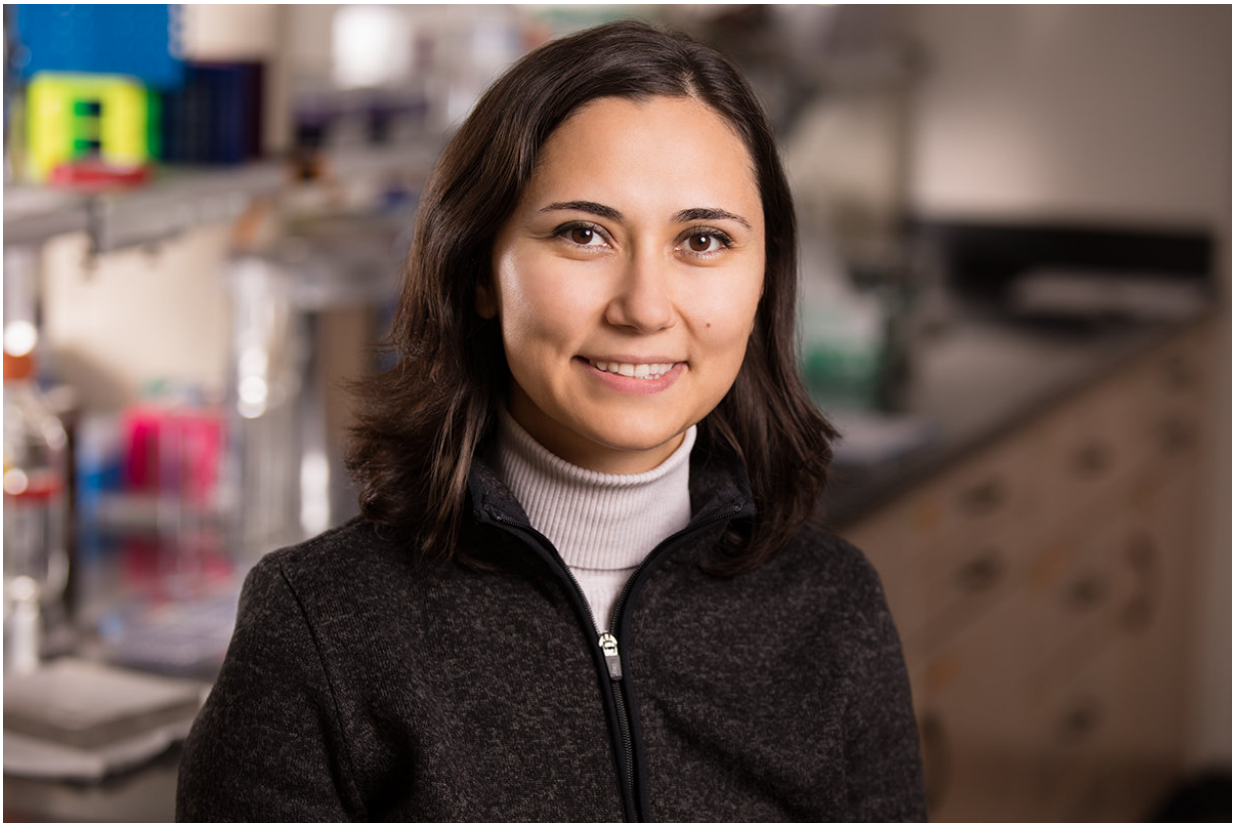


Hormone therapy combination may benefit health without increasing cancer risk

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A team led by food science and human nutrition professor Zeynep Madak-Erdogan found that treating ovariectomized mice with a combination of conjugated estrogens and the drug bazedoxifene improved metabolism and prevented the weight gain often associated with low estrogen levels without posing increased risk to their reproductive tissues. Credit: L. Brian Stauffer

Treating ovariectomized mice with a combination of conjugated estrogens and the drug bazedoxifene triggers the expression of genes that improve metabolism and prevent weight gain – without stimulating the uterus and increasing risks of reproductive cancer, a new study suggests.

