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The beneficial effects of controlled mobilization and loading on tissue healing are well documented in the scientific literature. Similarly, the detrimental effects of prolonged under-loading and immobilization are also well known. In the following sections we provide a brief overview of selected clinical topics with references. These studies form the foundation behind the science of unloading and progressive loading used in rehabilitation and training with the AlterG Anti-Gravity Treadmill®.

1. EFFECTS OF LOADING ON TISSUE HEALING

Progressive Loading In Healing

Rehabilitation programs are designed to help individuals optimize recovery with respect to the healing process. The goal is restoration of normal, or near normal, anatomical and physiological function to help return patients to their lifestyles and activities. Proper understanding of the anatomy, physiological processes, and pathomechanics are important to maximize the potential of therapeutic interventions.

Injury recovery can be divided into three stages: 1) Acute Inflammatory, 2) Regeneration and Repair, and 3) Remodeling. Achieving goals in each stage before advancing to the next is important to ensure a smooth progression for the patient (1).

Traditional orthopedic protocols separate patients into two categories to help them prevent damage to healing tissue and move them forward to the next stage of recovery. Patients are usually classified as: 1) Partial Weight Bearing or 2) Weight Bearing As Tolerated. The key to rehabilitation in both categories is the ability to mobilize patients early to prevent post-injury/post-operative sequelae that could slow progress.

Stage I: Acute Inflammatory Stage

In most injuries, there is an associated inflammatory reaction that may have objective findings characterized by pain, rubor, erythema, and ecchymosis. This phase can last between 48-72 hours depending on the severity of the injury. In this stage, extremities can be immobilized with braces or weight bearing limited to protect healing tissue. While this is important, there can be negative effects from restricting activity and limiting loading to surrounding tissue. Muscle atrophy can occur, bone density can be affected, and scar tissue can accumulate. (1,2)

Early mobilization after surgery can play a role in helping reduce the above sequelae and increase tissue strength, improve orientation of healing muscle fibers, encourage resorption of scar tissue, and decrease muscle atrophy/

weakness. Gentle exercise during this phase can be a way to improve range of motion and minimize loss of strength during this phase. (1,2,3)

Stage II: Regeneration and Repair

During this phase of recovery from 2 days to 6 weeks after injury, tissue is being repaired and regeneration of new healthy collagen takes place. Protected mobilization through exercise plays a critical role in this stage to restore full range of motion and return muscle strength to normal. The challenge for patients in this stage is to avoid being too aggressive with activities, as injured tissue will not likely be at full strength but the absence of pain may lead patients to do too much.

Controlled activity is important in this phase to track progress, as well as note any unusual responses in the healing area. Progressive loading also allows controlled stress to be applied to the healing tissue, to try and influence alignment and mobility of the scar. By preventing adhesions and encouraging proper remodeling, the hope is that patients can attain successful outcomes with their recovery (3,4)

Stage III: Remodeling

This last stage can last up to 12 months from the injury, as the tissue continues to remodel and gain strength. During this stage, there may still be some strength deficits and it will be important to work out muscle imbalances and asymmetries to prevent the likelihood of re-injury. Gradual incorporation of more aggressive activities will allow the patient to assess readiness of healing tissue to stresses and prevent overload during this phase (3,5)

CONCLUSION: Controlled Loading Is Important For Encouraging Early Mobilization While Protecting Healing Tissue

2. EFFECTS OF LOADING ON BONE

Bone, like muscle, is an adaptable tissue capable of repair, regeneration, and remodeling in response to environmental (particularly mechanical) signals. Bones are exposed to both stress (ie, load) and strain (ie, deformation) with weight-bearing exercise. Wolff's law states that bone develops the structure most suited to resist the forces acting upon it.

