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Influence of 8 Weeks of Tabata High-Intensity Interval Training and Nanocurcumin Supplementation on Inflammation and Cardiorespiratory Health among Overweight Elderly Women

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ABSTRACT: Nanocurcumin (NaC) and high-intensity interval training (HIIT) play crucial role in weight and inflammation control. The purpose of the current study was to evaluate the separate and combined effects of 8 weeks of Tabata-HIIT and NaC supplementation on the NOD-like receptor family pyrin domain-containing 3 (*NLRP3*) inflammasome, long non-coding RNA myocardial infarction associated transcript (*lncRNA MIAT*) expression, body composition, and cardiorespiratory health in elderly overweight women. A total of 48 healthy overweight elderly women were randomly divided into four groups: NaC, Tabata-HIIT+Pla, Tabata-HIIT+NaC, and placebo. Participants underwent a Tabata HIIT program (2 days per week, at 80～0% of maximal HR) and NaC supplementation (daily 80 mg in two 40 mg capsules) for 8 weeks. Blood sampling, cardiorespiratory hemodynamic responses, and body composition evaluations were obtained before and after treadmill stress testing at the baseline timepoint and following 8 weeks of intervention. The mRNA of *lncRNA-MIAT* and *NLRP3* were measured by real-time polymerase chain reaction. After 8 weeks, a significant improvement was observed in body composition and cardiorespiratory hemodynamics in the Tabata-HIIT groups compared to the NaC alone and placebo groups ($P<0.05$). Tabata training, both with and without the addition of nano curcumin supplementation, did not result significant effect on the resting levels of *lncRNA-MIAT* expression ($P>0.05$). Nevertheless, NaC supplementation along with Tabata training led to a significant reduction in *NLRP3* inflammasome. In addition, NaC supplementation in overweight/pre-obese women improved systemic inflammation during treadmill stress testing. These findings indicating the suppressive effects of non-pharmacologic interventions on the sympathetic system and downregulation of the inflammasome.

Keywords: high intensity interval training, inflammasome, metabolic syndrome, myocardial infarction associated transcript, nanocurcumin

INTRODUCTION

Aging is a serious concern worldwide and is associated with progressive changes in the vital organs (Westbury et al., 2021). Among the aging population, obesity and overweight are growing globally. Obesity and overweight are associated with a number of physical health problems and healthcare expenditure (Mikkola et al., 2020). Obesity-related health problems include several chronic inflammatory conditions and metabolic diseases. The World Health Organization (WHO) defines obesity as excessive fat accumulation. The body mass index (BMI) gradually increases during most of adult life in both men and women (Villareal et al., 2005).

Over the past few decades, it has been proposed that inflammatory processes are involved in obesity. Notably, individuals with obesity possess chronic secretion of proinflammatory cytokines, particularly C-reactive protein, and the cytokines interleukin (IL)-6 and IL-1β (Kouba et al., 2022). Recently, the NOD-like receptor family pyrin domain-containing 3 (*NLRP3*) inflammasome has been recognized as a complex of several proteins that play a critical role in the inflammatory response and diabetes (Lu et al., 2022). Interestingly, aging is associated with a decrease in fat free mass, an increase in fat mass, and a chronic low-grade inflammatory status that impacts the downstream *NLRP3* inflammasome and causes increased levels of proinflammatory mediators (Gomarasca et al., 2022).

Long non-coding RNAs (lncRNAs) are RNA molecules that are longer than 200 nucleotides. Their dysregulation has been linked to the development of several diseases,

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including diabetes. Emerging evidence suggests the vital role of lncRNAs in regulating *NLRP3* inflammasome activity (Alfaifi et al., 2021).

The myocardial infarction-associated transcript (*MIAT*) is identified as an lncRNA, and is involved in various physiological and pathological processes, such as myocardial infarction and microvascular dysfunction (Liao et al., 2016). A recent study reported that individuals with abdominal obesity showed a 6.35-fold higher expression of *lncRNA MIAT* compared to healthy controls. In addition, smoking and alcoholism were associated with high *MIAT* expression, with a 5.41- and 5.74-fold changes, respectively, compared to healthy subjects (Alfaifi et al., 2021).

Increasing evidence has shown that non-pharmacologic treatment strategies such as physical activity and herbal therapy are beneficial in the management of metabolic syndrome in overweight and obese patients (Hooshmand Moghadam et al., 2021). It is well-established that chronic exercise training is an efficient non-pharmacologic strategy for the prevention and treatment of several chronic inflammatory diseases. A large body of scientific evidence has contributed to establishing a positive correlation between regular exercise and anti-inflammatory status, which appears to be a crucial strategy for improving health, mainly in chronic diseases (da Luz Scheffer and Latini, 2020; Gomarasca et al., 2022). In contrast, the industrialization of societies has affected various aspects of lifestyle, including physical activity, and recent reports have indicated that sedentary lifestyles have significantly increased since the coronavirus disease 2019 (COVID-19) pandemic (Amini et al., 2021). Thus, it is essential to provide options for exercise training, such as high-intensity interval training (HIIT), that are practical, inexpensive, and safe and can be performed in a variety of locations (Souza et al., 2020).

Previous studies have reported that HIIT training can significantly decrease inflammatory markers by improving visceral adipose tissue and body composition (Nunes et al., 2019; Hooshmand Moghadam et al., 2021). In addition, the researchers reported that among interval exercises, Tabata-HIIT protocols might be particularly useful during the COVID-19 pandemic.

Domaradzki et al. (2020) reported that Tabata exercises are effective in controlling and reducing body weight and have an impact on several body composition indicators. In addition, Liang et al. (2020) demonstrated that HIIT appears to be effective as moderate-intensity continuous training to reduce β-amyloid deposition by regulating *NLRP3* inflammasome activity. Recently, in a related research, Gomarasca et al. (2022) demonstrated an applied 12-week Nordic walking regime that affected the resting expression of *NLRP3* inflammasome. Similarly, another study related to resistance training programs in elderly women demonstrated the downregulation of *NLRP3* protein (Mejías-Peña et al., 2017).

