Exercise training to reduce cardiovascular risk in patients with metabolic syndrome and type 2 diabetes mellitus : how does it work?

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1. Abstract

Metabolic syndrome (MetS) - a clustering of pathological conditions, including abdominal obesity, hypertension, dyslipidemia and hyperglycaemia - is closely associated with the development of type 2 diabetes mellitus (T2DM) and a high risk of cardiovascular disease.

A combination of multigenetic predisposition and lifestyle choices accounts for the varying inter-individual risk to develop MetS and T2DM, as well as for the individual amount of the increase in cardiovascular risk in those patients. A physically active lifestyle can offset about half of the genetically mediated cardiovascular risk. Yet, the extent to which standardized exercise programmes can reduce cardiovascular risk differs between patients. Exercise parameters, such as frequency, intensity, type and duration or number of repetitions, differentially target metabolic function, vascular health and physical fitness. In addition, exercise-induced molecular mechanisms are modulated by other patient-specific variables, such as age, diet and medication.

This review discusses molecular and cellular mechanisms underlying the effects of exercise training on cardiovascular risk specifically in patients with MetS and T2DM.

key words: exercise training, diabetes, signalling, glycaemic control, inflammation

2. Introduction

Patients with metabolic syndrome (MetS) suffer from a number of pathologic conditions, including abdominal obesity, hypertension, dyslipidemia and hyperglycaemia. Those factors strongly predispose MetS patients to type 2 diabetes (T2DM) and cardiovascular disease. A chronically positive caloric balance leads to overloading of adipose tissue lipid storage capacity. As a result, free fatty acid (FFA) - induced cellular stress responses feed, among other, hepatic and systemic inflammatory processes and a reduction in skeletal muscle insulin sensitivity.[1] Products of fatty acid metabolism and advanced glycated end-products, accumulating due to hyperglycaemia, upregulate and activate various pattern recognition receptors, thereby aggravating cytokine synthesis in innate immune cells and inflammatory aspects of vascular disease.[2-7]

Activation of innate immune cells feeds back into their metabolism: all cellular processes, including mitochondrial adenosine triphosphate (ATP) generation, take second place to the perceived need to defend against a pathogen. Hence, a "broken" Krebs cycle was observed in activated, pro-inflammatory "M1" type macrophages.[8, 9] Krebs cycle intermediates then feed synthesis of pro-inflammatory molecules instead of ATP.[10]

Metabo-inflammatory processes are strongly influenced by the patient´s genetic and epigenetic background as well as their lifestyle choices (***Figure 1***). Importantly, even in patients with unfavourable genetic background a healthy lifestyle can significantly reduce cardiovascular risk to levels below that of patients with a beneficial genetic background but unhealthy lifestyles.[11] Exercise training (ET) is an integral component of a lifestyle benefitting cardiovascular health with the ability to improve distinct target parameters (glucose control, lipid status, physical fitness).[1, 12, 13] Interestingly, exercise parameters – frequency, intensity, type and duration - appear to target different physiological responses. Endurance training usually leads to improved oxygen uptake and vascular function, while resistance training with increasing workloads causes skeletal muscle hypertrophy. Hence, combined endurance/resistance training programmes have been reported superior for targeting glycaemic control, anti-inflammatory effects or body composition.[12, 14-19] In the accompanying paper by Kemps et al. (pp XXX of this issue), target parameters of ET in T2DM patients and suitable exercise parameters are discussed from a clinical perspective, while here we discuss the underlying molecular principles.

3. Contraction-induced molecular mechanisms

During the contraction cycle, intracellular cytoplasmic calcium levels fluctuate and ATP is dephosphorylated by myosin (***Figure 2***). The relative kinetics of those two signals can be modulated

by type, intensity and duration of exercise as well as by the cellular content of fuels such as glycogen, and impacts on exercise effects. Other factors, such as sympathetic activation take a modulating role (***Figure 2***).

