# Chronic Muscle Disuse

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Periods of muscle disuse promote diminished muscle quality along with muscle atrophy that is characterized by reductions in muscle fiber cross-sectional area (CSA). Skeletal muscle disuse may be brought about by chronic sedentarism, periods of immobilization due to injury, bed rest as result of illness, or even exposure to microgravity. Such inactivity elicits functional and metabolic derangements in the affected tissue including marked mitochondrial alterations that contribute to the impaired metabolic health and degree of atrophy in the muscle. These impairments within the tissue prompt a net increase in catabolic processes in conjunction with reductions in skeletal muscle protein synthesis. Skeletal muscle mitochondrial decline and atrophy are underlying features of many diseases and they exacerbate disease progression and reduced mobility with aging. Thus, understanding the molecular underpinnings of muscle mitochondrial deficits with prolonged inactivity is of considerable interest.

skeletal muscle atrophy | mitochondrial quality control | mitochondrial biogenesis | mitophagy | autophagy

## 1. Introduction

The adaptability of skeletal muscle to various external stimuli has profound ramifications for overall health. It is well-established that chronic exercise supports favourable adaptions in muscle that contribute to improved metabolic fitness, longevity and the absence of various diseases. In contrast, chronic muscle inactivity promotes diminished muscle quality along with muscle atrophy that is characterized by reductions in muscle fiber cross-sectional area (CSA), the net result of increased catabolism concomitant with reduced skeletal muscle protein synthesis [1][2][3][4][5][6]. Indeed, muscle atrophy is a prominent feature of numerous pathophysiological conditions, including metabolic diseases, cancers, AIDS, and respiratory diseases, among numerous others, and leads to further disease progression and reduced mobility with aging [7][8]. In the absence of disease, skeletal muscle disuse may be brought about by chronic sedentarism, periods of immobilization due to injury, bed rest as result of illness, or for a select few, exposure to microgravity. In these cases, muscle atrophy may occur in the affected limb or more broadly throughout the body, creating functional and metabolic derangements in the affected tissue. Given the frequent recruitment and activation of slow-twitch oxidative fibers for the maintenance of posture and other routine tasks, muscles with a predominantly type I fiber composition such as the soleus are more susceptible to chronic disuse than muscles with a more mixed fiber complexion, such as the gastrocnemius [9][10][11]. Prolonged inactivity promotes the acquisition of the structural, biochemical and mechanical properties of a glycolytic tissue within these type I fibers, and generates metabolic dysfunction emanating from the mitochondrial network. Thus, the effects of

muscle atrophy with prolonged inactivity are variable and determined, in part, by the composition of fiber types within the affected tissue [9][12][13][14].

The World Health Organization posits that insufficient physical activity is the leading risk factor for the advancement of non-communicable diseases and diminished quality of life, and is a global phenomenon that requires a substantial and coordinated effort among nations to remediate the pervasive sedentarism [15]. The consequences of muscle atrophy are substantial, with implications in functional decline, disability, disease and premature death. Even during prescribed periods of muscle disuse, as part of therapeutic intervention following injury or illness, the resultant atrophy in the muscle can prove detrimental by delaying, impairing or even preventing adequate recovery, often despite rehabilitative intervention strategies [16][17][18][19][20].

# 2. Models of Muscle Disuse

## 2.1. Human Models of Muscle Disuse

Chronic inactivity in humans provides the most direct study of the conditions that bring about muscle wasting in patient populations. Unilateral limb immobilization/casting, as well as bed rest studies present the two most commonly used approaches for studying muscle wasting conditions in human subjects, and are particularly useful in studying muscle decline in the absence of associated comorbidities. Unilateral limb immobilization involves fixing a joint, such as the elbow or knee, in the flexed position while maintaining the limb suspended above the ground. This approach has been used for decades to compare the effects of muscle disuse in one limb, compared to the contralateral, unaffected limb [21]. The ability to localize muscle disuse with this model closely mimics the unloading that occurs following musculoskeletal injuries in the clinical setting, and allows for direct comparisons within the same subject, while eliciting pronounced reductions in CSA and muscle mass [22][23][24]. In fact, reports indicate that limb immobilization is capable of inducing 0.44% reduction in vastus lateralis mass per day [24][25][26]. Bed rest studies have also long been employed to simulate, not only prolonged periods of inactivity following injury or illness, but additionally, the muscle wasting conditions brought about by space flight [27]. Dry-immersion bed rest studies go one step further by positioning a subject in the supine position within a waterproof barrier and suspending them in thermoneutral water, in order to most accurately recreate the complete unloading that is experienced by astronauts in space [28]. The additional benefit of dry-immersion bed rest is the higher rate and greater extent at which neuromuscular adaptations are achieved, compared to traditional bed rest [28]. Both bed rest and limb immobilization studies allow effective countermeasures to be tested, in order to prevent, offset, or reverse the decline in muscle observed with disuse, while also providing a relevant model of the wasting associated with diseases and aging. In a clinical setting, brought into recent focus as a result of the COVID-19 pandemic, is the significant respiratory muscle atrophy and dysfunction resulting from mechanical ventilation in the intensive care unit. Respiratory muscle atrophy and dysfunction can occur in just 18 h following assisted ventilation [29][30]. Samples derived from these patients, although scarce, allow for direct study of the myopathy that makes these subjects unable to return to normal, unsupported ventilation [31][32].

