BY LAURIE MEYERS [research profile]

TREATING PREDIABETES
Exercise, Metformin, Or Both?

Barry Braun, PhD, here with Arlo, is exploring the combined effect of exercise and metformin on insulin resistance

PHOTOGRAPHS BY CHRISTOPHER BROWN

BARRY BRAUN, PHD

Occupation
Assistant Professor, Department of Exercise Science, University of Massachusetts, Amherst

Professional Focus
Exercise and metabolism

Outside Interests
Competitive running, snowshoe racing, and spending time with family

Research Funding
ADA Junior Faculty Award

More than 20 million Americans have prediabetes, a condition in which blood glucose levels are higher than normal, but not high enough to be diagnosed as diabetes. Prediabetes can lead to type 2 diabetes, and it also increases one's risk of developing cardiovascular disease.

It's these concerns that have researchers searching for treatment options, and there have

been some promising results: Several studies have shown that both metformin (Glucophage) and exercise can reduce the risk of developing type 2. However, these studies had participants taking metformin or exercising—not both.

Barry Braun, PhD, wonders whether the drug and regular exercise, used together, would be even more effective at treating prediabetes. He has designed a study to try to find out.

Background

But first, some background on prediabetes: Your body needs insulin to help it absorb glucose. Sometimes, heredity, extra weight, or other unknown factors make your body less "sensitive" to insulin; it's unable to recognize and use it. This is called insulin resistance, and it causes your muscle, liver, and fat cells to become progressively less able to absorb all the glucose in your blood. The pancreas responds by pumping out more and more insulin in an effort to keep up with the cell resistance. When the pancreas loses its ability to keep up, the result is type 2 diabetes.

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The Power Of Two

Braun's study will include 28 people who have prediabetes and are sedentary and overweight. Braun is particularly seeking out subjects who have family histories of type 2 diabetes.

These 28 people will complete three test days—once a week for three weeks—and they will be split into two groups. One group will get metformin, the other a placebo.

Food intake and physical activity will be strictly controlled before each of the three test days. These test days will involve some physical activity, a muscle biopsy, the administering of a glucose clamp to measure insulin sensitivity, and some "real world" activities to see how the participants function outside of a laboratory setting.

The Test Days

At the start of each of the test days, the participants will do one of the following: sit for 30 minutes, exercise for 30 minutes, or exercise for 60 minutes. (By the end of the 3 weeks, all 28 will have completed each activity.)

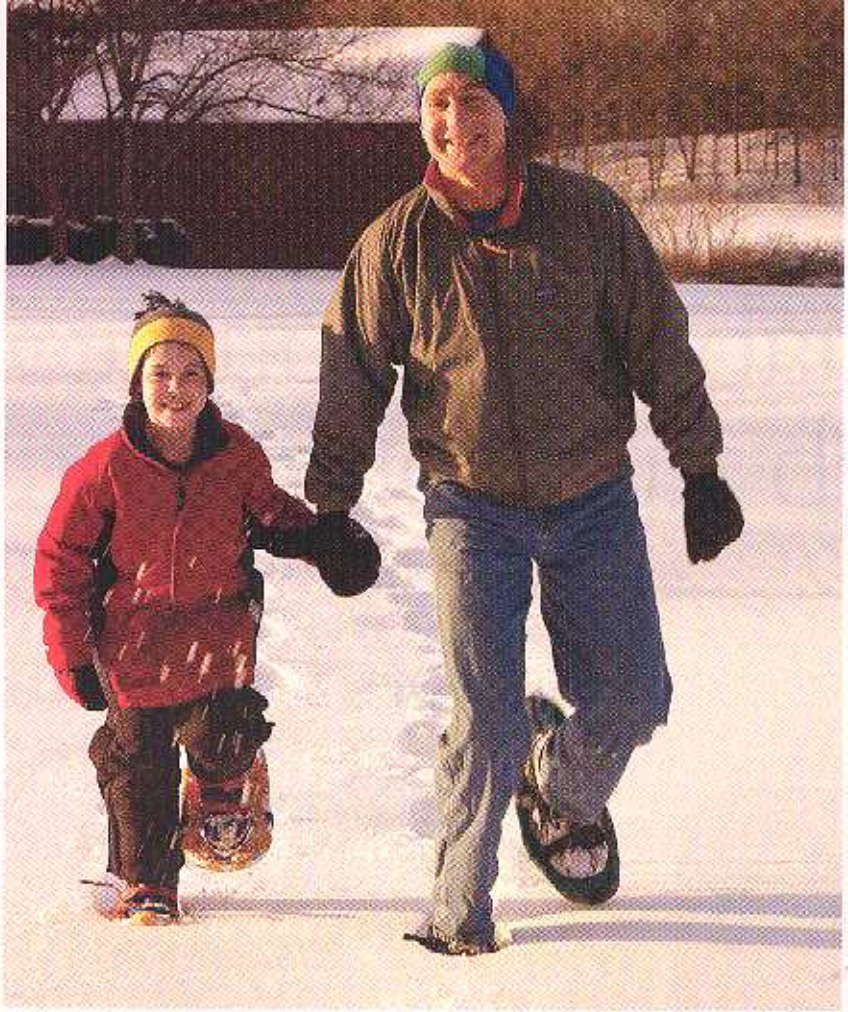
Stuart Chipkin, MD, will take muscle biopsies, and the cells will be frozen for later study. A glucose clamp will be administered to measure insulin sensitivity. This clamp will involve two intravenous (IV) catheters; one will sample blood every 5 minutes to determine glucose levels. The other catheter will administer insulin and a glucose isotope (used to measure how insulin sensitive participants' livers are), as well as a variable level of regular glucose based on the 5-minute measurements.

