REHABILITATIVE CONDITIONING

MECHANOTHERAPEUTIC EXERCISE PRESCRIPTION

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The idea that exercise is medicine is now widely accepted[1]. In sports medicine the accurate prescription of therapeutic resistance exercise following acute muscle injury is essential for successful return to sport, particularly as muscle injuries comprise 10 to 55% of all injuries occurring in sports[2].

It is concerning then that exercise prescription is not a part of the agenda for training doctors[3,4]. If exercise is medicine, is the correct dosage being prescribed to optimise muscle regeneration?

This article aims to outline the concept of resistance exercise load to facilitate mechanotransduction in regenerating muscle tissue following muscle injury. Secondly, it aims to provide guidance to assist clinicians in prescribing exercise parameters to optimise recovery.

MUSCLE INJURY CLASSIFICATION

Exercise prescription for muscle injuries has to take into account the severity of tissue damage. The biological effect of the isolated exercise load provided will be more influenced by the degree of tissue damage than by the mechanism and location of the injury. As such, guidelines for mechanotherapeutic exercise loading can be applied for all conservatively managed injuries on a classification gradient from grade I to grade IV (as described by the Aspetar Muscle Injuries Clinical Guide 3.0)[5]. Caution would be increased with episodes of re-injury and modified as required relative to mechanism and location.

Grade 0 injuries, which in essence remain undisruptive to muscle and remain undetectable to MRI, are likely to heal at a far greater rate and may be managed appropriately with normal tissue loading guidelines.

EXERCISE PRESCRIPTION IN SPORTS MEDICINE

Practitioners of exercise therapy commonly cite the American College of Sports Medicine Position Stand recommendations[6] to guide their rehabilitative exercise prescription. The suggested load parameters for muscle strengthening are often stated as >80% 1 repetition maximum (%1RM) for 1 to 6 repetitions, for 2 to 6 sets[6], however in clinical physiotherapy practice, practitioners often apply the less specific prescription of 3 sets of 10 repetitions. Even the lower parameter outlined (and perhaps often overlooked) in the ACSM guidelines of 50 to 60% 1RM for novices[6]

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is likely to be too much stimulus for many injuries, particularly those which are more extensive.

Caution is required in applying loading parameters for healthy tissue when dealing with a maladaptive or pathologically altered muscle, as the response is likely to be different from normal muscle and may disrupt healing. Currently, the optimal amount of load needed to promote muscle healing has not been identified.

Mechanotherapeutic load should be tailored to take into account the optimal likely response to the intervention. The objective of exercise should be identified as to whether it aims to modify injured tissue or strengthen supportive musculature. Cook and Docking[7] succinctly describe the need to meet but not exceed the 'capacity' of the injured tissue – enough to sustain muscle synthesis through repair, but less than the maximal load for that tissue, which may cause breakdown.

If exercise is medicine, then the dosage applied (intensity and volume of load), particularly in states of tissue fragility, needs to be appropriately considered.

MECHANOTRANSDUCTION

Mechanotransduction is the biological process by which mechanical load is received and converted into a cellular response leading to structural change of the tissue. Mechanotherapy has been described to be the "specific prescription of therapeutic exercise to promote repair and remodelling in injured tissue"[8].

MECHANICAL LOAD PERTURBATIONS

Active muscle contraction and movement during exercise leads to combinations of multidirectional shear and compressive forces at the level of the whole muscle, fascicles, single fibres and sarcomeres. Deformation of the tissue is not uniform and includes rotational and twisting forces, making it difficult to define the isolated forces transmitted.

The sliding filament theory of skeletal muscle states that contraction is fuelled by adenosine triphosphate hydrolysis and involves sodium-potassium interaction and calcium exchange[9]. This process modulates energy production, tissue blood flow and substrate utilisation[10].

During muscular contraction, the deformation of the muscular cell, cytoskeleton and extra cellular matrix (ECM) will transmit these variable forces across the tissue. This structural perturbation subsequently results in metabolic signalling cascades.

In injured tissue, this process is disrupted secondary to damage to the myofibril cells responsible for active contraction. Muscle injury is characterised by myofibril retraction, haemorrhage and extracellular calcium transfer into the tissue. This is followed by limited myofibril necrotisation and release of inflammatory and immune cells.

