gal-1 directs the acquired immune response towards type 2, concurrently inhibiting the secretion of Interferon-gamma (IFN γ), TNF α , IL-2, and IL-12 while facilitating the production of type 2 cytokine IL-5 (26, 27). Some studies suggest that Gal-1 may inhibit effector T lymphocytes and consequently suppress the potent immune response initiated by pro-inflammatory cytokines (28). The anti-inflammatory properties of Gal-1 have been confirmed in several models of chronic inflammatory and autoimmune diseases, including experimental autoimmune encephalomyelitis, arthritis, uveitis, hepatitis, and diabetes (29, 30). The use of human recombinant galectin-1 induces reduced secretion of type 1 cytokines (TNF- α , IL-1 β , IL-12, and IFN- γ) and inflammation suppression in the digestive tract, specifically through the induction of apoptosis in IFN- γ -producing effector T lymphocytes (31). Increased concentration and predominance of the immunosuppressive activity of Gal-1 restrict the local chronic inflammatory response by inhibiting the activity of infiltrating leukocytes and the secretion of inflammation mediators.

A recent study showed that inflammation, accompanied by the production of pro-inflammatory cytokines (IL-1 β , TNF, IL-13), intensifies the binding of Gal-1 to enterocytes and subsequent modulation, which triggers a compensatory effect on enterocytes to protect the epithelium and restore intestinal homeostasis (32). Increased concentration of Gal-1 may be the sign of its protective effect on local intestinal mucosa.

CONCLUSION

Our study substantiates the critical role of galectin-1 (Gal-1) in the pathogenesis of metabolic syndrome (MetS) and ulcerative colitis (UC). We noted increased Gal-1 levels, both systemically and locally, among individuals with MetS, suggesting that Gal-1 might exert a protective and immunosuppressive effect in these conditions. This elevation in Gal-1 concentrations could represent a physiological response aimed at mitigating the chronic low-grade inflammation inherent in MetS and UC. This observation underscores the potential of Gal-1 as a novel diagnostic marker and a potential therapeutic target in the management of MetS and UC. Our findings pave the way for further investigation into the role of Gal-1 in these conditions and warrant further studies to elucidate the therapeutic potential of modulating Gal-1 in the management of UC and MetS.

ACKNOWLEDGMENTS

We would like to acknowledge the invaluable contributions and support of all individuals and institutions involved in this research.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest regarding this research on the modulatory role of Galectin-1 in Ulcerative Colitis with comorbid Metabolic Syndrome.

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