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Effects of Regular Habitual Exercise on Platelet Energetics in Male Recreational Contact Sports Student-Athletes: A Cross-Sectional Study

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Keywords: athletes | ATP | lactate | oxidative phosphorylation | platelets | PRP

ABSTRACT

Background and Aims: Recently, an increasing number of athletes (from recreational to professional) have chosen autologous platelet-rich plasma (PRP) therapy to treat their sports-related injuries. However, its clinical outcomes vary among individuals and are thought to be influenced mainly by the athletes' PRP quality and physical condition. Thus, for successful PRP therapy, it is crucial to evaluate platelet activities in addition to soluble bioactive factors. In previous studies, we examined male professional athletes and female elite student-athletes. To expand the findings, in this study, we focused on male recreational student-athletes and characterized their platelet energetics.

Methods: PRP was prepared from healthy male soccer club members (college student-athletes, CA) and sedentary adults of similar ages (non-athletes, NA) at rest. Plasma lactate, platelet adenosine triphosphate (ATP), and oxygen (O_2) consumption levels were quantified using biochemical and bioelectrical methods.

Results: The body composition indices of the CA generally showed characteristics that fell between those of professional athletes and the NA. Changes in platelet lactate, ATP, or O_2 consumption levels, during the 24 h incubation period did not differ significantly between the two groups. Nevertheless, the changes in ATP levels were strongly and positively correlated with those in O_2 consumption only in the CA group.

Conclusions: Energy generation in CAs' platelets is suggested to be more closely related to O_2 consumption than that of the NA. Habitual exercise may impact platelet energetics as well as muscle cell energetics; however, further validation should be conducted with large samples to provide more insights into this hypothesis.

Tomoharu Mochizuki and Takashi Ushiki contributed equally to this study.

1 | Introduction

Platelet-rich plasma (PRP) therapy is currently the most popular modality for tissue regenerative therapy among athletes, regardless of their physical performance level [1]. Based on their clinical experience, many sports health professionals share the impression that athletes with many common sports injuries respond well to PRP [2]. However, their increasing popularity is mainly due to athletes' desires rather than etiological reasons or medical benefits [1]. Thus, PRP therapy is usually selected as the first-line therapy, and the issue of lack of strong evidence or standardized treatment protocols is considered trivial in clinical settings. Basic research on the biomedical basis for PRP therapy is widely deemed necessary. However, orthopedic physicians have expanded the indications and frequently use PRP in injured athletes. Therefore, the clinical outcomes of PRP therapy vary among individuals. Moreover, in contrast to its frequent use, the literature suggests that the benefit of PRP therapy is often marginal or that there is no benefit beyond specific etiologies [1]. PRP composition, for example, the quality and quantity of growth factors, should be further investigated along with patients' systemic and local health conditions to correct this conflicting situation and optimize therapy outcomes.

Since soluble bioactive factors, including positive and negative factors for cell growth, have been vigorously investigated by many groups, we focused on platelets, which are the major cell components in PRP, and studied their biology and physiology over the past 3 years. In previous studies investigating platelet energetics in male professional and female collegiate elite athletes [3–6], we found that platelet adenosine triphosphate (ATP) levels were lower in professional and elite athletes than in their counterparts. However, ATP generation was augmented in the skeletal muscles of the athletes. However, to date, no convincing data have been published explaining the mechanisms underlying this phenomenon.

To address this question, in this study, we modified the experimental design to exclude the influence of in vivo circulatory conditions, suppress platelet activation, and highlight changes in individual platelet parameters. In addition, we focused on recreational athletes but not contract sports student-athletes (soccer players), who were expected to express the transitional physical characteristics from sedentary adults to professional athletes and probably platelet energetics.

2 | Methods

2.1 | Study Design

The Niigata University School of Medicine has several athletic groups, including a soccer club, in which medical students participate in recreational soccer and conduct official and recreational games against other medical schools. This cross-sectional study was conducted among male soccer club members (college student-athletes, CA; $n = 19$; aged 19–25 years) at rest. Their counterparts were male sedentary medical staff and graduate students (non-athletes, NA; $n = 19$, aged 23–45 years) at rest. The inclusion criteria were as follows: negative for Human Immunodeficiency Virus, human hepatitis B Virus, human hepatitis C Virus, or syphilis antibodies; no smoking history; no chronic systemic diseases regardless of medical control; engagement in daily physical training on-season (for CA); no regular exercise habits (for NA) indicating no daily moderate-intensity physical exercise [7]; and agreement to provide informed consent. Notably, current recommendations prescribe at least moderate-intensity physical activity, requiring ≥ 3 metabolic equivalents for ≥ 30 min almost daily, generating ≈approximately 1000 kcal/week [7].

Blood was collected at the beginning of spring break and immediately after the academic year-end examination (for CA). Notably, CA are not necessarily considered elite athletes, and their physical activity and amount of daily exercise vary among individuals.

To validate the effects of regular exercise on physical conditions in the CA group, professional athletes were also invited to participate in this study. Blood samples were collected from professional soccer athletes ($n = 19$, aged 19–37 years) from the J1 League (the top division of the Japan Professional Football League) during their official medical examinations immediately after the regular season.

The Ethics Committee for Human Participants of Niigata University, Niigata, Japan, approved the study design and consent forms for all procedures (approval no. 2021-0126). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, 1964, and revised in 2013. All participants provided written informed consent.

2.2 | PRP Preparation

Peripheral blood was collected in glass vacuum blood collection tubes (Vacutainer; BD Biosciences, Franklin Lakes, NJ, USA) containing 1.5 mL of A-formulation acid-citrate-dextrose (Terumo, Tokyo, Japan). After incubation for 20–24 h, PRP was prepared from whole blood samples by horizontal centrifugation (415 *g*, 10 min). The upper plasma fraction of the PRP was pooled into a plastic tube, gently mixed, and aliquoted into 0.5 mL sample tubes with minimized air inclusion by adding 0.6 mL. The samples were incubated by intermittent stirring with a tube roller mixer at ambient temperature (20°C–23°C) as described previously [8].

