Title: Blood flow restriction training in rehabilitation following anterior cruciate ligament reconstructive surgery: A Review

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Abstract

Anterior cruciate ligament (ACL) rupture is a highly prevalent orthopaedic injury, resulting in substantial skeletal muscle atrophy due to changes in muscle protein balance and satellite cell abundance. Neural activation problems also contribute to strength loss, impacting upon a patients' physical function and rehabilitative capacity. Heavy loads typically required for muscle hypertrophy and strength adaptations are contraindicated due to graft strain and concomitant cartilage, meniscal and bone pathologies associated with ACL reconstruction. Strength of the quadriceps is a fundamental component for the ability to reduce shearing and torsional strains on the ACL with ground contact, and forms a critical component of ACL rehabilitation. Given the dangers of early post-operative heavy-loading, low-load blood flow restriction (BFR) training may provide an alternative rehabilitation tool for practitioners. Passive BFR can attenuate early muscle atrophy and strength loss, and may be more effective with the addition of novel, complementary therapies such as neuromuscular electrical stimulation. Upon ambulation, aerobic and resistance exercise with BFR can stimulate muscle hypertrophy and strength adaptations and resolve activation problems. This may occur through increasing muscle protein synthesis and satellite cell proliferation, decreasing muscle protein breakdown and improving muscle activation via altered recruitment patterns. Thus, BFR training may provide an effective rehabilitation tool that does not place heavy loads and force through the tibiofemoral joint. This may reduce the risk of damaging the graft, cartilage, meniscus or other intra-articular structures, providing thorough screening prior to use is followed by correct, evidence-informed application.

Key words: Blood flow restriction; strength; rehabilitation; anterior cruciate ligament

1. Introduction

The anterior cruciate ligament (ACL) is the most frequently injured knee ligament, with over 120,000 injuries occurring annually in the United States.[(1)] It is among the most commonly studied orthopedic injuries, thus the rehabilitation techniques used post-surgery have evolved over the last number of decades. Over this period practitioners have moved from their approach of minimal muscle activity and full immobilization to one of increased muscle activation and range of movement (ROM) in the early stages following surgery.[(2–4)] A major consequence of ACL injury and subsequent surgery is thigh muscle atrophy,[(5)] which contributes to thigh muscle weakness[(6)] in the first 12 weeks post-surgery[(7)] and can remain for over 2 years post-operation.[(8)] There are many short[(9)] and long term[(10)] consequences of ACL surgery such as decreased protein turnover,[(11)] strength loss,[(6)] muscle activation problems,[(12)] an increased risk of osteoarthritis[(13)] and re-injury.[(14)] The effects of muscle atrophy are unavoidable given the reduced weight bearing and unloading context of ACL rehabilitation.[(15)] This is particularly evident post-operatively due to graft strains,[(16)] cartilage damage,[(17)] bone bruising and meniscal injury,[(18)] which serve as contraindications to heavy load exercise to regain muscle strength and size. Thus, clinicians are faced with the task of finding alternative rehabilitation tools.

Blood flow restriction (BFR) training has been proposed as a tool for early rehabilitation post-ACL surgery[(19,20)] due to its low-load nature and hypertrophic capacity.[(21)] Our recent meta-analysis indicated that low-load BFR training is a safe and effective clinical rehabilitation tool when applied correctly.[(22)] Despite limited published research to date,[(19,20,23)] to our knowledge there are several ongoing clinical ACL trials examing the use of BFR in rehabilitation. However, the various means by which BFR may affect the numerous consequences of ACL surgery have not been discussed in detail. Therefore, the purpose of this review is to examine the consequences of ACL reconstruction surgery, and discuss how BFR can be used to target specific aspects of the rehabilitation process.

