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## An Endocrinologist's Perspective: Effects of Disease on Nutrient Metabolism and Muscle Loss

Marcus DaSilva Goncalves, MD, PhD, is entering his third year of a four-year research fellowship in the Division of Endocrinology at New York-Presbyterian/Weill Cornell Medical Center. It is the final phase in what will be his more than 15-year journey to become a physician-scientist when he completes his fellowship in 2018. In actuality, however, his goal to understand the complex interplay of metabolic organs to store and metabolize nutrients began to take shape in his youth.

“This desire started when I was 12 years old and I realized I could modify my own body composition by changing my diet and exercise regimen,” notes Dr. Goncalves. “I searched the fields of nutrition and exercise physiology to learn more about the mechanisms behind these changes but I was not satisfied with the quality of the evidence I found.”

His preoccupation with the subject and the paucity of information led him to Johns Hopkins University as an undergraduate studying biomedical



Dr. Marcus D. Goncalves

engineering. “Here I learned the engineering, mathematical, and computational tools that are essential to understanding the feedback regulation

*(continued on page 2)*

## Acromegaly: Addressing a Rare Endocrine Disorder

While small pituitary adenomas are common, affecting about 17 percent of the U.S. population, research suggests that most of these tumors do not cause symptoms and rarely produce excess growth hormone. According to the National Institutes of Health, scientists estimate that three to four out of every million people develop acromegaly each year.

“In almost all cases, acromegaly is due to a growth hormone-producing tumor of the pituitary gland,” says Pamela U. Freda, MD, Clinical Director of the Neuroendocrine Unit in the Division of Endocrinology and Co-Director of The Pituitary Center at New York-Presbyterian/Columbia University Medical Center.

Because the clinical diagnosis of acromegaly is often missed, these numbers likely don't reflect the true frequency of this rare and often disfiguring disease – the most common features being abnormal growth of the hands and feet. Overgrowth of bone

and cartilage often leads to arthritis; body organs, including the heart, may also enlarge. Acromegaly is currently under-recognized and under-diagnosed, notes Dr. Freda, who for much of her career has specialized in the diagnosis, treatment, and research of this disease.

“The diagnosis of acromegaly is typically not made until patients experience signs and symptoms of the disease for an average of seven to eight years,” she says. “As acromegaly cannot be detected on routine laboratory testing, the diagnosis needs to be first considered based on history and physical examination findings and then confirmed biochemically by measurement of a serum IGF-1 level and measurement of GH suppression during an oral glucose tolerance test. Early recognition is crucial because acromegaly is associated with many comorbidities, including hypertension, diabetes, and arthritis, that can significantly reduce survival.

*(continued on page 3)*

## Nutrient Metabolism and Muscle Loss (continued from page 1)

of nutrients and metabolic hormones in the body,” says Dr. Goncalves, who started in his freshman year doing laboratory research. “I was involved in a project looking at how yeast cells communicate with each other via small proteins – much like hormones in the body. This was my first insight into hormone function and regulation and my introduction to the basis of endocrinology. I wanted to know which hormones were responsible for regulating muscle and fat in a larger organism with many cells rather than a single-cell microorganism.”

Dr. Goncalves took these tools with him as he moved on to his master’s studies in biomedical engineering at Johns Hopkins and PhD studies in cell biology and physiology at the University of Pennsylvania. At the latter, his research involved investigating the regulation of several types of hormones that regulate skeletal muscle mass and glucose homeostasis, as well as the role of myostatin on muscle growth and metabolism.



*Cross-sectional images of the chest taken from two mice with lung cancer: one with cachexia and one without*

improve muscle mass and function in the mdx mouse model of Duchenne muscular dystrophy. Study data showed that targeting activin receptor type IIB improved skeletal muscle mass and functional strength, providing a therapeutic rationale for use of this molecule in treating skeletal myopathies.

During this time,

Dr. Goncalves also led research on the differential effects of chemotherapy on the metabolic activity of skeletal muscle in patients with melanoma. Using molecular imaging with [18F]-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT), the researchers showed that FDG-PET/CT can reveal baseline metabolic differences between different muscles of the body and detect and quantify differential changes in the metabolic activity of skeletal muscle associated with different chemotherapies.