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Figure 1 illustrates the experimental protocol. PRP preparations were quantified every 24 h, and the subtracted values were analyzed.

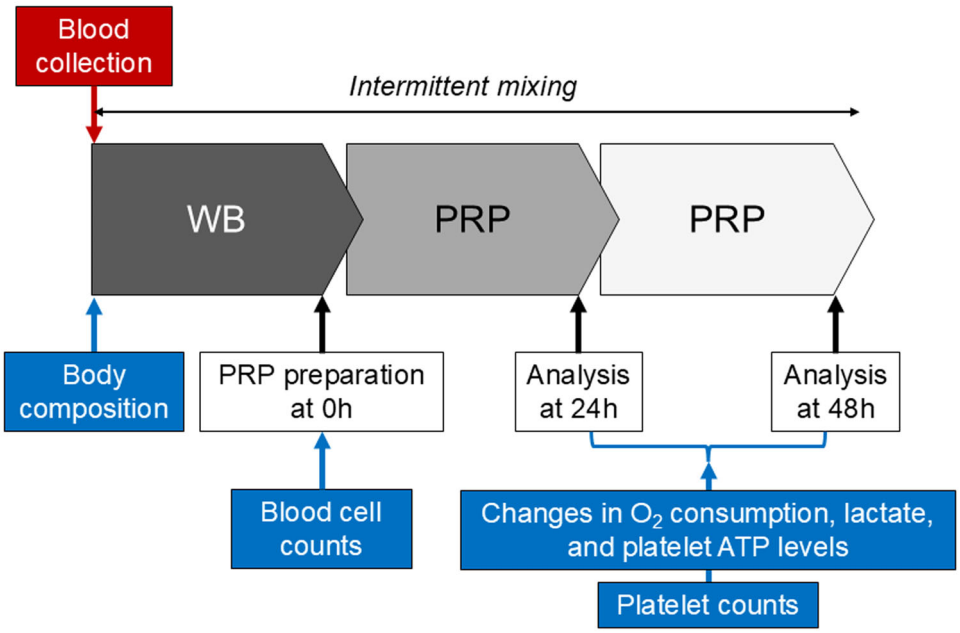

FIGURE 1 | Summary of experimental design and schedule. PRP, platelet-rich plasma; WB, whole blood.

2.3 | Platelet Oxygen Consumption Levels

Oxygen (O_2) consumption was measured using a Mitocell Respirometry System, which comprised a 782-oxygen meter and an RC300 respiration cell with a 1302 electrode (Strathkelvin Instruments Limited, North Lanarkshire, Scotland, UK), as previously described [9].

According to the manufacturer's instructions, the oxygen electrode was calibrated with air-saturated phosphate-buffered saline (PBS) (Calibration "high") and 0.01 M disodium tetraborate solution containing a small amount of sodium sulfite (Calibration "zero"). Calibration was repeated for each measurement, and the inner wall of the cell was cleaned with a Kimwipe to prevent possible carryover of oxygen content from the saturated PBS and samples.

For sample preparation, PRP fractions were prepared as described above, and platelet-poor plasma (PPP) fractions were prepared by further centrifugation to exclude cellular components. PRP and PPP fractions were fully added to 0.5 mL microtubes to minimize air space and air bubble formation and gently stirred intermittently for 24 h at room temperature. At the end of the incubation period (at 24 h), platelets were excluded from the PRP samples to prevent unexpected adhesion of platelets and large molecules to the polyethylene membrane covering the electrode and to avoid membrane clogging.

When transferred to the respiratory cells, the platelet-free fractions were handled carefully to minimize contact with air. The dissolved oxygen (DO) levels were measured with stirring at 21.0°C–21.4°C, and the plateau levels were recorded as the DO concentrations. O_2 consumption at 24 h (Figure 1) was calculated by subtracting the measured DO levels of PRP from those of PPP and normalized by platelet count. All samples were measured in quadruplicate.

Similarly, O_2 consumption was determined at 48 h. The subtraction of the 24-h data from the 48-h data provided the platelet-dependent net O_2 consumption during this 24-h period.

2.4 | Plasma Lactate Levels

The lactate levels in extracellular plasma were determined using a lactate meter with specific test strips based on the lactate oxidase enzyme electrode method (Lactate Pro2; Arkray, Kyoto, Japan) [10]. Since the lactate levels in stored whole blood samples largely depend on the glycolysis of red blood cells, time-course changes in the form of PRP, which excludes red blood cells, were monitored from 24 to 48 h to determine the lactate levels released by platelets.

During the initial incubation of whole blood samples, plasma lactate levels increased drastically depending on the quantity and activity of red blood cells. In contrast, PRP preparation minimized the increase in lactate levels.

2.5 | Platelet ATP Levels

At 24 h and 48 h of analysis, non-fixed living platelets suspended in 100 μL Dulbecco's PBS were adjusted to 40–60 × 10^4/μL and stored at −80°C until needed, typically within 2 weeks. After thawing, platelet ATP levels were determined using a luminescence ATP assay kit (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) and a luminescencer (AB-2200, Atto Corp., Tokyo, Japan) [11] and normalized by platelet count. Changes in platelet ATP levels during the last 24 h were calculated by subtracting the 24-h data from the 48-h data.

2.6 | Body Composition

Immediately before blood collection, body composition was determined using a bathroom weighing scale (HCS-FS03; ECLEAR, ELECOM, Osaka, Japan) equipped with a unique magnetic resonance imaging-based program that accurately evaluates body fat percentage (BFP) based on measured bioelectrical impedance and body weight [12]. The body mass index (BMI), BFP, skeletal muscle percentage (SMP), and basal metabolic ratio (BMR) were automatically determined using this weighing scale.

