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Exercise training in metabolic myopathies

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INFO ARTICLE

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ABSTRACT

Metabolic myopathies encompass muscle glycogenoses (GSD) and disorders of muscle fat oxidation (FAOD). FAODs and GSDs can be divided into two main clinical phenotypes; those with static symptoms related to fixed muscle weakness and atrophy, and those with dynamic, exercise-related symptoms that are brought about by a deficient supply of ATP. Together with mitochondrial myopathies, metabolic myopathies are unique among muscle diseases, as the limitation in exercise performance is not solely caused by structural damage of muscle, but also or exclusively related to energy deficiency. ATP consumption can increase 50–100-fold in contracting, healthy muscle from rest to exercise, and testing patients with exercise is therefore an appropriate approach to disclose limitations in work capacity and endurance in metabolic myopathies. Muscles rely almost exclusively on muscle glycogen in the initial stages of exercise and at high work intensities. Thus, patients with GSDs typically have symptoms early in exercise, have low peak work capacities and develop painful contractures in exercised muscles. Muscle relies on fat oxidation at rest and to a great extent during prolonged exercise, and therefore, patients with FAODs typically develop symptoms later in exercise than patients with GSDs. Due to the exercise-related symptoms in metabolic myopathies, patients generally have been advised to shun physical training. However, immobility is associated with multiple health issues, and may even cause unwanted metabolic adaptations, such as increased dependence on glycogen use and a reduced capacity for fatty acid oxidation, which is detrimental in GSDs. Training has not been studied systematically in any FAODs and in just a few GSDs. However, studies on single bouts of exercise in most metabolic myopathies show that particularly moderate intensity aerobic exercise is well tolerated in these conditions. Even low-intensity resistance training of short duration is tolerated in McArdle disease. Training in patients with FAOD potentially can also expand the metabolic bottleneck by increasing expression of the defective, but partially functional enzyme. Exercise performance in metabolic myopathies can be improved by different fuel supplementations and dietary interventions and should be considered as adjunct therapy to exercise training.

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Abbreviations: GSD, glycogen storage disease; ATP, adenosine triphosphate; PHK, phosphorylase kinase; CK, creatine kinase; GDE, glycogen debranching enzyme; PGM, phosphoglucomutase; PFK, phosphofructokinase; GAA, α-1,4-glucosidase; VO_{2peak}, peak oxygen consumption; TCA-cycle, tricarboxylic acid cycle; ERT, enzyme replacement therapy.

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1. Introduction

Metabolic myopathies are genetic diseases caused by mutations in genes coding for enzymes involved in muscle glycogen, glucose or fat metabolism [1–4]. Disorders of muscle carbohydrate and fat metabolism can phenotypically present in infancy, where the clinical picture is dominated by hypotonia, hepatomegaly and hypoglycemia. Later onset of symptoms is associated with a higher residual enzyme activity of the affected enzyme and thus, a genotype/phenotype relationship exists for most of the disorders [4]. Later onset is dominated by skeletal muscle symptoms, presenting either as loss of muscle mass and strength (static symptoms) or as exercise-related symptoms of muscle pain and contractures (dynamic symptoms), often related with exercise-induced muscle damage, which in severe cases may cause myoglobinuria and even kidney failure (Fig. 1). In patients with static symptoms, muscle wasting and fixed weakness are brought about by loss of muscle tissue caused by structural damages which in part, relates to the abnormal accumulation of glycogen or lipids intracellularly that disrupt contractile function. A direct toxic effect of deregulated autophagy and non-combusted acyl-carnitines in disorders lipid metabolism may also play a role in this muscle wasting. In conditions with primarily exercise-induced and dynamic symptoms, impairment of muscular performance is caused by a reduced substrate supply to either muscle fat or carbohydrate oxidation, which inhibits skeletal muscle ATP production [5]. The division of metabolic myopathies into those with static and dynamic symptoms is not strict, and it has become increasing clear that many metabolic myopathies overlap phenotypically in their disease course.

