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ORIGINAL ARTICLE

Effects of dietary protein combined with high-intensity exercise in restoring skin health in male rats

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ABSTRACT

BACKGROUND
Protein is essential for skin integrity, while exercise modulates cellular and molecular processes that regulate autophagy, mitochondrial biogenesis, and collagen synthesis. This study evaluates the combined effects of dietary protein restriction and varying exercise intensities on epidermal thickness, autophagy markers (LC3, p62), mitochondrial biogenesis (PGC1α), and collagen synthesis (Col1a1, Col3a1) in male Wistar rats.

METHODS
An experimental laboratory study was conducted involving 32 male Wistar rats. They were randomized into 8 groups: control, low protein, low intensity, group IV, moderate intensity, moderate intensity low protein, high intensity, and high intensity low protein. Low protein diet (5%) compared to the control (24%) was given for 60 days, while the exercise regimen was eight weeks of treadmill exercise (low/10 m per minute, moderate/20 m per minute, and high intensity/30 m per minute) for 30 minutes a day, five days a week. Epidermal thickness, LC3, p62, PGC1α, Col1a1, and Col3a1 mRNA expression were measured at the end of the study. One-way ANOVA/Kruskal-Wallis followed by Tukey HSD/Mann–Whitney test was used to analyze the data.

RESULTS
A low-protein diet significantly reduced epidermal thickness ($p=0.048$), increased LC3 ($p=0.043$) and p62 ($p=0.011$), indicating impaired skin regeneration and autophagy. However, exercise, especially at high intensities with low protein, mitigated this effect by increasing both LC3 ($p=0.011$) and PGC1α ($p=0.011$).

CONCLUSIONS
These findings highlight the compensatory role of exercise in maintaining tissue integrity under protein-deprived conditions in male rats. High-intensity exercise potentially enhances autophagy and mitochondrial biogenesis.

Keywords : Autophagy, collagen synthesis, epidermal thickness, exercise, protein restriction, rats

INTRODUCTION

Serving as both a protective shield and an active regulator, the skin is essential for defending against environmental factors, maintaining thermal balance, and enabling immune and sensory functions.[1] Its ability to regenerate and maintain structural integrity relies on a delicate balance of nutrients, particularly proteins, which are essential for the synthesis of structural components such as collagen and elastin.[2,3] Collagen, the primary structural protein in the skin, provides tensile strength and elasticity, while keratinocytes facilitate the renewal of the epidermal layer.[4,5]

Protein deficiency has been shown to impair skin regeneration, leading to reduced collagen synthesis and compromised structural integrity.[6,7] In contrast, exercise is known to stimulate molecular pathways that promote tissue repair and remodeling.[8–10] These include the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), a transcriptional coactivator involved in mitochondrial biogenesis and energy metabolism, and autophagy, which enables cells to break down and reuse damaged organelles and proteins.[11–14]

Exercise intensity plays a pivotal role in determining its physiological effects.[15] Low-to-moderate intensity exercise is often associated with moderate improvements in tissue health, while high-intensity exercise is linked to more pronounced activation of molecular pathways, including autophagy and mitochondrial function.[16–18] Additionally, mechanical loading during exercise has been shown to enhance collagen production and improve connective tissue strength via transforming growth factor beta (TGF-β), PGC1α, and interleukin 15 (IL15) signaling.[6,10]

Despite these insights, the interaction between dietary protein intake and exercise intensity in skin regeneration remains poorly understood. Most studies have focused on either nutritional or mechanical factors in isolation, leaving a gap in understanding their combined effects.[8,10,16,19]

Previous studies investigating the effects of exercise on skin health in animals or humans have produced inconsistent results. Crane et al.[10] reported that treadmill exercise in mice increased IL-15 in skeletal muscles, controlled by AMP-activated protein kinase (AMPK), which then induced PGC1α production and increased collagen synthesis. On the contrary, a human study performed by Nishikori et al.[20] showed that resistance exercise is superior to aerobic exercise in increasing dermal thickness, in addition to its beneficial effects on the elasticity of the skin and dermal structure. While studies in muscle indicate that high-intensity interval training is superior to moderate-intensity interval training in increasing AMPK, mitochondrial biogenesis, autophagy, and mitophagy in rats,[21–23] such molecular pathways have not been thoroughly examined in the skin. Deficiency of protein affects fibroblast activities, thus decreasing collagen formation, which might be correlated with mitochondrial biogenesis and autophagy in the skin.[6,24,25] These conflicting outcomes suggest that the effects of exercise on skin structure may depend on the intensity of exercise and nutritional status.