While the impacts of HIIT on cardiorespiratory fitness are now quite clear, the efficacy of a regular Tabata-HIIT program on the *NLRP3* inflammasome and, particularly, *lncRNA-MIAT* expression genes and hemodynamic indices such as maximal heart rate (MHR), systolic blood pressure (SBP), and myocardial volume oxygen (MVO_2) in overweight/pre-obese women has not yet been investigated.

In recent years, growing research has implicated the potential benefits of antioxidant supplementation for regulating reactive oxygen species levels (Mason et al., 2020). Among the most well-known types of natural anti-inflammatory compounds, curcumin has a long history of medicinal use due to its anti-inflammatory and antioxidant properties (Jäger et al., 2019). Nevertheless, poor solubility, low absorption from the gut, rapid metabolism, systemic elimination, and poor systemic bioavailability are major drawbacks to the therapeutic potential of curcumin (Anand et al., 2007; Prasad et al., 2014). Consequently, its therapeutic actions are significantly diminished. The mixed findings in previous studies revealed that the formulated curcumin, nanocurcumin (NaC), had better bioavailability and biological activities than its unformulated counterpart (Ahmadi et al., 2018; Hatamipour et al., 2019; Kamel Oroumieh et al., 2021). Shamsi-Goushki et al. (2020) showed that NaC supplementation is an effective agent in lowering blood lipids and increasing high-density lipoprotein, and its lipid-improving effects are significantly higher than those of curcumin. Furthermore, it has been reported that NaC may have protective effects against chronic inflammatory diseases and metabolic syndrome (Dolati et al., 2020). Moreover, Ashtary-Larky et al. (2021) reported that NaC supplementation may decline cardiovascular disease risk by improving glycemic and lipid profiles, inflammation, and SBP. Given the lack of evidence supporting pharmacological measures, further research into the efficacy of chronic non pharmacological interventions on the *NLRP3* inflammasome and *lncRNA-MIAT* gene expression is crucial. Moreover, few studies have been conducted into the simultaneous effects of chronic Tabata-HIIT and NaC supplementation on the *NLRP3* inflammasome and *lncRNA-MIAT* gene expression and cardiorespiratory hemodynamic responses to treadmill stress testing among overweight/pre-obese elder women. Therefore, to address this knowledge gap, we conducted a randomized controlled trial to evaluate the effects of 8 weeks of NaC supplementation intake alone and in combination with Tabata-HIIT on the *NLRP3* inflammasome and *lncRNA-MIAT* genes expression and the cardiorespiratory hemodynamic [MHR, recovery heart rate (RHR), SBP, MVO_2, oxygen saturation % (SpO_2%), maximal oxygen consumption (VO_2max), and oxygen pulse

(O_2 pulse)] and body composition indices [percent body fat (PBF), body adiposity index (BAI), waist-to-hip ratio (WHR), and BMI] in overweight/pre-obese elderly women.

Overweight and obesity in adults are increasing globally. Although various factors can increase the body weight, this increase is often due to the limitations of activities in outdoor spaces and the lack of gyms and sports clubs. The obesity burden in Iran, for example, is disproportionately higher among women than men. Moreover, compared to men, women suffer a disproportionate burden of obesity and overweight, which adversely affects their health (Nglazi and Ataguba, 2022). Furthermore, due to biological conditions associated with age in women, most subjects used in training or supplemental interventions are male. Therefore, there is a lack of research into the effectiveness of non-pharmacological factors in overweight/pre-obese women.

In this study, we evaluated the effects of non-pharmacological measures (Tabata-HIIT training and NaC supplementation) on body weight in women. Given the need for HIIT training for weight management post-pandemic and its relationship with systemic inflammation, the anti-inflammatory and antioxidant impacts of NaC and regular physical activity were evaluated.

It was hypothesized that: (1) the treadmill stress testing (Bruce protocol) in the 8 weeks of Tabata-HIIT exercises and NaC supplementation interventions would result in greater responses in the mRNA expression of the genes examined and hemodynamic indices in the elderly women with overweight/pre-obese; and (2) the combined strategies of Tabata-HIIT exercises and NaC supplementation, when compared to each of these strategies, would improve cardiovascular physiological and inflammatory responses to a greater extent.

MATERIALS AND METHODS

Study design and ethical consideration

This study was designed as a double-blind, randomized, placebo-controlled trial and was performed between September 2021 and February 2022. A total of 48 apparently healthy, sedentary (less than 30 min a day of moderate-intensity physical activity for 3 days a week in the past 6 months) (Amini et al., 2021), overweight or pre-obese (BMI>28 kg/m^2) women aged 40～60 years were recruited.

The subjects were randomly allocated into four groups: high-intensity interval training+placebo (Tabata-HIIT+Pla), NaC supplementation, high intensity interval training+nanocurcumin (Tabata-HIIT+NaC), and placebo (Pla). The subjects in the NaC and Tabata-HIIT+NaC groups ingested two 40 mg NaC capsules per day (80 mg/d) for 8 weeks. Women in the Pla and Tabata-HIIT+Pla groups received two placebo capsules every day. Assessments were made at four stages: baseline, immediately after treadmill stress testing (Bruce protocol), both prior to and after 8 weeks period of the Tabata-HIIT exercise and/or NaC supplementation interventions (Fig. 1).

The study design was approved by the University of Mazandaran Institution Ethics Committee (IR.UMZ.REC.1401.008) and was conducted according to the Helsinki Declaration (2013). All participants were familiarized with details of the research. Informed consent was obtained from all participants. Personal information was omitted from the patient data.

