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The Effect of Probiotic Supplementation on Serum Interleukin -23 Levels among Ulcerative Colitis Patients: a Pilot Study and Secondary Output

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Abstract

Background and aims: Interleukin (IL)-23 has gained particular attention as a proinflammatory cytokine playing key roles in the pathogenesis of ulcerative colitis. Recently, probiotics have been used more frequently in treating ulcerative colitis for induction and maintenance of remission. This study aimed to evaluate the effect of probiotic supplementation on IL-23 levels after remission induction in mild-to-moderately active ulcerative colitis patients in Jordan.

Methods: This is a pilot, multicenter, randomized, placebo-controlled, double-blind parallel-arms study. Twenty-four ulcerative colitis patients (11 men, 13 women) were randomly assigned to receive 3×10^{10} probiotic 10 billion active cells or three capsules of placebo daily for six weeks. Partial mayo score and serum level of IL-23 were measured at baseline and after six weeks.

Results: There was a significant difference in the mean Partial Mayo score between the probiotic group and the placebo group at the end of the study (1.33 ± 0.49 vs 3.42 ± 1.78) ($p<0.001$). The probiotics' IL-23 level was insignificantly reduced compared to the placebo group ($p>0.05$). Similarly, there were no significant differences in the mean or percentage change in the IL-23 level between the two groups ($p>0.05$).

Conclusions: Probiotic supplementation had an insignificant suppressive effect on IL-23 levels. However, it still offered a beneficial therapeutic effect for patients with ulcerative colitis, as evidenced by an improvement in the Partial Mayo score.

Keywords: Ulcerative colitis, Probiotics, Interleukin-23

INTRODUCTION

Inflammatory bowel diseases (IBD) are systemic immune-mediated conditions associated with inflammation of the gut tissue, including Crohn's disease (CD) and ulcerative colitis (UC) [1]. IBDs commonly affect young adults, leading to considerable consequences impacting their quality of life

[2,3]. The pathogenesis remains uncertain, but studies have approved a clear interaction of complicated mechanisms causing an imbalance between pro- and anti-inflammatory signaling [4,5]. Both innate and adaptive immune systems are tightly involved in the pathogenesis of IBD6.

The dominant pro-inflammatory cytokine that plays a key role in IBD pathogenesis is tumor necrosis factor (TNF)-α^7. Recently, the interleukin (IL)-23 and IL-23/IL-17 axes have gained particular attention as proinflammatory cytokines play key roles in modulating mucosal immunity and triggering and maintaining chronic intestinal inflammation [8-10]. IL-23 is a proinflammatory cytokine, expressed mainly in T cells, natural killer (NK) cells, and natural killer T (NKT) cells [11]. It has a key role in the pathogenesis of several immune-mediated inflammatory diseases via recruiting several inflammatory cells and Th17 cells. IL-23 is essential for differentiating CD4 T naïve cells into Th17 cells [12,13]. It promotes Th17 cells to produce TNF-a, IL-17, IL-6, IL-22, granulocyte-macrophage colony-stimulating factor, and other novel factors known to be associated with initiating autoimmune inflammation [13,14]. Increased expression of the IL-23p19 gene was reported to have a role in the pathogenesis of ulcerative colitis [15].

IBD treatment is a multi-disciplinary process that continually needs adjuvant and alternative options to enhance pharmacological treatment [16]. Probiotics are one of these options that are being extensively explored. With the growth of evidence supporting the vital role of microbiota in gut homeostasis [17], probiotics have been more frequently used in treating IBD and in the induction of remission [18] . However, whether there is a role or how probiotics can modulate Th17 cell fate in the gut remains weakly realized. The proposed mechanism of how probiotics work in UC is shown (Figure 1). It is suggested that administration of *L. acidophilus* suppresses Th17 cell-mediated secretion of pro-inflammatory cytokine IL-17 through downregulation of IL-23, TGFβ1 expression, and downstream phosphorylation of p-STAT3 [18].

