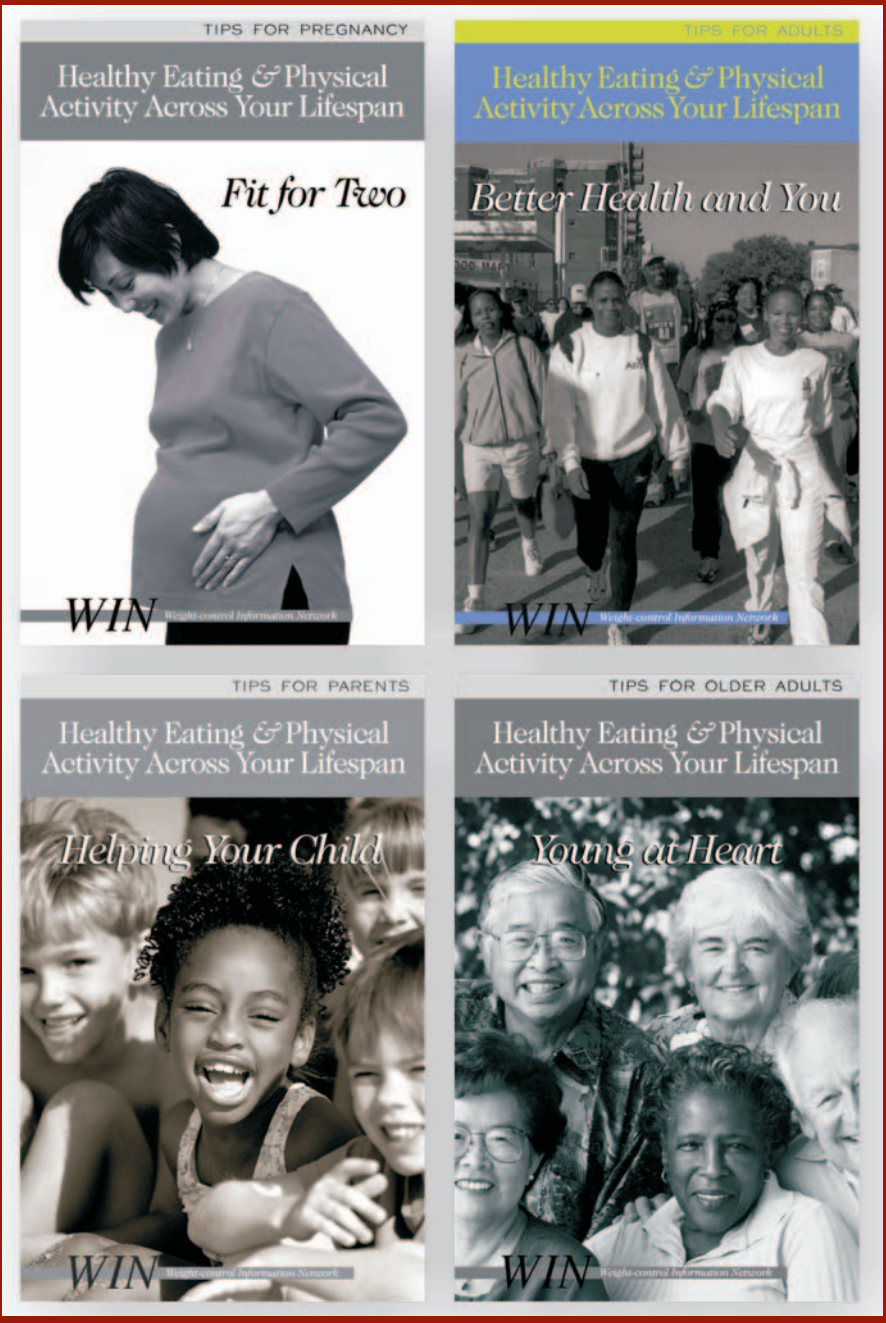


The NIDDK's Weight-control Information Network (WIN) provides the general public and health professionals with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues. WIN's series of publications, entitled "Healthy Eating and Physical Activity Across Your Lifespan," is available in English and Spanish and addresses people of all ages.