2.7 | Statistical Analysis

Data were presented as box plots using SigmaPlot (version 14.5; Systat Software Inc., Palo Alto, CA, USA). For multiple comparisons, statistical differences were confirmed using a one-way analysis of variance on ranks, followed by the Tukey test. Statistical differences were confirmed using the Student's *t*-test to compare both groups. When the data failed to pass the normality or equal variance tests, the Mann–Whitney rank-sum test was performed (SigmaPlot version 14.5). Differences were considered statistically significant at $p < 0.05$.

The correlation between the two indices was compared using Spearman's correlation analysis, and the correlation coefficients were calculated using the SigmaPlot software. The correlation strength was defined as very strong (0.8–1.0), strong (0.6–0.79), moderate (0.4–0.59), weak (0.2–0.39), and very weak (0–0.19).

3 | Results

The age, body composition indices, and static platelet ATP levels of both groups are summarized in Figure 2. Of the three

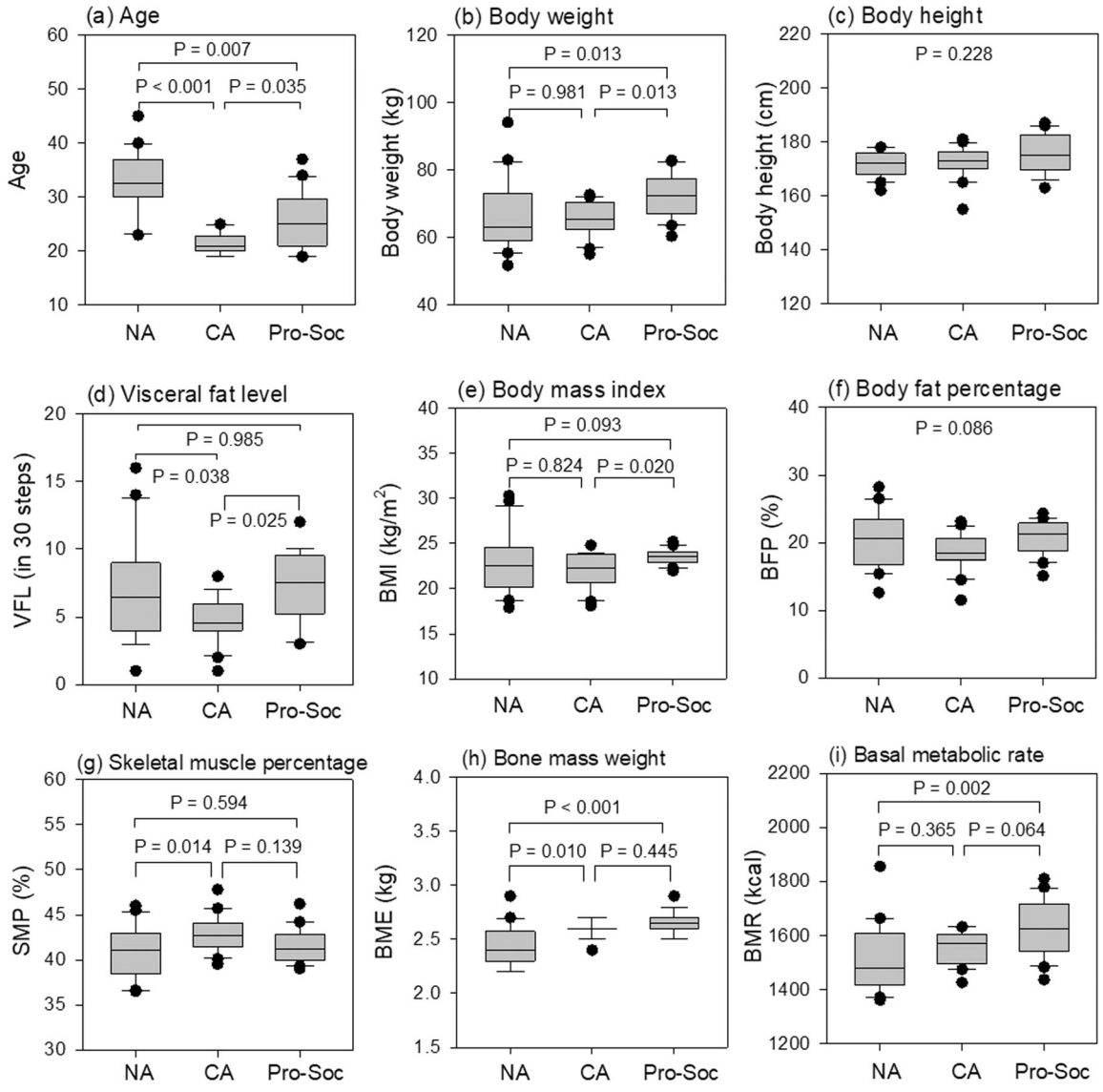

FIGURE 2 | Body composition indexes in sedentary nonathletic control participants (NA), college athletes (CA), and professional soccer players (Pro-Soc). (a) Age, (b) body weight, (c) body height, (d) visceral fat level (VFL), (e) body mass index (BMI), (f) body fat percentage (BFP), (g) skeletal muscle percentage (SMP), (h) bone mass weight (BMW), and (i) basal metabolic rate (BMR) at the time of blood collection. Statistical analyses were performed using a one-way analysis of variance on ranks, followed by the Tukey test. ($n = 19$ per group).

groups, chronological age was significantly the highest in the NA group (Figure 2a); However, because of the characteristic tendencies expected in persons with a sedentary lifestyle, for example, in Visceral Fat Level (VFL), BFP, SMP, bone mass weight, and BMR, the NA group was examined as a counterpart of the CA group in the following sections. In terms of body weight and height, the CA group fell between the NA and professional soccer athlete groups (Figure 2b,c). Similar tendencies were observed in BMW and BMR (Figure 2h,i). In contrast, the CA group exhibited the lowest values in VFL and BFP (Figure 2d,f) but had the highest SMP (Figure 2g). The CA and NA groups had lower BMI than the professional soccer player group (Figure 2e).

