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Review

Blood Flow Restriction Exercise as a Novel Conservative Standard in Patients with Knee Osteoarthritis—A Narrative Review

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Abstract: Knee osteoarthritis is a prevalent joint disease affecting millions of individuals globally. While total knee arthroplasty is an effective treatment for advanced stages of KOA, it may not be suitable for earlier stages or younger patients. Supervised exercise therapy has proven to be the first-line treatment of preference in tackling pain and disability caused by KOA. However, the high intensities required to induce positive muscle adaptations are not indicated in this population, as this is often accompanied by pain, discomfort, and frustration, leaving low-load resistance training as the only feasible method of treatment. Recently, the use of blood flow restriction training has begun to emerge as a substitute for high-load resistance training. With BFRT, a cuff is applied around the proximal aspect of the affected limb, causing partial arterial and full venous occlusion, thereby inducing localized hypoxia and the accumulation of metabolites, mimicking the effects of high-load resistance training, albeit with low loads. Consequently, BFRT might offer a suitable and more effective alternative for KOA patients who are not (yet) eligible for TKA compared to traditional exercise therapy. This review aims to summarize the current evidence as regards the application of Blood Flow Restriction in exercise therapy for knee osteoarthritis patients, with particular consideration of the underlying mechanisms and its safety, as well as general guidelines for practical implementation in clinical practice. In doing so, this narrative review aims to create a framework for translating from theory into practice.

Keywords: blood flow restriction; BFR; KAATSU; knee osteoarthritis; strength training

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1. Introduction

Osteoarthritis (OA) is a common and debilitating whole-joint disease affecting millions of people worldwide [1]. For knee osteoarthritis (KOA), the prevalence is estimated at around 23% in people aged over 40, which is expected to increase due to aging, obesity, and the lack of disease-modifying OA drugs [2]. Furthermore, this whole-joint disease has various personal, social, and economic consequences for patients, their environment, and society.

While there are a variety of possible treatments for KOA involving braces, exercise therapy, oral or topical non-steroidal anti-inflammatory drugs, intra-articular injections, and total knee arthroplasty (TKA), it can be stated that not every patient benefits from a similar intervention [3]. While TKA is a common and effective treatment for KOA, especially in the elderly with typically higher Kellgren-Lawrence scores, it is found less suitable for younger, more active patients [4]. As the decision for TKA strongly depends on the patients' remaining functionality, quality of life (QoL), and structural degradation, surgery is often not the preferred method of treatment at the onset of KOA [5,6]. Nevertheless, a significant amount of time is often spent with a diminished QoL, while aiming to maintain a certain level of physical activity, albeit accompanied by pain, discomfort, and frustration. To tackle these problems and improve the QoL, many of these patients might benefit more from customized exercise therapy, infiltrations, and weight loss in order to maintain a healthy lifestyle and reduce work abstinence while postponing primary TKAs and preventing revision TKAs, thus simultaneously reducing the social economic burden [3,7,8].

As supervised exercise therapy has proven to be effective in tackling pain and disability caused by KOA, it is often promoted as the first line of treatment [3,7–9]. Within the relatively young KOA population, the need for customized exercise therapy to strengthen the lower limb muscles and prevent the weakened joint structures from being loaded excessively is indisputable. By improving muscle force and patient function, respective exercise therapy can improve the patient's QoL substantially [10,11].

However, while conservative exercise therapy is strongly encouraged for those individuals diagnosed with KOA, low-load resistance training (LLRT) is often the only feasible method of treatment as this does not exacerbate joint pain and inflammation. However, high-load strength training (HLRT) effectively enables both strength and hypertrophic muscle adaptations [12]. Therefore, the American College of Sports Medicine (ASCM) guidelines recommend training intensities of at least 70% of 1 Repetition Maximum (RM) when wanting to induce strength increments [13].

Unfortunately, these levels of exercise intensity also imply substantial loading of the degenerated intra- and peri-articular structures, making its implementation in OA-associated exercise therapy often not feasible [14]. However, due to its significant correlation with function, lower limb strength training, specifically targeting the Quadriceps, remains crucial in the rehabilitation of KOA [15]. By improving both muscle mass and strength of the Quadriceps, the stability of the knee joint increases while also improving shock-absorbing capabilities [16].

