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ORIGINAL ARTICLE

Effect of acute downhill running on bone markers in responders and non-responders

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Abstract

Summary This study showed that procollagen type 1 amino-terminal pro-peptide and N-MID osteocalcin significantly increased after exercise independent of the form of muscle contraction. Thus, these preliminary results will be useful for future studies that will consider bone turnover characteristics of responders and non-responders to acute and chronic aerobic exercise.

Introduction The aim of the current study was to compare the effects of acute flat running (FR) and downhill running (DHR) on bone turnover markers in men.

Methods Fourteen healthy young active men performed three exercise tests in a counterbalanced order, including rest condition, FR, and DHR, at 60% maximal aerobic capacity on a treadmill with 0 and − 12% inclines. Blood samples were taken in the pre-exercise, immediately post-exercise, and 24-h post-exercise periods, and bone markers included total procollagen type 1 amino-terminal pro-peptide (total PINP) and N-MID osteocalcin.

Results Total P1NP significantly increased after exercise independent of the form of muscle contraction ($p > 0.05$). N-MID osteocalcin increased after DHR by 17% compared to after pre-exercise, but the difference did not reach significance ($p = 0.07$; partial eta square, 0.21). Biomarker responses to exercise were dependent on the exercise form and independent of hormone type in half of the participants who were classified as responders. Physiological parameters and changes in muscle voluntary contraction did not explain the differences between responders and non-responders.

Conclusion The effect of acute DHR on bone turnover is determined by biomarker type and participant characteristics. Future studies should discriminate between the characteristics of responders and those of non-responders.

Keywords Bone markers · Downhill running · Eccentric exercise · Responders

Introduction

The role of physical activity, with an emphasis on intensity rather than volume, on bone turnover markers has been reported. For example, a recent meta-analysis found discrepant outcomes and does not support the recommendation of walking alone to prevent osteoporosis, and suggested that further trials are needed to confirm this recommendation [1]. A randomised controlled study found that 12 months of moderate-intensity aerobic exercise did not affect total body bone mineral density or bone mineral content in overweight/obese postmenopausal women [2]. Scott et al. [3] examined the effect of acute exercise intensity (55%, 65%, and 75% $\dot{V}O_{2max}$) of 60 min of running on markers of bone resorption (COOH-terminal telopeptide region of collagen type 1) and formation (terminal pro-peptides of procollagen type 1 (total PINP), N-MID osteocalcin and bone-alkaline phosphatase). Results showed significant similar transient decreases at hour 3 in all sessions compared with baseline. Total PINP appeared to increase during exercise sessions, with a higher increase during the 75% maximal aerobic capacity (VO_{2max}) session, but the difference was not significant compared with the values at baseline and other intensities. Thus, the influence of acute exercise intensity on bone turnover is inclusive.

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The effect of exercise on bone turnover could be attributed to body impact rather than exercise intensity. For example, 15 physically active individuals participated in jumping with the ankle plantar flexors at 65% of maximal ground reaction force until exhaustion, and there was a tendency toward an increase in a marker of bone formation (total PINP) 1 day after the exercise, whereas a marker of bone resorption (carboxyterminal cross-linked telopeptide) significantly increased 2 days after the exercise [4]. An acute exercise session of high-intensity low-impact interval cycling at 90% maximal work load (W_{max}) for 1 min of work followed by 1 min of rest repeated six times increased bone turnover markers at 5 min after exercise and diminished them 1 and 24 h post-exercise. Another study investigated changes in metabolic markers of bone turnover immediately after exercise, 1 h post-exercise, and 24 h post-exercise after 30 min of jogging or water exercise at 60–70% of predicted maximal heart rate ($HR_{max\text{-}predicted}$) compared with a control trial in ten healthy active young females. Results showed no significant effects of time or trial condition on bone metabolic markers (osteocalcin, bone-specific alkaline phosphatase, and cross-linked N telopeptides) [5]. Therefore, exercise form apart from intensity and impact must be investigated.

