NIDDK

Recent Advances & Emerging Opportunities

Obesity

January 2022

This is a chapter from the NIDDK's Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK's mission and is available at: *www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities*

U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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The trans-NIH Obesity Research Task Force was established to accelerate progress in obesity research across the NIH, given the importance of the obesity epidemic as a major public health problem and its relevance to the missions of most of the NIH Institutes, Centers, and Offices. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, Dr. Griffin P. Rodgers; the Director of the National Heart, Lung, and Blood Institute, Dr. Gary H. Gibbons; and the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Dr. Diana W. Bianchi. The Task Force holds two to three seminars each year, covering a broad range of topics to accelerate research to develop new and innovative prevention and treatment strategies for obesity and to close knowledge gaps.

On September 3, 2021, the Task Force convened a symposium on obesity and COVID-19 where 4 distinguished scientists highlighted their research on obesity, vaccine response, SARS-CoV-2 infection, and the resulting disease of COVID-19. A summary of this seminar is in this chapter.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who have obesity may develop 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.[1] 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.[2,3] 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 (social determinants of health) such as a lack of healthy, affordable food and places to exercise in many communities, sedentary jobs, and other conditions that influence what, when, and how much people eat. Diet, activity, and aspects of our environment also may 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.

Individuals who have obesity may develop devastating health problems, face reduced life expectancy, and experience stigma and discrimination.

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 for children and adults in health care, home, community, 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.

More than 40 percent of U.S. adults and more than 19 percent of children and adolescents have obesity.[1,2,3]

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 to promote collaboration and enhance obesity research across the NIH.

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

The NIDDK supports basic, clinical, and translational research to discover how body weight is regulated and to design and evaluate approaches for preventing and treating obesity.

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[1] *Hales CM, et al. 2020. CDC. National Center for Health Statistics Data Brief No. 360.*

[2] *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.*

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

THE DIET DEBATE

Weighing in on the Diet Debate: Low-carbohydrate Versus Low-fat: By comparing the effects of a plant-based, low-fat diet for 2 weeks to an animal-based, low-carbohydrate diet for 2 weeks in adult men and women, researchers have shown that while each diet had benefits, the low-fat diet led to less caloric intake and a significant loss of body fat. Two competing models of obesity contrast the roles of dietary fat and carbohydrate. According to the carbohydrate-insulin model, a diet high in carbohydrates results in elevated insulin levels after a meal, which is thought to cause increased hunger and calorie consumption. Alternatively, the passive overconsumption model predicts that high-fat, energy-dense (calorie-dense) foods promote increased caloric intake and weight gain.

To determine the impact of each diet on caloric intake, hormone levels, and body weight, 20 adult volunteers without diabetes were admitted for 4 continuous weeks to the National Institutes of Health Clinical Center and randomly assigned to receive either a plant-based, low-fat diet or an animal-based, low-carbohydrate diet for 2 weeks followed immediately by the alternate diet for 2 weeks. They received three meals a day plus snacks and could eat as much or as little as desired. Both diets were minimally processed and contained approximately the same amount of protein. When on a low-fat diet, participants ate 550-700 fewer calories per day than when on the low-carbohydrate diet. Despite the large differences in calorie intake, they reported no differences in hunger, enjoyment of meals, or fullness between the two diets. People lost weight on both diets, but only the low-fat diet led to a substantial loss of body fat. However, the low-carbohydrate diet resulted in lower blood glucose (sugar) and insulin levels compared with the low-fat diet.

Since the low-fat diet led to less caloric intake and the low-carbohydrate diet did not result in weight gain, the validity of both competing models of obesity is challenged. However, the study is limited by the tightly controlled clinical environment, which makes it difficult to generalize results to real-world settings where factors such as food costs, food availability, and meal preparation constraints can make adherence to a diet challenging. These findings suggest that regulation of calorie intake is more complex than these models propose. More research is needed to determine the long-term effects of both diets.

Hall KD, Guo J, Courville AB,...Chung ST. Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake. Nat Med 27: 344-353, 2021.

> *When on a low-fat diet, participants ate 550-700 fewer calories per day than when on the low-carbohydrate diet.*

GENETIC UNDERPINNINGS OF OBESITY

Large-scale Genetic Study Identifies Genes That Increase Risk of Obesity While Protecting Against Other Metabolic Diseases: A new analysis of genetic data sets has revealed regions of the genome that are linked to both elevated levels of body fat and protection from some of the negative health impacts of obesity. Obesity is a major risk factor for cardiometabolic diseases such as type 2 diabetes, heart disease, and related conditions, and people living with obesity tend to have unhealthy glucose (sugar) and lipid levels in their blood and high blood pressure. But scientists have observed that up to 45 percent of people with obesity have healthy blood pressure and blood glucose/lipid levels, and therefore may not be at high risk of diabetes and cardiovascular disease. The reasons why this group of people remains healthy have been poorly understood.

