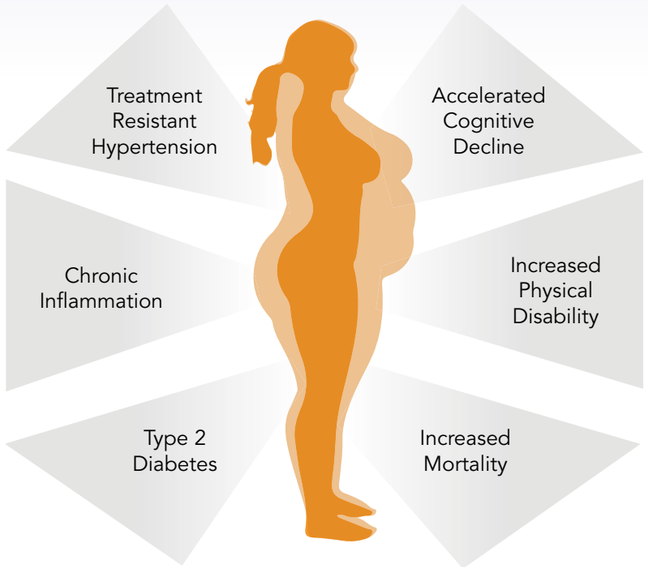
Is the magic in the muscle?

Targeting skeletal muscle to improve cardiometabolic function in ageing

Dr Joshua T Butcher and his team from the Oklahoma State University College of Veterinary Medicine, USA, investigate the similarities between the co-morbidities associated with obesity and ageing, and specifically how skeletal muscle mass and function can be used to uncouple diseases from accompanying pathology. While we all know that exercise is beneficial for weight loss, an important underlying benefit of exercise is increased muscle mass and function. Indeed, many of the benefits of exercise occur in an independent manner to changes in fat. This suggests that weight loss should not necessarily be a focus of exercise. Research in the Butcher Lab explores the skeletal muscle and aims to convey the benefits of exercise onto a patient (both human and animal), independent of exercise itself. Of course, if the body can successfully be 'fooled' into believing it has exercised, then the applications could help patients unable to exercise, and increase the health and life-span of older and obese patients.

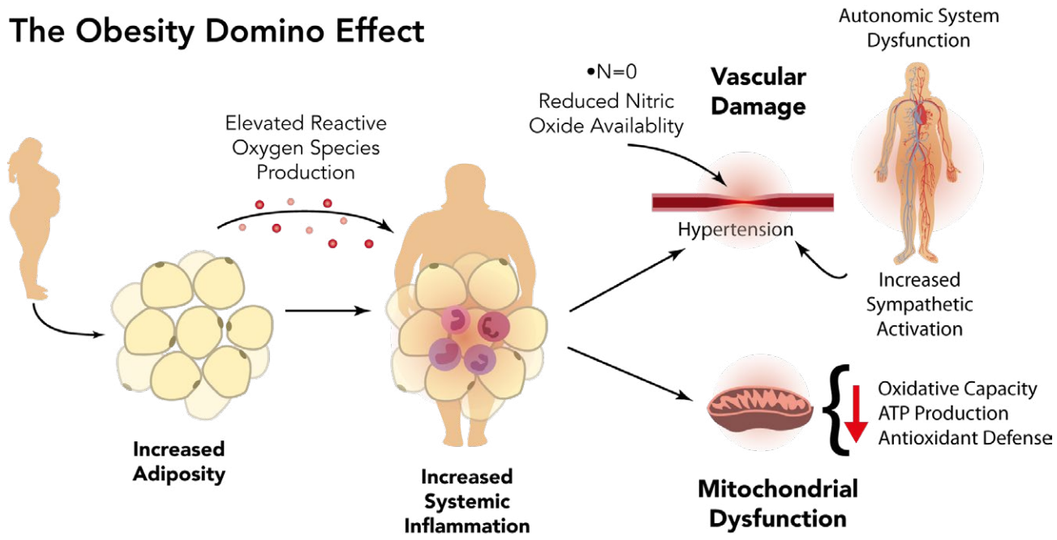
The human body is remarkably complex and many of its components, especially in the context of diseases states, remain poorly defined or even largely unexplored.

That complexity takes on a whole new level as we have to consider not only the interconnectivity of the elements within ourselves, but also the differences that occur between species, and our ever-changing shared environment. The One Health concept recognises the interconnectedness between the health of people, animals, and the environment. The complexity of this One Health concept brings with it new frontiers for discovering interventions and therapies for diseases. It involves collaboration across human and animal health, as well as the environment. There are lessons to learn from animals and a complete understanding of animal health can drive innovative solutions in human medicine, and vice versa.



Dr Joshua T Butcher is attempting to incorporate these ideas into his research paradigm. He is an assistant professor in the Department of Physiological Sciences at the Oklahoma State University College of Veterinary Medicine (CVM) in Stillwater, Oklahoma, USA. Butcher is a classically-trained cardiovascular physiologist with a background in analytical chemistry. His work at CVM involves examining the dynamic interplay of muscle mass on cardiovascular disease, obesity, and ageing.