The changes in mitochondrial O_2 consumption, plasma lactate levels, and platelet ATP levels during the last 24-h incubation are shown in Figure 3. No significant differences were observed between these parameters. However, similar tendencies (NA ≥ CA) were observed in changes in O_2 consumption (ΔO_2 consumption) and platelet ATP levels (ΔPlatelet ATP) (Figure 3a,c); in contrast, an opposite change (NA ≤ CA) was observed in plasma lactate levels (ΔLactate) (Figure 3b).

The correlations between platelet parameters, that is, changes in mitochondrial O_2 consumption, plasma lactate, and platelet ATP levels, are shown in Figure 4. A strong positive correlation was found between ΔPlatelet ATP and ΔO_2 consumption levels ($R = 0.628$) in the CA group. This correlation was statistically significant ($p = 0.00398$). In contrast, this correlation was weakly negative in the NA group ($R = -0.100$, $p = 0.678$) (Figure 4b vs. Figure 4a). For the remaining correlations, neither moderate nor high correlations were observed in either group (Figure 4c–f).

The correlations between BMR and platelet parameters are shown in Figure 5. The correlation between BMR and Δplasma lactate levels ($R = 0.326$, $p = 0.169$) and Δplatelet ATP levels ($R = -0.213$, $p = 0.373$) was weakly positive and weakly negative, respectively, in the CA group (Figure 5d,f). The correlation between BMR and Δplatelet ATP levels was weakly positive in the NA group (Figure 5e). In the remaining correlations, neither moderate nor high correlations were observed in either group (Figure 5a–c).

The correlations between SMP and platelet parameters are shown in Figure 6. The correlation between SMP and Δplatelet ATP levels ($R = 0.306$, $p = 0.199$) was weakly positive in the CA group (Figure 6f). In the remaining correlations, neither moderate nor high correlations were observed in either group (Figure 6a–e).

The correlations between BFP and platelet parameters are shown in Figure 7. The correlation between BFP and ΔO_2 consumption levels ($R = 0.219$, $p = 0.361$) was weakly positive in the CA group (Figure 7b). In the remaining correlations, neither moderate nor high correlations were observed in either group (Figure 7a,c–f).

4 | Discussion

The main finding of this study was that although individual parameters related to platelet energetics did not differ between

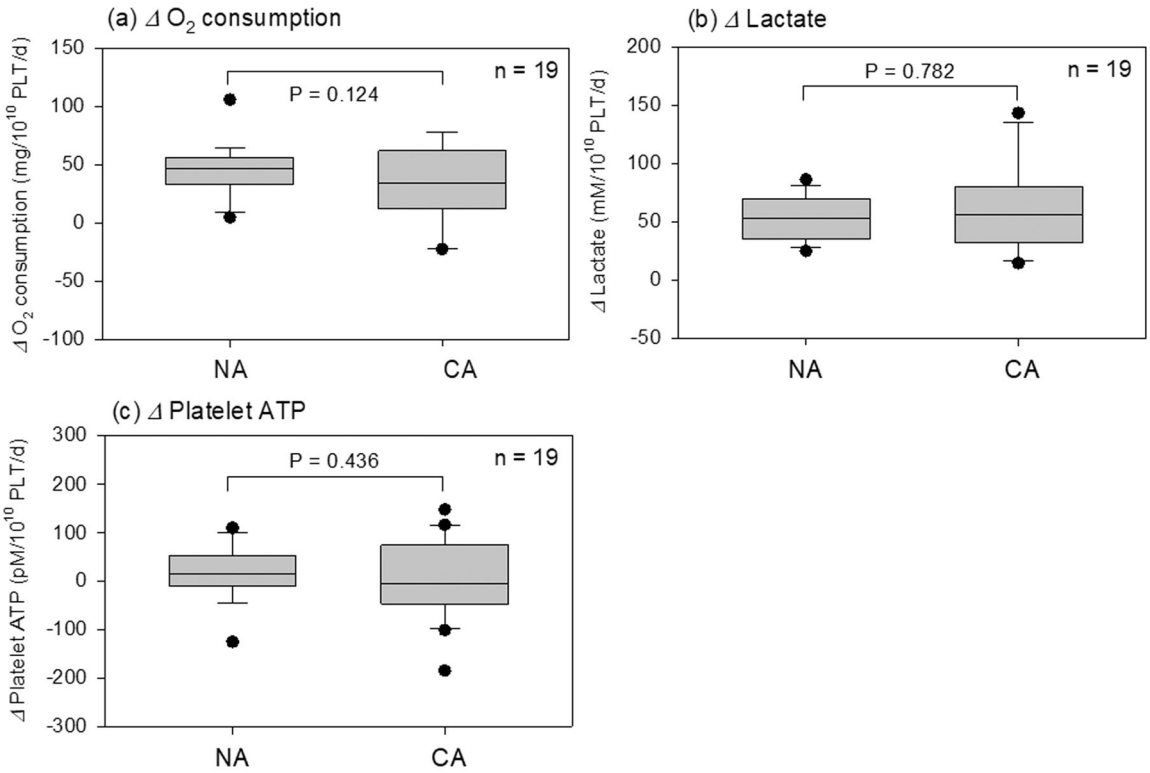

FIGURE 3 | Changes in platelet parameters, including (a) mitochondrial O_2 consumption levels, (b) plasma lactate levels, and (c) platelet ATP levels of non-athletes (NA) and college athletes (CA) during the last 24 h (from 24 to 48 h of analysis). No statistical significances were found between any comparisons (a and c: Student *t*-test, b: Mann–Whitney U test). $n = 19$ per group.