The effect of muscle contraction, as concentric and eccentric, on bone metabolism turnover has been studied during resistance exercise. For example, 8 weeks of training at a higher ratio of eccentric to concentric leg press (eccentric overloaded ≥ 100% 1-RM concentric leg press) was superior to a low ratio in increasing leg press strength and leg lean mass, and bone mineral mass increased only in overloaded eccentric training that exceeded 100% (138% 1-RM) [6]. Different forms of concentric and eccentric exercise are expected to have different effects on bone turnover. For example, the effect of a strength exercise that has an eccentric action on bone density occurs not only through mechanical loading but also through biochemical changes in free ionised calcium and blood pH [7]. Further, eccentric exercise is known to increase inflammatory markers and muscle damage and that the responses of bone turnover markers might be affected by the increases in inflammatory markers and muscle damage. Whether eccentric contraction during aerobic exercise will induce bone metabolic turnover remains to be examined. Boudenot et al. [8] suggested that traditional endurance exercises offer a modest impact on bone, whereas downhill exercises produce a high impact and involve eccentric muscle contractions that are particularly osteogenic. Thus, the role of acute eccentric aerobic exercise on bone turnover is not fully understood.

Eccentric aerobic exercises, such as those performed downhill have been recommended as they induce many health aspects. For example, eccentric cycling increased the level of fat oxidation at a low metabolic cost compared with concentric cycling [9], and moderate-intensity eccentric aerobic exercise has been acknowledged as a proper modality of exercise suitable for individuals who are elderly or have limited capacity [10]. Eccentric exercise has not shown any adverse events, even among adults with chronic cardiorespiratory disease [11]. Thus, as some downhill activities are natural and can be included in daily life, such as using stairs, and has been proposed as a modality exercise for elderly and very sedentary individuals, the current study aimed to examine the acute effect of downhill running (DHR) on bone turnover markers.

Methods

Participant characteristics

Fourteen healthy active men (age, 24.8 ± 5.7 years; body mass index [BMI], 23.4 ± 3.3 kg/m^2, VO_{2max}, 48.9 ± 3.1 mL/kg/min) who engaged in regular aerobic exercise training >2 h a week were recruited for the study. The exclusion criterion was involvement in resistance training in the past 2 months. Eligible men who expressed interest in participating were provided an overview of the study and asked to give written informed consent.

Study design

The study included primary and experimental exercise visits at the Laboratory of Cardiovascular Physiology at College of Sports Science & Physical Activity, King Saud University (KSU), Riyadh, Saudi Arabia. The primary visits aimed to measure VO_{2max} and determine DHR speed. Experimental exercise visits included three exercise conditions in a counterbalanced order interspersed with a 4-week washout period to provide adequate time after eccentric exercise. During the washout period, the participants were asked to keep their normal daily diet, rest the day before the experimental days, and fast overnight before the experiment. The experimental exercise conditions included flat running (FR), DHR, and rest (NoRun). Blood samples were collected and maximal voluntary contraction (MVC) was performed in all experimental visits pre-exercise, immediately post-exercise, and 24 h post-exercise. The study was approved by the KSU Institutional Review Board (IRB No. E-16-1831).

Primary visits

Participants visited twice to determine exercise intensity speed at 60% VO_{2max} during FR and DHR. In the first visit, the participants performed a graded exercise test to exhaustion as previously explained [12]. The second visit consisted of four stages of DHR at − 12% inclination started at 6 or 7 km/h for 3 min and increased by 1 km/h each stage. Simple regression was computed to determine the equation

of the relationship between speed and oxygen consumption during the incremental test for every participant, and the equation was used to determine the speed that elicits the exercise intensity at 60% VO_{2max} during the DHR test. A Hans Rudolf mask and Polar heart rate chest strap were worn during all exercise tests. Expired air was collected and the gas exchange was analysed using The Parvo Medics Analyser Module (TrueOne®2400 Metabolic Measurement System, Parvo Medics, Inc., USA). Gas and air flow calibration were performed before each test, and a qualified exercise physiologist mentored the tests.

Experimental visits

The experiments consisted of three visits: FR, DHR, and NoRun. The participants rested on a chair during the NoRun condition, whereas FR and DHR consisted of running at speed that elicits 60% VO_{2max} for 40 min distributed to five stages of 8 min interspersed with 2 min of low-speed running at speed that elicits 30% VO_{2max} after every 8-min slot. The inclination of FR was 0%, while that for DHR was − 12%. The 2-min interval run at low speed was previously suggested to avoid intolerance due to expected muscle damage during DHR [13]. Expired air was collected and HR was monitored in the aforementioned exercise sessions.

