

The physiology of exercise intolerance in patients with myalgic encephalomyelitis (ME) and the utility of graded exercise therapy

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ABSTRACT

This review discusses the suitability of graded exercise therapy for the treatment of myalgic encephalomyelitis (ME), based on current knowledge of the underlying physiology of the condition and the physiological effects of exertion on ME patients. A large body of peer-reviewed scientific literature supports the hypothesis that with ME an initial over-exertion (a period of metabolic stress) in conjunction with viral infection depletes concentrations of the metabolic regulator glutathione, initiating a cascade of physiological dysfunction. The immune system and muscle metabolism (including the muscles of the cardiovascular system) continually compete for glutathione, inducing a state of constant stress that renders the condition chronic. The impairment of a range of functions means that subtly different suites of symptoms are apparent for different patients. Graded exercise therapy has proven useful for a minority of these, and the exacerbation of symptoms for the majority is not subjective but has a physiological basis. Blanket recommendation of graded exercise therapy is not prudent for such a heterogeneous group of patients, most of which are likely to respond negatively to physical activity.

Following exercise, patients with myalgic encephalomyelitis (ME) uniquely exhibit exacerbated symptoms and a suite of measurable physiological changes indicative of stress (sub-optimal metabolic performance; e.g. reduced respiration and heart rate, increased glycolysis and lactic acid production, and concomitant limitation of activity¹⁻⁵). Although these symptoms may not be universal⁶, a significant subgroup of ME patients are affected in this manner⁷. The issue of exercise is critical for the treatment of the condition as one school of thought recommends "graded exercise therapy" as a general remedy for ME whilst another recognises that exercise intolerance may have an underlying physiological cause that may actually be aggravated by physical exertion. This difference of opinion influences policy: graded exercise therapy is one of the principal recommendations of the current NICE draft guidelines for the treatment of patients "mildly to moderately affected" by ME (p. 21, lines 20 to 23)⁸.

Although recent general reviews of ME exist⁹⁻¹¹, our aim is to specifically review evidence for the mechanisms by which physical activity affects ME patients, and to investigate how graded exercise therapy may help or hinder recovery.

Although no single randomised controlled study has yet attempted to investigate every aspect of ME, the combined weight of empirical evidence to date indicates that the condition is characterised by a complex series of events involving reserves of metabolic regulators such as glutathione, muscle metabolism and the cardiovascular system. A significant body of literature suggests that these imbalances are associated with a dysfunctional immune system impaired by viral infection. Indeed, a hallmark of ME is a range of symptoms, varying in extent between patients, suggesting that a range of functions are impaired to greater or lesser degrees.

ME typically follows a flu-like illness, with elevated concentrations of viral particles subsequently detectable in blood and muscle tissues¹². Post-viral fatigue is a well established possible consequence of infection by a range of different viruses¹³⁻¹⁷, with enteroviruses specifically implicated in the case of ME – elevated concentrations of viral RNA sequences resembling coxsackie virus B are detectable in muscle tissue¹². Furthermore, the majority of the limited number of ME patients so far treated with antiviral drugs (interferons) were able to return to work following treatment¹⁸, also suggestive of a persistent 'smoldering infection'¹⁹.

Crucially, post-viral fatigue is not related to the muscle disuse and deconditioning that can result from the initial period of illness¹². Indeed, the mechanism underpinning post-viral fatigue is a multifaceted physiological imbalance. Nijs and co-workers²⁰ found that, for ME patients, graded exercise resulted in faulty regulation of the immune system, specifically increased activity of the enzymes "elastase" and "RNase L". RNase L is a key component in the cell's virus detection system and is up-regulated in response to viral infection. However, elastase degrades RNase L and is normally involved in removing it from the cell when concentrations are too high. Why should both be highly expressed in ME patients? Elastase is activated and degrades the RNase L in the absence of metabolic regulators such as glutathione. (Glutathione is an amino acid complex that modifies enzyme activity throughout the body, and ME patients exhibit either lower concentrations or an imbalance between its active and inactive forms²¹⁻²³.) Thus the simultaneous over-activation and mis-regulation of this part of the immune system can be explained by glutathione depletion. A range of factors contribute to glutathione depletion in the general population, including infection, the oxidative stress induced by strenuous or sustained exercise, and the long-term elevation of the stress hormones cortisol and adrenalin²⁴. Furthermore, glutathione is also involved in sustaining respiration (i.e. the production of chemical energy compounds such as ATP in the mitochondria) thereby providing energy for active tissues such as muscle. Thus muscle tissue effectively competes with the immune system for glutathione²⁵ – sustained physical activity reduces the amount of glutathione available to the immune system, resulting in immune dysfunction. Conversely, an overactive immune system reduces the amount of energy available for muscle tissue, also exacerbating oxidative stress, and can account for both the chronic fatigue and pain (by inducing lactic acid production) that characterise ME.