Recently, the use of blood flow restriction training (BFRT) combined with low-load resistance training has emerged as a possible substitute for high-load strength training. With BFRT, a cuff is applied around the proximal aspect of the affected limb, causing partial arterial and full venous occlusion, thereby inducing localized hypoxia and the accumulation of metabolites, mimicking the effects of high load resistance training, albeit without heavy loads [17]. Consequently, BFRT might offer a suitable and more effective alternative for KOA patients who are not (yet) eligible for TKA compared to traditional exercise therapy. Therefore, this review aims to summarize the current evidence as regards the application of BFRT in exercise therapy for KOA patients, with particular consideration of the underlying mechanisms and its safety, as well as general guidelines for practical implementation in clinical practice. In doing so, this narrative review aims to create a framework for translating from theory in to practice.

2. Methodological Considerations

This review article encompasses the literature search on four main aspects: (1) The effects of BFRT in KOA; (2) mechanisms thought to be responsible for the effects of BFRT on muscle hypertrophy, strength and pain reduction; (3) considerations towards safety; and (4) practical implementation within a KOA-population. PubMed was searched from database inception to April 2024 and included previous review articles and consensus statements regarding the mechanisms, safety, and application of BFR, as well as the literature focusing on KOA. Only English-written papers concerning human adults (+19 years) that made a significant contribution to the body of knowledge on this topic were included for review. By combining both research domains, as shown in Table 1, 40 articles were initially retrieved, of which 37 were found eligible. Additionally, 31 articles were included through hand searching and reference lists of obtained articles, resulting in a total of 68 articles.

Table 1. Domain-specific search strategy in PubMed.

Research Domain	Search Strategy	Hits
Blood Flow Restriction	("blood flow restriction training" OR "BFR training" OR "blood flow restriction exercise" OR "BFR exercise" OR "blood flow restriction therapy" OR "BFR therapy" OR "blood-flow restriction" OR BFR OR "occlusion training" OR "occlusion therapy" OR "Blood Flow Restriction Therapy"[Mesh])	7277
Knee Osteoarthritis	"knee osteoarthr *" or "KOA" or "gonarthrosis"	35,349

A truncation wildcard or asterisk * was applied to represent any number of letters at the end of the word.

3. Results

3.1. Effect of BFRT in KOA

Research in strength training physiology has shown overwhelming evidence that hypertrophic muscle adaptations can be induced at much lower exercise intensities than the intensities assumed to be crucial to muscle mass gains by combining LLRT with blood-flow restriction [18]. For example, the systematic review (SR) and meta-analysis (MA) from Lixandrao and colleagues [19] demonstrated that BFR with LLRT results in similar increases in muscle mass compared to HLRT, which is supported by the SR from Hughes et al. in 2017 [17]. In line with these studies, a recent study by Hu and colleagues showed the additional effect of BFR in 112 patients with KOA, as the BFR group significantly improved in terms of strength, range of motion (ROM), quality of life (QoL), and ability of daily living (ADL) compared to a control group [14].

Beside resistance training, which is the preferred exercise modality to induce muscle hypertrophy and -strength, it appears that enhanced levels of metabolic accumulation and ischemia during BFRT, combined with aerobic activities at low intensities (e.g., walking, cycling, rowing), also increase muscle volume and strength compared to aerobic exercises without BFR [20–22]. For example, the study by Abe et al. (2010) indicated a significant increase in strength (11%) and thigh muscle mass volume (10.7%) after 6 weeks of walking 20 min 5×/week, whereas no significant increases in the group without BFR were found [21]. This is particularly interesting for the KOA population, which is encouraged to perform joint-friendly aerobic activities like walking and cycling on a regular basis to safeguard joint load-bearing capacity and a healthy body mass index (BMI). As these activities alone have little effect on muscle strength and size, the implementation of BFR would allow KOA patients to achieve strength and muscle mass increments whilst maintaining joint loading tolerance and a healthy cardiovascular profile.

In terms of pain, Ferraz et al. (2018) showed that the pain score according to the WOMAC subscale within KOA patients was reduced significantly in both the LLRT-group and low load-BFRT group compared to HLRT, although positive muscle adaptations in terms of hypertrophy and strength were only found in the latter two [23]. In line with these findings, Bryk et al. (2016) found that in patients with KOA, LL-BFRT resulted in similar benefits in function and quadriceps strength compared to HLRT, with HLRT inducing higher levels of anterior knee pain during training sessions compared to LL-BFRT [24]. Therefore, evidence suggests that BFRT is a more effective training strategy than LLRT alone in individuals with KOA, as it appears to replicate the improvements in strength and muscle growth seen with HLRT without the need for high intensities, which might increase pain, discomfort, and reduced adherence to therapy.

