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ORIGINAL ARTICLE

Effects of 4 Weeks of Beta-Alanine Intake on Inflammatory Cytokines after 10 km Long Distance Running Exercise

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PURPOSE: This study aimed to examine the immunological effects of β-alanine intake for 4 weeks on immune function changes after long-distance exercise and the possibility of β-alanine intake as an effective exercise supplement to improve exercise performance and maintain immune function.

METHODS: Eighteen male college students were randomly assigned to two groups, one with two capsules of 250 mg β-alanine and the other with placebo without a nutritional effect. The participants took one capsule each in the morning and evening after the meals. This study was conducted in a double-blinded manner. To analyze the inflammatory cytokines expressed during exercise, a 10 km long-running exercise was performed, and blood was collected from the forearm vein a total of 4 times (at rest, immediately after exercise, 30 minutes, and 60 minutes in recovery).

RESULTS: As a result of analyzing the level of inflammatory cytokine IL-6, compared to the placebo group, the β-alanine intake group decreased significantly to 60 minutes after recovery from long-distance aerobic exercise, and both groups showed a significant difference between both periods ($p < .001$). However, there was no significant difference between the groups based on the measurement period before and after intake. As a result of analyzing the level of TNF-α, the expression of TNF-α in the placebo group was significantly decreased from immediately after long-distance aerobic exercise to 60 minutes after recovery, but in the β-alanine group, TNF-β expression did not occur immediately after exercise, and there was no significant difference until the recovery period; thus, there was no statistically significant difference between the two periods. In addition, there was no significant difference between the groups in terms of the measurement period before and after intake.

CONCLUSIONS: Based on the above results, β-alanine intake for 4 weeks is thought to be effective in maintaining temporarily reduced immune function after long-distance exercise by reducing the level of inflammatory cytokines in the study participants.

Key words: β-alanine, Carnosine, Immune system, Cytokine, IL-6, TNF-α

INTRODUCTION

The immune system plays an important role in the recovery process of the body and tissue after exercise [1], and performs an action to maintain the homeostasis of the body [2]. However, exercise at an intensity that exceeds the maintenance of homeostasis in the body lowers the body's immune function and resistance ability due to external stimuli, and may cause oxidative stress, muscle fatigue, and muscle injury [3]. Attempts are being made to minimize such negative effects through research based on sports science in various fields [4]. In addition, various methods for improving fatigue recovery ability and immune function and managing inflammation after exercise through intake of nutritional supplements and dietary supplements have been suggested [3].

In the past, intake of exercise supplements was intended to induce effective exercise performance by increasing energy generation, exercise-related metabolic control, and energy use efficiency to improve exercise performance. For the purpose of preventing and recovering from fatigue and maintaining immune function, ergogenic aids such as taurine, cre-

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atine, carnosine, beta-alanine, vitamins, lactate, and arginine have been proven to be effective.

Among them, β-alanine is a non-protein amino acid that is endogenously produced in the liver and has been identified as a rate-regulated precursor for carnosine synthesis [5,6]. In addition, it was found that the carnosine precursor, β-alanine, was supplemented through the diet to increase the carnosine concentration in the muscle [7,8] and attenuate exercise-induced reductions in pH [9], supporting the concept that carnosine plays a significant role in buffering exercise-induced acidosis.

Carnosine, synthesized by the combination of β-alanine and histidine, is a naturally occurring dipeptide with numerous potential physiological functions and is formed by combining its constituent amino acids, L-histidine and β-alanine, with the assistance of the enzyme carnosine synthetase [10]. Carnosine acts as an intramuscular buffer, especially during high-intensity activity [11]. In addition to acting as an intramuscular buffer, carnosine has been shown to play various physiological roles in the body, such as reducing ROS expression and release of inflammatory factors in the body due to antioxidant and anti-inflammatory effects that suppress cell membrane damage caused by oxidative [12,13]. Increasing the content can significantly improve inflammatory and oxidative damage [14], potentially reducing neurodegenerative degradation associated with inflammatory responses to stress, thereby improving cognitive function and mood conditions [15-18].

Many previous studies support the possibility that carnosine may affect some health-related mechanisms, including antioxidant properties, anti-aging, immune enhancement, and neurotransmitter action [10]. This is because carnosine is widely regarded as an important anti-saccharide that acts to prevent reactions that can affect the body's protein structure and function [10]. Advanced glycated end products are associated with ageing processes and diabetes complications, but carnosine can improve the development of metabolic diseases or diabetes complications by reducing the release of cytokines that regulate the immune system by reducing the formation of these end products.