Obesity

Obesity has risen to epidemic levels in the U.S. Obese individuals suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. A strong risk factor for type 2 diabetes, obesity is also associated with other health conditions within the NIDDK's mission, including, for example, urinary incontinence, gallbladder disease, and the fatty liver disease nonalcoholic steatohepatitis.

Nearly 31 percent of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height. Furthermore, while obesity and overweight have risen in the population in general, the greatest increases observed over approximately the past two decades have been in the prevalence of extreme obesity; those who are severely obese are most at risk for serious health problems. Levels of childhood overweight have also escalated in the past several decades; approximately 16 percent of children and teens ages 6 through 19 are now overweight. (This document uses the terms overweight and obesity interchangeably for children and adolescents because there is no generally accepted definition for obesity, as distinct from overweight, in this age group.) The levels of pediatric overweight have ominous implications for the development of serious diseases both during youth and later in adulthood. Overweight and obesity also disproportionately affect racial and ethnic minority populations, and those of lower socioeconomic status.

The increased prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behavior and factors in the environment that promote increased caloric intake and sedentary lifestyles. Thus, the NIDDK has been supporting a multidimensional research portfolio on obesity ranging from basic studies to large clinical trials. This research includes, for example, investigations to elucidate the hormones and signaling pathways that influence appetite and energy expenditure; exploration of genetic factors that predispose individuals to obesity; studies of nutrition, including diet composition; research encompassing physical activity; and studies aimed toward obesity prevention through the development and testing of modifications of environmental factors in schools, the home, and other settings. The NIDDK additionally supports research on eating disorders that are associated with obesity in some people.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. To help bring the results of research to the public and health care providers, the NIDDK also sponsors education and information programs. Given the importance of the obesity epidemic as a public health problem, and its relevance to the mission of the NIDDK, the Institute has played a leading role in the NIH Obesity Research Task Force. Established by the NIH Director and co-chaired by the Directors of the NIDDK and the National Heart, Lung, and Blood Institute, the Task Force also includes representatives from numerous other NIH Institutes, Centers, and Offices. A major effort of the Task Force has been the development, with extensive input from external scientists and the public, of the *Strategic Plan for NIH Obesity Research*, published in August 2004 (*http://obesityresearch.nih.gov/About/strategic-plan.htm*).

ROLE OF GENETICS IN OBESITY

Identification of Genetic Mutations Associated with Obesity and Risk for Type 2 Diabetes in Children and Adults: The complexity of the genetics of obesity and type 2 diabetes poses significant challenges to the identification of genes associated with these conditions, as variations in many genes likely contribute to susceptibility. Recently, a group of researchers used a genetic approach to identify a specific region of a human chromosome as the likely location of a gene associated with childhood obesity (chromosomes are the large genetic structures that contain genes). The researchers subsequently pinpointed mutations in a gene within this region as associated with both obesity and type 2 diabetes in children and adults. This gene, called *ENPP1*, was

previously known to encode a protein that disrupts signaling by the hormone insulin; it does this by inhibiting actions of a critical cellular partner for insulin, the insulin receptor. Importantly, reduced responsiveness to insulin signaling (insulin resistance) can lead to type 2 diabetes. Further experimental analysis indicated that *ENPP1* protein levels are higher in children with obesity-associated mutations in the *ENPP1* gene. The scientists also found that one form of the *ENPP1* gene is "turned on" specifically in cells with particular relevance to obesity and diabetes: fat cells, pancreatic beta cells (which produce insulin), and liver cells. This study suggests a genetic mechanism for the link between childhood obesity and the high risk of type 2 diabetes in adolescence and early adulthood, and may help in the search for additional predisposing genes. Furthermore, these findings present new opportunities for strategies to prevent and treat obesity and diabetes.