3.2. Mechanisms of BFRT

3.2.1. Hypertrophy and Strength

By limiting the arterial inflow whilst fully occluding the venous outflow using a personalized limb occlusion pressure (LOP), localized hypoxia is created, enhancing the accumulation of metabolites such as lactate, hydrogen ions, inorganic, and dihydrogen phosphate [25,26]. This metabolic stress has been suggested to be a primary factor responsible for anabolic/anticatabolic muscle adaptations by activating numerous other mechanisms such as increased type II muscle fiber recruitment, mechanotransduction, cell swelling, muscle damage, as well as satellite cell activation [17,25,27,28]. Important to note is that although these mechanisms might all induce anabolic muscle adaptations separately, it is assumed they contribute to a complex network altogether mediating positive muscle protein synthesis (MPS) and concomitant muscle mass and muscle strength gains. Lastly, other mechanisms, such as reactive oxygen species (ROS) and increases in growth hormone, are often mentioned to explain increases in muscle mass and strength. However, due to the low-graded and contradictory evidence, these proposed mechanisms are not further discussed within this paper. An overview of the proposed mechanisms can be found in Figure 1.

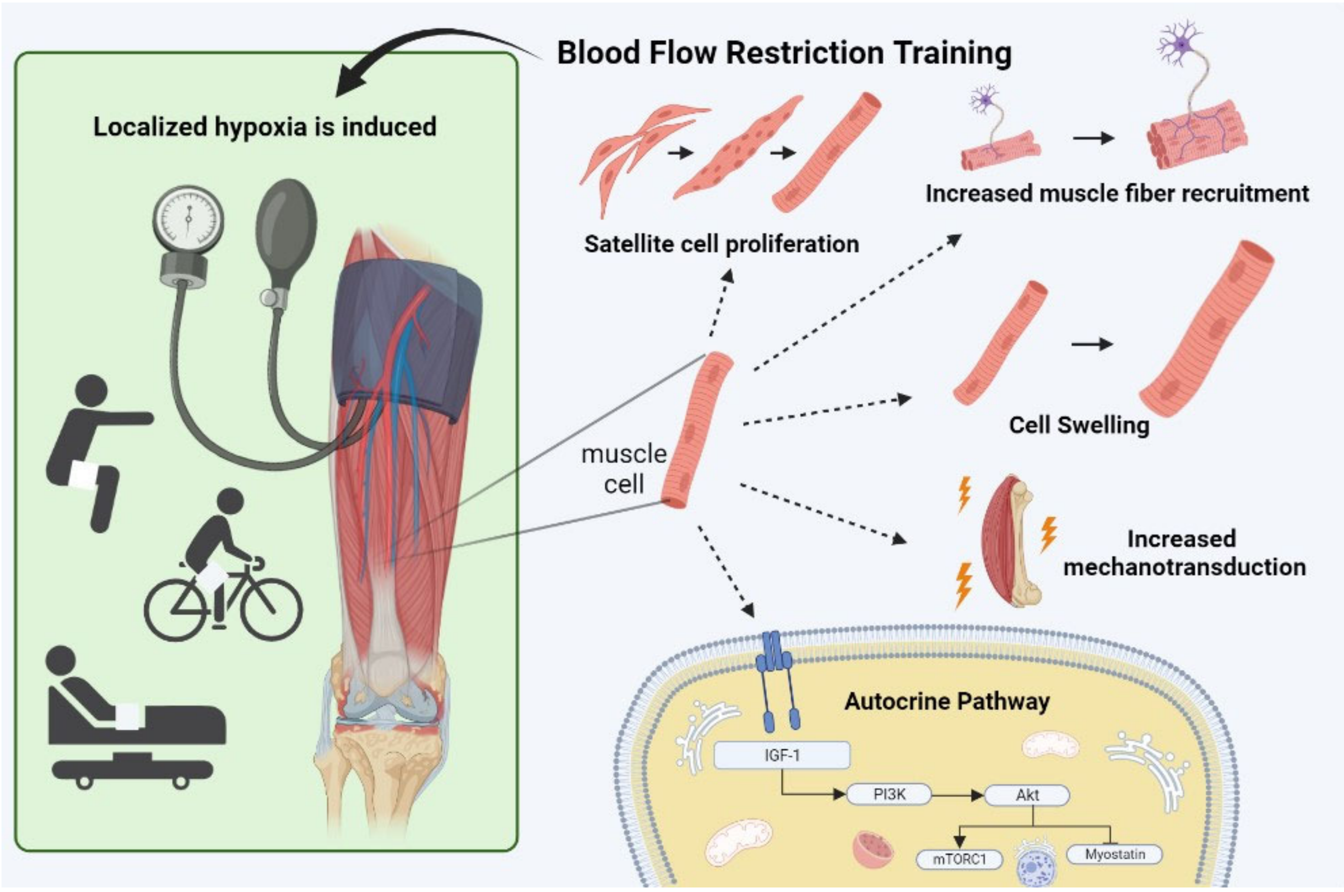

Figure 1. Overview of mechanisms using Blood Flow Restriction.

3.2.2. Muscle Fiber Recruitment

Muscle fiber recruitment has been shown to play an essential role in the observed effects of BFRT. The recruitment of type II muscle fibers seems to be important for inducing muscle hypertrophy, as these have a higher occurrence of signaling proteins compared to type I muscle fibers [29,30]. Muscle fibers are recruited according to the 'size principle', in which the smaller motor units associated with type I muscle fibers are activated initially at lower intensities, whereas the larger motor units related to type II muscle fibers are recruited at higher exercise intensities. Since the level of MPS is determined by the amount of muscle fibers activated, it is generally accepted that higher intensities (>70% of 1 Repetition Maximum (1RM)) are required to induce positive muscle adaptations in terms of hypertrophy and strength, as HLRT recruits both type I and type II muscle fibers (whereas LLRT mostly recruits type I fibers) [13]. Interestingly, previous research using integrated electromyography (iEMG) has demonstrated that during BFRT, recruitment of type II muscle fibers happens even at low intensities (~20% 1RM), due to the low oxygen levels and