Inclusion and exclusion criteria

Women with abdominal obesity (waist circumference>80 cm, BMI>28 kg/m^2, or body fat>30%) were invited to participate in this. Because the current study protocol was implemented during the COVID-19 pandemic, one exclusion criterion for our study was having at least one sign/symptom of acute respiratory disease. In addition, all women were tested for arterial SpO_2 using a pulse oximeter to rule out the potential presence of "silent hypoxemia," and those below the threshold of 95% SpO_2 were excluded from the study. The classification of overweight/obesity based on BMI was obtained using WHO international criteria, where a BMI of 25.0～29.9 kg/m^2 is defined as overweight, and a BMI greater than 30.0 kg/m^2 is defined as obesity. In line with previous research (Nunes et al., 2019; WHO, 2020; Budi Mulia et al., 2021), abdominal obesity and overweight were also defined using the waist circumference measurement of >80 cm for Asian females (WHO, 2020). Participants who completed less than 85% of the total exercise sessions were eliminated from the study process. Participants were required to take at least 85% of the curcumin supplement. The other exclusion criteria for our study were allergy to curcumin, intake of dietary supplements, and herbal green tea consumption. Only participants with no history of smoking or other tobacco consumption were included.

Assessments and measurements

***General characteristics and dietary intake*:** Interviews were conducted to fill out the questionnaires, which included general health and physical activity history questionnaires. Then, physical examination and assessments of vital parameters (systolic and diastolic blood pressure, resting and MHR, and resting electrocardiogram) were performed. In addition, the subjects' dietary status was determined using Nutritionist-4 software (version 7.0; N-Squared Computing), using g/d values from the 24-h food recall.

***Anthropometric measurement*:** At the participant's preliminary visit to the laboratory, anthropometric measurements were taken during the morning hours. Weight (at begin-

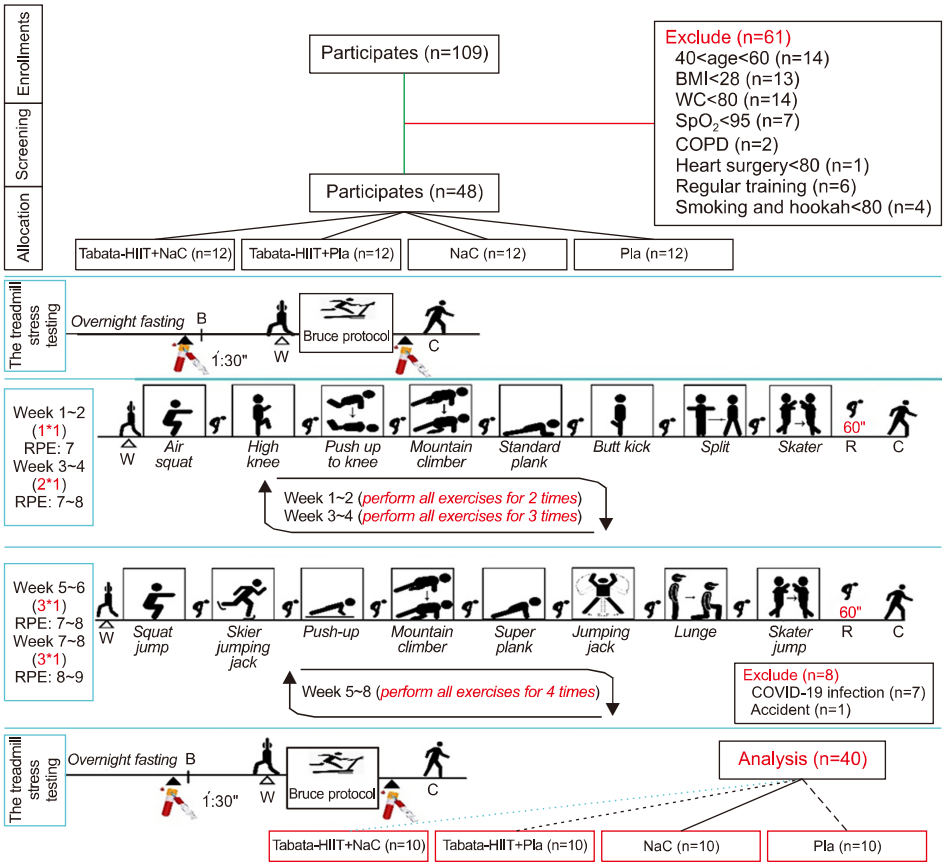

Fig. 1. Schematic representation of training protocol. BMI, body mass index; WC, waist circumference; SpO_2, oxygen saturation; COPD, chronic obstructive pulmonary disease; Tabata-HIIT+NaC, high intensity interval training+nanocurcumin group; Tabata-HIIT+Pla, high intensity interval training+placebo group; NaC, nanocurcumin supplementation group; Pla, placebo group; B, breakfast; W, warm-up; C, cool-down; R, recovery time; RPE, rating of perceived exertion. (1*1) represents the ratio of 20 s of exercise to 20 s of recovery time.

ning and end) was measured with subjects in light clothing and no shoes using an electronic digital medical scale with a stadiometer (Seca®), which was accurate to 0.1 kg. Height (at the beginning) was measured in the standing position to the nearest 0.1 cm using a flexible stadiometer. BMI, WHR, and body composition percentages were measured using a body composition analyzer system (BoCA×1, Medigate, Inc.). These assessments were also carried out manually in the standing position.

***Cardiorespiratory hemodynamic measurements*:** Hemodynamic assessments were made at four stages; baseline, immediately after treadmill stress testing (Bruce protocol) both prior to and after 8 weeks period of the Tabata-HIIT exercise and/or NaC supplementation interventions. During treadmill stress testing, this was done both before and after 8 weeks of the Tabata-HIIT exercise and/or NaC supplementation interventions, heart rate (HR) and blood pressure were continuously monitored using a 12-lead electrocardiogram. Myocardial oxygen consumption (MVO_2) was calculated according to the following formula: $MVO_2 = HR \times SBP$ (Ahmadian et al., 2022). Continuous SpO_2 measurements were taken from a wearable finger pulse oximeter (Model PO16, Brisk). Age and gender were inputted into the treadmill device and the HR and BP information was measured through the device. VO_2max was assessed via treadmill stress testing (Bruce protocol). In this protocol, the activity on the treadmill continues until maximum oxygen consumption reaches a plateau, and at this moment the device automatically begins to calculate the VO_2max. After determining the oxygen consumption, the oxygen pulse is used to calculate the HR ratio according to the following formula: O_2 pulse (mL/beat) = VO_2/HR ratio (Wasserman et al., 1987).

