

NIDDK

Recent Advances & Emerging Opportunities

January 2024

Obesity



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:

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



National Institute of
Diabetes and Digestive
and Kidney Diseases

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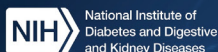
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NIH Obesity Research Task Force Symposium

Medications to Treat Obesity: Past, Present, and Future



September 8, 2023

Natcher Conference Center • Building 45 • NIH Campus • Bethesda, MD



The NIH-wide Obesity Research Task Force was established to accelerate progress in obesity research across 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 NIDDK, 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 seminars each year, covering a broad range of topics. On September 8, 2023, the Task Force convened a symposium on medications to treat obesity where seven distinguished scientists highlighted their research in this field, and two individuals who have used these medications shared their personal perspectives and experiences. 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 NIDDK's mission. Nearly 42 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.^{1,2} Nearly 20 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.^{1,3} 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 biological 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.

NIDDK supports a multidimensional research portfolio on obesity, spanning basic, clinical, and translational research. This research is coordinated through NIDDK's Office of Obesity Research and supported by NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases and Division of Digestive Diseases and Nutrition. 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.

Nearly 42 percent of U.S. adults and nearly 20 percent of children and adolescents have obesity.

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 NIH.

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.

¹ Stierman B, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files—Development of files and prevalence estimates for selected health outcomes. Centers for Disease Control and Prevention. National Health Statistics Reports 158, 2021.

² Although higher BMI levels generally reflect higher levels of body fat on a population level, BMI does not directly measure body fat or take into consideration age, biological sex, or health risks of populations other than non-Hispanic White.

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).

TIMING MEALS TO IMPROVE HEALTH

How Meal Timing May Reduce Obesity and Improve Metabolic Health: Scientists have revealed a mechanism behind why eating late at night can be linked to weight gain and metabolic disease in a study in mice. The connection between meal timing, sleep, and obesity is well known, but poorly understood. Research shows that eating during inactive periods (at night for people and during the day for nocturnal mice) can disrupt the body's internal molecular "clock," leading to an impairment of numerous physiological processes across the day/night cycle, including energy (calorie) intake and energy expenditure. This mistimed feeding can also alter fat tissue and contribute to weight gain. Understanding how meal timing affects metabolism could help the development of interventions for obesity.

To explore the reasons behind mistimed feeding and weight gain, researchers fed male mice a high-fat diet either exclusively during their inactive or their active period. Within 1 week, mice fed during their inactive period gained more weight and experienced decreased energy expenditure compared to those fed only in the active period, replicating what has been previously shown. This result led the team to investigate whether fat tissue metabolism differed based on the meal timing. Using mice that were genetically altered to have enhanced thermogenesis—or heat released by fat cells burning calories—they found that the mice fed during the inactive period did not gain weight and had improved glucose (sugar) tolerance, a measure of metabolic health, compared to mice without enhanced thermogenesis fed the same food during the same time of day, suggesting that thermogenesis protects against weight gain resulting from inactive period meals. Next, they sought to determine the specific metabolic underpinnings of this protection and identified the molecule creatine, which the body stores to use as energy, as the likely metabolic mechanism through which restricting feeding to the active period improves health. Indeed, genetic disruption of creatine synthesis in fat cells reduced the metabolic benefits of feeding restricted to the active period.

Scientists have revealed a mechanism behind why eating at night can be linked to weight gain and metabolic disease.

Taken together, these results expand upon our knowledge of the mechanisms that underlie the benefits of restricting eating to active periods. Time-restricted feeding in people is a promising approach to decrease body weight and improve metabolic health with few side effects. However, given that many people are unable to maintain this schedule for reasons including shift work, sleep loss, and the social aspect that people tend to dine in the evening, more research could help inform the design of behavioral and therapeutic interventions.

Hepler C, Weidemann BJ, Waldeck NJ,...Bass J. Time-restricted feeding mitigates obesity through adipocyte thermogenesis. Science 378: 276-284, 2022.