The novelty of the present study resides in its combination of dietary protein deficiency with different exercise intensities to assess skin-specific responses at both structural and molecular levels. While it is established that protein malnutrition diminishes epidermal thickness and dermal collagen content,[25] prior research has not explored whether varying exercise intensities can alleviate these effects. The objective of this study was to evaluate the combined effects of dietary protein restriction and varying exercise intensities on epidermal thickness, autophagy markers (microtubule-associated protein light chain 3/LC3, sequestosome 1/p62), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and collagen synthesis (collagen type I alpha 1 chain/Col1a1, collagen type III alpha 1 chain/Col3a1) in male Wistar rats.

METHODS

Research design

This experimental laboratory study was conducted in two stages in two laboratories, namely the Animal Laboratory of Universitas Padjadjaran, Jatinangor, Indonesia and the Maranatha Biomedical Research Laboratory of Universitas Kristen Maranatha, Bandung, Indonesia. From July to December 2022, the rats were acclimated and fed their respective diets for

60 days in the Animal Laboratory of Universitas Padjadjaran, while from January to March 2023, the treadmill exercises were performed in the Maranatha Biomedical Research Laboratory of Universitas Kristen Maranatha.

Study subjects

The sample size in this study was determined using the formula n = (DF/k) + 1,[26] where *n* is the number of subjects per group, DF represents the degrees of freedom for the desired error (ranging from 10 to 20), and k is the total number of groups (8 in this study). Using the lower limit of DF (10), the minimum required sample size per group was calculated as (10/8) + 1 = 2.25, which was rounded up to 3. For the upper limit of DF (20), the calculation yielded (20/8) + 1 = 3.5, rounded up to 4. Thus, the sample size per group ranged between 3 and 4 rats. To meet these criteria, the total number of subjects was determined by multiplying the number of groups by the sample size per group, resulting in a range of 24 to 32 rats. In this study, a total of 32 male Wistar rats were used, ensuring that the error degrees of freedom remained within the acceptable range for statistical validity. The inclusion criteria were healthy male Wistar rats aged 8–10 weeks, weighing 200–250 grams, with normal physical activity and feeding behavior during a one-week acclimatization period. The exclusion criteria were rats showing signs of illness, injury, abnormal behavior, failure to complete the exercise protocol, or those that died before the study endpoint.

A total of 32 rats were randomly divided into eight groups, with four rats per group: group I = control group (no intervention); group II = low-protein diet; group III = low-intensity exercise; group IV = low-intensity exercise + low-protein diet; group V = moderate-intensity exercise; group VI = moderate-intensity exercise + low-protein diet; group VII = high-intensity exercise; group VIII = high-intensity exercise + low-protein diet.

The rats were purchased from PT Biofarma, Bandung, Indonesia. The rats were placed in standard cages and were fed a normal pelleted or low protein rat diet (Prospets, PHARCI, Bandung), with free access to drinking water (ad libitum). The rats were housed in the Animal Laboratory of Universitas Padjadjaran, Jatinangor, Indonesia. The environmental conditions included a 12-hour dark and light cycle, an ambient temperature of 22°C-24°C, and a stable humidity of 60%. The rats were acclimatized to the set environment for two weeks.

Diet composition

The low-protein diet containing 5% protein was given at a dose of 10 grams per day (38 kcal), compared to the 14% protein content of the control diet given at a dose of 20 grams (60.2 kcal), and was administered for 60 days.[27] Rats were acclimated to their respective diets for one week prior to the start of the experimental procedures.

Treadmill exercise protocol

The rats acclimated to treadmill speed 2 weeks before the beginning of different intensities of exercise. The subjects performed treadmill exercise at low (10 m/min), moderate (20 m/min), and high (30 m/min) intensities, with sessions scheduled for 30 minutes a day, 5 days a week, for an 8-week period.[28] The intensities for the exercise protocol were selected based on the lactate threshold, referencing a previously published study.[29]

Experimental procedure

During the experimental phase, diet and exercise protocols were administered under the supervision of the research team, while the actual implementation, including treadmill operation and diet monitoring of the rats during sessions, was conducted by experienced animal facility staff, following detailed instructions to ensure consistency and animal welfare.

Hematoxylin and eosin (H&E) staining

Using H&E staining, epidermal thickness was histologically evaluated. Dorsal skin was collected post-mortem, fixed in 10% neutral-buffered formalin, embedded in paraffin, cut into 5 µm sections, and stained. Thickness was measured from light microscope images using image analysis software.