Within the contracting myocyte, the increase in adenosine monophosphate (AMP) in relation to ATP is sensed by the AMP-activated kinase (AMPK).[20] AMPK activation upon rise of the AMP-to-ATP ratio generally results in an increase of processes providing ATP, such as mitochondrial beta-oxidation and glucose uptake into the cell, and in downregulation of competing ATP-consuming processes not immediately needed for survival, including fatty acid biosynthesis.[21-25] Exercise intensity affects the choice of substrates with fatty acid oxidation increasing until about 60% of the individual´s maximal oxygen uptake capacity (VO_2max), then reaching a plateau. Glucose utilization instead increases further with increasing exercise intensity. Thus, at high exercise intensity, glucose outweighs FFAs as substrate for mitochondrial oxidation in healthy individuals.[26, 27]

One important downstream mediator of AMPK signalling is the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α target genes mostly serve mitochondrial biogenesis and FFA oxidation, but extend to anti-inflammatory processes, muscle growth and angiogenesis.[28-30] Differential effects of exercise type and intensity on skeletal muscle growth versus energy metabolism are mediated by differential PGC-1α splicing.[31] The two prominent PGC-1α isoforms - PGC-1α1 and PGC-1α4 - activate a large number of genes in common, but each isoform also governs their own specific gene set.[31] PGC-1α1 regulates genes involved in mitochondrial oxidation and fuel supply, while PGC-1α4 also regulates genes mediating skeletal muscle hypertrophy, including *IGF1* and myostatin.[31] Consistently, resistance exercise or a combination of resistance and endurance exercise increase expression of PGC-1α4 more than endurance training alone.[31]

Contraction-related calcium fluxes modulate AMPK signalling at several levels. Calcium-dependent kinases phosphorylate AMPK, thereby modulating its activity.[32] Calcium also increases the activity of the protein kinase B (PKB), which relieves the inhibition of the mammalian target of Rapamycin (mTOR) by AMPK.[33] Resistance training also activates mTOR leading to the induction of protein synthesis serving skeletal muscle hypertrophy.[34] Intriguingly, glucose tolerance remains normal in PKB overexpressing mice on a high-fat diet, but not in the overfed wild type controls.[35] Therefore, the interplay between AMPK signalling (which favours glucose and FFA utilization for ATP synthesis) and PKB/mTOR signalling (which prefers protein synthesis) represents another mechanism explaining why combining improved glucose handling in patients with T2DM through combined resistance training and endurance training.[33-41]

Systemic inflammation is a hallmark of MetS, T2DM and coronary disease. ET programs have repeatedly been shown to reduce systemic inflammation, as well as the activation state of innate immune cells.[42, 43] One mechanism, by which ET can relieve the inflammatory load in T2DM could be an increased FFA uptake into the skeletal muscle. This reduces plasma FFA levels and their activation of toll-like receptors (***Figure 1***).[4-7] In line with this, recent research has pointed to the mitochondria linking metabolic and anti-inflammatory effects of ET.[10, 44] AMPK signalling is impaired in inflammatory activation of macrophages, caused by saturated fatty acids.[6, 7] Improved FFA removal by the active skeletal muscle might therefore also act to relieve AMPK activity and improve mitochondrial oxidative function.[13, 45] In line with this, skeletal muscle mitochondrial oxidative capacity - more so than mitochondrial density - appears to mediate the beneficial effects of exercise on T2DM-associated metabolic and cardiovascular structural and functional impairments.[46, 47]

Skeletal muscle cells release a number of mediators during or upon exercise, which link local contractile activity to systemic inflammatory state. Examples include not only cytokines and growth factors, but also metabolites, long and short non-coding RNAs and cell-derived vesicles.[48] Brain-derived neurotrophic factor (BDNF) and interleukin-6 (IL-6), support AMPK signalling and result in improved FFA oxidation.[45] The resulting reduction of pattern-recognition receptor ligands in long-term ET programmes may contribute to the shift in the cytokine profile.[2, 4, 13] Long and short non-coding RNAs (e.g. microRNA) are released into the circulation as a means of inter-organ communication and differ with exercise parameters and the patient´s training status and underlying disease.[49-55] Associations between microRNA (miRs), transcriptional regulators (HDAC4, NRF1) and levels of circulating effectors (IGF-1, IL-10, testosterone) support the notion of distinct regulatory networks activated by acute resistance versus endurance exercise.[49, 53] Of note, alterations in circulating miR levels do not simply mirror local tissue miR levels, but resemble an integration between release and uptake by several different tissues.[51, 55, 56] Hence, better integrated OMICs studies - accounting for the patient´s genetic makeup, pathology, medication, training status and exercise parameters, combined with assessment of nucleic acids, (lipo-)proteins and multi-molecular complexes, such as extracellular vesicles, in various tissues will be more informative on systemic regulatory mechanisms than assessment of only individual players. [45, 48]

