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Assessing the effect of probiotic consumption on metabolic acidosis in patients with end-stage renal disease; a randomized, double-blind clinical trial

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ABSTRACT

Introduction: Patients with end-stage renal disease (ESRD) frequently experience disturbances in acid–base homeostasis, which contribute to adverse clinical outcomes and complicate management. Emerging evidence suggests that modulation of the gut microbiota through probiotic supplementation may influence systemic metabolic and respiratory parameters.

Objectives: This study aimed to evaluate the effect of probiotic supplementation on acid–base homeostasis compared with standard care.

Materials and Methods: This randomized, double-blind, controlled clinical trial was conducted at Loghman Hakim hospital, Tehran, Iran, between 2023 and 2024. Twenty-one patients with ESRD and metabolic acidosis were included in the final analysis. Participants were randomized to the intervention group (n = 12) receive daily probiotic supplementation (Cap Lactocare, 10^9 CFU, once after lunch for three months) plus standard care, or standard care alone (n = 9). Arterial blood gas parameters (ABG), including pH, carbon dioxide (PCO_2), and bicarbonate (HCO_3^-), were measured before and after intervention, and statistical analyses were performed using non-parametric tests to compare within- and between-group changes.

Results: The final analysis included 12 probiotic and 9 control patients. Before intervention, ABG parameters showed no significant differences in pH, PCO_2), and HCO_3^-. After intervention, the probiotic group demonstrated significantly higher pH (7.39 vs. 7.36), lower PCO_2 (39.26 vs. 41.72 mm Hg), and elevated HCO_3^- (27.22 vs. 24.51 mmol/L) compared with controls ($P < 0.05$). Within-group analyses confirmed significant improvements in pH (Δ +1.93%) and HCO_3^- (Δ +32.78%) alongside a reduction in PCO_2 (Δ –5.80%) in the probiotic group ($P < 0.05$), whereas the control group showed increases in pH (Δ +1.37%) and HCO_3^- (Δ +16.99%) ($P < 0.05$), without significant change in PCO_2 ($P = 0.931$).

Conclusion: Probiotic supplementation in patients with ESRD indicated a more comprehensive modulation of both metabolic and respiratory components of acid–base homeostasis compared with standard care.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials with code (IRCT20230608058421N1; https://irct.behdasht.gov.ir/trial/70981), and ethical code from Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1402.099).

Implication for health policy/practice/research/medical education:
The results of this clinical trial study indicated that probiotic supplementation in patients with end-stage renal disease (ESRD) led to a more comprehensive improvement in acid–base homeostasis compared with standard care. These findings highlight the potential of probiotics as an effective adjunctive therapy for optimizing both respiratory and metabolic components of acid–base balance in this patient population.

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Clinical Trial

Introduction

Chronic kidney disease (CKD) represents a major global health challenge, affecting 10 to 15% of the population (1) and over 700 million individuals worldwide and imposing substantial economic burdens on healthcare systems, with annual costs exceeding $80 billion in the United States alone (2). End-stage renal disease (ESRD), the terminal phase of CKD, is characterized by profound renal dysfunction, leading to the accumulation of uremic toxins, systemic inflammation, and a heightened risk of cardiovascular morbidity and mortality (3-5). Among the myriad complications, metabolic acidosis stands out as a prevalent and insidious feature, arising from impaired bicarbonate reabsorption and organic acid retention, which exacerbates protein catabolism, muscle wasting, and bone demineralization (6,7). This acidotic environment not only accelerates CKD progression but also intertwines with the malnutrition-inflammation complex syndrome, amplifying oxidative stress and endothelial dysfunction, thereby contributing to the dismal prognosis in ESRD patients reliant on dialysis (8). Addressing metabolic acidosis is thus imperative for mitigating these cascading effects, underscoring the urgent need for innovative therapeutic strategies beyond conventional alkali supplementation.

