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Trends in Endocrinology & Metabolism

Review

Effects of Blood Flow Restriction Exercise and Possible Applications in Type 2 Diabetes

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Blood flow restriction resistance training (BFRT) employs partial vascular occlusion of exercising muscles via inflation cuffs. Compared with high-load resistance training, mechanical load is markedly reduced with BFRT, but induces similar gains in muscle mass and strength. BFRT is thus an effective training strategy for people with physical limitations. Recent research indicates that BFRT has beneficial effects on glucose and mitochondrial metabolism. BFRT may therefore qualify as a valuable exercise alternative for individuals with type 2 diabetes (T2D), a disorder characterized by impaired glucose metabolism, musculoskeletal decline, and exacerbated progression of sarcopenia. This review covers the effects of BFRT in healthy populations and in persons with impaired physical fitness, the mechanisms of action of this novel training modality, and possible applications for individuals with T2D.

Highlights

Blood flow restriction resistance training (BFRT), that is exercising under partial vascular occlusion via inflation cuffs – can induce gains in skeletal muscle mass and strength similar to those seen with classical resistance training, albeit with marked lower training load.

Mechanistically, BFRT leads to accumulation of metabolites in myocytes and triggers the recruitment of higher-threshold motoneurons, induces cell swelling, and promotes protein biosynthesis, resulting in increased muscle mass and strength. Furthermore, low myocellular oxygen tension can induce angiogenesis, increase reactive oxygen species (ROS) production, mitochondrial biogenesis, and glucose transporter (GLUT) 4 expression.

In addition to impaired glucose metabolism and physical fitness, individuals with type 2 diabetes are at increased risk of sarcopenia. For these individuals, low-load BFRT may be an effective exercise modality.

Blood Flow Restriction Training as an Alternative for Maintaining Physical Performance and Health?

Endurance training typically improves cardiorespiratory fitness [1] which is associated with lower mortality from any cause as well as reduced cardiovascular disease risk [2]. In addition, individuals with higher muscle mass and strength are at lower risk of death [3]. Classical resistance training (RT) effectively improves skeletal muscle mass and strength as well as glycemic control [4,5]. In that sense, exercise training holds great promise for the prevention and management of metabolic diseases such as type 2 diabetes (T2D) (Box 1).

However, to achieve health benefits from RT, loads equating to 70% or more of the individual **one-repetition maximum** (**1-RM**; see Glossary) are often recommended [6]. High muscle-tendon loads may not be suitable for people with physical limitations or clinical populations who are affected by muscle wasting and reduced muscle strength. Effective alternative countermeasures are therefore urgently needed for these individuals to avoid frailty. One promising exercise modality is **blood flow restriction training (BFRT)** (Box 2).

It has been shown that blood flow restriction (BFR) alone, even without concomitant exercise training, can be effective in mitigating the reductions in muscle strength and **atrophy** that result from immobilization [7]. Interestingly, BFR without exercise prevented reductions of muscle strength and leg circumference in cast-immobilized patients [8] as well as declines of muscular weakness induced by chronic unloading [9]. Along these lines, previous studies showed that BFR without exercise diminishes both postoperative muscle atrophy [10] and bed-rest-related muscle atrophy [11].

This training modality typically utilizes loads as low as 20–40% of an individual's 1-RM for 2–4 sets of exercise to or near volitional failure. BFR is usually maintained between sets with a total restriction time of 5–10 minutes [12] (Box 3).

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Box 1. The Relevance of Exercise for Type 2 Diabetes (T2D)

Accounting for ~40% of total body weight, skeletal muscle is a key metabolic organ that is essential for energy homeostasis and glucose disposal both at rest and during exercise. Owing to its heterogeneous but highly plastic nature, mammalian skeletal muscle can adapt to a variety of stimuli and different tasks. The basis of muscle plasticity lies in the adaptability of skeletal muscle fibers. Based on specific ultrastructural and metabolic attributes, there are three different fiber types in humans, fast type 2A and 2X fibers and slow type 1 fibers [84]. Although endurance training can increase the proportion of type 1 and 2A fibers, physical inactivity promotes a shift towards type 2A and 2X fibers [85]. This has implications not only for performance but also for metabolic diseases such as T2D, as the different fibers also differ with regard to their glucose handling capacity [86]. Chronic energy imbalance and physical inactivity lead to myocellular maladaptation. The skeletal muscle of individuals with T2D displays impaired insulin-stimulated glucose transport and consequent lower glycogen synthesis, reflecting insulin resistance [15]. Decreased mitochondrial function and hence diminished lipid oxidation capacity are other characteristics of insulin-resistant individuals. This, in combination with increased systemic lipid influx, facilitates ectopic lipid accumulation in skeletal muscle. Regular exercise can improve myocellular mitochondrial function and boost fatty acid oxidation capacity [87]. Importantly, even a single bout of exercise is a potent stimulus to increase glucose disposal by activating 5′-AMP-activated protein kinase (AMPK) leading to insulin-independent glucose transporter (GLUT) 4 translocation and enhancing glucose uptake and glycogen storage, thereby rapidly reducing T2D-associated abnormalities [88]. Regular exercise with repeated muscle contractions therefore provides the basis for metabolic health and the prevention and management of T2D.