Bone undergoes constant remodeling through a series of bone resorption and bone formation steps that repair bone microtrauma, enhance bone strength in regions of high load,

and buffers fluxes in serum calcium level. (6,7) Osteoporosis is a condition known to reflect reduced bone quantity and quality, a problem that is accelerated by the impact of inactivity and reduced muscle mass on bone signaling. In general, unloading of the skeleton through disuse promotes reduced bone mass, whereas loading promotes increased bone mass. (8,9) Examples of scientific studies of disuse include prolonged bed rest and space flight, both resulting in accelerated bone loss. (10) At the other end of the spectrum repetitive overloading of bone can lead to stress fractures in athletes or fragility fractures in elderly persons with osteoporotic bone. The positive impact of exercise on bone mass varies at different stages of life, with exercise during the prepubertal skeletal growth period preferentially favoring greater bone mass gains, whereas exercise later in life promotes less gain, but reduces expected age-related losses. (11) Recovery of bone mass later in life is difficult in part due to a reduction in pluripotential stem cells and a low potential for musculoskeletal regeneration. (12) Laboratory studies of limb loading in animals show that although mechanical stress results in very small gains in total bone, these increments occur at skeletal surfaces subjected to the highest strain where they are most needed to reduce fracture risk. Experiments utilizing such models have demonstrated that to optimize bone formation, mechanical loading must be dynamic rather than static (13) and must be cyclical including rest periods. (14) This pattern of loading results in a greater than 100 fold increase in fatigue resistance (15) even though there is a much smaller absolute gain in bone mass. Recent interest has focused on the possibility that mechanical signals may increase the mesenchymal stem cell pool and drive differentiation of cells away from fat cells toward osteoblasts (12, 16) by stimulating expression of critical proteins (17). This exercise-induced expansion in stem cells could partially offset their age-associated reduction and further support a unique mechanism by which exercise promotes bone health.

Which Has The Greater Effect On Bone: Muscle Forces or Weight Bearing Forces?

Total bone mineral content is more strongly associated with muscle mass than with fat mass or total body mass, supporting the idea that muscle forces are closely interrelated with bone mass. (18) Muscle forces are generated both with impact and non-impact exercise, so it is difficult to separate the effects of gravity alone from muscle forces (19) on bone mass. It is clear that muscle forces and weight bearing forces have an effect on bone quality and there is evidence that the relative impact of each varies based on the skeletal location. Experiments have demonstrated that the majority of the forces generated within the femur during walking are the result of muscle forces and less the result of weight bearing. (19, 20) Laboratory experiments using a jumping rat model

support the idea that contracting musculature alone, without the landing impact, can stimulate bone formation. (21) On the other hand, critical weight bearing skeletal sites including the femoral neck appear to be highly sensitive to impact loading and may require upright weight bearing to maintain bone mineral content and structure. (22) As an example, competitive male cyclists generate very high leg muscle forces, but their bone density at all measured skeletal sites including the femoral neck is lower than that of non-athletes. (23, 24)

CONCLUSION: Evidence Strongly Supports Controlled Loading Of Bone To Facilitate Bone Health And Healing From Injury

One of the most important concepts in musculoskeletal health is the understanding that loading accelerates healing of bone, but the response is dose-dependent. Proper loading facilitates bone health, whereas repetitive overloading can produce injury. For these reasons, patients with musculoskeletal injuries and those who have recently undergone surgery are now being treated with controlled physical activity that loads their healing tissues. (25)

3. EFFECTS OF LOADING ON CARTILAGE

Hyaline articular cartilage provides the contact surface for synovial joints. This avascular and aneural tissue, has a high water content allowing it to withstand significant amounts of pressure and distribute forces evenly. (26,27) The result is a near frictionless environment under physiological conditions (28). Maintaining homeostasis for any tissue is important to preserve its mechanical abilities and allow it to serve its purpose. With osteoarthritis cases (OA) increasing as the population ages, making it the most common cause of disability, it becomes urgent to understand how to preserve and maintain cartilage health to help slow and stop the disease. (29)

Mechanical loading is important to regulate structure and function of musculoskeletal tissues. But it is well known that excessive force, overloading, can also be detrimental. For cartilage, overloading can lead to changes in tissue morphology, matrix, and mechanical abilities (30, 31). While there are few studies measuring the effects of overloading on cartilage in humans, there is information about shifts in balance of tissue remodeling in favor of catabolic over anabolic activity in numerous animal and 3D models (32). Injurious mechanical loads can be traumatic in nature or the result of cumulative impact forces at high peak stress.