To determine whether genetics may play a role, a team of researchers analyzed data from hundreds of thousands of people, mainly of European descent, who had previously been assessed for body fat and disease risk markers. They identified 62 regions of the genome that have a seemingly paradoxical association of increased risk of obesity and favorable effects on cardiometabolic outcomes. Genes identified within these regions point to both known and novel ways in which excess body fat can become uncoupled from cardiometabolic diseases. For example, some of these body fat-increasing genes are associated with storage of the excess fat beneath the skin, as opposed to storage around the internal organs where fat is metabolically harmful. Further analyses identified genes that are functionally implicated in improved blood glucose levels, insulin signaling, regulation and development of fat cells, and energy (calorie) expenditure. Moreover, genes were identified that are linked to both increased body fat and changes in the nature of some of the fat tissue, from calorie-storing "white" fat to a form called "brown" or "beige" fat, a process that can increase calorie burning and promote

healthy metabolism. These results are helping to clarify the complex genetic underpinnings of obesity, and the genes identified may represent targets for new therapies to reduce cardiometabolic risk associated with excess body fat.

Huang LO, Rauch A, Mazzaferro E,...Loos RJF. Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities. Nat Metab 3: 228-243, 2021.

A new analysis has revealed regions of the genome that are linked to both elevated levels of body fat and protection from some of the negative health impacts of obesity.

MOLECULAR UNDERPINNINGS OF EXERCISE

Succinate Regulates Muscle Adaptations to Exercise in Mice and Humans: Researchers have identified succinate, a small molecule produced through metabolism, as a signal in both mice and humans that triggers muscle remodeling and strength building in response to exercise. Muscle remodeling is the mechanism by which we get stronger in response to exercise, and it is thought to have other health benefits as well. Muscle adaptations require rapid cell-to-cell communication, but the signals originating from the contracting muscle that drive these processes are unknown.

In this study, researchers used small-molecule analysis to track the accumulation of metabolites secreted into the fluid between cells and into the circulation from acutely exercised muscle in both mice and humans. First, mice were exercised on a treadmill, and muscle samples were isolated and analyzed. In addition, the researchers recruited young, healthy men of normal weight and collected blood samples (which can be used to study the fluid composition between muscle cells) while the men exercised on a bicycle for 1 hour and during recovery. Notably, the researchers discovered that succinate was selectively and rapidly released by both mouse and human muscle during exercise—an unexpected finding since succinate was not previously thought to be able to move freely out of cells. However, during exercise the interior of muscle cells becomes transiently and mildly acidic and in this acidic environment, succinate is converted into a form that can be transported out of the muscle cells by acid-dependent succinate transporters. Once released from the contracting muscle cells, succinate binds to the protein SUCNR1, which is present on non-muscle cells also located in the muscle (tissue or fiber). Following acute exercise, the succinate-SUCNR1 binding then sends a signal that is critical to induce muscle remodeling and muscle strengthening. Importantly, the succinate-SUCNR1 signaling also appears to be associated with another benefit of exercise—improved insulin sensitivity—and the research team found that the extent of this effect correlated with the peak exercise succinate concentration in humans.

This study suggests that succinate may play a key role as a signal that mediates muscle adaptation and remodeling responses to exercise. Further research could provide insight into whether dietary succinate supplementation or other therapeutic approaches could trigger the succinate-SUCNR1 signaling pathway to initiate muscle adaptations similar to those seen through exercise, and whether it is safe to do so.

Reddy A, Bozi LHM, Yaghi OK,...Chouchani ET. pH-gated succinate secretion regulates muscle remodeling in response to exercise. Cell 183: 62-75, 2020.

POWERS

Preventing regain of lost weight is the most difficult challenge in the treatment of obesity. Individuals with overweight/obesity can alter dietary intake and physical activity to lose a significant amount of excess weight, but they will usually experience weight regain despite their best efforts. There is considerable evidence that various physiological adaptations occur that counter lifestyle attempts to maintain reduced weight.