RNA extraction and quantitative real-time polymerase chain reaction (PCR)

Blood sampling was carried out at the Monitoring and Evaluation Center of Health University of Mazandaran, Iran. Ten milliliters of blood was collected from each participant both prior to and after the treadmill stress testing (Bruce protocol), both before and after the 8 weeks of Tabata-HIIT exercise and/or NaC supplementation intervention.

Total RNA, including *lncRNA-MIAT* and *NLRP3* inflammasome coding, was extracted using a commercial kit (Yekta Tajhiz Co.), according to the manufacturer's instructions. The concentration and purity of the extracted RNA were measured via agarose gel electrophoresis and spectrophotometry (model NDNM96, NanoDrop Iranian). Complementary DNA (cDNA) was synthesized using a cDNA kit (Yekta Tajhiz Co.). Detection and measurement of mRNA (*MIAT* and *NLRP3* inflammasome) was performed using real-time PCR (Rotor-Gene 6000, Corbett Research) (Table 1). Target gene expression was quantified using the $2^{-\Delta\Delta C_T}$ formula (Livak and Schmittgen, 2001).

Table 1. Forward and reverse primers used in real-time polymerase chain reaction

Genes	Primers	Sequence	Access number	Base pair
β-Actin	Forward	CGGGAAATCGTGCGTGAC	NM_001101.5	109
	Reverse	GCTCGTAGCTCTTCTCCAGGG		
NLRP3 inflammasome	Forward	GAGCCTCAACAAACGCTACAC	NM_183395.3	151
	Reverse	ATCGGGGTCAAACAGCAACT		
LncRNA-MIAT	Forward	AAAGGGAGTTAGTGGATTTGAGTT	NR_003491.3	116
	Reverse	AAGTTCTGCTCAGTTGTCTAAAATG		

Treadmill stress testing (Bruce protocol)

The experimental procedures were explained to all participants prior to the exercise test. Data were collected under standard environmental conditions (temperature, 24～26°C; barometric pressure, 760 mm/Hg; relative humidity, 50～60%). The details of the treadmill stress testing (Bruce protocol) have been described elsewhere (Dabidi Roshan et al., 2023). In brief, participants performed treadmill testing under the experimental protocol, based on the predicted maximum HR that was previously piloted on a separate visit and prior to the actual experiment. The criteria for terminating the exercise electrocardiography test were based on ACC/AHA 2002 guideline update for exercise testing by Gibbons et al. (2002).

Tabata-HIIT exercise program

The details of the Tabata-HIIT exercise program were explained to all participants in the preliminary and practice sessions. The body weight-based exercise training program, adhering to the overload principle (i.e., increasing sets), exercise complexity, and rating of perceived exertion (RPE) scale, was adapted from previous studies with some modifications (Chin et al., 2020). The Borg RPE scale ranges from 0 (nothing at all) to 10 (extremely strong) and was used in this study (Abonie et al., 2023). The participants performed the exercise training program twice a week for 8 weeks. Training sessions began with 2 sets and ended with 4 sets. The Tabata-HIIT exercise program was performed with 8 sequences in a series of 20 s of work and 20 s of rest (ratio 1/1) and each set lasted for 5 min. The duration of each exercise movement was 20 s for the first week, 25 s for the second and third weeks, and 30 s for the fourth week (Table 2). Furthermore, the exercises were selected so that almost all muscle groups were used in each training session. During the first 4 weeks, the exercises were simple and corresponded to sequence 8. Each set included 8 exercises: air squats, high knee, push up to knee, mountain climber, standard plank, butt kickers, split, and skater. After the subjects' fitness improved from baseline and in order to strengthen the same muscle groups, more complex exercises were selected for the second 4 weeks: squat jump, skier jumping jack, push up, mountain climber, super plank, jumping jack, lunge, and skater jump. Exercise intensity was based on the predicted MHR (220 minus age) and ranged from approximately 80～90% of the maximum HR (170～180 bpm). Each exercise session consisted of 10 min of warm-up and 5 min of cool down. The recovery period between each set and exercise movement was 60 s. Subjects were advised to avoid any training or activity that they had not performed prior to the start of the study.

NaC supplementation intervention

The NaC supplementation protocol was designed based on the results of a previous study (Jazayeri-Tehrani et al., 2019). For analysis by high-performance liquid chromatography, NaC capsules were produced by the Nanotechnology Research Center of Mashhad University of Medical Sciences and registered under IRC number 1228225765. The NaC and placebo capsules were purchased by the Exir Nano Sina Company. The sinacurcumin® dose was 80 mg/d (two 40-mg capsules per day, one capsule at breakfast and another at dinner) for 8 weeks. The supplements were distributed once every two weeks, and consumption status was assessed weekly by phone. Accordingly, every subject in the NaC supplementation and Tabata-HIIT+NaC groups received the NaC capsules.