Meyre D, Bouatia-Naji N, Tounian A, Samson C, Lecoeur C, Vatin V, Ghoussaini M, Wachter C, Hercberg S, Charpentier G, Patsch W, Pattou F, Charles MA, Tounian P, Clement K, Jouret B, Weill J, Maddux BA, Goldfine ID, Walley A, Boutin P, Dina C, and Froguel P: Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. Nat Genet *37: 863-867, 2005.*

LINKS BETWEEN OBESITY AND RISK OF TYPE 2 DIABETES

Obesity and Insulin Resistance Linked by a Circulating Protein: Researchers have identified a circulating protein that seems to contribute to insulin resistance in obese people and those with type 2 diabetes. Retinol binding protein 4, RBP4, is a protein secreted by fat cells, and its suppression may have therapeutic benefits. The researchers found that engineering mice to lack RBP4 showed improved insulin sensitivity, whereas inducing high levels of RBP4 protein expression, or administering purified RBP4 protein, resulted in insulin resistance. The putative negative effects of elevated RBP4 protein levels in mice have been reinforced by the observation that RBP4 is also elevated in humans with obesity and type 2 diabetes. Thus, RBP4 is a factor that may play a causative role in the development of insulin resistance and type 2 diabetes, and it may be a valuable clinical target for new drug therapies. Laboratory studies have already shown that a drug that promotes excretion of RBP4 in urine can improve insulin sensitivity in obese mice. With further investigations, it may be possible to translate these promising results of basic research into clinically-oriented studies that may benefit obese, insulin-resistant individuals who are prone to or affected by type 2 diabetes.

Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, and Kahn BB: Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature *436: 356-362, 2005.*

FIDGETING AND BODY WEIGHT

Possible Role for Non-Exercise Activity in Preventing Obesity: Scientists are gaining insights into factors that influence weight gain—a problem that is on the rise in America. Today approximately 64 percent of U.S. adults age 20 and over are overweight or obese, with nearly 31 percent meeting criteria for obesity. Weight gain occurs whenever a person's energy intake exceeds his or her energy expenditure; however, it is challenging to tease out what distinguishes people who gain weight from those who do not. It is surprisingly difficult to precisely track every calorie a person consumes and every calorie he or she expends. Recent work has taken a major step in addressing the latter problem with a novel approach to assessing activity level. Researchers recruited 20 volunteers, 10 of whom were lean and 10 of whom were mildly obese, but all of whom were self-described "couch potatoes." For two weeks, the volunteers, who were wearing sensors that monitored their activity, followed their usual day-to-day activities and did not adopt any new exercise routines. During this time, the scientists collected data twice per second to determine whether the volunteers were sitting, standing, or lying down. They found that the lean subjects stood and/or moved, on average, two hours longer per day than those in the obese group. This type of energy expenditure is called "non-exercise activity thermogenesis," or NEAT. Thus, an important factor in maintaining leanness appears to be the expenditure of energy through movements that are not a component of intentional exercise.

Levine J, Lanningham-Foster L, McCrady S, Krizan A, Olson L, Kane P, Jensen M, Clark M: Interindividual variation in posture allocation: possible role in human obesity. Science *307: 584-586, 2005.*

Lifestyle Modification Plus Medication Proves More Effective than Medication Alone for Weight Loss in Obese Adults

People who are obese are at risk for serious health problems, such as type 2 diabetes and cardiovascular disease, yet losing weight and maintaining weight loss are difficult to achieve. A new study shows that treatment with a lifestyle modification program of diet, exercise and behavioral therapy, when used in combination with the weight-loss medication sibutramine, resulted in significantly greater weight loss among obese adults than treatment with the medication alone.

A total of 224 obese adults participated in the one-year study. Participants were randomly assigned to one of four groups: 1) weight-loss medication alone; 2) lifestyle modification alone; 3) weight-loss medication plus lifestyle modification; and 4) weight-loss medication plus brief physician-mediated therapy. All groups were prescribed a 1,200 to 1,500 calorie diet and the same exercise plan. Participants in the group receiving weight-loss medication therapy alone met with primary care physicians eight times for 10 to 15 minute visits, but were not instructed to keep food or activity records and were provided only general information on diet and exercise. Participants assigned to the lifestyle modification therapy attended a total of 30 group meetings, each lasting 90 minutes. During the meetings participants were instructed to complete and share weekly assignments, which included keeping detailed daily food and physical activity records. Those participants in the combined therapy group received both the lifestyle modification therapy and the weight-loss medication. Participants in the medication plus brief physician-mediated therapy group met with primary care physicians eight times for 10 to 15 minute visits during which they were also given homework assignments which included keeping daily food and activity records.