Blood sample and MVC measurements

Fasting blood samples were drawn by a well-trained phlebotomist at three time points: pre-, immediately post-, and 24 h post-exercise for the three experimental conditions. The blood analysis was performed at Prince Mutaib bin Abdullah Chair for Biomarkers of Osteoporosis (PMCO) at KSU. Serum total PINP, N-MID osteocalcin and β-CTx were determined using Roche Elecsys modular analytics (Cobas e411) electrochemiluminescence immunoassay (Roche Diagnostics, GmbH, Mannheim, Germany). For total PINP, intra- and inter-assay CVs were 1.8 and 2.3%, respectively with a lower detection limit (LOD) of 5.0 ng/L. For osteocalcin, intra- and inter-assay CVs were 4 and 6.5%, respectively with LOD of 0.50 ng/L. For β-CTx, intra- and inter-assay CVs were 4.6 and 4.7%, respectively with LOD of 0.01 ng/L.

The measurement of MVC for the quadriceps muscles was performed using a BioDex (Biodex Medical Systems, Inc., New York, USA) at three time points in all experimental conditions. The average of three MVC trials was calculated for each time point.

Statistical analysis

Data were analysed using SPSS (version 21; IBM). Continuous data are presented as mean ± standard deviation (SD) for variables following Gaussian distribution. All continuous variables were checked for normality using the Kolmogorov-Smirnov test. A repeated measures two-way analysis of variance (ANOVA) was used to analyse all variables. When Mauchly's sphericity test indicated a minimal level of violation (> 0.75), and the degrees of freedom were corrected using Huynh-Feldt correction and when the sphericity was < 0.75, Greenhouse-Geisser correction was used. A post hoc Tukey analysis was performed to identify where the significant differences occurred. Correlations between variables were assessed using Pearson's correlation analysis and differences between pre- and post were assessed using paired sample t test. A p value < 0.05 was considered statistically significant.

Results

Repeated measures ANOVA showed no significant differences in N-MID osteocalcin among the FR, DHR, and NoRun conditions at pre-, post-, and 24-h post-exercise, although the increase in DHR was borderline significant (p = 0.08). The values of total PINP significantly increased post-exercise for the FR and DHR conditions compared with baseline, while the DHR values were significantly higher than pre-exercise ($p < 0.01$). A post-exercise ANOVA test showed that FR and DHR values were significantly greater than NoRun values ($p = 0.02$). Although the mean value was greater at DHR than FR, it did not approach statistical significance ($p = 0.69$), while effect size (partial eta square = 0.09) between FR and DHR was observed at post-exercise (Table 1).

The coefficients of variation in individual responses of total PINP and N-MID osteocalcin at pre-, post-, and 24-h post-exercise were 25–39% in all conditions except post-DHR, which was > 40% for total PINP and N-MID osteocalcin. There were no significant correlations between percent changes from pre- and post-DHR of total PINP and N-MID osteocalcin and physiological parameters (Table 2). Furthermore, β-CTx data showed no significant difference between pre- and post-exercise bouts of FR (497.1 ± 182.4 and 430.7 ± 124.4 ng/L, $p = 0.12$) and DHR (421.5 ± 163.4 and 412.3 ± 153.4 ng/L, $p = 0.60$).

Figure 1 shows that the percent changes in the two biomarkers had the same trend and magnitude for the majority of participants during FR, which was also observed during DHR, whereas the change in each biomarker was different during DHR than FR. The participants were divided into two groups based on changes in total PINP during DHR: in group 1, total PINP increased ($n = 7$); in group 2, total PINP decreased or did not change ($n = 7$). The results showed no significant intergroup differences in BMI, VO_{2max}, energy expenditure (EE), or respiratory exchange ratio (RER). The

Table 1 Total PINP and N-MID osteocalcin responses at pre-, immediately post-, and 24 h post-flat running (FR), downhill running (DHR), and control no running rest (NoRun) ($n = 14$)

Parameter	Pre-	Post-	24 h	p value (Greenhouse-Geisser)	Partial eta square
P1NP (ng/mL)					
FR	90.9 ± 30.5	102.8 ± 35.7^{A}	94.4 ± 32.7^{B}	0.008	0.36
DHR	93.2 ± 29.9	114.9 ± 51.9^{A}	84.5 ± 37.4^{B}	0.004	0.37
NoRun	89.4 ± 31.7	83.5 ± 25.3$^{*\#}$	95.6 ± 34.2 ^{AB}	0.01	0.34
p value	0.79	0.02	0.20		
Osteocalcin (ng/mL)					
FR	38.2 ± 14.9	37.7 ± 11.3	35.9 ± 9.4	0.42	0.05
DHR	35.3 ± 10.5	41.6 ± 20.7	35.4 ± 10.2	0.08	0.21
NoRun	34.8 ± 13.5	34.3 ± 10.1	35.8 ± 12.1	0.48	0.06
p value	0.51	0.12	0.50		

