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ADVANCES IN ENDOCRINOLOGY

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Pathways to Diabetes Prevention: It's All Relative

In 2015, **Magdalena M. Bogun, MD**, an endocrinologist in the Naomi Berrie Diabetes Center at NewYork-Presbyterian/Columbia University Irving Medical Center, was one of four physicians selected to participate in the TrialNet Emerging Leaders Program designed to promote the engagement of new investigators in diabetes clinical research. Dr. Bogun focused her research on the natural history of type 1 diabetes drawing on data from TrialNet, an international network of leading academic institutions, physicians, scientists, and healthcare teams that conduct investigations on the study, prevention, and early treatment of type 1 diabetes (T1D).

"My investigation was a longitudinal study of insulin secretion in patients who have had metabolic testing both before and after diagnosis of T1D," says Dr. Bogun. "We found that insulin production decreases long before a patient is actually diagnosed with type 1 diabetes. Now that we know that a reduction in insulin production begins earlier on, we can diagnose T1D earlier in patients with antibody screening. So the question became how do we reach these individuals."

Dr. Magdalena M. Bogun

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Regulating Metabolism in the Setting of Cancer

In 2018, physician-scientist **Marcus DaSilva Goncalves, MD, PhD**, joined the Division of Endocrinology at NewYork-Presbyterian/Weill Cornell Medical Center following a four-year research fellowship in endocrinology in the laboratory of **Lewis C. Cantley, PhD**, Meyer Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. Throughout his 15-year career, Dr. Goncalves has studied muscle loss during critical illness, basic mechanisms of skeletal muscle growth and metabolism, insulin signaling, and developing new radiologic methods to assess skeletal muscle quality and function. Now with the establishment of the Goncalves Lab at Weill Cornell, he will continue to pursue basic science investigations into the interactions between the endocrine system and cancer. "Our mission is to better understand the hormones, cytokines, and metabolites that regulate systemic metabolism in the setting of cancer, and how these factors are changed with dietary interventions," says Dr. Goncalves, who has received funding from the Lung Cancer Research Foundation and a National Cancer Institute Career Development Award. The lab is currently focused on two main investigations: cachexia syndrome and how diet affects cancer metabolism.

The Cachexia Conundrum

By some estimates, nearly one-third of cancer deaths can be attributed to cachexia, a wasting syndrome characterized by a dramatic loss of skeletal muscle mass and often accompanied by significant weight loss. Cachexia occurs in many cancers, usually in the advanced stages of the disease, and is most commonly seen in pancreatic and gastric cancer, as well as lung, esophageal, colorectal, and head and neck cancer.

"Cachexia syndrome causes patients to waste away and die of frailty and immobility," says Dr. Goncalves.

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Pathways to Diabetes Prevention: It's All Relative *(continued from page 1)*

The Genetic Connection

Columbia is participating in the NIH TrialNet Pathway to Prevention, which offers free screenings at more than 200 TrialNet locations to relatives of people with T1D to evaluate their personal risk of developing the disease. This unique screening can identify the early stages of T1D years before any symptoms appear. Research has shown that relatives of individuals with T1D are 15 times more likely to develop the disease than the general population. The increased risk is linked to the presence of five diabetes-related autoantibodies. Based on the TrialNet data, the Juvenile Diabetes Research Foundation, American Diabetes Association, and the Endocrine Society now classify having two or more of these autoantibodies as early stage T1D.

"Our goal is to see which of these patients' relatives will actually develop diabetes," says Dr. Bogun. "People who screen positive for two or more diabetes-related autoantibodies are almost 100 percent likely to develop diabetes in their lifetime. The problem is that we don't know when – three, five, or 10 years in the future."

The criteria for testing include individuals between the ages of one and 45 who have an immediate family member with T1D, and those between the ages of one and 20 who have an extended family member with T1D.