The NIDDK convened a workshop, "Physiology of the Weight-reduced State," in June 2019 to explore the potential biological mechanisms that account for adaptations in appetite and energy (calorie) expenditure. The workshop was chaired by Drs. Rudolph L. Leibel of Columbia University and Kevin D. Hall of NIDDK, and it brought together researchers who study the regulation of eating behavior and energy expenditure and clinical scientists who are experienced in weight loss and weight maintenance interventions. Sessions focused on describing physiologic and metabolic changes that occur during the weight-reduced state in humans; studies examining the altered regulation of energy intake and energy expenditure after weight loss; and experimental approaches applied to the study of the weight-reduced state, particularly those such as metabolomics and proteomics, new genetics strategies, and neuroimaging. The goals of the presentations and discussions were to identify the state of knowledge regarding the biological mechanisms that oppose weight-loss maintenance, gaps in that knowledge, strategies to identify those pathways that are altered by weight loss, and new therapeutic targets for improving success in weight maintenance after weight loss.

Outcomes from the workshop included: (1) there is an equilibrium weight "set point" that is a function of physiology, genes, and environment; (2) changes in hunger and energy expenditure are the balancing factors that drive weight back to its set point; (3) increased appetite and reduced energy expenditure will likely persist until weight is restored to a set point; (4) variability in adaptation may account for some of the individual variability in weight loss maintenance; and (5) although current therapies have improved adherence and response to weight-loss and weight-maintenance interventions, new therapies are needed to prolong the weight-loss phase, reduce appetitive and metabolic adaptation during the weight-maintenance phase, and alter the weight set point.

As a result of the workshop, the NIDDK launched the Physiology of the Weight-reduced State (POWERS) clinical trial consortium, which will seek to characterize the physiological mechanisms underlying individual variability in maintenance of reduced weight over time. This could reveal new therapeutic targets for interventions aimed at maintaining weight loss. Investigators will study adults with obesity before and after weight loss achieved through a behavioral/lifestyle intervention to explore the physiologic mechanisms that regulate energy intake and metabolic adaptation.

The clinical sites are at Columbia University and Drexel University (the Drexel award is comprised of investigators from Drexel, Tufts, and the University of Pennsylvania). The data coordinating center is at the University of Pittsburgh. The primary governing body of the consortium is a Steering Committee comprised of investigators from the clinical sites and coordinating center as well as an NIDDK project scientist. The Committee will employ common protocol elements that ensure enough participants can be enrolled and extensively studied to provide insight into the duration and extent of metabolic adaptation following weight loss. In accordance with NIDDK data sharing policies, all data produced by the consortium will be made publicly available.

Through this bold new initiative, novel approaches to achieving and maintaining weight loss based upon a better understanding of the interaction of genes and environment can be realized.

Credit to Drs. Laughlin, Osganian, Yanovski, and Lynch for sampling from their manuscript: Laughlin MR, Osganian SK, Yanovski SZ, and Lynch CJ. Physiology of the weight-reduced state: A report from a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Obesity (Silver Spring). 29 Suppl 1: S5-S8, 2021.

NIH Seminar Series: Obesity and COVID-19

Since early 2020, the world has been in the midst of a deadly pandemic due to the SARS-CoV-2 virus and the resulting disease, COVID-19. COVID-19 has claimed millions of lives and changed the ways in which each of us relates to and navigates the world. For more than a year, many people were sheltered at home, where eating and physical activity routines were disrupted. Many people also encountered the added stress of loss of employment or dealt with illness in themselves or loved ones. These factors can contribute to an increase in obesity-promoting behaviors. Obesity, among many other diseases such as type 2 diabetes, is a known risk factor for severe illness and even death from COVID-19 in people of any age. Obesity trends continue to rise in the United States despite recognition of its many adverse health effects. The highest obesity prevalence has been in certain racial and ethnic minority populations, further contributing to the disparate outcomes seen in COVID-19. While we now have several vaccines available to help protect us against this deadly virus, obesity has been shown to impact an individual's immune response to certain vaccines; this is an important consideration for COVID vaccination as well. Given the global public health significance of obesity and COVID-19, the research community recognizes the need to accelerate development of new and innovative prevention and treatment strategies for obesity and to close knowledge gaps with the goal of translation into more effective patient care. To that end, four leading scientists highlighted their research at a September 2021 virtual symposium organized as part of the NIH Obesity Research Task Force Seminar Series. The research presented was supported by NIDDK and other NIH Institutes.

