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Expression of Gut Microbiota-Derived Metabolites and Their Association with Mucosal Inflammation in Ulcerative Colitis Patients

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ABSTRACT

Background
Ulcerative colitis (UC) is a chronic inflammatory bowel disease marked by mucosal inflammation and disruption of gut microbial homeostasis. Emerging evidence highlights the significance of gut microbiota-derived metabolites, including short-chain fatty acids (SCFAs) and tryptophan derivatives, in modulating intestinal inflammation and mucosal integrity.

Objective
To investigate the concentrations of key gut microbial metabolites in UC patients and evaluate their association with histological inflammation severity

Methodology
a cross-sectional study was conducted on 110 patients diagnosed with UC. Baseline clinical data were recorded, including disease duration, severity (based on histology using the Geboes scoring system), and medication history. Fecal samples were analyzed for levels of butyrate, propionate, acetate, indole-3-propionic acid (IPA), deoxycholic acid (DCA), and trimethylamine-N-oxide (TMAO) using standard biochemical methods. Correlations between metabolite levels and mucosal inflammation scores were analyzed using Pearson's correlation, and comparisons across severity groups were assessed with Mann-Whitney U and ANOVA tests.

Results
The mean levels of butyrate (8.9 ± 2.1 µmol/g), propionate (6.5 ± 1.6 µmol/g), and IPA (2.0 ± 0.6 µmol/g) were significantly below normal reference ranges. Butyrate and IPA showed moderate to strong negative correlations with histological inflammation ($r = -0.54$ and -0.62; $p < 0.001$). TMAO was positively correlated with inflammation severity ($r = 0.31$, $p = 0.002$) and significantly elevated in moderate/severe cases (6.1 ± 1.9 µmol/g vs. 4.8 ± 1.6 µmol/g, $p = 0.006$).

Conclusion
UC patients exhibited reduced levels of beneficial microbial metabolites, particularly SCFAs and IPA, which were inversely associated with inflammation severity. These findings support the potential role of microbiota-targeted therapies in UC management.

Keywords: Ulcerative colitis, gut microbiota, short-chain fatty acids, indole-3-propionic acid, mucosal inflammation, TMAO, Geboes score

INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) characterized by continuous mucosal inflammation, primarily affecting the colon and rectum.[1] Although the precise etiology of UC remains elusive, it is increasingly recognized that a complex interplay between genetic susceptibility, immune dysregulation, environmental factors, and the gut microbiome contributes to disease pathogenesis.[2] Among these, the role of gut microbiota and their metabolic by-products has gained significant attention in recent years, as advances in metagenomics and metabolomics have revealed a strong link between microbial composition, metabolite production, and mucosal immune responses in UC patients.[3]

The gut microbiota consists of trillions of microorganisms that maintain intestinal homeostasis through metabolic, immunological, and barrier-supporting functions. Dysbiosis, an imbalance in the gut microbial community, has been consistently observed in UC and is characterized by reduced microbial diversity and depletion of beneficial commensals such as Faecalibacteriumprausnitzii and Bifidobacterium species alongside an enrichment of pro-inflammatory pathobionts such as Escherichia coli and Enterococcus faecalis.[4] These microbial shifts are not only structural but also functional, resulting in altered production of microbial metabolites with immunomodulatory properties.

Among the most studied gut microbiota-derived metabolites are short-chain fatty acids (SCFAs), bile acids, tryptophan metabolites, and trimethylamine N-oxide (TMAO). SCFAs, particularly butyrate, acetate, and propionate, are generated through bacterial fermentation of dietary fibers and play a crucial role in maintaining epithelial integrity, modulating mucosal immune responses, and suppressing inflammation.[5] In UC, decreased levels of SCFAs, especially butyrate, have been associated with impaired regulatory T-cell activity and increased intestinal permeability, contributing to disease flare-ups and chronic mucosal injury.[6]

The interaction between these microbial metabolites and host mucosal immunity is of paramount interest in UC research. Metabolites can directly influence epithelial cells, dendritic cells, macrophages, and lymphocytes within the gut mucosa, thereby shaping the cytokine milieu and inflammatory cascades.[7] Disruption in this metabolite-immune axis is believed to perpetuate the inflammatory state in UC.[8] Recent studies using metabolomics profiling in stool and serum samples of UC patients have revealed specific metabolite signatures that correlate with disease severity, histological inflammation, and response to therapy.[9]

Despite these advancements, there is a need for further research to delineate the expression patterns of gut microbiota-derived metabolites in UC and to establish their mechanistic association with mucosal inflammation. Understanding these molecular interactions may not only provide insights into disease pathogenesis but also open avenues for novel diagnostic biomarkers and metabolite-targeted therapeutic strategies. Therefore, this study aims to evaluate the expression of key gut microbiota-derived metabolites and investigate their association with histological and endoscopic markers of mucosal inflammation in patients with ulcerative colitis.

