Diabetes drug shows promise in fighting lethal cancer complication

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Insulin resistance, the hallmark of type 2 diabetes and a condition often associated with obesity, is paradoxically also an apparent contributor to muscle wasting and severe fat loss that accompanies some cancers, according to new research.

And in an animal study, a diabetes drug that promotes insulin sensitivity slowed the progression of muscle wasting and fat loss, the main consequences of a syndrome called cachexia, in mice with colon cancer tumors.

Though it remains unknown whether that drug, rosiglitazone, has potential to prevent cachexia in humans with cancer, the finding led researchers to believe that curbing insulin resistance in cancer patients could improve their quality of life.

Research suggests that cachexia is responsible for between one-fifth and one-third of all cancer deaths.

The insulin resistance and cachexia both appear to be connected to inflammation induced either by tumors themselves or by secretions from tumors that activate an immune response, the researchers say.

"Insulin resistance usually follows obesity. In this case, it precedes uncontrollable fat loss," said Martha Belury, senior author of the study and a professor of human nutrition at Ohio State University. "The insulin resistance is the process we've identified that occurs soon after tumors

form. So if we can change that part of the disease, we might be able to change the progression and trajectory of how fast fat and muscle are lost as well. That's our goal."

The research appears online and is scheduled for future print publication in the *International Journal of Cancer*.

Belury and colleagues conducted two experiments. In the first, the researchers sought to demonstrate that animals developed insulin resistance shortly after they developed cancer and before muscle and fat loss became evident. In the second, they tested the effectiveness of the insulin sensitizing drug rosiglitazone against that same tendency toward insulin resistance.

The scientists injected mice with colon cancer cells to mimic one of several digestive-system cancers strongly associated with the development of cachexia. Less than two weeks after the cancer started growing, these mice had become insulin resistant. Control mice without tumors had normal insulin sensitivity. Insulin resistance means that the presence of insulin does not initiate the transfer of sugar, or glucose, from the blood into the tissues, where it is used for energy.

Just three days later, the mice with cancer weighed, on average, 20 percent less than control mice with no tumors; weight loss of at least 5 percent is considered to be a sign of cachexia in humans. By day 19, the total muscle weight in mice with cancer decreased by 29 percent and the weight of their fat tissue dropped by 73 percent. Such rapid loss of muscle and fat indicated these mice had indeed developed cachexia.

"These data provide evidence that in mice with colon cancer tumors, insulin resistance may be involved in the development of cachexia rather than occur as a result of cachexia," Belury said. "And the key here is that people and animals with cachexia do not want to be losing weight. They

can eat more and it doesn't matter. There's something internally that's driving this fat and muscle loss."

In the second study, the scientists tested whether rosiglitazone could "rescue" the insulin resistance in mice with colon cancer.

In this study, mice were fed a high-fat diet and randomized into three groups: mice with and without tumors receiving a saline solution as a control, and mice with tumors treated with daily injections of rosiglitazone.

Within eight days, the mice with cancer receiving the rosiglitazone showed more sensitivity to insulin than did the mice with tumors that received no medication. The insulin sensitivity of the medicated mice matched that of mice without tumors.

Similarly, the mice receiving rosiglitazone actually gained weight in this study, as did the mice without tumors. The mice with tumors receiving no treatment lost fat tissue, suggesting they were experiencing the onset of cachexia - despite the high-fat diet they were eating.

In addition to stopping fat and muscle loss, the rosiglitazone also dramatically reduced two biological markers present when proteins break down, particularly in muscles, and a third marker that indicates cells are eating their own amino acids in an attempt to survive.

"We found that those markers of protein and muscle degradation are increased in mice with cachexia, and then when we gave them rosiglitazone, that significantly slowed that degradation," Belury said.

It's too soon to know whether the same drug would have the same effect on humans with cancer, Belury noted. Not all people with cancer develop cachexia, and it's difficult to catch cachexia before severe weight loss

has already occurred. And by the time muscles begin to break down, the entire body reacts to the release of amino acids, meaning treatment at that time would have to take such reactions into account.

"For this research, we wanted to catch cachexia as it was having an influence on muscle wasting without the wasting muscle having an influence back on the cachexia," Belury said.

In future studies, the scientists plan to further test the timing and dosage of rosiglitazone and other insulin sensitizers to see if the experiments produce a "prominent, universal effect," Belury said.

Source: The Ohio State University (news : web)