2. Current issues and consequences of ACL reconstruction

2.1 Muscle atrophy and strength loss

Muscle atrophy and strength loss are major consequences of ACL injury.[5] An ACL-deficient or reconstructed tibiofemoral joint is depicted by decreased muscle strength and torque generating capacity,[24] which are attributed to muscle atrophy[25,26] and impaired muscle activation.[27,28] A most frequent finding is weakness of the quadriceps muscle group, in particular the vastus lateralis and medialis muscles.[29,30] A recent prospective case series examining lower limb muscle volume before and after ACL reconstruction surgery reported 15% atrophy in the vastus lateralis and rectus femoris compared to the contralateral, unaffected limb pre-surgery, and an excess of 20% in asymmetry in the vastus lateralis, medialis and intermedius and rectus femoris post-surgery.[5] Additionally, anatomical changes of atrophy remained during early improvements in muscle activation and strength, and explain a large portion of weakness of the thigh muscles in the first 12 weeks post-surgery.[7] Quadriceps strength deficit can exceed a 20% loss of normal muscle strength 6 months after ACL reconstruction,[31] and such weakness can remain for over 2 years' post-operation.[8] Mounting evidence demonstrates that muscle weakness can be observed in the quadriceps muscles of asymptomatic patients who have returned to their normal, full pre-injury activity levels after surgery[31,32] and such deficits can persist for years following reconstruction of the ACL.[33]

The quadriceps muscle groups extend the tibiofemoral joint, which is often restricted in terms of movement following ACL surgery to preserve the graft.[34] Weakness of this muscle group is disabling[24] and may contribute to more global dysfunction,[35] whilst also increasing the risk of re-injury[36] and early onset of osteoarthritis.[37] The loss of strength due to muscle atrophy and decreased muscle activation is unavoidable due to the necessary restrictions placed upon the post-injury and post-surgery recovery process, such as reduced load and weight bearing to ensure the graft is not over strained in the early stages of recovery. However, muscle atrophy and impaired voluntary force control negatively impact knee function following ACL surgery.[12] Additionally, there are permanent anatomical changes associated with ACL reconstruction. For example, a recent study found changes in sonoelastographic strain ratio in medial distal femoral cartilage within the operated tibiofemoral joint,[38] which the authors suggested may indicate early structural changes following ACL reconstruction. These aspects all impact upon the patients' physical function, quality of life and their recovery process. To effectively combat the observed atrophy and strength loss following ACL reconstruction, and thus improve physical function and the rehabilitation process, it is important to understand the mechanisms of such changes.

2. Mechanisms of muscle atrophy and strength loss

The mechanisms underpinning the two defining aspects of strength loss, muscle atrophy[25,26] and decreased neural activation,[27,28] are well-documented. Atrophy of skeletal muscle, manifested as loss of muscle mass,[39] occurs in the early post-operative period of unloading[40] following ACL reconstruction surgery. The atrophy is observed in the affected limb and is due to intrinsic processes such as changes in muscle protein synthesis. There is a decline in muscle protein synthesis[41] and an increase in breakdown[42] which both likely contribute to changes in muscle protein balance and loss of muscle mass.[39] Significant muscle atrophy and strength loss alongside increases in muscle myostatin messenger ribonucleic acid (mRNA) expression and muscle atrophy F-box (MAFBx) mRNA expression, which are markers of muscle atrophy, have been observed after only 5 days of disuse.[43] This short period of disuse was also found to lower myofibrillar protein synthesis rates and induce anabolic resistance to protein ingestion.[11] Other aspects such as reduced mitochondrial function and gene expression[44] and reduced satellite cell proliferation[45] within the vastus medialis have been associated with muscle atrophy.

Loss of strength is typically of greater magnitude than the loss of muscle mass,[46] which is attributable to clinical deficits in voluntary activation following ACL surgery.[47] Such neuromuscular coordination deficits are typically both short and long term[48] and can persist at 12 months post-surgery.[49] Moreover, diminished control of voluntary force capacity of the quadriceps impairs knee function.[12] Given the debilitating impact of loss of muscle strength on a patient’s physical function and rehabilitative capacity, the primary aims of ACL rehabilitation are focussed on regaining muscle size, strength and pre-injury activation levels to alleviate instability symptoms and restore normal physical functional activity.[50]

3. Principles of ACL rehabilitation

3.1 The primary goals of ACL rehabilitation

The principle goal of rehabilitation is to return an individual to normal function with a low risk of re-injury. The overall objective of ACL rehabilitation is to reduce the shearing and torsional strain through the ACL during activities of increasingly dynamic and complex nature[51] alongside tackling the deficit in muscle activation that is common following ACL surgery.[28,47,48] As the ACL is ruptured during activities which involve large knee abduction moments in short time frames[52] successful rehabilitation involves reducing the risk of this occurring in competitive scenarios.

