Principle of Nutritional Supplementation and Blood-Flow Restriction Training to Enhance Musculoskeletal Rehabilitation in Patients with Arthritis

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Abstract

Resistance training forms a key component of holistic care within orthopaedics. Blood-Flow Restriction Training (BFRT) is an increasingly popular alternative technique to stimulate comparable muscular gains to traditional resistance training. Indeed, BFRT may be more suitable for orthopaedic populations who cannot tolerate the high intensity of traditional resistance training. BFRT appears to stimulate multiple physiological changes to induce Muscular Protein Synthesis (MPS). Specifically, increased anabolic signalling within the akt/mTOR pathway appears to be a central mediator. Nutritional supplementation is a common method to support muscular gains in resistance training. Protein and creatine are amongst those most well documented in the literature. Protein supplementation may enhance muscular gains by potentiation of MPS *via* the akt/mTOR pathway when combined with resistance training. Creatine supplementation appears to have an ergogenic effect with subsequent positive impacts on body composition and recovery. There is minimal literature considering the benefits of combined nutritional supplementation and BFRT and no available literature considering orthopaedic populations as the study group. Nevertheless, the literature cites numerous benefits to protein and creatine supplementation in traditional resistance training. In conclusion, this advocates for further studies to see if BFRT can be enhanced with protein and/or creatine supplementation.

Keywords: Orthopaedics • Musculoskeletal • Supplements • Arthritis

Introduction

Muscular strength is a crucial consideration for effective Musculoskeletal (MSK) rehabilitation in acute and chronic orthopaedic settings. Historically, this has comprised resistance training to enhance muscular strength. Blood-Flow Restriction Training (BFRT) is an emerging technique demonstrating efficacy in orthopaedic rehabilitation [1, 2]. This method involves partial vascular limb occlusion, specifically venous occlusion, using proximally placed inflatable cuffs. With the cuffs placed, the patient then performs Low-Load (LL) exercises which in turn leads to muscle hypertrophy and strength gains. The exact mechanism underlying these muscular and functional changes is yet to be established. However, there are various theories explaining how BFRT may induce muscular growth including metabolite accumulation such as lactate, increased Growth Hormone (GH) secretion, increased levels of circulating Insulin-like Growth Factor 1 (IGF-1), increased recruitment of fast-twitch muscle fibres and downstream stimulation of intracellular anabolic pathways such as the akt/ mammalian Target Of Rapamycin (mTOR) pathway (discussed later) [3].

To stimulate increases in muscular size and strength, it is generally recommended that resistance training utilises high-intensity exercises with 70% of an individual's one Repetition Maximum (1RM) [4]. Despite this, post-surgical and elderly patients may be unable to tolerate such high intensities due to several factors, including pain and co-morbidities [5, 6]. Thus, BFRT presents an attractive clinical approach as it allows comparable muscular gains to high-intensity resistance training yet with as little as 30% of a patients 1RM and in shorter periods [1]. Other cited clinical benefits include hypoalgesia increasing patient engagement and reduced joint stress due to the use of lower loads [5, 7].

With the benefits of BFRT discussed, one must then consider how to optimise the delivery of BFRT. Nutritional supplementation may present one aspect in which muscular gains with BFRT could be enhanced. The use of nutritional supplements to bolster muscular gains and improve athletic performance with traditional high-intensity resistance training is well-documented within the literature [8-10].

To target nutritional supplementation, one must consider muscular energy metabolism and the hypertrophic changes stimulated by resistance training. Briefly, Adenosine Tri-Phosphate (ATP) represents the primary energy source for skeletal muscle contraction (Figure 1). Based on the intensity and the timing of the exercise, ATP may be derived from various sources in either an anaerobic or aerobic fashion [11]. Higher intensity exercise favours the anaerobic breakdown of Phosphocreatine (PCr) and muscle glycogen into lactate [11]. Over time and with lower intensity exercise, aerobic utilisation of free-fatty acids *via* B-oxidation and oxidative phosphorylation of plasma glucose and glucose derived from glycogen stores is preferred [11]. Following exercise, several tissue adaptations occur, namely mitochondrial biogenesis and muscular hypertrophy (Figure 2) [12]. For muscular hypertrophy to occur there must be an increased rate of muscle synthesis relative to breakdown. Following resistance training, muscle synthesis primarily centres upon activation of the akt/mTOR pathway. mTOR is stimulated by both the growth factor IGF-1 and independently in a mechanosensitive fashion [12]. Activation of mTOR causes downstream modulation of translational signalling and subsequently favours Muscle Protein Synthesis (MPS) [12, 13]. Further details reviewing the molecular and cellular changes underpinning muscle hypertrophy can be found in [14].