4. Mechanical forces mediating exercise-induced signalling mechanisms

Exercise acutely applies mechanical strains and stresses to the muscle itself, but also to the heart and vasculature.[57] Within the muscle, not only myocytes, but also fibroblasts, macrophages and vascular cells respond to mechanical forces.[58, 59] In the contracting muscle, tension changes are sensed by focal adhesions and ion channels and initiate signalling cascades resulting in altered deposition and remodelling of extracellular matrix (***Figure 1***).[58, 60, 61] Force intensity appears to

modulate individual signalling mechanisms, as has been shown for kinases downstream of MAPK and for the matrix-metalloprotease-2, which can impact on both, matrix stiffness and angiogenesis.[59, 61-64] Low-intensity and endurance training, especially in trained individuals, stimulates MAPK-ERK to induce cell proliferation and survival, while high-power resistance training activates MAPK-JNK which is associated with pro-apoptotic functions.[65-67] Differential effects in skeletal muscle fibre types might exist and other cues such as hormones are likely to interact.[59]

The heart releases – among other factors - natriuretic peptides in response to strain. Natriuretic peptides can induce lipolysis in human adipocytes and increase plasma non-esterified fatty acids, thus potentially linking mechanical forces in ET to metabolism.[68, 69] In support of this claim, natriuretic peptide plasma levels are lower in persons with obesity, MetS and T2DM.[70-73] An improvement of exercise capacity was associated with increased levels of B-type natriuretic peptides in heart failure patients.[74] Whether natriuretic peptides are causally involved in ET metabolic effects in T2DM patients, or whether the above-mentioned studies rather point to non-causal associations in responsive individuals remains unanswered. A recent murine study could not observe exercise-mediated increases in natriuretic peptides.[75] Neprilysin inhibitors might provide a pharmacological support strategy here and can help to unravel mechanistic links.[76]

In the local and systemic vasculature, shear stress increase during exercise mediates endothelial survival and function, including regulation of vascular tone and angiogenesis (***Figure 2***).[77, 78] Flow patterns and velocity distinctly affect cellular signalling mechanisms via inter-cellular junctions and luminal membrane proteins, including syndecans and glypicans which connect to the glycocalyx.[79-84] The probably best-studied response of endothelial cells to physiological shear stress is the synthesis of nitric oxide (NO). The transcription factor KLF2 links the mechanosensors to expression of the endothelial NO synthase, while kinases, such as PKB, and Ca^{2+} entry through ion channels enhance its activity.[79, 82, 83, 85-87] In addition, lower superoxide generation via NADPH oxidases and mitochondria together with enhanced superoxide dismutation protect NO levels.[88-90] Hence, vascular NO bioavailability is increased under atheroprotective flow. NO not only induces vasorelaxation and anti-thrombotic endothelial mechanisms, but also activates protective enzymes such as SIRT1.[91-93] Apart from eNOS, KLF2 also influences the release of inflammatory cytokines and adhesion molecules, which are involved in vascular inflammation.[94, 95] Hence, shear stress crucially mediates anti-atherosclerotic effects of regular ET on the vasculature in T2DM and MetS.[96-98]

5. Exercise-induced adrenergic signalling mechanisms

Sufficiently intense exercise increases adrenergic signalling, which governs not only adaptations in cardiac and skeletal muscle contraction force and perfusion but also metabolic adjustments.[99-104] These include an initial reduction in insulin release (required for glucose release from the liver),

increases in adipocyte lipolysis (resulting in the release of FFAs) and glycogenolysis within skeletal muscle (providing an endogenous fuel). Epinephrine and norepinephrine levels increase in T2DM patients during exercise to a similar or even greater extent than in healthy controls, albeit slower and more prolonged.[105] This might explain slower FFA release into the plasma in response to moderate-intensity endurance exercise in T2DM patients observed in one study.[106] Others reported a normal increase of norepinephrine levels during acute exercise in T2DM patients with normal heart rate response, but only a small increase in epinephrine.[107]

A bout of acute endurance exercise initially decreases plasma glucose in T2DM patients but not in non-diabetic controls. Further, the subsequent increase in plasma glucose occurred earlier and was greater compared to non-diabetic controls.[108-111] Whether this was due to likely through reduced insulin sensitivity remains to be discussed, as a large part of exercise-mediated glucose uptake into skeletal muscle cells is insulin-independent.[25, 112]