The current understanding of metabolic acidosis in ESRD highlights its bidirectional interplay with gut microbiota dysbiosis, a hallmark of advanced CKD (9). Dysbiosis fosters the overproduction of protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, through bacterial fermentation of aromatic amino acids, which compromise intestinal barrier integrity and promote systemic inflammation and oxidative stress (5,10). Probiotic interventions, particularly those involving strains like Lactobacillus and Bifidobacterium, have emerged as promising modulators of this gut-kidney axis, demonstrating reductions in inflammation and uremic toxins (11). For instance, synbiotic supplementation has been associated with improved lipid profiles, suggesting a protective role against oxidative damage (12,13). In CKD patients, probiotic administration has shown potential to lower blood urea nitrogen and serum phosphate, potentially buffering acid-base imbalances via increased short-chain fatty acid production (14). These findings collectively indicate that microbiota-targeted therapies could attenuate the metabolic derangements underlying acidosis.

In previous studies, we found limited direct evidence of probiotic effectiveness on metabolic acidosis as a primary endpoint. Moreover, dietary confounders and the absence of long-term data obscure causal links between probiotics and clinical outcomes like acidosis correction. These gaps highlight the need for additional research to clarify the therapeutic potential of probiotics in ESRD, ensuring robust evidence to guide clinical practice and optimize patient management.

Objectives

This double-blind clinical trial was designed to evaluate the effect of probiotic consumption on metabolic acidosis in patients with ESRD, using arterial blood gas parameters (ABG) including pH, partial pressure of carbon dioxide (PCO_2), and bicarbonate (HCO_3^-) as primary outcome measures, while also aimed to evaluate whether probiotic supplementation improves clinical indicators of acidosis management and enhancement of patient symptoms.

Materials and Methods

Study design and participants

This randomized, double-blind, controlled clinical trial followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline for writing trial protocols (15) and the CONSORT (Consolidated Standards of Reporting Trials) guideline for reporting results (16). The study was conducted at Loghman Hakim hospital in Tehran, Iran, between 2023 and 2024. A total of 24 ESRD patients provided written informed consent and were randomized in equal numbers to the probiotic or control group. During follow-up, no patients were lost in the probiotic group, whereas 3 patients in the control group did not undergo final ABG analysis, resulting in 21 patients (12 probiotic, 9 control) included in the final analysis.

Inclusion and exclusion criteria

Adult patients (≥18 years) with a confirmed diagnosis of ESRD undergoing maintenance treatment, presence of metabolic acidosis as evidenced by ABG analysis, and willingness to provide written informed consent and participate in the study. Patients with prior or concurrent use of probiotic supplementation during the study period, those with gastrointestinal disorders that could interfere with probiotic absorption, individuals who declined participation, and those unable to complete follow-up assessments were excluded.

Sample size

For sample size determination, a significance level of 0.05 and a study power of 0.8 were selected. The ratio of sample size between the intervention and control groups was based on pH values reported in the study by Borges et al (17), with a mean pH difference of 0.7 obtained from that study. The standard deviation was considered to be 0.6, with a margin of error of 0.05. Assuming a dropout rate of 0%, the calculated sample size was 12 patients per group, resulting in a total of 24 participants. The formula used for this superiority trial was derived from the comparison of two independent means using the t-test (18).

Randomization/allocation

Participants were randomized in a 1:1 ratio to either the probiotic or control group using a computer-generated random sequence to ensure unbiased allocation.

Concealment of group assignment was maintained through sequentially numbered, opaque, sealed envelopes prepared by an independent researcher not involved in patient recruitment or outcome assessment.

Blinding

This study was conducted as a double-blind clinical trial in which both participants and outcome assessors were unaware of group allocation. Randomization was performed to assign patients either to the probiotic or control arm. The probiotic group received probiotic capsules containing the active supplement, while the control group received standard care. Allocation codes were concealed and maintained by an independent researcher not involved in patient care or data analysis. Blinding was preserved throughout the intervention and assessment phases, with decoding performed only after completion of statistical analyses to minimize bias in outcome evaluation.