Recently, the therapeutic potential of carnosine was reviewed in a study by Artioli et al. [19], including effects on aging that could be improved by β-alanine or carnosine supplementation, neuroprotective transmission effects, and tumor growth inhibition effects. Studies demonstrating the therapeutic effect on a wide variety of subjects and conditions are being actively conducted [20-22]. Caruso et al. [23] reported that increased carnosine inhibited the release of lipopolysaccharide and IL-6 by interferon-γ-activated macrophages, and carnosine supplementation in overweight or obese pre-diabetic patients with glucose, triglycerides, and final It has been shown to attenuate the level of glycation end products and TNF-α expression [24,25], thereby reducing the risk of diabetic complications and oxidative stress-related diseases, and showing its effectiveness as a therapeutic agent to improve chronic diseases. Further studies are needed to substantiate it. Therefore, it is meaningful to examine the immunological effects of physiological changes in the body following β-alanine intake.

As a result of analyzing the effect of β-alanine supplements on performance in various exercise types and program structures, the effect of β -alanine supplements on performance varies with exercise time and intensity [26]. Saunders et al. [27] observed that exercise lasting from 0.5 to 10 minutes showed the best results, but short exercise (< 0.5 minutes) did not improve performance, and Hobson [28] showed that --alanine was most effective during exercise for 60 to 240 seconds, which means high-intensity exercise.

However, despite many previous studies demonstrating the effectiveness of β-alanine, few studies have conducted long-term endurance exercise, and even the protocol for long-term aerobic exercise is limited to studies using cycle ergometers. In addition, most of the studies on β-alanine intake are conducted using a resistive exercise protocol, focusing only on the effect of improving exercise performance as an adjuvant to improve muscle power or performance of subjects due to increased carnosine concentration. Trexler et al. [29] reported that more long-term exercise is needed to demonstrate the effectiveness of β-alanine in endurance performance exceeding 25 minutes, and in previous study related to endurance exercise, based on the fact that long-distance running exercises such as marathons cause acute inflammatory response, changes in blood lipid indicators, and various physiological changes, considering that long-distance running can be a high-intensity aerobic exercise depending on the subjects' personal physical level, It is thought that the reduction of blood fatigue substances along with the improvement of exercise performance during moderate-intensity aerobic exercise at a low r of intake of β-alanine supplements for 4 weeks will have a positive effect on the temporarily elevated immune system. It is thought that the reduction of blood fatigue substances along with the improvement of exercise performance during moderate-intensity aerobic exercise at a low-speed of intake of β-alanine supplements for 4 weeks will have a positive effect on the temporarily elevated immune system.

Therefore, this study analyzed the immune mechanisms appearing during long-distance aerobic exercise, and examined the effects of β-ala-

nine orally on inflammatory cytokines TNF-α and IL-6, which are immunomodulatory factors, increased after long-distance aerobic exercise by oral intake for 4 weeks. The purpose of this study is to examine the possibility that alanine intake will be usefully used as an effective exercise aid for immune function and inflammatory response.

METHODS

1. Subjects

The power test was performed using G*Power 3.1.9.2 (Franz Faul, University of Kiel, Kiel, Germany). The power test was performed using G*Power 3.1.9.2 (Franz Faul, University of Kiel, Kiel, Germany). An estimated sample size of 12 was calculated utilizing data from Santana et al [26], an α of 0.05 with a power of 0.8. Our study, the sample size was set to 20, but the power of 0.95 was obtained by analyzing the data of 18 that were finally successful except for 2, which was abandoned.

As the results of the IRB approval did not come out during the course of this study, the study had no choice but to proceed without IRB approval. Therefore, prior to the study, detailed research contents and procedures for this study were explained to all the study subjects, and among those who voluntarily expressed their intention to participate, the study was conducted with those who submitted an individual participation consent form.

In order to prove the effect of β-alanine intake to 18 male college students, the subjects of this study were randomly assigned to 9 ingestion groups and 9 in the control group to which the placebo effect was given. The physical characteristics of the subjects of this study are as presented in Table 1.

As a result of the pre-independent sample t-test for the two groups, there was no significant difference in all items, thus securing the homogeneity of the two groups.