Material and Methods

Evidence-based nutritional supplementation

Countless nutritional supplements are quoted within the literature. Supplementation with creatine and protein are amongst the most extensively researched. For this review, protein and creatine supplementation will be considered as strategies to enhance musculoskeletal rehabilitation with BFRT.

Protein supplementation

The use of protein supplementation in resistance training is well documented [8, 15]. As mentioned, when skeletal muscle homeostasis favours MPS over Muscle Protein Breakdown (MPB), muscular gains occur. MPS rates can be increased both by resistance training and consumption of protein or Essential Amino Acids (EAA). Indeed, it is believed resistance training acts to potentiate MPS response to EAA feeding thus promoting muscular hypertrophy [16]. In support of this, a large meta-analysis concluded that healthy adults performing prolonged resistance training significantly enhanced muscular gains in strength and size through concurrent dietary supplementation of protein [8]. Mechanistically, it is believed that the increased intracellular concentration of EAAs following protein ingestion leads to subsequent activation of mTORC1 signalling [16]. However, the exact translational and intracellular changes that underpin the anabolic responses with protein ingestion is still debated [16].

Creatine supplementation

Creatine is a naturally occurring compound, present in red meat and seafood. As discussed, creatine, specifically phosphocreatine, is essential for maintaining ATP stores and thereby ensuring optimal

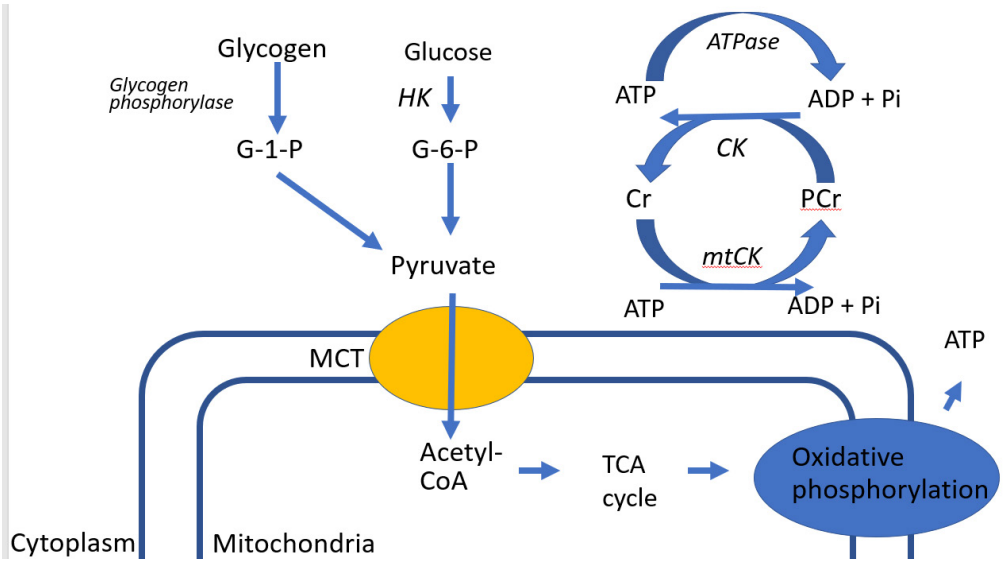

Figure 1. ATP represents the major source of fuel for skeletal muscle metabolism. It may be derived from extracellular and intracellular sources. Initially, and during intense exercise, phosphocreatine (PCr) is used in the resynthesis of ATP from ADP. Breakdown of glycogen into glucose and utilisation of extracellular glucose is favoured during intense exercise. Glucose proceeds to be metabolised firstly *via* glycolysis generating small quantities of ATP through substrate-level phosphorylation. It later enters the mitochondria as pyruvate where it is converted to acetyl-CoA and generates larger quantities of ATP in the TCA cycle and oxidative phosphorylation [11]. "HK, Hexokinase; Cr, Creatine; mtCK, Mitochondrial Creatine Kinase; MCT, Monocarboxylase Transporter".

