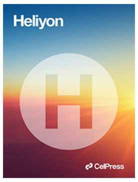
Heliyon 8 (2022) e11051

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Acute effects of low load resistance training with blood flow restriction on serum growth hormone, insulin-like growth factor-1, and testosterone in patients with mild to moderate unilateral knee osteoarthritis

Yangguang Chen [a,1], Junguo Wang [b,1], Shuoqi Li [c,*], Yinghao Li [a,**]

[a] College of Physical Education, Zhengzhou Shengda University, Zhengzhou, Henan, China
[b] Center for Osteoarticular and Trauma Surgery, Qingdao Hospital of Traditional Chinese Medicine (Qingdao Hiser Hospital), Qingdao, Shandong, China
[c] College of Physical Education, Yangzhou University, Yangzhou, Zhejiang, China

ARTICLE INFO

Keywords:
Blood flow restriction exercise
Knee osteoarthritis
Myogenic hormones

ABSTRACT

Objective: To investigate the acute effects of blood flow restriction (BFR) with single-leg low load resistance exercise and high load resistance exercise on serum insulin-like growth factor-1 (IGF-1), growth hormone (GH), and testosterone in patients with unilateral knee osteoarthritis (OA).

Methods: This study recruited 18 postmenopausal female patients with mild to moderate unilateral knee OA, which was then followed by randomly conducting three resistance exercise protocols by drawing lots: 1. A 30% 1-repetition maximum (1-RM) resistance exercise with BFR of 70% arterial occlusive pressure (AOP) (BFR group); 2. A 70% 1-RM resistance exercise without BFR (RES group); 3. A 30% 1-RM resistance exercise without BFR (CON group). Blood lactate (BLA) and muscle growth related hormone levels were tested at 4-time points: before exercise, immediately after exercise, 15 min after exercise, and 30 min after exercise.

Results: There was no statistical difference between the indexes in each group before exercise, but the different exercise had different effects on each index and also an interactive effect ($P < 0.05$). The increase of rating of perceived exertion in the BFR and RES groups, which were of similar magnitude, was greater compared to the levels in the CON group ($P < 0.05$). Post-exercise BLA levels were lower in the CON group in comparison to the BFR and RES groups ($P < 0.05$). Rather than the RES group, GH levels of the BFR group were also significantly higher than the CON group ($P < 0.05$) at 15 min post-exercise. At post- and 15 min after exercise, the CON group recorded significantly lower IGF-1 levels compared to the BFR and RES groups ($P < 0.05$). At post- and 15 min after exercise, the CON group ($P < 0.05$) reflected the lowest testosterone levels, followed by the RES group ($P < 0.05$), and the highest in the BFR group ($P < 0.05$).

Conclusions: Myogenesis-related hormones in women with unilateral knee OA could be increased by high load resistance exercise and low load resistance exercise with BFR on unaffected limb.

1. Introduction

Osteoarthritis (OA) is a dynamic, progressive disease causing significant disability and loss of function [1]. The decline of physical function caused by OA is one of the significant clinical manifestations of female patients with knee OA [2, 3]. Studies demonstrated that the incidence rate of knee osteoarthritis in female is 2–3 times that in male [4, 5], which may be due to the difference in biomechanical environment during walking caused by the different strength [6] and muscle activation modes [7] between female and male. Hence, improving muscle strength and promoting physical function recovery is an important goal of rehabilitation of female knee OA.

Resistance exercise is a traditional method to improve muscle mass and muscle strength [8], Nevertheless, the capacity to tolerate the high mechanical stresses directed onto the joints during heavy resistance training varies among individuals. A combination low load resistance training and blood flow restriction (BFR) could elicit parallel impacts as high load resistance training, which has recently led to its frequent use in

---

* Corresponding author.

** Corresponding author.

E-mail addresses: lsq728738864@gmail.com (S. Li), zhengzhouliyinghao@163.com (Y. Li).

[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.heliyon.2022.e11051
Received 13 May 2022; Received in revised form 5 September 2022; Accepted 7 October 2022

the rehabilitation of knee OA [9]. The basic principle that BFR exercise promotes muscle hypertrophy is partly due to the fact that the pressurized cuff restricts the inflow of arteries, leading to local hypoxia and greater lactate accumulation, while blocking venous outflow, resulting in continuous stimulation of afferent nerves [10]. These strong stimuli can promote the body to secrete growth related hormones, which is conducive to muscle hypertrophy [11]. Additionally, a study [12] revealed that single-leg BFR training effectively improved the muscle strength of the contralateral limb in healthy adults, known as the crossover effect. This event might result from the systemic circulation of myogenic-related hormones. Due to the affected leg of a patient with unilateral knee osteoarthritis may be accompanied by greater risk during resistance exercise [13], it may be safer to use the unaffected leg for resistance exercise with BFR. This provides a new idea for sports rehabilitation of patients with unilateral knee OA. Nonetheless, the effect of unilateral limb exercise on serum myogenesis-related hormones in patients with knee OA remains unclear.

