Muscling in on cancer

Shedding light on her ongoing studies, fat metabolism expert Dr Vera Mazurak explains how she aims to develop nutritional interventions to halt or even reverse muscle loss in chronic diseases, especially cancer.

What attracted you to the study of nutrition and metabolism?

The human body has always fascinated me – the biology and physiology is so complex, yet so perfectly coordinated. Food fuels that biology, but illness complicates it. I became hooked on research while working in a lab for a summer studying the effects of a nutrition solution on the immune system in a model of a model of gut resection. I knew there was a lot more I had to learn!

Could you define sarcopenia and myosteatosis, within the context of your research?

Sarcopenia refers to muscle depletion associated with poor outcomes – disability and death. However, since sarcopenia was first used to describe the physiological loss of muscle in ageing, ‘myopenia’ is the preferred term to indicate the presence of clinically relevant muscle wasting due to illness at any age. Myopenia, therefore, is a more appropriate term for the muscle loss we have observed in cancer patients.

Myosteatosis, derived from ‘myo’, meaning muscle, and ‘steatosis’, meaning fat, is sometimes referred to as low muscle density. While muscle normally contains a small amount of fat as an energy source, myosteatosis reflects an elevated fat content and is a pathological condition.

Why do the natures of these pathologies remain unresolved?

While it has long been known that diseases like cancer are associated with muscle loss, most studies explore mechanisms using animal models or cell culture, which may not reflect the pathology and underlying mechanisms in humans. Also, the observation that people with cancer exhibit myosteatosis is relatively new, made possible by the emerging use of computerised tomography (CT) images to characterise body composition in cancer patients.

How important are animal models to your research?

Animal models are very important to control for diet and genetic variation, however, it is essential that the results are applicable to humans. The animal model we are currently using represents the delivery of therapy for treatment of colorectal cancer in humans. The animals are fed meals resembling Westernised human diets with respect to all macro- and micronutrients, including quantity and composition of dietary lipids. We can then determine the effect of tumour, drug therapy and dietary components on muscle health.

Can you give an insight into technological advances that have permitted new explorations of physiological and pathological variation in muscle?

I believe the biggest recent advancement is the application of CT images to explore body composition in cancer patients. CT techniques exhibit specificity and precision and have been extensively validated in body composition research. This approach is able to quantify muscle and fat depots and also reveal features such as excess inter- and intra-myocellular lipid accumulation within muscle tissue. All of this information is available in the patient record because oncologists use CT images for a different reason, to determine the size and location of the tumour the size and location of the tumour and then later, its response to the treatment. The capacity to assess genetic material for predictors of muscle wasting, and further, response of that muscle to various interventions, is also enabling new explorations of muscle pathology in people with cancer.

Have your animal studies proved helpful towards defining mechanisms for eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA) in preventing or treating pathology?

We observed improvement in muscle health in a clinical trial where we provided EPA and DHA to lung cancer patients undergoing treatment for the disease. In the animal model described, we demonstrated that tumour-bearing animals exhibit considerable muscle loss and elevated muscle triglyceride content, which are accelerated following chemotherapy. When a Westernised diet was supplemented with fish oil (2.7 per cent EPA and DHA), fatty acid enrichment of the muscle tissue occurred within seven days at 2 and 4 per cent respectively, similar to the enrichment reported in a human study after three weeks of supplementation with fish oil. Triglyceride accumulation in muscle was prevented by dietary supplementation with EPA and DHA prior to and during treatment. At present, there are no other reports of the effects of EPA and DHA on lipid infiltration of muscle in the neoplastic state.

What is your hope for the future therapeutic interventions for cancer?

There is still much to learn about metabolism during each stage of the cancer trajectory, and subsequently what nutrients people with cancer may require compared to healthy people. Knowing this information, we can tailor our interventions towards individuals who are newly diagnosed undergoing treatment or recovering from therapy.

However, very little research money invested in chronic disease is directed towards nutrition, in spite of the knowledge that diet and lifestyle play an integral role in the development of these conditions. I should like to see nutrition research in the realm of cancer care prioritised for funding.
Bodybuilding to fight cancer

Trials of nutritional supplements that deliver polyunsaturated fats at the University of Alberta, Canada, have demonstrated improvements in the effectiveness of chemotherapy treatment, as well as an increase in muscle mass in cancer patients. With their nutrition-focused approach, the team has identified for the first time a relationship between supplementation of n-3 fatty acids and infiltration of muscle by fats.

UNINTENTIONAL WEIGHT LOSS is a hallmark of cancer. Once the diagnosis is made, the disease itself, accompanying anxiety and the side effects of chemotherapy, can all reduce appetite. Many cancer patients see weight loss as beneficial; for obese people in particular, loss of a small percentage of body mass each week may not initially be a concern. However, over the course of weeks of chemotherapy and recovery afterwards, maintenance of sufficient weight, essential to coping with and fighting the disease, can become a life-threatening issue. Malnutrition causes the body to access the energy and protein resources of lean body mass, as well as adipose tissue, leading to muscle atrophy and thus reduced stamina, frailty and disability. So in combination, the extra energy requirements needed to fight cancer, the toxicity of generalised treatment with chemotherapy, and structural and functional changes in both body composition and muscle ultimately significantly impact upon cancer patients' quality of life. Loss of muscle mass and density also predict length of survival in cancer patients.

In recent studies, Mazurak has explored the effects of dietary supplementation with fish oils high in Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) in humans as well as animal models of cancer: "I approach my research by identifying the underlying alteration in metabolism and then determine how nutrients could overcome, modify or correct these deficits," she explains. In both contexts, the studies have shown dramatic improvement in maintenance of both muscle quality and quantity.

MEASURING MYOPENIA AND MYOSTEATOSIS

In cancer, muscle tissue breaks down quickly and synthesis of new muscle cells declines. Independently of body mass index (BMI), skeletal muscle depletion – myopenia – has been shown to directly predict a decrease in a cancer patient's survival. Until Mazurak and Murphy's recent investigations, less was known about alterations in fat metabolism in cancer and what effects cancer-induced changes might have on a patient's functional state, quality of life and survival prospects.

Information about patient weight loss is generally self-reported and medical records seldom contain detailed information about a patient's BMI or height. For Mazurak's explorations, therefore, computerised tomography (CT) scans, which are taken for initial diagnosis and localisation of tumours and then at intervals for treatment monitoring purposes, have proved an invaluable source of data. CT scans provide a precise means of recording and measuring key components of body composition: fat (including subcutaneous, visceral and intramuscular) and protein. Setting the third lumbar vertebra as the landmark, Mazurak can input scans of the same patient taken over time to an analysis program called Slice-o-matic, which then allows her not only to see, but also to quantify, the changes in the patient's fat and muscle tissues as they unfold, and also mount comparisons of the trajectory of disease and its impacts on muscular and adipose tissue between patients with the same BMI.

Working backwards from the date of death, Mazurak's group has found that, about 180 days beforehand, the effects of malnutrition on body composition intensify and loss of adipose tissue and muscle occur at an accelerated rate. With Murphy, she therefore sought to find out when a nutritional intervention might have most impact; electing to explore this question in lung cancer patients, who, even if their weight loss is mild, are less likely than some other cancer patients to be successfully treated with chemotherapy.

FATTY ACID METABOLISM

In lung cancer patients, phospholipids and the fatty acids they carry – omega-3, omega-6, polyunsaturated fatty acids – in the blood...
The weight and skeletal muscle of those patients receiving fish oil supplements were maintained and the quantity of intermuscular adipose tissue was also reduced.