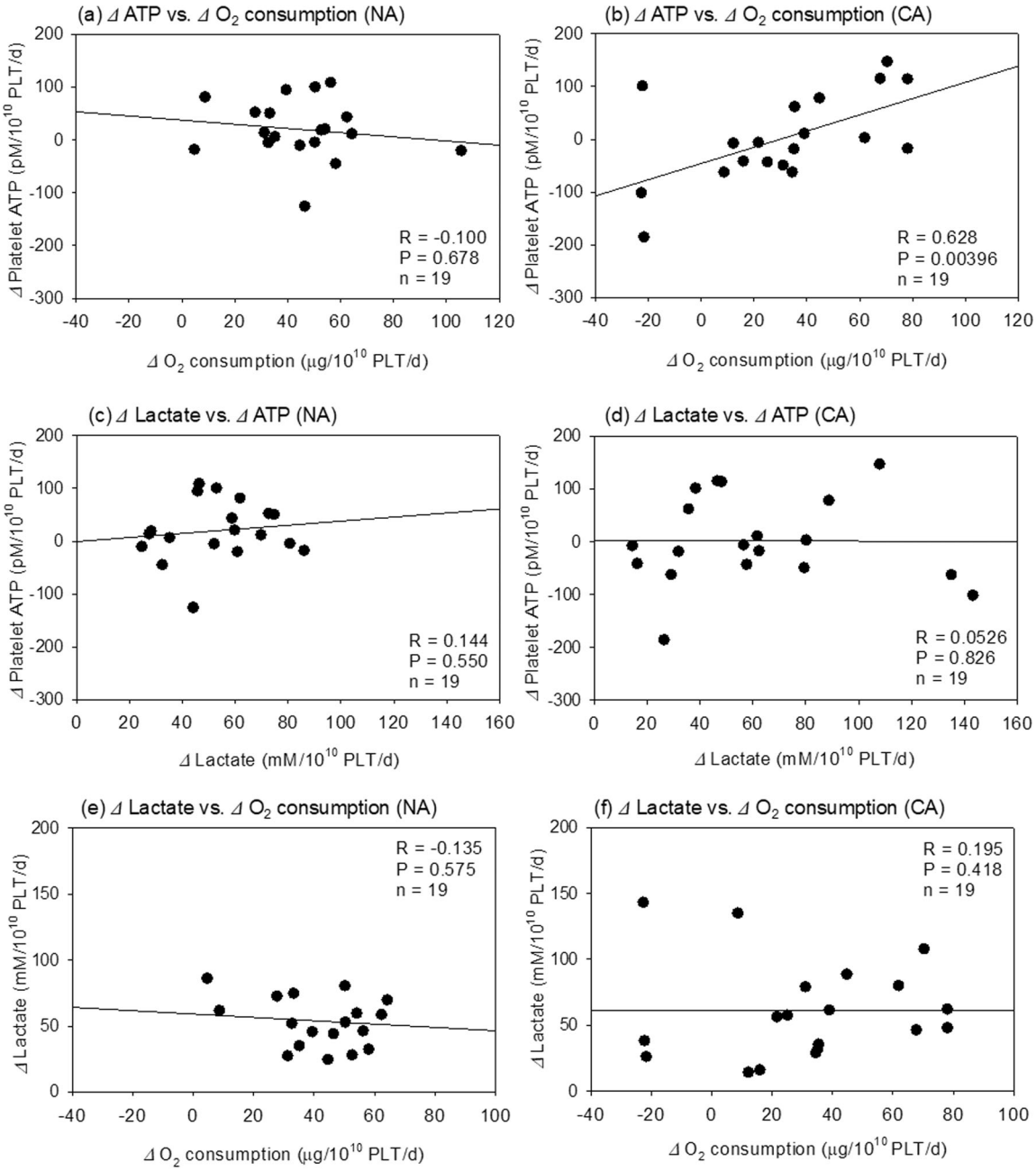

FIGURE 4 | Correlations among platelet parameters during the last 24 h. (a and b) Changes in platelet ATP levels vs. changes in mitochondrial O_2 consumption levels in nonathletic control participants (NA) and college athletes (CA). (c and d) Changes in plasma lactate levels vs. changes in platelet ATP levels in NA and CA. (e and f) Changes in plasma lactate levels vs. changes in mitochondrial O_2 consumption levels in NA and CA. "*R*," "*P*," and "*n*" represent Spearman's correlation coefficient, probability, and number of samples, respectively.

the two groups, the strong and positive correlation of O_2 consumption with ATP levels was observed only in the CA group. Based on this finding, we raised a hypothesis that, regardless of athletic performance levels, regular habitual exercise could modulate the energy generation system in platelets. Generally, anaerobic glycolysis dominates ATP generation in human platelets [13]. However, regular exercise, particularly aerobic physical training, can switch the power unit from glycolysis to aerobic mitochondrial oxidative phosphorylation (OXPHOS), as observed in skeletal muscles [14]. Furthermore, the similarity between platelet and muscle energetics, a concept suggested by Braganza et al. [15], can also be applied to young recreational student-athletes.