The goal will be to maintain a constant glucose level—in this case, the fasting level of 90 mg/dl. Depending on how the body handles insulin, the glucose infusion could vary widely. "It's kind of like a garden hose," Braun says. "If you're more sensitive to the insulin being infused, in order to maintain the constant level, we'd need to turn up the stream of glucose. On the other hand, if you're overweight, sedentary, and not very sensitive, you won't need much glucose, so the stream would be more like a trickle."

At the end of the study, these resistance levels will be analyzed along with the presence (or absence) of metformin in combination with the three different levels of activity.

But it's the comparison of laboratory results with a real world test that Braun's really interested in.

He wants to be able to compare the controlled laboratory data to results from an environment that more closely resembles daily life. So, before leaving the lab, the participants will receive a standard lunch—with the same number of calories, balanced at 50 percent carbohydrates, 20 percent protein, and 30 percent fat. They also will receive dinner and



Braun and his son, Samson, ready for a day of snowshoe racing.

breakfast to eat at home. The participants will receive pedometers, and to ensure that they keep up a consistent level of activity, they will be given a target number of steps to aim for between lunch and breakfast the next morning.

While out in the "real" world, participants will be outfitted with a self-contained continuous glucose monitoring system that goes under the skin. The monitor will measure glucose levels in the interstitial fluid (the fluid surrounding body cells) every 5 minutes and store the readings.

Then What?

What does Braun hope or expect to find with these tests?

In collaboration with Laurie Goodyear, PhD, of the Joslin Diabetes Center, graduate students in Braun's lab will be analyzing the cells from the muscle biopsies. Braun wants to examine cellular energy patterns. He's particularly interested in an enzyme called AMP kinase, which is present in skeletal, muscle, and fat cells. "AMP kinase seems to be a switch that makes a cell more likely to store or more likely to use energy," says Braun. In other words, AMP kinase functions kind of like a thermostat. But instead of monitoring temperature, it is sensitive to the balance between energy coming into the system (in response to eating) and energy going out of the system (for example, through exercise).

"Depending on the relative balance between energy coming in and energy going out, AMP kinase can turn on or turn off a host of metabolic systems—for instance, the oxidation of fat or the uptake of glucose in the blood—designed to restore the cell back to a target state. We don't know how AMP kinase does this, what the actual signals are that it is responding to, or how many other cell energy sensors exist."

Braun also wants to see "if the change matches up with other changes. If the amount of AMP kinase is doubled, would that match up to twice as much sensitivity to insulin?"

As for the metformin and exercise, "I expect that together they will have a partially additive effect—that 30 minutes of exercise with metformin will match the effects of 60 minutes of just exercise." Also, if you have problems with the side effects of metformin, exercising could allow you to take a lower dose and still receive the same benefits.

And if he finds that the two do work well together? "I'd really like to understand how much the AMP kinase plays a role."

Finally, Braun hopes that what they find in the lab also translates into changes in people's lives. "We have a mission statement for the lab. What we do is try to optimize the use of exercise to reduce insulin resistance and treat or prevent type 2."