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# Less fat, more hair and younger skin—study shows benefits from calorie-restricted diet

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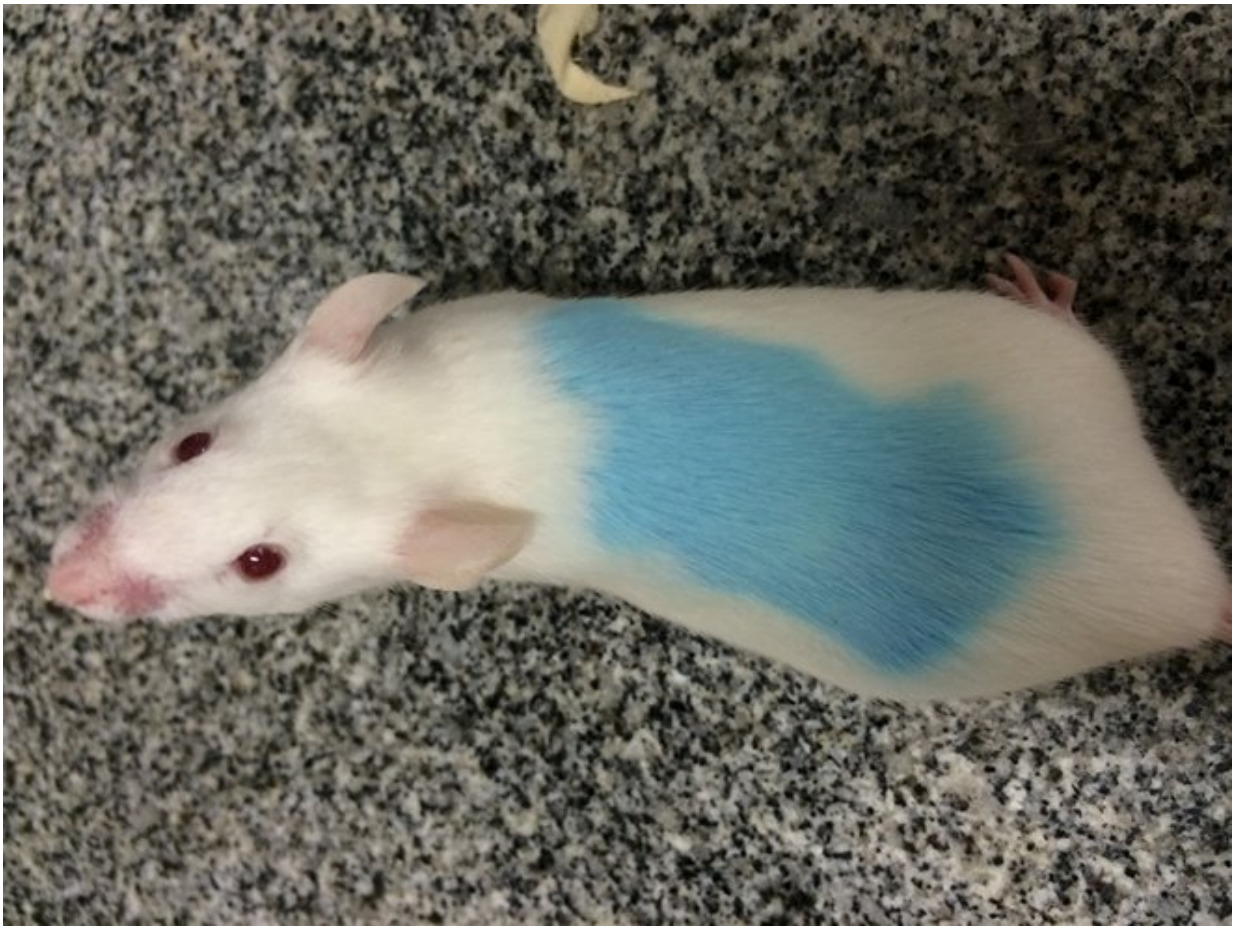

A study shows that caloric restriction diet reduces body fat and increases fur production in mice. This research from the University of São Paulo, in Brazil, was published in *Cell Reports*. Credit: Alicia Kowaltowski / USP

Caloric restriction diets have been associated with health benefits, but their effects on the skin have not been previously demonstrated. Research conducted at the University of São Paulo (USP) in Brazil shows that controlling calories helps mice live longer, although it reduces the reserves of fat in adipose tissue needed to keep the body warm. To offset this effect of the diet, the skin of the mice stimulated fur growth and increased blood flow to warm the skin.

The authors also observed changes in cell metabolism. The mice displayed an adaptive response to remain warm—and alive—in conditions when food was limited.

The research was conducted during Maria Fernanda Forni's postdoctoral fellowship at USP's Chemistry Institute with support from FAPESP and supervision by Alicia Kowaltowski. The results of the study were published in September in the journal *Cell Reports*. "The changes in fur and skin were highly perceptible," Kowaltowski said. "These changes are interesting because they appeared after only a few months when the animals were not yet old."

The experiment involved two groups of mice and lasted six months. In one of the groups, the mice were allowed to eat as much as they wanted at all times and became obese. The others were fed a diet with only 60 percent of the calories consumed by the other group on average.

After six months, the body mass of the mice fed a caloric restriction (CR) diet was 40 percent lower than that of the mice fed an unrestricted diet. This change was not due to the mice losing weight; the mice fed a CR diet did not gain as much weight as the mice that could eat ad libitum. As the fat that helps keep the body warm diminished in CR mice, the adaptive response of their skin was to stimulate fur growth, and after six months, their fur was more uniform, thicker and longer.