METHODOLOGY

This study was designed as a cross-sectional analytical study aimed at evaluating the expression of gut microbiota-derived metabolites and their association with mucosal inflammation in patients diagnosed with ulcerative colitis (UC). The study was conducted in the Department of Pathology, Ayub Medical College, Abbottabad. The total duration of the study was six months, from 1st December 2023 to 30th May 2024.

A total of 110 patients were enrolled in the study. The sample size was calculated using standard statistical methods, keeping a confidence level of 95%, a margin of error of 5%, and an estimated prevalence of altered metabolite expression of 32.7% among UC patients.10 A non-probability purposive sampling technique was employed. Patients fulfilling the inclusion criteria were consecutively recruited from the outpatient and inpatient departments of gastroenterology and surgery.

The inclusion criteria involved patients aged 18 to 65 years, clinically and endoscopically diagnosed cases of ulcerative colitis, those with recent colonoscopic biopsies available for analysis, and those who consented to participate in the study. Patients with Crohn's disease or indeterminate colitis, those with the use of antibiotics or probiotics within the past 4 weeks, those with a history of recent gastrointestinal surgery, those with systemic infections, malignancies, or other autoimmune diseases, and pregnant or lactating females were excluded from the study.

After obtaining ethical approval from the Institutional Review Board of Ayub Medical College, written informed consent was obtained from each patient. Clinical history, demographic information, and relevant medical records were reviewed. Fresh stool samples were collected in sterile containers. Samples were immediately stored at –80°C to preserve metabolite integrity until further analysis. Formalin-fixed paraffin-embedded (FFPE) colonic biopsy tissues were retrieved from the pathology archives for mucosal inflammation scoring and histopathological confirmation.

Stool samples were processed for metabolomic profiling using high-performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS). The targeted metabolites included short-chain fatty acids (SCFAs): Butyrate, propionate, acetate, tryptophan metabolites: Indole-3-propionic acid, indole-3-acetic acid, secondary bile acids: Deoxycholic acid, lithocholic acid, and other markers: Trimethylamine-N-oxide (TMAO).

Hematoxylin and eosin (H&E)-stained colonic biopsy sections were evaluated by a qualified pathologist blinded to the metabolite results. Geboes' score was used to grade mucosal inflammation.[11] Patients were classified based on severity: mild, moderate, or severe inflammation. Data were entered into a structured proforma that included demographic details, clinical presentation, medication history, metabolite concentrations, and histological inflammation scores.

Data were analyzed using SPSS version 26. Descriptive statistics (mean ± SD) were calculated for continuous variables, and frequencies (%) were calculated for categorical variables. Correlation analysis was performed using Pearson correlation to assess associations between metabolite levels and mucosal inflammation scores. Mann-Whitney U tests were applied to compare metabolite levels between patients with mild versus moderate/severe inflammation. ANOVA tests were used for multiple group comparisons. A p-value of <0.05 was considered statistically significant.

RESULT

The study included 110 patients diagnosed with ulcerative colitis. The mean age of participants was 41.3 ± 11.9 years, with a nearly equal gender distribution: 57 (51.8%) males and 53 (48.2%) females. The average disease duration was 4.8 ± 2.8 years. Based on histological scoring using the Geboes system, 36 (32.7%) patients had mild inflammation, 46 (41.8%) had moderate, and 28 (25.5%) had severe inflammation. Regarding treatment, 71 (64.5%) of the patients were receiving immunosuppressants, while 82 (74.5%) were on 5-aminosalicylic acid (5-ASA) therapy. Only 13 (11.8%) had used antibiotics in the past three months. (Table 1)

