High Fat, High Calorie Diet Leads to NASH and Liver Cancer in Mice

But a simple improvement in dietary intake reversed fatty liver disease and staved off cancer.

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Mice fed a Western diet high in calories and fat develop non-alcoholic steatohepatitis (NASH) and progress to developing liver cancer as well as kidney and heart disease. The findings, published in Cellular and Molecular Gastroenterology and Hepatology, also showed that switching the Western diet for one with appropriate amounts of macronutrients reversed the development of NASH and, subsequently, prevented cancer and related death.

Arising from the accumulation of fat in the liver, non-alcoholic fatty liver disease (NAFLD) and its more severe form, NASH, are responsible for a growing proportion of advanced liver disease worldwide. As a result of inflammation, NAFLD can lead to the buildup of scar tissue (fibrosis), cirrhosis (advanced scarring) and even hepatocellular carcinoma (HCC), the most common type of liver cancer. With no effective approved medical therapies, disease management is dependent on lifestyle changes such as weight loss and exercise.

The gut, brain, liver and adipose tissue all play a role in the development of NASH. But the mechanism of progression of liver steatosis (fat accumulation) through worsening stages to liver cancer is not entirely clear.

Debanjan Dhar, PhD, of the University of California San Diego, and colleagues sought to understand these underlying mechanisms of NASH progression in mice bred to indulge in overeating and fed a Western diet high in fats, cholesterol and calories.

First, these mice were fed a Western diet for 12 weeks to develop NASH and 24 weeks to develop liver cancer. Next, they were switched over to a standard diet to reverse NASH development.

Mice that were fed a Western diet quickly began showing signs of steatosis, NASH, fibrosis and even kidney damage. By weeks 1 and 2, these mice had steatosis, progressing to NASH at week 4 as well as severe fibrosis and kidney injury at week 12. By week 24, the mice had developed liver cancer and had impaired survival.

But when the Western diet was replaced with a standard diet, the mice with NASH recovered and did not progress to liver cancer.

“While the mice that continued on a Western diet developed HCC and had an increased risk of death, 100% of the mice that stopped the diet survived the length of the study without developing HCC,” said Dhar, in a press release. “This indicates that NASH and HCC may be a preventable disease and that diet plays a crucial role in the disease outcome.”

In these mice, switching to a better diet also lowered liver fat, improved the ability to process glucose. What’s more, and levels of certain cytokines (immune system chemical messengers), which spiked with NASH, were restored to normal. While NASH development was heralded by alterations in the gut lining and inflammation, the gut microbiome also appeared to change as NASH progressed to liver cancer.

Further, this mouse model for overeating reflected the mechanisms and genetics of NASH progression to liver cancer in humans. “Our animal model provides an important pre-clinical testing platform to study the safety and efficacy of drugs that are currently being developed, as well as to test the repurposing of other drugs that are already FDA approved for other diseases,” said Dhar.

Click here to read the study in Cellular and Molecular Gastroenterology and Hepatology.

Click here to learn more about fatty liver disease.
