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Oral hormone therapy shown to significantly alter metabolome of menopausal women

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Groundbreaking research led by a team of scientists including a University of Massachusetts Amherst biostatistician shows that oral hormone therapy (HT) significantly alters the metabolome of postmenopausal women. This finding, which examined blood specimens from the landmark Women's Health Initiative (WHI) study, may help explain the disease risks and protective effects associated with different regimens of hormone therapy.

"This is the first analysis of the metabolomic effects of hormone therapy conducted within the framework of a randomized clinical trial," says Raji Balasubramanian, associate professor in the School of Public Health and Health Sciences, whose research connects biostatistics, molecular epidemiology and women's health.

Balasubramanian, in collaboration with Dr. Kathryn M. Rexrode at Brigham and Women's Hospital, a teaching affiliate of Harvard Medical School, and colleagues at the Broad Institute of Harvard and MIT, Harvard's T.H. Chan School of Public Health, Brown University and several institutions in Spain, wanted to study whether hormone therapy alters the universe of small molecule metabolites. "The answer was a resounding yes," says Balasubramanian, lead author of the paper published in *Circulation: Genomic and Precision Medicine*.

The WHI's hormone therapy trials in the 1990s examined the effects on coronary heart disease (CHD), breast cancer and other conditions of two hormone therapies—estrogen alone and a combination of estrogen and

progestin. The combination therapy was found to significantly increase CHD risk by 29%; estrogen alone was found to decrease CHD risk by 9%, although this effect was not statistically significant.

"Our focus was on cardiovascular disease and understanding at a molecular level why these two hormone therapy regimens had disparate effects in regard to cardiovascular disease," Balasubramanian says.

Using liquid chromatography mass spectrometry (LC-MS) techniques, researchers at the Broad Institute measured 481 metabolites in blood specimens from the WHI hormone therapy trial participants: 503 from women in the estrogen-only group, half of whom were on placebo; and 431 in the estrogen plus progestin group, with half on placebo. The research team recorded measurements obtained right before hormone therapy began and one year later, when the women were still on active treatment or placebo.

The findings revealed "profound changes in the metabolome, spanning a wide range of classes including lipids, amino acids and other small molecule metabolites," Balasubramanian says. In fact, 62% of metabolites were significantly changed with estrogen-alone therapy, and 52% with estrogen plus progestin.

While most of the changes in metabolites were consistent with each type of hormone therapy, 22 metabolites were identified that had discordant effects. Twelve of those were associated with CHD risk in an evaluation of an independent WHI dataset.

With estrogen-alone treatment, the changes in all 12 metabolites provided a protective CHD effect. With estrogen plus progestin, 11 metabolites were unchanged. The amino acid lysine was significantly altered by both hormone therapies, but in the opposite direction. Estrogen-alone therapy increased lysine levels, providing a protective

effect, and estrogen plus progestin decreased lysine levels, elevating CHD risk.

"Getting a handle on what subset of metabolites had differential changes between the two drugs related to cardiovascular diseases might point to the molecular underpinnings of the difference in risk between the two treatments," Balasubramanian explains.

UMass Amherst 2020 graduate Ryan Sheehan contributed to the data analytic aspects of the study and continues to work in Balasubramanian's lab as a research associate. Taking part in the study was "the best experience a student could have," he says. "Not only was I able to contribute my own skills and knowledge to this important paper, but also I was able to learn so much about the processes that go on with professional research. The amount of time and attention to detail that went into each step is something I will try to mimic in my own work as I progress in my professional career."

The study also lays the groundwork for identifying other hormone therapy-related metabolomic changes in a broader age group of women and how those changes are associated with differential risks for other health conditions, such as breast cancer, depending on the hormone regimen.

"We're excited to contribute to advancing research in women's health," Balasubramanian says.

More information: Raji Balasubramanian et al, Metabolomic Effects of Hormone Therapy and Associations With Coronary Heart Disease Among Postmenopausal Women, *Circulation: Genomic and Precision Medicine* (2020). DOI: 10.1161/CIRCGEN.119.002977