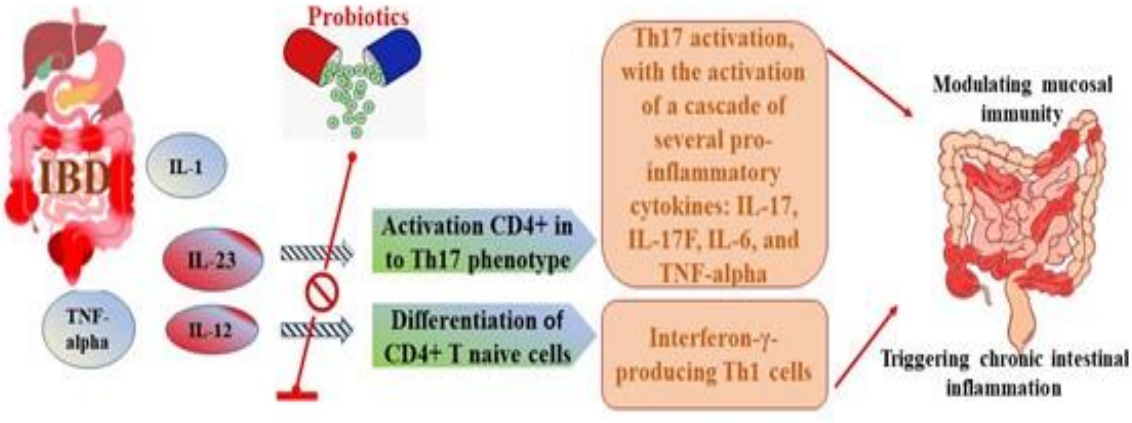

Figure 1. Probiotics suppress Th17 cell-mediated secretion of pro-inflammatory cytokine IL-17 through downregulation of IL-23. Abbreviations: CD4+, cluster of differentiation 4; IL, interleukin; IBD, inflammatory bowel disease; TNF, tumor necrosis factor

Also, administration of *Bifidobacterium breve* and *Lactobacillus rhamnosus* GG probiotics inhibits lipopolysaccharide-(LPS—) activated expression of IL-23 in cultured intestinal cells via inhibition of histone acetylation and enhancement of DNA methylation [19].

In this study, we aimed to evaluate the effects of probiotic supplementation on IL-23 levels after remission induction in mild-to-moderately active UC patients in Jordan. This is the first study to assess the probiotic effect of IL-23 in UC in humans.

MATERIALS AND METHODS

Study protocol and population

This study is a pilot, multicenter, randomized, placebo-controlled, double-blind parallel-arms conducted between 13th January 2020 and 10th March 2022, completed during the COVID-19 pandemic at the Hospital of Jordan University of and Al Basher Hospital. It was approved by the Institutional Review Board of Jordan University Hospital and Al-Bashir Hospital and by the Deanship of Academic Research at The University of Jordan, Amman, Jordan. Also, it was registered at ClinicalTrials.gov with the number NCT04223479. The Declaration of Helsinki informed the study. Informed consent was obtained from all patients who agreed to participate in the study.

Patients were included in the study if they were adults aged between 18-65 years with mild to moderate UC (as defined by Modified Mayo Disease Activity Index [PMS] score 3–9) and were on 5-ASA with or without azathioprine for at least three months). The exclusion criteria were concurrent enteric infection; use of antibiotics within the past two weeks; receiving biological treatment; change in the dose of oral 5-ASA within the past four weeks; use of rectal 5-ASA or steroids within seven days before entry into the study; hospitalization need; imminent need for surgery; lactating and pregnant women; those who received any investigational medicines within three months; and patients with significant hepatic, renal, endocrine, respiratory, neurological, or cardiovascular diseases.

