DOI: 10.1111/apha.13086

EXACTA

ACTA PHYSIOLOGICA

Skeletal muscle in the fight against chronic diseases

The causes for the development of chronic diseases such as diabetes, cardiovascular disease or cancer are multifactorial and often influence each other. With increasing age, the risk for developing type 2 diabetes increases and the risk to suffer from cardiovascular and chronic kidney disease is increased once a patient is diabetic. Besides pharmacological treatment, there is one strategy to combat the development or progress of most chronic disease: physical activity. Research is going on to understand the impact of skeletal muscle and exercise on improving the health status in, for example, diabetes and cancer at the cellular and molecular level or signalling pathways. This review will give a short overview of the latest reports published in *Acta Physiologica* about the complex interplay of skeletal muscle, immune system, kidney and cardiovascular system in chronic diseases.

The skeletal muscle makes up about 40% of human body weight and therefore represents the largest organ of the body in non-obese individuals.[1,2] Skeletal muscles are divided into type I (slow-twitch) and type II (fast-twitch) fibres[3] and can provide either short-term maximum strength or endurance over long time periods.[2] Skeletal muscle represents the primary tissue that is responsible for postprandial glucose processing.[4] In addition to its role in locomotion, skeletal muscles are also fundamental for whole-body metabolic health. Skeletal muscle is also an endocrine tissue and plays a key role in regulating the metabolism by synthesizing and releasing humoral factors called myokines.[2,4]

Multiple factors cause loss of muscle: hormone imbalances and chronic inflammation as well as genetic factors, injuries and unfavourable lifestyle patterns. Loss of muscle mass comes along with loss of quality of life, mortality risk and disability.[2] Muscle atrophy is characterized by a disruption in skeletal muscle protein turnover, impaired phosphorylation of key proteins of skeletal muscle protein synthesis and diminished regenerative capacity.[5] The symptoms of muscle atrophy in most cases are temporary. For operations in ER, tourniquets are used to create a bloodless field for musculoskeletal reconstructive procedures.[3] Use of tourniquets is associated with muscle weakness, post-operative swelling, oedema and numbness.[6] The skeletal muscle type II fibres exhibit a severe structural damage, neuromuscular junctions show a dysfunction, and an inflammatory response occurs in this tourniquet-induced ischaemia reperfusion injury. Although sometimes a full recovery cannot be achieved, the anti-inflammatory drug dexamethasone improved neuromuscular function and skeletal muscle contraction in mice that are treated with the drug in the first week after surgery.[3,6]

However, muscle loss in older age cannot be avoided completely. By the age of 50, humans have lost about 10% of their muscle mass and the process continues with one more per cent for every further year.[5] The sensitivity of aged muscle to stimuli for the maintenance of muscle is impaired.[2] Ageing comes along with cellular damage and a decline in physical function over time due to a decline in skeletal muscle mass and muscle function, called sarcopenia.[5] At the molecular level, ageing is associated with an impairment of the Notch, Wnt and MRF signalling pathways.[5] The process of ageing is not only caused by metabolic dysregulation, but is also affected by environmental influences like nutrition and physical activity.[2]

To date, no successful pharmacological treatment of sarcopenia is available. Thus, exercise is still the most effective way to counteract muscle loss. The positive effect of exercise is very likely associated with additional health benefits, for example increase in strength and reduction in blood pressure and glucose tolerance.[2] To analyse how exercise increases muscle mass and whole-body health in older subjects on the molecular level, the effect of striated muscle activator of Rho signalling (STARS) was examined. STARS is highly expressed in cardiac, skeletal and smooth muscles, increases actin polymerization and is likely involved in muscle cell development and repair.[5] In older subjects, STARS is downregulated at the protein level, hypothesizing that STARS can be activated in response to exercise. However, no changes in the level of STARS signalling pathway proteins of older humans were detected in response to an acute bout of exercise, suggesting that there are more, so far uncharacterized factors that act at the molecular level.[5]

However, when examining age-related muscle loss one has to be aware of the fact that there are some difficulties in discriminating between age-related physiological changes and disease-related processes in physiology of humans. ROS metabolism in mitochondria is for example affected in a similar way by either diabetes mellitus or age-related biochemical processes.[7]

Physical inactivity causes a decline in insulin sensitivity and a decrease in insulin-stimulated glucose uptake. This results in a reduction of muscle mass and increased obesity

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and often in the development of chronic diseases.[1,8] Exercise improves whole-body glucose tolerance and increases the insulin sensitivity.[9] At the molecular level, muscle contraction activates the transport of glucose. Exercise increases the insulin sensitivity in skeletal muscle. This results in a decrease in the insulin concentration needed to induce 50% of the maximum response.[10] Regular physical activity reduces the risk of several chronic diseases, for example type 2 diabetes, cardiovascular diseases, dementia, depression and several types of cancer.[9,11] Both, young and old subjects benefit from endurance training, for example increased insulin sensitivity. Sogaard et al analysed whether high-intensity interval training (HIIT) has the same effect. People aged about 63 who performed a 6-week HIIT showed increased insulin sensitivity, reduced cholesterol levels and lost body weight. HIIT therefore represents an alternative to endurance training.[8]