Real-time PCR analysis

Quantitative real-time PCR (qPCR) was utilized to analyze the expression levels of PGC1α, LC3, p62, Col1a1, and Col3a1. Total RNA was extracted from skin tissues using Genezol (GZR200, Geneaid Biotech Ltd., Taiwan), and qPCR reactions were conducted with the SensiFAST SYBR No-ROX One-Step RT-PCR Kit (BIO-72005, Bioline, UK). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was employed as the housekeeping

gene, and relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. The primers used were as follows: GAPDH (F: GTTACCAGGGCTGCCTTCTC, R: GATGGTGATGGGTTTCCCGT), LC3 (F: GGTCCAGTTGTGCCTTTATTG, R: GTGTGTGGGTTGTGTACGTCG), P62 (F: CTAGGCATCGAGGTTGACATT, R: CTTGGCTGAGTACCACTCTTATC), Col1a1 (F: GACATGTTCAGCTTTGTGGACCC, R: AGGGACCCTTAGGCCATTGTGTA), Col3a1 (F: TTTGGCACAGCAGTCCAATGTA, R: GACAGATCCCGAGTCGCAGA), and PGC1α (F: GTGCAGCCAAGACTCTGTAT, R: CTCGAATATGTTCGCGGGCT).

Statistical analysis

Shapiro-Wilk and Levene's tests assessed normality and homogeneity of variances. One-way ANOVA with Tukey's post hoc was applied to normal, homoscedastic data, while the Kruskal-Wallis and Mann-Whitney U tests were used for non-normal or heteroscedastic data. Statistical significance was set at $p<0.05$. Epidermal thickness was shown as mean ± SEM, and fold change data in box and whisker plots represented medians, ranges, and interquartile ranges.

Ethical clearance

All animal protocols of the experiment were approved by the Research Ethics Committee, Universitas Kristen Maranatha, Bandung, under number 144/KEP/VI/2023.

RESULTS

The effects of low protein and different intensities of exercise on epidermal thickness

After 8 weeks of treadmill exercise, the rats were sacrificed and the epidermal thickness of their skins was measured (Table 1). Statistical analysis using one-way ANOVA demonstrated a significant difference across groups (p=0.034). Post hoc Tukey HSD testing revealed a significant difference between group I (controls) and group II (low-protein diet) (p=0.048), with no significant differences observed among the remaining groups. Exercise, particularly at high intensity, potentially increased epidermal thickness, although not statistically significant, with group VII (high-intensity exercise) and group VIII (high-intensity exercise + low-protein diet) demonstrating near-normal values but not statistically significant compared to the control group (p=0.997 and p=0.999, respectively) or group II (low-protein diet) (p=0.183 and p=0.158, respectively). This suggests a compensatory effect of exercise under nutrient-deprived conditions.

The effects of low protein and different intensities of exercise on LC3 and p62 mRNA expression

Real-time PCR was conducted to examine mRNA expression of LC3 and p62 autophagy markers in skin tissue, with GAPDH as the housekeeping gene (Table 1).

The Kruskal-Wallis test showed a significant difference between groups for LC3 (p=0.006). The median of LC3 gene expression increased significantly in group II (2.37), group III (2.30), group IV (2.24), group V (1.64), group VI (1.94), and group VIII (3.11), compared to the control group (1.06). In contrast, the median of LC3 gene expression decreased significantly in group V (1.64) and group VII (1.54) compared to group III (2.30); in group V (1.64) and group VII (1.54) compared to group IV (2.24); in group IV (2.24), group V (1.64), group VI (1.94), and group VII (1.54) compared to group VIII (3.11).

Table 1. Median distribution of epidermal thickness, LC3, and p62 gene expression after 8 weeks of intervention, by treatment groups

Variables	Treatment groups								p value
	I (n=4)	II (n=4)	III (n=4)	IV (n=4)	V (n=4)	VI (n=4)	VII (n=4)	VIII (n=4)	
Epidermal thickness (μm)	253.48	165.23	232.48	233.85	200.24	189.51	224.61	233.93	0.034*
LC3 (au)	1.06	2.37	2.30	2.24	1.64	1.94	1.54	3.11	0.006**
p62 gene (au)	1.02	3.53	3.19	2.65	1.30	2.21	1.55	0.57	0.012**

