



As described in this chapter, researchers are studying new approaches to increase brown fat levels in people as a strategy to combat metabolic disorders. The human body contains multiple types of fat. White fat stores calories, and too much white fat increases the risk for the myriad co-morbidities associated with obesity, such as type 2 diabetes. A less abundant type of fat called brown fat burns calories and may help regulate blood glucose (sugar) and cholesterol. In a recent study, NIDDK intramural researchers examined whether the drug mirabegron can increase the levels of brown fat in healthy women to potentially fight the negative effects of weight gain. (This drug is currently approved for treating a different condition, overactive bladder.) As measured by body scans known as PET/CT, shown here, they found that brown fat activity increased after 28 days of mirabegron treatment (magenta arrow, right panel) compared to day 1 of the study (magenta arrow, left panel). The women also had increased insulin sensitivity, a marker of reduced diabetes risk. Examining other health outcomes, the researchers found improvements in some heart disease risk markers, although at the amount of drug used in the study, higher than the currently approved dosage, the participants also had increased heart rate and blood pressure. In future research, scientists could examine the effects of this drug in people with insulin resistance, a risk factor for developing type 2 diabetes, and test other potential medications that work similarly, to see if they have reduced cardiovascular risks. This chapter also includes a summary of a research advance by another team of scientists, who studied the effects of mirabegron on beige fat in a different group of people. The results from these studies could thus lead to a safer, effective way to activate brown/beige fat and potentially treat metabolic disease.

*Images courtesy of Dr. Aaron M. Cypess, NIDDK. Republished with permission of the American Society for Clinical Investigation, from Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity, O'Mara AE, Johnson JW, Linderman JD,...Cypess AM, J Clin Invest, Volume 130 (5), Copyright 2020; permission conveyed through Copyright Clearance Center, Inc.*

# Obesity

*Obesity has risen to epidemic levels in the United States. Individuals who have obesity may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission. More than 40 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.<sup>1</sup> More than 19 percent of children and adolescents also have obesity, and thus are at increased risk for developing serious diseases both during their youth and later in adulthood.<sup>2,3</sup> Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically disadvantaged.*

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also modify biologic factors in ways that promote obesity. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions.

The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental interventions in families and in health care and other settings, using a variety of approaches and technologies; surgical interventions; and combinations of strategies. In parallel, NIDDK-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches.

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter.

## **BARIATRIC SURGERY: NEW INSIGHTS INTO EFFECTS ON WEIGHT LOSS AND METABOLISM**

### **Comparing Surgical Treatment and Non-surgical Care for Long-term Weight Loss:**

Researchers have found that people with severe obesity who underwent bariatric surgery had significantly more short- and long-term weight loss compared to those who did not have surgery. Bariatric surgery can be an effective tool for treating severe obesity, leading to significant weight loss and improved health outcomes. However, few people with severe obesity opt to undergo bariatric surgery. This suggests that more data are needed about the long-term outcomes in people who have undergone bariatric surgery compared to those who have not had surgery, to help inform clinical decision making.

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<sup>1</sup> Hales CM, et al. 2020. CDC. National Center for Health Statistics Data Brief No. 360.

<sup>2</sup> Fryar CD, et al. 2020. CDC. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats.

<sup>3</sup> For children and adolescents, obesity refers to a BMI at or greater than the 95<sup>th</sup> percentile on growth charts (which are based on previous national surveys).

To help fill this knowledge gap, scientists analyzed data from the health records of women and men with severe obesity enrolled in a managed health care system. The study sample included over 31,000 people who had undergone a bariatric surgery procedure—either Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG)—as well as nearly 88,000 people who did not have bariatric surgery. Those who did not have surgery received usual medical care, which typically did not include treatment specifically for obesity. The scientists examined the level of total weight loss at 1, 5, and 10 years post-surgery, and at similar timepoints for those in the non-surgical group. After 1 year, people who had RYGB or SG lost about 28 and 23 percent of their body weight, respectively, which was much higher than the 0.2 percent weight loss observed in the non-surgical group. After 5 years, there was some weight regain in the people who had bariatric surgery, so the total weight loss decreased to about 22 percent in the RYGB group and 16 percent in the SG group. However, those levels still exceeded the 2.2 percent weight loss seen in the non-surgical group after 5 years. After 10 years, significant differences persisted: 20 percent weight loss in the RYGB group and 4.8 percent in the non-surgical group. The 10-year data could not be assessed for the SG group because it is a more recent procedure, though it is now the most common form of bariatric surgery. Although the data showed that people who underwent bariatric surgery regained weight over time, regain to within 5 percent of their pre-surgical weight was rare.