What interests Butcher and his team, including Emily Nunan, a dual degree DVM/PhD student, is whether manipulating muscle mass can help prevent cardiometabolic diseases that accompany obesity – a group of common but often preventable conditions, including diabetes, heart attack, stroke, and non-alcoholic fatty liver disease – especially in older patients. And by 'manipulating', he means using exercise mimetics directly



targeting skeletal muscle mass and function, independent of changes in actual activity.

MIMICKING EXERCISE

Exercise mimetics are natural or synthetic pharmaceutics that mimic the effects of exercise by activating critical regulators in the body, particularly those that allow for muscle growth or maintenance, especially after injury. Of course, most of us immediately think of anabolic steroids, common and often abused performance-enhancing drugs that certainly result in overall increases in muscle mass. However, long-term use of these drugs are accompanied with increasingly negative side effects. There are other pathways that can be targeted (for example myostatin, PGC1α) that could offer mechanisms to better health, especially for the elderly and obese facing the threat of the overall decline in muscle function and the morbidities listed earlier. At the very least, by targeting skeletal muscle and keeping it healthy in obesity and ageing, via exercise or an exercise mimetic, a patient – be it human or animal – has a better chance of increasing their health and potentially their life span.

MUSCLE AND DISEASE

Rodents and exotic animals are the focus of Butcher's basic science laboratory at CVM. The researchers in the lab directly manipulate muscle mass in mice, using a combination of genetic, pharmaceutical, or nutritional techniques, to not only determine the overall effects on muscle mass and function, but determine whether these positive impacts on muscle also translate into better cardiometabolic health overall (eg, glucose homeostasis, kidney and vascular function). Based on this, they can examine whether the healthier muscle can 'buffer' against a disease and, if so, how. The question then becomes whether this mechanism can be clinically translated, and if prompting this mechanism through pharmacological intervention could help those patients who are unable to physically exercise.

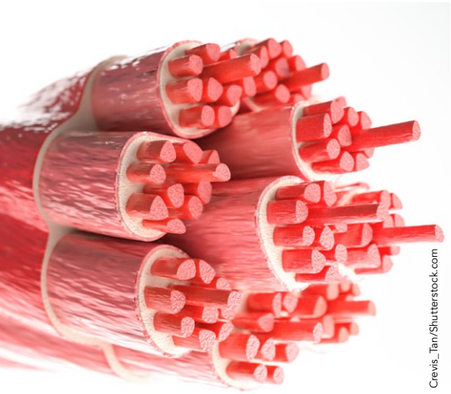
Skeletal muscles work when we want them to work, and when we work them, it's good for our whole body.

One of their current areas of research explores the correlation between decreased muscle function and increased obesity-derived cardiometabolic function in younger patients, a correlation that bears remarkable resemblance to what occurs naturally in the elderly. The elderly also experience marked loss of skeletal muscle mass and function (a term called sarcopenia) and this also occurs with dramatic increases in the risk of developing cardiometabolic disease.

The human body has three types of muscle tissue: cardiac muscle, which is confined to the heart itself and responsible for coordinated movement for pumping blood; smooth muscle, a spatially diverse muscle making up the various organs, including blood vessels and the digestive tract; and skeletal muscle. While cardiac and smooth muscles are controlled by the autonomic nervous system and are therefore involuntary – they work without us thinking about them – skeletal muscles, which make up most of the muscles in the human body, are voluntary. Indeed, while it's hard to imagine because skeletal muscle is fairly spread out within the body, it is the largest organ in most animals, including humans. Skeletal muscles work when we want them to work, and when we work them, it's good for our body as a whole. When we lose skeletal muscle health because of ageing, we develop a condition called sarcopenia. Butcher believes this has links to other diseases associated with ageing.

In his research, Butcher has also noticed that many of the key indices that define the pathology of ageing also define the pathology of obesity. His concern is that in the USA, the current trajectory of obesity will see an increasing number of

Research in the Butcher Lab aims to manipulate muscle mass to help prevent cardiometabolic diseases that accompany obesity.



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older adults displaying a convergence of these pathologies, a condition called sarcopenic obesity.

AGEING AND OBESITY

In humans, sarcopenia normally kicks in after the age of about 50, and is associated with loss of skeletal muscle mass and quality. This accelerates the overall decline in muscle function. If a person doesn't exercise or remain active, they can lose about one percent of muscle mass annually. Such reductions in muscle mass and function also accompany obesity. Much of this results from a negative impact from nearby adipose, or fatty, tissue. Muscles not needed for weight-bearing are especially vulnerable. Butcher's research with mice shows that obesity also reduces the body's production of regenerative muscle stem cells.