Table 1. Physical characteristics of subjects

Variable	β-alanine (n=9)	Placebo (n=9)	*p*-value
Age (yr)	20.78±1.2	20.33±4.36	.06
Height (cm)	175.89±5.04	175.11±6.11	.89
Weight (kg)	73.99±9.67	73.3±10.11	.91
Body fat (%)	19.09±4.83	19.44±6.97	.14
Muscle mass (kg)	33.82±3.52	33.64±3.58	.88

M±SD.

2. Procedure

1) Experimental Design

This study was conducted in the Sports Science Lab of E University located in S-city, Gyeonggi-do and an outdoor track 400 m in the Sports Park located in Y-city, Gyeonggi-do. A maximum exercise load test was performed to evaluate the aerobic exercise capacity of the study subjects before running for 10 km, and a wash-out period of 24 hours was applied after the exercise load test. For the 10km long-distance running exercise, the exercise intensity of the study subjects was set based on the results of the maximum exercise load test. The study subjects arrived at the outdoor track 30 minutes before the 10 km run in advance, took sufficient rest, and performed warm-up and stretching exercises. This study was conducted according to the research procedure in Fig. 1.

2) β-alanine Supplements

In order to exclude the psychological effects of β-alanine supplement intake, all study subjects were randomly assigned to the β-alanine intake group (BA) and the placebo group (PO) by a double-blind method. research was conducted. The duration of β-alanine intake was set to 4 weeks based on a study by Sale et al. [30]. In addition, a study by Dolan et al. [31] found that 3.2 g to 6 g daily was an appropriate dose, and 500 mg per day was taken referring to the results of the study that showed

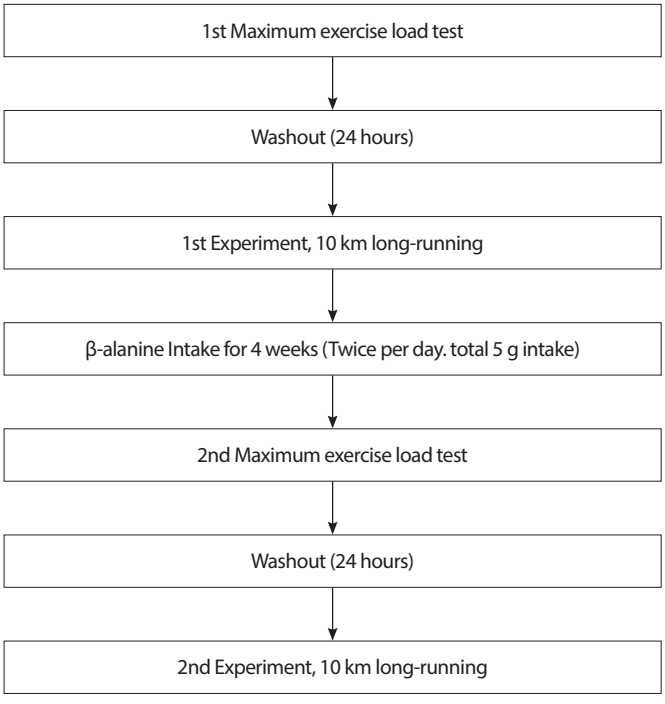

Fig. 1. Experimental Design.

that tingling skin abnormalities were confirmed when taking more than 6 g. The intake time was set after breakfast and dinner, referring to Jordon's study, and 250 mg was divided and consumed voluntarily at 10 am and 6 pm, respectively [32]. Meanwhile, in the placebo group, starch powder was added to the gelatin capsule and ingested at the same time. In order to check whether or not to take the drug, all study subjects were asked to fill out an intake record to determine the intake rate.

3) Long-distance Aerobic Exercise

The subjects of the study performed a 10 km running exercise twice in total, and had them run the same distance on a 400 m outdoor track at the same time. Two types of wireless electronic heart rate monitors (H10 Polar, M5 SUUNTO) were worn before the 10 km running exercise, and the heart rate was measured while resting for 30 minutes before the experiment. The exercise intensity was 64-76% of the maximum heart rate (HRmax), which is the medium-intensity exercise intensity suggested by ACSM, considering that a 10 km run is a long distance based on the aerobic exercise ability of the study subjects through the first maximum exercise load test. The average heart rate was set to 146 ± 22 bpm [33], and after the resting heart rate and lactate level were confirmed, the selected study subjects completed the race while maintaining the target heart rate. Lactic acid, blood glucose, blood and heart rate were measured at rest before exercise, immediately after running for 10 km, at 30 minutes in the recovery period, and at 60 minutes in the recovery period. The 10 km running exercise method was designed with reference to the exercise protocol of Santana et al. [26].