Overall, the researchers found that, for people with severe obesity, both RYGB and SG resulted in much more short- and long-term weight loss compared to non-surgical care. Bariatric surgery has serious surgical risks, and lifetime risk remains unknown; however, severe obesity also increases risks for serious diseases. Thus, this study contributes important new information for people with severe obesity and their health care providers as they consider both the risks and benefits of different treatment approaches.

Arterburn DE, Johnson E, Coleman KJ,...Haneuse S. *Weight outcomes of sleeve gastrectomy and gastric bypass compared to nonsurgical treatment.* *Ann Surg* PMID: 32187033, 2020.

**Diet Versus Surgery for Metabolic Health: Weighing the Benefits for People with Obesity and Type 2 Diabetes:** New research shows that the metabolic benefits of gastric bypass surgery and diet in people with obesity and type 2 diabetes are similar and related to weight loss itself with no evidence of clinically significant effects independent of weight loss.

Studies have suggested that surgical procedures to treat obesity that involve bypass of part of the gastrointestinal tract, such as Roux-en-Y gastric bypass, have unique therapeutic effects on blood glucose (sugar) control that are independent of weight loss. However, results of such studies are complicated by the differences in weight loss among people who undergo procedures. To investigate these effects further, researchers in this study evaluated markers of glucose control before and after matched amounts of weight loss induced either by gastric bypass surgery or diet alone in 22 women and men with obesity and type 2 diabetes. The scientists used techniques to measure how well an individual metabolizes glucose and how sensitive an individual is to insulin. Following weight loss of about 18 percent of their initial weight, participants had their blood glucose tested after a meal. Levels of blood glucose were lower in both the surgery and diet groups than before weight loss, indicating metabolic improvements. There was a higher initial peak, followed by a decrease, in blood glucose in the surgery group after food consumption, likely due to the marked increase in rate of delivery of nutrients into circulation due to a restructured gastrointestinal tract. The researchers also found that insulin sensitivity (a measure of how well the body responds to insulin) in the liver, skeletal muscle, and adipose (fat) tissue increased similarly in both groups after weight loss. In addition, beta cell function (a measure of insulin secretion relative to insulin sensitivity) increased similarly in both groups.

The nearly identical benefits of matched weight loss in the surgery and diet groups underscore the profound effects of substantial weight loss on metabolic function in people with type 2 diabetes, and these results challenge the notion that gastric bypass surgery has clinically meaningful effects on metabolic health that are independent of weight loss. However, there remains difficulty in achieving

and maintaining substantial weight loss with diet and other lifestyle changes alone. Therefore, further research is needed to attain the same long-term metabolic outcomes in people with obesity and type 2 diabetes without surgical intervention.

*Yoshino M, Kayser BD, Yoshino J,...Klein S. Effects of diet versus gastric bypass on metabolic function in diabetes. N Engl J Med 383: 721-732, 2020.*

## STIMULATING BEIGE FAT FORMATION

### **Beige Is All the Rage: Drug Treatment Stimulates Beige Fat Formation Resulting in Metabolic Health Benefits in People with Obesity:**

Researchers have shown that treatment with the drug mirabegron, which is approved to treat overactive bladder, stimulates the formation of beige fat tissue in people with insulin resistance and overweight/obesity resulting in several metabolic health benefits, including improved blood glucose (sugar) metabolism. Among different types of fat tissue, brown fat is a form of fat that burns calories (energy) to generate heat, unlike white fat, which is more abundant in the body and stores energy. Beige fat cells, which have similar energy-burning properties to brown fat, can be formed in white fat by cold exposure or through activation of the protein  $\beta$  (beta)3 adrenergic receptor ( $\beta$ 3AR), which is present in fat cells and some bladder cells and can be stimulated by mirabegron. Recent studies in mice have demonstrated that beige fat cells can improve glucose metabolism. However, no study had demonstrated a link between beige fat and glucose metabolism in humans.