Limiting Eating Times to Improve Health of People Who Work Around the Clock: In a study to improve the health of people who do shift work, researchers found that time-restricted eating was feasible for firefighters on 24-hour schedules and led to cardiometabolic benefits, particularly for those who had health risks when the study began. Shift work disrupts cycles of sleeping, eating, and activity, and it is associated with cardiovascular and metabolic disease. Thus, the researchers developed an intervention to reduce these health risks while being compatible with shift-work schedules and the nature of firefighting work, and they tested this in a clinical trial.

Researchers found that time-restricted eating was feasible for firefighters on 24-hour shift work and led to health benefits for those with cardiometabolic risks.

The intervention focused on time-restricted eating (TRE), limiting calorie intake to a 10-hour window per day most days of the week for 12 weeks. As an innovative strategy to inform recruitment and other aspects of the study design, the researchers consulted with fire departments and related organizations and did a 24-hour ride-along to understand the participants' shift-work lifestyle. The study participants, 137 firefighters working 24-hour shifts, were recruited from a local fire-rescue department. Over 90 percent were male, reflecting the fire department's demographics, and were from different racial groups and ethnicities; a majority were White though race was unknown for some participants. The researchers randomly assigned the participants to either the TRE group or a standard of care group. They advised both groups to follow a Mediterranean diet (e.g.,

eating more fruits and vegetables, olive oil, and fish); collected thousands of time-stamped food and beverage records, which the firefighters logged using an app on their smartphones; and examined health measures. The results showed that TRE was feasible, as the firefighters in the TRE group reduced their eating time from around 14 hours per day when the study began to about 11 hours per day. Among the subset of participants who had elevated risk factors before the intervention began, those in the TRE group had improved blood glucose (sugar) and diastolic blood pressure by the end of the study, compared to the standard of care group. Among all the participants, those in the TRE group had improvements in a blood lipid, VLDL, and better quality of life measures compared to the standard of care group. Some health improvements were seen in both groups (e.g., systolic blood pressure), possibly associated with dietary changes. No adverse events were reported.

These encouraging results show health benefits of time-restricted eating for people doing shift work and open the way to potential future studies with larger numbers of participants, including more women, and that explore longer-term health effects.

Manoogian ENC, Zadorian A, Lo HC,...Panda S. Feasibility of time-restricted eating and impacts on cardiometabolic health in 24-h shift workers: the Healthy Heroes randomized control trial. Cell Metab 34: 1442-1456.e7, 2022.

EXAMINING THE EFFECTS OF WEIGHT-LOSS SURGERIES

Weight-Loss Surgery That Reprograms the Body's Internal Clock to Improve Metabolism and Eating Behavior: Scientists studying gastric bypass surgery, a treatment for severe obesity that also ameliorates type 2 diabetes, discovered that, in mice, this surgery reprograms the biological day/night "clock" to adjust the timing and amount of food consumption and improve glucose (sugar) metabolism. In designing the study, they sought to explore a potential connection between weight-loss surgery and the body's innate molecular clock based on previous research. Past studies showed that this clock synchronizes metabolism, eating, and other processes with 24-hour day/night cycles, and that risks for obesity and type 2 diabetes increase when day/night cycles are disrupted, for example, when people do shift work.

For their study, the researchers compared mice that had Roux-en-Y gastric bypass (RYGB) surgery to those of

similar body weight that did not have the surgery, with both groups on a high-fat diet. While a high-fat diet typically alters the amount and timing of food intake in mice, those that had RYGB surgery ate less overall and shifted more of their food consumption to the time in the day/night cycle when mice normally eat. The researchers then analyzed different tissues for potential effects on genes encoding clock functions, which exist throughout the body, and found that RYGB surgery led to changes in the activity of clock genes in the liver, an organ with important roles in glucose metabolism. To further test the relevance of the clock to surgical outcomes, they examined mice that lacked a key clock gene. They discovered that, compared to other mice, the clock-deficient mice lost less weight after RYGB surgery and did not have improvements in glucose metabolism. Thus, a functional clock was needed for these beneficial effects.