The degree of cellular damage will reflect the degree of contraction possible post-injury – and loading may need to be delayed until the bridge between the ECM and connective tissue scar has formed (approximately 10 days)[2].

SIGNALLING CASCADES

In response to mechanical deformation, there are simultaneous developmental and degradative mechanisms which require

balance to ensure synthesis rather than breakdown is the product of tissue loading[11].

The magnitude and influence of specific signal pathway activation depends on the intensity, duration and mode of exercise stimulus provided and on external environmental factors[10].

Mechanosensory pathways include phosphoinositide 3-kinase (PI-3K), which leads to phosphorylation of either protein kinase B or mTor (mammalian target of rapamycin). The latter, mTor, may be a key modulator of cell synthesis, however the mechanism by which it is mechanically activated remains unclear[11]. The former, (protein kinase B or AKT) is a critical node to balance synthesis and degradation and has a firmly established role in muscle atrophy.

Other signalling pathways include mitrogen-activated protein kinases (responsible for receptor signals to the cell nucleus)[11], as well as the focal adhesion kinase protein pathway, which assists transmission of contractile force through muscle tissue and is important for integrin signalling[10].

Changes in cellular calcium concentration are generally recognised as essential for cellular signalling following the action potential required for active contraction. The direct deformation of muscle cells via loading, allows calcium influx through damage to the sarcolemma or stretch-activated channels[12,13].

Other post-translational mechanisms to assist protein synthesis include ribosomal protein S6K (p70) and binding protein (4E-BP1)[10].

Concurrent degradative post-translational mechanisms would include Forkhead box O (FOXO) transcription factors and two muscle-specific components of the ubiquitin-proteasome pathway – muscle atrophy F box and muscle RING finger 110 which control protein breakdown.

REPARATIVE CELL RESPONSE

The process of protein synthesis as a response to tissue exercise loading has been discussed in detail[14], but includes three stages: destruction/inflammation, repair and remodelling.

When loading injured tissue, it must be acknowledged that prior to load application, tissue cells are already structurally damaged and undergoing a process of repair. As such, a greater understanding of the response to mechanical load is required to highlight key elements which assist the reparative process.

Inflammatory stage

The primary stage of response to load involves the inflammatory response to tissue damage, the immune response and the release of both wound and growth hormones. During inflammation it has been found that mechanical loading results in platelet-derived growth factor expression to assist tissue repair[15,16].

Various growth factors (e.g. fibroblast growth factor, insulin growth factor 1/2 and transforming growth factor) activate myogenic precursor cells to initiate the first stages of protein synthesis. Care must be taken to refrain from excessive load due to the likely presence of inflammatory mediators when tissue cells are already damaged. Equilibrium is required to facilitate the positive and negative effects of inflammatory cells on tissue repair. For example, macrophage invasion is characteristic of the inflammatory response to injury and can cause cellular damage by release of free radicals[17]. However, such cells may also assist muscle repair, through the release of growth factors and cytokine-mediated signalling. Secondly, muscle-derived nitric oxide can inhibit the inflammatory cell invasion of healthy muscle tissue and prevent cell destruction from free radicals[17].

Repair stage

The repair stage involves myofibril regeneration and extension into the developing connective tissue scar, where the ruptured ends of myofibrils need to recover their continuity. This occurs via early granulation, construction of the ECM scaffold and fibroblast invasion.

> ***The stress applied to the regenerating tissue must be balanced to ensure that homoestasis between anabolism and catabolism is maintained to prevent further tissue destruction, inflammation and delayed repair***

During tissue repair, loading activates satellite cells and fibroblasts, facilitating differentiation into myoblasts and myofibroblasts respectively. These cells are formed inside the basement membranes which act as a scaffold for reconstructing myofibrils. This allows formation of the musculotendinous junctions into the connective tissue scar and growth of new muscle protein cells[18].

