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**Unit 5: Respiration, Internal Environment,
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Skeletal muscle performance and ageing – Tieland 2018

1. The world population is ageing rapidly. Since 1980, the number of people aged 60 years and over has doubled to approximately 810 million. The elderly population will continue to grow to approximately 2 billion in 2050. As society ages, the incidence of physical performance limitation will increase as well. In western society, as much as 42% of those over 60 years of age have difficulties in performing activities of daily living (e.g. walking speed or standing up from a chair), and >30% are confronted with physical disabilities. These physical limitations increase the risk of falls, institutionalization, co-morbidity, and premature death.
2. While there are a number of contributors to physical limitations with advancing age, one of the more prominent contributors is undoubtedly a reduction in skeletal muscle performance. One of the hallmark changes of ageing that is linked to reductions in muscle performance is the loss of skeletal muscle mass, which is commonly referred to as sarcopenia.

The body consists of more than 500 skeletal muscles which are controlled by the nervous system and which connects and supports the skeletal system. Skeletal muscles consist of muscle fibres, each containing sarcomeres, which are the smallest repeating functional units in the muscle. Via a series of complex events, sarcomeres are responsible for muscle contraction and relaxation. This allows the body to perform a wide variety of different movements, ranging from fast and powerful movements to small and fine motions. Since skeletal muscles are responsible for all the voluntary movements, logically, skeletal muscles are essential for optimal physical performance. Physiological changes, such as a loss of motor units, changes in fibre type, muscle fibre atrophy, and reduced neuromuscular activation, could affect the velocity, force, and strength of movements, leading to reduced physical performance, potentially leading to functional disability and institutionalization.

3. Not only are skeletal muscles important for physical performance, they are also an important contributing factor in maintaining optimal health throughout life. As such, skeletal muscles are involved in different metabolic pathways. Since muscles are the primary site for the insulin-stimulated glucose uptake from the blood, the muscles are crucial in maintaining glucose homeostasis. Muscles are also involved in other metabolic functions providing a site for fatty acid metabolism and glycogen synthesis. Metabolic disturbances in muscle could, therefore, lead to insulin resistance, the metabolic syndrome, and obesity. Furthermore, muscles interact with other organs via the excretion of myokines, which can exert autocrine, paracrine, or endocrine effects. Myokines support the metabolic function of different tissues, such as the bones, pancreas, liver, and adipose tissue. The metabolic function of skeletal muscle and the role of myokines both illustrate the importance of the muscles in maintaining optimal health throughout life.
4. At the myocellular level, many studies have reported a substantial decrease in muscle fibre size in the elderly. This reduction in muscle fibre size has been shown to be fibre type specific, with 10–40% smaller type II fibres observed in the elderly as compared with young adults. In contrast, type I muscle fibre size seems to be largely sustained with ageing. The type I, or slow twitch fibres, are recruited first and, as such, are mainly responsible for endurance-type activities. The type II, or fast twitch fibres, are recruited later and predominantly responsible for higher intensity or highly fatiguing activities. The reduction in type II fibres may therefore result in a decline in muscle strength in the elderly and may decrease the ability to rise from a chair or to lift a heavy load.

The decline in type II muscle fibre size is reported in some studies to be accompanied by an age-related reduction in type II muscle fibre satellite cell content and function. These satellite cells are the stem cell of human muscular tissue and essential for skeletal muscle fibre growth, repair, and regeneration throughout human life. The specific reduction in type II muscle fibre satellite cell content and function could therefore possibly represent a key factor responsible for specific type II muscle fibre atrophy with ageing.

The primary cause of skeletal muscle loss is the disruption in the regulation of skeletal muscle protein turnover, leading to a negative balance between muscle protein synthesis and muscle protein breakdown.

In addition to the pronounced muscle atrophy, a reduction in the force per unit area of skeletal muscle is also observed at the single fibre and whole muscle level in the elderly. For instance, when the rat plantar flexor muscle group is electrically stimulated (eliminating the potential neural impairments in force production) and force is expressed relative to muscle mass (controlling for size), aged rats (24 months) exhibit a 34% reduction in 'muscle quality'.