Note: Values presented as medians; I: control; II: Low protein diet; III: Low-intensity exercise; IV: Low-intensity exercise + low protein diet; V: Moderate-intensity exercise; VI: Moderate-intensity exercise + low protein diet; VII: High-intensity exercise; VIII: High-intensity exercise + low protein diet

au: arbitrary unit; LC3: microtubule-associated protein light chain 3; P62: sequestosome 1, *=significant, $p<0.05$, **=very significant at $p<0.01$

The Kruskal-Wallis test showed a significant difference between groups for p62 (p=0.012). The median of p62 gene expression was increased in group II (3.53), group III (3.19), group IV (2.65), group V (1.30), and group VI (2.21), compared to the control group (1.02). In contrast, the median of p62 gene expression decreased significantly in group V (1.30) and group VII (1.55) compared to group II (3.53); in group V (1.30), group VI (2.21), and group VII (1.55) compared to group III (3.19); in group V (1.30) and group VII (1.55) compared to group IV (2.65); also in group V (1.30) compared to group VI (2.21).

The effects of low protein diet and different exercise intensities on mitochondrial biogenesis and collagen synthesis mRNA expression

Real-time PCR was conducted to examine mRNA expression of PGC1α, a mitochondrial biogenesis marker, and Col1a1 and Col3a1, collagen synthesis markers, from the skin tissue. GAPDH was used as a housekeeping gene, and the result is shown in Table 2.

The Kruskal-Wallis test showed a significant difference between groups for PGC1α (p=0.046). The median of PGC1α gene expression was increased in group III (5.96), group IV (9.74), group V (6.25), group VI (4.69), group VII (4.20), and group VIII (12.51), compared to the control group (1.09). A significant decrease in the median of PGC1α gene expression was found in group V (6.25), group VI (4.69), and group VII (4.20), compared to group IV (9.74); also in group V (6.25) compared to group VII (4.20).

The Kruskal-Wallis test showed a significant difference between groups for Col1a1 (p = 0.036), while a non-significant difference was found for Col3a1 (p=0.078). The median of Col1a1 gene expression increased in group III (3.22), group IV (2.46), group V (2.03), group VII (4.36), and group VIII (6.62), compared to group I (0.89); also in group VII (4.36) compared to group II (2.49). A significant decrease of Col1a1 gene expression was found in group VI (1.57) compared to group III (3.22) and in group IV (2.46), group V (2.03), and grup VI (1.57) compared to group VII (4.36); also in group VI (1.57) compared to group VIII (6.62) (Table 2).

Table 2. Median difference of PGC1α, Col1a1, and Col3a1 gene expression after 8 weeks of intervention, by treatment groups

Variables	Treatment groups								p value
	I (n=4)	II (n=4)	III (n=4)	IV (n=4)	V (n=4)	VI (n=4)	VII (n=4)	VIII (n=4)	
PGC1α (au)	1.09	6.87	5. 96	9.74	6.25	4.69	4.20	12.51	0.046*
Col1a1 (au)	0.89	2.49	3.22	2.46	2.03	1.57	4.36	6.62	0.036*
Col3a1 (au)	1.09	3.74	3.77	4.92	6.70	2.46	3.06	7.25	0.078

Note: Values presented as medians; I: control; II: Low protein diet; III: Low-intensity exercise; IV: Low-intensity exercise + low protein diet; V: Moderate-intensity exercise; VI: Moderate-intensity exercise + low protein diet; VII: High-intensity exercise; VIII: High-intensity exercise + low protein diet; au: arbitrary unit; PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Col1a1: collagen type I alpha 1 chain; Col3a1: collagen type III alpha 1 chain, *=significant at p<0.05

DISCUSSION

The findings highlight the impact of protein intake and exercise intensity on epidermal thickness, which is essential for skin health and its ability to regenerate. The significant reduction in epidermal thickness observed in group II (the low-protein diet group) compared to group I (the control group) highlights the detrimental effects of protein deficiency on skin structure. This finding is consistent with previous research showing that protein malnutrition impairs dermal extracellular matrix production and delays skin regeneration.[25,30,31] Interestingly, exercise appeared to mitigate the negative effects of protein restriction, particularly in groups VII and VIII (the high-intensity exercise groups). While the increase in epidermal thickness in these two groups was not statistically significant compared to groups I and II (control group and low-protein diet group), the observed trend suggests a potential compensatory role of exercise. This may be attributed to mechanical stimulation during exercise, which is known to activate growth factors such as transforming growth factor beta (TGFβ), interleukin-15 (IL-15), and insulin-like growth factor-1 (IGF-1), which promote collagen synthesis and tissue repair.[10,32,33]