University of Illinois food science and human nutrition professor Zeynep Madak-Erdogan led a group of researchers who explored the effects of conjugated estrogens and bazedoxifene on the liver by analyzing gene transcription and the metabolism of about 150 chemicals in the blood. The findings were reported in a paper published in the online journal *PLOS One*.

Bazedoxifene is commonly prescribed in combination with conjugated estrogens to prevent postmenopausal osteoporosis. It is among a class of compounds known as selective estrogen receptor modulators, which bind to estrogen receptors and either promote or block their activity.

"Once women enter menopause and estrogens are lost, their metabolism is rewired, in the sense that they often start gaining weight, their bad cholesterol increases, their good cholesterol decreases and they may become pre-diabetic," Madak-Erdogan said. "If they are prescribed a combination of bazedoxifene and conjugated estrogens, these symptoms often improve."

"We wanted to see why this drug combination is helpful, so we used a genomewide approach where we looked at the gene expression profiles in the liver," Madak-Erdogan said. "Because the liver is a major organ in metabolic control and regulates many of the chemicals in the blood, we looked at blood serum composition as well."

The scientists fed 48 eight-week-old mice a [high-fat diet](#) in which 45 percent of the calories came from fat. To mimic the low-estrogen state of menopause, 40 of the mice had their ovaries removed when they

reached 10 weeks old. The mice then were randomly divided into five groups, each of which was treated for six weeks with a different combination of conjugated estrogens and bazedoxifene.

The scientists measured the mice's food intake and body weight weekly, and performed MRIs before treatment and at four weeks post-treatment to measure each animal's whole body mass and lean body mass.

After the treatment period, the scientists euthanized the mice and weighed their adipose (fat) tissue, including their [white adipose tissue](#), which stores energy in the form of lipids; and their mesenteric and perirenal adipose tissues, two forms of abdominal fat associated with the development of type 2 diabetes, insulin resistance, inflammation and other obesity-related diseases.

Using liver samples from each treatment group, the scientists examined the expression of various genes within the mice's livers and measured the levels of nearly 150 metabolites in their blood, including cholesterol, free fatty acids and glucose.

Treatment with bazedoxifene and conjugated estrogens decreased the expression of genes along three parallel metabolic pathways that affect liver health – reducing lipid accumulation, levels of inflammation and reactive oxygen species pathways in the liver, Madak-Erdogan said.

The researchers found that eight metabolites associated with the weight and health of the liver were down-regulated by the estrogen supplements – including several metabolites known to be misregulated in people with nonalcoholic fatty [liver](#) disease.

"Treatment with conjugated estrogens and bazedoxifene also prevented the [weight gain](#) that is often associated with postmenopausal decreases in [estrogen](#) and consuming a high-fat diet," Madak-Erdogan said. "Animals

in the treatment group had less fat mass and lower body weights than their peers in the control group. And their uterus and mesenteric white adipose tissue weighed significantly less than those of their peers."

Recent studies suggesting that hormone replacement therapy increases women's risks of reproductive cancers have prompted physicians to exercise caution in prescribing hormones – despite evidence that HRT may improve women's metabolic functioning, lessen weight gain and lower their risks of serious health conditions such as cardiovascular disease and diabetes, Madak-Erdogan said.

"Although hormone therapy could reduce postmenopausal [weight](#) gain and many serious metabolic problems, physicians tend to avoid prescribing it because of concerns about elevating women's risks of reproductive cancers," Madak-Erdogan said. "Our study suggests that the combination of conjugated estrogens and bazedoxifene could improve metabolism without posing increased risk to the reproductive tissues."

More information: Karen Lee Ann Chen et al. Bazedoxifene and conjugated estrogen combination maintains metabolic homeostasis and benefits liver health, *PLOS ONE* (2017). [DOI: 10.1371/journal.pone.0189911](#)

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