In the last decade, exercise as a therapy for patients affected by muscle diseases has been studied extensively, and results have shown that the older notion, that muscle contraction may accelerate the disease process is not true. Therefore, exercise therapy is now becoming a mainstay in the rehabilitation of patients with muscle diseases. In metabolic myopathies, however, exercise as a therapy may seem counter intuitive for patients and clinicians, because exercise usually is the cause of symptoms and is often not well tolerated by patients. However, exercise in metabolic myopathies may be important for several reasons. Firstly, the exercise intolerance experienced by most people with metabolic myopathies is in part caused by a sedentary lifestyle. Immobility is associated, not only with skeletal muscle atrophy, but also with metabolic alterations that can lead to increased dependence on glycogen and a reduced capacity for fatty acid oxidation [6], which can be detrimental for persons affected by muscle glycogenoses. Secondly, exercise provides a powerful adaptive mechanism for metabolic change in skeletal muscle. Thus, exercise may alter skeletal muscle substrate metabolism in ways that are specifically beneficial for patients with metabolic myopathies, and thereby improving exercise tolerance and ability to combust either alterative fuels or, for disorders of fatty acid oxidation, increase the residual level of enzyme and thereby expanding the metabolic bottleneck. Thirdly, a regular exercise program has the potential to improve general health and fitness and improve quality of life, like in healthy subjects, if executed properly [7,8].

In this review, the effect of exercise on carbohydrate and fat oxidation and how that relates to patients with metabolic myopathies is described, and the few studies, which have examined the effect of regular exercise training in these conditions will be addressed. As a particular issue for metabolic myopathies, fuel supplements may play an important role for enhancing exercise performance, and this will also be covered by the review. Clinical presentation, disease course and management of the metabolic myopathies have been reviewed in detail elsewhere [1,2,4,9–12].

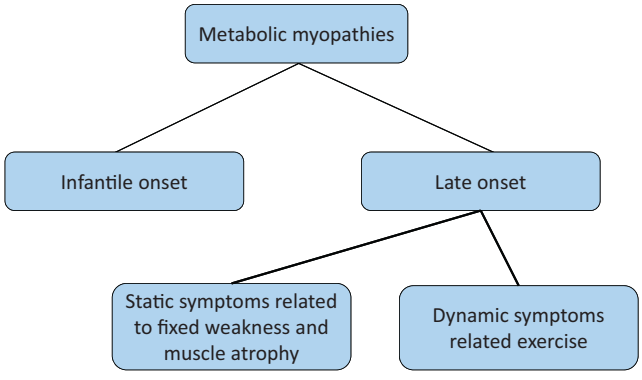

Fig. 1 – Clinical presentation of disorders of muscle carbohydrate and lipid metabolism. Static muscular symptoms are used to describe muscle affection in GSDs that present with progressive skeletal muscle weakness and wasting, i.e. fixed weakness. Dynamic exercise-induced muscular symptoms are provoked by exercise or other strenuous activities that increase muscular energy requirements, and these symptoms resolve with rest when energy demands diminish.

2. Energy metabolism in exercise

Energy is needed for multiple cellular processes, but in healthy contracting skeletal muscle, two processes by far drain most of the available energy. One is the ATPase that directly drives the shortening of the sarcomere via myosin and actin interaction, and the other is the different ion ATPases, most notably the sodium–potassium and calcium ATPases. ATP for these processes comes from a variety of fuel sources in skeletal muscle, and the understanding of how these fuels are burned at different stages of exercise is important to understand the pathophysiology and symptomatology of metabolic myopathies. At rest, skeletal muscle relies almost exclusively on oxidation of fat to produce ATP for the myocytes. During exercise, fuel use is dependent on exercise type, intensity and duration. In strength exercise, muscle tension usually rises above arterial pressure and accordingly, fuel is preferentially supplied from anaerobic glycolysis. With this type of exercise, muscle relies heavily on the anaerobic breakdown of muscle glycogen and subsequent anaerobic glycolysis with the formation of lactate. It follows that this type of exercise is not tolerated well in disorder of muscle glycogenolysis or glycolysis, i.e. most muscle glycogenoses. In aerobic or endurance exercise, the oxidized fuels depend on