To achieve this; the knee extensors and flexors and hip extensors must be strong enough to overcome the shearing forces at the knee associated with foot contact with the floor.[53] The hip abductors must be strong enough to overcome the torsional force at the knee associated with foot contact.[54] The co-activation synergies of the muscles around the knee and hip must be able to respond to the short time frames required to stabilise the knee during dynamic movement tasks,[49,55] and the kinematic strategy adopted during dynamic tasks must retain the centre of mass over the centre of pressure and reduce knee valgus to reduce strain and torsional loads associated with foot contact.[54] In addition, the neurophysiological and biomechanical demand is greater on an individual during reactive and unpredictable environments.[56]

Fundamental to these requirements, are the capabilities of the muscles of the knee and hip to produce an appropriate amount of force within a short period of time to overcome the magnitude and direction of forces associated with the ground contact period of sport specific tasks. Put simply, the muscles of the knee and hip must be strong enough to cope with the demands of the increasing forces that the individual will be subjected to when completing more demanding tasks. As strength is such a fundamental component of being able to reduce the shearing and torsional strains on the ACL during the demands of higher ground reaction forces associated with unpredicted changes of direction commonly found in sport, ensuring that an individual is strong enough is a critical component of an ACL rehabilitation programme.

3.2 Why are heavy loads contraindicated?

Developing muscle strength typically requires the repeated recruitment of high threshold motor units to induce the tissue strain or the physiological response required for an adaptive response.[57] In order to achieve this, training interventions typically demand volumes of work which require the muscles to produce >65-70% one repetition maximum (1RM).[58] However, there are a several contraindications to such heavy load exercise. Completing this intensity of work may produce strain loads which the recently reconstructed ACL is unable to tolerate.[34] Graft failure due to excess strain is a primary concern[59] across the two commonly used grafts to repair an ACL, bone-patellar tendon bone autograft[60] and the hamstring autograft.[61] Over-strain of the graft may result in an adverse response and prolong the duration of rehabilitation. Concomitant injuries after acute ACL tears are common,[18] including collateral ligament sprains, cartilage damage and meniscal pathologies.[62] Additionally, subchondral bone lesions, or bone bruising, have been reported to occur in greater than 80% of patients with a complete ACL rupture in the acute phase[63,64] and have been associated with meniscal tears.[65] Such pathologies associated with ACL tear and reconstruction reduce the load bearing capacity of the tibiofemoral joint. However, equally the longer the muscle is inactive the more likely it is to atrophy[43] and be unable to produce the forces required to reduce the shearing and torsional strains associated with unpredicted changes of direction.[51]

To ensure successful ACL rehabilitation and reduce time scale of recovery, it seems logical to find ways to increase muscle strength and size without placing unwanted strain loads on the tibiofemoral joint. Blood flow restricted exercise could provide a convenient solution to this problem as the loads required to produce physiological adaptations in muscle strength and size are lower than traditionally used.[21] At present, no clear effect of BFR has been found proximal to the cuff, thus BFR may be most beneficial for rehabilitation of the muscles that control the tibiofemoral joint as opposed to the hip.

4. Blood flow restriction training

4.1 Overview of application and adaptations

The past twenty years has seen BFR exercise emerge as a novel method of training, with an extensive literature base. It involves restriction of blood flow to the working muscle via partial and full restriction of arterial and venous blood flow, respectively.(66) It is commonly applied to both lower and upper limbs using pneumatic tourniquets,(67) inflatable cuffs(68) and elastic wraps.(69) Early research identified the capability of BFR to stimulate muscle hypertrophy and strength gains when combined with low-load resistance(70) and low-intensity aerobic(71) exercise. To date, a definitive mechanism(s) underpinning adaptations to low-load BFR training has not been pragmatically identified; however, several potential mechanisms have been proposed and reviewed in depth.(66,72,73) These proposed mechanisms include: cell swelling;(74) increased muscle fibre recruitment;(75) increased muscle protein synthesis;(76) and increased corticomotor excitability.(77)