After one year, patients in the weight-loss medication plus lifestyle modification (combined therapy) group, lost an average of more than 26 pounds—more than double the weight loss seen with medication alone (11 pounds). Interestingly, those participants in the combined therapy group who were most successful were those who frequently recorded their food intake. Those participants with high adherence to food-intake record keeping lost more than twice as much weight as those with low adherence (41.5 *versus* 17 pounds).

One limitation of the study is that it only included obese patients who were otherwise healthy and excluded obese patients with health problems possibly related to their obesity, such as hypertension, cardiovascular disease, cerebrovascular disease, kidney disease, liver disease, and diabetes. Because many obese patients also have other conditions that can adversely affect their health, physicians should carefully monitor patients enrolled in weight-loss programs that include weight-loss medications.

The findings of the study are consistent with the NIH's *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. These guidelines, developed by the National Heart, Lung, and Blood Institute in collaboration with the NIDDK, recommend that weight-loss medications be used in a supportive role to a comprehensive program of behavioral treatment, diet therapy, and increased physical activity. The guidelines also recommend that physicians prescribe a regimen of lifestyle therapy for at least six months before adding weight-loss medication to the regimen. That is, lifestyle modification should be the first line of treatment for obesity, but for obese adults who cannot lose enough weight to improve their health, medication used as an adjunct can help. A recent editorial in the *New England Journal of Medicine* underscores not only the need for improved medical approaches to treating obesity but also the potential dangers and limitations of weight-loss drugs. Weight-loss medication will be most effective when combined with a reduced-calorie diet and increased physical activity.

Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, Hesson LA, Osei SY, Kaplan R, and Stunkard AJ: Randomized trial of lifestyle modification and pharmacotherapy for obesity. N Engl J Med 353: 2111-20, 2005.

Yanovski SZ: Pharmacotherapy for obesity—promise and uncertainty. N Engl J Med 353: 2187-2189, 2005.

NIDDK's Weight-control Information Network (WIN)

The NIDDK's Weight-control Information Network (WIN) provides the general public and health professionals with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues. This information includes fact sheets and brochures for the public, as well as WIN Notes, a periodic newsletter for health professionals and consumers. Through its information services, WIN reaches out to people of all ages, and to diverse ethnic and racial groups.

In addition to developing science-based fact sheets and brochures, WIN conducts a variety of ongoing outreach activities to primary care providers, registered dietitians, fitness professionals, health educators, community organizers and others. Recent promotional efforts include a focus on the benefits of regular physical activity, tips to help overweight children, weight loss and nutrition myths, and portion control.

To promote the availability of its brochure series, "Cómo Alimentarse y Mantenerse Activo Durante Toda La Vida" ("Healthy Eating and Physical Activity Across Your Life Span"), WIN recently conducted an outreach effort in U.S. cities with a high proportion of low-income Latino residents. The cities were Los Angeles, New York, Miami, and Washington, D.C. The "Toda La Vida" series of booklets, available in English and Spanish, provide Spanish-speaking adults, older adults, parents, and pregnant women with tips on how to build regular physical activity and healthful eating into these four stages of life and beyond.

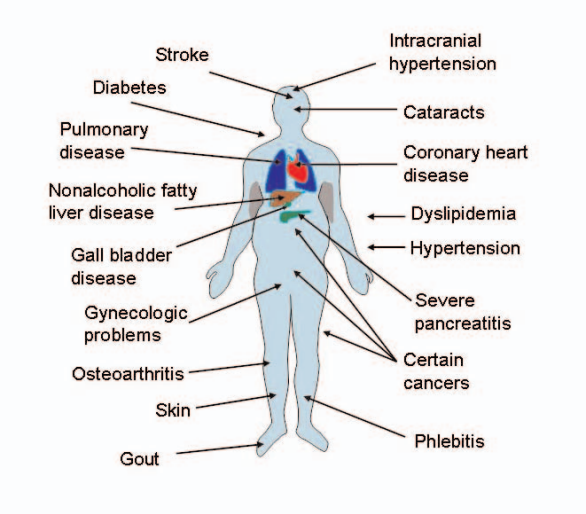
WIN's "Sisters Together: Move More, Eat Better," is a national initiative that encourages African American women to maintain a healthy weight by becoming more physically active and eating more healthful foods. Among its publications are: "Celebrate the Beauty of Youth!," "Fit and Fabulous as You Mature," "Energize Yourself and Your Family," and "Walking...A Step in the Right Direction." WIN conducts ongoing outreach efforts to historically Black colleges and universities and various community venues to promote the availability of "Sisters Together" brochures.