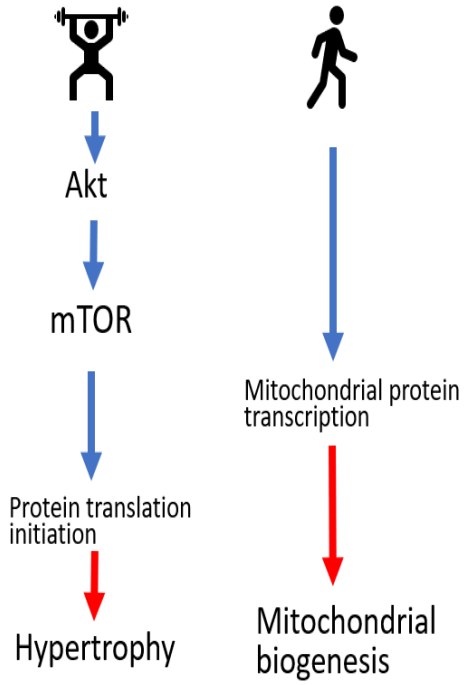

Figure 2. Numerous intracellular signalling pathways are activated in response to a variety of primary signals resulting from exercise. This diagram simplifies two of the intracellular pathways activated in response to exercise. Muscular adaptations are different depending upon the type of exercise performed. Resistance training causes activation of the akt/mTOR pathway initiating intracellular signalling pathways associated with muscular hypertrophy. Mitochondrial biogenesis is increased during endurance exercise [12].

energy capacity during exercise. Thus, creatine supplementation bolsters intramuscular stores of phosphocreatine and confers an ergogenic advantage. The mechanism is currently unexplained, yet enhanced glycogen synthesis, increased anaerobic threshold and greater shuttling of ATP from mitochondria thereby increasing aerobic capacity, are all possible explanations. Logically, increased exercise capacity appears to allow greater increases in muscular strength and mass. However, creatine supplementation may have further benefits such as enhancement of recovery and injury prevention. From an orthopaedic perspective, creatine supplementation is efficacious in the prevention of muscular atrophy following limb immobilization and thus during rehabilitation [17].

Nutritional supplementation in BFRT

There is a distinct lack of high-quality Randomised Controlled Trials (RCTs) considering the benefits of protein supplementation in combination with BFRT. A recent small RCT looked at the benefits of protein supplementation in 30 healthy older males undergoing low-load BFRT (Table 1) [18]. Over 8 weeks, the subjects were allocated to three groups: those receiving BFRT with protein supplementation, those receiving BFRT and placebo and those receiving no training but protein supplementation. Subject to their group allocation, lower limb BFRT was performed three times a week with 20%-30% of the individuals 1RM utilised. For those receiving protein supplementation, these participants were given 15 grams of collagen hydrolysate daily. The authors opted for collagen hydrolysate based on several previous studies that suggested collagen hydrolysate appears to raise concentrations of hydroxyproline-glycine concentrations which exert a positive, and therefore hypertrophic effect, on the mTOR pathway. Thigh muscle Cross-Sectional Area (CSA) and muscle strength were used as functional measures of BFRT. Conversely, circulating Reactive Oxygen Species (ROS) and IGF-1 were used to measure the efficacy of the intervention as increases in these levels have been postulated to stimulate MPS. Similar to findings of other reviews, BFRT produced a highly statistically significant increase in thigh muscle CSA compared to the control group performing no BFRT. The BFRT and collagen supplementation group showed a 6.7% increase in CSA whilst the BFRT with no supplementation group showed a 5.7% increase. Interestingly, the addition of collagen supplementation appeared to provide no statistically significant advantage in increasing muscle CSA. None of the other measures appeared to reach statistical significance over the 8-week intervention period. The authors acknowledged that post-exercise protein supplementation may produce only a small effect in untrained individuals as demonstrated in previous studies by Morton, R.W., et al. The changes in circulating IGF-1 and ROS were conflicting with what was expected. However, previous studies examining IGF-1 have yielded variable results and studies utilising circulating ROS levels as a marker of efficacy are limited. Nevertheless, the lack of change in muscular strength may prove clinically significant within orthopaedic rehabilitation. With only a small sample size, repeated RCTs with larger sample sizes and a variety of age groups may increase our understanding of any possible benefits of protein supplementation [8].

