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Kidney Weight: The Pre-Clinical Analysis on the Influence of Probiotic Supplementation in Malnutrition

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ABSTRACT

A study showed malnutrition, encompassing both obesity and undernutrition, is a serious metabolic condition that leads to health complications, including kidney injury. Probiotics have been proposed as a potential adjuvant therapy to improve compensatory kidney function. However, research on the effects of probiotic intervention on kidney morphological changes across different nutritional statuses remains limited. This exploratory pilot study involved 24 male isogenic Sprague Dawley rats (n=24; 7-8 weeks old), which were divided into six groups (n=4): undernourished (KU), undernourished-probiotics (KU-P), normal (KN), normal-probiotics (KN-P), obese (KO), and obese-probiotics (KO-P). The rats underwent a 10-day dietary period, followed by a 44-day treatment period, and were terminated on day 45. The kidneys were then extracted and weighed using an analytical scale. Kidney weight data were analyzed using a non-parametric Kruskal-Wallis test, followed by post hoc Dwass-Steel-Critchlow-Fligner (DSCF) tests. Findings revealed a significant difference in kidney weight among the groups (p=0.001), with a substantial effect size. Descriptive trends showed that the obese (KO) group had the highest kidney weights, while the undernourished (KU) group had the lowest. The normal-probiotic group (KN-P) showed a trend toward increased kidney weight compared with the undernourished group (KU); however, conservative pairwise comparisons did not reach statistical significance (p>0.05) due to the limited sample size. Nutritional status is the primary factor influencing kidney weight. While probiotics demonstrated a corrective effect on kidney morphology in the normal group, their efficacy in supplementation requires further evaluation, particularly in undernourished and obese conditions.

INTRODUCTION

Malnutrition represents a significant metabolic challenge that adversely affects quality of life and contributes to patient morbidity and mortality (Serón-Arbeloa et al., 2022). This condition, encompassing both undernutrition and obesity, can lead to severe health complications, particularly in pediatric and adult populations (Hegazi et al., 2024; Soliman et al., 2021). The World Health Organization (WHO) has identified malnutrition as a primary global public health threat, affecting an estimated 20–60% of hospitalized patients (World Health Organization, 2021). Furthermore, the United Nations Children's Fund (UNICEF) reports that approximately one in seven children under the age of five (14%) suffers from stunting, over half (>50%) experience micronutrient deficiencies, and the prevalence of overweight and obesity in children is escalating (United Nations Children's Fund, 2024). Recent data from Indonesia indicate a pressing concern: 24.9% of 3,891 children are affected by the triple burden of malnutrition, underscoring the urgent need for intervention (Andriani et al., 2023).

Malnutrition is known to impair the function and recovery of every organ system (Ravichandran et al., 2022). The kidneys are a primary organ targeted by complications secondary

to malnutrition, which include nephropathy, encephalopathy, anorexia, albumin depletion, inadequate nutrient intake, ghrelin and leptin imbalances, metabolic disturbances, and intestinal dysbiosis (Moldovan et al., 2025). Consequently, malnutrition can precipitate a decline in renal function, potentially culminating in chronic kidney disease (CKD). A significant ramification of this condition is a reduction in hemoglobin (Hb) levels, which, in turn, leads to diminished quality of life for the patient (Van Haalen et al., 2020).

To date, no standardized laboratory criteria exist for the definitive diagnosis of malnutrition in patients with Chronic Kidney Disease (CKD) (Sheikh et al., 2022). Nevertheless, a cohort study in Indonesia reported that 42% of 388 CKD patients were at high risk for malnutrition (Kotha et al., 2025). Moreover, a separate study of 1,277 patients with CKD demonstrated that 89% were at risk for malnutrition, with 64.9% classified as having a moderate to high risk (Yu et al., 2025). Therefore, malnutrition currently constitutes the most common clinical manifestation in individuals with CKD (Xi et al., 2023).