In addition, there is evidence that BFRT may trigger microvascular changes, including capillary neoformation and thickening of the perivascular basal membrane, as well as mitochondrial adaptations such as decreased mitochondrial **reactive oxygen species (ROS)** production within myocytes [13,14]. These adaptations may also make BFRT suitable for populations such as individuals with T2D, who suffer from vascular complications, alterations of mitochondrial function in several tissues, including skeletal muscle, and associated musculoskeletal problems such as muscle weakness [15].

This review addresses the effects of BFR combined with resistance and aerobic training in healthy humans and populations with impaired physical fitness, followed by exploration of the mechanisms of action of BFRT, and concludes with potential applications of BFRT in individuals with T2D.

Blood Flow Restriction Combined with Resistance Training

Several recent studies have investigated the hypertrophic effect of BFRT in the upper and lower limbs in trained and untrained healthy individuals [14,16–18]. Although studies often differ in the percentage of occlusion and the intensity and frequency of training, they commonly describe beneficial effects on muscle mass and preserved or improved muscle function. The changes in muscle size with BFRT are greater than a repetition-matched control group exercising without BFR, and are often comparable with that observed following traditional high-load (HL) RT [19]. If a low-load (LL)

Box 2. What Is Blood Flow Restriction Training?

BFRT originated in Japan and has become a popular and effective training method in the athletic population as well as in healthy and elderly individuals and in rehabilitation medicine. The major difference to classical RT lies in the reduced blood flow to the exercising limb. BFRT uses inflatable cuffs that partially occlude arterial blood flow and completely restrict venous return in working skeletal muscle proximal or distal to the cuffs during exercise [89]. By doing so, mechanical loading can be markedly reduced with BFRT. Recent research suggests that BFRT is as effective as RT for improving muscle mass and, to a lesser extent, muscle strength, despite markedly lower training loads [90]. The main mechanism of action of BFRT remains unknown, but likely involves venous blood pooling as a consequence of blood flow restriction to the exercising limb, which induces cell swelling. Cell swelling in combination with the accumulation of metabolites such as lactate can initiate intramyocellular signaling pathways that promote skeletal muscle hypertrophy [57] (see Figure 1 in the main text). There is evidence that muscle growth is supported by SC activation and incorporation into existing skeletal muscle, thereby increasing myonuclear number [64]. In addition, fast-twitch muscle fibers are recruited early on despite the LL nature of the training modality, which further facilitates muscle adaptations [50]. An area of recent interest is the impact that BFRT may have on reducing sensations of pain and discomfort. BFRT may reduce pain sensitivity by increasing the endogenous production of β-endorphin in active, young and healthy individuals [91] or in the context of rehabilitation [16]. Hence, BFRT could also be useful for individuals affected by acute and/or chronic pain.

Box 3. A Commonly Used Blood Flow Restriction Training Protocol

The recommended frequency of BFRT to achieve skeletal muscle strength adaptations and hypertrophy are 2–3 times per week for longer periods (>3 weeks) or 1–2 times per day for shorter durations (1–3 weeks) [12]. Further, loads as low as 20–40% of an individual's one-repetition maximum (1-RM) for 2–4 sets of exercise are typically used in BFRT protocols in which the total volume adds up to ~75 repetitions. The volume follows a scheme from 30 repetitions in the first set and 15 repetitions in sets 2–4. It is recommended to exercise to or near to volitional failure. The rest periods between the sets should be between 30 s and 1 minute with the cuffs remaining inflated during rest. This equals a total restriction time of 5–10 minutes per exercise. The amount of pressure required to occlude the blood flow in a limb is related to limb size, the individual's blood pressure, the cuff material/width, and the device used. It is recommended to assess the individual limb occlusion pressure (LOP) [92], in other words the minimal pressure required to occlude arterial blood flow before the start of the training so as to perform BFRT with ~40–80% of LOP (Table I).

Table I. Suggested BFRT Protocol [12]

Frequency	2–3 times per week (>3 weeks) or 1–2 times per day (1–3 weeks)
Load	20–40% 1-RM
Restriction time	5–10 minutes per exercise
Sets	2–4
Repetitions	30 × 15 × 15 × 15 or sets to volitional failure
Rest between sets	30–60 s
LOP	40–80% LOP

group without BFR is allowed to exercise to failure, then muscle growth is similar to that of BFRT [17]. However, the exercise volume required to achieve these similar muscular adaptations is reduced with the application of BFR. Strength is also increased following BFRT, although the changes are often less than those observed following traditional HL training [20]. This is probably related to the fact that training modes with higher loads often perform better on maximal strength tests than those with lower loads. This may be due to differences in neural adaptation, but may also reflect local changes in the muscle that occur independently of muscle growth [21,22].

Taken together, in healthy and active individuals, BFRT can induce similar changes in muscle size as traditional HL exercise. In addition, although strength is also increased, this is usually to a lesser extent than that observed following HL resistance exercise. Both mechanical stress and metabolite accumulation account for muscle hypertrophy, but their contributions may vary proportionately in RT and BFRT. Figure 1 summarizes the potential mechanisms of BFRT.