Data presented as mean ± SD. Repeated measures analysis of variance (ANOVA) with post hoc Bonferroni test was performed. A and B indicates significance at the pre- and post-levels. ANOVA was performed, and * and # indicate significance in the FR and DHR conditions. p values were considered significant at the < 0.05 level

same was found after the participants were divided based on changes in N-MID osteocalcin.

Figure 2 showed no correlation between percent changes of bone markers (total PINP and N-MID osteocalcin) and percent change of MVC from pre- and post-DHR ($r = 0.05$ and 0.21, respectively).

Discussion

In the present study, there was a transient increase in total PINP immediately after exercise independent of exercise form. It decreased 24 h post-exercise, but the response of the NoRun condition was inconsistent. On the other hand, N-MID osteocalcin did not change at all time points except for a modest but non-significant increase (17%) immediately after the DHR condition compared to pre-exercise. This means that the effect of acute exercise on the mean value of bone markers is affected by the type of biomarker and muscle contraction. Individual responses to FR and DHR revealed a similar trend in the percent changes in bone markers (total PINP and N-MID osteocalcin) for approximately half of the participants.

Table 2 Correlations between changes in bone markers (TOTAL PINP and N-MID osteocalcin) at pre- and post-DHR and physiological parameters

Δ Post–pre (%)	BMI	VO_{2max}	EE	RER
P1NP	− 0.35 (0.22)	0.21 (0.49)	− 0.34 (0.23)	− 0.01 (0.96)
Osteocalcin	− 0.41 (0.14)	0.34 (0.26)	− 0.34 (0.23)	− 0.06 (0.82)

Data presented as coefficient (r) values and significance is considered at $p < 0.05$

BMI body mass index, *DHR* downhill running, *EE* energy expenditure, *P1NP* procollagen type 1 amino-terminal pro-peptide, *RER* respiratory exchange ratio, VO_{2max} maximal aerobic capacity

Thus, it is important to classify healthy active men into responders and non-responders to accurately recommend eccentric DHR for bone health. Finally, physiological parameters including changes in MVC did not explain changes in bone markers after acute aerobic exercise involving either eccentric or concentric contraction.

The current findings of a transient increase in total PINP and no change in N-MID osteocalcin after acute aerobic exercise are consistent with several previous studies. Scott et al. [3] found that total PINP increases transiently after acute weight-bearing exercise and remains unchanged during recovery time and in the 1–4 days after exercise independent of exercise intensity. Total PINP tended to increase on day 1 after a very strenuous single bout of exhaustive high-impact exercise but remain unchanged immediately and 2 h post-exercise [4]. On the contrary, acute exhaustive running influenced resorption but not formation markers including total PINP, which did not change 2 h and 1–4 days after the exercise [14]. It should be noted that there was no significant difference between pre- and post-β-CTx at FR and DHR, which indirectly indicate that exercise intensity was not sufficient to induce bone turnover and changes in bone markers. Thus, a transient increase of PINP to acute exercise may be exercise intensity dependent, but further studies are required to confirm this conclusion.

There was no change in N-MID osteocalcin after DHR, although the percent change and effect size was greater than FR. It is unclear whether increasing DHR intensity or duration would have an effect, and previous studies suggested no response of N-MID osteocalcin to different acute exercise forms [15]. Brisk walking at 50% VO_{2max} for 90 min did not induce any significant changes in N-MID osteocalcin concentration among postmenopausal women [16]. A short-term maximal effort using a modified Wingate test did not induce any change in N-MID osteocalcin at 5 or 60 min after exercise in athletic