Notwithstanding the prevalent effects of malnutrition in patients with Chronic Kidney Disease (CKD), a therapeutic dilemma exists in managing diminished renal function. This condition elevates the risk of drug toxicity, adverse drug interactions, and suboptimal therapeutic outcomes. Given that adverse drug reactions are often unavoidable, there is a pressing need for further investigation (Alhassani et al., 2021). Moreover, research specifically focused on pharmacological agents with minimal potential for renal drug interactions remains limited (Papotti et al., 2021).

Probiotics, as an adjuvant therapy, have emerged as a potential agent for ameliorating impaired renal function. Previous clinical research has demonstrated that a 2-month probiotic intervention significantly increased serum albumin levels in malnourished patients compared with a control group (Pan et al., 2021). Furthermore, a meta-analysis revealed that probiotic administration in patients with CKD was associated with significant reductions in blood urea nitrogen (BUN) and C-reactive protein (CRP) levels (Liu et al., 2024). However, literature investigating the effects of probiotics on renal morphological changes across different nutritional statuses is limited. Therefore, the present study aims to explore the effect of probiotics on kidney organ weight as a manifestation of morphological alterations that may occur concurrently with improvements in metabolic function and systemic homeostasis.

METHOD

Animals

The experimental animals used in this study were male isogenic Sprague Dawley rats (n=24; age 7-8 weeks) with no physical deformities. The animals were procured from Animal Vet Laboratory Services (Bogor, 16680), a collaborating animal provider with the Institut Pertanian Bogor (IPB). To prevent baseline bias, subjects were assigned to the three primary nutritional status groups using block randomization based on initial body weight, ensuring homogenous mean weights at the start of the study. Each main group was subsequently subdivided into control and probiotic intervention groups. The total number of animals (n=24) across the six resulting groups (Undernutrition-Control [KU], Undernutrition-Probiotic [KU-P], Normal-Control [KN], Normal-Probiotic [KN-P], Obese [KO], and Obese-Probiotic [KO-P]) satisfied the minimum sample size requirement as determined by Federer's formula.

All subjects were housed in standard polycarbonate cages (4 rats per cage; 60 x 40 x 20 cm) in a controlled environment with a 12-hour light/dark cycle, a temperature maintained at 22±2°C, and a humidity of 55±5%. General health and body condition were monitored weekly to ensure adherence to the dietary protocols and to assess animal welfare. The study adhered to the humane endpoints established by the institutional ethics committee; however, no animals required early euthanasia during the experimental period. This reporting follows the ARRIVE guidelines 2.0 for pre-clinical animal research (du Sert et al., 2020).

Undernutrition & obesity protocol

Animals in both the undernutrition and normal groups were fed a standard rat chow procured from Indofeed PT. Sadewa Animal Feed. The chow's composition was as follows: water

(12%), ash (14%), crude protein (15%), crude fat (2%), crude fiber (14%), calcium (0.8%), phosphorus (0.5%), and amino acids (lysine 0.7%; methionine + cystine 0.5%). The normal group was provided with chow and drinking water ad libitum. In contrast, the undernutrition group underwent caloric restriction, receiving a daily food ration equivalent to 60-70% of the average daily intake of the normal group. The obesity group was administered a 45% high-fat diet (HFD) composed of corn meal, soybean meal, fish meal, sunflower seeds, flaxseed, sesame seeds, wheat bran, lard, dry molasses, a vitamin/mineral mix, calcium lignosulfonate, calcium carbonate, ferrous sulfate, potassium sulfate, a toxin binder, and TBHQ. The detailed nutritional profile of the HFD is presented in Table 1. These dietary protocols to induce undernutrition and obesity were initiated 10 days prior to the start of the experiment and were maintained until euthanasia on day 45. Throughout the treatment period, the body weight of animals in the undernutrition group was monitored weekly to ensure a consistent 10-15% weight reduction. Conversely, animals in the obesity group were managed to sustain a consistent weight gain of 10-15%. All animals across all groups had ad libitum access to clean drinking water throughout the study.