Analysis of gut microbiota-derived metabolites showed that the mean butyrate concentration was 8.9 ± 2.1 µmol/g, which was below the normal reference range of 10–15 µmol/g. Propionate and acetate levels were 6.5 ± 1.6 µmol/g and 17.6 ± 3.4 µmol/g, respectively—both falling toward the lower end of their respective normal ranges. Indole-3-propionic acid (IPA), a tryptophan metabolite with anti-inflammatory properties, was also reduced (2.0 ± 0.6 µmol/g; normal: 2.5–4.0 µmol/g). In contrast, trimethylamine-N-oxide (TMAO), which has been implicated in inflammatory processes, showed a mean value of 5.7 ± 1.8 µmol/g, approaching the upper normal limit (<6 µmol/g). Deoxycholic acid (DCA) levels were within normal limits (3.2 ± 1.0 µmol/g). (Table 2)

Correlation analysis revealed that higher mucosal inflammation (as assessed by Geboes score) was significantly associated with lower concentrations of butyrate ($r = –0.54$, $p < 0.001$), propionate ($r = –0.38$, $p = 0.001$), acetate ($r = –0.21$, $p = 0.045$), and IPA ($r = –0.62$, $p < 0.001$). Conversely, TMAO showed a weak but statistically significant positive correlation with inflammation ($r = 0.31$, $p = 0.002$), while DCA did not correlate significantly ($p = 0.270$). (Table 3)

Further comparisons between patients with mild disease (n = 36) and those with moderate to severe inflammation (n = 74) demonstrated significantly lower metabolite levels in the latter group. Butyrate was markedly reduced in moderate/severe cases (8.2 ± 1.9 µmol/g) compared to mild cases (10.4 ± 1.8 µmol/g; $p < 0.001$). Similar trends were seen for propionate (6.1 ± 1.5 vs. 7.2 ± 1.3 µmol/g; $p = 0.002$) and IPA (1.8 ± 0.6 vs. 2.4 ± 0.5 µmol/g; $p < 0.001$). In contrast, TMAO was significantly elevated in patients with more severe inflammation (6.1 ± 1.9 vs. 4.8 ± 1.6 µmol/g; $p = 0.006$). (Table 4)

ANOVA confirmed these trends across the three histological severity groups, with significant variation in butyrate ($F = 9.85$, $p < 0.001$), propionate ($F = 5.48$, $p = 0.006$), IPA ($F = 11.32$, $p < 0.001$), and TMAO ($F = 4.91$, $p = 0.009$) levels. Post hoc Tukey analysis highlighted a stepwise decline in beneficial metabolites with increasing inflammation severity (Severe < Moderate < Mild), while TMAO showed a progressive increase (Severe > Mild). These findings underscore the inverse relationship between

beneficial microbial metabolites and intestinal inflammation in UC patients, along with a potentially pro-inflammatory role of TMAO. (Table 5)

Table 1: Baseline Characteristics of Ulcerative Colitis Patients (n = 110)

Variable	Mean ± SD / n (%)
Age (years)	41.3 ± 11.9
Gender	
Male	57 (51.8%)
Female	53 (48.2%)
Duration of Disease (years)	4.8± 2.8
Disease Severity (Histology)	
Mild	36 (32.7%)
Moderate	46 (41.8%)
Severe	28 (25.5%)
Current Use of Immunosuppressants	71 (64.5%)
Use of 5-ASA	82 (74.5%)
History of Antibiotic Use (last 3 months)	13 (11.8%)
This table shows the demographic and clinical characteristics of UC patients included in the study. Disease severity was based on histological evaluation using Geboes scoring.	

Table 2: Mean Concentrations of Gut Microbiota-Derived Metabolites in UC Patients

Metabolite	Mean ± SD (µmol/g)	Reference Range (Normal)*
Butyrate	8.9 ± 2.1	10–15
Propionate	6.5 ± 1.6	5–10
Acetate	17.6 ± 3.4	15–25
Indole-3-propionic acid (IPA)	2.0 ± 0.6	2.5–4.0
Deoxycholic acid (DCA)	3.2 ± 1.0	2–5
Trimethylamine-N-oxide (TMAO)	5.7 ± 1.8	<6
**Reference ranges are approximate values obtained from healthy control profiles reported in previous microbiota-metabolite studies. The mean values indicate a relative reduction in beneficial SCFAs and tryptophan metabolites in UC patients.*		

Table 3: Correlation between Metabolite Levels and Mucosal Inflammation Scores (Geboes Score)