In this study, SMP and VFL values were significantly lower in the CA group but not BMI, BFP, or BMR values. Possible differences in their original body shape may have masked the effects of regular exercise. However, considering the tendency of BMR to increase, regular exercise seems to impact their metabolism. BMR is undoubtedly influenced primarily by skeletal muscle metabolism [16], and this causal relationship is often emphasized in the media and widely accepted among

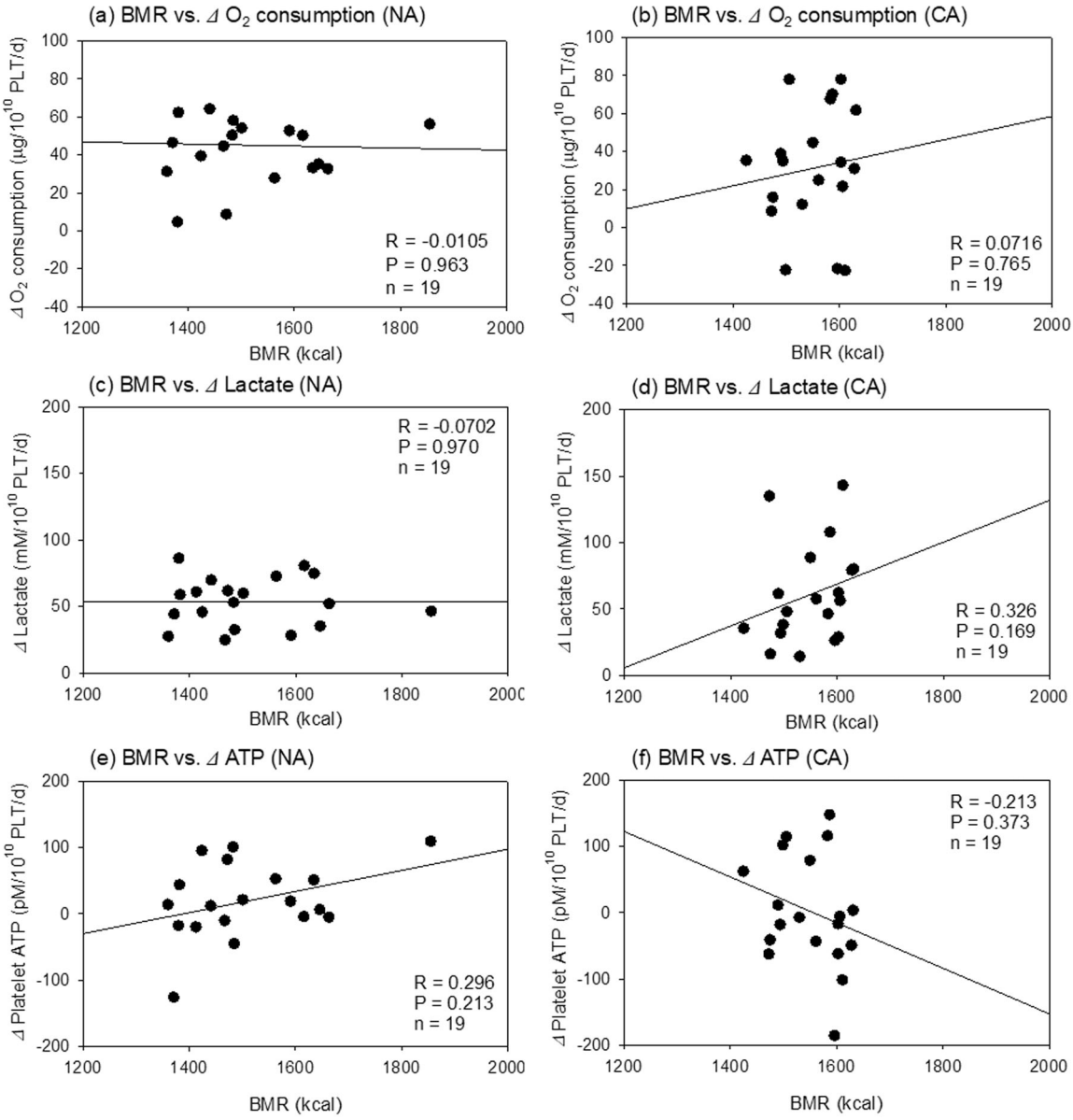

FIGURE 5 | Correlations between basal metabolic rate (BMR) and platelet parameters. (a and b) BMR vs. changes in mitochondrial O_2 consumption levels during the last 24 h in nonathletic control participants (NA) and college athletes (CA). (c and d) BMR vs. changes in plasma lactate levels during the last 24 h in NA and CA. (e and f) BMR vs. changes in platelet ATP levels during the last 24 h in NA and CA. "*R*," "*P*," and "*n*" represent Spearman's correlation coefficient, probability, and number of samples, respectively.

people. However, other organs are also involved in resting energy expenditure. The brain and liver have significantly higher rates per kilogram in young adults with normal weight than muscle and fat [17]. Thus, due to this minor occupational rate of muscle activity, regular exercise may not have a clearly discernible influence on BMR in the CA group. More appropriate physical parameters are required to precisely evaluate the influence of regular exercise and examine its direct impact on platelet energetics.

The effects of acute exercise on platelets and the coagulation system have been reported frequently. In contrast, the effects of chronic exercise probably depend on the types of exercise and are poorly understood [18, 19]. Based on our published and unpublished preliminary data, it can be summarized that platelet coagulation and fibrinolysis are activated in athletes. However, since fibrinolytic changes are more pronounced, the hemostatic balance is improved. Decreased coagulation activity may indirectly decrease platelet activity and responsiveness. The present biochemical findings add another possible mechanism for decreased platelet activity to the hematological scenario.