Electrical pulse stimulation (EPS) serves as an in vitro model for exercise in skeletal muscle. Using EPS can help understanding the impact of skeletal muscle on metabolic regulation by analysing a complex multidirectional cross-talk between different tissues.[9] Skeletal muscle is an endocrine organ. The humoral factors that are expressed and released are termed myokines.[1] Myokines are part of a complex network and can either act locally or on other organs, such as liver, adipose tissue, brain and pancreas.[1,9,11] Synthesis and release of myokines are regulated by differentiation, induction of insulin resistance or exercise.[4]

The expression of myokines after exercise is enhanced.[1] Circulating IL-6 is for example increased following exercise due to increases in skeletal muscle IL-6 synthesis and secretion.[4] Very likely, the contractile activity of a skeletal muscle influences its secretory function. The beneficial health effect of exercise might be induced by myokines released by contracting skeletal muscle. On the contrary, altered secretion of myokines likely increases the risk of cardiovascular diseases and type 2 diabetes.[1,11] However, in most cases, the contribution of myokines induced by physical activity to the development of diseases so far remains unexplored at the molecular level.[1] For better understanding the multifaceted interplay of exercise physiology and to identify novel myokines, the EPS of cultured skeletal muscle cells is a promising tool.[9] Electrical pulse stimulation enables mRNA expression studies, signalling pathway and protein expression analyses and the detection of metabolic effects. The replacement of dysfunctional muscle tissue in terms of regenerative medicine and tissue engineering can be possible future applications of EPS.[9]

Although most myokines are upregulated after exercise, several are also downregulated: myostatin is predominantly expressed by skeletal muscle and its expression is downregulated in response to long-term physical activity.[4,11,12] Myostatin plays a role in skeletal muscle homeostasis and is a negative regulator of muscle growth.[11,12] Mutations in the myostatin gene cause a hypermuscular phenotype, known from the Belgian Blue breed cattle.[11] Mice that did not express myostatin showed reduced adipose tissue and also improved insulin sensitivity.[12] The expression of myostatin in skeletal muscle cells was associated with impaired insulin sensitivity.[11] Thus, myostatin affects glucose metabolism and the expression of myostatin in muscle was higher in type 2 diabetes subjects.[12]

A reduced response of skeletal muscle tissue to insulin, called insulin resistance, is likely the primary defect leading to development of type 2 diabetes.[4,13] In a second step, progressive β-cell failure occurs and type 2 diabetes develops.[13] Diabetes mellitus is the most prevalent endocrinopathy in the world and often results in chronic kidney disease.[14] Diabetes leads to numerous metabolic disturbances such as enhanced hepatic gluconeogenesis and impaired glucose uptake.[1] A deficit of regular physical exercise results in a decline in insulin sensitivity and reduces insulin-stimulated glucose uptake and is one of the main factors causing a chronic disease such as diabetes.[1] A combined endurance and strength training is the most beneficial type of exercise to improve glycaemic control.[1] Nowadays, studies of the impact of type 2 diabetes on myokine production are limited. Skeletal muscle from diabetic and non-diabetic subjects was differentiated to myotubes to study their secretory profile. Myotubes from type 2 diabetes patients showed decreases in glucose uptake and glycogen synthesis. In parallel, they also showed differences in the secretory profile compared to non-diabetic subjects; for example, the amounts of IL-6, IL-8 and TNF-α were increased. This leads to the suggestion that the altered secretion of a number of myokines in patients plays a role in the response of skeletal muscle to type 2 diabetes.[4]

Similar to myokines, thyroid hormones exhibit a role in glucose homeostasis. As diabetes mellitus has been associated with thyroid dysfunctions, it was suggested that thyroid hormones can be used to treat glycaemia and insulin resistance.[14] Diabetic rats showed decreased thyroid function and a disrupted function of tissues involved in glucose homeostasis. Due to an increased amount of inflammatory cytokines, a chronic low-grade inflammation state arose and even might be causative for the above-mentioned disrupted functions. These symptoms lead to the assumption that a deficit of thyroid hormones might be associated with insulin resistance in skeletal muscle. Therefore, thyroid hormones might be a therapeutic treatment to improve glycaemia and insulin response and combat the inflammation state. In diabetic rats, treatment with triiodothyronine (T3) reduced glycaemia and improved insulin sensitivity. The inflammatory cytokine expression in the skeletal muscle

was negatively influenced by T3.[14] The result confirms that thyroid hormones are potential therapeutics for the treatment of diabetes.

