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Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions

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Abstract

Peripheral muscle dysfunction is an important systemic consequence of cystic fibrosis (CF) with major clinical implications, such as exercise intolerance and reduced quality of life. Evidence is now accumulating that lack of physical activity is unlikely to be the sole explanation for peripheral muscle dysfunction of patients with CF. Particularly, the demonstration of CFTR expression in both murine and human skeletal muscle suggests the potential implication of intrinsic CF-related factors.

By combining data from both human and animal models, this review describes CF peripheral muscle abnormalities and critically reviews the advances in understanding the impact of the underlying mechanisms. We also describe how peripheral muscles respond to intervention in this population. Methodological concerns and directions for future research are also considered.

Peripheral muscle atrophy and weakness is prevalent in patients with CF and associated with reduced aerobic and anaerobic performances. Further investigations are however needed to confirm alterations in peripheral muscle endurance and fatigability. Physical inactivity is probably the major contributor of peripheral muscle abnormalities in patients with CF with mild-to-moderate phenotypes. However, the relative influence of additional factors (e.g. inflammation, metabolic abnormalities) probably increases with disease severity making specific and individualized interventions necessary in severe patients. Exercise training is the most effective intervention to address peripheral muscle dysfunction but other strategies, such as neuromuscular electrical stimulation and nutritional or hormonal supplementation may be of interest in some patients. Investigations are needed to determine whether pharmacological interventions such as CFTR modulators are effective to address this condition. To better elucidate the etiology of peripheral muscle dysfunction in CF, future studies should combine measurements at the cellular level with indices of muscle function and monitor physical activity levels to account for its potential effects on muscle function.
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1. Introduction

Cystic fibrosis (CF) is a multisystem genetic disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The defect of this anion channel, normally present in the epithelial membrane, leads to pancreatic insufficiency and chronic airway infections with progressive loss of lung function. Despite recent improvements in therapeutics (e.g. [1]), there is currently no curative treatment for CF, making improvements in patients' functional status, well-being and longevity essential clinical goals.

Although respiratory failure is a major cause of mortality in the end stages of the disease, impairments in lung function do not explain all aspects of the disability experienced by patients

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with CF. There are several secondary manifestations of the disease and recent evidences suggest a key role of peripheral muscle function as an important systemic consequence of CF. Larger muscle mass has been shown to be positively associated with increased survival in CF [2]. Skeletal muscle weakness is also associated with important clinical problems such as reduced aerobic capacity [3,4], which is in turn associated with impaired quality of life [5] and represents one of the best markers of prognosis and survival in CF [6–8].

Some mechanisms underlying peripheral muscle abnormalities have been identified (e.g. physical inactivity [3] and inflammation [9], among others factors detailed in this review). However, there is still much to learn about the relative influence of other potential factors contributing to this systemic manifestation of CF. Particularly, the demonstration of CFTR expression in human skeletal muscle [10] leaves open the debate whether CF peripheral muscle dysfunction mainly reflects deconditioning or whether intrinsic CF-related factors can be involved. This is a key research question with important clinical implications as determining factors underlying peripheral muscle dysfunction in CF will help identify viable treatment strategies. Peripheral muscle dysfunction can be prevented and/or the function can be improved, notably by exercise training, but novel alternatives or additional therapeutic approaches also need to be investigated. Furthermore, because of the likely heterogeneity in mechanisms of muscle dysfunction depending on CF genotypes and phenotypes, there is a need for individualized therapeutic strategies based on appropriate patient evaluations.

The purpose of this review is to provide an overview on peripheral muscle abnormalities in patients with CF, with particular emphasis on (1) the structural and functional alterations, (2) the clinical consequences of peripheral muscle dysfunction, (3) its etiology and (4) the effects of therapeutic interventions on peripheral muscle function. Some methodological considerations and suggestions for future research are also proposed.

2. Scope

The focus is set only on peripheral muscles as respiratory muscles are a distinct area of investigation. This review includes studies which investigated various CF-related genotypes and phenotypes and considers children, adolescents and adults of both genders with various levels of habitual physical activity (PA). It would be tempting to refer to other chronic respiratory disorders when data specific to CF are lacking, as pulmonary diseases share some common mechanisms underlying peripheral muscle dysfunction. A large amount of data is available on skeletal muscle function in patients with chronic obstructive pulmonary disease (COPD) [11], mainly because of the high prevalence of COPD worldwide and the fact that skeletal muscle dysfunction in COPD has been extensively studied for at least two decades [11]. However, several specificities impede extrapolation of evidences underlying COPD-related peripheral muscle dysfunction to patients with CF. For example, the negative effect of aging on muscle function is a major concern in COPD patients, who may also cumulate many years of physical inactivity as compared to pediatric or young adults with CF, where aging involves muscle growth, until the third decade of life. On the other hand, defects in CFTR expression and function may contribute to unique skeletal muscle dysfunction in CF. Thus, findings related to other respiratory diseases will be mentioned only sparingly, when appropriate.

3. Peripheral muscle abnormalities in CF

3.1. Muscle atrophy

Body mass index (BMI) is the most popular method to assess malnutrition in a routine clinical practice. A cut-off value of 18.5 kg/m^2 is often used in adults with CF [12]. It is recommended that children with CF maintain a BMI $\geq$50th percentile, whereas a BMI percentile of 20 has been suggested as a critical threshold for nutritional failure [13]. However, BMI has some limitations as it does not inform on body composition (e.g. percentage of fat-free mass, FFM). Although there are no accepted criteria to define low muscle mass, a FFM <5th percentile has been often used in both children [13] and adults [14] with CF. Using this criterion, the prevalence of hidden FFM depletion (i.e. low FFM despite preserved values of BMI) has been found to range from 14 to 38% in patients with CF [13–16]. Another important notion is that the loss of FFM is not homogeneously distributed throughout the body and a graded pattern of FFM loss in legs > arms > trunk was found in adults with CF [14]. This is consistent with previous reports in COPD [17] and underlines the particular vulnerability of lower limb muscles to atrophy in CF. CF has long been associated with poor nutrition. However, overweight and even obesity has lately become a concern in CF. In a recent single center-based study, the prevalence of overweight and obesity was 15% and 8%, respectively [18]. Beyond being associated with cardiovascular and metabolic disorders, a high BMI may mask a loss of FFM. Altogether, these data highlight the importance of measuring body composition for early and accurate muscle atrophy detection in both children and adults with CF. Dual-energy X-ray absorptiometry is considered as the reference method in assessing FFM in CF [19] whereas skinfold thickness and bioelectrical impedance (Lukaski equation) may, respectively, overestimate and underestimate FFM in these patients [19].

3.2. Muscle strength

Most of the studies investigated the lower limb muscle strength by measuring the maximal isometric voluntary force of the quadriceps. The majority of them showed that quadriceps strength is reduced in patients with CF (Fig. 1). However, the true prevalence of lower limb weakness in CF remains uncertain as most of these studies had small sample sizes (Fig. 1) and were carried out in reference centers, where the patient population may be biased toward more severe patients.

While in COPD patients in vitro contractile properties of vastus lateralis muscle bundles were found to be preserved [20], no studies are currently available regarding in vitro peripheral skeletal muscle contractility (e.g. quadriceps fibers) in CF. Divangahi et al.

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