Data analysis

Within-group comparisons were made using paired sam-

Table 2. Eight-week Tabata-HIIT exercise program used in this study

Tabata-HIIT program	Session/week (number)	Work/rest (s)	1~2 weeks	3~4 weeks	5~6 weeks	7~8 weeks
Low-volume	2	1/1 (20/20)	(2×5/1×1)[1)]	3×5/2×1	4×5/3×1	4×5/3×1
RPE (Borg scale 10)		–	7	7~8	7~8	8~9
S&C exercises		–	S	S	S&C	S&C

[1)]Example; (2×5/1×1)=2 (sets)×5 min (8 sequences with a ratio of 20/20 s)/1×1 min (rest between sets).
HIIT, high intensity interval training; RPE, rating of perceived exertion; S, simple; C, complex.

ple *t*-tests. All analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp.). The Shapiro-Wilk test was used to check the normality of the data distributions of continuous variables. Between-group comparisons were performed using two-way repeated measure ANOVA followed by the least significant difference *post-hoc* test (Bonferroni test) for all indices examined. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Body composition following 8 weeks of Tabata HIIT and NaC supplementation

The body composition of the participants is shown in Fig. 2. A significant main effect for time was noted for PBF (P=0.001) and BAI (P<0.001), with values being significantly lower at 8 weeks in comparison to baseline in the Tabata-HIIT+Pla, Pla, and Tabata-HIIT+NaC groups. Although no significant effect for time was noted for BMI and WHR, it should be noted that significant differences between groups were noted for WHR after the 8 weeks. No significant differences were noted between or within groups for BMI.

Cardiorespiratory hemodynamic responses following 8 weeks of Tabata HIIT and NaC supplementation

The cardiovascular hemodynamic responses of the participants were measured using a treadmill stress test (Fig. 3). A main effect for time was detected for RHR (P< 0.001), SBP (P<0.001), DBP (P<0.04) and MVO_2 (P< 0.03), with values being significantly greater at 1 min post-test in comparison to the baseline at 8 weeks. Furthermore, at 5 min after the treadmill stress testing in comparison to baseline of post 8 weeks just for RHR. The RHR values were found to be significantly greater in the Tabata-HIIT+Pla group in comparison to the placebo group at 1-min (P<0.05) and 5-min post-test (P<0.02). Likewise, MVO_2 at 1-min post-test (P<0.03).

Following 8 weeks, a significant main effect for time was noted for RHR (P<0.04) and MVO_2 (P<0.03) at 5-min post-test at 8 weeks, with values being significantly lower in the NaC group in comparison to baseline (0 weeks). Furthermore, the MVO_2 values were significantly lower at 8 weeks post-training in the NaC group in comparison to baseline (P<0.03). A significant main effect for time was noted for SBP (P<0.04) and DBP (P<0.02), with values being significantly lower at 8 weeks for the Tabata-HIIT+NaC group in comparison to baseline. It al-

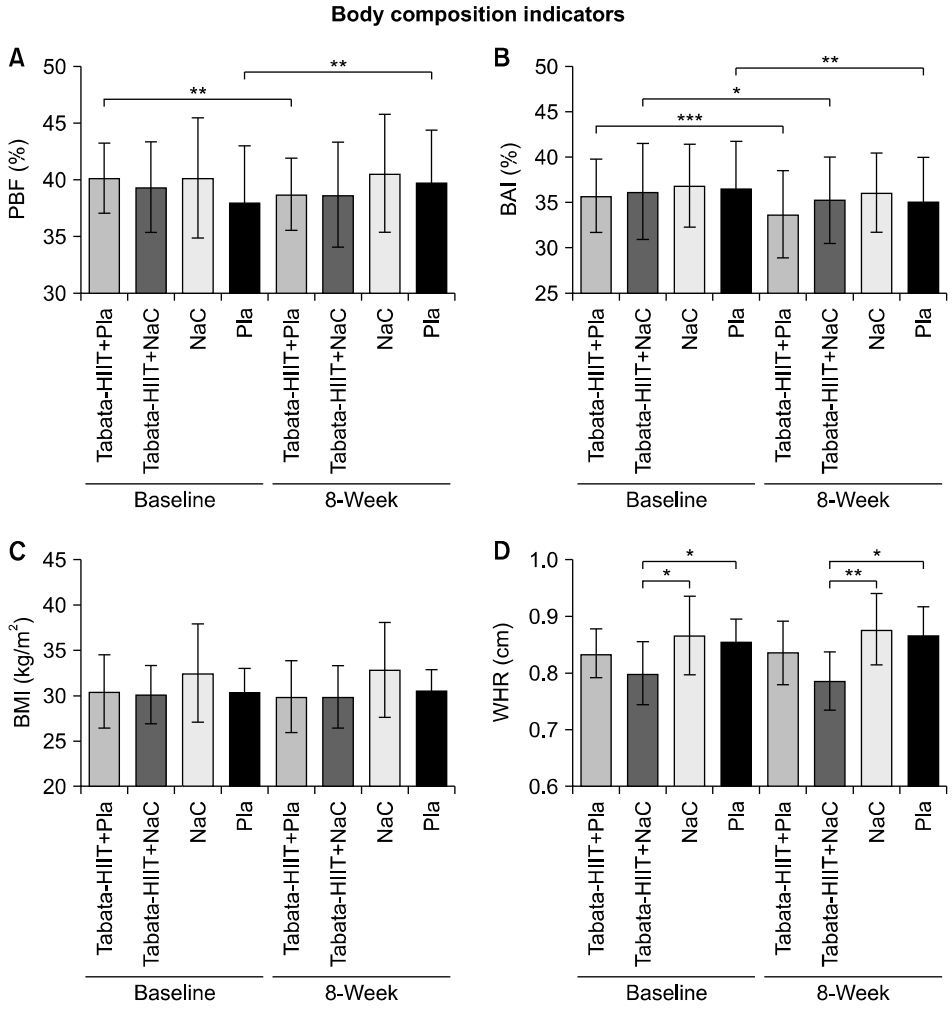

Fig. 2. Body composition indicators after 8-week Tabata-high intensity interval training (HIIT) and nanocurcumin (NaC) supplementation in elderly overweight women. (A) Changes in percent body fat (PBF). (B) Changes in body adiposity index (BAI). (C) Changes in body mass index (BMI). (D) Changes in waist-to-hip ratio (WHR). Asterisks denote significant main effects for time (P<0.05). *P<0.05, **P<0.01, and ***P<0.001. Pla, placebo.

