Muscling in on Sarcopenia, Myopenia and Myosteatosis: Definitions and Interventions

Defining Sarcopenia, Myopenia and Myosteatosis

There is building appreciation for the importance of body composition in conferring risk of disease. Body composition is a collective term used to describe the composite tissues (muscle, fat, organs, bone) in the body. The amount of muscle and fat are important determinants of nutritional requirements. Over the adult life course, one of the most significant changes that occurs is a loss of muscle mass often accompanied by increases in fat mass. Alterations in body composition can result from, result in, or influence the natural history of human health disorders.

The understanding of body composition in relation to health outcomes has developed in tandem with an ability to quantify tissues using image-based methods such as computed tomography (CT), dual x-ray absorptiometry (DXA) and magnetic resonance imaging (MRI). Image-based approaches permit the observation that sarcopenia is not restricted to people who appear thin or wasted but is prevalent in every category of body mass index (BMI) including those who would be considered to be overweight and obese. Skeletal muscle mass and whether muscle is being lost, is masked by the overall bulk of body weight of an individual, making image-based approaches essential to specifically quantify muscle. Reliance on measures of weight, weight loss and BMI are insufficient to determine health risk.

Application of body composition techniques that enable one to 'look inside' the body has revealed divergent behavior of muscle and adipose tissue during aging and chronic disease. These two major

Body composition phenotypes

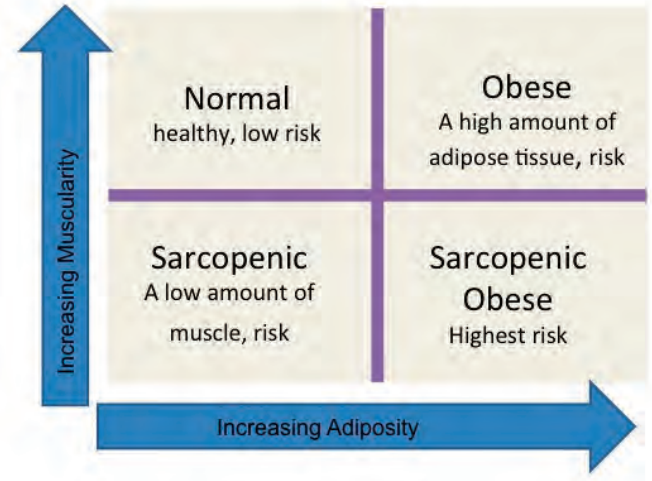
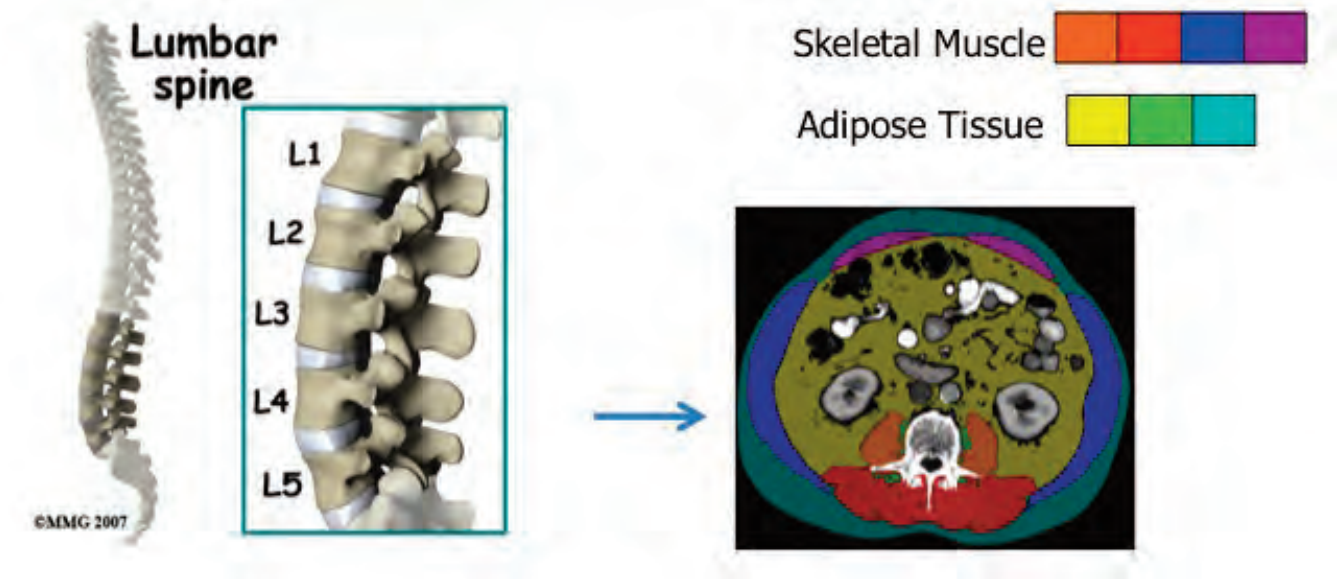