Blood Flow Restriction Combined with Aerobic Training

BFR can also be combined with aerobic exercise (AE) to derive further benefits from mechanical stimuli. Walk training with BFR twice per day, 6 days per week for 3 weeks resulted in an increase of muscle mass by 4–7%, as assessed by magnetic resonance imaging and an 8–10% increase of dynamic and isometric strength in healthy young men. By contrast, walking without BFR had no effect on muscle size or strength [23]. In addition, only 15 minutes of low-intensity cycle exercise training at 40% of the **maximal oxygen consumption (VO_2max)** with BFR thrice weekly for 8 weeks resulted in muscle hypertrophy and improved VO_2max in young healthy men, whereas the control group without BFR showed no improvements [24]. Along these lines, using a within-subject design, this study showed that interval cycling with three sessions per week for 6 weeks resulted in increased leg oxygen delivery and decreased lactate release in the BFR leg, which was unchanged in the control leg of physically active, young healthy men [25]. The increased oxygen delivery after BFR was likely mediated by increased resting femoral artery diameter, without effects on mitochondrial function, indicating that BFR mainly improved oxygen delivery in this study. When healthy and recreationally active men performed an acute running session either with or without BFR or in systemic hypoxia, only the exercise session with BFR

Glossary

5′-AMP-activated protein kinase (AMPK): a protein kinase that acts as a cellular energy sensor by sensing low ATP levels. AMPK activates cellular glucose and fatty acid uptake upon falling energy levels, thereby playing an important role in maintaining cellular energy homeostasis.
Acetyl-CoA carboxylase (ACC): the enzyme that catalyzes the carboxylation of acetyl-CoA to malonyl-CoA. Malonyl-CoA is used as substrate for the biosynthesis of fatty acids.
Angiogenesis: the formation of new blood vessels.
Atrophy: the partial or complete wasting of tissue mass, typically skeletal muscle.
Blood flow restriction training (BFRT): a training modality that partially occludes arterial blood flow and completely restricts venous blood flow by inflatable cuffs during exercise. This training modality typically utilizes loads as low as 20–40% of an individual's 1-RM.
Growth hormone (GH): a growth-stimulating peptide hormone that is released from the pituitary gland.
Hepatocyte growth factor (HGF): a paracrine cellular growth factor secreted by stromal and mesenchymal cells. During BFRT, HGF release is induced by NO and leads to activation of SCs.
Hypoxia-inducible factor 1α (HIF-1α): an important oxygen-dependent transcriptional regulator for adaptive cellular response to low oxygen tension or hypoxia. HIF-1α is a subunit of hypoxia-inducible factor.
Insulin-like growth factor 1 (IGF-1): an essential factor in controlling cell growth that has structural similarities to insulin. As a result of BFRT, IGF-1 may promote muscle hypertrophy by aiding fusion of SCs with existing myofibers.
Intramyocellular lipids: lipids stored as droplets in skeletal myofibers.
Limb occlusion pressure (LOP): the minimum pressure necessary to occlude arterial blood flow via an inflating cuff.
Lipotoxicity: the deleterious effects of the accumulation of lipid intermediates in non-adipose tissues which impairs cellular homeostasis and disrupts tissue function.
Mammalian target of rapamycin (mTOR): a serine/threonine protein kinase that phosphorylates and activates other macromolecules. mTOR induces protein synthesis and leads to muscle hypertrophy.

resulted in increased oxidative stress, **5′-AMP-activated protein kinase (AMPK)** signaling, and **peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)** mRNA in the vastus lateralis muscle [26]. AMPK plays a key role in mitochondrial homeostasis by modulating autophagy and mitochondrial biogenesis, resulting in the replacement of defective mitochondria with new functioning mitochondria and thereby contributing to mitochondrial homeostasis in skeletal muscle [27]. Furthermore, AMPK is involved in the regulation of glucose uptake and glucose transporter (GLUT) 4 trafficking following exercise. Increased glucose uptake in ischemic tissues is primarily achieved by translocation of GLUT4 from its intracellular compartments to the sarcolemma. In addition, ischemic preconditioning can activate AMPK in a protein kinase C (PKC)-dependent manner and induce GLUT4 expression [28].

BFR combined with AE affects aerobic metabolism and endurance performance, and may also have modest additional effects on muscle mass and strength. This is in contrast to the classical perception that AE alone does not impact on muscle size and strength. Although studies with this training modality are limited and inconsistent, particularly at lower intensities, the effects on endurance and strength make this training method potentially suitable for concomitant improvement of musculoskeletal and cardiovascular health.

Effects of Blood Flow Restriction in Elderly Populations and Persons with Impaired Physical Ability

The development of new exercise strategies in an effort to decrease the risk for **sarcopenia** is of particular importance in older adults or in the context of rehabilitation from postoperative musculoskeletal injuries, where humans are often unable to complete high-intensity RT. Also for these individuals, BFRT is an effective intervention to induce muscle hypertrophy and strength gains [29]. Further studies assessing the potential of BFRT in postsurgery rehabilitation showed improved skeletal muscle hypertrophy and strength to a similar extent as HL-RT, with a greater reduction in pain and joint effusion, leading to greater stability and mobility, and hence improvements in physical function and quality of life [30]. The authors conclude that BFRT may be an appropriate training method, especially for early rehabilitation. Low-intensity BFR in combination with elastic bands twice per week for 6 or 12 weeks resulted in improved muscular hypertrophy and muscle strength without a decrease in vascular function in cohorts of older women and men [31,32]. By contrast, no effects were observed in the group without BFR. Based on these results, BFRT seems be a safe way to prevent and alleviate sarcopenia. Moreover, seated leg extension, leg curl, and horizontal leg press with BFR twice per week for 12 weeks led to similar increases of muscle cross sectional area (CSA) and strength compared with RT in older adults [33]. BFRT three times per week for 4 weeks improved vascular endothelial function and peripheral blood circulation in healthy elderly individuals [34]. BFRT has also been proposed as a valuable exercise option for patients with coronary artery disease. In that sense, twice-weekly BFRT for 8 weeks improved systolic blood pressure and muscle strength in these patients [35].