metabolite accumulation induced by vascular occlusion, which causes the type I fibers to fatigue more rapidly [28,31–33]. Furthermore, group III and IV afferents located within a muscle are also stimulated by these metabolic processes. Stimulation of these afferents causes inhibition of the alpha motor neuron, thereby further enhancing muscle fiber recruitment to maintain adequate muscle force and protect against conduction failure [28].

MPS occurs independently of exercise intensity if fatigue is reached. As BFRT effectively induces muscle fatigue due to significantly decreased venous return and arterial inflow, it enables optimal fiber recruitment for muscle hypertrophy purposes [28].

3.2.3. Mechanotransduction

When mechanical tension is applied to a muscle during exercise, a process called mechanotransduction is triggered. This process involves mechanosensors such as integrins and focal adhesions on the muscle cell membrane, which convert mechanical force into chemical signals. These signals activate anabolic and catabolic pathways within the muscle cell, leading to a shift in the balance of muscle protein synthesis and breakdown in favor of MPS [34,35]. Research has indeed shown that high-load resistance training, involving the recruitment of abundant type I and II fibers can increase the phosphorylation of the P70S6K-protein complex, thereby increasing MPS to a higher degree compared to LLRT alone [36,37]. As BFRT mimics this HLRT [31], this novel training method could similarly enhance mechanotransduction and therefore increase MPS [25].

3.2.4. Cell Swelling

Another mechanism that has been proposed to enhance MPS by applying BFRT is cell swelling. This phenomenon results from an increase in intracellular hydration and has been reported to stimulate protein synthesis and decrease proteolysis in various types of cells [38]. The increased accumulation of metabolites through venous occlusion creates a pressure gradient, thereby enhancing reperfusion and subsequent intracellular swelling. This swelling, which is often referred to as 'the pump', is believed to initiate a signaling response within muscle cells in order to reinforce the muscle's structural integrity over time [39]. While some studies have reported positive effects of passive blood flow restriction on inducing anabolic muscle adaptations and reducing atrophy [40,41], other studies have not found significant differences in MPS between BFR with rest and rest alone [42]. Therefore, more research is needed to fully understand the potential benefits of cellular swelling on muscle adaptations.