As humans age, they lose the sex hormones – testosterone in men and oestrogen in women. The results are a decrease in muscle size and strength, higher blood-sugar levels, and accelerated fat deposition – conditions also observed in obese individuals. Fat, however, is not always a bad thing. Indeed, fat is a crucial component of cell health – it literally keeps our bodies from falling apart. The issue about whether it's healthy or not depends on how much of it there is and where it is. Fatty tissue deposited under the skin – termed subcutaneous adipose tissue, or SAT – serves a broadly protective purpose; but if fatty tissue collects around vital organs – termed visceral adipose tissue, or VAT – it can present a threat, especially if it becomes inflamed. As humans age, VAT accumulation increases, but this is also the case when they become obese.

RECREATING OBESITY

By using pharmaceutics or genetic manipulation, Butcher and his team have recreated obesity conditions in mice and noticed other links between obesity and ageing. One of those is the development of hypertension, or elevated blood pressure, leading to an increased risk of cardiovascular disease. Both ageing and obesity are also associated with decreasing levels of nitric oxide (NO) in the blood. NO is essential for opening blood vessels and helping blood flow more freely. Elevated levels of free radicals – oxygen-containing molecules with an uneven number of electrons – often go hand-in-hand with decreasing levels of NO. These highly reactive molecules latch on to healthy cells in the body, causing damage to other molecules, such as DNA, lipids, and proteins. This toxic environment of oxidant stress increases the risk of developing serious illnesses such as cancer.

One of the more obvious links between the conditions of obesity and ageing is the loss of glucose homeostasis – the body's ability to regulate its blood sugar levels. The outcome is a heightened risk of developing type 2 diabetes. Less known is that ageing and obesity are both linked to a breakdown in mitochondria, the cell compartments that generate energy for the cells to work. However, while the loss of mitochondrial function is a natural part of ageing, research shows that exercise in elderly subjects helps counteract the effects of ageing on mitochondria in skeletal muscles. In obese people, the breakdown of mitochondrial function is brought about by excess calorific intake overwhelming mitochondrial and cellular processes.

For every disease that resists our best efforts for treatment or cure, there's likely a fellow animal that has developed a natural resistance.

Here's the crux of Butcher's concern: if obesity and ageing share morbidities, what is the compound effect of a population with an increased prevalence of obesity as it starts ageing? Does obesity cause premature ageing of skeletal muscle and what are the implications of this in a younger population, especially when they become older? This should concern health authorities, especially in the many developed countries with rising rates of obesity. Encouraging the elderly and obese to exercise regularly is one way to minimise the risk of morbidities. Exercise is widely accepted to prevent or mitigate metabolic diseases such as type 2 diabetes and cardiovascular diseases. Furthermore, muscle-secreted factors called myokines facilitate communication between muscle and other organ tissues, helping to keep them healthy.

This raises a key question: given that we know how overwhelmingly beneficial exercise is to patients, how do we convey those benefits (specifically healthy skeletal muscle) onto a patient who is unable to exercise? There is a broad swathe of patients who are unable to exercise at a level that conveys benefit, consider for instance those confined to long-term hospital stays, physical injuries, or those limited by space, time, finances, or a pandemic. Therefore, it should be worthwhile to consider alternative ways to maintain healthy skeletal muscle, particularly approaches that deliver benefits to people unable to exercise.

Butcher and his team recognise the interconnectedness of the health of people and animals. Their aim is to better understand not only human health but also animal health. Hopefully, they can leverage their novel advances in understanding the role that skeletal muscle plays in health (and disease) and potentially increase healthspan, both for human and animal patients.

Behind the Research

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Research Objectives

The Butcher Lab investigates the dynamic interplay of muscle mass (a by-product of exercise) on cardiovascular disease, obesity, and ageing.

Detail

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Bio

Dr Joshua T Butcher is an assistant professor in the Department of Physiological Sciences at the Oklahoma State University College of Veterinary Medicine. He was awarded a PhD in cellular and integrative physiology from West Virginia University. His research interests lie in advancing One Health through examining the effect of skeletal muscle (dys)function on health and disease.

Emily Nunan is a dual degree DVM/PhD student at Oklahoma State University College of Veterinary Medicine. She completed a Bachelor of Science degree in biochemistry and molecular biology from Oklahoma State University.

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Collaborators
The most rewarding science is that which is accomplished with friends and we gratefully acknowledge our collaborators on this work, including Madhan Subramanian, Priya Balasubramanian, Pamela C Lovern, Ibra S Fancher, and João Brandão.

References

Nunan, E, Butcher, JT, et al (2022) Obesity as a premature aging phenotype — implications for sarcopenic obesity. *GeroScience* 44:1393–405. doi.org/10.1007/s11357-022-00567-7

Personal Response

How likely are we to see targeted therapy using exercise mimetics in the elderly in the USA?

"The world is experiencing a 'global greying' phenomenon, largely due to the ability of our clinicians to overcome previously terminal diseases and extend life span in patients. However, the older patient population presents itself with additional challenges, especially in those with multiple comorbidities (like obesity). Given the loss of quality life in those with mobility challenges and the rising cost of disability, I'd bet that targeted skeletal muscle therapy via exercise mimetics gains significant traction within 10–15 years."

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