5. Excitation–contraction coupling (E-CC) involves the physiological processes that convert the neural signal for muscle activation (i.e. the muscle fibre action potential) into muscle contraction and subsequently into force development. Briefly, the action potential spreads throughout the muscle via the t-tubular system, activating the voltage-sensitive dihydropyridine receptors, which subsequently open the ryanodine receptors. This releases Ca^{2+} from the sarcoplasmic reticulum (SR) that binds to troponin C creating cross bridge formation, leading to muscle contraction and consequently to force production. After the contraction phase, Ca^{2+} is returned to the SR by the SR Ca^{2+} pump, allowing the muscle to relax. Theoretically, disruption at any point in the E-CC process results in reduced muscle performance.
6. In addition to changes in the E-CC processes, there are several other physiological contributors to reduced muscle quality with one being age-related changes in the muscle architectural structure. Skeletal muscle displays a strong structure–function relationship by which several architectural characteristics factor into its functional capacity.
7. With regard to muscle energetics, the vast majority of studies have focused on the effects of ageing on aerobic metabolism (i.e. mitochondrial function or oxidative phosphorylation). There is evidence that aerobic capacity, measured by the peak treadmill oxygen consumption (peak VO_2), which is the maximal ability to use oxygen to meet the energy demands of physical activity, may decline at an accelerated rate already after the age of 20, with a rate up to >20% per decade in community-dwelling men and women over 70.
8. The vast range of motions and forces that humans can achieve arises from the activity of more than 600 skeletal muscles, which are under the control of the nervous system. After processing sensory information about the body and its surroundings, the motor centres of the brain and spinal cord generate neural commands that effect coordinated, purposeful movements. The process is complex, as the nervous system is a cellular network of up to 10 billion neurons and 60 trillion synapses communicating together. The discharge behaviour of these neurons, including the motor neuron, represents a complex interplay between the excitatory and inhibitory synaptic inputs they receive and the cells' intrinsic electrical properties. The patterns of interneuronal connections and communication, as well as the discharge behaviours, are not permanently fixed; they show variability and can be reorganized.
9. Motor systems are organized hierarchically, with each level concerned with a different decision. The highest and most abstract level, likely requiring the prefrontal cortex, deals with the purpose of a movement. The next level, which is concerned with the formation of a motor plan, involves interactions between the posterior parietal and premotor areas of the cerebral cortex.

10. The premotor cortex conveys the spatial characteristics of a movement based on sensory information arising from the posterior parietal cortex about the situation (i.e. the environment) and about where the body is in space. The lowest level coordinates the space and time details of the muscle contractions needed to execute the planned movement. These supportive motor regions include the contralateral sensorimotor cortex, supplementary motor area, and the cingulate cortex. Control circuits located in the cerebellum and basal ganglia are then initiated to trigger activity in descending motor tracts, which signals the spinal interneurons and lower motor neurons to contract skeletal muscle fibres to produce movement.
11. Mitochondria are important cellular organelles that are responsible for the production of energy by both aerobic and anaerobic respiration and oxidative phosphorylation.

Not only the mitochondrial content is important for elderly skeletal muscle performance, the mitochondrial function (i.e. the ability to produce ATP) is important as well. High-energy phosphates (i.e. ATP and creatine phosphate) provide the chemical energy necessary to satisfy the energy cost of cross-bridge cycling and ion pump activity during muscle contraction and are therefore important for performance.

12. The adult human skeletal system consists of 206 bones, as well as a network of tendons, ligaments, and cartilage that connects them. The skeletal system provides form, support, and stability to the body, and when coupled with the muscular system, it permits movement. The basic fundamentals of form-function relationships suggest that any fundamental change in form (e.g. skeletal alignment) will affect elderly skeletal muscle performance.

In addition to skeletal aspects, connective tissue changes are also occurring with advancing age. These age-related changes include a reduction in tendon stiffness and in Young's modulus (the ratio of stress, or force per unit area, and strain, which is the ratio of deformation over initial length), suggesting that a deterioration in tendon material properties accounts for most of the decline in stiffness. During locomotion, the muscle-tendon system functions as a spring when the muscle lengthens while activated, before subsequently shortening. Thus, this unit effectively act as a shock absorber (i.e. they cyclically absorb and recover elastic recoil energy). Accordingly, changes in tendon properties likely alter the muscle spring properties and affect the degree of shortening of muscle fibres and the rate of force development upon contraction and, as such, physical performance in older adults.

13. Next to the role of hormones, inflammation, and insulin resistance, other biological factors may also be involved in elderly skeletal muscle performance. Several studies emphasize the important role of genetics on physical performance later in life. For instance, a twin study on the role of genes in physical performance in elderly (>75 years) found that about 33–50% of the variation in physical performance in elderly women could be attributed to age-related genetic factors. An example of age-related gene modulations is the reduced expression of vitamin D, as a low vitamin D level is associated with lower muscle mass and impaired physical performance. Another example is the two-fold higher level of myostatin protein and myostatin mRNA in elderly, compared with younger controls, which was associated with lower fat-free mass. Myostatin is a protein that acts as a negative regulator of muscle growth and has been linked to the development of sarcopenia. Inhibition of myostatin has been suggested as a promising therapeutic therapy for sarcopenia, which could affect skeletal muscle performance.

14. The ageing process is associated with a decline in appetite and food intake known as anorexia of ageing. Approximately, 21% of the older adults present with anorexia of ageing, and it is even more prevalent in frail and institutionalized elderly people. Anorexia and subsequent weight loss have been associated with adverse health outcomes, such as falls, immobility, and sarcopenia. Anorexia is closely related to malnutrition, which is highly prevalent among hospitalized elderly patients. Collectively, both macronutrients and micronutrients play an important role in impaired skeletal muscle performance in elderly.
15. The loss of exercise capacity with ageing is the net result of lack of regular physical exercise (i.e. inactivity), age-related functional, metabolic, and structural changes in the skeletal muscle and the neuromotor control, and disease-related functional impairment resulting from catabolic effects of chronic systemic illness (e.g. heart failure, COPD, and cancer). Developing a clear understanding of the many factors affecting elderly skeletal muscle performance and physical function has major implications for scientists, clinicians, and health professionals who are developing therapeutic interventions aiming to enhance muscle function and/or prevent mobility and physical limitations and, as such, support healthy ageing.