3. Variables

1) Body Composition

Body composition was measured twice before and after intake of β-alanine, and height, weight, body fat percentage, and muscle mass were measured using body composition analyzer(BSM370, H20N INBODY). Subjects fasted for more than 12 hours before measurement, wore simple clothes, and removed metal attachments.

2) Blood Analysis

All study subjects were instructed to limit drinking and excessive exercise and take rest for 48 hours before the start of the test. Blood was collected directly from the forearm vein by a professional nurse, and after collecting 3.5 mL of whole blood in 3.5 mL of SST, immediately mixed 5 to 10 times. All samples were stored it at room temperature for 30 minutes, spun it at 3,000 RPM for 10 minutes using a centrifuge, collected 1.0 mL of the separated supernatant, transfered to a container for transportation, and transported to Company N located in Y-city, Gyeonggi-do, below -20 degrees Celsius and analyzed. All of the collected research variables were measured and analyzed at the request of Gyeonggi-do N Company.

3) Inflammatory Cytokines

IL-6 and TNF-α were measured using the collected samples to examine the changes in inflammatory cytokines during long-distance aerobic exercise following ingestion of β-alanine. The measurement period was the first experiment, before ingestion of β-alanine, at rest (BE) before running for 10 km, immediately after exercise (AD), during the recovery period of 30 minutes (R30), and during the recovery period of 60 minutes (R60), blood was collected 4 times, and the second experiment After taking β-alanine for 4 weeks, blood was collected 4 times at rest (BE), immediately after exercise (AD), 30 minutes in recovery (R30), and 60 minutes in recovery (R60) before running for 10 km, for a total of 8 times.

(1) IL-6

The concentration of IL-6 was analyzed using Enzyme-Linked Immunosorbent Assay (ELISA), and a Colorimetric Microplate Reader VERSA Max (Molecular device, USA) was used as the test equipment. As a reagent, IL-6 high sensitivity was measured using BMS213HS (Invitrogen, USA).

(2) TNF-α

For the concentration analysis of TNF-α, ELISA was used, and Microplate Reader VERSA Max (Molecular device, USA) was used as the test equipment. As a reagent, TNF-α high sensitivity was measured using Quantikine HS Human TNF-α (R&D, USA).

2. Statistical analysis

For all data obtained in this study, the mean (M) and standard deviation (SD) of the measured variables were calculated using IBM SPSS ver 25.0. Two-way repeated measures ANOVA was performed to verify the main effect and the interaction effect between each period and group. When the main effect was found, the difference between before and after intake for the measured items was measured using a paired sample t test, and an independent t-test was performed to determine the differ-

ence between groups before and after ingestion. To analyze the effect of exercise ability within each group, one-way ANOVA was performed on the average difference between measurement periods (BE, AD, R30, R60). The least significant difference (LSD) post hoc test was performed. The statistical significance level of all measurement items was set at $\alpha < .05$ level.

RESULTS

1. Changes in IL-6 after 4 weeks of β-alanine Intake

Table 2 shows the results of the analysis of the interaction effect according to the measurement period and ingestion. Interaction effect between period × group ($p = .029$) and main effect between period ($p = .000$) were found, but there was no main effect between groups.

Table 3 shows the results of one-way ANOVA to analyze the average difference between measurement periods (BE, AD, R30, R60) within a group during long-distance aerobic exercise. Both the β-alanine intake group and the placebo group showed a significant increase immediately after exercise and then decreased until 60 minutes of recovery. R60 showed a greater decrease Table 3.

2. Changes in TNF-α after 4 weeks of β-alanine intake

Table 4 shows the results of analysis of the interaction effect according to the measurement period and ingestion. The interaction effect between period × group ($p = .042$) and the main effect between period ($p = .014$) were found, but there was no main effect between groups.

Table 5 shows the results of one-way ANOVA to analyze the average difference between measurement periods (BE, AD, R30, R60) within a group during long-distance aerobic exercise. Both the β-alanine intake group and the placebo group showed a significant increase immediately after exercise and then decreased until 60 minutes of recovery. The placebo group showed a greater decrease between the measurement periods (BE, AD, R30, R60) after β-alanine intake compared to the β-alanine intake group Table 5.