3.2.5. Muscle Damage

Exercise-induced muscle damage (EIMD) is a common consequence of strength training, which, from a mechanical perspective, is thought to be induced by overstretching the sarcomere with subsequent extracellular matrix degradation as well as disruption of the cytoskeletal matrix and z-disk streaming [43]. However, as BFRT is performed with low levels of mechanical stress, other mechanisms such as ischemia and subsequent reperfusion are likely responsible for muscle damage [44]. Furthermore, activation of stretch-activated calcium channels or transient receptor potential channels may also contribute to muscle damage by increasing intracellular calcium levels, which ultimately lead to muscle damage and necrosis [45,46].

Although EIMD is often associated with high levels of discomfort, it simultaneously triggers positive muscle adaptations, as EIMD has been claimed to be an important regulator of satellite cell (SC) proliferation. Following EIMD, satellite cells located under the basal lamina rapidly proliferate and subsequently contribute to muscle remodeling and muscle growth [25]. Indeed, several studies with HLRT have already shown that it produces significant levels of muscle damage due to the high loads and concomitant high mechanical stress placed upon muscles, compared with LLRT, to which KOA patients are often referred.

While the evidence for the effects of HLRT and LLRT on muscle damage is well established, the impact of BFRT on muscle damage appears to be more enigmatic. Although some studies found BFRT to induce only minimal levels of muscle damage [47,48], expressed in terms of delayed onset muscle soreness (DOMS) [47], creatine kinase [49], or interleukin (IL)-6 after [36] 24 h, other studies reported a larger degree of EIMD following BFRT, up to 48 h after exercise [50,51]. However, elevated levels of muscle soreness, CK, and IL-6 levels as a result of BFRT have especially been reported in individuals who are not accustomed to the high metabolic stress associated with BFR, particularly when performing BFRT until volitional failure [52].

Despite the inconclusive evidence on the extent of EIMD caused by BFRT, literature suggests that muscle degeneration and regeneration occur in response to exercise [53], resulting in an increased proliferation of satellite cells in both acute and chronic BFRT [54,55]. This proliferation could be explained by an increase in stretch-, hypoxia-, and/or contraction-induced nitric oxide (NO) secretion [55]. Furthermore, other mechanisms, such as increased levels of vascular endothelial growth factor (VEGF) and Hepatocyte Growth Factor (HGF) are associated with increased satellite cell proliferation and a concomitant increase in MPS and muscle hypertrophy [53,56].

3.2.6. Autocrine Pathway

Muscular hypertrophy and strength gains are primarily achieved through autocrine and paracrine actions, which stimulate protein synthesis by modulating anabolic and catabolic signaling pathways. The IGF-1/P13K/Akt signaling pathway is crucial in this process, promoting protein synthesis and suppressing proteolysis [25,57]. Within skeletal muscle, insulin growth factor (IGF-1) activates PI3K and Akt, triggering protein translation via mTORC1 induction, which regulates mRNA translation initiation and elongation [57].

Moreover, the upregulation of the IGF/PI3K/Akt pathway seems to inhibit myostatin expression, a negative regulator of muscle growth that hampers myoblast and myotube differentiation through Smad2/3 phosphorylation [57,58]. Previous studies have demonstrated a decrease in myostatin expression and significant increases in muscle mass and strength after 8 weeks of LL-BFRT, comparable to the effects of HLRT [59].

Nonetheless, further research is necessary to gain a comprehensive understanding of the underlying mechanisms responsible for these BFRT-induced effects.

3.2.7. Pain

Pain symptoms are associated with increased physical disability in patients with knee osteoarthritis [60,61]. Therefore, the primary objective of managing KOA is to alleviate pain while minimizing treatment-related adverse events. To control pain and improve physical function, oral non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are the two most prescribed analgesics, as 10% to 35% of OA patients report frequently using these drugs [62,63]. However, as these drugs involve an increased risk for gastrointestinal or cardiovascular complications, international guidelines as well as the National Institution for Health and Care Excellence strongly recommend exercise as a core therapy for reducing pain in KOA [7,8].

Indeed, resistance training has been found to be effective in reducing pain through the mechanism of exercise-induced hypoalgesia (EIH). The magnitude of this EIH appears to be greater with higher loads or prolonged exercise, as previous studies have shown that using an external load of >75% of 1RM resulted in significant pain reduction [64]. Unfortunately, regardless of its benefits for pain, joint function, and general (physical) health and well-being, HLRT is not feasible for many KOA patients due to their limitations in load-bearing capacity, pain threshold, and training background, making it very difficult to persevere and potentially harmful for some patients.

