

It's long been said you are what you eat—and a new in-depth, collaborative study reconfirms the maxim. The Miller School's Vascular Biology Institute, the Florida Heart Research Institute, and the founder of the South Beach Diet have teamed up to reveal the connections between diet and disease.

By Robyn Nissim

Photos by John Zillioux

OF MICE

MICE WHO CLOSELY MIMIC HUMANS' PROPENSITY TO OBESITY AND DIABETES inspired Keith Webster, Ph.D., to create a comprehensive, cross-collaborative study “measuring just about everything we can think of that is initiated by diet and ends up with diabetes and congestive heart failure,” says the director of the University of Miami Leonard M. Miller School of Medicine's Vascular Biology Institute (VBI). Helping to fund the basic science study and hoping to translate these findings into clinical applications are Paul Kurlansky, M.D., of the Florida Heart Research Institute, and Arthur Agatston, M.D., a voluntary associate professor of cardiology who is better known as the author and creator of the South Beach Diet. ■ “Diet studies are inherently very difficult to do in humans,” says Agatston, one of the modern gurus of dieting. “You can't blind people to what they're eating.” Yet there is increasing concern in the medical community about how what you eat can impact your health. And there is fear that Americans are going to suffer the consequences.



Arthur Agatston, M.D., right, is helping fund the research of Keith Webster, Ph.D., on the disease link between diet and diabetes.



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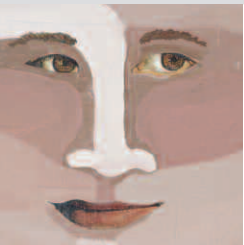
That concern is well founded: According to the American Diabetes Association, there are almost 21 million people, or 7 percent of the population in the United States, who are estimated to have diabetes. It is the fifth-deadliest disease in the United States and the only major disease with a death rate that is still rising. Cases of type 2 diabetes, which is associated with older age, obesity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity, have doubled in the last two decades.

“Somewhere between 55 and 70 percent of the adult population—depending upon whom you’re asking—is overweight in this country. Somewhere around 20 to 25 percent of the adult population is

“not very good representatives of human disease,” Webster notes. “Leptin-deficient mice tended to get very obese, their diabetes lasted for a short time, and then they reverted, whereas humans won’t revert back to a pre-diabetic state unless they’re treated.” The new mice are much more similar to humans who suffer from type 2 diabetes, who are typically overweight but not necessarily grossly obese, Webster says. “In many cases, people get insulin resistance and the symptoms of type 2 diabetes before they get obese, which is exactly what these mice do on a Western-style diet.”

With his new mice, Webster is analyzing the impact of the Agatston South Beach Diet on the obesity-related impact on type 2 diabetes. Webster has two sets of mice, one of which is on a Western

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obese. That’s incredible. Obese is on the far end of the spectrum—two standard deviations away from the norm. Obesity predisposes one to type 2 diabetes and has, aside from some of the obvious health risks, dramatic potential impact on the incidence of coronary heart disease and congestive heart failure. We’re only seeing the tip of the iceberg because this trend toward weight gain has only happened over the last 20 years. Over the next 20 years, we’re going to see the impact, the cumulative health impact, of having this problem,” says Kurlansky, the director of research at the Florida Heart Research Institute.

Animal studies have been conducted in the past to try to link diet and diabetes—to back up anecdotal evidence about the harmful effects of a Western-style diet, which is high in starch-type simple carbohydrates, with hard data. But the mice used were leptin-deficient, meaning they lacked an adipose tissue-derived hormone that signaled nutritional status to the brain’s hypothalamus. These mice were

diet (heavy on the mouse equivalent of cheeseburgers and fries), while the other set of mice is on the South Beach or Mediterranean-style diet, where all their fat was derived from fish oil and starch was reduced to a minimum. Both sets of mice are being fed the same amount of food. The key elements of the South Beach Diet, which were laid out in Agatston’s bestselling book, *The South Beach Diet: The Delicious, Doctor-Designed, Foolproof Plan for Fast and Healthy Weight Loss*, focused on using good fats along with good carbohydrates. Agatston created the diet initially to help improve the health of his patients, with the accompanying weight loss being an unexpected bonus.

Agatston’s and others’ studies have shown that eating “right” will have a positive impact on one’s health. So it may seem that we already know what’s going to happen to the sets of mice. But we don’t.

“Just recently, the Women’s Health Initiative showed that a low-fat diet did not work to protect



Paul Kurlansky, M.D., director of research at the Florida Heart Research Institute, warns that obesity will become a more severe public health problem over the next 20 years.

the heart,” Agatston points out. “Science has gone beyond low-fat foods to good fats and bad fats, but we’re checking into the role of inflammation in this whole process.”

“Everything is out there in terms of what we expect, but nobody knows exactly how obesity is related to diabetes. People have some idea, but we don’t know,” Webster says.

Webster’s work will in part focus on cytokines, which are small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis (the formation and development of blood cells). Cytokines generally act over short distances and short time spans and at very low concentration. They bind to specific membrane receptors, which then signal the cell via second messengers to alter its behavior. Understanding the signals that ping about the cellular level will help scientists create appropriate responses for the body when it hears the wrong message.