Investigators recruited 13 women and men, who had overweight/obesity along with either prediabetes or metabolic syndrome, and treated them with mirabegron at the maximal dose approved (50 mg/day) for 12 weeks. Following mirabegron treatment, more than half of the participants who had prediabetes prior to treatment no longer met criteria for that condition. This finding was consistent with overall improvement of glucose tolerance, a marker of how well the body handles blood glucose. Researchers then further examined the participants to measure the function of  $\beta$  cells, which produce the insulin

necessary for processing glucose, and how well other tissues respond to insulin (insulin sensitivity). The results indicated that an improvement in both measures led to the improved glucose tolerance. Typically, improved glucose tolerance in people with prediabetes or type 2 diabetes is associated with weight loss. However, interestingly, the participants in this study did not experience weight loss. When the researchers examined how mirabegron treatment affected certain molecular markers known to be present in beige fat, they saw an increase in several of these markers in white adipose tissue, indicating the formation of beige fat cells in response to the drug. These changes correlated with the improved glucose metabolism. The scientists then examined effects on skeletal muscle, and they found that mirabegron treatment induced a beneficial switch in the type of muscle fibers in this tissue, which could account for improvements in insulin sensitivity in muscle. Remarkably, neither  $\beta$  cells nor skeletal muscle cells have the  $\beta$ 3AR protein—and thus the beneficial effects of the drug must have been indirect, likely via mirabegron-induced changes in fat tissue. In further experiments, using muscle cells in laboratory culture dishes, the researchers deduced that the effects on fiber type were a result of white adipose tissue “beiging” and sending out a signal to the skeletal muscle cells.

This study demonstrated for the first time in people with overweight/obesity and insulin resistance that mirabegron treatment improves multiple measures of glucose metabolism by inducing beige fat formation in white adipose tissue. In contrast to the increase in beige fat, an increase in brown fat was not observed in this study, but another recent study conducted by intramural NIDDK researchers demonstrated that brown fat is activated by mirabegron in a group of healthy women. While more research is needed to determine the long-term effects of mirabegron treatment on metabolism and if mirabegron can delay the onset of or even reverse type 2 diabetes, the present study brings scientists closer to identifying a safe, effective way to induce beige fat formation and potentially treat metabolic disease.

*Finlin BS, Memetimin H, Zhu B,...Kern PA. The  $\beta$ 3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. J Clin Invest 130: 2319-2331, 2020.*

## UNDERSTANDING HOW HIGH-FAT FOODS AFFECT CALORIE CONSUMPTION

### Your Brain on High-fat Food: Why Diets May Fail:

Researchers have discovered that consumption of a high-fat diet (HFD) suppresses the desire to eat healthier, more nutritional food, and that this devaluation of healthy food is rooted in the brain.