Fat Metabolism and Obesity

Dr. Samuel Klein

Dr. Samuel Klein received his M.D. from Temple University in 1979, and an M.S. in Nutritional Biochemistry and Metabolism from MIT in 1984. He completed residency and a clinical nutrition fellowship at University Hospital in Boston, as well as fellowships at Harvard Medical School in Boston and Mt. Sinai Hospital in New York. He is currently the William H. Davenport Professor of Medicine and Nutritional Science at the Washington University School of Medicine in St. Louis, where he also serves as Director of the Washington University Clinical Nutrition Research Unit, Director of the Weight Management Center, and Associate Program Director of the General Clinical Research Center. He discussed the work from his laboratory at the February 2005 meeting of the NIDDK's Advisory Council. Some highlights of his talk are presented here in this "Scientific Presentation."

The ability of the human body to store excess energy as body fat has proved invaluable during human history for overcoming periods of famine. However, in the U.S. today, food is relatively plentiful, high-calorie food is comparatively inexpensive, and technologic advances have led many individuals into sedentary lifestyles. These and other factors have contributed to an upsurge in rates of overweight and obesity. Because excess body fat is associated with numerous serious diseases—including type 2 diabetes, heart disease, nonalcoholic fatty liver disease and many others—the health consequences of this trend toward increasing weight are severe. Through studies of fat metabolism, the Klein lab seeks to understand the metabolic effects of different weight-loss treatment approaches and the link between excess fat and the metabolic abnormalities seen in diseases associated with overweight and obesity.



Obesity is frequently associated with serious medical complications, as illustrated in this figure. Among these complications are higher than normal levels of unhealthy blood fats, and/or lower than normal levels of healthy blood fats ("dyslipidemia"); inflammation of blood veins ("phlebitis"); and joint pain caused by the accumulation of uric acid deposits ("gout"). Cancers more common in people with obesity include those of the breast, uterus, cervix, esophagus, pancreas, liver, kidney and prostate. Gynecological conditions sometimes associated with obesity include abnormal menstruation, infertility and polycystic ovarian syndrome; pulmonary (lung) problems include abnormal function and obstructed breathing during sleep (apnea).

Image courtesy of Dr. Samuel Klein.

Insights into the Regulation of Fat Metabolism

The body stores fat in molecules called triglycerides. When fat is burned for fuel, each triglyceride is broken into its component parts: three free fatty acid (FFA) molecules and one molecule of glycerol. The Klein lab studies fat metabolism by directly measuring the appearance

and disappearance of the FFA and glycerol in the body when fat is utilized for energy. The presence of excess FFA is known to stimulate the liver to release glucose and to contribute to type 2 diabetes by inhibiting the action of insulin. Excess FFA also stimulates the production of very low density lipoprotein (VLDL, which is the primary carrier of plasma triglycerides), and decreases high density lipoprotein-cholesterol (HDL-cholesterol, also known as "good cholesterol"). Both of these effects increase the risk of heart disease.

Dr. Klein and his colleagues measured fat metabolism (breakdown of fat into glycerol and FFA) in lean women and in obese women, and found that the latter have lower rates of FFA and glycerol release than their lean counterparts, when measured per gram of fat. However, because the obese women had so much more fat than the lean women, they had a much higher total amount of FFA and glycerol release. Thus, because excessive FFA is so unhealthy, the obese body may partially compensate by reducing the rate of fat metabolism—but cannot reduce it sufficiently to keep FFA at a healthy level.