The screening involves a blood test for the presence of diabetes-related biochemical autoantibodies (GAD 65, IA-2A, mIAA ICA, and ZnT8A). A positive antibody test is an early indication that damage to insulin-secreting cells may have begun. "Those who have at least two positive antibodies are given an oral glucose tolerance test, and then we test their glucose levels two hours later," says Dr. Bogun. "Essentially, it is like a stress test to diagnose type 1 diabetes sooner. If autoantibodies are present, participants are invited to be monitored with an oral glucose tolerance test every six months to detect high sugar levels and clinical onset of T1D."

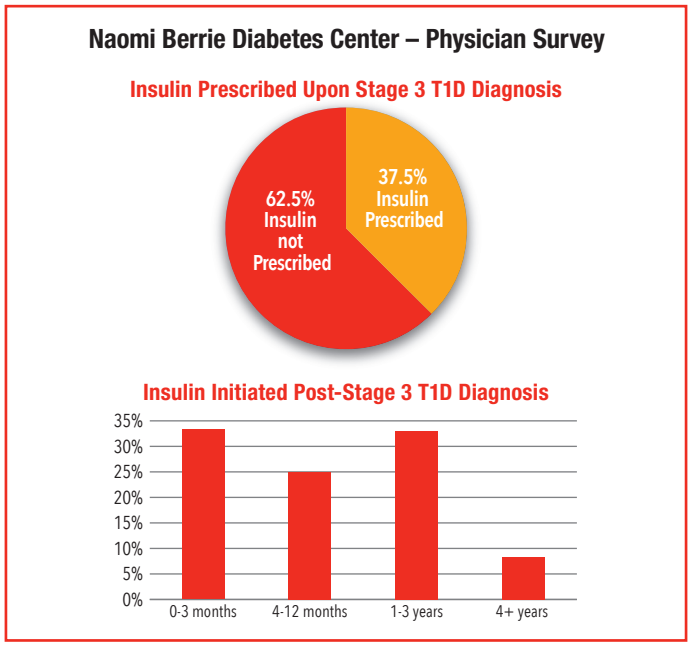
The Treatment Challenge

As per the current ADA guidelines, if an individual has an onset of clinical symptoms, HbA1c ≥ 6.5%, 2-hr plasma glucose (PG) ≥ 200 mg/dL during an oral glucose tolerance test (OGTT), or fasting plasma glucose ≥ 126 mg/dL2, the person would be classified as having stage 3 type 1 diabetes. "Because we are diagnosing type 1 diabetes so much earlier than in the past and not waiting until the patients exhibit symptoms, we are now faced with a scenario of how to treat them. My current research is trying to determine what is being advised and what is the best way to treat these patients who are being diagnosed much sooner," says Dr. Bogun. "Are they being told to check glucose levels and wait until they increase to treat? Does the provider start insulin right away? Right now, there is no standardized approach; it's patient-specific."

"We wanted to better understand how patients at our site who were diagnosed with new onset (stage 3) T1D through Pathway to Prevention in TrialNet were managed when initially diagnosed," continues Dr. Bogun. "To accomplish this, we sent short surveys to the physicians of 24 patients who were diagnosed with stage 3 T1D through the Pathway to Prevention trial." The survey showed:

- 37.5 percent were prescribed insulin upon diagnosis
- 44 percent were prescribed basal insulin
- 33 percent were prescribed rapid-acting insulin
- 22 percent were prescribed both basal and rapid-acting insulin

The survey additionally indicated that 55 percent of patients who were not prescribed insulin were asked to monitor glucose levels daily; 9 percent were asked to monitor weekly; and 36 percent before meals.



"The time between diagnosis and initiation of insulin treatment varied – nearly 60 percent of patients were prescribed insulin within a year of stage 3 T1D diagnosis," says Dr. Bogun. "Less than 10 percent of patients did not require insulin treatment more than four years after T1D diagnosis. "We plan to expand this study to all TrialNet centers to evaluate how various treatment options at diagnosis impact patient outcomes."