Dr. Barry Popkin from the University of North Carolina at Chapel Hill presented a global perspective of obesity and COVID-19. An analysis of multiple scientific studies revealed that individuals with overweight and obesity face a greater risk of severe consequences from COVID-19, including hospitalization, intensive clinical care, and death. Globally, there have been substantial decreases in physical activity due to virus control measures and isolation related to loss of employment. In most countries, there have been rapid increases in consumption of ultra-processed, less nutritious, and less expensive foods. Increased weight has been documented, and COVID-19-associated changes in diet and exercise patterns could continue to result in greater weight gain and risk of obesity worldwide. In addition, economic stressors and food insecurity in some countries could lead to undernutrition, which is also associated with reduced immune function and poor outcomes from COVID-19. Dr. Popkin noted that this research was done prior to the delta variant of SARS-CoV-2 becoming the dominant cause of COVID-19 worldwide.

Dr. Melinda Beck from the University of North Carolina at Chapel Hill presented her research on the immune response to influenza vaccination in the context of obesity and potential implications for human responses to COVID-19 vaccines. Obesity is a risk factor for poor outcomes from both influenza and SARS-CoV-2 infection. Using an animal model, her team found that influenza-infected mice with diet-induced obesity showed greater lung inflammation, immune dysfunction, and a higher mortality rate compared to influenza-infected lean mice. In a human influenza vaccine study, adults with obesity who received an influenza vaccine experienced a steeper decline in vaccine-induced, influenza-specific antibodies over time compared to vaccinated, healthy weight adults. Moreover, a certain type of immune cell called "T cells" that typically recognize and fight viral infections were also relatively impaired in adults with obesity. Compared to vaccinated, healthy weight adults, vaccinated adults with obesity were twice as likely to become infected with influenza. This is similar to what is observed in vaccinated elderly individuals. Based upon these results, there is recognition in the scientific community that metabolic disease can influence the immune response and that perhaps the response to COVID-19 vaccines in people with obesity may not be as robust compared to healthy weight adults.

Dr. Dirk Homann from the Icahn School of Medicine at Mount Sinai presented his research on diabetes and COVID-19. Preexisting diabetes is associated with an increased risk of severe COVID-19. However, new-onset diabetes has also been observed in patients with COVID-19, raising the question of whether a more complex connection between COVID-19 and diabetes exists. In laboratory studies using human pancreatic cells in culture, Dr. Homann's group saw no evidence of enhanced cell death or pronounced insulin depletion of SARS-CoV-2 infected cells. Although they did find that the protein "receptor" to which the SARS-CoV-2 virus binds is required for productive infection of pancreatic cells, they found no indication that the virus affects pancreatic cell functionality, thereby inducing diabetes. Dr. Homann's group's results thus far suggest that SARS-CoV-2 infection of pancreatic cells is unlikely to induce diabetes. This is a rapidly evolving area of research, with different laboratories finding different results under different conditions that together are helping to build a comprehensive picture of the impact of SARS-CoV-2 on the pancreas. Research remains ongoing to better understand the relationship of COVID-19 and diabetes.

Dr. Dana Dabelea from the University of Colorado concluded the series of presentations by describing her work through the NIH-supported Environmental influences on Child Health Outcomes (ECHO) program on obesity-related behaviors in children and families during the COVID-19 pandemic. Through a consortium of nationwide pediatric cohorts, Dr. Dabelea's group aimed to describe obesity-related behaviors in children during the pandemic, to identify socio-demographic groups who are at high risk for obesity-related behaviors, and to explore the extent to which behaviors are modified by parental coping strategies. They found that in the first 7 months of the pandemic, a substantial proportion of children did not meet recommended guidelines for healthy behaviors, including those for diet, physical activity, and screen time. Consistent with observed pre-pandemic disparities, healthier behaviors were seen among children who were younger, non-Hispanic White, and whose mothers had higher education levels. The vast majority of parents reported pandemic-related financial strain. Financial concerns and access to food as sources of stress were associated with increased intake of unhealthy foods, decreased exercise, and shorter sleep duration. Time-sensitive, ECHO-wide, ongoing studies are being conducted to examine changes in children's obesity-related behaviors that are occurring in tandem with societal changes related to the COVID-19 pandemic. Continued research is needed to understand the long-term effects of the pandemic on obesity-related behaviors and implications for children's health during COVID-19 and beyond.

The seminar included a lively discussion among speakers and participants on current challenges and opportunities. Continued research could reveal better strategies to prevent and treat obesity, thereby preventing many adverse health outcomes in general, as well as during the current and potential future pandemics.