The severity, nature and mechanism of muscle injury will reflect the degree to which the ECM and myofibrils are likely to be damaged, as well as the fragility of the connective tissue scar. The time lapsed since acute injury can also be a guideline of tissue capacity as animal models show that load to muscular failure following laceration only increases from 13.6% of control at 5 days, to 50% of control by day 14 post-injury[19]. Subsequently, between 14 and 56 days post-laceration, load to failure plateaus between 47 to 53% of control[19]. Caution is therefore advised, as it should not be assumed that tissue can be excessively externally loaded, simply due to time lapse since injury.

Active tissue mobilisation (without external resistance) during early healing enhances the penetration of myofibrils into the connective tissue scar, improves capillary in-growth and facilitates proper cellular orientation during this phase[2].

Remodelling stage

Remodelling is characterised by re-vascularisation and intramuscular innervation alongside myofibril regeneration. During this phase, mechanical loading provides reinforcement between regenerating myofibrils and the ECM to allow temporary lateral adhesions[19] for stress-shielding of the repair site. This also facilitates maturation of the connective tissue scar-musculotendinous attachments.

These reparative processes occur alongside an increase in the size and number of myocytes throughout the healing tissue, which is deemed a key limiting factor for regeneration contractility[20].

Of course, the stress applied to the regenerating tissue must be balanced to ensure that homeostasis between anabolism and catabolism is maintained to prevent further tissue destruction, inflammation and delayed repair. In previously injured tissue this balance is even more essential due to a greater chance of developing a catabolic state. It is suggested that scarred tissue has a different homeostatic set point at which it must be balanced[21]. As such, the exercise loading prescription used in healthy tissue should be modified to reflect this potential mismatch of catabolism and facilitate tissue synthesis.

REHABILITATIVE EXERCISE PRESCRIPTION GUIDELINES

Research currently does not outline the specific dosage of training principles (such as intensity and volume) for regenerating tissue. However, it is evident that training parameters should be modified to ensure appropriate metabolic stress, tension and tissue breakdown, without excessive failure and inflammation. Resistance training intensity must promote repair, synthesis and scar maturation.

The most common measurement of resistance exercise intensity is the percentage of one-repetition maximum (%1RM) and is formed by measuring the maximal force generated (or weight used) in one contraction (1RM). This is completed by progressing through increasing load amounts until only 1 repetition can be performed.

The difficulty in using this measure within an injured population is that clinicians may be unable to assess the maximal amount of resistance for one repetition due to the presence of an injury. Any repetition maximum is likely to be limited due to the load exceeding tissue tolerance. The use of contralateral or previous baseline measurements from the athlete is useful to guide intensity parameters. Alternately, clinicians may

use an intensity parameter guided by the number of consecutive repetitions which can be performed with a reduced load amount. As such the 'xRM' can be calculated (with x being the targeted number of repetitions).

Intensity

Until optimal parameters are identified by research, the 50% 1RM figure outlined by the ACSM guidelines for novices is likely to be a valuable guide for injured tissue. The specific %1RM prescribed should be guided by any reaction to loading. This may include evidence of excessive inflammation, swelling, loss of contractility/force reduction and pain response, both acutely and delayed following exercise.

Guided by clinical practice, it is suggested that isolated muscle loading should be commenced after 10 days rest (with only active range of motion) to protect the injury site during the primary stage of healing. Following this period a maximum of 40% 1RM should be used to assist mechanotransduction and prevent tissue catabolism.

Exercises should be prescribed at variable intensity at and below 40% 1RM for variable volume. This intensity figure sits below the suggested novice starting point and better reflects the capacity for healing tissue to be loaded.

Clinician discretion is required to set a starting %1RM figure relative to the site, nature and grading of the muscle injury, which can be assisted with radiological imaging.

To best aid mechanical repair and tissue regeneration it is advised to isolate and train the specific muscle group through both the concentric and eccentric phases of a muscle's specific action. Conjoining muscle groups, where the injured muscle has a secondary synergistic role, can be trained at higher intensity, as tolerated. While the injured muscle will be stimulated and such activity will contribute to the overall volume of stimulation, it is suggested that quantifying the degree of load in this instance is impossible in clinical practice. Instead clinicians should be cautious not to excessively load muscles anatomically close to the injury site and be watchful of immediate and delayed reaction to such loading.