It is well known that humans prefer to consume energy-rich, high-fat foods and that exposure to such diets can lead to overconsumption of calories, weight gain, and the numerous health complications that can accompany overweight/obesity. The urge to consume high-fat foods is compounded by an accompanying lack of desire to eat nutritional food that may be perceived as less palatable. However, the reasons behind this remain poorly understood. To determine how high-fat food affects calorie consumption, researchers split adult male and female mice into two groups. Both groups began with unlimited access to a nutritionally balanced standard diet (SD). One group remained on the SD for the duration of the study, while the other group was given unlimited access to both the SD and 60 percent HFD for 8 weeks, followed by removal of the HFD for a 2-week withdrawal period. HFD-exposed mice exhibited an immediate preference for the high-fat food in lieu of the healthier SD, and only the HFD-exposed mice increased total daily calorie consumption and gained weight. Every HFD-exposed mouse displayed a marked reduction in SD consumption, and, remarkably, HFD removal resulted in rapid weight loss and a failure to consume daily required calories from the SD. This self-restricted caloric deprivation indicated that the mice no longer valued SD food. Moreover, after 2 weeks without access to a HFD, body weight and caloric consumption did not recover to baseline levels, indicating a prolonged physiological adaptation. Since several brain circuits, namely in a region of the brain called the hypothalamus, govern the drive to eat, the researchers next recorded activity of brain cells called AgRP neurons in mice transitioned to and from a HFD and compared those to recordings from mice on a SD. Hunger activates AgRP neurons and stimulates the drive to eat; food intake then suppresses AgRP activity. When the researchers presented the mice with a SD, they observed robust inhibition of AgRP activity, followed by similar food intake in each feeding session. However, when mice were provided with a HFD, they had significantly reduced AgRP responses

to a SD—indicating that they no longer perceived SD as something that could alleviate their hunger. Notably, SD still did not quiet the hunger signals from AgRP neurons even after a 2-week HFD withdrawal, analogous to a strict diet in humans, emphasizing a prolonged effect from a HFD on this neural signaling system. In addition, the researchers observed changes in the brain chemical dopamine, known to play a critical role in reward pathways. Dopamine release was enhanced in mice that were fed a SD. However, after 1 week of HFD access, the scientists observed reduced dopamine release in response to a SD, further enforcing the concept of devaluation of nutritional food after exposure to a HFD.

Though these findings will need to be confirmed in humans, taken together, they reveal a neural basis behind why we may be driven toward calorie dense, highly palatable, less nutritional food and help explain the challenges of dieting in an obesogenic environment—where such food is readily available. Further research will be critical to developing therapeutics that can potentially target specific brain signaling pathways in response to certain diets.

*Mazzone CM, Liang-Guallpa J, Li C,...Krashes MJ. High-fat food biases hypothalamic and mesolimbic expression of consummatory drives. Nat Neurosci 23: 1253-1266, 2020.*

## MOLECULAR UNDERPINNINGS OF EXERCISE

We know exercise is good for us. It helps build muscle, burn fat, and can even improve our moods. But long before we notice changes in our physique, there are hidden, more immediate, molecular and cellular changes taking place inside our bodies—changes that could improve blood glucose (sugar), metabolism, or even stave off disease. It has been posited for some time that communication between different types of cells is critical for regulating metabolism and organ function, but the exact players involved remained unknown. Moreover, previous studies have examined selected changes in metabolic, cardiovascular, and immune pathways, but a systemic molecular response to exercise has not been fully characterized. In the recent advances described below, researchers performed a system-wide, comprehensive, molecular profiling before and after a brief bout of intense physical activity and investigated adaptive immune changes in response to sustained exercise. Their



findings provide insight into why exercise is beneficial to our health, highlight precise molecular factors involved, and have potential implications for diagnostic tests in a health care setting.

### **A Physiological Dance: How a Brief Bout of Exercise Initiates a Molecular Choreography of Events:**

Through a highly comprehensive analysis, researchers have revealed molecular changes involved in a choreography of biological processes, including metabolism, inflammation, cardiovascular function, and tissue repair, that occur in humans in response to an acute bout of exercise. By analyzing blood components before and after a controlled session of physical activity, they provide a window into the dynamic nature of the impact of exercise on human molecular physiology.