DISCUSSION

Stimulation by oxidative reaction in the body through exercise causes inflammation along with cell damage, and it is known that the secretion of various cytokines affects the inflammatory process in the body [34]. It activates the inflammatory mechanism of the human body through the synthesis and release of pro-inflammatory mediators such as cytokines [35], and among many items of pro-inflammatory cytokines, IL-6, TNF-α, CRP, etc. It is the most commonly studied indicator of performance [36+38]. The mechanism of cytokine expression has a series of temporal sequences and is known to appear differently in pathological inflamma-

Table 2. Results of Two-way ANOVA of IL-6

Variable	SS	df	MS	F	*p*-value
Groupr×Time	0.041	1	0.041	5.77	.029*
Time	4.807	1	4.807	671.13	.000***
Group	0.010	1	0.010	0.557	.466

M±SD.
*$p < .05$, ***$p < .001$.

Table 4. Results of Two-way ANOVA of TNF-α

Variable	SS	df	MS	F	*p*-value
Groupr×Time	7.789	1	7.789	4.889	.042*
Time	12.239	1	12.239	7.683	.014*
Group	14.480	1	14.480	0.256	.620

M±SD.
*$p < .05$.

Table 3. Changes in IL-6 during 10 km long-distance running exercise tests performed before and after intake

Variable	Group	BD (A)	AD (B)	R30 (C)	R60 (D)	f-value
IL-6 (pg/mL)	Before intakes					
	BA	$2.65 \pm 1.01^{b,c,d}$	4.6 ± 0.99^{a}	4.46 ± 0.93^{a}	4.36 ± 0.85^{a}	10.344***
	PO	$1.96 \pm 1.01^{b,c,d}$	3.76 ± 0.90^{a}	3.45 ± 0.86^{a}	2.93 ± 0.89^{a}	9.668***
	p-value	.638	.543	.479	.232	-
	After intakes					
	BA	$2.5 \pm 0.96^{b,c,d}$	$3.52 \pm 0.96^{a,d}$	$3.51 \pm 0.89^{a,d}$	$3.01 \pm 0.92^{a,b,c}$	14.51***
	PO	$2.13 \pm 1.01^{b,c,d}$	$3.55 \pm 0.87^{a,c,d}$	$3.2 \pm 0.89^{a,b,d}$	$2.86 \pm 0.89^{a,b,c}$	22.332***
	p-value	.797	.972	.805	.908	-

M±SD.
BD, Before Exercise; AD, After Exercise; R, Recovery; BA, β-alanine intakes; PO, Placebo.
^{a,b,c,d}significant difference among the measuring times within group.
***$p < .001$.

Table 5. Changes in TNF-α during 10 km long-distance running exercise tests performed before and after intakes

Variable	Group	BD (A)	AD (B)	R30 (C)	R60 (D)	f-value
TNF-α (pg/mL)	Before intakes					
	BA	0.63 ± 0.04[b]	0.75 ± 0.04[a,c,d]	0.66 ± 0.03[b]	0.66 ± 0.04[b]	7.721***
	PO	0.55 ± 0.02[b,c,d]	0.71 ± 0.03[a,c,d]	0.62 ± 0.03[a,b]	0.6 ± 0.03[a,b]	31.526***
	p-value	.147	.418	.204	.223	-
	After intakes					
	BA	0.48 ± 0.02	0.52 ± 0.03	0.5 ± 0.03[d]	0.47 ± 0.02[c]	2.308
	PO	0.53 ± 0.02[b]	0.59 ± 0.02[a,c,d]	0.52 ± 0.03[b]	0.54 ± 0.03[b]	6.687**
	p-value	.228	.131	.753	.091	-

M ± SD.
BD, Before Exercise; AD, After Exercise; R, Recovery; BA, β-alanine intakes; PO, Placebo.
[a,b,c,d]significant difference among the measuring times within group.
***$p < .001$.

tory stimulation and exercise situations [39]. Although the mechanism of IL-6 synthesis and secretion in muscle is not clear, it is reported that it is due to cellular stress [40], exercise-induced increase in reactive oxygen species (ROS) induces activation of TLR4, MyD88, and NF-kB signaling mechanisms in skeletal muscle, and inflammatory cytokines IL-6, TNF-α, IL-1β by expressing inflammatory genes such as [41], it can be said that an inflammatory response is caused.