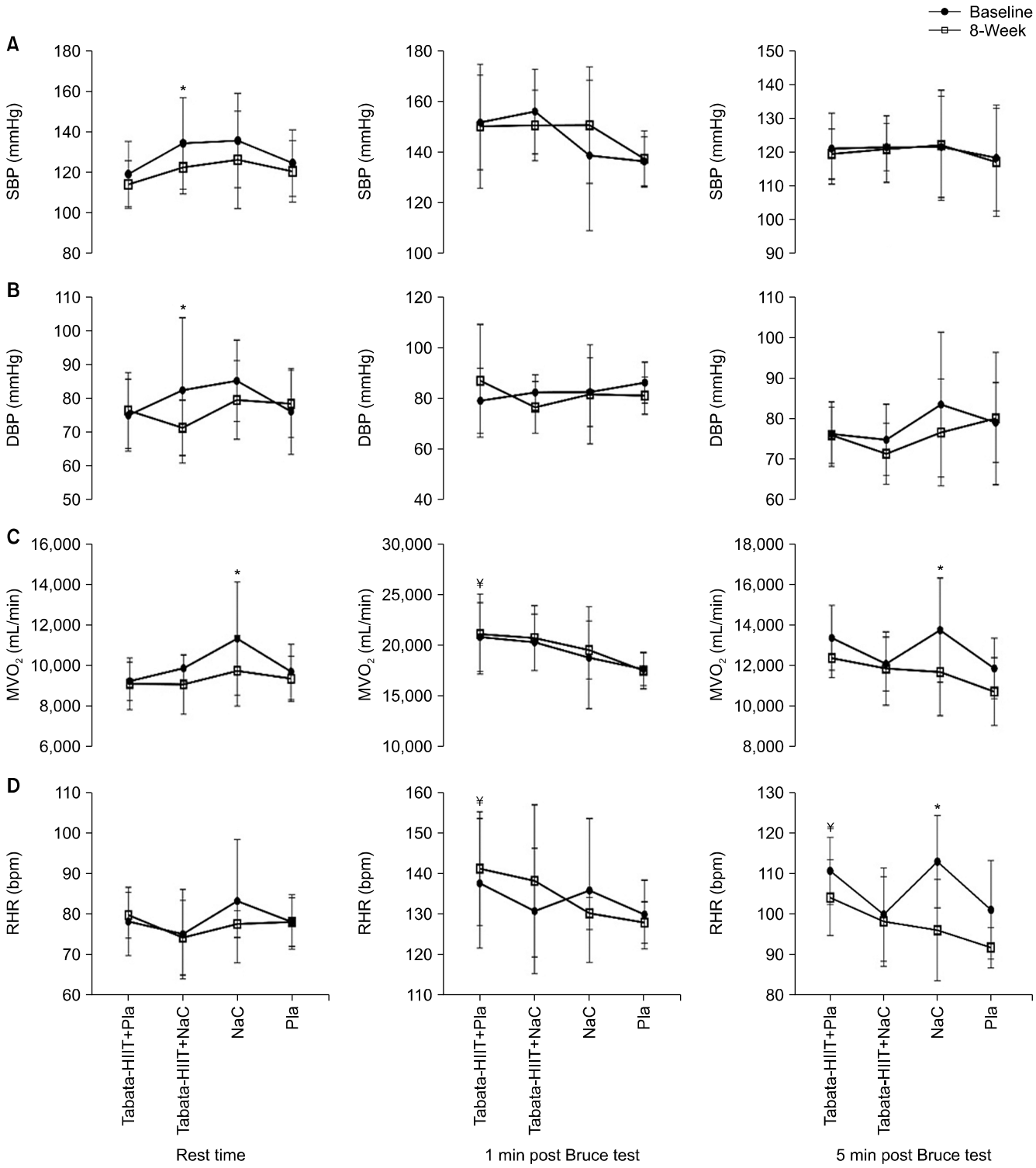

Fig. 3. Hemodynamic indicators after 8-week Tabata-high intensity interval training (HIIT) and nanocurcumin (NaC) supplementation in elderly overweight women. (A) Systolic blood pressure (SBP). (B) Diastolic blood pressure (DBP). (C) Myocardial volume oxygen (MVO_2). (D) Recovery heart rate (RHR). Asterisks denote significant main effects for time ($P<0.05$). *$P<0.05$. ¥ denotes a significant difference compared to control ($P<0.05$). Pla, placebo.

so should be noted that no significance differences were noted between the groups for any other hemodynamic indicator.

A significant main effect for time was noted for VO_2max ($P<0.001$, Fig. 4A), SpO_2 ($P<0.04$, Fig. 4B) and O_2 pulse ($P<0.002$, Fig. 4C). In all groups except the control group (Pla), VO_2max was greater at 8 weeks compared to baseline. Likewise, O_2 pulse. Moreover, for SpO_2, the values were significantly lower in the control group ($P=0.03$) after the 8 weeks ($P<0.03$). No significant differences between groups were noted for SpO_2, VO_2max, or O_2 pulse, neither at baseline or following 8 weeks.