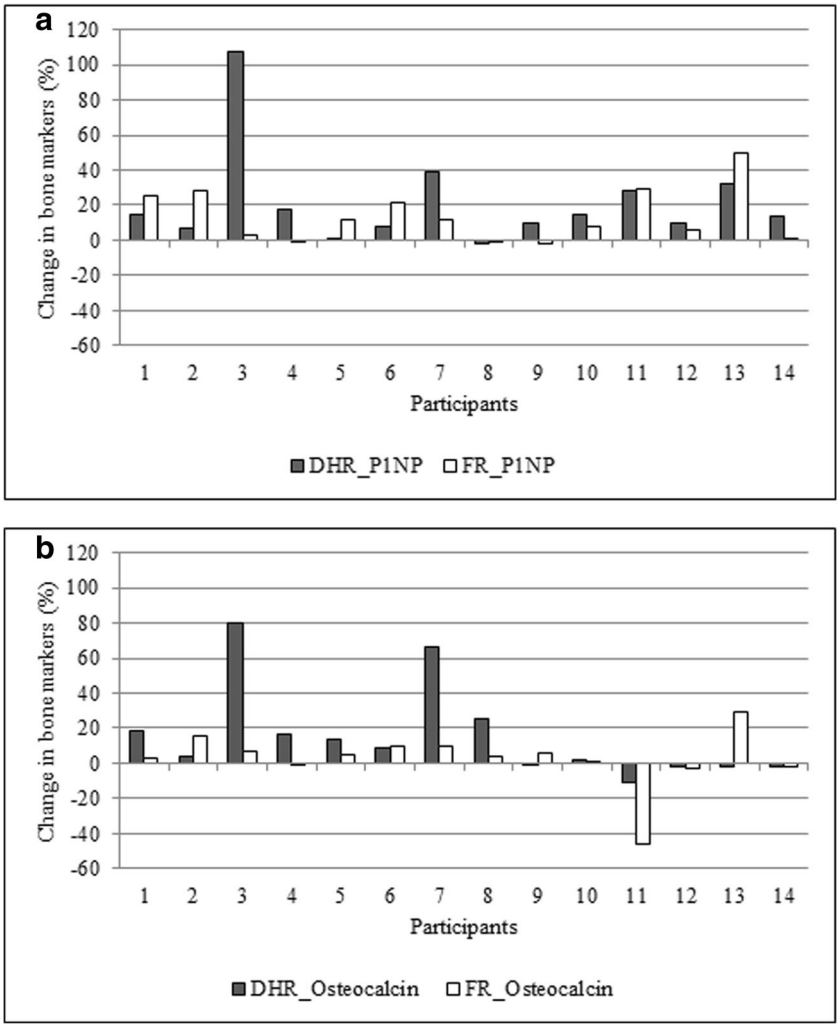

Fig. 1 Percent changes in bone markers **a** TOTAL PINP and **b** N-MID osteocalcin, from pre- to post-bouts of flat running (FR) and downhill running (DHR) per participant ($n = 14$)

males [17]. A 30-min cycling session performed at 80% VO_{2max} led to a transient increase in all formation markers except N-MID osteocalcin in young active males [18]. On the contrary, N-MID osteocalcin significantly increased by 11% at the end of a high-intensity exercise session at + 15% of the ventilatory threshold in male cyclists, whereas the N-MID osteocalcin levels did not change during moderate-intensity exercise performed at − 15% of the ventilatory

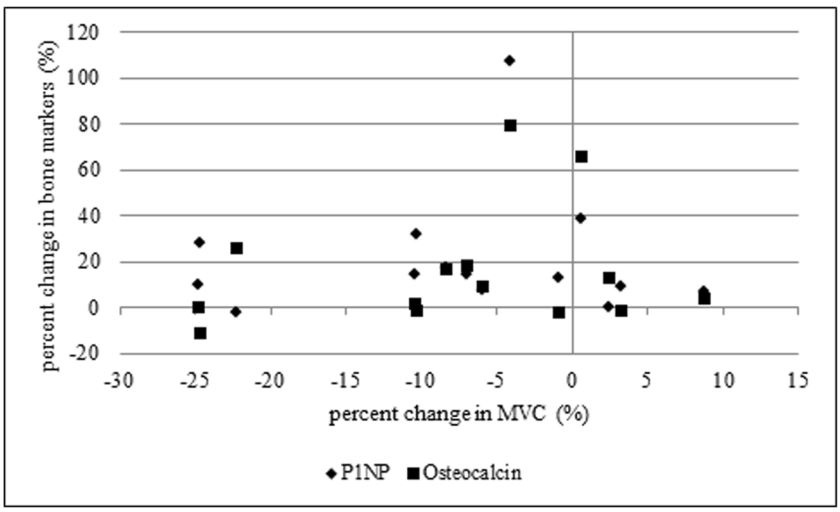

Fig. 2 Correlation between percent changes of bone markers (total PINP and N-MID osteocalcin) and percent change of maximal volitional contraction (MVC) pre- and post-DHR