Our previously published study [14] demonstrated that BFR training promotes the production of muscle growth-related hormones in healthy adults. Therefore, this study aims to elucidate the acute effects of BFR with single-leg low load resistance exercise and high load resistance exercise on insulin-like growth factor-1 (IGF-1), serum growth hormone (GH), and testosterone in patients with unilateral knee OA. The findings will provide the theoretical basis to assist researchers and physical therapists in developing a more scientific exercise strategy.

2. Methods

2.1. Research objects

This study recruited 18 postmenopausal female patients with mild to moderate unilateral knee OA. Multiple sources were utilised in recruiting the patients, including direct mailings, advertisements in popular newspapers, and several community approaches. Participants were eligible for recruitment if they fulfilled the following inclusion criteria: (1) postmenopausal female (2) aged between 40 and 70 years old, (3) symptomatic unilateral knee OA (4) Currently experiencing objective functional limitations and (5) not participating in any regular resistance training.

A two-stage protocol was employed in defining patients with knee OA: evidence of osteophytes based on radiographic imaging and either a grade 2 or 3 of the target knee upon bilateral standing anterior-posterior radiograph [15]. A certified radiologist or physiatrist performed the reading of the X-rays. Meanwhile, potential participants were excluded from this study if (1) their health status contradicted the use of a tourniquet (Such as cardiovascular disease, musculoskeletal injury, metabolic syndrome and severe obesity), (2) currently suffering from peripheral vascular disorders or any condition contradicting subjecting them to exercise training, and (3) high blood pressure defined by a diastolic blood pressure >100 mm Hg or resting systolic blood pressure >160 or <100 mm Hg [16]. Overall, patients with a history of other health conditions precluding safe participation were excluded. The experiments were performed upon receiving the written and oral consent of each participant. This study was conducted following The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964). Approval for this experiment was granted by the Ethics Committee of Qingdao Hospital of Traditional Chinese Medicine (Number: 2022-HYJ-247). The study was registered in the ISRCTN registry (Number: ISRCTN51633853). The sample size was estimated using G*power (Version 3.1.9.2) by assuming a post-hoc power (1-β err prob) of 0.99.

2.2. Experimental design

This study utilised a single-blind crossover experimental design. The participants undertook pre-tests and were trained to practice the motor movements the day before the formal test to enhance the test accuracy. Each participant had to perform the 1-repetition maximum (1-RM) test of the unaffected limb prior to the formal exercise, which was then followed by randomly conducting three resistance exercise tests by drawing lots: 1. A 30% 1-RM resistance exercise with BFR of 70% arterial occlusive pressure (AOP) (BFR group); 2. A 70% 1-RM resistance exercise without BFR (RES group); 3. A 30% 1-RM resistance exercise without BFR (CON group). The washout period of each test was 72 h. In order to avoid hormonal effects, the rhythmic test was performed in the afternoon (14:00 to 16:30). The blood collection site was the elbow vein and the blood samples were assessed for systemic biochemical markers. Specifically, blood sampling was conducted before and immediately after exercise, and subsequently at 15 min and 30 min post-exercise.

2.3. Maximum strength test

The exercise prescription guidelines proposed by the American College of Sports Medicine (ACSM) were followed in executing the participants'1-RM assessments [16]. Leg curl and extension of the unaffected limb were the main contents of the test. The participants had to familiarise themselves with the test procedure before executing a warm-up exercise, comprising numerous knee resistance exercises. The participants chose the initial weight (50%–70% 1-RM) during the test in line with the range of self-predictive ability. Upon completing each test, the load was amplified by 10%–20% until the participant could not execute the programmed frequency of repetitions. The participants maintained the same joint range of motion and speed. Resultantly, a 1-RM was achieved within four tests with a corresponding resting time of 3 min between each test. The 1-RM value was documented as the weight of the last executed test.