The low-load nature and hypertrophic capacity of BFR training identified its potential as a clinical rehabilitation tool; an alternative to heavy-load resistance training in populations that require muscle hypertrophy and strengths gains but in which heavy-loading of the musculoskeletal system is contraindicated.(21) Clinical research has demonstrated significant muscular adaptations in patients suffering from muscle atrophy and strength loss, including those with knee osteoarthritis,(78–80) sporadic inclusion body myositis,(81,82) older adults at risk of sarcopenia,(83,84) and ACL reconstruction patients.(19,20) Our recent meta-analysis examined the use of BFR training as a clinical rehabilitation tool, concluding that low-load BFR training was more effective at increasing muscle strength as opposed to low-load training alone, and may stimulate greater adaptations in muscle size and physical function during periods of rehabilitation.(22)

4.2 BFR in ACL rehabilitation: Overview of the current evidence

Within the context of ACL injury rehabilitation there is great promise for the use of BFR training, both with and without low-load exercise. Following surgery there is often a short period of unloading, which results in atrophy.[5] Passive BFR (four days post-surgery, 5 sets of 5 min BFR at 238 mmHg for ten days) has been used to attenuate knee flexor and extensor CSA decrease by approximately 50% compared to controls.[20] Following a period of unloading passive BFR was also found to compare more favorably to control and isometric exercise conditions at attenuating atrophy,[85] even at 50mmHg.[86] However, not all evidence is positive for this technique; one study found no attenuation of muscle atrophy following BFR or a control group in patients in the 2 weeks post ACL surgery (13.8 ± 1.1% vs. 13.1 ± 1.0%, respectively).[23] As well as attenuation of atrophy by BFR *per se*, augmentation of low-load resistance training with BFR has also been shown to be effective in attenuating muscle mass loss and weakness. A prospective study in ACL reconstruction patients demonstrated greater increases in cross-sectional area (CSA) and muscular strength in the BFR group compared to a control group when implementing low-load muscular training with moderate BFR in the first 16 weeks post-operation.[19] This has also been evidenced in healthy subjects who underwent a low-load BFR training protocol (3 sets to failure at 20% of maximum voluntary contraction (MVC), three times per week) during 30 days of unilateral lower limb suspension (ULLS).[87] Furthermore, low-load BFR training has been used in a case study on an injured female athlete following ACL surgery.[88] Over a 12 week period the authors reported an increase in thigh size/girth of the affected limb and an increase in lower extremity functional scale (LEFS) scores compared to pre-surgery values.

This summary of current research that has examined BFR in ACL rehabilitation and periods of brief unloading and muscle disuse highlights its potential for use as a rehabilitation tool. Specifically, the low-load nature of BFR training may be critical in the early post-operative phase to increase quadriceps muscle strength, hypertrophy, endurance and voluntary activation. This is without heavy loading of the tibiofemoral joint, thus allowing for preservation of the graft and reducing the risk of aggravating any concomitant cartilage, meniscal and bruising pathologies. Current, general

BFR research suggests it may be used in a progressive model through all stages of rehabilitation from early post-op to return to heavy load exercise[89] and pre-injury activity levels. The next section of this review will revisit this progressive model and discuss BFR application specific to ACL rehabilitation throughout each phase. It will examine how it may combat the mechanisms of muscle atrophy and strength loss previously discussed and update the model with more recent evidenced-based guidelines on safe and effective application.

4.3 BFR in ACL rehabilitation: A progressive model

Phase 1: Early post-operative with BFR

The primary goals of the early post-op phase are reducing joint effusion, pain control and combating muscle atrophy and strength loss. As aforementioned, muscle atrophy during early post-op unloading[39,40] is caused by a disturbance in muscle protein balance, namely a decrease in synthesis[41] and an increase in breakdown.[42] Passive BFR is thought to cause cell swelling that is evident after release of the cuff;[74] such acute cell swelling can stimulate protein synthesis and suppress breakdown[90,91] which may stimulate the anabolic effects of BFR previously described.[74,85,86] Enhanced mammalian target of rapamycin (mTOR) signalling in a rat skeletal muscle model has also been demonstrated with passive BFR.[92]

BFR can be applied using a protocol of 5 sets of 5 minutes occlusion followed by 3 minutes of rest and reperfusion to attenuate muscle mass and strength of the quadriceps muscles.[85,86,93] Additionally, voluntary isometric contractions during BFR may increase metabolic stress and cell swelling levels that may contribute to the hypertrophy process,[66,74] acting as a preparatory stepping stone to subsequent low-load rehabilitation. One study used a lower pressure,[86] but it was not completely effective; it may be that full limb occlusive pressure (LOP) is required for passive BFR application in this stage. This should begin a few days post-surgery permitting that inflammation, pain and swelling is not excessive, and patients have passed a risk assessment questionnaire.[94]

