Researchers find significant sex-based differences in obesity treatment in mice

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One size rarely fits all. This is a truism the field of nutrition sciences is increasingly taking to heart when it comes to obesity treatment.

According to the CDC, nearly 42% of U.S. adults are overweight or have obesity. This epidemic also affects about 20% of U.S. children.

The causes and effects of obesity are varied, affecting different populations and individuals in unique ways based on their age, sex,

genetics, and more. This means scientists and doctors need to consider individual-level factors in determining which obesity treatment is the most effective for each patient.

A recent publication by Ji-Young Lee in the *Journal of Nutritional Biochemistry* provides a step toward this individualized approach. Lee, professor and department head of nutritional sciences in the College of Agriculture, Health and Natural Resources, found that a potential obesity treatment works in different parts of the body in male versus female mouse models.

A lesser-known molecule, called nicotinamide adenine dinucleotide (NAD+), plays a critical role in generating energy in cells. And it may provide a key treatment option for obesity.

When your cells break glucose down, the reaction releases hydrogen molecules. NAD+ snatches up these loose hydrogen molecules, becoming NADH. NADH is then used to produce ATP in the mitochondria.

It follows that obesity and other metabolic disorders are associated with low NAD+ levels.

Lee's study looked at the impact of giving mouse models a form of vitamin B3, known as nicotinamide riboside (NR), that the body converts into NAD+.

In previous research with male mouse models, Lee found that feeding obese mice NR prevented the development of fatty liver disease. But the effect on female mice was unknown.

In the new study, Lee and her team discovered a novel difference—in female mice, the NR treatment worked in the adipose, or fatty, tissue,

rather than the liver.

"We have acknowledged that males and females are biologically different, and any treatment can be different, any drug can be different," Lee says.

The adipocytes, or adipose tissue cells, were smaller in females fed NR. Enlarged adipocytes are a hallmark of obesity and related complications.

The NR treatment also increased the mice's metabolic rate. Lee observed higher levels of voluntary activity, like running on a wheel, associated with this change.

Lee says this is a bit of a "chicken and egg" problem, as it's not clear if the NR treatment increased the metabolic rate first and that made the mice more likely to engage in physical activity, or if the NR treatment acted on the mice's central nervous system to prime them to engage in physical activity, which in turn increased their metabolic rate. Either way, this pattern helped prevent obesity in these mice.

Lee notes that the impact of the NR treatment was only significant in the older female mice (16 weeks old), in which she observed significant reductions in weight gain, fat mass, glucose intolerance, and cholesterol levels in the older mice.

Lee says her team likely only saw these effects in older mice because the younger mice (eight weeks old) were too healthy and did not have enough fat yet for the NR treatment to have any noticeable effect.

Lee hypothesizes that sex hormones may explain the difference of NR effects between the female and male mouse models. In a follow-up study, she will conduct the experiment by eliminating the estrogen production in female mice to see if that influences the outcome.

These findings underscore the growing importance of personalized nutrition that considers differences between patients, including sex.

"There is an increasing awareness in the field that we really need to do personalized treatment," Lee says. "It's not one-treatment-fits-all."

More information: Mi-Bo Kim et al, Nicotinamide riboside supplementation exerts an anti–obesity effect and prevents inflammation and fibrosis in white adipose tissue of female diet-induced obesity mice, *The Journal of Nutritional Biochemistry* (2022). DOI: 10.1016/j.jnutbio.2022.109058

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