Dr. Bogun has a message for clinicians about screening for type 1 diabetes. "I would strongly suggest that they have the relatives of their patients with type 1 diabetes screened through Pathway to Prevention – especially the children," she says. "When children are diagnosed with type 1 diabetes, they actually have less insulin-producing cells than adults who are diagnosed and they might get sicker. If we can identify those patients earlier they can receive the treatment they need earlier. And if they do not require treatment yet, we can give them the education necessary on how to test glucose levels and how to detect high blood sugar much earlier than what would otherwise be detected in the community."

Reference

Julie Behrend (Indiana University School of Medicine), Magdalena Bogun, Sarah Pollak, Robin Goland. Naomi Berrie Diabetes Center. *Management of Asymptomatic Patients Diagnosed with Type 1 Diabetes Through Pathway to Prevention in TrialNet.* Poster Presentation. 10th Annual NIDDK Medical Student Research Symposium. 2018.

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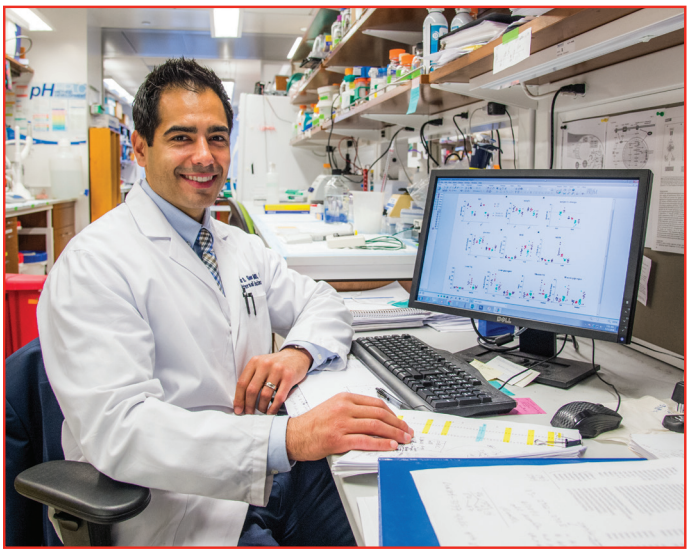
Regulating Metabolism in the Setting of Cancer *(continued from page 1)*

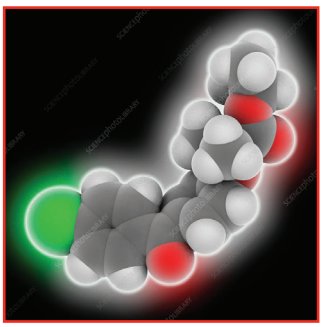


Dr. Marcus D. Goncalves

"The etiology of cachexia is completely unclear and there is no therapy. Cachexia affects a huge population of patients, and anything we can do to address this syndrome would make a big difference in a patient's quality of life while undergoing cancer treatment."

According to Dr. Goncalves, half of all patients with cancer experience cachexia at some phase in their therapy. "At the time of death, it's probably closer to 80 percent, and 20 to 30 percent of patients die from the wasting syndrome only. Those numbers for death are probably an underestimate because most patients get referred to hospice and the cause of death is really unknown."

As part of their research into this devastating and debilitating condition, Dr. Goncalves has developed a mouse model that recapitulates the cachexia syndrome as they seek interventions – either dietary or metabolic – to help prevent muscle wasting and fat loss. Concurrently, they are conducting a retrospective study of the medical records of patients with lung cancer at Memorial Sloan Kettering Cancer Center and at Weill Cornell to determine how much muscle they lose over time.



The effect of the drug fenofibrate (molecular model shown here) on cachexia is being studied in patients with non-small cell lung cancer (NSCLC) through a retrospective chart review, looking at change in skeletal muscle mass over time in comparison to untreated NSCLC patients.