The lack of significant differences among exercise groups may reflect the overriding impact of nutrient availability, suggesting that the effects may not surpass the threshold required to overcome protein deficiency. Despite the benefits of exercise, protein remains a critical factor for skin regeneration, and its deficiency likely limits the ability of exercise to fully restore epidermal thickness. Low-intensity exercise did not exhibit meaningful improvements in epidermal thickness, indicating that higher intensity may be necessary to stimulate significant regenerative responses. On the other hand, moderate intensity exercise might not sufficiently activate key molecular mechanisms, such as PGC1α and TGF-β signaling, which are crucial for collagen synthesis and tissue repair, while still inducing metabolic stress that hinders regeneration. In contrast, low intensity exercise imposes minimal stress, allowing for better maintenance of homeostasis, whereas high intensity exercise provides a robust stimulus that triggers significant adaptive responses, including enhanced collagen production, that finally increase epidermal thickness.

The results of this study provide insights into the regulation of autophagy in response to dietary protein restriction and exercise intensity, as indicated by changes in LC3 and p62 levels. LC3 is a marker of autophagosome formation, while p62 reflects the degradation of autophagic substrates. An increase in LC3 accompanied by a decrease in p62 indicates autophagy activation, whereas an increase in both LC3 and p62 suggests impaired autophagic flux or autophagy inhibition.[34] In groups II, III, and IV (the low-protein diet, low-intensity exercise, and low-intensity exercise + low-protein diet groups, respectively), LC3 was significantly elevated compared to group I, with concurrent increases in p62 levels. This pattern suggests that autophagy was initiated but not completed, pointing to autophagy inhibition. The impaired flux may result from insufficient substrate availability due to protein restriction or suboptimal stimulation of autophagic machinery at low exercise intensity.[35,36]

On the contrary, moderate-intensity exercise likely induced higher energy demands, leading to more effective autophagic clearance, as evidenced by increased LC3 and reduced p62 levels compared to low-intensity exercise. Although the statistical results did not show significant differences in group VI (the moderate intensity exercise + low protein diet group) compared to group II (the low protein diet group), the moderate exercise intensity level showed a lower level of p62, indicating greater effectiveness in the degradation process by the autophagolysosome. It is also intriguing to conclude that the effect of moderate-intensity exercise on autophagy in the skin is not as pronounced as its effect on skeletal muscle, as the skin is a metabolically less active organ during exercise.[37] As a result, the increase in autophagy in the skin is not as robust as in skeletal muscle. This difference may be due to the prioritization of autophagy activation in metabolically demanding tissues such as skeletal muscle, which require efficient energy production and mitochondrial quality control during physical activity.

Interestingly, high-intensity exercise led to improved autophagic flux, as evidenced by the decrease in p62 alongside elevated LC3 in group VIII (high-intensity exercise + low-protein diet), which exhibited the most favorable autophagic profile, with increased LC3 and reduced p62. This highlights the potential of high-intensity exercise to activate autophagy even under nutrient-deprived conditions. The enhanced autophagic flux likely plays a critical role in maintaining cellular homeostasis and promoting tissue repair under such stress.[12,38]

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a master regulator of mitochondrial biogenesis, showed significant upregulation in all exercise groups compared to the control. This indicates that even under protein-restricted conditions, exercise can stimulate mitochondrial biogenesis, likely through 5'-adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation, which is sensitive to the energy demands of physical activity.[10,39] However, reduced PGC1α expression in groups V and VII (the moderate intensity and high intensity exercise groups) compared to group IV (the low intensity exercise+ low protein group), suggests a possible threshold effect where the combination of higher intensity exercise and protein restriction may limit the capacity to sustain PGC1α expression. This could be attributed to increased oxidative stress or energy imbalances at higher exercise intensities, which may interfere with optimal PGC1α transcription.[14] The highest level of PGC1α observed in group VIII (high-intensity exercise + low-protein diet) reflects a robust adaptive response to combined metabolic and mechanical

stress. High-intensity exercise presumably activates AMPK, a key regulator of mitochondrial biogenesis, in response to increased energy demands, while protein restriction exacerbates the energy deficit, amplifying PGC1α expression. Additionally, the oxidative stress induced by high-intensity exercise, compounded by limited protein availability, may further enhance PGC1α activation to maintain mitochondrial function and reduce reactive oxygen species. This dual stress environment creates a synergistic effect, prioritizing mitochondrial biogenesis as a critical adaptive mechanism under nutrient-deprived conditions. These findings suggest that high-intensity exercise can compensate for protein restriction by enhancing mitochondrial function, although long-term sustainability of this response remains uncertain due to the dependence on protein for mitochondrial component synthesis.