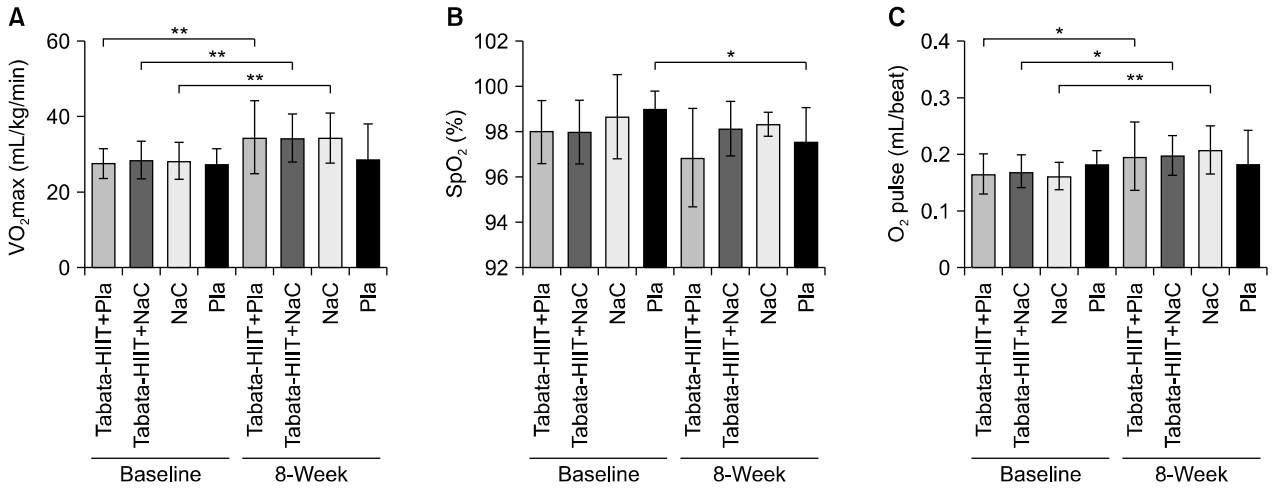

Fig. 4. Cardiorespiratory indicators after 8-week Tabata-high intensity interval training (HIIT) and nanocurcumin (NaC) supplementation in elderly overweight women. (A) Maximal oxygen consumption (VO_2max). (B) Oxygen saturation (SpO_2). (C) Oxygen pulse (O_2 pulse). Asterisks denote significant main effects for time (P<0.05). *P<0.05 and **P<0.01. Pla, placebo.

Gene expression responses following 8 weeks of Tabata HIIT and NaC supplementation

***NLRP3 inflammasome expression*:** At the start of the 8 weeks, the relative expression of *NLRP3* immediately post-test was increased in all participants compared to baseline (before the test). Although no significant change was noted for *NLRP3* relative expression at 8 weeks, we found a lower *NLRP3* relative expression in the Tabata-HIIT+Pla group compared to controls (Pla group; P=0.05). Notably, no significant main effect for time was found for *NLRP3* relative expression between pre-treatment and post-treatment (Fig. 5).

Following 8 weeks of treatment, the *NLRP3* relative expression was significantly greater in the placebo group (P<0.001) in comparison to baseline. Moreover, *NLRP3* relative expression at 8 weeks was significantly greater in the placebo group compared to the Tabata-HIIT+Pla (P=0.007), Tabata-HIIT+NaC (P=0.005), and NaC (P=0.04) groups.

***LncRNA-MIAT expression*:** Before the 8 weeks, the *MIAT* relative expression at immediately post-test was decreased in all participants (P=0.03) compared to baseline. After the 8 weeks, the *MIAT* relative expression was more increased in the NaC group than in the Tabata-HIIT+Pla group (P=0.03). Notably, no significant main effect for time was found for the *MIAT* relative expression after the 8 weeks of treatment compared to baseline (0 weeks) (Fig. 5).

Following the 8 weeks of Tabata HIIT and curcumin treatment, the *MIAT* relative expression was significantly greater in the NaC group compared to the control (P=0.01) and Tabata-HIIT+NaC (P=0.03) groups. No significant main effect for time was found for *MIAT* relative expression.

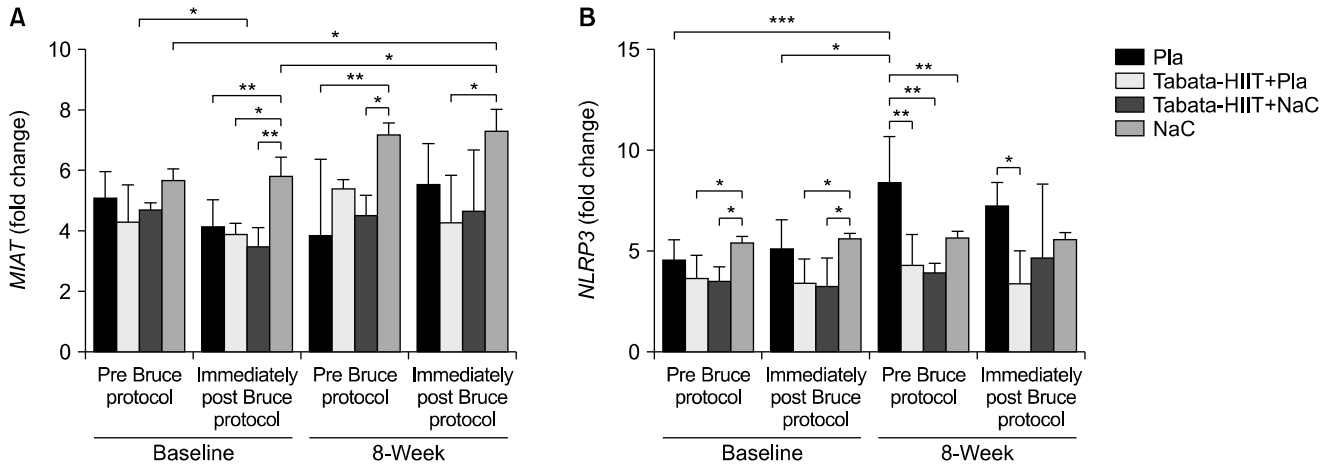

Fig. 5. NOD-like receptor family pyrin domain-containing 3 (*NLRP3*) and myocardial infarction associated transcript (*MIAT*) gene expression after 8 weeks of Tabata-high intensity interval training (HIIT) and nanocurcumin (NaC) supplementation in elderly overweight women. (A) *MIAT*. (B) *NLRP3*. Asterisks denote significant main effects for time (P<0.05). *P<0.05, **P<0.01, and ***P<0.001. Pla, placebo.