Figure based on: A population-based approach to define body-composition phenotypes. Prado CM, Siervo M, Mire E, Heymsfield SB, Stephan BC, Broyles S, Smith SR, Wells JC, Katzmarzyk PT. Am J Clin Nutr. 2014 Jun;99(6):1369-77. doi: 10.3945/ajcn.113.078576. Epub 2014 Apr 23

body components behave independently of one another. Four basic body composition phenotypes have been recently proposed based on muscularity and adiposity, each associated with their own risk for poor health outcomes. A low quantity of muscle tissue is termed sarcopenia. Sarcopenia was originally described in the elderly and is a term denoting a reduced quantity of skeletal muscle, generally defined as an absolute muscle mass >2 standard deviations below that typical of healthy adults, concurrent with loss of strength. Apart from aging, muscle loss can also occur as a result of illness. The presence of clinically relevant muscle wasting due to any illness and at any age is termed myopenia.

Computed Tomography (CT) Analysis: Methodology



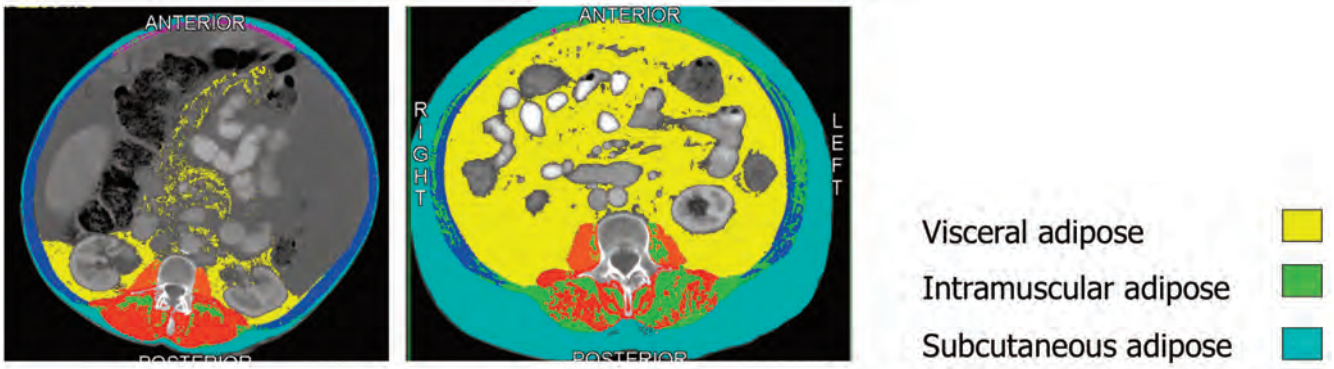
To quantify different tissues for body composition analysis, the 3rd lumbar vertebra, an established landmark in body composition analysis is used to consistently measure the same region of the body across patients. A single image is downloaded onto a software program (Sliceomatic from Tomovision). Each tissue has specific attenuation characteristics which are recognised by the program and allows us to distinguish between skeletal muscles and different types of adipose tissues. Each tissue of interest is color coded so that we can distinguish rectus abdominus, oblique and lateral abdominal muscles, psoas, paraspinal muscles, (depicted by orange, red, blue and purple respectively) whereas visceral adipose is depicted by yellow, intramuscular adipose by green and subcutaneous by turquoise

When a low amount of muscle (sarcopenia) is accompanied by a high level of adiposity (obesity) that person would be classified as being sarcopenic obese which is the highest health risk category. Apart from the quantity of muscle and fat, image-based approaches also reveal additional features such as excess lipid accumulation within muscle tissue.

