

Preclinical study shows ketogenic diet could enhance pancreatic cancer therapy

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A Ludwig Cancer Research preclinical study has demonstrated that a common weight-loss diet could enhance the efficacy of chemotherapy for pancreatic cancer. Published in the journal *Med*, the study shows that a ketogenic diet—or high fat, modest protein and very low carbohydrate intake—synergizes with chemotherapy to triple survival time compared to chemotherapy alone in rigorous mouse models of pancreatic ductal

adenocarcinoma (PDAC).

The researchers, led by Ludwig Princeton Branch Director Joshua Rabinowitz, also describe findings from an intricate examination of how ketogenic diets affect the metabolism of PDAC tumors, and identify mechanisms that might account for the therapeutic effect. Their findings are now being evaluated in a clinical trial (NCT04631445) testing the benefits of a [ketogenic diet](#) in PDAC patients receiving chemotherapy.

"There's been real progress against [pancreatic cancer](#) over the past two decades," said Rabinowitz, who is also a Professor in the Department of Chemistry and the Lewis-Sigler Institute for Integrative Genomics at Princeton University. "The problem is that, while a number of patients now see their tumors stabilize or shrink, the benefits of chemotherapy are very short lived. It often extends patients' lives six months to a year, but way too rarely do we see the three-plus years of extension in survival that people would, at a minimum, hope for."

Substantial preclinical evidence suggests that fasting, or diets that resemble fasting in their metabolic effects, could enhance therapy for a variety of cancers. The ketogenic diet mimics fasting by reducing circulating glucose and depressing levels of insulin, a hormone that drives tissues and tumors to consume the sugar. Insulin is an important promoter of [cancer](#) growth—especially in pancreatic tumors—while glucose is a critically important fuel for cancer cell proliferation. Rabinowitz's own studies previously revealed that PDAC tumors, despite their aggressive growth, are starved of glucose, which suggested they could be especially vulnerable to additional glucose deprivation.

In the current study, Rabinowitz and his colleagues conducted multiple experiments over many years—with early and ongoing support from Stand Up to Cancer—using mice that were engineered to develop PDAC or implanted with tumors that resembled those seen in patients. The

mice were fed either a normal, carbohydrate rich diet or a ketogenic diet and treated with a standard-of-care combination of chemotherapies—nab-paclitaxel (Abraxane), gemcitabine and cisplatin.

They found that the ketogenic diet alone did not affect tumor growth. But it did triple median survival time when combined with chemotherapy. Notably, while the therapeutic benefit did not depend on the immune system, only mice with intact immune systems were among the long-term survivors.

Rabinowitz and his team also conducted studies to explore the effects of the combination therapy on tumor metabolism. "We know that glucose is a major cancer fuel, and insulin is a cancer promoting hormone, and that the ketogenic diet in one stroke decreases both," said Rabinowitz. "We found in this study that the diet decreases levels of glucose more profoundly in the tumor than in healthy tissues and that it dramatically suppresses levels of insulin."

By depriving the body of sugar, the ketogenic diet forces the body to break down fats to generate molecules known as ketone bodies that can be burned by cells to generate energy. Chief among these is 3-hydroxybutyrate.

"One thing we noticed is that 3-hydroxybutyrate acts like a supercharged fuel that dumps electrons into cells, and tumor cells are wired for other reasons to be extra-good at taking up this fuel," said Rabinowitz.

"Fortuitously, too much of this super-charged fuel may be toxic to cancer."

This excess of electrons causes the generation of reactive oxygen species (ROS), extremely unstable molecules that are also generated by chemotherapy. ROS kill cancer cells by damaging DNA, membranes and other components of cells. This, the researchers hypothesize, may

enhance the antitumor effects of the chemotherapy.

"I think that the most exciting thing here is that we can take chemotherapy regimens that we know to be active, that offer patients the best chance in the clinic right now and, at least in mice, make them work substantially better by pairing them with a ketogenic [diet](#)," said Rabinowitz. "We hope that we'll see the same types of benefits in patients."

More information: Lifeng Yang et al, Ketogenic diet and chemotherapy combine to disrupt pancreatic cancer metabolism and growth, *Med* (2022). [DOI: 10.1016/j.medj.2021.12.008](https://doi.org/10.1016/j.medj.2021.12.008)

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