DISCUSSION

In this study, we tested whether 8 weeks of Tabata HIIT alone and in combination with NaC supplementation would affect the body composition, the expression of the *NLRP3 inflammasome* and *lncRNA-MIAT* genes, and the cardiorespiratory hemodynamic responses to the treadmill stress in overweight elderly women. We found that the body composition, VO_2max, and O_2 pulse were significantly greater at 8-week post-intervention in comparison to baseline, control and the NaC alone groups. In addition, 8 weeks of Tabata HIIT caused a significant improvement in RHR, SBP, and MVO_2. Meanwhile, Tabata-HIIT exercise combined with NaC supplementation for 8 weeks showed unique sympathetic suppressor and parasympathetic activating properties, as indicated by a decrease in the resting HR and SBP.

Eight weeks of non-pharmacological interventions led to a significant decrease in the *NLRP3 inflammasome* and *lncRNA-MIAT* expression after the treadmill stress test. Furthermore, the resting relative expressions of *NLRP3* and *lncRNA-MIAT* in the Tabata HIIT and Tabata-HIIT+NaC groups were lower at 8 weeks as compared to the placebo group and the baseline period. Tabata HIIT and curcumin supplementation can therefore be said to lower the expression of genes linked to inflammation. These protocols could downregulate the expression of these genes, indicating the suppressive effects of regular exercise and natural herbal supplementation (i.e., NaC) on the activation of the inflammasome. These novel findings provide evidence that a decrease in the chronic expression of *NLRP3* may reduce systemic inflammation.

It has been previously reported that the activation of *NLRP3* in adipose tissue stimulates the secretion of proinflammatory cytokines. Our results showed that Tabata-HIIT and Tabata-HIIT+NaC protocols could be effective in normalizing body composition measurements such as PBF, BAI, and WHR and the cardiorespiratory hemodynamic responses (VO_2max, O_2 pulse, MVO_2, SBP, and HR) in overweight elderly women. Therefore, taking a NaC supplement along with Tabata-HIIT exercises may have beneficial effects on cardiorespiratory hemodynamics in overweight elderly females.

In line with our findings, researchers have reported that regular physical activity could reduce inflammatory factors. Evidence has demonstrated that physical activity has inhibitory effects on inflammasome activation (Gomarasca et al., 2022). Meanwhile, other studies have shown that upregulation or downregulation of lncRNAs can inhibit *NLRP3* activation and reduce inflammatory responses (Lu et al., 2022). One *lncRNA*, *MIAT*, is involved in myocardial infarction, microvascular dysfunction, and diabetes mellitus development (Liao et al., 2016; Alfaifi et al., 2021). Alfaifi et al. (2021), reported MALAT was acknowledged as a unique serum index that predicts metabolic syndrome, providing a promising biomarker for future strategies to diagnose gestational diabetes mellitus. In addition, these researchers stated that high *MIAT* expression was also observed to be associated with smoking and alcoholism among patients with diabetes mellitus (Alfaifi et al., 2021).

Recent studies have demonstrated that nanomicelles and nanoparticles can increase the effectiveness of curcumin (Benameur et al., 2023). In the current study, we used the NaC capsule form, which contains 85% curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin. As suggested in most studies, curcumin is among the strongest anti-inflammatory agents (Anand et al., 2007; Prasad et al., 2014; Jäger et al., 2019). The results of our study also showed that although NaC supplementation for 8 weeks improved body composition and cardiorespiratory hemodynamic indices, this effect was lower compared to overweight elderly women who also performed Tabata-HIIT exercises. Similarly, the resting relative expressions of *NLRP3* and *lncRNA-MIAT* in the Tabata-HIIT+NaC and Tabata-HIIT groups were found to be lower at 8 weeks after non-pharmacological interventions, as compared to placebo group and baseline period. Therefore, it seems that NaC with Tabata-HIIT was able to reduce myocardial stress and relative inflammation probably via improvements in body composition or by reducing the cytokine levels.

Liang et al. (2020) reported that HIIT training (12 weeks, 5 d/week), is more effective than moderate-intensity continuous training for regulating *NLRP3* inflammasome activity. In our study, one session of treadmill stress testing in inactive elderly women caused an inflammatory response; however, one session of the treadmill stress testing after the combined strategies of Tabata-HIIT exercises and NaC supplementation reduced the inflammatory response and increased the *MIAT* gene expression. In line with our findings, Cardoso et al. (2021) reported that acute intense exercise was associated with tissue damage and inflammation. However, in our research, a significant decrease in *NLRP3* was observed in the Tabata-HIIT+NaC group. Domaradzki et al. (2020) demonstrated that HIIT was effective in reducing body mass, WHR, and PBF in overweight individuals, but exercise combined with diet resulted in a greater weight reduction than diet alone and increasing exercise intensity increased the magnitude of weight loss (Brown et al., 2018). In addition, the cardiovascular protective effects of NaC supplementation may be attributed to anti-inflammatory properties, which attenuate the metabolism of prostaglandins and lipoxygenases (Ashtary-Larky et al., 2021). Our study findings support this point of view, as we detected a decrease in %BAI, PBF, and WHR following 8 weeks of non-pharmacological intervention.

This experimental protocol provides information with respect to the chronic physiological adaptations to non-pharmacological interventions, including Tabata-HIIT with and without NaC supplementation. The findings from this investigation demonstrate the rate pressure product and myocardial oxygen consumption on the cardiovascular system during the treadmill stress testing and a lower resting *NLRP3* and *lncRNA-MIAT* expression in overweight elderly women after 8 weeks of non-pharmacological interventions. These findings indicate the suppressive effects of regular exercise and herbal supplementation (i.e., NaC) on the sympathetic system and the downregulation of inflammasome activity, especially the combined approach of Tabata HIIT and NaC. It is recommended that overweight elderly women take an NaC supplement along with Tabata HIIT. The results confirmed that inflammation induced by treadmill stress testing can be managed using long-term non-pharmacological strategies.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: VDR. Analysis and interpretation: SN. Data collection: SN. Writing the article: VDR, SN. Critical revision of the article: VDR. Final approval of the article: all authors. Statistical analysis: SN. Overall responsibility: VDR.

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