2.4. Exercise protocols

The exercise load of 30% 1-RM was utilised by the CON and BFR groups, whereas the exercise load of 70% 1-RM was used by the RES group. The healthy limbs in each test required six sets of knee extension and flexion exercises utilising a sitting posture bending exerciser (HS-SLC, Life Fitness, Schiller Park, IL, USA) and a sitting leg extension exerciser (HS-LE, Life Fitness, Schiller Park, IL, USA). Both devices used similar movement modes that required the back of the body to be adjacent to the seat, holding the handles with both hands, and modifying the calf's force point to the ankle joint. The eccentric contraction and concentric contraction were 3 s each, each set was repeated 15 times, with 1 min interval between each set. For the BFR group, the participants were required to wear a pneumatic cuff with 70% AOP on their unaffected limbs (SC12L, Hokanson, Bellevue, WA, USA). This device assumed a straight cuff with a 12 × 124 cm in sized nylon sleeve on the outside. The cuff was worn on the upper third of the thigh (proximal end of the legs) during the exercise. Specifically, the cuff was adjacent to the lower limbs and perpendicular to the limbs when fastened. The device was detached upon completing the exercise [17].

2.5. Blood flow pressure setting

Following the test method described in a previous study [18], the participants' blood flow occlusion pressures were evaluated with a BFR cuff and a Doppler probe (DV-600, Marted, Ribeirao Preto, Sao Paulo, Brazil) [18]. While maintaining a supine position, the cuff was positioned on the proximal end of the participants' unaffected thighs and inflated gradually (i.e., 1 mmHg) until pressure is attained in which no arterial pulse could be further detected. The arterial occlusion pressure was recorded as the minimum pressure in which no pulse was detected, and then the average value was taken after three tests.

2.6. Perceived exertion

The rating of perceived exertion (RPE) scale was used to evaluate subjective load before and after exercise. Participants were informed that a rating of 6 depicts a rating of 6 meant they sensed no exertion, whereas 20 reflects they were exerting maximum effort and unable to further exert themselves [19].

2.7. Blood sample

Blood sampling was performed at various time points as described in the study design. The serum samples were allowed to stand for 30 min, centrifuged at 3000 revolutions per min (rpm) for 15 min, and stored at -80 °C before usage. Serum IGF-1, GH, blood lactate (BLA), and testosterone were analysed using the double-antibody sandwich enzyme-linked immunosorbent assay (Enzyme-linked immunosorbent assay, ELISA).

2.8. Statistical analysis

Statistical analyses were performed using the SPSS 24.0 software (IBM, USA). Data normality was assessed using the Shapiro-Wilk normality test. All the data conformed to normality assumptions and they were presented as mean ± standard deviation (Mean ± SD). Alterations in testosterone, BLA, IGF-1, and GH levels at different periods were tested using a two-way repeated-measures analysis of variance (ANOVA). The same statistical test was employed in analysing the alterations of RPE at pre-and post-exercise. All the analyses for each group were checked for the main and interaction effects. If either of the two effects was significant, the multiple comparisons were conducted using the Newman-Keuls method. Statistical differences were considered at P-values less than 0.05.

3. Results

3.1. Participants' physical characteristics

Table 1 depicts the participants' physical characteristics. A total of 18 patients completed all the tests and exercise protocols, and no adverse effects were documented. Meanwhile, Table 2 presents the exercise load and cuff pressure used by patients during the exercise.

3.2. Changes in RPE

No statistical difference was detected in the RPE between the groups pre-exercise (Figure 1) but the influence of various exercise groups was different with a significant interaction effect ($P < 0.05$). The time effect of RPE was also significant ($P < 0.05$) as the RPE levels of each group post-exercise were significantly higher compared to pre-exercise. The increase in RPE in the BFR and RES groups, which were of similar magnitude, was greater compared to the levels in the CON group ($P < 0.05$).

Table 1. Physical characteristics of patients.

Variable	Mean ± standard deviation
Age (yr)	54.06 ± 4.45
Height (m)	1.63 ± 0.04
Weight (kg)	58.67 ± 5.91
BMI (kg/m^2)	22.10 ± 1.78
Affected limb (L:R)	11:7
SBP (mmHg)	132.22 ± 14.87
DBP (mmHg)	83.78 ± 8.42
Rest HR (beat/min)	71.83 ± 4.58
WOMAC Pain	8.05 ± 2.53
WOMAC Stiffness	4.16 ± 2.50
WOMAC Physical Function	20.79 ± 5.51

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HR = Heart rate; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Exercise load and cuff pressure.

Variable	Mean ± standard deviation
Leg extension 1-RM (kg)	42.16 ± 5.03
30% Leg extension 1-RM (kg)	12.65 ± 1.51
70% Leg extension 1-RM (kg)	29.51 ± 3.52
Leg curl 1-RM (kg)	43.12 ± 6.59
30% Leg curl 1-RM (kg)	12.94 ± 1.98
70% Leg curl 1-RM (kg)	30.18 ± 4.61
AOP (mmHg)	179.94 ± 98.26
70% AOP (mmHg)	125.96 ± 52.78

1-RM = 1 Repetition maximum; AOP = Arterial occlusion pressure.

