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Research statement and goals

I have a long-standing research interest in nutrition and exercise, and studying their integration *in vivo* in humans. My research translates to human health and performance by primarily focusing on the potential of exercise and nutrition to induce acute shifts in cellular and whole-body substrate metabolism. In addition, I also examine chronic adaptations, and functional significance, to prolonged exercise training and nutrient availability. I favor interdisciplinary approaches to human health related questions, and have incorporated physiological approaches to better understand the whole-human response to exercise and nutrition.

My research uses a variety of techniques. *In vivo* metabolic labeling through stable isotope tracers not only provides a window into the intricacies of protein (amino acid) metabolism, but also allows for high throughput proteomic-based approaches to better understand how muscle cells coordinate and adjust their proteome to my area of study. I also investigative aspects of carbohydrate metabolism through oral glucose tolerance tests, which seek to derive indices of insulin sensitivity in response to nutrition, exercise, and poor health. Finally, I employ more targeted approaches as well, such as Western/immunoblotting methods, to examine the molecular readouts that may be underpinning acute metabolic responses and chronic physiological adaptations. In general, my research incorporates both sports and clinical nutrition based protocols that directly assess the *in vivo* status across multiple human conditions, including athletes, aging, obesity, and chronic kidney disease patients. My overall goal is to perform translational research aimed at identifying cost-effective and sustainable strategies through diet and exercise manipulations to promote health and physical performance across the lifespan.

Exercise and nutritional regulation of skeletal muscle mass

My current research primarily encompasses the use of stable isotope tracers of amino acids to understand how exercise, nutrition, or disease may regulate skeletal muscle mass (e.g., protein synthesis). However, this method also traces the metabolic fate of amino acids at the whole body level (e.g., protein synthesis, breakdown, and oxidation). Protein ingestion and exercise are the two main anabolic stimuli to human skeletal muscle tissue for maximizing net muscle protein balance. Thus, the application of nutrition and exercise physiology approaches provides an understanding of the mechanisms regulating skeletal muscle mass under various human conditions. There are many potential sites of skeletal muscle mass regulation in response to acute exercise and food ingestion. For example, ingested protein needs to be digested into amino acids and absorbed into the blood in adequate amounts in order to provide a strong anabolic signal to skeletal muscle tissue. Hence, the digestion and absorption kinetics of ingested protein is an important regulatory factor for the stimulation of the postprandial muscle protein synthetic response. Unfortunately, commonly used methodologies to assess protein digestibility (e.g., ileal digestibility) are challenging to execute *in vivo* in humans due to their invasive nature, and the methods cannot be applied with exercise. Alternatively, intrinsic labeling of protein foods with stable isotope amino acids have been useful to provide an index of protein digestibility *in vivo* in humans, and can be used in the exercise-state. Moreover, the protein digestibility measurements can be coupled with measurements of muscle protein synthesis rates to provide a more complete picture of the factors regulating skeletal muscle mass. For this reason, our laboratory has developed intrinsically labeled eggs for *in vivo* assessments of protein digestion and absorption kinetics and the subsequent muscle protein synthetic response in humans.

My current investigations are aimed at the influence of nutrition and exercise on the regulation of muscle protein turnover in aging, obesity, and chronic kidney disease. These populations generally share a common theme of inactive lifestyles. In the context of aging, there is an observed anabolic resistance of muscle protein synthesis rates to protein ingestion. It is currently unclear if this anabolic resistance of aged muscles is underpinned by an intrinsic defect in the upstream mechanisms of muscle protein synthesis rates, or simply a manifestation of an inactive lifestyle. Currently, my research group is conducting studies to assess the anabolic responsiveness of muscle protein synthesis rates to acute resistance exercise in older women when compared to their younger counterparts. This work will provide a basic understanding of how aged muscles are responding to a fundamental

anabolic stimuli of resistance exercise alone or combined with feeding. In addition, this work will fill a knowledge gap to an understudied area of aging women. We are also conducting a prolonged resistance training study in middle-aged men and women to assess the influence of the protein density of the diet to support multiple facets of health and well-being including muscle, cognitive and psychological health. Collectively, these data will better define how nutrition and exercise can be used, separately or together, to support muscle health and physical performance with advancing age.

My current research has also focused on obesity, and is consonant with the increasing public health concern for obesity prevalence in US adults. Our research has demonstrated that anabolic resistance of muscle protein synthesis rates to protein-dense food ingestion also occurs in people with obesity. We have recently conducted a study to test whether an acute bout of resistance exercise prior to protein ingestion can recover the feeding-mediated responsiveness of muscle protein synthesis rates in people with obesity. This work demonstrated that excess fat mass diminishes the interactive nature of feeding and resistance exercise to stimulate muscle protein synthesis rates in sedentary young adults. Our focus of future research in this area is to re-sensitize the anabolic machinery and muscle protein synthesis rates with obesity by prescribing a more robust exercise prescription, at least until evident weight loss. However, the long-term consequences of obesity on muscles are not fully understood, and it is still not clear if weight loss can fully restore anabolic sensitivity to exercise and food ingestion. Notwithstanding, this initial work has provided a better understanding, and unique perspective, of the mechanisms driving human skeletal muscle remodeling in response to nutrition and exercise in people with excess fat mass. As such, this work will serve as preliminary data for future R01 applications to the National Institutes of Health (NIH).