Volume

Exercise volume should be inversely proportional to the exercise intensity. As the intensity level will be far below the maximal capacity of the entire muscle, volume should be guided by the individual's response to the intensity and should aim to remain between 12 to 20 repetitions per set. The number of sets can be guided by increasing signs of excessive loading and fatigue.

Loading progression

Beyond 6 weeks post-injury, progression should be extended beyond 40% 1RM as the healing process consolidates tissue capacity for load and can be increased to and beyond 50% 1RM.

Due to the fragile nature of regenerating tissue, subtle load progressions of 2% are suggested as a starting point[22]. However, progression should be individualised to each patient's response. In fact all exercise parameters of intensity and volume should be patient-dependent, as the nature of injury will always be individual-specific. Each injury will involve different degrees of macro and micro tissue damage, different molecular responses to load, different compensatory behaviour mechanisms and different nervous system thresholds to loading. However, the general principles of reduced intensity below normal tissue guidelines and slow progression of loading, remain useful as first steps to improve exercise prescription.

Rehabilitation programmes should be designed as a complete rehabilitative macrocycle which incorporates the healing phases of the injury and the planned exposure to therapy

Table 1

- *Accurate exercise prescription following acute muscle injury is an essential – although often overlooked – component of successful return to sport programmes.*
- *Current guidelines of resistance training exercise prescription (e.g. ACSM) do not succinctly reflect the role of exercise during the process of tissue healing.*
- *Early mechanotherapeutic exercise can prevent disuse atrophy and promote tissue regeneration/maturation through mechanical and biochemical means.*

Table 1: Mechanotransduction summary.

Table 2

- *Intensity of exercise (via %1RM) is an easily quantifiable variable for clinicians to modify to commence mechanotherapeutic loading.*
- *%1RM should be calculated in line with the contralateral limb or previous baseline performance parameters.*
- *40% 1RM, commenced 10 days post-injury with simple isolated loading exercises is an appropriate starting point. Days 0 to 10 should only include gentle range of motion exercise.*
- *Exercise volume should be inversely proportional to exercise intensity and guided in practice by an individual athlete's response of pain sensitivity and fatigue.*
- *Progression should take the form of 2% increases in load amount, with subsequent reduction in volume.*
- *Rehabilitation programme microcycles should incorporate additional indirect variables, such as contralateral limb exercise, neuromuscular control, proprioception and cardiovascular training.*

Table 2: Mechanotherapy exercise prescription guidelines.

Tissue capacity management

In regenerating tissue, failure load and ultimate tensile strength are both reduced, however sensitivity to load is increased as a protective tissue response. Loading parameters must be modified to ensure that they are not so high that it causes tissue reaction, inflammation, peripheral sensitivity and pain. Supplementary treatment to reduce tissue compensatory behaviour and pain should be employed as required and may include massage and manipulative therapies at the discretion of the clinician.

Rest times between sets should be increased as required and active recovery modalities such as gentle stretching or movement should be undertaken to facilitate tissue response. It is appropriate that the suggested rest parameters for hypertrophy and muscle endurance in non-injured tissues (1 to 3 minutes)[6] should also be modified. With no evidence available to specifically guide the rest between exercise sets, it is suggested that a minimum of 3 minutes should be used initially and modified according to patient progression.

Periodisation

Rehabilitation programmes should be designed as a complete rehabilitative macrocycle which incorporates the healing phases of the injury and the planned exposure to therapy.

This macrocycle can be sub-divided into mesocycles relative to the specific phase of healing and the degree of tissue regenerative capacity. For example, the primary phase of inflammation and early repair coincides with the lowest degree of tensile strength. As such, the immediate post-injury mesocyle from days 0 to 10 can focus on active movement without external resistance. The secondary mesocycle during the repair phase should switch focus to mechanotherapeutic loading.

Each week can be again sub-divided into microcycles of specific exercise sessions, incorporating rest days to promote the recovery of healing tissue. Rehabilitation plans should also consider the prescription of alternate sessions where other factors can be trained (e.g. contralateral limb strengthening, neuromuscular control training without external resistance, proprioceptive training and cardiovascular training). Of course these aspects may also be integrated into the specific mechanotherapy training sessions as required, but caution should be taken with the overall volume of loading (direct and indirect) placed on the healing tissue.