This study in mice demonstrates the role of the body's molecular clock in weight loss, eating times, and glucose metabolism after RYGB surgery for obesity. If the molecular clock has a similar role in RYGB surgical outcomes in humans, researchers could study whether adjusting meal and snack times may yield more health benefits. Further research on the effects of different bariatric (weight loss) surgical procedures could also lead to new, less invasive treatment approaches.

Ye Y, Abu El Hajja M, Obeid R,...Mokadem M. Gastric bypass alters diurnal feeding behavior and reprograms the hepatic clock to regulate endogenous glucose flux. JCI Insight 8: e166618, 2023.

Substance Produced by Gut Following Bariatric Surgery Regulates Metabolic Health in Mice: New research in mice has identified a key player produced by the gut that links surgical and dietary weight-loss therapies to improvements in metabolic and digestive health. Interventions such as bariatric surgery or a high-fiber diet can protect against the development of metabolic diseases like type 2 diabetes. Some health benefits from bariatric surgery can even occur independently from weight loss, although exactly how this happens is not clear. Further research on mechanisms underlying these effects may one day lead to new ways to treat metabolic diseases.

A substance produced by the gut called Reg3g is important for conferring improvements in metabolic and digestive health following bariatric surgery.

Reg3g is an antimicrobial peptide (a mini version of a protein) produced in the small intestine to help prevent resident bacteria from invading the intestinal wall. Because previous studies have shown that Reg3g confers health benefits in addition to its antibacterial properties, the researchers sought to examine whether Reg3g can also contribute to the health effects of bariatric surgery or a high-fiber diet and offer protection against metabolic diseases like type 2 diabetes. The researchers found that levels of Reg3g ramp up in mice after a type of bariatric surgery called vertical sleeve gastrectomy (VSG). To determine if Reg3g was responsible for the beneficial metabolic effects of VSG, the researchers performed VSG on male mice that were genetically altered to lack Reg3g. When compared to normal mice, the mice lacking Reg3g slowly regained weight and did not show improvements in blood glucose (sugar) levels and insulin production, implicating Reg3g in weight loss maintenance and better metabolic health after bariatric surgery. The researchers also saw improved metabolic health when they administered Reg3g to mice who did not undergo surgery, pointing to a possible role for Reg3g in protection against

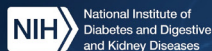
type 2 diabetes. When the researchers looked at the microbiome (the community of microbes in the gut) following VSG or a high-fiber diet, they found that these interventions changed the composition of the microbiome by boosting levels of certain beneficial bacteria, which in turn stimulated Reg3g production. Furthermore, Reg3g was found to play an important role in improving gut function, such as strengthening the gut barrier and reducing cellular stress in the small intestine.

These results suggest that changes to the microbiome due to bariatric surgery or a high-fiber diet stimulate production of Reg3g, which in turn mediates a variety of health benefits. Interestingly, the researchers also found that Reg3g is elevated following VSG in young people with obesity. If Reg3g causes similar metabolic effects in humans as in mice, it could mean that Reg3g-based treatments might have therapeutic value for people with metabolic diseases like type 2 diabetes.

Shin JH, Bozadjieva-Kramer N, Shao Y,...Seeley RJ. The gut peptide Reg3g links the small intestine microbiome to the regulation of energy balance, glucose levels, and gut function. Cell Metab 34: 1765-1778, 2022.