Possible Mechanisms of Action of Blood Flow Restriction Training and Applications for the Management of Type 2 Diabetes

Preservation of muscular function is essential for metabolic health, especially in individuals with T2D, a group of patients who are particularly affected by increased cardiovascular risk [36] and exacerbated progression of sarcopenia [37]. Because diminished muscle mass and function are related to reduced glucose disposal capacity [38], preserving muscle mass and function is of high priority in this patient group. The particularities of T2D skeletal muscle pathophysiology derive from impaired nonoxidative muscle glucose disposal and concomitant white adipose tissue dysfunction and ectopic lipid deposition due to hyperinsulinemia [15]. Peripheral insulin resistance ensues after excessive lipid availability and increased **non-esterified fatty acid**

Maximal oxygen consumption (VO_2max): the maximum amount of oxygen that an individual can take up during maximum exertion. The VO_2max capacity is measured by respiratory gas analysis during a graded exercise test.
Mitogen-activated protein kinases (MAPKs): kinases that play an important role in signal transduction by modifying nuclear gene transcription following changes in the cellular environment.
Nitric oxide synthase (NOS): upon activation, NOS converts L-arginine to nitric oxide (NO), an important signaling molecule. The abundant isoform in skeletal muscle is neuronal NOS.
Non-esterified fatty acids (NEFAs): fatty acids that are released via lipolysis from triglycerides.
One-repetition maximum (1-RM): the maximum weight that a person can lift once in a defined range of motion.
Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α): a master regulator of key mitochondrial genes.
Reactive oxygen species (ROS): unstable oxygen-containing reactive species that can react with other molecules in a cell and can cause damage to DNA, RNA, and proteins.
Sarcopenia: age-related loss of skeletal muscle mass and muscle function.
Satellite cells (SCs): quiescent precursors of skeletal muscle cells and the oldest adult stem cells. After activation, SCs are able to fuse with existing muscle fibers.
Vascular endothelial growth factor (VEGF): an important signaling molecule that is activated by hypoxic conditions and mainly induces angiogenesis.