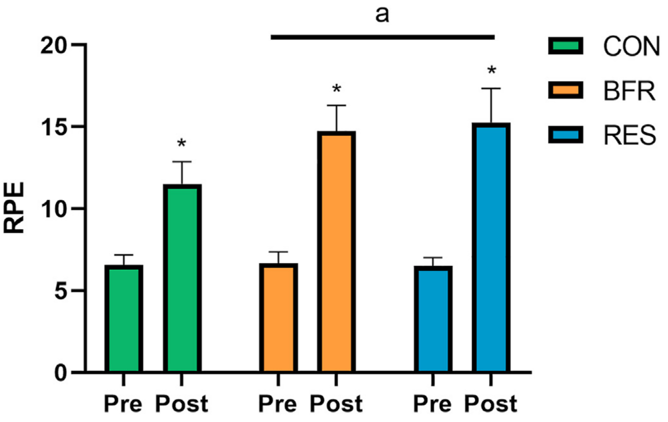


Figure 1. The effects of resistance exercise on RPE on each groups. Note: * represents a significant difference compared with Pre; a represents a significant difference compared with CON group.

3.3. Changes in blood lactate

Following Figure 2, the BLA was not statistically different between the groups pre-exercise. Meanwhile, the influence of different exercise groups was significantly different with a statistically significant interaction effect ($P < 0.05$). Additionally, the time effect of RPE was significant ($P < 0.05$). Post-exercise BLA levels were lower in the CON group in comparison to the BFR and RES groups ($P < 0.05$). At 15 min post-exercise, the LOW group reflected significantly lower average BLA compared to that of the HIGH group. The CON group recorded the lowest average BLA compared that the two other groups ($P < 0.05$). The BLA was not statistically different between the groups at 30 min post-exercise.

3.4. Changes in growth hormone

Figure 3 presents the GH levels in the various experimental groups. Resultantly, no statistical difference was detected in GH levels between the groups pre-exercise. The effects of BFR varied at different pressures, with a significant interaction effect ($P < 0.05$). A significant result was also recorded for the time effect of GH ($P < 0.05$). Meanwhile, GH levels were not statistically different between the groups immediately post-exercise and 15 min later. Rather than the RES group, GH levels of the BFR group were also significantly higher than the CON group ($P < 0.05$) at 15 min post-exercise.

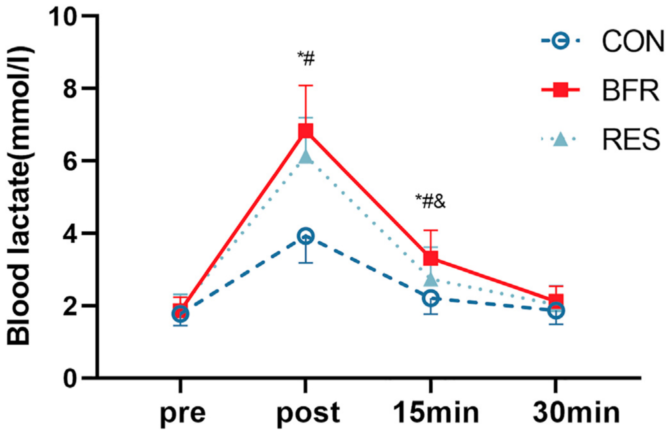


Figure 2. Changes of BLA before and after exercise in each group. Note: * represents a significant difference between the CON group and the BFR group; # represents a significant difference between the CON group and the RES group; & represents a significant difference between the BFR group and the RES group.

3.5. Changes in insulin-like growth factor 1

Although no statistical difference was recorded in IGF-1 levels between the groups pre-exercise (Figure 4), the effect of BFR differed at various pressures with a significant interaction effect ($P < 0.05$). The time-effect of IGF-1 was also significant ($P < 0.05$). Specifically, at post- and 15 min after exercise, the CON group recorded significantly lower IGF-1 levels compared to the BFR and RES groups ($P < 0.05$). Meanwhile, no between-group statistical difference was recorded in the IGF-1 at 30 min post-exercise.