Two fat depots exist within skeletal muscle with varying functions. Fat within muscle cells is associated with microscopic lipid droplets that is utilised for energy within the muscle (intramyocellular fat). Lipid droplets are located near the mitochondria, the energy producing organelle within the cell. Visible fat within the fascia surrounding the muscle cells is comprised of adipocytes (intermuscular fat) that may be referred to as "ectopic fat". Myosteatosis, or a pathological accumulation of fat, describes abnormal retention of lipids within muscle tissue reflecting an impairment of normal processes of synthesis and elimination of triglyceride. Myosteatosis is relatively recently characterised, however, interest has been raised by its relationship to insulin resistance, poor physical function and most recently, survival (reviewed Aubrey et al 2014).

Features of muscle wasting, including myosteatosis have been described in other conditions such as aging, obesity and type 2 diabetes. Myopenia and myosteatosis have recently been reported to be independent risk factors for mortality in cancer patients.

Muscle mass and strength are critical components in maintaining physical function, mobility and vitality. Low muscle mass increases the



The figure illustrates the extremes of variation in fat mass observed using CT images at the third lumbar vertebrae. These are images of patients with metastatic disease. Some patients present with such a small amount of adipose tissue, that it would similar to pinching the skin on the back of your hand. The other image depicts an abundance of subcutaneous adipose tissue and their internal organs are embedded in vast amounts of visceral adipose tissue. In this particular patient, you can see extensive infiltration of fat into the muscles as indicated by the green

risk of becoming immobilised and if the person becomes hospitalized, length of stay is longer and treatments are less effective. Other costs of severe muscle wasting include low quality of life, burden on caregivers and utilization of health care costs.

Mechanisms underlying myopenia and myosteatosis

Several mechanisms may contribute to muscle loss and/or myosteatosis. Dysfunctions in mitochondria, altered pathways of anabolism, and elevated inflammation disrupt protein synthesis and catabolism. Mechanisms for muscle loss have been largely explored using preclinical models and few studies have been conducted in humans to determine the causes of muscle loss and development of myosteatosis. To add further complexity to the problem, muscle loss, and potentially myosteatosis, is accelerated by many chronic disease, injury, surgical procedures, acute illnesses and obesity. Existence of more than one of these conditions simultaneously will exacerbate an already altered body composition. Little is known about the biological features of muscle, how to modify muscle loss and myosteatosis, and the capacity to reverse these pathologies with any given treatment. Procurement of human muscle is essential to be able to identify the key biological alterations associated with muscle loss.

A view to improve myopenia and myosteatosis

Our research program approaches the problem of myopenia and myosteatosis by applying principles of metabolism and nutrition with an aim to define effective interventions. Several underlying factors contributing to muscle loss, including catabolic humoral mediators (i.e. pro-inflammatory cytokines), anabolic failure (i.e. insulin insensitivity) and activation of proteolytic systems. In addition, a deficit of nutrients required for muscle anabolism may also be contributing to muscle loss.