Collagen 1A1 (Col1a1), which encodes collagen type I, demonstrated significant upregulation in multiple exercise groups, particularly at high exercise intensity. This aligns with previous findings that exercise-induced mechanical loading promotes collagen synthesis through TGF-β, IL15, and PGC1α signaling.[3,6,10] The significant differences in Col1a1 expression suggest that type I collagen synthesis is more responsive to exercise-induced mechanical stress, likely due to its structural role in providing tensile strength to tissues.[40,41] The decrease in Col1a1 expression in group IV (low intensity exercise + low protein diet), group V (moderate intensity exercise), and group VI (moderate intensity exercise + low protein diet) compared to groups III and VII (low intensity and high intensity exercise groups) suggests that low intensity exercise combined with low protein and also moderate intensity exercise by itself may not provide sufficient mechanical or metabolic stimulation to enhance collagen synthesis under protein-restricted conditions. High intensity exercise, on the other hand, likely generates robust mechanical stress and activates pathways such as the PGC1α and TGF-β pathways, which drive collagen production even when protein intake is limited. The non-linear response of Col1a1 to exercise intensity highlights the complex interplay between mechanical load, nutrient availability, and cellular signaling in regulating collagen synthesis.

In contrast, Col3a1, which encodes collagen type III, did not show statistically significant differences among the groups. This could be because collagen type III plays a more transient role in early wound healing and tissue repair, often being replaced by type I collagen in later stages of remodeling.[40,41] The lack of significant differences may reflect the timing of tissue sampling, where type III collagen synthesis might have already declined as part of the natural remodeling process. Alternatively, type III collagen may be less sensitive to the mechanical and metabolic stimuli of exercise compared to type I collagen.

The limitation of this study is the single time point of tissue sampling, which cannot capture the dynamic process of autophagy, mitochondrial biogenesis, and collagen synthesis at different time points. The study did not investigate collagen density and other markers of autophagy which may strengthen the effects of different exercise intensities on autophagy and collagen synthesis. The model of different intensities of exercise using male Wistar rats may not fully represent responses in human studies, thus limiting the clinical implication of the study. Future studies might explore the long-term effects of protein restriction and its mechanism after different exercise intensities to provide greater detail for clinical and nutritional practices.

The results of this study suggest that high-intensity exercise may be an effective adjunct therapy to temporarily counteract the adverse effects of protein deficiency on skin health. Molecular markers involved in autophagy, mitochondrial biogenesis, and collagen synthesis may be promoted by high-intensity exercise to preserve skin architecture as well as tissue repair, despite the nutrient starvation state. Clinically, this demonstrates the therapeutic potential of structured high-intensity exercise to aid in the healing of wounds, prevent skin atrophy, and increase skin resistance in malnourished, chronically ill patients, or in elderly patients with muscle and skin wasting. The integration of exercise into the management plan of patients at risk of impaired tissue repair may provide a low-cost, non-pharmacological strategy for enhancing recovery and maintaining skin integrity in clinical and community health settings.

CONCLUSIONS

This study provides compelling evidence that high-intensity exercise can mitigate the adverse effects of a low-protein diet on skin structure and molecular pathways associated with autophagy

and collagen synthesis. By enhancing autophagy and upregulating PGC1α and Col1a1, exercise emerges as a potent intervention to support tissue health under nutrient-deprived conditions. These findings highlight the potential of combining dietary and physical strategies for optimizing skin regeneration and tissue remodeling.

Conflict of Interest

Competing interests: no relevant disclosures.

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Author Contributions

JWG, RL, and FK initiated the research idea; FK, VMT, and HG carried out the animal experiment; JWG, DG, DKJ directed the hematoxylin and eosin staining and real-time PCR; JWG, RL, VMT, and DG managed data analysis and interpretation; JWG, RL, DG, and DKJ prepared the manuscript drafting. All authors have read and approved the final manuscript.

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Data Availability Statement

Original data used in this study may be requested directly from the corresponding author.

Declaration of Use of AI in Scientific Writing

The authors used Grammarly to improve English writing, ChatGPT to improve the quality of the writing, and then all authors reviewed and edited the content before submitting the manuscript.

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