## 2.2. Animal Models of Muscle Disuse

In many cases employing animal models of muscle inactivity offers greater flexibility and the ability to control for potential confounding variables, while also mimicking many of the relevant disuse atrophy-generating conditions that may affect humans [33][34]. In animals, hindlimb suspension and hindlimb immobilization are two common approaches for inducing disuse-atrophy, particularly in mice and rats. Hindlimb suspension involves affixing orthopedic tape to the tail of the animal and attaching the tape to a metal swivel located at the top of the cage, thus, allowing for unhindered 360° rotation and movement around the cage using the forelimbs [35][36][37][38]. The hindlimb suspension technique was first developed nearly 50 years ago by the National Aeronautics and Space Agency, in order to simulate weightlessness, and thus, makes the approach particularly useful for studying the effects of musculoskeletal unloading [39][40]. Similar to immobilization in humans, rodent hindlimb immobilization involves fixing one limb with a plastic brace, or within a plastic tube, in order to maintain the joint in a flexed position [36]. In this way, disuse can be accomplished by using, either a fixed dorsiflexion of the ankle joint to induce atrophy of the tibialis anterior and extensor digitorum longus, or fixed plantarflexion to produce atrophy of the gastrocnemius, plantaris, and soleus [41][42][43]. The benefits of employing hindlimb immobilization include the ability to compare the effects of disuse to the contralateral limb of the same animal, while restricting muscle contraction. Additionally, these techniques offer a relatively simple, cost effective approach to induce reductions in muscle CSA, mass, and strength in as little as one week [44]. Another model that may be applied to rodents involves confined housing via small cages that restrict movement, and thus, limit physical activity so as to replicate chronic sedentarism [45][46][47][48]. This model of restricted movement is useful in studies interested in observing the systemic effects of muscle inactivity such as the changes in glucose metabolism and insulin resistance, along with the muscle atrophy and myopathy that ensues [45][48][49]. Likewise, an added benefit to any of these aforementioned rodent models is the ability to study corrective interventions, such as re-training to minimize or to reverse the detrimental effects of muscle disuse.

In contrast to these relatively non-invasive techniques, denervation, or similarly, nerve crushing and tetrodotoxin (TTX) cuffing, provide surgical methods of inducing muscle disuse, and have applicability to severe spinal cord or neuronal injury, as well as aging [50]. Denervation involves the excision of a small (~2–3 mm) segment of the nerve innervating the target muscle. Generally the tibial nerve is targeted in rats, while the sciatic nerve is used in mice, thus, affecting the lower hindlimb muscles [36][51][52]. Denervation of the nerve completely abolishes nerve-muscle communication via neuromotor and neurotrophic inputs, leading to rapid atrophy of the tissue. Nerve crushing is similar to denervation, however it requires the application of a force to the nerve with adequate pressure to temporarily ablate neural input to the muscle, while still allowing for neural regeneration and re-innervation to occur over time [36][53][54]. Alternatively, treatment with the sodium channel blocking drug TTX provides a chemical approach to denervation. TTX cuffing around the nerve maintains axonal continuity to the muscle and vascular beds, along with the flow of trophic factors that are otherwise lost with mechanical denervation, yet eliminates the impulse conduction from the nerve to muscle in order to prevent muscle contraction [53][54]. Each of these approaches are both suitable and sufficient for inducing muscle disuse-induced atrophy as well as metabolic myopathy. However, the choice of which model is best depends on the context and application of the experiments, and any conclusions made using one technique should be carefully applied and contrasted with those obtained via other disuse methodologies or model organisms.

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