### A Concentration on Cachexia

Dr. Goncalves then entered the Medical Science Training Program (MD/PhD program) at the University of Pennsylvania School of Medicine in 2012. “I pursued medicine to develop a more complete understanding of human physiology and pathophysiology,” he notes. “I observed the dramatic effects that disease can have on nutrient metabolism. Cancer is one example where a small cellular change can alter metabolism so greatly that the body loses its ability to maintain essential nutrients like triglyceride and amino acids. This cachexia syndrome causes patients to waste away and die of frailty and immobility. It has no clear diagnostic methodology, no known mechanism, and no FDA-approved treatment.”

Following medical school, with his interest in this area solidified, Dr. Goncalves narrowed his attention on studies of the mechanisms that lead to muscle loss in patients with cancer. His ultimate goal is to develop effective treatments that prolong and improve quality of life with a complementary goal of bridging the gap between science and medicine in the field of endocrinology, nutrition, and exercise physiology. “Many clinicians fail to understand the basic mechanisms that control energy balance and many researchers do not appreciate the biopsychosocial approach to medical treatment,” says Dr. Goncalves. As a physician-scientist, and with training that crosses biomedicine, basic science, and patient care, Dr. Goncalves now brings a unique perspective to studying disease-related muscle loss in model organisms and through to clinical trials.

For the past two years Dr. Goncalves has been an endocrinology research fellow in the laboratory of **Lewis C. Cantley, PhD**, Meyer Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. In addition to muscle loss in cancer, Dr. Goncalves is also interested in muscle loss during critical illness, basic mechanisms of skeletal muscle growth and metabolism, insulin signaling, and developing new radiologic methods

*(continued on page 4)*

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**— Dr. Marcus D. Goncalves**

“While looking for a lab to join, I was offered a project by an endocrinologist who was also a physician-scientist,” notes Dr. Goncalves. “He was investigating a drug that increases muscle size in a mouse but, for reasons unknown, the mice went on to lose all of their body fat. The project couldn’t have been more perfect for me. The research was focused on a protein called myostatin which, when you take this protein away, causes the muscles to get much bigger. So it releases a stop signal that’s naturally present. While this has not been proven, I believe myostatin is a muscle hormone that works together with catabolic steroids to break down the muscle fiber. Muscle fibers are the body’s reservoir for amino acids so it makes sense that muscle is called upon to release amino acids in times of metabolic need. When you take the myostatin away, catabolism is being shut down, tipping the balance towards protein synthesis and anabolism.

“The implications for treatments targeting myostatin are vast,” continues Dr. Goncalves. “Involuntary loss of skeletal muscle (termed sarcopenia) is associated with many common diseases, including sepsis, chronic obstructive pulmonary disease, HIV infection, burn trauma, and cancer.” As proof of principle, Dr. Goncalves participated in a study targeting myostatin’s receptor (activin receptor type IIB) to

## Acromegaly: Addressing a Rare Endocrine Disorder (continued from page 1)

The diagnosis should be suspected in a patient with the characteristic clinical findings.”

Dr. Freda is one of four endocrinologists in Columbia’s Neuroendocrine Unit. Under the direction of **Sharon L. Wardlaw, MD**, the Unit treats patients with the full range of disorders of the pituitary gland. These include nonfunctioning pituitary tumors, Cushing’s disease, prolactinomas, and other types of tumors in the region such as craniopharyngiomas, as well as hypopituitarism, diabetes insipidus, lymphocytic hypophysitis, and other diseases that affect the pituitary or hypothalamus. “Ours is very much a multidisciplinary team approach to these neuroendocrine disorders and we work very closely with neurosurgery, neuroradiology, neuro-oncology, and radiation oncology in the care of our patients,” says Dr. Freda.

### Integrated Clinical and Research Endeavors

According to Dr. Freda, the main goal of therapy for acromegaly is to achieve biochemical control, including suppression of GH and IGF-1 normalization. “Transsphenoidal surgery is the most effective treatment for relieving the signs and symptoms of the tumor mass effect and can be curative in many patients,” explains Dr. Freda. “In selected patients, medical therapy can be used initially. In patients who are not successfully treated by surgery alone, we institute medical approaches that include therapy with



MRI of a pituitary tumor

somatostatin analogues and/or a growth hormone-receptor antagonist. Some patients also undergo radiotherapy, which can take many years to take effect. So in the interim, medical therapy is also begun.”