The patients who met the eligibility criteria and agreed to participate were randomly assigned to receive either 3×10^{10} of probiotic 10 billion active cells© (Jamieson Laboratories, Canada N8W5B5) capsules (each capsule containing (1×10^{10} CFU/g) of *Lactobacillus paracasei* (A234) (1.5×10^{9}), *Lactobacillus gasseri* (A237) (1×10^{9}), *Lactobacillus rhamnosus* (A119) (1×10^{9}), *Lactobacillus rhamnosus* (A193) (1×10^{9}), *Lactobacillus acidophilus* (A118) (0.5×10^{9}), *Lactobacillus Plantarum* (A138) (0.5×10^{9}), *Lactobacillus casei* (A179) (0.3×10^{9}), *Lactobacillus reuteri* (A113) (0.3×10^{9}), *Lactococcus lactis* (A328) (0.2×10^{9}), *Bifidobacterium animalis subsp. Lactis* (A026) (2×10^{9}), *Bifidobacterium breve* (A055) (1×10^{9}), *Bifidobacterium longum* subsp. *Longum* (A027) (0.39×10^{9}), *Bifidobacterium bifidum*(A058) (0.3×10^{9}), *Bifidobacterium longum* subsp. *Infantis* (A041) (0.01×10^{9}) species.) Or three capsules of placebo (containing polysaccharide) daily for six weeks. Probiotic 10 Billion Active Cell© contains all eight strains in VSL#3, an internationally recognized probiotic supplement unavailable in Jordan. VSL#3 has been used in studies involving the UC Disease Activity Index to assess clinical activity and is among the most studied probiotic strains. Moreover, VSL#3 has been reported to be safe and effective in achieving clinical response and inducing clinical remission in mild-to-moderately active ulcerative colitis, with a reported response rate of 77% [20-22].

The randomizations were done using a

website-generated random number table (www.randomization.com), stratified by sex. The randomization number was strictly given according to the order of the patient's enrollment, with each patient assigned the first available number on the randomization list. Randomization was carried out in a double-blind manner using 1:1 allocation to the two groups. The physicians, patients, health care providers, lab technicians, and researchers were all blinded for treatment.

Data collection and IL-23 measurements

An interviewer-administered structured questionnaire collected data on age, body weight, education level, previous and current health problems, family history of IBD, physical activity, and use of supplements. A 10-ml venous blood sample was collected on a yellow-capped serum separator tube with inert barrier gel and clot activator (plain tube) from the participants. The blood samples were left clotted at room temperature (25°C) for 15 minutes, then centrifuged at 4000 rpm for 15 minutes at four °C (Centrifuge Rotina 38R, Hettichi, Germany). The separated serum was placed in an Eppendorf tube for automated analysis. IL-23 in serum samples was measured by a two-site sandwich Enzyme-Linked Immunosorbent Assay (ELISA) using a commercially available kit (Human IL-23 ELISA Kit, PicoKine™, USA).

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Science (IBM® SPSS® Statistics; Version 21.0, version for Windows, 2019, USA). The mean and standard error of the mean (SEM) were calculated for the continuous variables. Frequencies and percentages were used to describe categorical variables. To ensure the normal distribution of continuous variables, the Shapiro-Wilk test was applied. Independent samples T-test was used to detect differences between placebo and probiotics groups regarding constant variables. A paired *t*-test assessed within-group changes in IL-23 levels from baseline to end line. A P value < 0.05 was considered statistically significant.

RESULTS

Thirty consecutive adult UC patients met the inclusion criteria and agreed to participate in the study. However, only 24 patients completed the study (11 men, 13 women). Six patients dropped out due to a lack of follow-up or discontinued the intervention (change in medication type or dose; pregnancy).

The general characteristics of the twenty-four UC patients are presented in Table 1. The mean age was (39.0 ± 14), 54.2% of patients were female, 70% had no other comorbidities, and half were non-smokers. The mean PMS score at the baseline was 4.7 ± 1.3 for the probiotic group vs. 4.3±1.8 for the placebo group (p =0.479). The mean PMS score after the intervention was significantly different for probiotics (1.33 ± 0.49) compared to the placebo group (3.42 ± 1.78) (p<0.001). The other biochemical parameters (CRP, TNF-a, IL-6, 1, and 10) were published elsewhere [23]. However, the mean percent of change for CRP was -4.31 ± 9.60 for the probiotics group and 3.2 ± 5.17 for the placebo group (p =0.040), for IL-6, was 14.73 ± 13.71 for the probiotics group and 5.94 ± 12.48 for the placebo group (p =0.174), for IL-1 was 19.00 ± 49.85 for the probiotics group and 13.60 ± 40.51 for the placebo group (p =0.787), for IL-10, was 38.91 ± 44.26 for the probiotics group and -10.54 ± 44.90 for the placebo group (p =0.024), TNF-a was 5.45 ± 24.02 for the probiotics group and -0.84 ± 23.29 for the placebo group (p =0.550).