To understand how exercise is beneficial to our health, a team of researchers set out to identify the precise molecular fluctuations that are triggered by physical activity and which lead to improved health and fitness. In this study, they took hundreds of thousands of measurements from 36 male and female participants, ages 40 to 75 years; many of the participants also had insulin resistance, a condition associated with obesity, diabetes, and prediabetes. Before a treadmill test, the researchers took a baseline blood sample. Participants then wore an oxygen-measuring mask and exercised for about 8 to 12 minutes, until they reached peak oxygen consumption—the gold standard for measuring aerobic fitness. The researchers took blood samples from participants 2 minutes, 15 minutes, 30 minutes and 60 minutes after they stopped exercising. It turns out that shortly after exercise, the body experiences a whirlwind of molecular activity. Molecular markers of an immune response, inflammation, and “oxidative stress” spiked sharply in most people directly following exercise, which is indicative of skeletal muscle strain and tissue healing as the body begins to recover. They also saw an increase in markers of lipid (fat) metabolism. Exercise also triggered the release of several hormones to restore metabolic balance, and the researchers observed a distinct positive correlation between glucose and insulin levels; insulin secretion enhances the body’s ability to absorb glucose to meet higher energy demands. The team also observed a decrease in the appetite-associated hormones leptin and ghrelin, similar to previous studies. This finding suggests a role of physical activity in appetite regulation. Moreover, as part of the study, they

compared the molecular response of individuals who had insulin resistance to those who could process glucose properly. Several biological pathways were altered in individuals with insulin resistance, including a dampened immune response post-exercise. Finally, the team noticed clear associations between sets of molecules and peak oxygen consumption. For example, higher levels of molecules known to reflect poor metabolic health were associated with lower peak oxygen while healthy molecular profiles were associated with higher peak oxygen, therefore indicating enhanced cardiopulmonary capacity. These associations allowed the team to develop prediction models of fitness revealing potential resting blood biomarkers of peak oxygen consumption.

Taken together, these findings provide a first-of-its-kind comprehensive profile of post-exercise molecular fluctuations and illustrate the complex interplay between multiple biological processes. The results provide a window into why exercise is good for us and offer the potential to someday be implemented into health care settings as a personalized blood test for fitness to determine an optimal fitness regimen.

*Contrepois K, Wu S, Moneghetti KJ, Snyder MP. Molecular choreography of acute exercise. Cell 181: 1112-1130.e16, 2020.*

### **The Role of an Immune Protein in Metabolic Conditioning of Muscle to Sustained Exercise:**

Researchers have discovered that the immune protein interleukin-13 (IL-13) is activated by exercise, sustained by endurance training, and leads to enhanced muscle efficiency and improved blood glucose (sugar) in a coordinated manner that improves metabolic fitness.

It is known that exercise reduces the risk of developing many conditions, including metabolic syndrome and obesity, and previous studies suggested that immune signals may mediate the metabolic effects of exercise. To identify circulating factors induced by exercise, scientists examined a panel of proteins from the blood plasma of normal-weight sedentary women, endurance-trained female athletes, and women with obesity. They found that endurance-trained women had substantially higher levels of circulating IL-13, which is made by immune cells embedded in skeletal muscle, compared with the other groups. They found similar results when they analyzed blood plasma of normal-weight sedentary and endurance-trained men: male athletes had significantly higher levels of

IL-13 than their non-athletic counterparts. To gain more insight into the effects of IL-13, the scientists examined mice with and without this immune protein. When they genetically deleted IL-13 in mice and performed treadmill-running tests, the mice lacking the protein displayed a substantial reduction in running time and distance. Next, the researchers examined the levels of activity of genes in muscle tissue samples from normal and IL-13-deficient mice, with and without exercise. The results were consistent with the notion that exercise promotes a metabolic switch in muscle tissue from burning glucose as fuel to burning fatty acids, or the building blocks of fat, which maximizes energy efficiency. This metabolic reprogramming was lost in IL-13-deficient mice. Furthermore, the researchers found that endurance training, through IL-13 signaling, improved the running capacity and blood glucose levels of both male and female mice compared to untrained animals.

These results demonstrate that endurance exercise activates an adaptive response, which is an interaction between immune cells and muscle cells, that leads to a metabolic conditioning of muscle as a strategy for sustained physical activity while improving glucose tolerance. This research highlights the importance of immune signaling in metabolic fitness.