3.6. Changes in testosterone

Figure 5 depicts the between-group comparison of testosterone levels pre-exercise. No statistical difference was detected in testosterone levels between the groups pre-exercise. A significant interaction effect ($P < 0.05$) was recorded in line with the influence of BFR at various pressures. Likewise, the time effect of testosterone was significant ($P < 0.05$). At post- and 15 min after exercise, the CON group ($P < 0.05$) reflected the lowest testosterone levels, followed by the RES group ($P < 0.05$), and the highest in the BFR group ($P < 0.05$). At 30 min post-exercise, the testosterone levels of the CON group was significantly lower in comparison to the BFR and RES groups ($P < 0.05$).

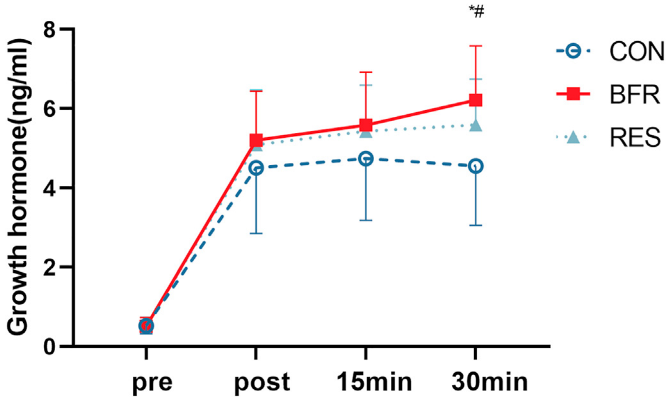


Figure 3. Changes of GH before and after exercise in each group. Note: * represents a significant difference between the CON group and the BFR group; # represents a significant difference between the CON group and the RES group.

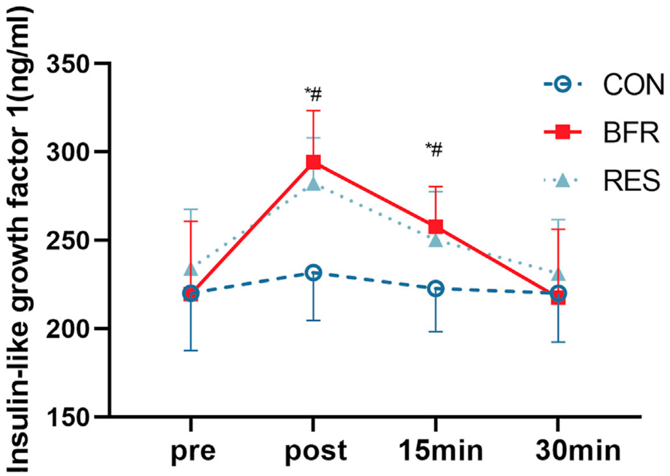


Figure 4. Changes of IGF-1 before and after exercise in each group. Note: * represents a significant difference between the CON group and the BFR group; # represents a significant difference between the CON group and the RES group.

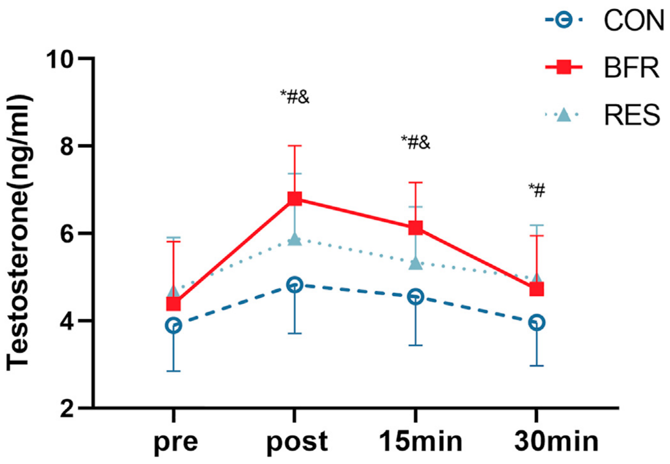


Figure 5. Changes of testosterone before and after exercise in each group. Note: * represents a significant difference between the CON group and the BFR group; # represents a significant difference between the CON group and the RES group; & represents a significant difference between the BFR group and the RES group.

4. Discussion

Results from this study revealed that both BFR and RES groups recorded a significant increase in myogenic-related hormones post-exercise, which was significantly higher compared to that of the CON group. Notably, the BFR group demonstrated higher testosterone secretion levels compared to the RES group post-exercise. These findings highlighted that a combination of BFR and low load resistance exercise is more conducive to the secretion of testosterone levels than high load resistance exercise, Hence, the proposed programmes seem better in enhancing muscle growth.