Similarly, there is nearly no available literature studying the therapeutic benefits of creatine supplementation in combination with BFRT. One small RCT published in the Montengrin Journal of Sports Science and Medicine appeared to dispute the use of creatine supplementation with BFRT [19]. In this study, 15 healthy young males were randomly allocated into three intervention groups. These consisted of BFRT, BFRT with creatine monophosphate (CrM) supplementation and BFRT with CrM and Hydroxymethylbutyrate (HMB). HMB is an additional nutritional

Table 1. A summary of the available literature and their study methodology in papers that consider protein or creatine supplementation in BFRT.

Title of Study	Study Design	Participant details	Groups	Training protocol	Supplement details	Outcome measures	Results
Effects of Blood Flow Restriction Training with Protein Supplementation on Muscle Mass And Strength in Older Men. (Centner et al, 2019)	Randomised Controlled Trial	30 healthy older males All over 50 years old Untrained-weekly exercise less than 60 minutes per week	BFRT with collagen supplementation (BFRT+C) BFRT with no supplementation (silicon dioxide placebo used) (BFRT+P) No BFRT and collagen supplementation (CONT)	8 weeks of 3 sessions per week of lower limb BFRT: 45-degree leg press 1 set with 30 repetitions of 20% 1RM 3 additional sets with 15 repetitions 30 seconds inter-set rest interval 1RM was increased from 20% to 30% at week 4.	15 grams of collagen hydrolysate provided by the Collagen Research Institute in Kiel, Germany. Mixed with 250ml of water. Once daily consumption/	Thigh muscular CSA measured using MRI. Isometric 1RM using 90-degree leg press device. Systemic IGF-1. Measured at the beginning and end of the 8-week intervention period via blood sample. Total ROS production pre- and post- exercise. Measured in the first session and the last session via capillary blood sample. Only in BFRT+C and BFRT+P.	Statistically significant increase in muscle CSA in BFRT+C ($p<0.001$) and BFRT+P ($p<0.001$) but no statistically significant difference between the groups. No statistically significant changes in isometric 1RM in all groups. Increases observed in BFRT+C and BFRT+P. No significant differences between groups. No difference in changes in IGF-1 between experimental groups. However, all groups showed an increase over the intervention period. ROS production decreased pre- to post-exercise in all groups. ROS levels remained similar between treatment groups over the first and last training session
Neuromuscular Adaptations after Blood Flow Restriction Training Combined with Nutritional Supplementation: A Preliminary Study (Chulvi-Medrano et al, 2019)	Randomised Controlled Trial	15 healthy young males 20-30 years old Resistance-trained for at least 6 months	BFRT with hydroxymethyl butyrate (HMB) and creatine monohydrate (CrM) supplementation (BFRT+CrM+HMB) BFRT with creatine monohydrate (BFRT+CrM) BFRT with no supplementation (no placebo used) (BFRT)	3 weeks of 2 sessions per week of upper limb BFRT: Bicep curls at 30% of maximal isometric volumetric contraction (MIVC) and a total occlusion pressure (TOP) of 30% 3 sets of 15 repetitions 30 second inter-set rest interval	Creatine monohydrate 0.3gram/kg of body weight. 3 grams of HMB (Scitec Nutrition®). Supplementation was given 10 minutes prior to training sessions.	MIVC was measured in the dominant arm using a load cell device (Mutonic® SP51 "HiLine" V6.10). Participants were given two attempts with the highest selected for analysis. Biceps muscle thickness measured in kg using ultrasound technique (Sonosite M-Turbo) Both were measured at the beginning of the training protocol and at the end	No significant effect on MIVC. Biceps muscle thickness statistically increased across all three groups. BFRT had a significant difference from pre- to post-training ($p<0.05$) BFRT was significantly different from BFRT+CrM+HMB group at post-training ($p<0.05$) with values of 3.96 kg ± 0.15 kg and 3.62 kg ± 0.17 kg respectively.