Intervention

Participants in the intervention arm were instructed to consume the probiotic (Regflor capsule [200 mg bifidobacterium infantis]; Darukala company, Iran) provided to them once daily after lunch for a duration of three months. The probiotic administered was Cap Lactocare containing 10^9 colony forming unit (CFU), delivered in capsule form throughout the study period. To ensure accurate monitoring and minimize potential confounding factors, participants were asked to report any new illnesses or the initiation of additional medications during the intervention. The control group received standard medical care for ESRD without probiotic supplementation. Adherence to the intervention was monitored through patient interviews and capsule counts at follow-up visits.

Data collection

All participants provided written informed consent before enrollment. Demographic data, including age, sex, and body mass index, as well as clinical comorbidities (type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, hypothyroidism, and anemia), were collected through structured patient interviews at baseline. Eligible patients were then randomized into probiotic and control groups, with the probiotic group receiving supplementation and the control group receiving standard care. The ABG parameters (including pH, PCO_2, and HCO_3^-) were measured before and after the intervention using standardized laboratory procedures and were compared between and within groups.

Outcomes measurement

The primary outcomes were changes in ABG parameters, including pH, PCO_2, and HCO_3^-. These parameters were measured in both the probiotic and control groups before and after the intervention to evaluate differences in acid–base homeostasis. Between-group comparisons were performed to assess whether probiotic supplementation resulted in greater improvements relative to standard care, while within-group analyses determined the extent of change over time in each treatment arm.

Statistical analysis

All statistical analyses were conducted using SPSS version 27 (IBM Corp., USA). The Kolmogorov–Smirnov test confirmed that all continuous variables were not normally distributed, and Levene's test was applied to assess variance equality. Accordingly, non-parametric methods were used: the Wilcoxon signed-rank test for within-group comparisons of continuous variables, the Mann–Whitney U test for between-group comparisons of continuous variables, and the chi-square test for between-group comparisons of categorical variables. Continuous data were expressed as mean ± standard deviation or interquartile range, and categorical data as frequencies and percentages. A two-tailed P value < 0.05 was considered statistically significant.

Results

In this study, a total of 32 patients were initially assessed for eligibility, of whom 8 were excluded (5 did not meet the inclusion criteria and 3 declined participation). The remaining 24 patients were randomized in equal numbers to the probiotic group (n=12) and the control group (n=12). All participants in the probiotic arm received the allocated intervention, while those in the control arm received standard care without probiotic supplementation. During follow-up, no patients were lost in the probiotic group, whereas 3 patients in the control group did not undergo final ABG analysis. Consequently, 12 patients in the probiotic group and 9 patients in the control group were included in the final analysis (Figure 1).

The results comprised 21 patients with ESRD, including 12 who received probiotic supplementation and 9 assigned to the control group without probiotic therapy. Baseline demographic and clinical characteristics were generally comparable between the two groups. Female participants were more frequent in the probiotic group, whereas cardiovascular disease was equally represented across both groups, with no significant differences observed. Type 2 diabetes mellitus, hypertension, and dyslipidemia were present in both groups with similar distributions. Less common conditions, such as hypothyroidism and anemia, were observed only in the probiotic group, though without statistically significant differences. Age and body mass index were also comparable between groups. Overall, statistical analyses confirmed that the two groups were well balanced at baseline with respect to demographic and clinical variables (Table 1).

The comparative analysis of ABG parameters between the probiotic and control groups revealed no significant