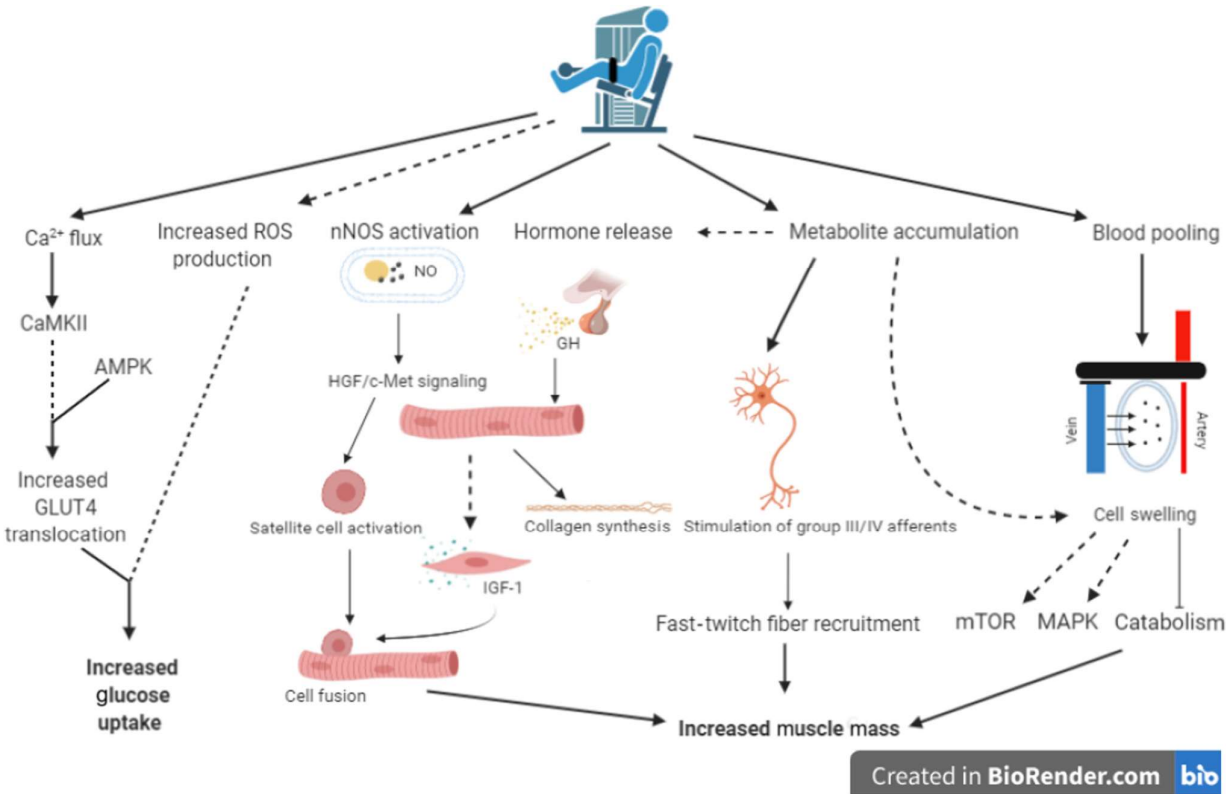

Figure 1. Effects of Blood Flow Restriction Training (BFRT) on Changes in Muscle Mass. BFRT initiates several cellular pathways that eventually result in increased muscle mass, strength, and glucose uptake. Muscle contraction leads to Ca^{2+} influx and phosphorylation of CAMKII in skeletal muscle, and, together with AMPK, results in increased GLUT4 translocation to the plasma membrane. Together with elevated ROS production, these pathways result in increased insulin-independent glucose uptake. nNOS regulates satellite cell activity through induction of HGF/c-Met signaling. Metabolite accumulation results in augmented hormone release. The rise in GH induces collagen synthesis which has a protective effect on skeletal muscle. GH also induces the release of IGF-1, which promotes satellite cells to fuse with existing myofibers. In addition, metabolite accumulation can also stimulate group III/IV afferent neurons, which results in recruitment of fast-twitch fibers despite low training loads. Lastly, BFRT also induces cell swelling through fluid influx, which can induce anabolic pathways by activating mTOR and MAPK, with simultaneous inhibition of catabolism. Broken lines represent speculative associations. Abbreviations: AMPK, AMP-activated protein kinase; CAMKII, calmodulin-dependent protein kinase; GH, growth hormone; GLUT4, glucose transporter 4; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor 1; mTOR, mammalian target of rapamycin; nNOS, neuronal nitric oxide synthase; ROS, reactive oxygen species. Figure created with BioRender.com.

(NEFA) influx to the skeletal muscle, leading to excessive deposition of **intramyocellular lipids** and impaired mitochondrial function and insulin signaling caused by **lipotoxic** intermediates such as diacylglycerols and ceramides [15]. These abnormalities may lead to an increased risk of developing micro- and macrovascular diabetes-related complications. Regular physical activity and exercise in T2D have been shown to decelerate disease progression and reduce the risk for cardiovascular complications [1,2,5]. Nevertheless, the perceived strain during exercise is higher in T2D compared with glucose-tolerant persons, and has been shown to reduce exercise adherence and compliance [39]. This may further reduce their physical fitness and aggravate the underlying metabolic condition. Thus, current research focuses on efficient, targeted exercise alternatives with lower loads that can effectively produce metabolic benefits in T2D. Mechanisms of BFRT derived from current research suggest that this training method may offer metabolic benefits for individuals with T2D. Figure 2 depicts the particularities of skeletal muscle metabolism in patients with T2D and exemplifies how BFRT could specifically improve muscle function in these individuals.