Table 1. General Characteristics of Participants (n=24)

Variables	mean±SEM
PMS score	4.13 ± 1.26
Age (year)	39.42 ± 11.0
Physical activity (MET-minutes/weeks)	4454.74 ± 1273.2
Body Mass Index (Kg/m^2)	24.94 ± 6.3
Variables	**N (%)**
Sex	
Male	11 (45.8)
Female	13 (54.2)
Marital status	
Married	18 (75.0)
Single	6 (25.0)
Education	
primary education	4 (16.7)
Secondary education	5 (20.8)
Diploma	2 (8.3)
Bachelor/master	13 (54.2)
Working status	
Yes	12 (50.0)
No	12 (50.0)
Physical activity level	
Light intensity activities	2 (8.7)
Moderate intensity activities	17 (73.9)
Vigorous-intensity activities	4 (17.4)
Smoking	
Yes	4 (16.7)
No	12 (50.0)
Previous	1 (4.2)
Passive	7 (29.2)
Hookah uses	
Yes	6 (25.0)
No	18 (75.0)
Chronic health problems	
Yes	7 (29.2)
No	17 (70.8)
Type of medications used	
Mesalamine alone	22 (91.7)
Mesalamine and Azathioprine	2 (8.3)
Mesalamine type	
Pentasa	16 (66.7)
Asacol	5 (20.8)
Salazopyrin	3 (12.5)
Family history of IBD	
Yes	5 (20.8)
No	19 (79.2)
Use of probiotics before at least one year	
Yes	3 (12.5)
No	21 (87.5)

PMS, partial Mayo score; MET, metabolic equivalent for the task; IBD, inflammatory bowel disease.

Table 2 shows the baseline and end line and the mean and percentage of changes in PMS score and IL-23 for participants. There were no significant differences in baseline IL-23 levels among probiotic and placebo groups. In the end, there was no significant difference in the mean IL-23 level between the probiotic and placebo group [(247.44 ± 8.83) vs (257.56 ± 12.74), p=0.523]. Similarly, the probiotic group had an insignificantly lower mean and percent of change in the IL-23 level (19.22 ± 9.85 and 8.86 ± 4.23, respectively, p =0.828) compared to the placebo group (22.63 ± 11.96 and 11.07 ± 5.53, respectively, p=0.752).

Table 2. Baseline, endline, mean and percentage of change in values of Partial Mayo score and Interleukin-23 (pg/ml) for participants (n=24).

Variables	Probiotics group (n=12)	Placebo group (n=12)	*p*-value*
PMS score at baseline	4.7 ± 1.3	4.3 ± 1.8	0.479
PMS score at endline	1.33 ± 0.49	3.42 ± 1.78	**0.001**
Baseline	227.02 ± 10.25	202.00 ± 10.86	0.110
Endline	247.44 ± 8.83	257.56 ± 12.74	0.523
Mean of change	19.22 ± 9.85	22.63 ± 11.96	0.828
Percentage of change	8.86 ± 4.23	11.07 ± 5.53	0.752

Data presented as mean ± SEM. PMS, partial Mayo score
**P* values were obtained from one-way ANOVA to test for differences between groups and *Fisher's* LSD post hoc. *P*-value < 0.05 was indicated as statistically significant.

DISCUSSION

IBD is considered a consequence of abnormal immune responses in the gastrointestinal tract. It has been recognized that CD is modulated with Th1 cytokines while UC is associated with Th2 cytokines [17,24]. IL-23 is a pro-inflammatory cytokine produced in response to microbial pathogens, and it is vital for differentiating CD4 T naïve cells into Th17 cells [13]. Th17 cells and IL-17 expression were significantly enhanced in the inflamed gut of CD and UC patients [25,26]. With the accumulation of evidence supporting the significant role of microbiota in gut homeostasis [24], probiotics have been more frequently used in treating IBD, especially UC [18]. However, studies on the probiotic effect on the IL-23 level are limited.