threshold [19]. It should be noted that prolonged aerobic exercise may lead to a decrease in N-MID osteocalcin, which could be attributed to a decrease in haemoconcentration [20]. Studies on the response of N-MID osteocalcin to high-impact exercises are also scarce. A short-term high-impact jump did not affect N-MID osteocalcin level [21], whereas it was significantly higher after plyometric exercise compared with intermittent running in untrained college-aged men observed immediately and 1 h after exercise [21]. Thus, the current high impact of acute eccentric DHR on N-MID osteocalcin level was not confirmed.

There were no correlations between changes in bone markers and physiological parameters, such as VO_{2max}, EE, and BMI. It was reported that physical fitness levels measured using VO_{2peak} at baseline and after aerobic intervention did not correlate with changes in bone formation markers including N-MID osteocalcin [22]. Although chronic energy balance, particularly negative energy balance, affects bone metabolism including N-MID osteocalcin [23], the latter has a role in systemic energy and carbohydrate metabolism [3]. EE in the current study did not correlate with the response of N-MID osteocalcin. N-MID osteocalcin is inversely associated with adiposity in obese adolescents [24], a finding that differs from that of the current cohort. It should be noted that the current finding was of acute exercise, so it cannot be extended to a chronic condition.

Individual variations affected the responses of bone turnover markers. Individual responses showed similar response patterns of the two formation markers (total PINP and N-MID osteocalcin) for more than half of the participants. These variations among homogeneous participants could be attributed to several factors such as exercise-induced lactate concentration, metabolic acidosis, and basal values [20]; however, these variables have not been investigated in the current study. Furthermore, eccentric exercise relies on the residual force enhancement theory that occurs after active muscle lengthening, for which large variations were found, suggesting that there are responders and non-responders in this action [25]. We recently reported a correlation between change in MVC and fat oxidation rate [12], but such a correlation was not found between changes in bone turnover and changes in MVC in the current study; thus, MVC is not expected to be the main factor in bone marker variations. Further studies are required to examine the bone turnover characteristics of responders and non-responders to acute and chronic aerobic exercise.

Strengths and limitations

The strengths of this study include the control resting day condition to disseminate any day-to-day variation [7] and the three measurement time points including 24 h post-exercise. A measurement at 24-h post-exercise is suggested to be included for all bone markers since a delayed response of bone turnover after acute exercise has been reported in several studies [20]. Treadmill speed was set based on relative exercise intensity rather than absolute workload, whereas the gas exchange analysis was measured during all sessions. However, the study also has some limitations. It did not include bone resorption markers testing, which would have allowed to see whether the effect observed in total PINP relates to a global increase in bone turnover or a more specific effect on bone formation. [26]. The participants were recruited based on their engagement in regular aerobic exercise, but individual variations in biomarker responses might require further control of the sports type. It was not possible to properly discriminate between the physiological parameters of the responders and non-responders because of the small sample size. Lastly, the baseline N-MID osteocalcin level among the current participants was high; thus, the changes may not be as pronounced as in sedentary individuals and may require higher intensity levels for active individuals [20, 27]. Changes in β-CTx supported the importance of increasing the intensity of exercise among active individuals. As the present findings are mostly preliminary, future studies are needed to investigate the characteristics of responders versus non-responders based on the responses of bone biomarker markers in acute and chronic interventions, and to perform these among patients at risk for osteoporotic fracture whom are significantly different from the current group.

Conclusion

Total PINP is sensitive to aerobic acute exercise independent of muscle contraction type. The mean total PINP and N-MID osteocalcin levels increased greater after DHR than after FR. Similar trends of these biomarkers in response to exercise form were observed in half of the participants. The characteristics of the responders and non-responders were not explained by physiological parameters or percent changes in MVC.

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Contributions SA, SY, and NA designed the study; SA supervised the data collection process; and SY supervised the blood analysis. SA wrote the first draft of manuscript, SY and NA carefully revised some sections. JR intellectually contributed to the final version of the paper. All authors approved the final draft for publication submission.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval The study was approved by the KSU Institutional Review Board (IRB No. E-16-1831).

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