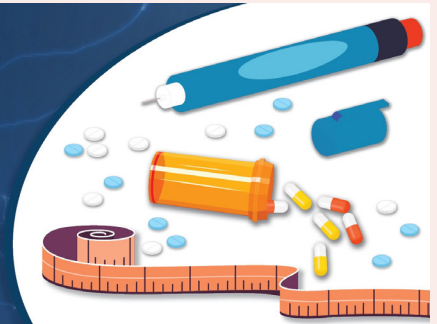
NIH Obesity Research Task Force Symposium

Medications to Treat Obesity: Past, Present, and Future



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Medications to Treat Obesity: Past, Present, and Future

The epidemic of obesity continues to rise in the United States in adults and children. Obesity increases risk for diseases and conditions such as type 2 diabetes, cardiovascular disease, and some types of cancer and cancer-related death, and it also complicates the management of a myriad of diseases. While enormous progress has been made in the pharmacological management of diseases and conditions closely integrated with excess body weight, such as hypertension and type 2 diabetes, the treatment of obesity itself has proven largely resistant to therapy, with anti-obesity medications of the past often delivering insufficient efficacy and safety concerns that limited use and resulted in the removal of drugs from the market. While lifestyle and behavioral interventions help many people lose weight, some people cannot lose enough weight to improve health with lifestyle treatments alone, and even among those who do, weight loss is often difficult to maintain. Recent advances are now inspiring the pursuit of next-generation anti-obesity medications that appear capable of safely achieving significant and sustained body weight loss. With increasing knowledge, there is real potential to vastly expand therapeutic options for obesity treatment, allowing for more personalized and effective approaches to care. To that end, seven leading scientists highlighted their research at a September 2023 symposium organized as part of the NIH Obesity Research Task Force Seminar Series.

The research presented was supported by NIDDK, other NIH Institutes, and other sources.

Dr. Matthias Tschöp of the German research center Helmholtz Zentrum München presented an overview of obesity drug development ranging from diet pills of the past up to the current transformative era of obesity pharmacotherapies capable of safely inducing substantial amounts of weight loss. One class of medications that is particularly promising for the management of obesity is incretin-based therapies. Incretins are hormones secreted by the gut in response to food ingestion, which then regulate blood glucose (sugar) and delay stomach emptying, but also have effects on multiple other organs, including the brain. Medications that mimic these hormones have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes for more than a decade, but due to their significant effects on body weight, some have also been approved for obesity treatment. Some of the new medications lead to weight losses approaching those seen with bariatric surgery, and recent preliminary data suggest they may also reduce the risk of cardiovascular disease and death for some people with obesity. Additional medications are in the research and development pipeline, including hormones targeting multiple receptors and combination therapies, with a goal of increasing efficacy while minimizing adverse effects.

FEATURE

Dr. Randy Seeley of the University of Michigan presented his research on the mechanisms by which incretin-based drugs work in the brain to treat obesity. He described the concept of a “set point,” a term that describes a weight range the body strives to maintain, and one which is elevated in a setting of obesity. The set point is regulated by key hormones that act in the brain and by genetics, as well as by calorie intake and expenditure, and it provides a potential explanation for why it can be difficult for people on a diet to maintain weight loss over time as the body is driven back toward a predetermined set point. Through a series of experiments in rodents, Dr. Seeley showed that overfeeding or calorie restriction will expectedly cause weight gain or loss, respectively. However, when the animals returned to eating normally, they very quickly returned to their set point. He went on to show that when rodents were administered obesity medications that target the brain, their set points appeared to become lower, leading to substantial weight loss that was maintained while receiving the drug.

Dr. Domenica Rubino of the Washington Center for Weight Management and Research presented her research on the incretin-based drug semaglutide for obesity treatment in adults through the Semaglutide Treatment Effect in People with obesity (STEP) clinical trials. The STEP program evaluates the safety and efficacy of semaglutide in a diverse population of adults with obesity and with or without type 2 diabetes. Semaglutide resulted in significant and sustained weight loss of 15 to 20 percent of body weight. In addition, the treatment improved cardiac risk factors such as blood pressure, reduced blood glucose levels, and decreased incidence of fatty liver. Participants reported improvements in health-related quality of life and a better sense of control over cravings, along with well-tolerated, primarily gastrointestinal side effects such as nausea, which can be affected by adjusting the dose. Evidence thus far supports the efficacious and safe use of semaglutide for weight management in adults with obesity.