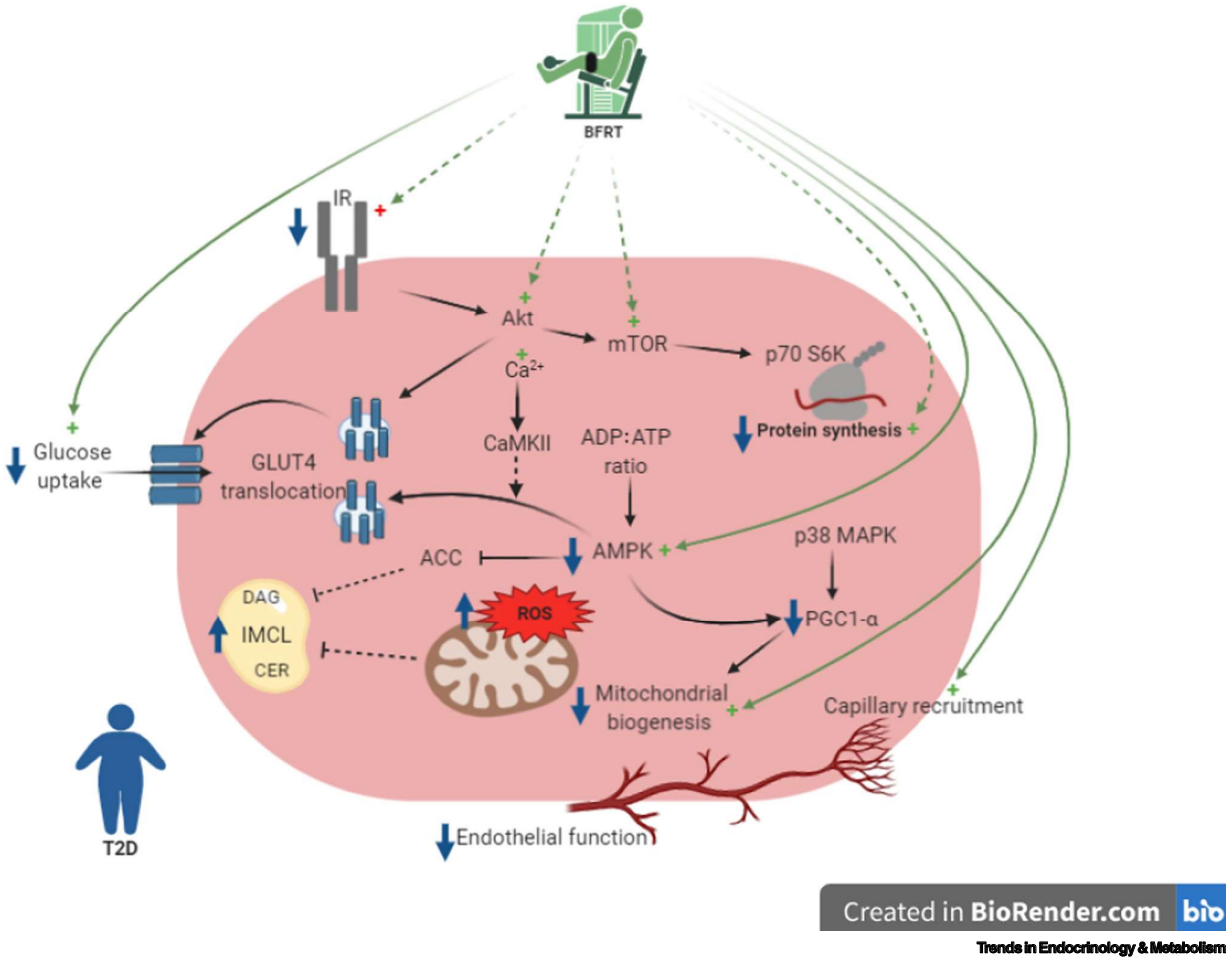

Figure 2. Proposed Mechanisms of Blood Flow Restriction Training (BFRT) in Improving Skeletal Muscle Metabolism in Type 2 Diabetes (T2D). BFRT improves contraction-mediated GLUT4 translocation via the Ca^{2+}/CAMKII-pathway and activated AMPK, thereby increasing glucose uptake. By activating the mTOR/p70S6K and p38MAPK/PGC-1α signaling cascades, BFRT leads to increased protein synthesis and mitochondrial biogenesis, which is probably impaired in T2D. Improved mitochondrial function promotes oxidation of IMCL, thereby reducing lipotoxic intermediates such as DAG and ceramides. In addition, BFRT increases the ADP:ATP ratio, which leads to the phosphorylation and activation of AMPK. Consequently, AMPK phosphorylates and inhibits ACC, which promotes mitochondrial fatty acid oxidation and can further decrease IMCL content. Finally, low myocellular oxygen tension during BFRT can induce angiogenesis and aid capillary recruitment, which benefits individuals with endothelial dysfunction. Abbreviations: ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; CER, ceramides; DAG, diacylglycerols; CAMKII, calmodulin-dependent protein kinase; GLUT4, glucose transporter type 4; IMCL, intramyocellular lipids; IR, insulin receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; p70 S6K, ribosomal protein S6 kinase; ROS, reactive oxygen species. Green arrows indicate the effects of BFRT; blue arrows indicate impairments that are generally found in T2D. Figure created with BioRender.com.

Vascular Adaptations

It has been shown that 8 weeks of BFRT can improve vascular conductance and venous compliance, as assessed via plethysmography in men and women [40]. This change was more pronounced than when utilizing LL training to or near to failure without blood flow restriction (i.e., an effect specific to blood flow restriction). Along these lines, 6 weeks of low-intensity BFR, or moderate-intensity or high-intensity RT, increased calf vascular conductance compared with non-exercise conditions in young healthy men [41]. Similarly, BFRT stimulates **angiogenesis** by inducing ischemia and shear stress in healthy, active men [42]. These findings were supported by increased mRNA expression

of **vascular endothelial growth factor (VEGF)**, VEGF receptor 2, **hypoxia-inducible factor 1α (HIF-1α)**, and endothelial **nitric oxide synthase (eNOS)** after BFRT [42]. Moreover, compared with passive sitting as the control condition, four sets of unilateral BFRT resulted in higher levels of angiotensin-converting enzyme 2 and an increased number of vasculogenic progenitor cells, which underlies the vascular regeneration effect of BFRT on skeletal muscle [43].

Effects on Mitochondrial Function

Although changes in mitochondrial function usually occur with AE, there is evidence that BFRT also evokes changes in mitochondrial bioenergetics. In that regard, BFRT improved mitochondrial respiratory function and mitochondrial protein synthesis to a similar degree as RT, despite lower training loads [44]. Although citrate synthase activity, a marker of mitochondrial content, did not change with either type of training, both regimes increased **acetyl-CoA carboxylase (ACC)** and p38 **mitogen-activated protein kinase (MAPK)** phosphorylation. ACC, a downstream target of AMPK, may indicate activation of this kinase, whereas p38 MAPK activation may stem from increased training-induced ROS production. Low oxygen tension during occlusion or mechanical stress could lead to the production of ROS – important signaling molecules that are probably involved in muscle remodeling [45] and mitochondrial biogenesis [4]. Although the mechanism by which ROS induces muscle hypertrophy has not been fully elucidated, it seems that exercise-derived ROS can influence muscle growth via MAPK signaling [46]. In individuals with congestive heart failure, BFRT performed thrice weekly for 6 weeks, improved complex I-related muscle mitochondrial function when compared with an untreated control group [47]. It has also been described that sirtuins, that are activated by exercise training as well as by repeated ischemia–reperfusion cycles such as those occurring during BFRT, may impact on mitochondrial biogenesis and function [48,49].