Table 1. High fat diet chow's composition 45% per 100gr

Component	Weight (gr)	Calories (kcal)
Total fat	23.32	209.99
Protein	18.01	72.06
Carbohydrates	44.43	177.76
Total energy		≈ 460 kkal

Probiotic administration

Following a 10-day preparatory period for the undernutrition and obesity groups, probiotic administration commenced in the designated treatment groups. The three probiotic-treated groups (KU-P, KN-P, and KO-P) received a daily probiotic supplement via oral gavage for 44 consecutive days, in addition to their respective dietary and water protocols. The probiotic used in this study was L-bio® (Lapi Laboratories, Indonesia), a commercially available multispecies supplement approved by the Indonesian National Agency of Drug and Food Control (BPOM). According to the product label, it contains the following bacterial strains: *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W55, *Lactobacillus casei* W56, *Lactobacillus salivarius* W57, and *Lactobacillus lactis* W58.

The dosage was calculated to mimic a standard maintenance dose adjusted for the rat model. Each 1-gram sachet contains 10^8 CFU. We administered 0.1g of the powder diluted in 1 mL of distilled water per rat daily. This resulted in a daily intake of $1x10^7$ CFU/rat/day. This specific dosage was selected to evaluate the effects of a standard dietary supplementation level, consistent with previous pilot studies (Wang et al., 2021). To ensure viability, fresh suspensions were prepared daily immediately prior to gavage, using sachets from a single manufacturing batch stored at 4°C until use.

Tissue extraction

Upon completion of the experimental period, all animals were euthanized via isoflurane inhalation followed by cardiac puncture. The primary organs of interest for this study were the right and left kidneys, which were harvested through an intra-abdominal surgical procedure performed post-euthanasia on day 45. Immediately following excision, the kidneys were placed in 10 mL sample containers with 0.9% NaCl solution and stored at -4°C for subsequent analysis. This overnight storage protocol was implemented to enable simultaneous batch processing of all samples. While we acknowledge that cold storage may induce minor physicochemical changes, the protocol was applied identically to all specimens to ensure that any systematic error remained uniform across all experimental groups. On the following day, the kidneys from all six groups (KU, KU-P, KN, KN-P, KO, and KO-P) were cleared of surrounding visceral fat. Kidney weight, the primary outcome in this study, was measured using an analytical balance with a precision of 0.0001 g. All tissue extraction and storage procedures were conducted under the supervision of qualified laboratory personnel and followed methodologies adapted from da Fonseca et al. (2025) and Budisulistyo et al. (2023). Other researchers utilized other organs extracted during the procedure for separate investigations.

Statistical analysis

All statistical analyses were performed using Jamovi© software (version 2.7.2.0), with a significance level of $p<0.05$ adopted for this study. The software application followed the guidelines established by Sihombing et al. (2024). The statistical analysis was performed on coded datasets, with the analyst blinded to the specific treatment groups to minimize bias. Additionally, due to the small sample size (n=4), kidney organ weight data were analyzed using the non-parametric Kruskal-Wallis test. To quantify the magnitude of the differences, the effect size was calculated using Epsilon-squared (ε^2). Post-hoc pairwise comparisons were performed using the Dwass-Steel-Critchlow-Fligner (DSCF) test to identify specific between-group differences. A significance level of $p<0.05$ was maintained. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Lampung (No. 356/UN26.18/PP.05.02.00/2025).

RESULTS

The outcome parameter measured in this study was kidney weight. The kidney weight results for each group are presented in Table 2.