The current study reported that probiotic supplements lead to a variable reduction in the IL-23 level. A similar result was observed by Bamola et al., who conducted a double-blind, randomized, placebo-controlled study on administering *Bacillus clausii* UBBC-07 (MTCC 5472) to UC and CD patients for four weeks [27]. Using the animal module, Chen et al. showed that administration of *L. acidophilus* to the mouse colon inhibited the colitis-mediated increase in TGFβ1 and IL-23 expression, thus implicating a decrease in TGFβ1 and IL-23 expression upon *L. acidophilus* treatment [18]. Another study by Ghadimi et al. using intestinally cultured probiotics revealed that Bifidobacterium breve and *Lactobacillus rhamnosus* GG (LGG) inhibited histone acetylation and enhanced DNA methylation, which inhibit lipopolysaccharide-(LPS-) activated expression of IL-23. Thus, giving another possible mechanism for *L. acidophilus*-mediated downregulation of IL-23 [19].

A possible explanation of the probiotic's IL-23 downregulatory effects is the reduction of TNF-α expression [18], as previous studies have stated that nuclear factor- (NF) κB, a critical mediator of TNF-α signaling, regulates the transcription of the IL-23p19 gene [28]. Leccese et al. suggested that deeper molecular analysis to characterize the interactions of probiotics with immune cell signaling cascades is vital in identifying probiotic strains able to inhibit the activation of IL-23/Th17 axis without increasing TNF-α or inhibition of IL-10 as potential side effects, so it became a more effective therapeutic strategy for UC and CD [29]. Moreover, the *Lactobacillus and Bifidobacterium* strains were reported to interfere with the IL-23/Th17 axis similarly to how the anti-inflammatory drug 6-Mercaptopurine works while also stimulating the expression of the anti-inflammatory cytokine IL-10 [30-31]. However, probiotics have a strain-specific immunomodulatory nature [29] and it is important to determine the effective concentrations of commensal probiotics on the expression of proinflammatory cytokines and relevant effectors [18].

Our study showed that probiotics significantly improved the Partial Mayo Score compared to the control group despite the absence of a significant effect on IL-23. This could be due to alterations in other cytokines that we did not measure. A study by Isidro et al. investigated the impact of VSL#3 on macrophages and their cytokine secretion profile. It demonstrated that VSL#3 maintained the proinflammatory status of M1 macrophages by increasing the production of G-CSF, IL-1β, IL-6, and IL-23 while maintaining high levels of IL-12. Additionally, VSL#3 influenced M2 and Mφ macrophages by increasing the production of IL-8, IL-12, TNF-α, eotaxin, GRO, and MIP-1. Concurrently, it induced the production of anti-inflammatory cytokines IL-10, IL-13, and IL-1Ra by M2 macrophages and pro-healing factors TGF-α, EGF, FGF-2, and VEGF by both M2 and Mφ macrophages [32]. Furthermore, it has been shown that Bifidobacteria-containing probiotics can promote mucin production, regulate cell death, and decrease inflammation [33]. This could also explain the improvement in patients' Partial Mayo Score.

Strength and limitation: Our study is the first clinical study on the effect of probiotics on IL-23 in UC patients in Jordan. The small sample size was the study's major limitation, in addition to the lack of data analysis for other inflammatory biomarkers related to UC, such as TNF-α and IL-17. Further studies are needed to investigate the long-term effects of probiotics on IL-23 in mild to moderately active UC patients.

CONCLUSION

The probiotic supplementation used in this study had a beneficial therapeutic effect for patients with UC as an add-on treatment despite the insignificant suppressive effect on the IL-23 level. To study the change of IL-23 in patients with IBD, similar studies using single and mixed probiotics in a larger sample are recommended. Also, studies on histopathological levels to investigate the changes in intestinal inflammation are required.

Ethical consideration: The study was approved by the Institutional Review Board of Jordan University Hospital and Al-Bashir Hospital and by the Deanship of Academic Research at the University of Jordan, Amman, Jordan.

Data availability: The data underlying this article cannot be shared publicly due to

the privacy of individuals who participated in the study.