In a previous study, as a result of ingesting 3.4 g of β-alanine and 3.4 g of arginine per day for 2 weeks to elite soldiers, it was shown that TNF-α and CRP significantly decreased in the intake group [42], a study showing that IL-6 decreased and IL-10 increased immediately after resistance exercise as a result of administering 2 g of L-carnosine and 2 g of β-alanine per day for 2 weeks to the general public [43] also showed a decrease in the levels of IL-6 and TNF-α immediately after exercise in the intake group, consistent with the results of previous studies. Animal data also showed that injection of β-alanine to mice induced by myocardial ischemia/reperfusion significantly reduced TNF-α and IL-6 [44], and the injection of glutamine and β-alanine to mice treated with resistance exercise showed TNF-α, IL-6, IL-1β decreased, and IL-10 increased [45] which is consistent with the results of this study.

In conclusion, it can be understood that the increase in ROS and the imbalance of cytokines caused by oxidative stress during the 10 km long-distance running exercise increased the expression of inflammatory cytokines. It is thought that the decrease and inflammatory cytokine expression were directly affected, thereby reducing the levels of IL-6 and TNF-α. This is because in the study of Liu et al. [46], histidine and carnosine supplementation significantly inhibited the release of pro-inflammatory cytokines, and the levels of IL-6 and TNF-α were significantly decreased, resulting in decreased CRP. Research results suggesting that the release could be explained can be said to support this. In the case of CRP in this study, the intake group decreased significantly compared to the control group, but the number of subjects participating in this study was small, so there was no statistically significant difference. In addition, since the 10 km long-distance running intensity of moderate intensity, about 64-76% of HRmax conducted in this study, was not able to observe the change in the CRP level of the subjects, and the change in CRP was limited to interpret the results in this study.

The limitation of this study was that various blood variables could not be observed because experimental conditions and costs should be considered during the experiment, and levels of infectious cytokines were confirmed to confirm the effectiveness of the adjuvant to reduce the expression of inflammatory factors temporarily increased after exercise. In this study, there was no significant difference between the groups due to the small number of subjects, and the initial inflammatory response was lower than the measurement range of the test reagent because they were male students in their 20 seconds with healthy physical strength without chronic inflammatory diseases. In addition, significant changes could not be observed because the moderate intensity of the 10 km long-distance running did not affect the subjects' inflammatory cytokine levels, and there were limitations in controlling the subjects' lifestyle, diet, drinking, smoking, and weather conditions at outdoor experiments.

In future studies, the correlation between cytokine release and how β-alanine intake affects the complementary mechanism of cytokine, and it is thought to be a study that can support the clear pattern of expression of immune factors and the therapeutic effect of β-alanine.

CONCLUSION

This study investigated the effect of 4 weeks of β-alanine intake on inflammatory cytokines, which is an immune regulator increased after long-distance running exercise, and investigated the immunological changes through exercise nutrition through physiological changes in the body following β-alanine intake. This study was conducted with the purpose of suggesting the possibility that β-alanine intake could be usefully used as an effective exercise aid not only to improve exercise performance but also to maintain immune function, and the following conclusions were obtained.

β-alanine intake for 4 weeks significantly decreased the levels of inflammatory cytokines IL-6 and TNF-α from immediately after moderate-intensity long-distance running exercise to 60 minutes of recovery, and weakened the expression level of inflammatory cytokines immediately after exercise. It had a positive effect on maintaining immune function.

Summarizing the above results based on the change pattern of the variables observed in this study, the immune factors and fatigue substances in the blood during moderate-intensity exercise showed a significant increase as the exercise duration increased, and that the immune modulators according to the intake of β-alanine showed a significant increase. It was concluded that there was a difference in their expression patterns. β-alanine intake has a positive effect on physiological changes in the body, maintenance of temporarily reduced immune function and anti-inflammatory function, which occur during moderate or higher-intensity exercise. It is judged to be worthy of use as a genic-aid. In addition, in order to improve diabetes exacerbation and complications related to the expression of cytokines regulating the immune system, and to improve metabolic diseases, additional evidence demonstrating the effectiveness as a therapeutic agent to improve blood sugar and insulin control and diabetic complications in diabetic patients If the research proceeds, it can be thought that β-alanine can be used more diversely as a therapeutic agent beyond an exercise aid.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: HW Moon; Data curation: SY Jin; Formal analysis: SY Jin, HW Moon; Funding acquisition: HW Moon, JS Kim; Methodology: SY Jin, HW Moon; Project administration: SY Jin, HW Moon, JS Kim; Visualization: SY Jin, JS Kim; Writing-original draft: SY Jin, HW Moon, JS Kim; Writing-review & editing: SY Jin, HW Moon, HY Kim.

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