Table 2. Kidney weight (gr)

No	KU	KU-P	KN	KN-P	KO	KO-P
1	1.78	1.79	1.82	1.95	2.33	2.47
2	1.59	1.71	1.79	1.87	2.24	2.19
3	1.51	1.84	1.94	2.07	1.98	2.35
4	1.68	1.94	1.84	2.03	1.98	2.68
Mean (SD)	1.64 (0.12)	1.82 (0.10)	1.85 (0.07)	1.98 (0.09)	2.13 (0.18)	2.42 (0.21)

The results showed variations in kidney weight (gr) across the different experimental groups. The mean kidney organ weights (± SD) for the undernutrition-control (KU), undernutrition-probiotic (KU-P), normal-control (KN), normal-probiotic (KN-P), obesity-control (KO), and obesity-probiotic (KO-P) groups were 1.64±0.12gr, 1.82±0.10gr, 1.85±0.07gr, 1.98±0.09gr, 2.13±0.18gr, and 2.42±0.21gr, respectively. The normal-control (KN) group demonstrated a mean kidney weight of 1.85±0.07gr. In the absence of pathological findings, this value was established as the physiological baseline for this specific cohort and substrain, serving as the internal reference for assessing atrophy or hypertrophy.

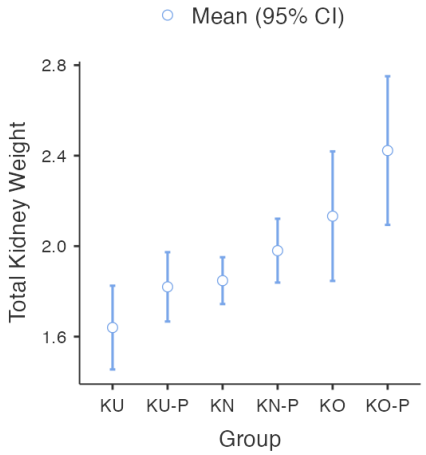

Figure 1. Descriptive plot of kidney weight treatment group

The visual data presented in Figure 1 indicate that the undernutrition-control (KU) group possessed the lowest mean total kidney weight among all experimental groups. Conversely, the obesity-probiotic (KO-P) group exhibited the highest mean total kidney weight. To statistically validate these observed differences while accounting for the small sample size (n=4), the data were analyzed using the non-parametric Kruskal-Wallis test, as shown in Table 3.

Table 3. Kruskal-Wallis test

Kruskal-Wallis Test	χ^2	df	p-value	ε^2
Kidney weight total	20.2	5	0.001	0.879

The Kruskal-Wallis analysis revealed a statistically significant difference in kidney organ weight among the groups ($\chi^2(5)=20.2$; $p=0.001$). Furthermore, the analysis demonstrated a substantial effect size ($\varepsilon^2=0.879$), indicating that the nutritional intervention accounted for 87.9% of the variance in kidney weight. This suggests a robust biological effect despite the small sample size. Further post hoc analyses are presented in Table 4.

Table 4. Dwass-Steel-Critchlow-Fligner (DSCF) test

		KU	KU-P	KN	KN-P	KO	KO-P
KU	Wilcoxon statistic (W)	—	2.858	3.266	3.266	3.286	3.266
	p-value	—	0.330	0.190	0.190	0.185	0.190
KU-P	Wilcoxon statistic (W)		—	0.624	2.858	3.286	3.266
	p-value		—	0.998	0.330	0.185	0.190
KN	Wilcoxon statistic (W)			—	2.858	3.286	3.266
	p-value			—	0.330	0.185	0.190
KN-P	Wilcoxon statistic (W)				—	1.643	3.266
	p-value				—	0.855	0.190
KO	Wilcoxon statistic (W)					—	2.464
	p-value					—	0.504

Post-hoc pairwise comparisons using the DSCF test revealed substantial separations in rank sums, particularly between the Undernourished (KU) and Obese (KO) groups ($W=3.286$) and between the Undernourished (KU) and Normal-Probiotic (KN-P) groups ($W=3.266$). However, due to the conservative adjustment for multiple comparisons with small sample sizes ($n=4$), these pairwise differences did not reach statistical significance ($p>0.05$).

DISCUSSION

The results of this study demonstrate a marked morphological disparity in kidney organ weight between the obesity (KO) and undernutrition (KU) groups. While the conservative post-hoc analysis did not yield a statistically significant p-value ($p > 0.05$) due to the limited sample size, the descriptive trends show a clear divergence from the normal baseline: obesity was associated with organ enlargement (hypertrophy) relative to the normal group, whereas undernutrition was associated with reduced organ mass (atrophy). This observable disparity also held true for their probiotic-treated counterparts (KO-P vs. KU-P).