“We know that obese tissue produces some dangerous cytokines, but we don’t know how those dangerous cytokines make a person insulin-resistant or hypoglycemic. And the reason for doing these experiments in animals rather than humans—the next phase is to do that in humans—is you can’t take out the target tissue from a human study. So we will be taking out skeletal muscle tissue, heart tissue, and adipose tissue, and we will be looking at, in addition to the stem cells, the molecular biology of that tissue and why is it insulin resistant,” Webster says.

Two things that aren’t known and that are really critically important are the precise relationships between all those parameters that need to be measured. The VBI will be looking at a panel of up to 72 different cytokines, a massive increase from the handful that other studies have examined. “We hope to find which ones really respond to diet and which ones are really related to the insulin resistance,” Webster notes.

One of the most important of these cytokines is called tumor necrosis factor alpha (TNF-alpha), and its levels always go up in inflammatory disease. “We think that this might be the major signaling from obese tissue to mediate diabetes and insulin resistance. We also think that these inflammatory cytokines are floating around with the stem cells, and the stem cells in the bloodstream are also communicating with the stem cells in the bone marrow. These inflammatory cytokines may be killing or modifying the stem cells so that they’re not as good as the stem cells from a healthy mouse or a person, and this may be at the root cause of the diabetes. This might be why obesity and bad diet ultimately cause people to become diabetic,” says Webster.

The second hypothesis being tested is whether the stem cells themselves are causing most of the damage. When you get a defect in stem cells that are circulating,

you end up with a defect in the repair processes that the stem cells are normally doing. If you have adipose tissue producing dangerous or inflammatory cytokines that are destroying the stem cells, then they can no longer repair the vessels. “Therefore, you get vascular dysfunction, which can contribute to heart problems and a lot of the problems that are associated with diabetes. The major cause of death in the diabetic population is cardiac disease, so you get vascular disease and then you get heart disease and then you get heart failure—and this could all be initiated by cytokine-related effects on the stem cells,” Webster surmises.

“So we’re taking all these samples and doing all these assays to see if we can reverse the diabetes—and we think we can—and see if we can reverse the obesity—and we think we can. And the key question is whether we can reverse defects in the stem cells,” says Webster.

body fat was measured by X-ray scanning, and plasma cytokines were measured by antibody microarray. Leopoldo Raij, M.D., professor of medicine and an internationally acclaimed expert in hypertension, will monitor blood pressure parameters of the mice during dietary regimes. At selected time points, stem cells were isolated from bone marrow and cultured.

The Western diet group 1 mice were extremely insulin resistant and hyperglycemic at ten weeks and displayed multiple signs of type 2 diabetes. They tended to sleep more and move around a lot less. At 20 weeks, some of these mice began to display evidence of liver damage.

In contrast, the South Beach group 2 mice had normal glycemic levels and were healthy with no signs of diabetes even at 20 weeks. Group 1 mice that were switched to the South Beach Diet showed clear signs of improved insulin sensitivity and glycemic control

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Leopoldo Raij, M.D., an expert on hypertension, is studying blood pressure parameters and oxidative stress in the experimental mice.



Toni Yeasky and Iliana Cesar are conducting experiments comparing the effects of a Western diet versus the South Beach Diet in mice.

“The important thing is that, from a medical point of view, we need to understand what works, what doesn’t work, why it works, and why it doesn’t work. So what this project is attempting to do is to better understand obesity on a very physiologic, cellular level. The reason why we’re starting in an animal model is because we’re dealing with very complex processes here. In an animal model, you can control many of the processes, and you can also adjust the time. For a person to become obese, it may take 15 or 20 years. For a mouse to become obese, it may take four to six weeks in a laboratory setting,” Kurlansky says.

The first set of experiments in this program was initiated early this year by VBI investigators Toni Yeasky, Iliana Cesar, and Amber Wilson. The two groups of mice were maintained on their respective diets for 20 weeks, after which some of the group 1 mice were switched to the South Beach Diet. Blood was drawn weekly and profiled for markers of type 2 diabetes,

after six weeks. An extremely novel finding was that insulin resistance correlated very closely with an accumulation of the inflammatory cytokine monocyte chemoattractant protein-1 (MCP-1), but not with tumor necrosis-a (TNF-alpha) or interleukin-6. The latter two cytokines are widely believed—but not proven—to be responsible for insulin resistance.

Another finding was that the group 1 mice had significant myocardial hypertrophy (heart enlargement) that increased progressively to 20 weeks.

Stem cells were taken from the bone marrow of diabetic group 1 and healthy group 2 mice. These cells are currently under culture, and preliminary indications are that cells from the diabetic mice are growth retarded.

The second group of mice in the study are already at 20 weeks. These mice will be used exclusively for stem cell isolations and tissue collections. “We will culture stem cells from tissues isolated from extremely diabetic and normal, healthy mice,

as well as mice in which the diabetes has been reversed. These cells will be examined for gene expression by microarray, cytokine production, growth, and differentiation. We expect to find differences in these cells that could be linked to the role of diabetes in heart disease as well as the link between obesity and diabetes,” says Webster.

“What’s really important in all of these experiments is to see if you can reverse the process. This study may not answer that, but it might give some insights,” Kurlansky says.

The Florida Heart Research Institute and South Beach Diet Doctor Arthur Agatston are confident that this comprehensive study is going to give hard science answers to some clinically related questions. They’ve both given \$100,000 each to fund the early phases of the research, but Agatston says he’s planning “on committing to this research for the long-term.

“I think we’re going to find the key to a lot of diseases, not just vascular.”