Thus, following an initial period of stress, glutathione concentrations may be too low for the optimal function of both the immune system and muscle tissues, paving the way for both persistent viral infection and fatigue, both of which feedback from each other to render the condition chronic.

This situation is compounded by the fact that glutathione not only has a supporting role in the immune response but also directly inhibits the replication of enteroviruses by blocking the formation of one particular protein (glycoprotein B) shared by all – including coxsackie viruses. Indeed, glutathione concentration is a major factor influencing the expression of other persistent viral infections such as HIV²⁶⁻²⁹. Thus glutathione depletion not only suppresses the immune system, it leaves the body particularly defenceless against enteroviruses. Sustained exercise or stress can deplete glutathione concentrations to the point where viral RNA is no longer prevented from replicating, aiding either an initial infection or the renewed replication of previously blocked viral RNA present in muscle tissue and blood^{27, 29}. Thus glutathione depletion is a strong candidate for 'the trigger for reactivation of endogenous latent viruses' in ME³⁰. A small number of studies demonstrate that foods rich in glutathione or direct glutathione injection help to relieve fatigue in ME patients, and may clear active viral infections^{31, 32}.

Although the above studies have concentrated on skeletal muscle, the heart (and the postural leg muscle involved in pumping blood back to the heart) is not exempt from glutathione depletion. Thus the above mechanism can also account for the range of cardiovascular problems associated with ME, including orthostatic (standing) intolerance (reviewed by Spence and Stewart³³). Patients with orthostatic intolerance 'have continuous disability and commonly have exercise intolerance'³³.

Together, this evidence suggests that chronic fatigue in ME is symptomatic of the following sequence of events: a period of infection or strenuous physical or mental activity results in glutathione depletion; this renders the immune system relatively ineffective, particularly against enterovirus infection; the immune system becomes constantly activated (and inefficiently governed) because it has insufficient resources (glutathione) to completely rid the body of viral particles; the constantly elevated energy demand of the immune system detracts from other metabolic functions (particularly energy-demanding systems such as skeletal muscles and the cardiovascular system); limitation of respiratory and cardiovascular systems further locks the patient into a vicious cycle of inefficient energy production and use; increased reliance on anaerobic metabolism leads to lactic acid production and associated muscle pain.

Clearly, the performance of energy-demanding activities such as exercise can only aggravate this situation. Indeed, 82 % of ME patients in a recent study stated that graded exercise therapy worsened their condition, and only 5 % found it useful (compared to 70 – 75 % of patients who found either pain management or 'pacing' of daily activities useful)³⁴. Furthermore, the Canadian Clinical Treatment Protocol warns that "externally paced 'Graded Exercise Programs' or programs based on the premise that patients are

misperceiving their activity limits or illness must be avoided"³⁵. If exercise is so detrimental, why is graded exercise therapy often recommended as a treatment for ME? Firstly, many of the studies cited here are recent, and the information and implications have perhaps not yet filtered up to policy makers. Secondly, the reclassification of ME as an ambiguous 'chronic fatigue syndrome' (CFS) by members of the psychiatric profession assumes that the symptoms have no physiological basis and are best treated with the traditional psychiatric method of facing and overcoming a problem, rather than direct removal of the problem at source. However, this approach jumps from hypothesis to treatment without investigating the mechanisms involved, perhaps explaining why "no psychiatrist has ever cured an ME patient using psychiatric treatments"¹⁹. Psychiatry, by definition, should not have authority over the treatment of physiological disorders, particularly those that occur chiefly in muscle tissues. Graded exercise therapy is founded on, and perpetuates, the myth that ME patients are simply malingering, while most are frustrated by their incapacity to satisfactorily conduct critical aspects of daily life³⁴.

ME is a heterogeneous disorder that affects different patients to varying degrees and with subtly different suites of symptoms. At best, graded exercise therapy has relieved symptoms for (but not cured) a tiny minority of patients, whilst the weight of empirical evidence indicates that exercise has direct and persistently negative impacts on the physiology and quality of life of a significant subgroup of ME patients. Any universally applied therapy is unlikely to address the heterogeneity of ME, and graded exercise is particularly unsuitable as it may worsen the condition, and should not be generally recommended without a high degree of confidence that it will not be applied to susceptible patients: it is difficult to conceive of a more inappropriate therapy for ME. By increasing the risk of relapse and overall health risks, rather than reducing them, graded exercise therapy also risks increasing the burden of illness on society at large. The present review suggests that an approach based on treatment of the underlying physiological dysfunction will be more fruitful.

Abbreviations

ATP = Adenosine triphosphate, RNase L = 2',5'-oligoadenylate (2-5A) synthetase/Ribonuclease L

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