Muscle: An endocrine organ linking physical activity and development of chronic non-communicable diseases/diabetes mellitus

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Abstract

Sedentary lifestyle is one of the principal causes of non-communicable diseases worldwide. Recently, muscles have been recognized as an important source of cytokines and myokines, molecules with autocrine, paracrine, and endocrine function, and far-reaching effects. It has been postulated that muscles through cytokines can modulate low-grade chronic inflammation, a feature of non-communicable diseases, such as type 2 diabetes, and therefore play an important role in disease postponement and successful treatment. Therefore, physical activity is an integral part of treatment guidelines for type 2 diabetes. Despite increasing evidence of anti-inflammatory effect of PA, much more research is needed to pinpoint the type and intensity of activity with the largest anti-inflammatory effect, as well as the type of patients which would benefit most from this approach, especially in terms of improvement of cardiovascular outcomes.

Key words: Cardiovascular outcome; chronic inflammation; diabetes type 2; muscles; myokines

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1. Introduction

Approximately 50% of total body weight consists of roughly 600 mainly skeletal muscles. Recently, endocrine function of skeletal muscles has become recognized, and more and more muscle-derived factors termed myokines with autocrine, paracrine, and endocrine function are being detected [1]. Mentioned myokines potentially have far-reaching effects on non-muscle tissue and thereby could provide a molecular link between muscle function and chronic non-communicable diseases [2,3].

Physical inactivity is one of the leading causes of deaths that can be prevented worldwide [4]. A sedentary lifestyle is estimated as being the principal cause for approximately 21–25% of breast and colon cancer burden, 27% of diabetes, and approximately 30% of ischemic heart disease burden, respectively. Furthermore, it may also play a role in the development of neuropsychiatric disorders [5-13].

A persistent, chronic inflammation is one of the prominent features of physical inactivity, which potentiates the development of insulin resistance, atherosclerosis, malignant growth, and cell degeneration [14]. It has been related to an excess of adipose tissue and production of the pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. Recently, additional source of pro-inflammatory cytokines has been found in skeletal muscles [15]. For example, the reduced expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) in inactive skeletal muscle leads to a low-level inflammatory response, which then has negative impacts on other tissues such as pancreatic β-cells [16]. In addition, PGC-1α reduces the activity of the nuclear factor-κB (NF-κB), the main regulator of pro-inflammatory gene expression [17]. Therefore, through production of pro-inflammatory cytokines, inactive muscles might negatively affect other organs, and ultimately, lead to disease development [18].

The beneficial effects of exercise transcend function of skeletal muscles. Moderate exercise has been shown to increase life span and improve neuromuscular and neurological performance in animal models, while in humans, it contributes to improvement of glycemic control, hyperlipidemia, and hypertension [19]. Large population observational studies consistently show reduced inflammatory biomarkers in adults with higher levels of physical activity and fitness, even after adjustment for potential confounders [20,21]. Many of these effects occur also in elderly individuals who started physical activity at an advanced age highlighting the efficacy and potency of exercise as an intervention for the prevention and/or treatment for various diseases; one of such examples being type 2 diabetes [22].

To date, the molecular mechanisms that link physical activity to health remain yet not fully elucidated. Nevertheless, several hypotheses have been proposed. For example, the exercise-related reduction in systemic inflammation being among the most revisited ones [23] and involving the muscle-fat crosstalk through the network of myokines and cytokines [24], such as IL-6 and IL-15. Regular physical activity acutely increases the release of adrenaline, cortisol, growth hormone, prolactin, and other factors with immunomodulatory effects [25,26]. Importantly, however, long-term training is associated with decreased circulating levels of the stress hormones. Moreover, exercise reduces the expression of Toll-like receptors at the surface of monocytes that have been implicated as mediators of systemic inflammation [27]. On the other hand, high intensity exercise bouts trigger systemic inflammation, lead to a subsequent immunodepression, and thus can increase the risk for infections [28]. Muscle function, inflammation, and exercise are hence intrinsically linked in a complex manner [29]. Induction of beneficial versus detrimental effects therefore seems highly context-specific and might depend on the amplitude and frequency of exercise as well as variables in secretion.