While catecholamines serve to adapt the cardiovascular system to an acute challenge, chronic employment of catecholamines to compensate a reduction of cardiac output cause systemic dysregulations in signalling mechanisms, as seen in heart failure. Regular ET can normalize catecholamine levels at rest, also in T2DM.[113, 114]

The exact mechanisms by which acute and regular exercise modulate the release and uptake of glucose and FFA in T2DM patients still remain to be elucidated. Heterogeneous observations are likely through individual combinations of patient characteristics (state of insulin insensitivity and chronotropic competence) and exercise parameters (type, intensity).[104, 105, 115] Considering the wide range of functions regulated by the various adrenergic receptors beyond exerting chronotropic and inotropic effects – including lipolysis, thermoregulation and vasorelaxation – further studies also need to look at the role of genetic variations in genes encoding components of the adrenergic system when assessing the effect of exercise programmes. [116-118]

6. Interaction of exercise with other determinants

A number of modifiable and non-modifiable variables interact with the individuals´ response to exercise, including diet, pharmacotherapy, age, sex and the genetic background (***Figure 2***). There is a definitive lack of knowledge regarding most of these interactions. Hence, further research into those matters is warranted to provide better guidance in combining medication and diet with personalized exercise programmes to optimize the benefit for the individual patient.

6.1. Modifiable determinants

Interventional lifestyle change programmes in patients with MetS and T2DM recommend to simultaneously target diet and exercise to achieve a larger effect on body weight reduction and glucose handling.[119] It is currently under debate, however, how exactly an optimal diet for patients with T2DM should be composed.[120] Recent evidence has led to a change in recommendations, now avoiding simple fat reduction, but focusing more on the quality of each nutrient component - i.e. complex versus refined carbohydrates and sugars, saturated versus mono- and polyunsaturated fats and trans fats.[121] While large studies, such as the PURE study, can help provide associative evidence on diet and cardiovascular mortality[121], there is still too little information on the interaction between diets of different micro- and macronutrient composition and exercise. Diet and exercise can interact on several mechanistic levels: Diet and frequency of exercise influence intracellular glycogen content, which in turn modulates the activation of AMPK.[122-126] Further, low-to-moderate and high intensity interval training have distinct effects on insulin sensitivity. Dietary supplements, such as L-carnitine, affect lipid oxidation during exercise in healthy athletes, but it also conveys cardiovascular risk by yet unknown mechanisms.[127, 128] Further attention in this respect needs therefore also been given to the gut miocrobiome, which is affected by both, diet and exercise and via its metabolites modulates cardiovascular risk. [129, 130]

Interaction of pharmacologic treatment of MeTS and T2DM, or their cardiovascular co-morbidities with exercise effects have only recently gained attention. Hence, knowledge is still severely limited and mostly regards specific interactions.[131] Exercise-induced hyperglycaemia is normally counteracted by hepatic glucose release. Sulfonylureas, and potentially also other insulin secretagogues, might therefore increase hyperglycaemic risk during exercise, albeit less so for metformin.[132-134] Sodium-glucose co-transporter type 2 inhibitors may provide an alternative treatment to accompany exercise for T2DM patients.[135] Beta-blockers reduce sensing of hypoglycaemia in diabetic patients, but might - counter-intuitively - increase liver glucose production.[136, 137] In patients requiring insulin, long- and short-acting formulations can be used to avoid exercise hyper- and hypo-glycaemia.[138-140] Nevertheless, blood glucose levels need to be well monitored when combining these pharmacologic treatments with exercise in T2DM patients. An impairment of mitochondrial function by metformin has been observed, but it is currently unknown whether exercise can still improve mitochondrial function and mass despite metformin treatment in T2DM patients and which exercise conditions might be best suited in combination with this important pharmacological tool, also acknowledging sex-specific metformin excretion.[141-144] Statins, while lowering plasma cholesterol levels, are also associated with an increased risk for T2DM.[145, 146] Addition of exercise to statin treatment is more effective in improving insulin sensitivity, reducing inflammation, and increasing exercise capacity than statin treatment alone.[147] Individual adaptation

of statin type and dose, as well as vitamin D or Q10 replacement might potentially help to limit statin-induced muscle pain potentially help maintain exercise adherence.[148]