Skeletal Muscle Fiber Type-Specific Adaptations

BFRT recruits fast-twitch fibers despite utilizing low loads. These fast-twitch type 2 fibers are innervated by high-threshold motoneurons, which are usually recruited only at high loads or when performing resistance exercise to task failure [50]. The parallel recruitment of both type 1 and 2 fibers is also reflected by similar increases in type 1 and 2 myofibrillar cross-section areas in response to 19 days of training in healthy males [51]. The early recruitment of type 2 fibers is important for training adaptation because muscular adaptations are suggested to be more pronounced in fast-twitch fibers than in slow-twitch fibers [52]. Increases in muscle mass may in turn aid improved glucose clearance [53]. Of note, studies employing muscle biopsies to study single fiber type-specific adaptations in LL and HL regimes are limited, and future studies will be necessary to improve our understanding of fiber type-specific adaptations. Exercise training can also induce NOS-mediated conversion of L-arginine into nitric oxide (NO) [54]. NO, another reactive species, can induce muscle growth via the activation and proliferation of muscle **satellite cells (SCs)** [55]. Anderson *et al.* hypothesized that the resulting spike in NO production in response to training stimulates the release of **hepatocyte growth factor (HGF)** and its subsequent binding to the c-Met receptor on SCs which leads to their activation and hence to an increase in muscle mass [56].

Cell Swelling-Mediated Muscle Hypertrophy

Skeletal muscle hypertrophy occurs when rates of myofibrillar protein synthesis exceed the rates of breakdown. One mechanism hypothesized to drive skeletal muscle hypertrophy following BFR is acute cell swelling. Transmembrane water channel proteins such as aquaporin 4 likely facilitate fluid influx from the extracellular to the intracellular space. Moreover, the accumulation of metabolites in muscle fibers increases the osmotic gradient and additionally supports extracellular-to-intracellular fluid influx [57]. Cell swelling initiates an anabolic response with simultaneous inhibition of protein breakdown [58], and activates **mammalian target of rapamycin (mTOR)** and MAPK

signaling pathways [59]. In addition to anti-catabolic effects, further studies suggested that cell swelling promotes protein sparing [60].

Loenneke *et al.* hypothesized that muscle cell swelling may be a primary mechanism of the observed benefits of BFR, independently of exercise [57]. The authors speculated that cell swelling induces a cascade of intracellular signaling events via an intrinsic volume sensor that leads to activation of a so far unidentified tyrosine kinase, subsequently resulting in the activation of mTOR and MAPK pathways and induction of muscle anabolism [57]. Taken together, one possible mechanism for how BFRT induces skeletal muscle hypertrophy comprises cell swelling that may activate mTOR and MAPK signaling pathways.

Hormone Signaling

Elevated blood lactate in response to BFRT may stimulate **growth hormone (GH)** release from the pituitary gland [61]. GH seems to have a protective effect on skeletal muscle because exogenous GH administration for 14 days and consequent local **insulin-like growth factor 1 (IGF-1)** signaling resulted in an increase in muscle collagen synthesis and tendon collagen I mRNA expression in adult humans [62]. GH promotes anabolic pathways via stimulation of IGF-1 synthesis in several tissues (i.e., primary liver as well as muscle cells) [63]. Consequently, IGF-1 may enhance SC fusion with existing muscle fibers, thereby facilitating the integration of new myonuclei and maintaining optimal DNA-to-protein ratios [64]. In that direction, short-term LL-BFRT led to a marked increase in SC content and myonuclear number in human skeletal muscle [51]. However, several studies have shown that acute anabolic hormones such as GH, IGF-1, insulin, noradrenalin, and testosterone are not involved in mediating skeletal muscle hypertrophy [65,66]. In fact, 10 weeks of BFR-walking training induced GH release in older women, but the GH response assessed from blood sampling in the morning and immediately after the training session did not correlate with skeletal muscle hypertrophy [65]. Likewise, increase of muscle CSA did not differ after 15 weeks of RT designed to acutely elevate GH, IGF-1, and testosterone concentrations or of RT designed to maintain basal hormone concentrations in young healthy men [66]. Although administration of recombinant GH promotes collagen synthesis in tendons and skeletal muscles, it failed to increase muscle protein synthesis [62]. BFR induces the release of anabolic hormones such as GH, IGF-1, and testosterone that can activate intracellular signaling events promoting SC activation. Although hormonal changes induced by training may promote extracellular matrix remodeling, they do not seem to be associated with skeletal muscle hypertrophy.