The renal enlargement observed in the obesity groups can be attributed to the compensatory effect of an elevated metabolism to process a surplus nutrient intake (Friedman et al., 2024). However, the precise mechanisms linking changes in microbiota composition to the development of obesity are not yet fully understood, owing to the complex etiology of this disease (Wiciński et al., 2020). Meanwhile, the undernutrition group showed that low kidney organ weight may indicate atrophy resulting from nutritional deficiency. This reduction in organ mass can be attributed to the body's adaptive mechanisms in response to albumin depletion, inadequate nutrient intake, and the metabolic imbalances commonly associated with undernutrition (Cheng et al., 2023; Tong et al., 2024). Such organ atrophy typically results from immune-mediated disruptions in homeostasis (Wensveen et al., 2024). This finding underscores the serious concern of undernutrition, particularly as patients with renal disorders are often at high risk for developing malnutrition (Otis et al., 2025).

Probiotics offer a compensatory effect by improving renal function, which can be indicated by a quantitatively higher mean kidney weight compared to non-obese groups (Kuo et al., 2023). However, in the present study, the probiotic intervention did not significantly reduce kidney weight in obese rats. This finding contrasts with a meta-analysis, which demonstrated that probiotic administration can decrease body mass index, visceral and subcutaneous fat area, body

fat percentage, and fat mass compared with controls (Machado-Oliveira et al., 2024). On the other hand, our descriptive results suggest that probiotics trended toward increasing mean kidney weight in both undernourished and obese groups, with the most notable increase in obese rats (KO-P=2.42gr vs. KO=2.13gr). Importantly, this increase in mass was not accompanied by adverse morphological changes, as no gross kidney stones or obstructions were observed. While micro-steatosis cannot be excluded without histopathology, no overt fatty changes were visible to the naked eye.

However, we interpret these results with caution. Unlike in undernutrition, renal enlargement in obesity often reflects compensatory hyperfiltration and hypertrophy rather than improved health. Although no gross pathological alterations were visible, the increased mass in the KO-P group may indicate an exacerbated hypertrophic response. Additionally, without histological verification, it remains unclear if this increase represents beneficial tissue growth or pathological structural adaptation. Nevertheless, this interpretation requires further confirmation through assessments such as glomerular filtration rate (GFR), as hypertrophy can also be a compensatory mechanism for declining renal function (Riska et al., 2023).

On another note, probiotic administration increased the mean kidney weight in the undernutrition cohort (KU=1.64 g vs. KU-P=1.82 g). Although this increase was not statistically significant, it suggests a potential role for probiotics as agents that may restore organ function (Huang et al., 2025). In the context of undernutrition, the observed increase in kidney weight in the probiotic group (KU-P) compared to controls suggests a potential reversal of malnutrition-induced atrophy. Malnutrition is known to cause significant organ wasting and a reduction in renal mass due to protein-energy deficit. This increase in kidney mass can be interpreted as a 'restoration of organ structural integrity' following nutrient-deprivation atrophy, rather than pathological enlargement. This notion is further supported by the descriptive trend observed between the normal-probiotic group (KN-P) and the undernutrition-control group (KU). However, the conservative pairwise statistical adjustment did not reach significance. This improvement indicates that probiotics can act as an adjuvant therapy, potentially enhancing the efficiency of micro- and macronutrient absorption in the gut and reducing inflammation, thereby facilitating optimal organ recovery (Wang et al., 2021). This finding is consistent with previous research, which reported that probiotic consumption was associated with a 27% reduction in the prevalence of CKD (Xie et al., 2025).