Combining this with neuromuscular electrical stimulation (NMES), which is commonly used to combat muscle atrophy and strength loss following ACL surgery[29,95] and can prevent the decrease in muscle protein synthesis during unloading,[96,97] may have a greater effect in attenuating atrophy and strength loss. Although this is a novel concept, studies combining low-intensity NMES with BFR have found increases in muscle size and strength.[98,99] NMES of the quadriceps does not involve transmission of large forces through the tibiofemoral joint, thus exhibiting a low risk of damaging the graft or exacerbating any cartilage, meniscal or bone injuries. Early increases in muscle strength and size are necessary to perform voluntary training later in the rehabilitation process,[100] and there is debate over whether passive BFR alone is truly effective.[23] Thus, we are proposing NMES with BFR as an updated and potentially more effective approach to the early post-op phase. For an overview of optimal parameters for NMES, see Spector *et al.*[101]

Phase 2: Post-operative ambulation with BFR

The primary goals of this phase are to further attenuate atrophy and strength loss, improve quadriceps activation and control, and normalise gait kinematics. Full knee extension is required to start gait re-education;[94] if a patient starts to undertake high volumes of walking with a pathological gait pattern, there is opportunity for further injury or tissue overload of other structures supporting that movement pattern.[54] Providing patients have full ROM, BFR walking activities can help meet the goals of this phase.

Unloaded isotonic work acts as a prerequisite for regaining muscle strength and size during low-load resistance rehabilitation. Combining activities such as walking with BFR has been shown to increase muscle size and strength[71] and multiple aspects of physical function;[102] it may therefore be used to increase muscle size and strength in early ambulation post-ACL surgery. Once patients are able, cycling can also be combined with BFR; low-intensity cycling with BFR can concurrently increase muscle hypertrophy and aerobic capacity.[103] It may also promote muscle deoxygenation and metabolic strain, thus further stimulating endurance adaptations in the quadriceps to combat the post-surgery loss of muscular endurance.[104] BFR should be prescribed at a pressure between 40-80% LOP;

aerobic exercise intensity is typically prescribed at a low percentage of VO_2max or heart rate reserve, depending upon on the mode of exercise.

Phase 3: Low-load resistance training with BFR

Once patients have full range knee flexion and extension and gait is normalised, low-load resistance training is normally introduced. This is to accelerate the hypertrophy process and improve strength to begin a return to full weight bearing and pre-injury activity levels. The strength and hypertrophy adaptations from low-load resistance training with BFR are well-documented,(105) with our recent review and meta-analysis concluding that low-load BFR training is an effective, tolerable and useful clinical MSK rehabilitation tool.(22) During this phase of the model, progressive and individualised low-load resistance training on 2-3 days per week using a low-load between 20-30% 1RM is sufficient for muscle size and strength adaptations,(22,66) using an occlusive pressure of 40-80% LOP.(106)

Low-load resistance training with BFR has been shown to increase muscle protein synthesis,(76,107) which may be a result of activation of the mTOR signalling pathway that is thought to be an important cellular mechanism for enhanced muscle protein synthesis with BFR exercise.(76,108) Such increases in muscle protein synthesis with low-loads can help recover and increase muscle size without loading the tibiofemoral joint with the heavy loads traditionally required for such an adaptation.(58) Low-load BFR resistance exercise may also be used to combat the reduced muscle satellite cell abundance observed during periods of unloading following ACL surgery.(45) Proliferation of myogenic stem cells and addition of myonuclei to human skeletal muscle, accompanied by substantial myofibre hypertrophy, has been demonstrated following 23 training sessions in just under 3 weeks.(109)

Regarding strength, the early preferential recruitment of type II fast-twitch fibres at low-loads due to the hypoxic muscular environment generated during BFR exercise is thought to be an important mechanism behind strength adaptations at such low loads.(73) With BFR exercise, it appears that the normal size principle of muscle recruitment(110) is reversed.(21) Fast-twitch fibres, which are more susceptible to atrophy and activation deficits during unloading[111] and are normally only recruited at high intensities of muscular work, are recruited earlier. Indeed, several studies have demonstrated increased muscle activation during low-load BFR resistance exercise.[112,113] Greater internal activation intensity has been found relative to external load during low-load BFR resistance exercise,[75,114] suggesting type II fibres are preferentially recruited. Such preferential recruitment of the fibres that are more susceptible to atrophy[111] during the early stages of ACL rehabilitation may help combat activation problems whilst also triggering muscle hypertrophy and recovery of strength.