Acute exercise leads to an increase in IL-6, magnitude of which is type and duration of exercise, glycogen content, and involved muscle related. This further leads to increased hepatic glucose production and adipose tissue lipolysis during PA and enhances insulin sensitivity [1,30]. Unlike, in other inflammatory cascades, IL-6 increase during PA is not preceded by an increase in TNF-α (mentioned is on the contrary downregulated) or IL-1β but rather IL-1RA, IL-10, and sTNF-R which creates anti-inflammatory environment and might be responsible for the atheroprotective effects of regular physical activity [14,31,32]. Regarding the type of PA, the most prominent result is seen in the combined aerobic
and resistance activity with a reduction of IL-1β, IL-6, TNF-α, IFN-γ, leptin, and resistin and an increase of anti-inflammatory IL-4, IL-10, and adiponectin [33]. Moreover, stress hormones, such as epinephrine which are higher during an exercise bout, reduce the TNF-α levels and add to physical activity induced anti-inflammatory milieu, similarly as cortisol, whose secretion can also be higher during exercise and can be under IL-6 control [26].

1.1. Irisin, a magic ‘exercise pill’?
The discovery of irisin, a very promising myokine, led to research of its connection and possible pivotal role in fighting obesity [34]. In humans, irisin was linked to exercise [35]. Even an acute bout of exercise might increase irisin concentration and it seems that the increase occurs after both aerobic as well as strength (anaerobic) type of workout. Interestingly, the highest increase is related to high cardiorespiratory fitness (almost double in fit individuals compared to untrained) [36].

As the irisin should lead to the increased energy expenditure by stimulating the formation of “brown” fat tissue, it was at some point pronounced to be the “exercise pill” by many public media. The contradiction still exists about its role in glucose metabolism and glucose homeostasis. Meta-analysis published in 2017 [37] points to the promising role of irisin in fighting type 2 diabetes mellitus through its impact on weight, metabolic parameters, and glucose but mainly based on animal models studies. The role of irisin in diabetes mellitus prevention and irisin therapy in humans is still not clear, and its receptors are yet to be detected.

1.2. Diabetes, aerobic and anaerobic physical activity, and inflammation
Type 2 diabetes is an example of chronic metabolic disease in whose prevention and treatment physical activity plays an important role. Patients with type 2 diabetes have elevations in inflammatory plasma markers as well as endothelial dysfunction. C-reactive protein (CRP), IL, and TNF-α seem to be of specific importance for the low-grade systemic inflammation observed in diabetic subjects [38,39]. Due to mentioned, current guidelines specifically suggest regular physical activity as a backbone of diabetes management. According to the ADA, 150 min of aerobic physical activity of moderate intensity improves glycemic control, HbA1c as well as cardiometabolic risk factors of patients with type 2 diabetes, while resistance and strength training improve muscle mass, muscular blood flow, glucose utilization, and insulin sensitivity [40]. The effects of aerobic and resistance/strength training on diabetes-related chronic inflammation are pronounced in case of supervised and vigorous regular activity and are seen as hs-CRP decreases as well as improvement in other biomarkers of inflammation and insulin sensitivity and might suggest beneficial effects of PA on cardiovascular morbidity and mortality [33,41].

Despite increasing evidence of anti-inflammatory effect of PA, much more research is needed to pinpoint the type and intensity of activity with the largest anti-inflammatory effect, as well as the type of patients that would benefit most from this approach. Moreover, future research directed to improvement of cardiovascular outcomes with PA and subsequent PA-related decrease of systemic inflammation in patients with type 2 diabetes is appreciated [42]. Animal studies suggest different effects of endurance training and aerobic training on antioxidant and inflammatory markers; endurance training increases the antioxidant activity while exhaustive exercises increase inflammation [43].

Moreover, aging and physical inactivity related sarcopenia can be responsible for lower myokine levels, especially irisin, which might in the future be used as a prognostic biomarker of diabetes-related inflammatory response on a muscle level [44]. Additional studies are needed to identify the molecular mechanisms underlying the anti-inflammatory effect of exercise and the sites where this action is predominantly exerted while inflammatory biomarkers originate from multiple sources, such as visceral adipose tissue, as well as muscles, and their interplay might be responsible for long-term cardioprotective effects.

Author contributions
All authors contributed equally in writing of the manuscript.

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