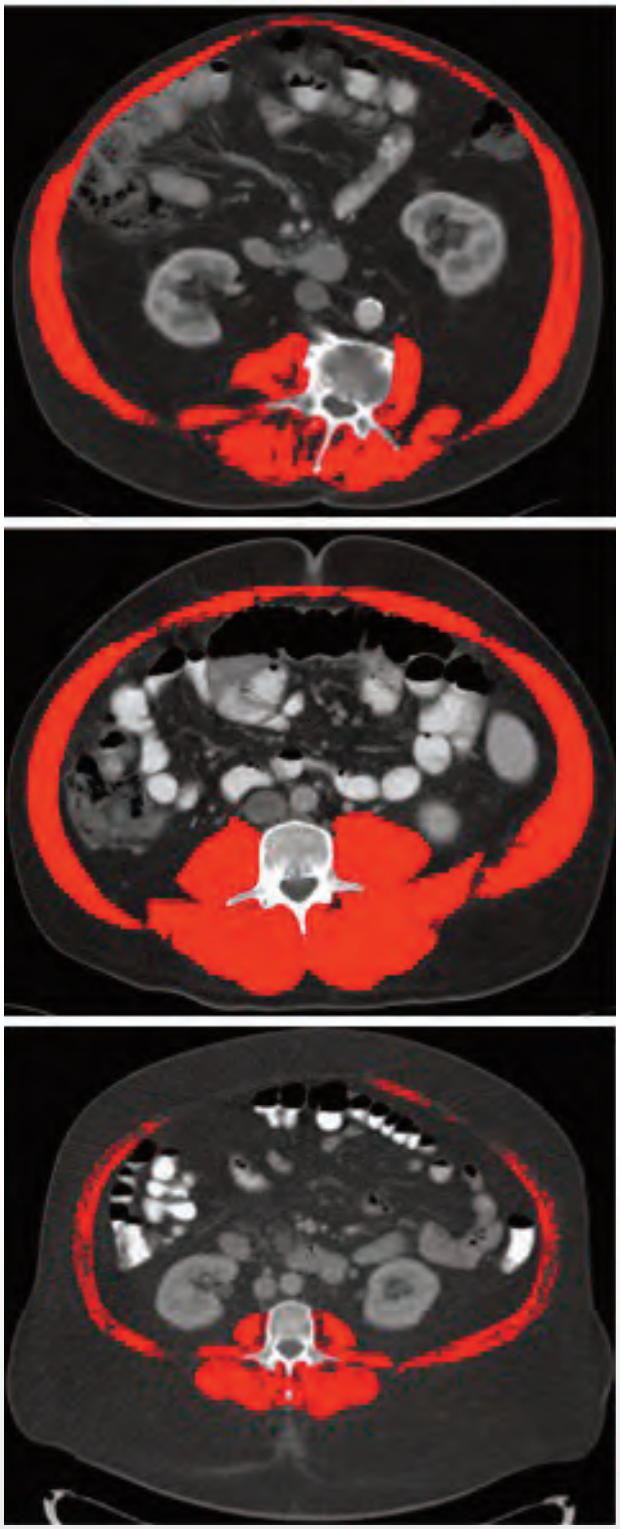
Our major focus to date has been on people who have cancer. While sarcopenia and myosteatosis have a high prevalence among people with age-related chronic diseases, cancer patients have unique features that make them excellent candidates for the study of muscle wasting and myosteatosis: the availability of high resolution CT images and the agreement of a high proportion of patients to muscle biopsy during cancer surgery. CT images taken for cancer diagnosis and follow-up enable an unprecedented ability to test for myopenia and myosteatosis in large numbers of patients, including repeated measurements over time. Our team also has access to human muscle biopsies to obtain material for the study of muscle wasting. A painful and invasive percutaneous biopsy (standard method) is not typically justified in many vulnerable, ill or elderly subjects.

What do we know about nutritional intervention for muscle loss?

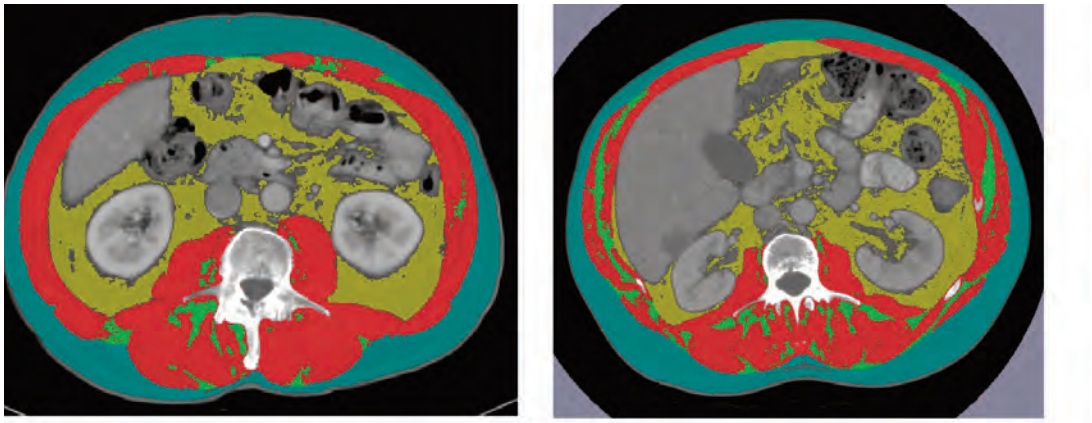
In patients diagnosed with lung cancer, low muscle mass is prevalent and loss of muscle occurs at an accelerated rate during treatment. In a recent clinical trial, we reported some patients lost up to 5.2kg of muscle from time of diagnosis to the end of first line chemotherapy treatment (approximately 16 weeks for the majority of patients). Loss of skeletal muscle mass in this population appeared to generally occur concurrently with elevated fat deposition into muscle. We have reported a more intense loss of muscle in people who have low levels of the n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in their blood. Given that low muscle mass carries an independent risk for death and disability, and that low concentrations of EPA and DHA are independently and strongly related to the presence of myopenia and loss of muscle over treatment, an important relationship between skeletal muscle metabolism and n-3 fatty acid supply emerged from this work. Following these clinical observations, we aimed to determine mechanisms for the beneficial effects we observed.