Metabolite	Pearson's r	p-value	Interpretation
Butyrate	–0.54	<0.001	Moderate negative correlation
Propionate	–0.38	0.001	Weak negative correlation
Acetate	–0.21	0.045	Weak negative correlation
Indole-3-propionic acid	–0.62	<0.001	Strong negative correlation
Deoxycholic acid	0.10	0.270	Not significant
TMAO	0.31	0.002	Weak positive correlation
**Negative correlations indicate that higher metabolite concentrations are associated with lower mucosal inflammation severity. Statistical significance: $p < 0.05$*			

Table 4: Comparison of Metabolite Levels between Mild and Moderate/Severe UC Patients (Mann-Whitney U Test)

Metabolite	Mild (n = 36) Mean ± SD	Moderate/Severe (n = 74) Mean ± SD	p-value
Butyrate (µmol/g)	10.4 ± 1.8	8.2 ± 1.9	<0.001
Propionate (µmol/g)	7.2 ± 1.3	6.1 ± 1.5	0.002
Indole-3-propionic acid	2.4 ± 0.5	1.8 ± 0.6	<0.001
TMAO (µmol/g)	4.8 ± 1.6	6.1 ± 1.9	0.006
Mann-Whitney U test revealed significantly lower levels of beneficial metabolites in patients with higher inflammation severity. TMAO was significantly elevated in moderate/severe cases. $p < 0.05$is considered as significant.			

Table 5: Metabolite Levels According to Histological Inflammation Severity

Metabolite	F-statistic	p-value	Post Hoc (Tukey) Comparison
Butyrate	9.85	<0.001	Severe < Moderate < Mild
Propionate	5.48	0.006	Severe < Mild
Indole-3-propionic acid	11.32	<0.001	Severe < Moderate < Mild
TMAO	4.91	0.009	Severe > Mild
ANOVA revealed significant variation in metabolite levels across inflammation grades. Tukey's post hoc test confirmed statistically significant group differences. $p < 0.05$ is considered as statistically significant.			

DISCUSSION

This study evaluated the levels of gut microbiota-derived metabolites in ulcerative colitis (UC) patients and their correlation with histological inflammation. The key findings include significantly reduced levels of beneficial short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, as well as indole-3-propionic acid (IPA), in patients with moderate to severe inflammation. Conversely, the pro-inflammatory metabolite trimethylamine-N-oxide (TMAO) was significantly elevated in patients with greater histological disease severity.

Our findings are consistent with prior research demonstrating the role of microbial dysbiosis and metabolite imbalances in UC pathophysiology.[12] Butyrate, known for its anti-inflammatory and mucosal healing properties, was significantly lower in moderate and severe UC patients (mean: 8.2 ± 1.9 µmol/g) compared to those with mild disease (mean: 10.4 ± 1.8 µmol/g). This aligns with studies by He et al. (2021) and Zhaoet al. (2021), which reported reduced butyrate-producing bacteria (such as Faecalibacteriumprausnitzii) in UC patients, correlating with lower fecal butyrate levels and increased mucosal inflammation.[13, 14] Butyrate acts through mechanisms such as inhibition of histone deacetylases and enhancement of regulatory T cell activity, both of which are compromised in inflamed colonic mucosa.

Similarly, propionate and acetate, other SCFAs derived from microbial fermentation, were also significantly reduced in patients with more severe inflammation. Although their anti-inflammatory roles are less potent than butyrate, studies like that of Bilotta et al. (2021) have suggested that propionate contributes to epithelial barrier integrity and immune regulation, further supporting our observations.[15]

The significantly lower levels of indole-3-propionic acid (IPA) in moderate/severe UC patients (1.8 ± 0.6 µmol/g vs. 2.4 ± 0.5 µmol/g in mild UC; $p < 0.001$) are noteworthy. IPA, a tryptophan-derived metabolite produced by Clostridium sporogenes and other anaerobes, has been shown to activate the pregnane X receptor (PXR), thereby exerting anti-inflammatory effects and maintaining gut barrier function. Our findings are supported by studies such as Gao et al. (2025), which reported reduced serum and fecal IPA in active UC patients. These reductions suggest a compromised microbial capacity for tryptophan metabolism in dysbiotic states.[16]

Interestingly, TMAO, a metabolite derived from dietary choline and carnitine metabolism, was elevated in moderate/severe UC cases (6.1 ± 1.9 µmol/g vs. 4.8 ± 1.6 µmol/g in mild UC; $p = 0.006$), and positively correlated with inflammation severity ($r = 0.31$, $p = 0.002$). While TMAO is more commonly studied in the context of cardiovascular disease, recent research by Wang et al., 2023 has implicated elevated TMAO in promoting systemic and gut inflammation by enhancing cytokine production and impairing epithelial function.[17] Our findings support the growing evidence of TMAO's role in gut inflammation, although causality remains to be established.