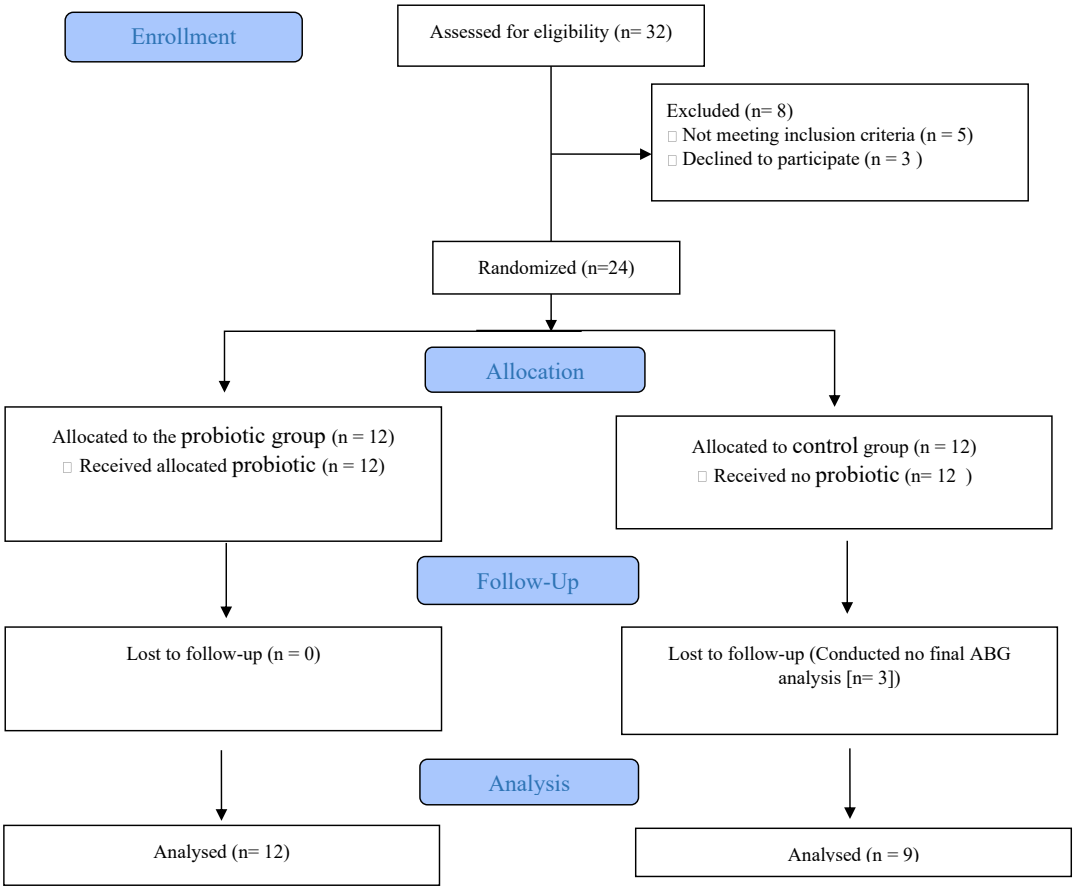

Figure 1. CONSORT flow diagram of the study selection.

differences before the intervention, with both groups demonstrating similar baseline values across pH, PCO_2, and HCO_3^- levels. Following the intervention, however, distinct changes were observed: the probiotic group exhibited a notable improvement in acid–base balance, reflected by a higher pH, lower carbon dioxide levels, and elevated bicarbonate concentrations compared to the control group. These post-intervention differences were statistically significant, indicating that probiotic administration was associated with a more favorable modulation of respiratory and metabolic components of acid–base homeostasis relative to standard care (Table 2).

Within-group analyses of ABG parameters revealed that both probiotic and control groups achieved significant improvements in the normalization of pH and HCO_3^- levels after the intervention, though the extent

Table 1. Comparison of demographic characteristics and underlying disease among treatment groups

Qualitative variables	Treatment group				*P* value*
	Probiotic (n = 12)		Control (n = 9)		
	No.	%	No.	%	
Female gender (n = 7)	5	71.4	2	28.6	0.350
CVD (n = 8)	4	50	4	50	0.604
T2DM (n = 16)	9	56.2	7	43.8	0.882
Hypertension (n = 11)	6	54.5	4	45.5	0.801
Dyslipidemia (n = 6)	3	50	3	50	0.676
Hypothyroidism (n = 1)	1	100	0	0	0.375
Anemia (n = 3)	3	100	0	0	0.105
Quantitative variables	**Mean ± SD**	**IQR (Q1 - Q3)**	**Mean ± SD**	**IQR (Q1 - Q3)**	***P* value****
Age (year)	64.4 ± 16.3	62 – 76	54.6 ± 10.7	46 - 62	0.058
BMI (kg/m^2)	27.35 ± 3.47	25.40 – 29.89	30.04 ± 1.32	29.32 – 31.17	0.111