supplement that may be ergogenic and lead to the enhancement of aerobic and anaerobic capacity. Some of its effects may relate to the stimulation of the discussed mTOR. Interestingly, one review by had stipulated that combining creatine and HMB supplementation may boost sports performance and have a positive effect on body composition [10]. Upon allocation, individuals performed upper limb BFRT twice a week for three weeks. Maximal Isometric Voluntary Contraction (MIVC) of elbow flexion was used as an outcome measure for muscular strength and biceps muscle thickness was used to examine the effects on muscular hypertrophy. In terms of MIVC, there were no significant changes in strength demonstrated in all groups. Although there was a non-statistically significant increase in strength, the authors suggested that these findings may be explained by the short intervention period. Nevertheless, the BFRT caused a statistically significant increase in muscle mass regardless of supplementation. Yet, supplementation appeared to confer no advantage over BFRT without supplementation. Whilst this study provides a unique perspective on

creatine supplementation with BFRT, this may represent a weaker source of evidence-based on the relatively short length of the study, the lack of placebo, the lack of dietary monitoring, the use of upper limb BFRT-which is relatively understudied-and the very small sample size.

Results and Discussion

The field is severely lacking studies examining the combined effects benefits of protein and/or creatine supplementation with BFRT. Ideally, several large multi-centred RCTs would need to be conducted with a range of homogenous patient populations. Within orthopaedics, it would be particularly pertinent to conduct these studies on older patients and those undergoing rehabilitation following orthopaedic surgery. For example, elderly patients represent a considerable source of orthopaedic referrals [20]. Increasing age is associated with muscle loss or sarcopenia. Thus, the preservation of muscle through nutrition and exercise is of paramount importance to combat sarcopenia and for maximising functional capacity [21]. A recent review appeared to support the augmentation of resistance training with nutritional supplementation to combat sarcopenia [22]. Conversely, the meta-analysis conducted disputed the use of protein supplementation in resistance training of elderly populations, stating that there appeared to be no significant increases in muscle mass or strength with protein supplementation [23]. Overall, BFRT is effective in older populations, thus nutritional supplementation may prove fruitful in certain orthopaedic populations [24].

There are several factors to consider when supplementing protein including dose, quality and timing. Returning to an elderly population, some have recommended that elderly populations consume a higher amount of daily protein to combat sarcopenia and its sequelae. Therefore, a patient-centred approach to supplementation may be advocated in those undergoing BFRT and future studies must consider protein dose when utilizing BFRT. When considering protein quality, leucine is an EAA that is of particular interest as it maximally stimulates MPS independently of other EAAs [22]. In support of this, a 2006 study, found protein supplementation with proportionally higher levels of leucine were more effective at stimulating MPS than protein sources that were relatively leucine-poor [25]. Whey protein is a protein supplement that appears to be effective in raising EAAs and leucine concentrations thus leading to stimulation of MPS [22]. Given its widespread availability, whey protein may be a suitable choice for future studies. Meta-analysis appears to suggest the timing of protein consumption relative to resistance exercise appears to have little effect on hypertrophy [26]. However, contextualising an elderly population, it seems to be more important to ensure protein distribution is kept even throughout the day to bolster MPS [22]. Therefore, the study design should factor in the current research to ensure any effect is detected.

Thus far, studies have individually considered protein supplementation and creatine supplementation with BFRT. There is mixed evidence to suggest that resistance training with both creatine and protein supplementation may lead to greater muscular gains [27]. Conversely, this may not be the case in elderly populations [28, 29]. Therefore, future studies may consider the possible benefits of co-supplementation of protein and creatine supplementation in the context of BFRT.

Whilst supplementation is generally assumed to be generally safe [17, 30, 31]. Orthopaedic populations may be co-morbid thus supplementation may not be recommended for all patient populations. Protein supplementation may have negative health effects on insulin resistance and kidney function [32]. Thus, protein supplementation may not be advisable in those with renal disease and diabetes. Similarly, creatine supplementation may have deleterious effects on kidney function thus caution is recommended in patients with pre-existing renal disease [33].

Conclusion

Overall, creatine and protein supplementation has generally been shown to be efficacious in those undergoing resistance training with multiple reviews noting increased strength and muscle mass. BFRT is a safe alternative to high-load resistance training and may be particularly beneficial in orthopaedic populations. Presently, it is unclear whether supplementing protein or creatine may enhance muscular gains in BFRT. However, the evidence base is weak. In conclusion, this review highlights the lack of quality RCTs and advocates increased research in this area to establish whether nutritional supplementation is a viable adjuvant for enhancement of muscular gains with BFRT.

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