Complementing the Neuroendocrine Unit’s clinical programs is a robust research program funded by the National Institutes of Health and industry. The Unit has the only NIH-funded research program for acromegaly in the country and the only NIH-funded research program for pituitary disease in the New York area. These programs offer patients the opportunity for novel diagnostic and therapeutic options for their pituitary tumors above and beyond those routinely available.

“For the past 20 years my research has focused on acromegaly,” says Dr. Freda, who is internationally recognized for her clinical and research program. “Our Neuroendocrine team at Columbia is widely known for our rigorous acromegaly research program and high quality clinical care of pituitary tumor patients.”

Dr. Freda and her colleagues have established and follow prospectively a uniquely large cohort of patients with acromegaly that has grown considerably over the years. “We have undertaken many studies based on this cohort,” she says. “Much of our research has aimed to determine how best to diagnose the disease and to determine whether or not patients are cured after treatment.”

Dr. Freda’s major research interests focus on clinical and translational investigations. In one series of studies of newly diagnosed and postoperative patients with acromegaly, she examined serum



Dr. Pamela U. Freda

IGF-1 levels relative to the upper normal limit related to insulin sensitivity, serum cardiovascular risk markers, and body composition. The researchers found that active acromegaly presents a unique combination of features associated with cardiovascular risk, reduced insulin sensitivity, yet lower body fat and lower levels of some serum cardiovascular risk markers, a pattern that is reversed in remission. “The percentage of the upper limit of normal of IGF-1 levels strongly predicts these features,” says Dr. Freda. “Our findings suggest that of all the factors insulin resistance is the most strongly related to disease activity and potentially to the increased cardiovascular risk in active acromegaly.”

In another study, the results of which were published in *Endocrine Practice*, the Columbia researchers took part in ACROSTUDY, an observational registry intended to collect safety and efficacy data on pegvisomant, a growth hormone receptor antagonist, in the treatment of acromegaly. The global safety surveillance study, which was set in 14 countries and 373 sites, analyzed safety, MRI readings, and treatment outcomes in 710 subjects who received at least one pegvisomant dose during and up to five years of follow-up. The ACROSTUDY data indicate that pegvisomant used as the sole medical therapy is a safe and effective medical treatment for this disease. The reported low incidence of pituitary tumor size increase and liver enzyme elevations support the positive benefit-risk of pegvisomant.

“Even though acromegaly is rare, its progression is insidious,” says Dr. Freda. “Increased clinical vigilance and earlier diagnosis can make a real difference in the lives of patients.”

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## Advances in Endocrinology

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### Nutrient Metabolism and Muscle Loss (continued from page 2)

to assess skeletal muscle quality and function. The first year of his fellowship was dedicated to patient care, dividing his time between endocrinology consults at New York-Presbyterian/Weill Cornell and oncology consults at Memorial Sloan Kettering Cancer Center. He is now deep into the research component of his fellowship, continuing his work on mouse models of cancer and cachexia. He also collaborates with **Kenneth P. Olive, PhD**, Director of the Small Animal Imaging Shared Resource in the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center, on a pancreatic mouse model looking at both histology and metabolism.

“We have a few different genetic models where the mice spontaneously develop tumors,” says Dr. Goncalves. “They all develop the same metabolic disease as patients with cancer. As an endocrinologist, I ask different questions than the muscle-specific or cancer-specific biologists. I’m interested more in skeletal muscle metabolism and why the muscle is breaking down from a metabolic point of view rather than a cancer point of view. Some researchers believe that the muscle breakdown is purely from inflammation. I think that other hormones are altered – especially testosterone, insulin-like growth factor, and cortisol.”

According to Dr. Goncalves, treatments for cancer-induced muscle loss are basically non-existent. “Protein or amino acid supplements are sometimes used which may or may not work. Some groups have tried medications off-label such as beta blockers or nonsteroidal anti-inflammatories. These also have very weak data related to results. So the field is wide open for something that can help – even a little – which can make a big difference in a patient’s quality of life while undergoing cancer treatment.”

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