In executing their function, probiotics play a crucial role in maintaining intestinal and systemic health by producing various metabolites, primarily short-chain fatty acids (SCFAs) such as acetate (C2), propionate (C3), and butyrate (C4) (Nisa et al., 2025). These compounds serve as a primary energy source for intestinal epithelial cells, which in turn can enhance gut barrier integrity and exert anti-inflammatory effects (Shin et al., 2023). In addition to producing SCFAs, specific probiotic strains, such as *Bifidobacterium* and *Lactobacillus*, have been shown to modulate the intestinal microbial ecosystem (Marć et al., 2022). Their mechanism of action involves restoring microbial balance by increasing the population of beneficial bacteria while suppressing the growth of pathogenic microorganisms like Salmonella, Escherichia, and Staphylococcus (Sachdeva et al., 2024). This action not only contributes to an improved nutritional status but also helps to reduce the levels of chronic inflammation often associated with both undernutrition and obesity. These structural changes may be mediated through the gut-kidney axis; by modulating the gut microbiota and producing SCFAs, the intervention reduces the translocation of uremic toxins and inflammatory cytokines that contribute to renal wasting. Consequently, probiotic intervention offers a holistic and multifactorial approach, positioning it as a promising strategy for addressing the challenges of both undernutrition and obesity (Aponte et al., 2020; Chen et al., 2025).

Despite its merits, this exploratory study has several limitations. First, the scope was strictly limited to macroscopic morphological outcomes. A critical limitation is the absence of histological analysis (e.g., glomerular sizing) and serum biochemical markers (e.g., Creatinine, BUN). Without these functional data, we cannot definitively distinguish whether the observed increase in kidney weight, particularly in the obesity group, reflects beneficial tissue regeneration, pathological hypertrophy, or inflammatory edema. Therefore, the findings presented here should be interpreted as macroscopic morphological trends that warrant further microscopic verification.

Another limitation is the contrasting nature of the probiotic effect observed between the undernutrition (KU) and obesity (KO) groups. In the context of undernutrition, the probiotic-

induced increase in kidney weight appears to be a positive restorative effect, trending towards normalization. Conversely, in the context of obesity, the probiotic-induced increase in kidney weight could be interpreted as a negative effect, potentially exacerbating pathological hypertrophy. We also acknowledge that the lack of normalized data on rats' body/kidney weight is a constraint of this pilot study. Furthermore, the low probiotic dosage used (10^7 CFU/rat/day) may have contributed to suboptimal outcomes. While sufficient to observe trends in the normal group, it may have been suboptimal for overcoming the severe metabolic dysregulation in the obese and undernourished cohorts. Thus, this study should be viewed as a pilot dosing evaluation.

Future studies should incorporate a more comprehensive analysis by including body weight normalization and functional markers of kidney health, such as blood urea nitrogen (BUN), C-reactive protein (CRP), and albumin levels. The administration of a higher therapeutic dosage, ranging from 10^7 to 10^{10} CFU/mL, is also recommended for subsequent research (Wang et al., 2021). In addition to the treatment dose, it is recommended that probiotic administration focus on the quality of the specific probiotic strains being given, rather than simply the number of strains in a product, in accordance with their clinical relevance (McFarland, 2021).

CONCLUSION

The findings of this exploratory pilot study demonstrate that nutritional status is a primary factor influencing renal mass, with undernutrition driving atrophy and obesity driving hypertrophy. Probiotic supplementation showed a significant corrective effect on kidney morphology in the normal-nutrition group and a trend toward mass restoration in the undernourished group. However, in the obese group, probiotics further increased kidney mass, the implications of which (beneficial vs. hypertrophic) remain to be elucidated. These macroscopic results highlight the potential of the gut-kidney axis but underscore the necessity for future comprehensive studies utilizing histological and functional renal markers to validate efficacy.

AUTHOR'S DECLARATION

Authors' contributions and responsibilities

RAH: Conceptualization, investigation, writing original draft, visualization; **KNB:** Conceptualization, funding acquisition, writing original draft, visualization; **SWM**: Visualization, review & editing; **NIY:** formal analysis, review & editing. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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