In addition to damage from overloading, cartilage is susceptible to degeneration from immobilization combined with non-weightbearing. Prolonged immobilization in both

animal and human studies show cartilage thinning, tissue softening, and reduced proteoglycan content (32). So an inactive lifestyle, could serve to be equally as detrimental for cartilage health as an overactive one that leads to irreversible damage. Studies with patients immobilized for as short as 7 weeks to recover from ankle fractures show cartilage atrophy and reduced thickness in patellae and med tibia (33).

Moderate Mechanical Loading Is Important in Cartilage Health

While overloading and providing inadequate loads are both found to negatively affect cartilage homeostasis, there are studies that show moderate exercise is beneficial in maintaining cartilage health. Subjects that participated in these studies showed normal distribution of proteoglycans and improved glycosaminoglycan content (34, 35). The result was reduced pain and disability from knee OA (34). While the information is still insufficient regarding optimal exercise regimens, including dosage, length of intervention, or ideal loads, clinical observations of subjects suggest that physical activity is not detrimental if it is not painful and does not lead to overuse trauma (36).

CONCLUSION: Controlled Loading Is Important For Maintaining Cartilage Health

Understanding factors contributing to cartilage health is important to help control a growing problem with an aging population, osteoarthritis. Proper loading is not just critical for healthy individuals to preserve cartilage homeostasis; studies show that early controlled loading could be important in preventing sequelae post-injury/post-surgery. Further research on specific parameters regarding moderate exercise activity could be helpful in developing treatment strategies for facilitating and preserving cartilage health.

4. EFFECTS OF LOADING ON TENDONS

Changes in the structure and properties of tendon tissue have clearly been shown in response to both increased and reduced mechanical loading.

Increased loading leads to increased mechanical tendon stiffness, induction of collagen protein synthesis and changes in expression of matrix-related genes (37, 38). Several studies have shown that tendon unloading leads to reduced mechanical strength and stiffness and possible decreased synthesis of collagen proteins (39, 40).

In a study by Heinemeier et al (41) it was found that tendon mass was unaffected by a period of absolute unloading but there were demonstrable and substantial changes in

the mechanical properties as expected. This indicates that important changes must occur in the tendon-matrix even though the tendon size is unchanged. Such changes have been postulated to be alterations in collagen fibril content, size and density.

CONCLUSION: Controlled loading and unloading have considerable effects on tendon physiology and morphology

The clinical significance of this information with regards to PWB therapy is that there must be homeostasis within the tendon structure. In the presence of injury or recovery it may be important to reduce the mechanical stiffness of the tendon, or to negatively influence the genetic trigger of collagen protein synthesis to limit hypertrophy. However, it needs to be achieved without causing the changes described above in the absolute unloaded tendon where possible matrix and load-transfer mechanisms are compromised. Precise, controlled partial weight bearing technology can offer a treatment modality to manipulate our response to these factors.

5. EFFECTS OF CONTROLLED LOADING AND UNLOADING ON NEUROPHYSIOLOGY

Neurophysiological evidence has shown that neuroplastic activity can be enhanced when walking on a treadmill with body weight partially supported (42, 43). It is hypothesized that part of this neuroplastic reorganization is driven by an afferent barrage of non-nociceptive information that are peripherally potentiated by the process of ambulation. An example of this is when the trailing leg approaches terminal stance, the muscle spindles in the hip flexors sense elongation, and Golgi tendon organs in the plantarflexor muscles sense unloading as weight is transferred forward into swing. These afferent sensory cues facilitate stance-to-swing phase transitions and contribute to rhythmic, alternating lower extremity movements during gait (44, 45, 46, 47).

