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Review

Emerging therapeutic concepts for muscle and bone preservation/formation

J. Compston [a,*], K.C.H. Fearon [b,*]

[a] Bone Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[b] Department of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh EH16 4SB, UK

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1. Introduction

There are approximately six hundred named muscles in the human body with a great diversity of function and *gross* structure. In clinical practice, the main groups of muscles whose mechanical function may

* Corresponding authors.
E-mail addresses: jec1001@cam.ac.uk (J. Compston), K.fearon@ed.ac.uk (K.C.H. Fearon).

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influence the outcome of acute or chronic disease are the muscles associated with respiration (e.g. intercostal muscles and diaphragm) and those concerned with bipedal locomotion (e.g. muscles of the trunk and lower limb). However, in terms of clinical outcomes, it is also relevant to consider skeletal muscle as a metabolic 'whole' organ. Skeletal muscle represents 40% of total body mass, accounts for a major component of the anabolic protein response to feeding, modulates peripheral insulin resistance, is the main source of peripheral glutamine production, is an endocrine organ and has a role in regulatory crosstalk with adipose tissue and the immune system [9]. In clinical situations where muscle wasting may become severe, the metabolic role of muscle in homeostasis may be critical to survival. The aim of therapeutic intervention is therefore to maintain or regain the mass and both the mechanical *and* metabolic function of skeletal muscle.

2. Philosophy of intervention

In general, muscle loss occurs as a result of lack of movement, lack of nutrition, the specific effects of systemic disease (e.g. systemic inflammation) or a variable combination of all three. According to this view, intervention could therefore address the generic issues of exercise and adequate nutrition or the specific mediators associated with systemic disease (e.g. pro-inflammatory cytokines or hypoxia). An alternative approach is to determine conserved signalling pathways which independent of the disease, if blocked or stimulated, can result in net anabolism [15]. It must be stated, that often the disease process resulting in muscle wasting is associated with anorexia and fatigue and that without addressing the consequences of these symptoms (inadequate nutrition and lack of physical activity), then any targeted intervention will have a sub-optimal effect. Such logic leads to the inevitable conclusion that therapeutic intervention must be multimodal (Fig. 1).

It is also important to recognise that chronic disease rarely goes untreated and that any intervention strategy must take account of concomitant therapy. One extreme example is cancer-associated muscle loss. Cancer patients with advanced disease now routinely survive several years and during this time are exposed to the catabolic effects of surgery, radiotherapy or chemotherapy, some of which may be administered in repeated cycles and can induce significant muscle loss [6]. In this situation, muscle preserving therapy must counteract both the effects of the disease and its treatment.

Fig. 1. In order to optimise the response to any specific drug therapy for muscle wasting disease it is important to stabilise the clinical condition of the patient and to provide an adequate background level of exercise and nutrition.

3. Outcomes for therapeutic intervention

Whilst in health there is a relatively strong correlation between muscle mass and strength, it is uncertain whether this relationship pertains in the presence of systemic disease. For example, in cancer cachexia there is both a reduction in muscle mass and mechanical quality [40]. Recent studies have identified some of the precise mechanisms that account for such altered function in muscle wasting diseases [27]. Thus the assumption that an increase in muscle mass will be associated with increased function may not always hold (see results of recent phase III intervention trials in prevention of cancer associated weight-loss). For the short-term (e.g. quality of life related to physical functioning) the mechanical function of locomotor muscles is probably paramount for the patient. However, for survival, it may be both the mechanical function of respiratory muscles and the overall mass/metabolic function of muscle that is important.

4. Phase and duration of intervention

The classic testing of novel drugs in Phase I or II trials usually focuses on patients with advanced disease where other therapeutic options have been exhausted. However, recent efforts at devising classification systems for muscle wasting associated with chronic diseases (e.g. cancer cachexia [16]) have suggested that wasting may occur in phases that may or may not progress. The earliest phase is identified as pre-cachexia when muscle wasting may not yet have occurred, but patients are at high risk of progression and display metabolic features of the relevant wasting syndrome such as systemic inflammation. It is generally accepted that prevention at this stage with maintenance of muscle mass and function is not only likely to be the easier option but also gives the maximum duration for the intervention to act (during a period of relative clinical stability) and the maximum time for patient benefit. For example, the INTERCOM trial showed that 24 months of nutritional intervention coupled with exercise in COPD enhanced muscle strength and 6 min walk distance and decreased hospitalisation [43]. Shorter periods of intervention may not be either effective or give sufficient clinical benefit to justify additional expenditure.

5. Concept of mixed mechanisms of muscle wasting from different pathologies: will monotherapy be effective?

It is important to appreciate that the demographics of Western Society are changing profoundly with the number of patients over the age of eighty set to double in the next 20 years. A healthy individual will lose skeletal muscle mass at the rate of 0.5–1.0%/year after the age of 40 years. Such age-related sarcopenia is thought to be due, in part, to neuro-degeneration coupled with a variety of other factors [30]. For the average 70 year old/comorbid patient presenting with any of the common diseases associated with muscle loss (cancer, chronic kidney disease, chronic heart failure, chronic obstructive pulmonary disease), this naturally means that a significant but variable proportion of their overall reduced muscle mass will be due to such neurodegeneration. It is not known the extent to which muscle loss from diverse mechanisms can be managed with a single therapeutic approach.

6. Treatment of muscle wasting in the age of obesity

There is an epidemic of obesity in Western Society with >50% of all adults in the UK now having a BMI indicating overweight or frank obesity. The muscle mass of a healthy but obese individual is usually greater than the comparable non-obese individual. However, there is a sub-population of obese individuals who are generally co-morbid and