In previous studies [12, 20], it has been proved that BFR of one limb is beneficial to the strength improvement of the opposite limb, which is called the crossover effect of BFR exercise. In the study of Bowman et al. [12], the control group used 30% 1-RM load for 6 weeks of resistance training without BFR, while the BFR group applied unilateral BFR with 80% AOP on the exercise protocol of the control group. The results showed that the muscle strength and circumference of the limbs without BFR in the BFR group were significantly improved compared with the control group after intervention. It is speculated that the higher metabolic pressure may lead to the increase of synthesis related hormones, which may further promote muscle hypertrophy. This study further verified the possible mechanism of crossover effect on the basis of its research. In addition, the muscle strength and function of the affected leg are weak [21] and the risk of resistance exercise is high [13]. Therefore, restoring the function of the affected leg has become the primary goal of rehabilitation of patients with unilateral knee OA. The results of this study also provide a potential exercise prescription for the rehabilitation of patients with unilateral knee OA to reduce the exercise risk of the affected leg.

The GH is essential in bone growth and development. Young individuals subjected to low-intensity resistance exercise with BFR were reported to demonstrate high GH levels [22]. A study by Takarada et al. [23] posited that BFR resistance exercise of knee joint extension in five groups reflected increased GH levels by 290 times. Notably, the HIGH, LOW, and CON groups were about 28, 18, and 14 times higher, respectively. The present GH levels are lower compared to a previous report [24]. In addition, The present study depicts that peak GH levels are obtained in the range of 15–30 min post-exercise, which coincides with an earlier study [25]. The increased metabolic stress might explain the higher GH secretion levels in the BFR and RES groups, which were significantly higher compared to the CON group. Specific metabolic stress has been reported during resistance exercise. Moreover, BFR can further heighten the metabolic stress to facilitate the accumulation of metabolites and promote GH secretion [26]. A similar trend was demonstrated in the BLA index in this study (BFR group $\geq$ RES group $>$ CON group). Both high and low load resistance exercises with BFR increased the accumulation of metabolites in the body significantly compared with low load resistance exercise without BFR. This also confirms the above inference to a certain extent. In addition, GH can complete its biosynthesis and increase muscular adaptations mediated by IGF-1 [27], hence, the body's IGF-1 level might be affected to a certain degree following the increase of GH during exercise. Finally, estrogen may also affect the secretion of hormones such as GH after exercise [28]. However the participants in this study are all postmenopausal women, the influence of estrogen on the secretion of hormones after exercise is avoided to a certain extent.

The IGF-1 participates actively in cell growth and is highly similar to GH, but the acute response of resistance exercise to IGF-1 is still poorly understood. Serum IGF-1 was significantly increased following low BFR resistance [25], which contradicts the reports by Fujita et al. [29]. Both BFR and RES groups recorded a significant increase in IGF-1 levels post-exercise compared to the CON group. Meanwhile, comparisons between the BFR and RES groups revealed no statistically significant difference. Parallel effects on IGF-1 might be elicited in response to low and high load resistance exercises with BFR, which may be a potential option for traditional high load resistance exercise. The liver could be stimulated by circulating GH levels to secrete IGF-1 [30]. The present study reflects that a significant increase in IGF-1 and GH levels occurred following a low load resistance exercise with BFR. Hence, elevated GH levels may explain the elevated IGF-1 recorded in this study.

Testosterone, a cholesterol-derived steroid, plays a vital role in enhancing muscle synthesis and growth. Testosterone also inhibits the secretion of ubiquitin and is antagonistic to cortisol, thus reducing the breakdown of muscle protein [24, 25]. In the current study, the low load resistance exercise with the BFR group exhibited higher testosterone secretion levels compared to the high load resistance exercise group. This might be explained by the greater metabolic pressure induced by BFR. Lactic acid can promote cAMP generation in rat interstitial cells and stimulate the production of testosterone [26, 27], while BFR can increase the secretion of catecholamines [26]. Catecholamines can also be stimulated by β2-adrenergic receptors in the mouse testes.

Regarding the research linking OA to testosterone levels, the prevalence of knee OA has been associated with lower serum testosterone levels [31]. A positive association was also found in a previous study between medial tibial cartilage thickness and higher serum testosterone levels [32]. Meanwhile, a larger study involving men aged 60 years and above suffering from knee OA revealed positive relationships between men with less Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness and higher testosterone levels [30]. Meanwhile, women with higher testosterone levels were more likely to display better WOMAC function [33]. Hence, increasing testosterone levels is generally beneficial for patients with knee OA. This study increased circulating levels of testosterone by exercising the unaffected leg while keeping the affected leg safe, and this effect may also benefit the affected leg. This suggests that unilateral low load resistance training may be a potential exercise regimen that can increase testosterone levels knee OA patients.