In contrast to genetic features, epigenetic markers can be modified (e.g. by diet and exercise), thus modulating metabolic risk in the offspring.[149] Vice versa, epigenetic mechanisms might determine the response to exercise, and targeting these might provide a further means to optimize ET response.[150, 151]

6.2. Non-modifiable determinants of exercise effects

Sex-specific effects in substrate utilization and muscle anabolism at different exercise intensities are known well from healthy athletes and have recently also been observed in patients with MetS and T2DM.[99-103, 152-161] On the other hand, fasting glucose and triglyceride levels improved significantly in response to a 12-week endurance training programme, regardless of sex in middle-aged T2DM patients.[161] Sex hormones, with estrogen the most intensely studied, affect vascular function, fibrosis and immunity, thus conferring cardiovascular protection.[162-169] This effect deteriorates in post-menopausal women, but can be preserved to some degree by regular ET.[166, 170]

Exercise-mediated improvements in glucose handling and insulin sensitivity is less efficient in older than in younger mice and humans.[171] Moreover, age modulated the hypertrophic effects of resistance training.[172] Adrenergic β2-receptor sensitivity, which falls sharply with advancing age, has been postulated as a responsible factor. However, treatment of older diabetic mice with a β2-agonist improved insulin sensitivity, indicating that age-associated loss of β2 sensitivity can be overcome pharmacologically.[171]

Response to exercise in patients with MetS and T2DM is also affected by the patient´s genetic makeup. Relevant mechanisms include the actual contraction process and metabolic adaptations to acute exercise[173, 174], the regenerative phase where exercise-induced muscle damage is repaired[175] and metabolic processes take place[118, 176, 177], as well as structural and metabolic adaptations to regularly repeated exercise.[178, 179] A recent study in over 2,800 individuals identified genes determining the success of lifestyle-mediated as well as pharmacologic interventions to improve insulin sensitivity, including the genes for hepatocyte nuclear factor 4α (*HNF4*) and neuronal differentiation 1 (*NEUROD1*).[180] Genetic predisposition might also modulate effects and side-effects of pharmacological treatments, as shown for statins, metformin and sulfonylureas.[141, 143, 181-184]

Murine studies point to the bi-directional interaction between voluntary wheel running and genetic mechanisms in determining VO_2max, thus linking genetic background with adherence.[185, 186] Since findings in mice cannot be directly translated to humans with their high diversity of genetic background, pathologies and life styles, big-data based methodologies are warranted in future

studies to better delineate the interaction between individual modifiable and non-modifiable factors influencing the patients´ response and adherence to exercise.

7. Conclusions

In conclusion, regular ET exerts pleiotropic effects, beneficial not only to metabolic, but also to cardiovascular endpoints in patients with MetS and T2DM. Exercise parameters, such as type, intensity and duration modulate effects on individual clinical target parameters. In addition, the patient's individual genetic background, as well as sex, age, diet and medication interact with exercise and confer risks as well as effectiveness to meet treatment goals.

Future studies need to delineate these multi-dimensional interactions and enable the delivery of personalized exercise programmes. Novel data exploitation methods in combination with telemedicine approaches can help to deal with the high degree of inter-individual variation in a human population as well as the difficulties to standardize lifestyle interventions. In addition, target parameters other than HbA_{1C} need to be taken into consideration when aiming to tackle cardiovascular risk, among them inflammation and blood pressure control.

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Conflicting Interests

The authors declare no conflicting interests.

9. Figure Legends

Figure 1: Effects of an exercise programme on target treatment parameters in T2DM and MetS are affected by modifiable and non-modifiable, patient-related parameters, in addition to exercise-related parameters.

Figure 2: Exercise-induced stimuli, such as calcium fluxes and ATP-to-AMP conversion initiate signalling events favouring substrate uptake and oxidation, and the synthesis of mitochondrial and contractile proteins. Systemic inflammatory status is improved by reduced circulating levels of fatty acid metabolites and glycated end-products and altered paracrine spectra of myocytes and immune cells. Mechanical forces initiate muscle and vascular remodelling and vascular nitric oxide availability. Jointly, those mechanisms lead to reduced plasma levels of LDL, glucose and inflammatory mediators and to improved vascular function. Depending on the individual´s age, sex, the parameters of the exercise programme, genetic background and medication, each of the listed mechanisms may be modulated, affecting the individual effect of ET.

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