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This study was registered at ClinicalTrials.gov with the number NCT04223479.

Declaration of competing interest: The authors declare no conflicts of interest.

Authors' contribution: LMA data acquisition, statistical analysis, interpreted the results, and data analysis. LMA, OK, and BA inducted and drafted the manuscript. MIY, YR, SH, and AA were involved in the concept and design of the study, data analysis and review and providing input on the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Abbreviations: 5-ASA, 5-aminosalicylic acid; **CD, Crohn's disease;** ELISA, Enzyme-Linked Immunosorbent Assay; IBD, inflammatory bowel disease; **IL, interleukin;** LPS, Lipopolysaccharide; MET, metabolic equivalent for task; NF, nuclear factor; **NK, natural killer; NKT, natural killer T;** PMS, Partial Mayo Score; Th, T helper; **TNF, tumor necrosis factor;** UC, ulcerative colitis; EGF, Epidermal Growth Factor; G-CSF, Granulocyte Colony Stimulating Factor; GRO, Growth-Related Oncogene; MIP-1, Macrophage Inhibitory Protein 1; VEGF, Vascular Endothelial Growth Factor; TGF-α, Transforming Growth Factor; M1, Classically activated or proinflammatory macrophage; M2, Alternatively activated or anti-inflammatory macrophage; Mφ, Unpolarized macrophage.

This study was registered at ClinicalTrials.gov with the number NCT04223479.

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تأثير مكملات البروبيوتيك على مستويات الإنترلوكين -23 في الدم بين مرضى التهاب القولون التقرحي: دراسة تجريبية ومخرجات ثانوية

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الملخص

الخلفية والأهداف: اكتسب الإنترلوكين-23 اهتمامًا خاصًا باعتباره سيتوكينًا مسببًا للالتهابات يلعب دورًا رئيسيًا في التسبب في التهاب القولون التقرحي. في الآونة الأخيرة، تم استخدام البروبيوتيك بشكل متكرر في علاج التهاب القولون التقرحي لتحفيز الدخول في فترة هدوء المرض والحفاظ عليها. تهدف هذه الدراسة إلى تقييم تأثير مكملات البروبيوتيك على مستويات الانترلوكين-23 بعد الدخول في مرحلة الهدوء في مرضى التهاب القولون التقرحي الخفيف إلى المتوسط الشدة في الأردن.

منهجية الدراسة: هذه دراسة تجريبية متعددة المراكز وعشوائية وخاضعة للتحكم بالدواء الوهمي ومزدوجة التعمية ومتوازية الأذرع. تم تعيين أربعة وعشرين مريضًا بالتهاب القولون التقرحي (11 رجلاً و13 امرأة) عشوائيًا لتلقي 3 × 10^{10} بروبيوتيك 10 مليار خلية نشطة أو ثلاث كبسولات من الدواء الوهمي يوميًا لمدة ستة أسابيع. تم تحديد درجة نشاط المرض من خلال مجموع مايو الجزئي وتم قياس مستوى انترلوكين-23 في المصل في بداية الدراسة وبعد ستة أسابيع.

النتائج: كان هناك فرق كبير في متوسط مجموع مايو الجزئي بين مجموعة البروبيوتيك ومجموعة الدواء الوهمي في نهاية الدراسة (1.33 ± 0.49 مقابل 3.42 ± 1.78) ($p < 0.001$). انخفض مستوى انترلوكين-23 في مجموعة البروبيوتيك بشكل طفيف مقارنة بمجموعة الدواء الوهمي ($p>0.05$). وبالمثل، لم تكن هناك فروق كبيرة في المتوسط أو النسبة المئوية للتغير في مستوى انترلوكين-23 بين المجموعتين ($p>0.05$).

الاستنتاجات: كان لمكملات البروبيوتيك تأثير قمعي ضئيل على مستويات انترلوكين-23 ومع ذلك، فقد قدمت تأثيرًا علاجيًا مفيدًا للمرضى الذين يعانون من التهاب القولون التقرحي، كما يتضح من التحسن في مجموع مايو الجزئي.

الكلمات الدالة: التهاب القولون التقرحي، انترلوكين-23، مكملات البروبيوتيك.