Understanding and Controlling Obesity in Women

Medical scientists focusing on obesity thought for many years that it was excessive abdominal or “belly” fat that increased the risks for health problems such as diabetes and cardiovascular disease.

This hypothesis was based largely on evidence that men tend to gain weight in the belly and that overweight men were at a higher risk for developing diabetes and cardiovascular disease. Overweight women, according to this hypothesis, were thought to be at a lower risk of cardiovascular disease than overweight men because women tended to gain weight under the skin throughout the body.

However, recognition that cardiovascular disease is the number one killer of women as well as men in the United States, and that the obesity epidemic is growing among both genders, has prompted a new look at the nature of obesity.

Overall, rates of obesity among Americans have grown dramatically over the past 20 years. In every state, at least a fifth of the population is now obese, and in 12 states concentrated in the South the prevalence of obesity is 30 percent or more, according to the U.S. Centers for Disease Control and Prevention. Nationwide, more than a third of adults are obese, CDC figures show.

In addition, 34 percent of adults are overweight—meaning that two-thirds of American adults are either obese or overweight and there appears to be no end in sight to this upward trajectory.

Moreover, health scientists have observed another troubling trend involving excess weight. “It seems to be affecting people at younger ages,” according to Dr. Matthew Rodeheffer, Assistant Professor of Comparative Medicine and of Molecular, Cellular and Developmental Biology.

Recently, in fact, rates of obesity and being overweight have been increasing among American women in the age group between 20 and 34 years old more rapidly than in any other age group for women or men, according to CDC figures. More than a third of children (ages 10 – 17) nationwide are obese or overweight, according to a 2011 report on obesity by the Trust for America’s Health and the Robert Wood Johnson Foundation.

Furthermore, recent analyses of data from population studies of women have indicated that obesity may actually be associated with greater health risks in women than men, said Rodeheffer, who has been studying obesity for nearly a decade. Obese women, in fact, are up to eight times more likely than obese men to develop secondary health conditions including diabetes and cardiovascular disease.

According to Rodeheffer, one of the limitations to understanding what is going on with respect to obesity and related health problems in women is that studies of obesity-related disease have been performed almost exclusively in men or male animals models.

Rodeheffer recently carried out experiments in animal models to determine whether there are differences between females and males in the molecular mechanisms that trigger weight gain due to diet. In these experiments, conducted in the fall of 2010, he wanted to begin to explore a fundamental question: what happens to fat cells at the start of obesity!
“Was it different in females and males, the same, similar? One short experiment told us it’s quite different,” he said in a recent interview in his laboratory.

Rodeheffer’s experiments showed that when a high-fat diet was introduced the cells that trigger the accumulation of fat – fat precursor cells – increased in the abdominal area in male mice. However, in females the increases in fat precursor cells occurred in both the abdominal area and under the skin throughout the body, with the introduction of a high-fat diet.

Hoping to continue this line of research which seeks to determine fundamental biological differences in how we accumulate fat, Rodeheffer applied for and was awarded a 2011 Pilot Project Program grant from Women’s Health Research at Yale.

One of the main goals in his ongoing study is to identify the cellular mechanisms that control the proliferation of fat (white adipose tissue) at the very outset of diet-induced obesity in female mice. Identifying and understanding these mechanisms is highly relevant to everyone’s health, but particularly important for the health of women because they experience greater obesity-related consequences.

Although there are several factors that contribute to obesity, the basic cause is regular consumption of more calories, in food, than are burned off in daily activities and exercise.

“I think it likely has as much to do with how much we eat as with what we eat. Our diets have changed substantially in the last several decades and the contributions of these dietary changes to the obesity epidemic are unknown,” Rodeheffer said.

“The purpose of our study is to characterize what’s going on in the biology, at the cellular level,” he said. “What we really want to understand are the signals in the body,” which tell fat precursor cells to activate and fat cells to proliferate, resulting in more white adipose tissue mass.

His hypothesis, though novel, is quite simple: the excessive accumulation of all white adipose tissue in women, both in the abdominal area and under the skin throughout the rest of the body, may contribute to the development of obesity-related pathologies such as heart disease and diabetes.

The practical benefit of Rodeheffer’s research lies in the potential for the development of therapeutics for the treatment of obesity, and the prevention and treatment of the related health consequences. Understanding the basics of how fat cell proliferation processes work is expected to enable him to identify molecular and cellular targets “so that we can do very directed drug development to combat obesity,” Rodeheffer said. Just as with other addictions, changing behaviors is key to managing and controlling overeating and poor eating habits, but providing a biological intervention can help many people start the process of gaining control over addictive behaviors and changing their lives.

Rodeheffer already has characterized when, during the onset of obesity, fat cells are induced to produce new fat cells, contributing to increased fat mass. “We are now focused on identifying the signals that cause the precursors to become fat cells,” he said. “Knowing the signals necessary for increased fat cell numbers in obesity will allow us to develop therapeutic strategies that directly target the pathways active in obesity.”

A thorough understanding of the molecular mechanisms that regulate white adipose tissue mass in women also has the potential to change how risk assessment is conducted for obese women, affecting how they are assessed with regard to the likelihood of developing heart disease, diabetes, infertility, cancer and other obesity-associated conditions. Better risk assessments mean more chances for prevention.
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Q & A with Matthew S. Rodeheffer, Ph.D.

Q: You hypothesize that accumulation of fat under the skin throughout the body and abdominal fat in women may contribute to obesity-related health problems. Can you explain this?

A: We all know that women and men accumulate fat differently, because we can see the difference. Women tend to accumulate more fat under the skin throughout the body than men and this fact was linked to the association of lower levels of heart disease and diabetes in women than men.

However, we have recently come to appreciate that women have incredibly high rates of heart disease, and studies have shown that obese women may actually have a greater risk of becoming diabetic than obese men. These findings suggest that fat distribution in women may not protect against the development of these obesity-associated diseases and that it may actually contribute to disease progression.

Q: Why is it important that your study relies on female animal models?

A: Almost all of the mechanistic studies of obesity to date have focused on males. In order to determine why females distribute fat differently than males, it is imperative that we study female models of obesity. In reality, studying the differences between males and females – specifically determining why adipocyte (fat cell) numbers increase in the fat under the skin in females when males do not demonstrate this response – may lead to a better general understanding of the signals that regulate fat mass in obesity.

Q: How will understanding the cellular mechanisms involved in the accumulation of fat help you begin to develop interventions to limit obesity in women?

A: In order to study how something happens you have to know when it happens. Our initial studies have characterized when, during the onset of obesity, fat precursor cells are induced to produce more mature fat cells, leading to increased fat mass. Now that we know when the precursor cells are activated, we can study the activated cells to determine what the signals are that control their activation in obesity.

Once we know the nature of the activating signals, we hope to develop strategies to interfere with the activation of fat precursor cells to potentially mitigate weight gain.

About the Investigator:
Dr. Matthew Rodeheffer

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A main goal of his laboratory is to determine how white adipose tissue (fat) mass is regulated normally, and how that regulation is altered in obesity. Given the recent appreciation of the obesity epidemic, his study is highly relevant to everyone’s health, but particularly important to women because women suffer greater obesity-related health consequences compared to men.

Women’s Health Research at Yale’s Pilot Project Program provides funding to Yale researchers to generate feasibility data for innovative scientific studies that can advance medical care. These findings are necessary to apply for and obtain larger external grants so the researchers can continue their investigations.

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