*Knudsen NH, Stanya KJ, Hyde AL,...Lee C-H. Interleukin-13 drives metabolic conditioning of muscle to endurance exercise. Science 368: eaat3987, 2020.*

## GUT MICROBIOME AND BODY WEIGHT

### How the Gut Microbiome Controls Daily

**Metabolic Rhythms:** New research has clarified how the microbes in the gut (*i.e.*, the gut microbiome) regulate mice's daily metabolic rhythms, affecting weight gain and metabolic health. An organism's metabolism changes in response to the cycle of day and night, and this "circadian rhythm" is associated with sleeping and feeding cycles. Some of these metabolic changes are regulated via modification to a cell's histones, the protein "spools" around which DNA is wound. Depending on histones' chemical modifications, they may allow or block access to genes, effectively turning specific genes on or off. Since the gut microbiome has also been linked to daily metabolic cycles, researchers asked if the microbiome uses host histone modification to control cyclic gene activity in the gut. To answer this question, the

scientists studied histone modifications in the small intestines of either normal or "germ-free" mice that lack all microorganisms. They found that histone modifications in germ-free mice's intestinal cells did not cycle daily as they did in normal mice. To study how the microbiome was causing this difference in histone modification, researchers surveyed the proteins, called histone deacetylases, which cause many of these modifications. The scientists identified one histone deacetylase in mice, HDAC3, that was not as abundant in germ-free mice as in normal mice and that, like the histone modifications, cycled differently in the presence or absence of a microbiome. Upon further study, researchers confirmed that the microbiome was required for HDAC3's recruitment to histones at target genes, suggesting that the microbiome was affecting HDAC3 activity. Studying a mouse model with an intact microbiome but without HDAC3 in its intestinal cells gave further clues to HDAC3's importance: a lack of HDAC3 resulted in disruptions in the daily activity cycles of over 2,700 genes in the intestinal lining. Taken together, these findings demonstrated that the microbiome controls HDAC3 activity to produce wide-reaching effects on the body. For example, many of HDAC3's target genes in the intestinal lining are involved in nutrient transport and metabolism. Furthermore, researchers discovered that HDAC3 controlled how intestinal cells took up nutrients during digestion, ultimately affecting the concentrations of metabolic products and lipids in the mice's blood. Because of these effects on nutrient uptake, the researchers also investigated HDAC3's role in diet-related obesity. They found that HDAC3 in the intestinal lining was required for the microbiome to promote obesity and other negative metabolic effects when mice were put on a high-fat diet. They even found that HDAC3 was important in weight gain induced by experimental jet lag, demonstrating another link between circadian rhythm, the microbiome, and obesity. Overall, these findings highlight a possible way in which the gut microbiome's regulation of its host's metabolism has significant impacts on metabolic health. Although future research is needed to determine if the microbiome and HDAC3 play similar roles in people, these experiments have identified possible new targets for the treatment of metabolic disease.

*Kuang Z, Wang Y, Li Y,...Hooper LV. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. Science 365: 1428-1434, 2019.*

# NIH Seminar Series: Obesity and Women's Health

## Obesity and Women's Health Virtual Symposium

September 10, 2020

NIH Obesity Research Task Force Seminar Series



Obesity prevalence continues to rise in the United States despite recognition of its many adverse health effects. More than two in three U.S. adults are considered to have overweight or obesity. Among women, although obesity and severe obesity have increased in all racial/ethnic groups over the past several years, the prevalence of both are greater in non-Hispanic Black women and Mexican American women compared to non-Hispanic White women. These disparities are particularly concerning given that obesity is a risk factor for adverse outcomes from the novel coronavirus, which has disparate outcomes in communities of color. In addition to its contribution to cardiovascular disease, breast cancer, and worse outcomes from COVID-19, obesity in women increases the risk for adverse conditions affecting almost every organ system including the reproductive system and lower urinary tract. To accelerate the development of new and innovative treatments for obesity in women and to close knowledge gaps, four leading scientists highlighted their research at a September 2020 virtual symposium. The research presented was supported by the NIDDK among other Institutes. The seminar was organized as part of the NIH Obesity Research Task Force Seminar Series.