Effects on Biomarkers of Inflammation

The effects of BFRT on inflammatory biomarkers are limited. Three weeks of BFRT compared with work-matched RT with low (20% 1-RM) or high intensities (70% 1-RM) increased the anti-inflammatory macrophage phenotype by 163% only in the BFRT group. Moreover, 3 days after training cessation the levels of proinflammatory macrophages were higher in the low-intensity RT group compared with BFRT. The authors also detected a decline of 18% in plasma interleukin 6 (IL-6) between before and 180 minutes after the BFRT session, whereas there was no change in the high-intensity control group [67]. Biweekly BFRT for 8 weeks tended to decrease the levels of inflammation biomarkers (i.e., CD40 ligand) posttraining [35]. Limited evidence indicates that BFRT may mediate an anti-inflammatory effect.

Effects on Glucose Metabolism

Christiansen *et al.* reported that BFR cycling training three times per week for 6 weeks resulted in increased GLUT4 expression and/or NO availability, which led to increased net glucose uptake in the BFR-trained leg compared with the leg trained without BFR in healthy humans [68]. Another study reported that biweekly BFRT for 8 weeks tended to decrease insulin levels and estimates of

HOMA-IR (homeostatic model assessment of insulin resistance) without reaching statistical significance [35]. In one uncontrolled study, the author reported that 3 months of BFRT applied to patients with metabolic syndrome led to a 10% decrease of glycated hemoglobin (HbA1c) and a low-density lipoprotein cholesterol reduction of 8% [69]. Although these studies did not directly pertain to patients with T2D, it is possible that BFRT could improve metabolic control in individuals with T2D by improving muscle mass and muscle metabolism, decreasing insulin levels, or increasing GLUT4 translocation. More data on metabolic and hormonal responses of BFRT, including plasma profiles of NEFA, catecholamines, and glucagon, will be necessary to improve the efficiency and understanding of BFRT in T2D [70,71].

Safety of Blood Flow Restriction Training

Diabetes can be accompanied by complications and comorbidities such as macrovascular (coronary artery disease) and microvascular complications (retinopathy, nephropathy, microalbuminuria) or autonomic neuropathy. These aspects, in addition to monitoring blood glucose concentration before, during, and after exercising to minimize the risk of hypoglycemia, need to be considered before using BFRT in this cohort. Of note, to date no studies are available regarding the safety of BFRT for patients with diabetes. Previous reviews, however, concluded that exercising with BFR appears to result in similar physiological responses compared with classical RT without BFR [12,72], which is considered to be safe for individuals with T2D [6].

Although blood pressure increases acutely following BFRT [73,74], this effect is often comparable with or less than that observed following traditional HL RT [75–77] and does not pose an additional risk for individuals with T2D. In addition, part of this augmentation in blood pressure can further be reduced by applying lower limb occlusion pressure [78].

With regard to potential compressive nerve damage risk, Mendonca *et al.* examined whether BFR with 60% and 80% arterial occlusion pressure had a negative effect on nerve conduction velocity in healthy young men. To this end, the study investigated both early (M wave) and late responses (H wave) to stimuli to assess nerve conduction velocity, and concluded that nerve conduction remained unaltered with BFRT [79].

The balance between coagulation and fibrinolytic activity also does not appear to be negatively impacted by the application of BFR [59,80,81]. This would suggest that the risk of blood clotting is not increased when LL exercise is completed with BFR.

Previous studies do not find prolonged changes in markers of muscle damage [82], making this training modality potentially suitable even for individuals with low physical fitness. In sum, BFRT can induce soreness, which can be reduced when individuals become accustomed to exercise, and other markers of muscle damage are only minimally affected.

Although BFR impacts on many body systems, discussion of safety generally focuses on effects on the cardiovascular system, coagulation, and muscle damage. The available literature suggests that general risks are not considerably elevated over exercise alone when BFR is applied appropriately [12,83]. Appropriate use includes LL/intensity exercise completed with the correct relative applied pressure – in other words, application of a pressure that accounts for the cuff that is used and the size of the limb to which it is applied. This ensures restriction of blood flow rather than occlusion.

Taken together, the available evidence indicates that BFR does not negatively impact on blood pressure, nerve conduction, blood coagulation, or muscle integrity, and does not raise additional

safety concerns beyond classical RT. Nevertheless, additional studies will be necessary to address specific risks for patients with diabetes.

Concluding Remarks

BFRT promotes muscle hypertrophy primarily through cell swelling and metabolite accumulation, which result in increased protein synthesis and fusion of SCs with existing myocytes. Low oxygen tension during BFR may further induce capillary neoformation and increase intracellular ROS production that may promote mitochondrial biogenesis and GLUT4 expression. Limited evidence indicates that BFRT may decrease insulin and HbA1c levels and increase GLUT4 translocation, and this may improve metabolic control in individuals with T2D. These adaptations may qualify BFRT as a potential training method to improve muscle function and glucose metabolism in persons with T2D (see Outstanding Questions). Although additional studies will be necessary to address specific risks for patients with diabetes, the available evidence indicates that the general risks of BFRT are not considerably greater than those of classical RT.

Outstanding Questions

Does BFRT impact on glycemic control and insulin sensitivity in individuals with T2D?

What is the interconnection between muscle strength, muscle mass, and metabolic changes in the context of BFRT?

Can BFRT alone prevent sarcopenia in newly diagnosed individuals with T2D, and combat sarcopenia in those with prolonged disease duration?

What are the molecular differences between classical resistance training and BFRT at the myocellular level in the context of T2D?

Does BFRT raise additional safety concerns specifically for individuals with T2D?

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