An animal model of cancer-chemotherapy was developed with an intent to recapitulate the human course of colorectal cancer. Similar to the observations from the human study, this model develops myosteatosis during tumor growth that is accelerated during chemotherapy. When the rats were provided EPA and DHA in their diet, fat accumulation in the muscle was negligible compared to the control group who received no supplemental fatty acids. These data suggest an ability of EPA and DHA to potentially prevent muscle loss and myosteatosis to improve muscle health.

Several diverse lines of evidence from the literature would support EPA and DHA influencing muscle health in many ways, both directly and indirectly, that tip the balance in favour of muscle anabolism and reduced fat infiltration. EPA and DHA may support the anabolic potential of muscle



These 3 images are of people with identical height and weight. According to conventional measures of determining risk, each of these individuals would be classified in the same way. However, it is clear that image 3 depicts an individual who would be at the highest risk given the low amount of muscle relative to a higher proportion of fat



These images depict the variation in muscle mass within individuals who have the same BMI. The individuals from whom these CT images are taken are the same age, height, weight and sex. The individual on the right has less muscle and more fat inside the muscle than the person on the right. The person on the right has an amount of muscle that would be categorised as sarcopenic

through improving insulin sensitivity which has been reported in several animal and human studies. Inflammatory mediators, such as the acute phase proteins and pro-inflammatory cytokines, also cited as factors contributing to muscle catabolism, have been reported to be reduced by EPA and DHA in cancer and a variety of other conditions. The metabolism of fat within the muscle is altered when EPA and DHA are increased in the muscle tissue. Collectively, these results studies suggest an important role for n-3 fatty acids in the maintenance of normal muscle mass and function that overall promote anabolism (improved insulin sensitivity, reduced inflammation) and prevent fat infiltration. Research is required to determine under what conditions these pathways are activated and how to optimise the inhibitory effect of EPA and DHA on muscle degradation and fat infiltration at a cellular level.

Summary and future directions

Myopenia (low muscle mass) and pathological fat accumulation in muscle (myosteatosis) increase the chances of poor outcomes, including death. Little is known of these features in human muscle and treatments for muscle loss in the cancer setting remain elusive. Multi-modal strategies that combine targeted nutrient interventions, exercise and anti-inflammatories aimed at addressing the multiple drivers of muscle pathology will be required to improve clinical outcomes. Collective work in humans suggests that disease associated alterations in muscle may be modifiable and potentially reversible. Current nutritional approaches are in the form of a "one size fits all" approach which may be insufficient given diversity in body compositions. For example, dietary guidelines for people with cancer are not optimal or evidence-based. Finding a treatment for low muscle mass is on the agenda of many pharmaceutical companies. To date, there are no approved drugs to reverse muscle loss, however several phase 2 and 3 trials are in progress investigating promising potential treatments for muscle loss that occurs during aging and disease.

The complex problem of disease associated muscle loss can only be addressed using multiple strategies to target various contributors. The European Palliative Care Research Centre together with The EAPC Research Network have initiated a Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia (the MENAC trial), a multicenter phase III randomised study that combines a high protein nutritional supplement containing n-3 fatty acids, with an anti-inflammatory drug as well as home-based resistance and aerobic exercise. This multi-faceted approach simultaneously tackles protein and energy intake, inflammation that drives muscle loss, while evoking an anabolic environment to minimize muscle loss that occurs in cancer patients as they undergo treatment.

The ability to modify muscle wasting and myosteatosis has a broad scope of application to

aging, diabetes, obesity and various forms of muscle atrophy, which share these common features. While treatment for these conditions remains limited, a number of mechanisms may contribute to the ability various drugs and nutrients to alter body composition, however, a more complete understanding of the features of the muscle characterised by wasting and fat infiltration is required.

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