"Fur has properties that insulate animals to retain warmth," Kowaltowski said. "We believe this is an adaptation present in mammals. Those that eat less have less fat, and they need more fur or body hair as thermal insulation."

Skin vascularization also changed. Compared with the obese group, the CR group had three times more blood vessels in their skin. This change increased blood flow to skin cells. Moreover, skin cell metabolism exhibited differences between the groups.

Conversely, signs of premature skin aging appeared in the overweight mice. "The change in vasoconstriction helped the slimmer mice stay warm, and their skin also remained young," Kowaltowski said.

In the second stage of the experiment, parts of the skin were shaved in both groups to confirm that the extra fur was helping CR mice keep warm. "We shaved the mice and observed their evolution for a month," Kowaltowski said.

The researchers measured the loss of body heat and found that thicker fur did, indeed, help the mice retain warmth. "CR mice lost muscle mass and became lethargic," Kowaltowski said. "This metabolic change directly resulted from the loss of body heat to the environment. The mice were unable to live well without fur."

Finally, the skin of the mice was dyed blue to investigate whether there was a difference between CR mice and overweight mice in terms of fur thickness. The result showed that CR mice had thicker fur than did overweight mice. "They lost less fur, and their fur remained thick for longer. This could be an adaptation to avoid energy expenditure on growing fur," Kowaltowski said.

"These discoveries are particularly significant since they reveal not just a

pronounced effect of the CR diet on skin, but also an adaptive mechanism to deal with the reduced insulation due to skin changes under conditions of lower caloric intake."

## Liver protection

In another study published in *Free Radical Biology and Medicine*, Kowaltowski's group showed that a CR diet protected the liver from damage due to temporary interruption of blood flow to the organ. "When we compared mice fed ad libitum with mice fed a CR diet, we found a huge difference," Kowaltowski said. "Approximately 25 percent of the liver was damaged in the former group, and only 1 percent was damaged in the latter."

The ischemia/reperfusion model used in the experiment consists of interrupting approximately 70 percent of blood flow to the liver for 40 minutes, simulating a heart attack. Data in the scientific literature suggest that this procedure induces a pathological increase in tissue calcium, which causes a breakdown in the function of mitochondria (organelles that produce energy for cells) and leads to the death of some liver cells.

"Calcium is important to regulate mitochondrial metabolism and increase ATP [adenosine triphosphate, the molecule that stores energy] production. However, an excessive amount of calcium causes the organelles to stop working properly. Therefore, our hypothesis was that the observed benefit of the diet was related to an increase in the capacity of the mitochondria to capture calcium from the intracellular medium without ceasing to produce energy," said Sergio Menezes-Filho, a researcher at IQ-USP and first author of the article.

In vitro experiments were performed to test the hypothesis and better understand the mechanisms involved. To accomplish this, the

researchers isolated mitochondria from both groups of mice, the control group was fed ad libitum and the study group fed a CR diet (60 percent of the control group's caloric intake).

The mitochondria were placed in incubation medium with a fluorescent probe that shone more brightly as the level of calcium increased.

"We added a small amount of calcium to the medium, and the fluorescence intensified. As the mitochondria captured the calcium, the brightness diminished. We added a little more. When the mitochondria reached maximum calcium uptake capacity, calcium began returning to the incubation medium, and fluorescence increased even without the addition of more calcium," Menezes-Filho explained.

In this experiment, the group observed that CR mouse mitochondria were able to absorb approximately 70 percent more calcium than were control mouse mitochondria without functional impairment.

Using mass spectrometry, the group found that there were more ATP molecules in the mitochondria extracted from the CR group than in those extracted from the control group. Marisa Medeiros, a professor at IQ-USP, collaborated in this part of the study.

"We do not yet know why the mitochondria of the mice fed ad libitum have less ATP, but this difference is certainly associated with their calcium uptake capacity," Kowaltowski said. "When we artificially matched the ATP levels in both groups by adding ATP to control mitochondria or reducing it in CR mitochondria, calcium uptake also became equal."

## Multiple benefits

"Simply telling people to eat less is not working. Obesity has become a

global epidemic. We are trying to understand how CR acts in the organism and which molecules are involved to identify targets for preventing or treating diseases associated with weight gain and age," Kowaltowski said.

The experiments performed to date show that dieting in laboratory animals has highly specific effects in different organs. For example, in the pancreas, dieting enables insulin-producing cells to better respond to a rise in blood sugar levels. In the brain, dieting has also been found to provide a benefit associated with mitochondrial calcium uptake capacity, which could prevent neuronal death in diseases such as Alzheimer's, Parkinson's, epilepsy and stroke, among others.

Ignacio Amigo, a researcher at IQ-USP, and Fernanda Menezes Cerqueira, currently at Ben-Gurion University of the Negev, Israel, also took part in the studies. "To date, in our research, we have evaluated the effects of CR in acute pathological situations, but we believe diet also has a subtler beneficial effect on physiological conditions and helps to regulate metabolism on a daily basis. This effect is what we plan to more thoroughly explore now," Kowaltowski said.

**More information:** Sergio L. Menezes-Filho et al, Caloric restriction protects livers from ischemia/reperfusion damage by preventing Ca 2+ -induced mitochondrial permeability transition, *Free Radical Biology and Medicine* (2017). DOI: 10.1016/j.freeradbiomed.2017.06.013

Maria Fernanda Forni et al. Caloric Restriction Promotes Structural and Metabolic Changes in the Skin, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.08.052

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