Phase 4: Heavy-load resistance training with low-load BFR training

The end goal of ACL rehabilitation is for patients to be able to resume heavy loading and return to, or exceed, their pre-injury strength and activity levels. Heavy-load resistance training is more effective at increasing muscle strength compared to low-load BFR training,[22] thus the latter may best be used as tool for effective and potentially quicker progression back to heavy exercise loads. Combination of low-intensity BFR resistance training with heavy-load training has been shown to increase muscle strength and size gains compared to low-load BFR training alone.[115] Once physically able, individuals can integrate low-load BFR training with high-load resistance training to re-introduce larger mechanical loads to structures of the MSK system. This can stimulate other adaptations alongside muscle size and strength, such as tendon stiffness - which may not be possible with low-load BFR training[116] - to contribute to further improvements in physical function. It is important that the patient is physically able to utilize the heavy loads required without an adverse reaction. Therefore, it is recommended that the patient should be able to exercise with the loads required to stimulate muscle and tendon adaptation of 65-70% pre-operative 1RM[58] when entering this advanced phase of rehabilitation.

4.3 BFR and other aspects of ACL rehabilitation: A summary

Research regarding the effect of BFR on concomitant injuries with ACL rupture and reconstruction is less advanced. At present, BFR is thought to have limited or no effect on tendon stiffness,[116] likely due to its low-force nature, and any intra-articular effects have yet to be pragmatically examined. One case study has shown an increase in serum bone alkaline phosphatase, a marker of bone formation, following low-load BFR resistance training in an individual suffering an osteochondral fracture,[117] suggesting BFR may have an impact on bone health. Further investigation of this may identify benefits for rehabilitating bone bruising following ACL rupture and reconstruction. Several clinical trials are proceeding, including one of our own, examining the effect of BFR during ACL rehabilitation. To our knowledge, trials examining the effect of BFR training following meniscus and articular cartilage repairs are underway. At our present situation, there is great potential with BFR training for increasing muscle hypertrophy, strength and combating muscle activation deficits following ACL surgery without overloading a recovering tibiofemoral joint and risk reversing the positive effects of the surgery, or worsening any concomitant pathologies.

5. Safety of BFR training

Given the delicacy of ACL reconstruction, it is important that rehabilitation is approached in a safe yet effective manner.[22] Despite concerns of disturbed hemodynamics and ischemic reperfusion injury,[118,119] the safety of BFR training has been extensively reviewed[119,120] and reported to provide no greater risk than traditional heavy-load training.[121] Reports of rhabdomyolosis have occurred,[122,123] however the cause was likely inappropriate and unclear prescription of BFR training.[22] However, BFR is safe if applied correctly - a recent questionnaire based study demonstrated that there is a wide variety of protocols used[124] despite well-documented guidelines in the literature.[22] To further ensure safety, an extensive and thorough screening must take place before implementing BFR;[22] for an overview see Kacin *et al.*, Hughes *et al*. and Patterson *et al.*[22,120,125]

6. Conclusion

Quadriceps muscle atrophy, strength loss and activation deficits can be combated with low-load BFR training. Passive, aerobic and low-load resistance training with BFR can stimulate adaptations in muscle size, strength and endurance and improve muscle activation without heavy loading of the tibiofemoral joint. BFR may reverse the decline in muscle protein synthesis and increase in breakdown, and the decrease in satellite cell abundance observed during unloading following ACL surgery. It may also preferentially recruit muscle fibres that are more susceptible to atrophy at low-loads which they are not normally engaged with low load exercise. Thus, if BFR is applied safety and correctly, it can provide an effective and appropriate rehabilitation tool as the low-load nature places less strain on the graft and any cartilage, meniscal and bruising injuries that are common with ACL rupture and reconstruction.

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