FUTURE RESEARCH

Future research should focus on the specific loading tolerance of regenerating muscle tissue to more accurately assist the design of resistance exercise interventions during rehabilitation. The relationship between other measures (e.g. maximal voluntary isometric contraction, electromyogram) and load intensity will also provide greater insight into the best method to optimally load regenerating muscle tissue.

Table 3

Ref	Method	Intervention	Control	Muscle	Outcome		Findings	Significance
					CLINICAL	PHYSIOLOGICAL		
(23)	Non-blinded, non-randomised case control	Autologous conditioning serum injections.	Non-incubated serum injections	Hamstring	Return to play		I: 16.6(SD± 0.9) vs C: 22.3 (SD± 1.2)	P value = 0.001
						Tissue oedema (via MRI)	MRI evidence of quicker regression of oedema in intervention group.	N/A
(24)	Prospective randomised controlled trial	Loading exercise (focus on lengthening)	Conventional hamstring exercise	Hamstring	Return to play		I: 28 days (SD± 15) vs C: 51 days (SD± 21)	P value = 0.001
(25)	Prospective randomised controlled trial	Static stretching, isolated progressive hamstring resistance exercise, and icing.	Progressive agility and trunk stabilisation exercises and icing.	Hamstring	Return to play		I: 37.4 days (SD± 27.6) vs C: 22.2 days (SD± 8.3)	P value = 0.2455 (NS)
(26)	Prospective randomised controlled trial	Loading exercise (focus on lengthening)	Conventional hamstring exercise	Hamstring	Return to play		I: 49 days (SD± 26) vs C: 86 days (SD± 3)	P value = <0.001
(27)	Randomised controlled trial with blinded comparisons in a 2×2 factorial design.	Non-thermal ultrasound	1. Exercise alone; 2. US + exercise; 3. No treatment	Gastrocnemius		Markers of skeletal regeneration: 96-hours post-injury muscle mass, contractile protein concentration, fibre cross-sectional area, number of nuclei per fibre, and myonuclear density.	No significant difference between 4 groups.	P value = 0.01 (NS)
(28)	Descriptive animal study	Pulsed ultrasound	No treatment	Gastrocnemius		Satellite cell proliferation at day 3.	I: 37.4mm2 (SD± 6.9) vs C: 19.1mm2 (SD± 3.9)	P value = <0.05
						Satellite cell proliferation at day 10	I: 12.4mm2 (SD± 4.5) vs C: 10.4mm2 (SD± 6.1) (NS)	(NS)
						Fibroblast proliferation at day 3.	I: 46.5mm2 (SD± 12.9) vs C: 56.1mm2 (SD± 9.9) (NS)	(NS)
						Fibroblast proliferation at day 10.	I: 27.4mm2 (SD± 11.8) vs C: 10.1mm2 (SD± 7.8)	P value = <0.05
(29)	Descriptive animal study	Low-level laser therapy (dose 1.0j)	No treatment	Tibialis anterior		Relative peak force at 6th contraction following sequence of tetanic contractions.	I: 151.27% ± 18.82 vs. C: 82.25% (SD ± 11.69)	P value = <0.05

Table 3: Comparison of interventions for acute muscle strain management. NS=no significant difference between groups. I=intervention group. C=control group. SD=standard deviation. US=ultrasound. Ref=reference.

Evaluation and comparison of specific intensity parameters on tissue regeneration is required to affirm the recommendations in this article.

CONCLUSIONS

All professionals using exercise as an intervention for those with muscle injury should be conscious and aware of how to apply exercise intensity to facilitate mechanotransduction and improve tissue regeneration. Resistance exercise with injured and regenerating tissue should be designed to do more than just 'strengthen' the tissue, with best practice considering the optimisation of the environment for the connective and healing tissue surrounding it.

The process of reasoning as to how exercise parameters should be modified in regenerating muscle and how the severity of muscle injury may influence early exercise loading is essential for all those involved in sports. The suggested guidelines may allow return to sport more rapidly.

References
Available at www.aspetar.com/journal

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