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Diabetes drugs affect hearts of men, women differently

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Widely used treatments for type 2 diabetes have different effects on the hearts of men and women, even as the drugs control blood sugar equally well in both sexes, according to researchers at Washington University School of Medicine in St. Louis. Janet B. McGill, M.D., and Robert J. Gropler, M.D., look through the PET scanner they and their colleagues used to study the heart's response to common diabetes therapies. They found large differences in heart metabolism between men and women taking widely used diabetes drugs. Credit: Robert J. Boston

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different effects on the hearts of men and women, even as the drugs control blood sugar equally well in both sexes, according to researchers at Washington University School of Medicine in St. Louis.

In particular, the commonly prescribed diabetes drug metformin had positive effects on heart function in women but not in men, who experienced a shift in metabolism thought to increase the risk of heart failure.

"We saw dramatic sex differences in how the heart responds to the different therapies," said senior author Robert J. Gropler, MD, professor of radiology. "Our study suggests that we need to better define which therapies are optimal for women with diabetes and which ones are optimal for men."

The study appears in the December issue of the *American Journal of Physiology - Heart and Circulatory Physiology*.

To the researchers' knowledge, this is the first study to investigate sex differences in the heart's response to diabetes treatments. In type 2 diabetes, the pancreas continues to make insulin, but the body can't use it effectively to move glucose out of the blood and into the tissues. And for reasons that are not entirely clear, patients with diabetes are at higher risk for heart failure.

"It is imperative that we gain understanding of diabetes medications and their impact on the heart in order to design optimal treatment regimens for patients," said Janet B. McGill, MD, professor of medicine and a study co-author who sees patients at Barnes-Jewish Hospital. "This study is a step in that direction."

The investigators evaluated commonly prescribed diabetes drugs in 78 patients, who were assigned to one of three groups. Under McGill's

supervision, the first group received metformin alone; the second received metformin plus rosiglitazone (Avandia); and the third received metformin plus Lovaza, which is a kind of fish oil.

Metformin reduces glucose production by the liver and helps the body become more sensitive to insulin. Rosiglitazone also improves insulin sensitivity and is known to move free fatty acids out of the blood. Lovaza is prescribed to lower blood levels of triglycerides, another type of fat.

Importantly, Gropler noted that when they compared the three groups without separating men and women, no differences in heart metabolism were seen. But when the patients were separated by sex, the drugs had very different and sometimes opposite effects on heart metabolism, even as blood sugar remained well-controlled in all patients.

"The most dramatic difference between men and women is with metformin alone," said Gropler, who also sees patients at Barnes-Jewish Hospital. "Our data show it to have a favorable effect on cardiac metabolism in women and an unfavorable one in men."

The research suggests that these divergent responses in men and women may provide at least a partial explanation for the conflicting data surrounding some diabetes drugs. Specifically, the proportion of men and women participating in a clinical trial may play an unappreciated role in whether drugs are found to be safe and effective.

There is particular controversy surrounding rosiglitazone. In 2010, the U.S. Food and Drug Administration (FDA) restricted rosiglitazone's use because of questions about cardiovascular safety. Based on a recent review of data, the FDA reversed its 2010 decision last month, lifting the restrictions.

In the current study, metformin caused the heart metabolism of men to move in an undesirable direction – burning less sugar and more fats. Chronic burning of fat by the heart, according to Gropler, leads to detrimental changes in the heart muscle, which can lead to heart failure.

"Instead of making heart metabolism more normal in men, metformin alone made it worse, looking even more like a diabetic heart," Gropler said. "But in women, metformin had the desired effect – lowering fat metabolism and increasing glucose uptake by the heart."

Taking either rosiglitazone or Lovaza with metformin seemed to mitigate some of the negative heart effects of metformin alone in men. But women, already benefiting from metformin, improved heart metabolism further by adding rosiglitazone, with the desired effect of reducing the heart's dependence on fat metabolism. Adding Lovaza did not have a strong effect in either direction for men or women.

Gropler pointed out that he and his colleagues have shown in previous work that even healthy men and women show differences in how their hearts burn fuel. Healthy male hearts tend to burn more glucose, while in women, healthy hearts tend to burn more fats. This difference may help explain why women with diabetes tend to get more aggressive heart failure than men: Women already burn more fats.

"We now know there are sex differences at baseline, both in the metabolism of healthy hearts and in the hearts of patients with diabetes," Gropler said. "We are adding the message that these sex differences persist in how patients respond to drugs. For patients with diabetes, we are going to have to be more attentive to sex differences when we design therapies."

Further complicating matters, the researchers also noted that the differences they observed in heart metabolism can't be measured with

conventional blood tests.

Unlike many heart studies that rely on blood sugar and cholesterol tests that anyone might get at a doctor visit, the Washington University researchers used positron emission tomography (PET) scans to image the heart and measure blood flow, oxygen consumption and fatty acid and glucose uptake by the heart, among other measures. They also took echocardiograms in conjunction with the PET scans and used stable isotopes to monitor whole-body metabolism and how this influences the heart.

Although the trial was relatively small in terms of the number of patients, it was unusually rigorous in the methods used to analyze heart metabolism, according to Gropler. He noted that only a handful of medical centers worldwide have the resources to perform such a study.

"If you use standard measurements, you're going to miss the sex differences we observed," Gropler said. "This may mean we have to do more complex imaging of the heart to better understand which therapies are best for which patients."

Provided by Washington University School of Medicine

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