Our clinical question as to why many sports-related injuries respond well to PRP and heal faster and more effectively remains unanswered. Recent guidelines recommend 30 min or more of daily, moderate-intensity physical exercise based on favorable biological adaptations and substantial health benefits [7]. To our understanding, it concerns patient health conditions and indicates that regular appropriate exercise has beneficial effects on the resistance potential against various diseases and the regenerative potential of injured tissues and organs. Unfortunately, it is

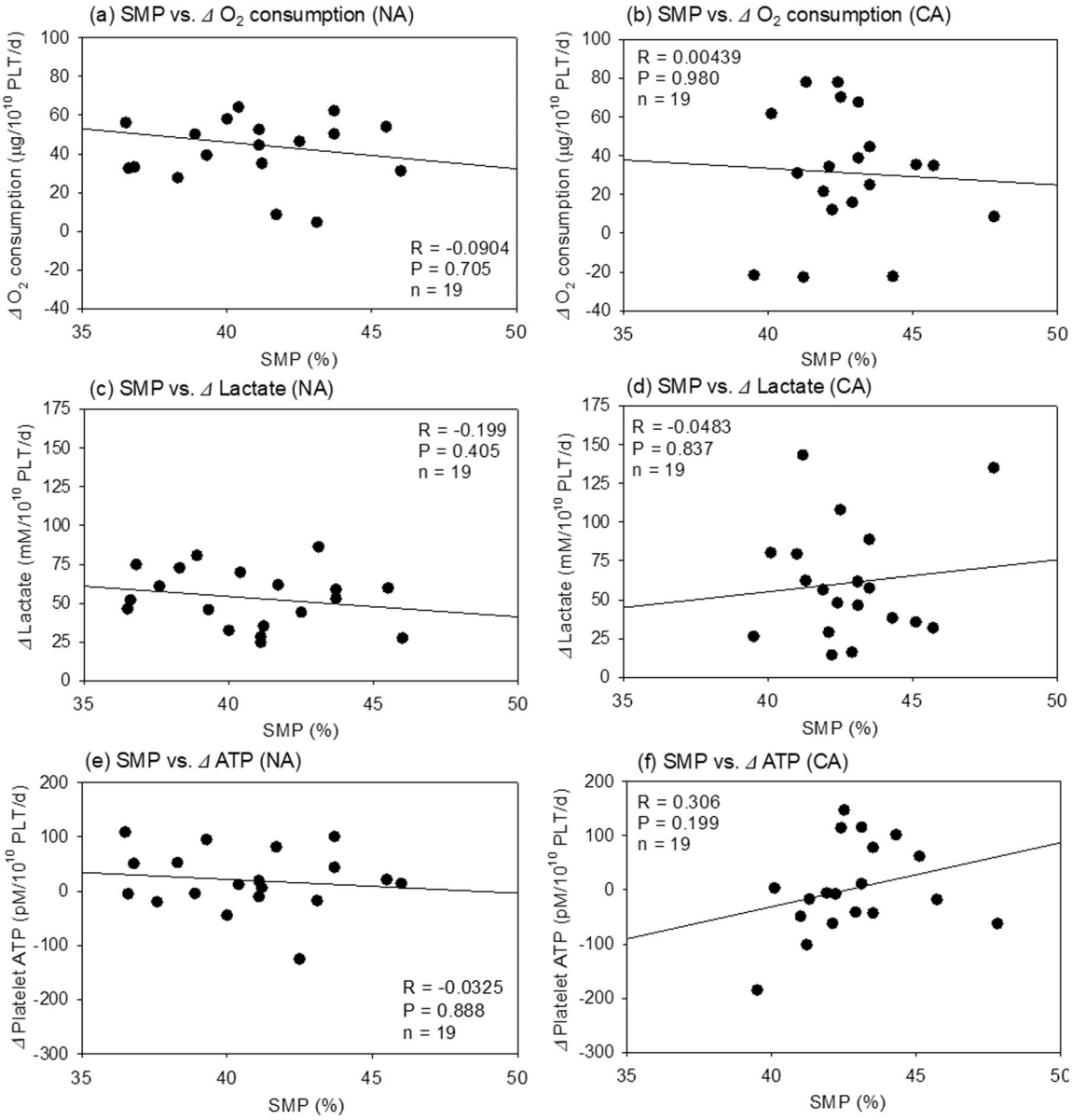

FIGURE 6 | Correlations between skeletal muscle percentage (SMP) and platelet parameters. (a and b) SMP vs. changes in mitochondrial O_2 consumption levels during the last 24 h in nonathletic control participants (NA) and college athletes (CA). (c and d) SMP vs. changes in plasma lactate levels during the last 24 h in NA and CA. (e and f) SMP vs. changes in platelet ATP levels during the last 24 h in NA and CA. "*R*," "*P*," and "*n*" represent Spearman's correlation coefficient, probability, and number of samples, respectively.

challenging to find an answer regarding platelet quality in a series of our athlete studies [11, 20–23] and the present study. A possible explanation is that decreased platelet activity and responsiveness may reduce unexpected platelet aggregation and subsequent loss of growth factors during PRP preparation. Further investigations are required to address this question and optimize PRP treatment for sports injuries.

5 | Limitations

First, the sample size adopted in this study was relatively small, and more samples are required to generalize the findings. Second, the CA group was heterogeneous in terms of physical ability and performance, and those who participated in this study did not necessarily have similar physical performance at qualified levels or regularly spend limited time on physical exercise. However, the findings of a preliminary study indicate that platelet energetics are similar to those of professional athletes [23]. Therefore, although they were hardworking medical college students, we considered this sample population sufficient to test our hypotheses raised in the study conducted on professional athletes. Third, significant differences in age were found among the groups, and similar generations could be selected, particularly in the CA and professional soccer player groups. In addition, recruitment during spring break was relatively difficult. It has often been indicated that aging can make platelets more reactive, increasing the risk of incidence of cardiovascular disease and thrombosis, and concomitantly decreasing platelet counts [24]. However, it is generally believed that such aging effects