Dr. Mercedes Carnethon from Northwestern University presented her research on the cardiovascular consequences of obesity in women. Her work focuses on multi-level risk factors including biological influences, individual health behaviors,

interpersonal and cultural aspects, and environmental factors. Vulnerable periods in a woman's life, such as the reproductive years and menopause, can trigger weight gain, which can in turn affect cardiovascular health. Individual behaviors including poor dietary intake and sleep disturbances (insomnia is more common in women than men) can all lead to metabolic disruptions like weight gain, altered glucose (sugar) metabolism, and hypertension. Moreover, social and environmental determinants such as income, education, socioeconomic status, and neighborhood safety disproportionately affect female-headed households and may increase risk for obesity in women in underserved minority communities. Finally, analyses have shown that weight loss interventions during critical periods of life when cardiovascular health declines are less effective in women than men. Further research is needed to tailor interventions to the cultural and interpersonal factors faced by women.

Dr. Richard Legro from Pennsylvania State University gave a thought-provoking presentation on obesity and female reproduction. Ample amounts of observational data suggest that obesity in women is associated with infertility and adverse pregnancy outcomes. However, Dr. Legro challenged this notion and questioned if the impact of obesity on fertility might be overestimated. He discussed results from several studies that assessed the impact of weight loss on pregnancy outcomes in women with obesity. One such study evaluated the effects of Roux-en-Y gastric bypass surgery on



female reproductive function and found that weight loss had no effect on the quality of ovulation. In another study that evaluated pregnancy outcomes after bariatric surgery, the investigators found that while weight loss was associated with reduced risk of gestational diabetes, the women who lost the most weight were at greater risk for preterm birth and for having infants that were smaller than average, compared to women with obesity who did not have surgical treatment. Finally, in the NIH-funded FIT-PLESE trial, researchers compared an intensive lifestyle intervention to a standard lifestyle intervention in women with obesity and unexplained infertility before the women had fertility treatment. While women in the intensive intervention group experienced greater improvements in metabolic syndrome, there were no differences between the two groups in healthy live births. Therefore, improvements in metabolic health did not equate to improvements in reproductive fitness. Dr. Legro concluded that while obesity is certainly a risk factor for many harmful conditions, obesity alone is not a major contributor to infertility and pregnancy complications.

Dr. Jennifer Ligibel from the Dana-Farber Cancer Institute at Harvard Medical School presented research linking obesity to breast cancer risk and outcomes. Observational evidence shows a strong link between obesity and breast cancer risk. In addition, obesity is linked to recurrence in breast cancer survivors and mortality rate. The strongest evidence that weight loss could reduce cancer risk comes from bariatric surgery studies—bariatric surgery was associated with a lower risk of cancer, including postmenopausal breast cancer, in women with severe obesity. The National Cancer Institute-supported **Breast Cancer WEight Loss (BWEL)**

clinical trial enrolled participants with stage II-III breast cancer who also had overweight/obesity, and randomly assigned them to either a health education and weight loss intervention group or a health education alone group to assess the impact of a weight loss intervention on survival. This large-scale study is ongoing. BWEL and other ongoing trials have the potential to provide more definitive evidence regarding whether weight loss and other lifestyle changes after cancer diagnosis could reduce the chance of recurrence and improve survival.

Dr. Leslee Subak from Stanford University presented research on lower urinary tract symptoms (LUTS) and obesity in women. LUTS include issues such as urinary incontinence (UI) or loss of bladder control, frequency of urination, and urgency of urination, among others. Urinary incontinence is highly prevalent among women and has a negative impact on quality of life. The biggest risk factor for developing UI is body weight, and the majority of women with UI have overweight or obesity. As part of the Program to Reduce Incontinence by Diet and Exercise (PRIDE), Dr. Subak described studies that assessed the effect of weight loss on UI. The studies found that a reduction in weight was associated with substantial improvements in UI and other urinary tract symptoms such as urgency. Similarly, the Longitudinal Assessment of Bariatric Surgery (LABS) observational study found that a substantial reduction in weight could lead to UI remission.

The seminar also included a lively discussion among speakers and participants on current challenges and opportunities. Continued research in this important area can potentially reveal better ways to prevent and treat obesity in women, thereby preventing many adverse health outcomes.