However, by applying BFR combined with LLRT, patients with a reduced load capacity might experience pain reduction while simultaneously benefiting from effects similar to HLRT, albeit without the need to implement heavy loads and high training intensities.

Indeed, several studies have found that BFRT with 80% of the limb occlusion pressure resulted in a greater EIH response compared to light and heavy load resistance, which was prolonged for 24 h in the exercising limb [65]. Furthermore, in contrast to LLRT alone, Korakakis et al. (2018) found significant pain reduction after LLRT + BFR during functional testing in patients with anterior knee pain, which was also sustained after a 45 min physiotherapy session [66]. In line with this, KOA patients reported less knee pain and discomfort in the BFR group compared to traditional HLRT [24]. Interestingly, while a recent study by Ogrezeanu and colleagues found an increase in pain pressure thresholds (PPTs) following leg extension with BFR at 80% Limb Occlusion Pressure (LOP) in end-stage KOA patients, their self-reported pain significantly worsened [67]. While this is in contrast to previous research claiming a pain-reducing effect with BFR, it can be argued that leg extensions with such high occlusion pressures are not suitable for end-stage KOA patients without gradual exposure to BFR, and the visual analog scale (VAS) does not differentiate between muscle pain and knee pain and does not take into account possible confounders such as the discomfort caused by the cuff pressure, mechanical load, or the nocebo effect of physiological stress [68].

Furthermore, the study by Hughes and Patterson (2020) found that BFRT led to a significant increase in peripheral blood beta-endorphin (BE) concentration, suggesting that BFRT may involve an opioid-mediated mechanism in EIH [65]. The activation of the endogenous opioid system and stimulation of BE production may contribute to EIH by inhibiting noxious-evoked activity, as BFRT evokes a high level of metabolic stress, which subsequently activates type III and IV afferents, thereby leading to a greater perception of intensity and discomfort. Additionally, other mechanisms have been proposed to explain the occurrence of EIH, including the recruitment of type II muscle fibers, a link between baroreceptors and pain pathways, ischemically and metabolically induced pain, as well as conditioned pain modulation (CPM) [69].

3.3. *Safety of Blood Flow Restriction*

BFRT has gained popularity in recent years for its ability to increase both muscle mass [19] and strength [70], improve physical function [20], and improve cardiorespiratory endurance capabilities within both resistance and aerobic training [22]. Based on the available literature, BFRT appears to be a safe exercise modality when used according to evidence-based guidelines [71]. In their study in 2006, Nakajima and colleagues reported serious adverse event rates of 0.055%, 0.008%, and 0.008% for deep venous thrombosis (DVT), pulmonary embolism (PE), and rhabdomyolysis, respectively [72]. Despite these low adverse event rates, it is necessary to consider its safety, especially when applied in a clinical population with altered perceptual, cardiovascular, or hemodynamic responses [73]. Within the BFRT literature, three primary areas of concern in terms of safety are often reported: venous thromboembolism (VTE), excessive hemodynamic/cardiovascular response, and rhabdomyolysis [74].

3.3.1. Risk for Venous Thromboembolism

The potential risk of VTE formation associated with BFRT has received considerable attention, particularly among individuals recovering from orthopedic surgery [75]. During the initial 6 weeks following orthopedic surgery, there is a significantly elevated risk for VTE [75]. However, current evidence indicates that the use of a tourniquet during surgery, which similarly induces “stasis”, albeit by applying much higher pressures over a prolonged period of time, does not appear to increase this risk for VTE by itself [76]. Therefore, the prospect of a brief (5–10 min per exercise) sub-occlusive pressure applied to KOA patients should alleviate concerns regarding VTE risk [71,74,75]. Furthermore, as studies showed no elevated levels of coagulation markers [77] but instead even provided preliminary evidence of elevated fibrinolytic markers such as tissue plasminogen activator (tPA), it can be stated that the risk for VTE is not higher with BFRT (incidence rates of 0.055% and 0.008% for DVT and PE, respectively) compared to traditional exercise [72].