Dr. Ania Jastreboff of Yale University School of Medicine presented her research on the incretin-based drug tirzepatide for obesity treatment in

adults, and she also provided a glimpse at new medications in the drug development pipeline. In a randomized, controlled clinical trial that enrolled more than 2,500 participants, nearly all participants lost weight while taking tirzepatide, while close to half of those lost more than 25 percent of their body weight. Participants on tirzepatide had a greater percent reduction in fat body mass than lean body mass, resulting in an overall improvement in body composition. Furthermore, of the participants who had prediabetes, nearly all reverted to normal blood glucose levels while taking tirzepatide, and cardiometabolic measures such as blood pressure improved. Participants taking the medication reported mild to moderate gastrointestinal adverse effects, and thus there is a need to titrate the dose for each patient. The efficacy, tolerability, and safety profiles of tirzepatide appear consistent with those of similar anti-obesity medications. Dr. Jastreboff previewed several new incretin-based and small molecule drugs currently in phase 2 and 3 clinical trials in the drug development pipeline.

Dr. Jack Yanovski of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at NIH highlighted his research on medications for the treatment of obesity in children and adolescents and gave an overview of the field. There are currently five FDA-approved drugs to treat obesity in children aged 12 to 16 years and one medication approved for children under age 12 years. Several approved medications to treat obesity in youth have limited efficacy and are associated with adverse side effects that could impede adherence. However, the same incretin-based drugs that work well in adults appear effective for weight reduction in adolescents when combined with lifestyle modification. Dr. Yanovski noted that highly effective approaches currently being studied in adults with obesity represent a treatment gap for children, especially for those under the age of 12 years. More research is necessary to gain a greater understanding of the biology of why obesity medications do not work for some youths, and a prime focus of research should also be to develop effective prevention strategies.

FEATURE

Dr. Louis Aronne of Weill Cornell Medicine presented his work on using medications to treat obesity in clinical practice. He described key principles to prescribing medication to treat obesity such as considering the patient's severity of disease, any comorbidities that may require medications that cause weight gain, potential adverse side effects and how to manage them, and affordability of the treatment. Dr. Aronne stressed the importance of an individualized, multipronged, stepwise approach. For example, the clinician should start a patient on a low dose of medication and slowly increase to assess tolerability and efficacy; if one medication is not effective, switch to another; and combination therapies can be evaluated to improve results. Dr. Aronne also highlighted case studies from his clinic that illustrate effective use of anti-obesity medications.

Dr. Ilhuoma Eneli of Children's Hospital Colorado presented research on access to obesity treatment and health equity. She described how disparities and inequity contribute to obesity through historical, social, economic, and policy contexts that have systematic effects on weight-related outcomes. Health care-related factors that drive disparities include the often high cost of treatment; location of treatment centers, with many in large, urban areas, limiting access to rural

populations; access to insurance; inadequate provider training; suboptimal diagnostic criteria that may not reflect health risks across different populations (e.g., Asian American populations); and bias/stigma. A related factor is insufficient diversity in clinical trials. Dr. Eneli discussed potential solutions to address structural and systemic factors that lead to inequity in obesity treatment, such as policy change to ensure affordable and accessible options for all. Solutions remain complex and nuanced, and they must occur at the individual, community, and structural levels and in health care environments to effectively address inequities as they pertain to obesity prevention and treatment strategies.

The seminar concluded with a panel discussion featuring two women with experience using obesity medications who shared their personal perspectives. Following their poignant testimonies, they were joined on the panel by the scientific speakers for a lively discussion with participants, moderated by Dr. Susan Yanovski, NIDDK, on current challenges and opportunities in this evolving landscape of transformative obesity medicine. Continued research could reveal better strategies to prevent and treat obesity with personalized approaches to improve health care for all.