Insights from these studies have inspired the use of body weight-supported treadmill training and have shown that the sensorimotor experience can improve walking speed, stride length, postural balance, and walking endurance (48). Furthermore, a functional magnetic resonance imaging investigation has shown that body weight support can influence activity within the primary sensorimotor cortex while performing an ankle dorsiflexion task (49).

CONCLUSION: Overall the current scientific evidence suggests that body weight support may be an efficacious therapy for improving walking performance.

6. UNLOADING TO ASSIST EXERCISE FOR OVERWEIGHT INDIVIDUALS

Global guidelines regarding the most appropriate level of exercise for health promotion in the general populations are varied, however there is no global discrepancy in supporting health promotion through physical exercises. Guidelines produced in 2009 by the Chief Medical Officer of the Department of Health in the United Kingdom recommends five 30 minute sessions per week of moderate intensity exercise (50). This is recommended to achieve health benefits and can equate to brisk walking. The American College of Sports Medicine recommends more than 150 minutes per week of moderate to intense physical activity may be needed for weight loss (51). While the American Institute of Medicine suggests 60 minutes per day of moderate intensity exercise is advantageous to control body weight (52).

Higher intensity (70-80% of maximal heart rate) exercise is suggested to promote a greater rate of fat burning (53). Speed interval training is proposed to increase metabolism during exercise, and also increase metabolism over a longer period of time post exercise completion (54). Unfortunately it becomes difficult for people who are overweight to achieve, let alone sustain, the recommended levels of exercise. Partial body weight support allows the overweight individual to experience their preferred body weight as well as achieve meaningful calorie expenditure (55).

Barone and Wang et al. (56) observed a reduction of 3cm in waist circumference in sedentary adults after 6 months of a supervised exercise routine, and that this in turn led to a modest reduction in systolic blood pressure. A reduction in abdominal fat and a modest reduction in systolic blood pressure indicate a reduction in cardiovascular risk factors (57).

Poor cardio-respiratory fitness levels have been linked with an average three fold increase risk of early death in overweight unfit men and women (58, 59). Exercise routines which aimed at improving cardio-respiratory fitness have been shown to be effective in reducing the risk of early mortality in sedentary adults (60, 61).

CONCLUSION: Partial body weight support has indirect effects on weight reduction by enabling exercise in individuals otherwise unable to do so.

7. EFFECTS OF PARTIAL BODY WEIGHT SUPPORT AND UNLOADING ON GAIT RETRAINING

Evidence shows that walking on a treadmill with body weight support facilitates swing-stance symmetry, increases hip extension during stance and reduces gastrocnemius and

stance phase muscle activity. This activity within the stance phase muscle groups was also shown to increase when ambulating at higher speeds with weight support (62).

It is clear from the literature that the process of supporting body weight when walking leads to long-term improvements and carryover in overground walking capabilities, especially walking speed (63, 64). It has been postulated that this improvement in walking speed may in part be due to manipulation of the product of net joint movement and angular velocity around the hip, and alterations in ankle power during late stance (Nadeau et al 1999).

Mulroy et al (63) examined gait parameters associated with responsiveness to body weight supported treadmill training. They concluded that a body weight supported treadmill training cohort exhibited an increase in overground walking speed. This cohort demonstrated more consistent overall kinesthetic changes around the hip and ankle during late stance. This group demonstrated an increase in maximal hip extension during late stance and was attributable to an increase in hip joint extension motion and decreased anterior pelvic tilt. In contrast Mulroy et al (63) also found a cohort that showed a limited response to training and they demonstrated increased anterior pelvic tilt, and greatly reduced plantar-flexion ROM and power during pre-swing compared to the improved group.

CONCLUSION: Use of body weight support and partial weight bearing can create desirable pathomechanical effects that can positively affect outcome.

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