No Effect of Liposuction on Fat Metabolism

Losing even a modest amount of weight, however, can improve an overweight person's metabolic profile very quickly. Indeed, there is a dramatic drop in the release rate of FFA associated with weight loss. There are also major improvements in blood glucose and insulin action. However, numerous studies have demonstrated that it is very difficult for people who lose weight to keep that weight off. So the Klein team investigated whether they could achieve the metabolic benefit of weight loss by simply removing fat from obese people using the cosmetic surgery known as liposuction.

They found that liposuction had no effect on metabolic risk factors, even when very large quantities of fat were removed. One possible explanation for this comes from the fact that liposuction only removes subcutaneous fat (fat in the layer just beneath the skin). It may be that the fat depots in and around organs such as liver or in muscle have adverse effects and cause insulin resistance, and other risk factors for heart disease seen in clinical obesity. Another possibility is that—when weight loss occurs because calories expended exceed calories consumed (as in successful diet and exercise programs)—fat cells shrink in size. In liposuction fat cells are removed, but the remaining cells do not become smaller. It is possible that the size of fat cells is a significant factor in regulating fat metabolism. This question will require further investigation.

Effects of Diet and Exercise on Fat Metabolism

Dr. Klein reviewed the work by his group and others that compares low-fat diets with low-carbohydrate diets, or with calorie-restricted diets. He noted that there was a remarkably consistent finding across investigators that little difference occurred in overall weight loss after a year or more on these diets, even though people on low-carbohydrate diets tend to lose more weight in the short term. However, he pointed out that the low-carbohydrate dieters do fare better with respect to several markers of cardiovascular disease, particularly their levels of triglycerides and HDL-cholesterol, which improve more in low-carbohydrate dieters than in low-fat dieters. More research will be necessary to establish the reasons for this difference, and whether it actually translates to improved health outcomes.

Of course, an exercise program is also considered to be a critical part of most weight-loss efforts. Dr. Klein noted that, in principle, it is simpler to avoid consumption of a high calorie item (or to substitute a "diet" version) than to burn the equivalent number of calories via exercise. Nonetheless, exercise is associated with successful maintenance of weight loss. Importantly, it is not clear whether successful weight loss is the result of dieting, or whether individuals who can maintain an exercise program are also particularly likely to adhere consistently to their diets.

Dr. Klein noted that exercise can be a powerful stimulus for the burning of fat as fuel. Examining the

body's ability to use fat for fuel during endurance exercise, the Klein lab noted that study volunteers used more fat during a particular session of exercise after 16 weeks of training than before training began. This means that the body is adapting in some fashion to the exercise program. The investigators discovered that the change occurred because muscle tissue becomes better adapted for consuming fat calories: specific proteins used in burning fat for fuel are increased after 16 weeks of training.

Effect of Gastric Bypass Surgery on Fat Metabolism and Fatty Liver Disease

In the last portion of his presentation, Dr. Klein turned to an important complication of obesity—nonalcoholic fatty liver disease (NAFLD). NAFLD is caused by a chronic excess of fat in the liver (steatosis), an increasingly common problem that is associated with obesity. The Klein lab examined rates of fat metabolism in patients who underwent gastric bypass surgery as a treatment for obesity. Unlike liposuction, which directly removes fat, the gastric bypass procedure causes a marked decrease in caloric intake.

The Klein study focused on patients who had steatosis. The patients were found to have a significant drop in the rate of FFA release following their surgeries. The investigators also showed that liver VLDL-triglyceride secretion rate decreased because of a marked decrease in the contribution of FFA derived from intrahepatic or visceral fat breakdown to VLDL-triglyceride production.

Building up and extending these impressive findings, Dr. Klein and colleagues are next planning to analyze the molecular mechanisms governing these changes in fat metabolism, as well as the processes that lead from steatosis to nonalcoholic steatohepatitis. The Klein lab is actively studying these challenging questions, while also investigating the ominous links between obesity and other diseases. These studies, combining basic and clinical investigations, are a powerful tool for providing valuable insights into the complex metabolic regulation that affects body weight, makes maintaining weight loss so difficult, and contributes to the many diseases associated with obesity.