Lastly, I have recently investigated the regulation of muscle mass in individuals on maintenance hemodialysis (MHD). This is a complex, yet pertinent, human model to explore the mechanisms by which nutrition and exercise regulate skeletal muscle mass. Specifically, individuals with end-stage renal disease, undergoing MHD, experience numerous metabolic and phenotypic derangements including skeletal muscle mass wasting. The underlying mechanisms of skeletal muscle wasting in individuals on MHD is not clear, but likely involves several factors, including: chronic inflammation, reduced protein intake, metabolic acidosis, insulin resistance, hormonal abnormalities, increased substrate oxidation, and nutrients/amino acid loss during dialysis. Moreover, catabolism is not only inherent to the dialysis procedure, but this catabolic state persists for hours, and even days, post-treatment. Thus, individuals on MHD spend a majority of the time in a catabolic-state. My research group has recently conducted an experiment to assess how MHD muscle responds to the ingestion of a protein dense meal on a non-dialysis day. This work demonstrated skeletal muscle subject to MHD is over stimulated in the basal state as muscle protein synthesis rates are ~2-fold elevated, coupled with increased proteolysis, when compared to age- and BMI-match controls. Moreover, protein digestion and amino acid absorption kinetics and the postprandial muscle protein synthetic response were severely impaired in individuals on MHD versus controls. Thus, individuals on MHD demonstrate an anabolic resistance of muscle protein synthesis rates to protein ingestion. Our work seems to confirm catabolic carryover even into non-treatment days, but also provides new insight that this condition induces negative consequences on MHD muscle protein metabolism. Our future research focus is to test if individuals on peritoneal dialysis (PD) also experience overt anabolic resistance to protein ingestion so that we may better define, and isolate, how detrimental dialysis treatment is to individuals with end-stage renal disease.

Collectively, we have published a number of manuscripts in high quality journals including: *American Journal of Clinical Nutrition* (impact factor: 6.77), *The Journal of Clinical Endocrinology and Metabolism* (5.455), *Medicine & Science in Sports & Exercise* (4.459) and *Journal of Nutrition* (4.145). These data have been leveraged into NIH grant applications that have not been funded. However, I believe I am currently equipped with

adequate experience and evidence for more competitive submissions, and this will be an impetus of my future grant writing efforts.

Other research

I also have an interest in applied exercise physiology to investigate the physiology of high performance. Investigating the physiological and performance outcomes of athletes provides relevant information on several levels. For example, generally an athlete can carry out repeated exercise tasks to a constant degree, and thus provides insight into the test-retest reliability of a method. Secondly, athletes are in a trained-state, thereby providing 'gold standard' responses to a particular exercise stimulus. This information is relevant when constructing a physiological continuum of worst (pathological) to optimal physiological responses to a particular feeding or exercise manipulation. Lastly, performance physiology often serves as a gateway in translational research for new scientific recruits (e.g., undergraduate research assistants) within our kinesiology program. Therefore, research in athletes can stimulate, and hold, their interest in exercise physiology based science, and potentially open a door to grow an interest in other lines of research. To this end, we have conducted externally funded studies to define optimal fueling strategies to support time trial performance in trained cyclists. In addition, we have investigated the impact of resistance exercise manipulations to modulate the post-exercise muscle protein synthetic response in trained weightlifters. Other interests of mine include the development of more sustainable and cost-effective strategies to improve the use of protein in the diet for muscle maintenance and health. Current protein recommendations have been defined by using maximal protein dosing to elicit a robust rise in postprandial muscle protein synthesis rates. Practical applications of maximal protein dosing for the stimulation of muscle protein synthesis rates, which have been developed based on isolated protein sources, may be challenging to achieve when considering other nutrient requirements. Defining the optimal protein dose would be useful as it seeks to maximize the use of dietary of amino acids for muscle protein synthesis while minimizing amino acid oxidative loss, thereby reducing the environmental strain from increased protein production. Potential strategies include eating protein as part of its natural food matrix (as opposed to an isolated form), incorporating regular exercise into a lifestyle, and eating a healthy distribution pattern of protein throughout the day.

Future directions

In conclusion, my future plans are to continue conducting research on aging, obesity, and individuals with chronic kidney disease with the goal of demonstrating the efficacy of exercise and diet quality to improve skeletal muscle mass and function. Moreover, I continually seek to innovate methods and test their utility *in vivo* in humans. We are currently adopting dynamic proteomics measurements in our interventions. Dynamic proteomics may be a promising and novel tool to screen for potential protein biomarkers involved in disease pathways or health *in vivo* in humans. However, these 'omics' based approaches need to be coupled with techniques that have proven physiological relevance (e.g., established measures of protein synthesis, oral glucose tolerance, substrate oxidation, etc.) to provide a valid functional reference for protein network changes.

My short-term research goal is to define optimal anabolic conditions through acute metabolic interventions. Outputs will provide the framework for developing effective prophylactic and therapeutic strategies to prevent disease and promote health throughout adult life. My primary long-term research goal is to continue my program of research by expanding into new areas that include the interactions between muscle, brain, and gut for overall health. I have already made efforts to achieve this goal through collaboration with colleagues both the University of Illinois and other institutions. The outcomes from my research program will contribute to public health policies, and improve standard health practices, to include exercise and diet quality as the forefront initiatives to improve overall health and physical performance across the lifespan.