Several limitations were inherent in this study. Only female patients with unilateral knee OA were recruited in this study, thus the findings are not generalizable to male patients. This study does not represent muscle hypertrophy effects of long-term intervention given the short-term follow-up periods. Likewise, this study only theoretically established the effect of unilateral limb exercise on systemic myogenesis. The potential systemic effect of unilateral limb exercise on the affected limb requires further investigation. It is not clear whether long-term unilateral BFR training will bring about the effect of muscle imbalance. In future studies, the participation group should be further expanded to include more patients requiring rehabilitation after musculoskeletal disorders. The long-term intervention effect of training on the unaffected and affected limbs should be explored in the future, and further pay attention to its impact on muscle strength imbalance on the basis of improving the muscle strength of the affected side. Finally, the safety-related issues and the dose-response relationship during exercise can be further investigated in longitudinal studies.

5. Conclusion

Myogenesis-related hormones in women with unilateral knee OA could be increased by high load resistance exercise and low load resistance exercise with BFR. Additionally, low load resistance exercise with BFR was more conducive to improve post-exercise serum testosterone levels in comparison to high load resistance exercise.

Declarations

Author contribution statement

Yangguang Chen and Junguo Wang: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yinghao Li and Shuoqi Li: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Funding statement

Yangguang Chen was supported by the project of the Education Department of Henan Province [ZDJH4372019].

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e11051.

Acknowledgments

Not applicable.

References

[1] A. Phinyomark, S.T. Osis, B.A. Hettinga, D. Kobsar, R. Ferber, Gender differences in gait kinematics for patients with knee osteoarthritis, BMC Muscoskel. Disord. 17 (1) (2016) 157.

[2] S. Harper, L. Roberts, A. Layne, et al., Blood-flow restriction resistance exercise for older adults with knee osteoarthritis: a pilot randomized clinical trial, J. Clin. Med. 8 (2) (2019) 265.

[3] R.F. Loeser, Age-related changes in the musculoskeletal system and the development of osteoarthritis, Clin. Geriatr. Med. 26 (3) (2010) 371–386.

[4] D.T. Felson, Y. Zhang, M.T. Hannan, et al., Risk factors for incident radiographic knee osteoarthritis in the elderly. The framingham study, Arthritis Rheum. 40 (4) (1997) 728–733.

[5] J.A. Buckwalter, D.R. Lappin, The disproportionate impact of chronic arthralgia and arthritis among women, Clin. Orthop. Relat. Res. 372 (2000) 159–168.

[6] J.G. San Juan, D.N. Suprak, S.M. Roach, M. Lyda, Lower extremity strength and range of motion in high school cross-country runners, Appl. Bionics Biomech. 2018 (2018) 1–5.

[7] K.K. White, S.S. Lee, A. Cutuk, A.R. Hargens, R.A. Pedowitz, EMG power spectra of intercollegiate athletes and anterior cruciate ligament injury risk in females, Med. Sci. Sports Exerc. 35 (3) (2003) 371–376.

[8] M.S. Cerqueira, W.H. de Brito Vieira, Effects of blood flow restriction exercise with very low load and low volume in patients with knee osteoarthritis: protocol for a randomized trial, Trials 20 (1) (2019) 135.

[9] B. Grantham, V. Korakakis, K. O'Sullivan, Does blood flow restriction training enhance clinical outcomes in knee osteoarthritis: a systematic review and meta-analysis, Phys. Ther. Sport 49 (2021) 37–49.

[10] T.M. Manini, B.C. Clark, Blood flow restricted exercise and skeletal muscle health, Exerc. Sport Sci. Rev. 37 (2) (2009) 78–85.

[11] Loenneke, C.A. Fahs, J.M. Wilson, M.G. Bemben, Blood flow restriction: the metabolite/volume threshold theory, Med. Hypotheses 77 (5) (2011) 748–752.

[12] E.N. Bowman, R. Elshaar, H. Milligan, et al., Proximal, distal, and contralateral effects of blood flow restriction training on the lower extremities: a randomized controlled trial, Sport Heal. A Multidiscip. Approach 11 (2) (2019) 149–156.

[13] P.T. Williams, Effects of running and walking on osteoarthritis and hip replacement risk, Med. Sci. Sports Exerc. 45 (7) (2013) 1292–1297.

[14] L. Yinghao, Y. Jing, W. Yongqi, et al., Effects of a blood flow restriction exercise under different pressures on testosterone, growth hormone, and insulin-like growth factor levels, J. Int. Med. Res. 49 (9) (2021), 030006052110395.