T2DM: Type 2 diabetes mellitus, CVD: Cardiovascular disease, SD: Standard Deviation, IQR: Interquartile Range. *Chi-square, **Mann-Whitney U.

of normalization was more pronounced in the probiotic group. Importantly, the probiotic group also demonstrated a significant reduction in PCO_2 levels, indicating enhanced respiratory regulation in addition to metabolic adjustment. In contrast, the control group exhibited no meaningful change in carbon dioxide, suggesting that its metabolic improvement was not accompanied by parallel respiratory adaptation. Taken together, these findings highlight that probiotic supplementation produced a more integrated and comprehensive modulation of acid–base homeostasis, encompassing both respiratory and metabolic components, compared with the control group (Table 3).

Discussion

The findings from this study demonstrate that probiotic supplementation in patients with ESRD significantly enhances ABG parameters, including increases in pH and HCO_3^- alongside reductions in PCO_2, relative to control groups. These improvements suggest a targeted modulation of acid-base homeostasis, addressing a critical aspect of metabolic dysregulation in ESRD where chronic metabolic acidosis is prevalent due to impaired renal acid excretion and bicarbonate reabsorption. Scientifically, this indicates that probiotics may influence systemic acid-base balance through mechanisms involving the gut-kidney axis, where microbial modulation could reduce the accumulation of uremic toxins and inflammatory mediators that exacerbate acidosis (5,19,20). Practically, such enhancements in ABG profiles could translate to better symptom management, potentially alleviating fatigue, muscle wasting, and bone demineralization associated with persistent acidosis in dialysis-dependent patients (6,7). By restoring a more balanced acid-base milieu, probiotic therapy emerges as a non-invasive adjunct to standard renal replacement therapies, offering a means to optimize physiological homeostasis without additional pharmacological burden.

Comparisons with existing literature underscore the novelty and alignment of these results within the broader context of microbiota-targeted interventions in CKD. Previous meta-analysis of randomized controlled trials by Yu et al has reported that probiotics, often in combination with prebiotics or synbiotics, effectively lower levels of gut-derived uremic toxins such as indoxyl sulfate, which contribute to inflammation and oxidative stress in ESRD (19). These toxins, produced via microbial fermentation of dietary proteins in a dysbiotic gut environment, have been linked to worsened acid-base disturbances through systemic inflammatory pathways (20,21). Our observed

Table 2. Comparative analysis of ABG parameters before and after the intervention between the two treatment groups

ABG parameters	Treatment group				*P* value*
	Probiotic (n = 12)		Control (n = 9)		
	Mean	SD	Mean	SD	
Before intervention					
pH	7.25	0.02	7.26	0.03	0.998
PCO_2 (mm Hg)	41.68	2.61	41.65	1.23	0.972
HCO_3^- (mmol/L)	20.50	1.21	20.95	2.34	0.917
After intervention					
pH	7.39	0.03	7.36	0.02	0.006
PCO_2 (mm Hg)	39.26	2.01	41.72	1.04	0.003
HCO_3^- (mmol/L)	27.22	2.64	24.51	0.73	0.007

ABG: Arterial Blood Gas, PCO_2: Partial pressure of carbon dioxide, HCO_3^-: Bicarbonate, *Mann-Whitney U.