3.3.2. Excessive Cardiovascular Response

A second area of concern is the excessive cardiovascular response through increased stimulation of type III and IV afferents, which might evoke the exercise pressor reflex (EPR). This EPR plays a strong role in the regulation of blood pressure and heart rate during exercise but appears to be dysregulated in patients with comorbidities such as hypertension (HTN), obesity, and/or diabetes [78,79]. As these systemic conditions (e.g., obesity, HTN) are commonly associated with KOA, exaggerated sympathetic nerve activity could manifest itself, leading to abnormal elevations in mean arterial pressure and coronary vasomotor tone, thereby increasing the risk of adverse cardiovascular events during exercise [78]. However, while BFRT has the capacity to increase the cardiovascular response to a similar degree compared to HLRT in both healthy and hypertensive individuals [80], this increase appears to be within normal ranges, despite medical comorbidities [81]. Furthermore, while comorbidities such as HTN should be taken into account, literature suggests that BFRT is capable of reducing postexercise systolic blood pressure to a greater degree compared to moderate-intensity resistance training in hypertensive women [82].

3.3.3. Rhabdomyolysis

Lastly, despite the low loads applied and the absence of mechanical disruption of myofibers, a few cases of rhabdomyolysis have been reported following BFRT [83–85], which is characterized by the excessive release of CK and muscle myoglobin into the bloodstream [86], although this does not always appear to be present [87]. While this is a serious side effect of resistance training, irrespective of the use of BFRT, its occurrence risk can likely be mitigated by gradually exposing the patient to BFRT, taking into account personal characteristics and previous experience with strength training [74].

4. Practical Guidelines to Enhance Safety and Optimize Training Effectiveness

To prevent potential adverse events from occurring and make this type of training accessible for a diverse (patient) population, the use of personalized limb occlusion pressures (LOP)—which is the minimal pressure necessary to fully occlude both the arterial and venous systems—is recommended to limit excessive stress on the vascular system [27]. The calculation of this personalized LOP allows practitioners to select a pressure at a certain percentage of this LOP to standardize the level of occlusion across patients with different body characteristics. However, it should be noted that individualized LOPs are determined at rest and do not consider muscle contractions, thereby producing a higher-than-anticipated pressure compared to resting conditions [88]. Therefore, in addition to using individualized LOPs, devices capable of autoregulation are recommended, as they consider the contraction-related pressure and thus further enhance the safety of BFRT [88]. Although it is a device-specific feature, these devices aim to ensure a constant LOP during resistance training sessions as they adjust limb occlusion level in function of muscle contraction and relaxation phase throughout BFRT [73].

Despite the fact that blood flow restriction training has been shown to be effective and well-tolerated in clinical settings, the current literature often lacks an individualized prescription of BFRT, especially regarding occlusive pressures, which should be tailored to ensure safe and effective application. For example, in the study of Segal et al. in patients with KOA risk factors [89], a low load BFRT protocol was administered in a cohort of women, which was replicated in a cohort of men using similar modalities. While the women demonstrated an increase in muscle strength, no significant improvement in strength was observed in the male cohort, despite the same BFR protocol being applied [90]. As men tend to have greater thigh circumference than women, it is conceivable that the same BFR pressure induced an insufficient BFR stimulus to enhance muscle strength.

Indeed, besides blood pressure and cuff width, previous studies used thigh circumference to determine limb occlusion pressure, with larger limbs requiring higher pressures to reach a similar degree of occlusion compared to smaller limbs [27]. These arbitrary pressures will have highly variable effects within heterogenous (patient or athletic) populations, possibly increasing the risk for adverse events [91] or reducing their effectiveness, depending on the level of occlusion, which cannot be estimated on the basis of thigh circumference. Although more research is necessary, individualized pressures between 40 and 80% LOP are generally recommended, with some studies showing the pressure to be inversely proportional to the load applied (i.e., when exercising at the low end of the load spectrum (~20% 1RM), higher pressures around 80% LOP should be applied) [92]. However, from a perceptual perspective, greater degrees of (muscle) discomfort have been linked to higher pressures, especially during the initial application period [93]. Therefore, while higher pressure might be advantageous for a given goal (e.g., pain reduction), it is important for practitioners to consider the associated perceptual demands. Employing lower, perhaps physiologically suboptimal pressures around 40% LOP at the outset of care may serve as a valuable approach to gradually acclimating KOA patients to the perceptual demands required for exercise adaptation. Furthermore, individual assessment of (relative)-contra indications using questionnaires, medical history, Virchow's Triad, and physical examination remains important, especially in post-surgical patients or patients with comorbidities such as hypertension, obesity, or diabetes [74,75].