[15] M.D. Kohn, A.A. Sassoon, N.D. Fernando, Classifications in brief: kellgren-lawrence classification of osteoarthritis, Clin. Orthop. Relat. Res. 474 (8) (2016) 1886–1893.

[16] American College of Sports Medicine, ACSM's Guidelines for Exercise Testing and Prescription, Wolters Kluwer, 2021.

[17] S.S. Kjeldsen, E.T. Næss-Schmidt, G.M. Hansen, J.F. Nielsen, P.W. Stubbs, Neuromuscular Effects of dorsiflexor training with and without blood flow restriction, Heliyon (2019).

[18] R. Rodrigues, R.B. Ferraz, C.O. Kurimori, et al., Low-load resistance training with blood-flow restriction in relation to muscle function, mass, and functionality in women with rheumatoid arthritis, Arthritis Care Res. 72 (6) (2020) 787–797.

[19] S. Dankel, S. Buckner, B. Counts, et al., The acute muscular response to two distinct blood flow restriction protocols, Phys. Int. 104 (1) (2017) 64–76.

[20] E.N. Bowman, R. Elshaar, H. Milligan, et al., Upper-extremity blood flow restriction: the proximal, distal, and contralateral effects—a randomized controlled trial, J. Shoulder Elbow Surg. 29 (6) (2020) 1267–1274.

[21] S.E.S. Terpstra, J.H.P.M. van der Velde, R. de Mutsert, et al., The association of clinical and structural knee osteoarthritis with physical activity in the middle-aged population: the NEO study, Osteoarth. Cartilage 29 (11) (2021) 1507–1514.

[22] J. Brumitt, M.K. Hutchison, D. Kang, et al., Blood flow restriction training for the rotator cuff: a randomized controlled trial, Int. J. Sports Physiol. Perform. 15 (8) (2020) 1175–1180.

[23] Y. Takarada, Y. Nakamura, S. Aruga, T. Onda, S. Miyazaki, N. Ishii, Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion, J. Appl. Physiol. 88 (1) (2000) 61–65.

[24] J.R. Pierce, B.C. Clark, L.L. Ploutz-Snyder, J.A. Kanaley, Growth hormone and muscle function responses to skeletal muscle ischemia, J. Appl. Physiol. 101 (6) (2006) 1588–1595.

[25] H. Takano, T. Morita, H. Iida, et al., Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow, Eur. J. Appl. Physiol. 95 (1) (2005) 65–73.

[26] H. Madarame, K. Sasaki, N. Ishii, Endocrine responses to upper- and lower-limb resistance exercises with blood flow restriction, Acta Physiol. Hung. 97 (2) (2010) 192–200.

[27] S.D. Patterson, M. Leggate, M.A. Nimmo, R.A. Ferguson, Circulating hormone and cytokine response to low-load resistance training with blood flow restriction in older men, Eur. J. Appl. Physiol. 113 (3) (2013) 713–719.

[28] Y. Nakamura, K. Aizawa, T. Imai, I. Kono, N. Mesaki, Hormonal responses to resistance exercise during different menstrual cycle states, Med. Sci. Sports Exerc. 43 (6) (2011) 967–973.

[29] C.S. Fry, E.L. Glynn, M.J. Drummond, et al., Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men, J. Appl. Physiol. 108 (5) (2010) 1199–1209.

[30] C.D. Scott, J.L. Martin, R.C. Baxter, Rat hepatocyte insulin-like growth factor I and binding protein: effect of growth hormone in vitro and in vivo, Endocrinology 116 (3) (1985) 1102–1107.

[31] S. Amani-Shalamzari, A. Sarikhani, C. Paton, et al., Occlusion training during specific futsal training improves aspects of physiological and physical performance, J. Sports Sci. Med. 19 (2) (2020) 374–382. http://www.ncbi.nlm.nih.gov/pubmed/32390731.

[32] M. Pires-Oliveira, A.L.G.C. Maragno, L.T. Parreiras-e-Silva, T. Chiavegatti, M.D. Gomes, R.O. Godinho, Testosterone represses ubiquitin ligases atrogin-1 and Murf-1 expression in an androgen-sensitive rat skeletal muscle in vivo, J. Appl. Physiol. 108 (2) (2010) 266–273.

[33] S shan Lu, Lau C. pang, Y fan Tung, P. Wang, Lactate and the effects of exercise on testosterone secretion: evidence for the involvement of a cAMP-mediated mechanism, Med. & Amp. Sci. Sport & Amp. Exerc 29 (8) (1997) 1048–1054.