"We can measure their skeletal muscle from their routine imaging studies, including CT scans and PET scans, which give us a lot of muscle data," says Dr. Goncalves. "Then we see if the patient was on a drug that has helped them over time. One drug that has come up in our studies in mice is fenofibrate, which is usually given for high triglyceride levels, a liver disorder associated with obesity. We have found that if we give it to mice with cachexia it prevents them from losing muscle mass. We're now looking in the charts of patients that have been on that drug. Did they do better or worse? We think we have a small signal there, but we're still working on the data."

Dr. Goncalves is in the planning stage for an observational trial of patients with lung cancer. "We'll be collecting blood samples and measuring the skeletal muscle of these patients, who we will follow over time to observe the metabolic changes that occur when they develop cachexia. Then the goal is to have an intervention trial where patients are actually given a therapy."

Diet and Cancer Metabolism

The researchers are also studying how diet affects cancer metabolism, using both mouse models and patient studies. "In a mouse model of colorectal cancer, we found that when you give those mice high amounts of sugar in the form of high fructose corn syrup the tumors get much bigger," says Dr. Goncalves. Identifying the metabolism of the tumors that change in the setting of both glucose and fructose, the researchers have been able to block that growth by modifying fructose 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."**
>
> **— Dr. Marcus D. Goncalves**

"In patients with endometrial cancer, we are giving them the opposite – low sugar, ketogenic diets – to see if that helps prevent the tumor from growing rapidly," says Dr. Goncalves, who chose endometrial cancer to target because of its high rate of PI3-kinase mutations. "That is a central node in the way insulin signals in all tissues of the body and is partly the reason I became interested in this project. As endocrinologists, we deal with insulin sensitivity in the skeletal muscle and in the liver. If you can block PI3-kinase signaling in the tumor, you block PI3-kinase signaling in all tissues of the body and you develop an insulin resistance similar to type 2 diabetes. Blocking that rise in insulin may prevent some of the complications that develop during cancer therapy. Similarly, I think we will eventually find that there are other mutations in metabolic pathways that predispose the tumor to be fast growing and modulate this growth by looking at fructose and changing the diet accordingly."

Addressing Loss of Appetite

Dr. Goncalves has long focused on how the body regulates food intake. "There are well-characterized pathways that are altered in obesity and regulate hormones such as leptin and insulin that control the hunger pathways in the brain," he says. "With cachexia those pathways are rewired in the opposite way – patients no longer have the sense of hunger or the way they taste or perceive food has changed."

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As Dr. Goncalves explains, a number of inflammatory cytokines and hormones that control appetite are deranged in the setting of cancer. "Some of those are the glucocorticoids and inflammatory cytokines, for example, the IL-6 superfamily, and a new cytokine, GDF15, which is increased in many chronic states, especially cancer. GDF15 has been shown to directly activate pathways in the brain that suppress appetite. There are now antibodies that block GDF15 and lead to an increase in appetite."

Dr. Goncalves is in discussions with industry to acquire a version of that antibody to test in his cachexia mouse model. "I think this discovery is a big leap forward in the cachexia field," he says. "Recently, several papers have highlighted significant benefits of blocking GDF15 in cancer models of cachexia."

Dr. Goncalves agrees that depending on the tumor and treatment, a wide array of problems can affect gut motility, taste sensation, and the hunger system. "It is so medically complex that you have to address each component from a medical perspective." To that end, Dr. Goncalves is collaborating with Weill Cornell colleagues in Geriatrics, Palliative Medicine, and Rehabilitation Medicine to establish a comprehensive care model to help patients with cachexia.

"Patients will receive both dietary and exercise information, as well as a hormone evaluation, all in one visit," he says. "There are not many clinics in the northeast that specifically serve cachexia. By providing supportive care, hormone evaluation, and vitamin and protein supplements, we hope that patients will eat a little more so that they can tolerate the therapy that will hopefully cure the cancer."

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