Deoxycholic acid (DCA) levels were not significantly associated with inflammation in our cohort, echoing mixed findings in the literature. While some studies suggest a protective role of secondary bile acids like DCA in gut homeostasis, others have shown pro-inflammatory effects depending on concentration and context.[18] In our cohort, DCA levels remained within the normal range and showed no significant correlation with disease severity, suggesting a limited role in UC pathogenesis, at least in the active phase.

Overall, our results emphasize the importance of microbial metabolites as both indicators and potential modulators of intestinal inflammation in UC. The inverse correlations of SCFAs and IPA with mucosal inflammation reinforce their therapeutic potential, as seen in trials investigating butyrate enemas and dietary modulation. Meanwhile, the positive correlation of TMAO with disease severity points toward emerging metabolic biomarkers of UC activity.

Mechanisms like inhibition of lipolysis in adipose tissue or inducing stress in β-cells (Zhang, 2012). Additionally, the manner in which ANGPTL8 increased for Pakistani women compared to outcome trajectories in Western populations (Wang et al., 2021) reinforces the idea that there are ethnic differences in the pathophysiology of GDM that could in part relate to the higher visceral adiposity in South Asians as well as the β-cell stress that this entails (Ahmed et al., 2022). This notion of ANGPTL8 contributing to IR via inhibition of insulin receptor signalling in skeletal muscle (Abu-Farha et al.,, 2016), potentially connects with known genetic predispositions for populations who experience heightened metabolic dysregulation.

The rs2278426 SNP (T allele), associated with a 2.1-fold impendency of GDM in our cohort, highlights the genetic basis for ANGPTL8 dysregulation in South Asians. This polymorphism has evidence for differences in the ANGPTL8 promoter activity (Dewey et al., 2016) and it may also compound the effect of high carbohydrate intake which is commmon in Pakistan on IR (the rs2278426 T allele variant could exacerbate IR). Also, we found that carbohydrate-rich diets independently increased ANGPTL8 levels in our analyses ($\beta = 0.23$) as also seen in mouse studies where the addition of glucose led to increased ANGPTL8 expression (Gusarova et al., 2015). Finally, socioeconomic differences (SES) further exacerbate risks about GDM: women with low SES had ANLPTL8 levels that were 15% greater than those of women with higher SES likely due to less available nutrient dense food and less access to prenatal healthcare. These findings illuminate the syndemic nature of GDM in Pakistan where biological, environmental, and structural contributors interact to drive metabolic dysfunction.

The high predictive performance of ANGPTL8 in the third trimester for postpartum dysglycemia (AUC=0.84) makes it a potential tool for risk stratification. Adding the screening of ANGPTL8 levels to routine prenatal care could identify pregnant women at high risk earlier so follow-up postpartum monitoring can be directed towards them. This is particularly important in Pakistan, where only 32% of women with gestational diabetes mellitus (GDM) are performed glucose tolerance testing (Ali et al., 2021). If the Lady Health Workers (LHW) of Pakistan were to adopt ANGPTL8 testing and training, this could help to reduce the urban-rural healthcare gap, especially in areas that do not have any specialized outreach. In addition to this, our findings on dietary factors suggest that culturally relevant interventions, such as replacing refined grains with lower glycemic index, could help improve ANGPTL8-induced insulin resistance (IR).

Limitations

Despite the robust associations observed, this study has several limitations. First, it is a cross-sectional design, which limits causal inference. Second, we did not include a healthy control group for direct comparison of metabolite levels. Third, dietary intake and other confounders affecting metabolite concentrations were not systematically controlled. Lastly, microbial profiling was not performed, which could have provided a clearer link between microbial species and metabolite production.

CONCLUSION

The present study confirms that UC patients exhibit distinct alterations in gut microbial metabolites, with significant reductions in anti-inflammatory compounds (butyrate, propionate, acetate, and IPA) and elevated levels of the potentially pro-inflammatory metabolite TMAO. These changes correlate with histological inflammation severity and support the potential role of microbial metabolomics in disease monitoring and targeted therapy in ulcerative colitis.

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