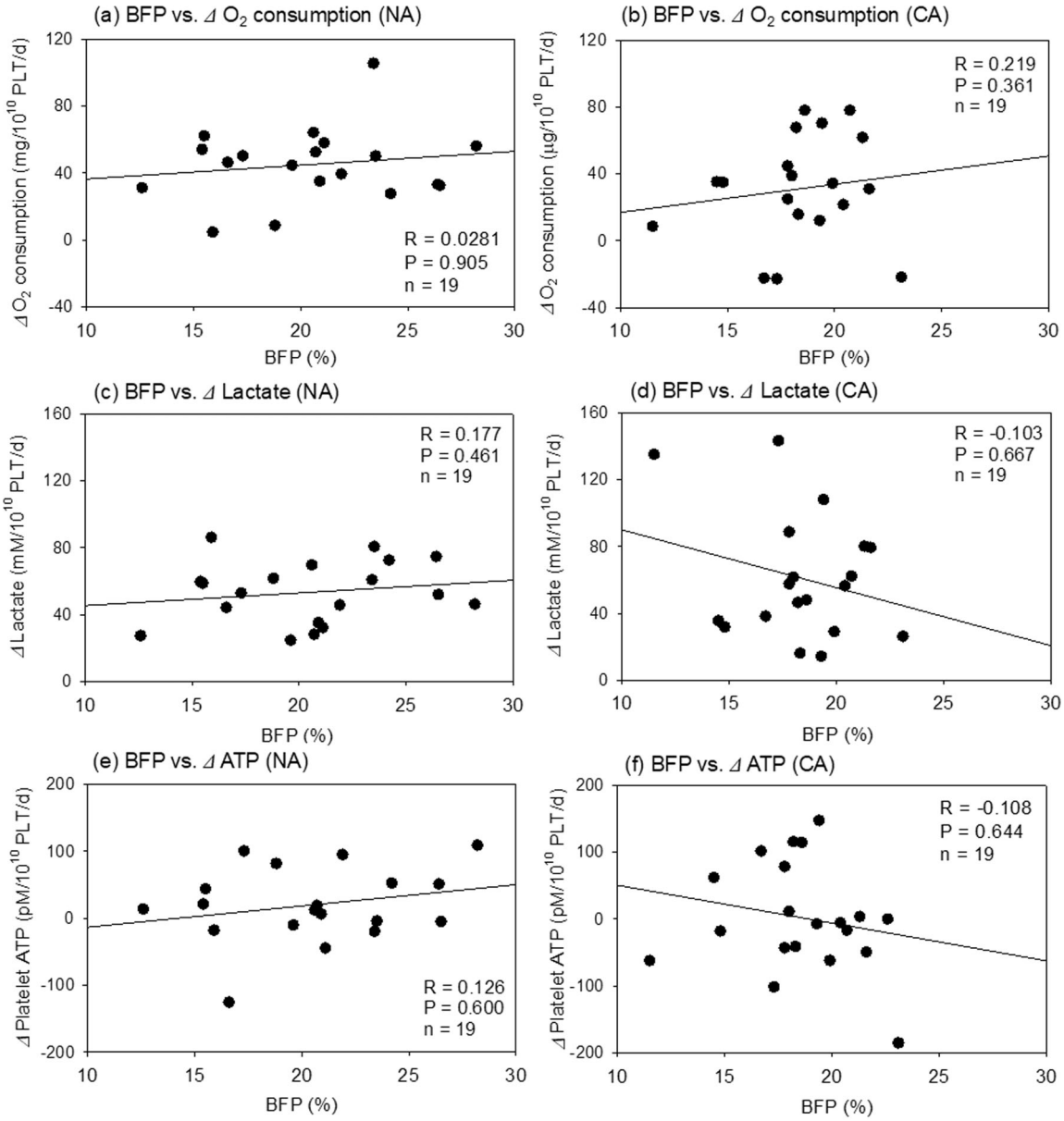

FIGURE 7 | Correlations between body fat percentage (BFP) and platelet parameters. (a and b) BFP vs. changes in mitochondrial O_2 consumption levels during the last 24 h in nonathletic control participants (NA) and college athletes (CA). (c and d) BFP vs. changes in plasma lactate levels during the last 24 h in NA and CA, and (e and f) BFP vs. changes in platelet ATP levels during the last 24 h in NA and CA. "*R*," "*P*," and "*n*" represent Spearman's correlation coefficient, probability, and number of samples, respectively.

become significant in the elderly (65 years or more) [25] or sometimes in the middle-aged population. Thus, we do not think these differences significantly influenced the purpose of this study. However, further investigations should be performed at various levels to validate our conclusions.

6 | Conclusions

Resting platelets generally undergo anaerobic glycolysis and aerobic mitochondrial OXPHOS to generate ATP. Despite the limited sample size, this correlation analysis suggests that platelet ATP generation may depend more on O_2 consumption in the CA group than in the NA group. To provide more insight into this hypothesis, further study with a sufficiently large sample size should be conducted. This possible change may also influence the quality and efficacy of PRP therapy.

Author Contributions

Tomoharu Mochizuki: conceptualization, investigation, writing – original draft, writing – review and editing, project administration, and funding acquisition. **Takashi Ushiki:** conceptualization, investigation, writing – original draft, writing – review and editing, supervision, project administration, and funding acquisition. **Hiroshi Koga:** investigation. **Katsuya Suzuki:** investigation. **Misato Sato:** investigation. **Mami Osawa:** investigation. **Masami Kamimura:** investigation. **Hajime Ishiguro:** investigation. **Tatsuya Suwabe:** investigation. **Tomoyuki Kawase:** conceptualization, methodology, writing – original draft, writing – review and editing, and funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author, T.K., upon reasonable request. The raw data are not publicly available because they were not deposited in any data deposit sites to protect participants' privacy. However, the authors confirm that the data supporting this study's findings are available within the article. All authors have read and approved the final version of the manuscript. Tomoyuki Kawase has full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency Statement

The lead author Tomoyuki Kawase affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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