Another proposed strategy to treat insulin resistance in skeletal muscle and thereby diabetes is the activation of the NAD^+-dependent protein deacetylase sirtuin 1 (SIRT1).[15] SIRT1 plays a role in changes in cellular energy status to adaptive changes in insulin signalling. The activity of SIRT1 is enhanced in skeletal muscle in calorie restriction and causes beneficial effects on glucose uptake stimulated by insulin. While lifelong overexpression of SIRT1 in skeletal muscle did not improve insulin resistance, it was suggested that a temporal overexpression of SIRT1 in muscle of adult mice would affect insulin sensitivity of skeletal muscle. However, this hypothesis could not be confirmed.[15]

The risk of cardiovascular disease is increased in patients with chronic kidney disease, due to a disturbed cardiac metabolism, a reduced glucose utilization and increase in the uptake of free fatty acids.[16,17] A reduction in vessel relaxation, which is so far reported for vessel ageing, was analysed in terms of chronic renal failure.[18] The analysis revealed new insights in arterial contractility in chronic renal failure in rats. The arteries showed an increase in stiffness, but the reasons for this are not completely understood. The contraction and relaxation rates were reduced in rats suffering from chronic renal failure. This might be due to a reduced intracellular Ca^{2+} clearance in vascular smooth muscle cells.[17,18]

Diabetes is also associated with an altered signalling between cardiomyocytes and coronary arteries, resulting in cardiovascular diseases. The Zucker diabetic fatty rat model of type 2 diabetes exhibits a reduced anticontractile influence of cardiomyocyte-rich perivascular tissue. Although the cause-effect relationship remains unclear, it was suggested that the dysfunctional crosstalk between cardiomyocyte-rich vascular tissue and coronary arteries exhibits changes in the production and release of vasoactive metabolites and that this is causative for the development of cardiovascular complications in type 2 diabetes.[16]

In kidneys of patients suffering from hypertensive chronic kidney disease, the level of the transcription factor HIF-1α is increased.[19] HIF-1 is a primary actor for sensing and responding to low oxygen.[20] In animal studies, the overactivation of HIF-1α in renal epithelial cells contributes to chronic kidney disease, suggesting that HIF-1α plays a role in initial glomerular injury and causes hypertension and progression to renal fibrosis.[19] The regulation by HIF-1 was also analysed in terms of skeletal muscle. During exercise, the skeletal muscle gets hypoxic and the HIF-1 pathway gets activated. Under normoxic conditions, a factor called PHD2 targets HIF-1 for proteasomal degradation. In experiments with mice, HIF-1 can be stabilized by knocking out PHD2. By doing so, it is possible to specifically examine the impact of HIF-1 without the need of hypoxia or exercise as trigger.[20]

Humans may lose muscle mass in severe chronic pathological conditions. Chronic diseases such as cancer induce cachexia.[21] Skeletal muscle wasting is a major problem of cancer.[22] Cachexia leads to weakness and physical disability and causes a reduction in quality of life, a reduced treatment tolerance response to therapy and thereby reduces the survival rate in cancer patients. People suffering from cancer and cancer-associated cachexia also have a higher risk to develop further chronic diseases such as diabetes, cardiovascular diseases and depressions. By now the molecular mechanisms, how cancer impacts skeletal muscle wasting is poorly characterized.[21,22] Skeletal muscle atrophy in cancer cachexia might be induced by a disturbed balance between protein synthesis and degradation.[21] Furthermore, a systemic inflammation was reported to be a major mediator of cancer cachexia. Cytokines such as IL-6, IGF-1/2, TNF-α and myostatin are released by the tumour, the immune system or the skeletal muscle. Besides the fact that an active lifestyle prevents cancer, it was suggested that long-term endurance training as a non-pharmacological approach prevents cancer-induced muscle wasting, for example by having an anti-inflammatory impact.[21,22] The reduction of TNF-related weak inducer of apoptosis (TWEAK) in skeletal muscle correlates with the reduction in tumour growth.[22] TWEAK is a regulator of the skeletal muscle mass.[21] Muscle-derived TWEAK increases cancer growth. Endurance training lowered the TWEAK level in the serum and in muscle. Thus, exercise training can counteract cancer-associated muscle loss among other things by preventing tumour-induced TWEAK signalling.[21,22]

In sum, current research reveals a beneficial impact of regular physical activity on the development and progression of chronic diseases. In particular, the discovery of myokines was a breakthrough in the understanding of how skeletal muscle communicates with other human organs. New insights into the regulatory effect of skeletal muscles to human organs serve as a platform for the generation of novel pharmacological treatment options.

CONFLICT OF INTEREST

None.

FUNDING INFORMATION

Bundesministerium für Bildung und Forschung (BMBF) iPS-Profiler, FKZ: 01EK1612B; Bundesministerium für Bildung und Forschung SysToxChip FKZ: 031A303A.

ORCID

R. Mrowka http://orcid.org/0000-0002-0991-3418
A. Westphal http://orcid.org/0000-0002-9626-2624

R. Mrowka
A. Westphal
Klinik für Innere Medizin III, AG Experimentelle Nephrologie, Universitätsklinikum Jena, Jena, Germany
Email: ralf.mrowka@med.uni-jena.de

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