Comparable to the heterogeneity in terms of LOP pressures applied, a lot of variety exists in terms of volume necessary to enhance muscular adaptations. However, according to Scott et al. and Loenneke et al. [94,95], two to three low-load BFRT sessions per week are sufficient for enhanced strength adaptations in clinical populations.

5. Practical Implementation

To maximize the benefits of this novel training method, Loenneke et al. [96] proposed a progressive model through which BFR can be applied in various stages of rehabilitation, including both voluntary resistance and aerobic exercise as well as passively, without exercise. While the latter can be applied during bedrest to diminish atrophy in some patients [40,41], it might simultaneously serve as an entry level for sedentary patients who are unaccustomed to BFRT. Next, following periods of (relative) rest, aerobic activities such as cycling or rowing are often recommended for patients with KOA to maintain their ROM and cardiovascular fitness whilst simultaneously maintaining muscle mass, as these non-weight-bearing activities are associated with lower levels of pain and discomfort. As the addition of BFR in cycling or walking activities has been proven to increase both muscle mass and strength [20,21,97], aerobic capacity [21,98], and functional capacity compared to aerobic exercise without BFR [99], it should be promoted and facilitated in patients with KOA. Similarly, as the training loads applied during BFR combined with resistance training, the intensities applied during aerobic BFR should be generally low, around 45% heart rate reserve or 40% VO2max [21,27,99].

Furthermore, recent evidence suggests that performing 4 sets of 15 repetitions instead of the traditional 30-15-15-15 scheme or sets until failure is similarly effective as an addition to low-load intensity training, thereby further reducing perceived barriers to blood flow restriction [74,100].

BFR training guidelines, based on the evidence as regards the implementation of BFR in training and musculoskeletal rehabilitation for patients with KOA, are summarized in Table 2.

Table 2. Proposed BFRT guidelines in patients with KOA.

	Resting State BFR Accommodation	Aerobic Training	Low-Load Resistance Training
Patient Profile	Sedentary patients; Patients starting to rehabilitate after a period of bedrest; Patients with anxiety for BFRT	All KOA patients	All KOA patients
LOP	70–100% LOP	<50% VO2max or HRR	40–80% LOP (depending on the patient's training status)
Training Frequency	1–2×/day during supine position	2–3×/week	2–3×/week
Restriction time	5 min	5–20 min per exercise	5–10 min per exercise
Repetitions & Rest Between Sets	3–5×/5 min, 3–5 min passive recovery	2–4×/5 min up to 2 × 10 min, 1–2 min active or passive recovery	60 reps—15/15/15/15, 30–60 s rest
Restriction Form	Intermittent	Continuous or intermittent	Continuous or intermittent
Type Of Exercise	None; Electrostimulation	Walking; Cycling; rowing	1. Quadriceps dominant 2. Hamstring dominant 3. Calf dominant
Expected Training Results	Prevention of muscle atrophy, familiarization with BFR	Optimization of cardiovascular response to aerobic stimuli; muscle volume and strength gains	Muscle volume and strength gains
Safety Guidelines	Use individualized LOP and autoregulated BFR devices, guaranteeing safe occlusion pressure levels	Use individualized LOP and autoregulated BFR devices, guaranteeing safe occlusion pressure levels	Use individualized LOP and autoregulated BFR devices, guaranteeing safe occlusion pressure levels

KOA = Knee Osteoarthritis; LOP = Limb Occlusion Pressure; HRR = Heart Rate Reserve; min = minutes; s = seconds; reps = repetitions.

6. Conclusions

As surgery is often not the preferred method of treatment for many KOA patients, conservative alternatives such as exercise therapy are generally promoted and facilitated. However, the intensity required to induce positive muscle adaptations with this exercise therapy implies substantial loading of the degenerated intra- and peri-articular structures, making its implementation in KOA patients often not possible. Instead, individualized blood flow restriction training might offer a feasible alternative, acting as a surrogate for high-load strength training while using low loads and promoting training responses during low-load aerobic or resistance activities, thereby improving muscle strength and mass, functional capacities, and ultimately quality of life in patients with KOA. Based on the exponentially growing literature, 2–3 BFR sessions per week with low loads or low intensities and individualized LOPs in a fixed or failure protocol appear optimal to maximize training effects, taking into account personal characteristics and safety guidelines. However, long-term follow-up research with larger populations is necessary to validate these short-term findings.

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