Table 3. Comparison of ABG parameters between the times before and after the intervention within each of the probiotic and control groups

ABG parameters	Measurement time				Changing rate (%)	*P* value*
	Before intervention		After intervention			
	Mean	SD	Mean	SD		
Probiotic (n = 12)						
pH	7.25	0.02	7.39	0.03	+1.93	<0.001
PCO_2 (mm Hg)	41.68	2.61	39.26	2.01	-5.80	0.007
HCO_3^- (mmol/L)	20.50	1.21	27.22	2.64	+32.78	<0.001
Control (n = 9)						
pH	7.26	0.03	7.36	0.02	+1.37	<0.001
PCO_2 (mm Hg)	41.65	1.23	41.72	1.04	+0.16	0.931
HCO_3^- (mmol/L)	20.95	2.34	24.51	0.73	+16.99	<0.001

ABG: Arterial Blood Gas, PCO_2: Partial pressure of carbon dioxide, HCO_3^-: Bicarbonate, *Wilcoxon signed-rank test.

improvements in pH, PCO_2, and HCO_3^- extend these findings by directly tying probiotic effects to ABG modulation, a less commonly assessed endpoint in prior studies that typically focused on inflammatory markers like C-reactive protein or gastrointestinal symptoms (19,22). For instance, network meta-analyses have ranked probiotics highly for alleviating uremic and inflammatory burdens in dialysis patients, with trends toward metabolic stabilization, though explicit ABG data remain sparse (19,23). These studies' results thus corroborate the therapeutic potential of probiotics in mitigating dysbiosis-driven complications while highlighting a more comprehensive impact on acid-base regulation than previously emphasized.

The strengths of this study lie in its controlled comparison of probiotic supplementation against controls, providing robust evidence for its specific effects on multiple ABG parameters, which collectively indicate a holistic improvement in acid-base homeostasis. This multi-faceted assessment strengthens the inference that probiotics exert a broader modulatory role beyond isolated toxin reduction, potentially through enhanced short-chain fatty acid production that supports epithelial integrity and reduces luminal pH alterations (23,24). However, limitations inferred from the study context include the potential for variability in probiotic strains, dosages, and patient adherence, which could influence the generalizability of these findings across diverse ESRD populations. Broader implications extend to clinical practice, where integrating probiotics into ESRD management protocols could enhance overall metabolic health, reduce reliance on alkali supplements for acidosis correction, and inform personalized nutrition strategies targeting the gut microbiota. Theoretically, these findings advance the understanding of the gut-kidney axis by illustrating how microbial interventions can recalibrate systemic homeostasis, paving the way for interdisciplinary research combining nephrology and microbiology to refine therapeutic paradigms.

Limitations of the study

This study has several limitations that should be considered. First, the relatively small sample size (21 patients completing final analysis) is a major constraint, as it may limit the generalizability of the findings and reduce statistical power. Second, the short intervention period of three months may not capture the long-term effects of probiotic supplementation on metabolic acidosis. Third, potential confounding factors were self-reported, which may have introduced reporting bias and affected the accuracy of outcome assessment.

Conclusion

This study demonstrated that probiotic supplementation in patients with ESRD led to significant improvements in ABG parameters compared with standard care. While both groups showed normalization of pH and bicarbonate levels, the probiotic group achieved greater metabolic correction, accompanied by a significant reduction in carbon dioxide, reflecting enhanced respiratory regulation. These findings suggest that probiotics may provide a more comprehensive modulation of acid–base homeostasis, integrating both metabolic and respiratory components, and thus represent a promising adjunctive strategy in the management of acid–base disturbances in this patient population.

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Authors' contribution

Conceptualization: Melika Gholizade and Farzaneh Futuhi.
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Project management: Zahra Sahraei.
Resources: All authors.
Supervision: All authors.
Writing—original draft: All authors.
Writing—review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Grammarly, https://app.scinito.ai/, and Copilot) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. This study was conducted at Loghman Hakim Hospital and is derived from the thesis work of Melika Gholizade

(Thesis#43005665), with the Ethical code (IR.SBMU.MSP.REC.1402.099; https://ethics.research.ac.ir/form/dhnda4rvohxxc26i.pdf), approved by the Shahid Beheshti University of Medical Sciences, Tehran, Iran on May 30, 2023. The study protocol was also registered as a clinical trial at the Iranian Registry of Clinical Trials (identifier: IRCT20230608058421N1; https://irct.behdasht.gov.ir/trial/70981). Accordingly, written informed consent was taken from all participants before any intervention. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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