



## **Advances**

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**NIDDK**

NATIONAL INSTITUTE OF  
DIABETES AND DIGESTIVE  
AND KIDNEY DISEASES

## ◆ *Obesity Linked to Unique Mix of Intestinal Bacteria and Bacterial Genes*

Scientists have discovered that bacteria that dwell in the human gut are associated with their host's obesity or leanness. This work provides clues to how knowledge of the gut microbial community might be used to counter human obesity.

Bacteria that inhabit the gut—the gut microbiota—perform important functions, including breaking down food that could not otherwise be digested. Mouse studies have also suggested that bacterial diversity in the gut may influence whether animal “hosts” are lean or obese, based on differences in the efficiency of specific types of bacteria to extract energy (calories) from food.

In a recent study of obese and lean adult twin sets and their mothers, researchers studied the human microbiota using fecal samples to determine whether host obesity, genetics, or environment is associated with the bacterial composition of the microbiota. To determine which types of bacteria were present in the gut, the researchers analyzed DNA sequences in a particular gene common to all bacteria to identify sequence variations unique to each type. Comparisons revealed that the proportion of different types of bacteria in the guts of obese twins differed from that in the lean twins. Actinobacteria were more abundant than Bacteroidetes bacteria in the obese twins. Conversely, Bacteroidetes were more numerous in the lean twins. Obesity was also associated with significantly less bacterial diversity overall than leanness. Additional analysis revealed that the microbiota of family members are more similar in bacterial composition than unrelated individuals. Surprisingly, the identical twins were not more similar in their gut microbes than fraternal twins, suggesting that composition of the gut microbiota is influenced more strongly by environmental factors than by an individual's genes. An analysis of bacterial genes represented in the “microbiome”—the combined DNA of the microbiota—found that although the precise composition of the types of bacteria in the gut differs among individuals, people share a “core microbiome” of common microbial genes harbored by the various bacteria. Additionally, comparison of non-core microbiome genes identified over 350 genes that were either enriched or depleted in the microbiomes of obese individuals. Among the genes enriched in the obese gut microbiome, many of which are involved in processing carbohydrates and other metabolic pathways, most were from Actinobacteria and others were from another group of bacteria, Firmicutes.

While this study does not demonstrate cause and effect—whether differences in human microbiota help cause obesity or leanness, or whether obesity or leanness leads to changes in gut microbes—earlier research has shown that the composition of gut microbiota can influence weight gain in mice. This study does demonstrate a significant link between obesity and the gut microbiome, including the identification of several hundred genes that represent biomarkers of unique gut bacterial activity in obese individuals. These biomarkers may lead to more personalized healthcare and potential probiotic interventions to modify the microbial content of the human gut.

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## ◆ *To Understand Bone Formation: Just Follow Your Gut*

Scientists made a surprising discovery that bone formation is regulated by levels of gut-derived serotonin, and a gene called *Lrp5* controls bone formation by inhibiting serotonin production. Bone is living tissue that constantly rebuilds as old bone tissue is broken down and new bone is formed. The *Lrp5* gene had previously been found to be important in bone formation. Mice lacking *Lrp5* have low bone mass due to a decrease in bone formation. In people, mutations in this gene are associated with bone diseases, including a form of osteoporosis. However, it was unknown how *Lrp5* regulated bone formation, whether it was acting directly on the bone, and what other cellular factors were involved.

To understand how *Lrp5* regulates bone formation, scientists first sought to identify factors controlled by *Lrp5* by determining whether any genes were turned on or off differently in bones of mice lacking *Lrp5* as compared to normal mice. In mice lacking *Lrp5*, they found that the gene turned on to the greatest extent is involved in serotonin synthesis, and the activity of this gene was also increased dramatically in gut cells. The animals also had abnormally high levels of serotonin. Only about 5 percent of the body's serotonin is produced in the brain, where it modulates mood, appetite, sleep, and other processes. The other 95 percent is made in the duodenum of the gastrointestinal tract, but the function of this gut-derived serotonin has been a matter of scientific debate.

With these clues about the importance of gut-derived serotonin, the scientists performed a series of experiments in mice to examine serotonin's role in bone formation. In one experiment, they found that administration of a chemical inhibitor of serotonin synthesis normalized bone formation in mice lacking *Lrp5*. In another experiment, they discovered that genetically turning off serotonin production in the gut protected against bone loss in a mouse model of menopause (a time period when women are at greater risk for loss of bone density). Overall, the research showed that increasing serotonin levels slowed the formation of new bone, while inhibiting serotonin production promoted it. In addition, the research demonstrated that *Lrp5* was not acting directly on the bone, but rather in the gut to regulate production of serotonin, which in turn travels through the body to bone cells to inhibit bone formation. Studies in a small number of people with bone diseases associated with mutations in *Lrp5* showed that the patients have abnormal serotonin levels. These preliminary observations suggest that serotonin may also be important in controlling bone formation in people. Most drugs for osteoporosis that are approved for use in people prevent the breakdown of bone, but do not promote the generation of new bone. The discovery that gut-derived serotonin inhibits bone formation in mice and possibly in people suggests that therapies to inhibit serotonin production in the gut, or to block its action on bone, could be a novel means by which to treat or preempt osteoporosis.

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## ◆ ***Maternal High-Fat Diet During Pregnancy Triggers Liver Disease in Offspring, in an Animal Model***

A new study highlights a risk of liver disease resulting from exposure to excess fat and calories during fetal development. Childhood obesity has been correlated with the dramatic rise in incidence of type 2 diabetes and nonalcoholic fatty liver disease among youth in the United States. Previous studies have shown that high-fat diets, obesity, and diabetes during pregnancy are associated with metabolic problems in the offspring. However, the mechanisms for these findings remain relatively unknown, and it can be difficult to distinguish between the effects of obesity and the effects of a diet that could lead to obesity. Current dietary guidelines for mothers with gestational diabetes include substituting fats for carbohydrates in the diet to help lower blood glucose levels. However, the results from this study suggest the importance of considering potential adverse effects of excess dietary fat when adjusting a diet.

Scientists recently explored the effects of a high-fat diet during pregnancy on liver disease in offspring, using an animal model in which some mothers were more susceptible to obesity and diabetes than others. These studies, done in non-human primates, suggest that a chronic high-fat diet results in a significantly increased risk of fetal fatty liver disease that persists after birth. This finding held true whether or not the mothers were themselves obese or had diabetes. Pregnant animals fed a high-fat, high-calorie diet produced offspring that had a three-fold increase in triglyceride fat in the liver. Furthermore, the offspring displayed evidence of increased liver stress during gestation, consistent with the development of fatty liver disease. Elevated levels of triglycerides persisted in the offspring following birth. Additionally, as the offspring grew, those from mothers fed a high-fat diet had a two-fold increase in percent body fat compared to offspring of mothers who ate a standard diet. Importantly, after female animals were consistently fed a high-fat diet for four years, switching them to a lower calorie, low-fat diet reduced fetal liver abnormalities in their subsequent offspring, even though some of the mothers remained obese and insulin resistant. These studies suggest that a maternal high-fat diet may result in increased fat transfer to the fetus, and that unhealthy levels of fats in maternal blood (rather than diabetes or obesity) could potentially be the predominant cause of some future metabolic disorders in offspring. However, it is also possible that the health effects observed in offspring were the result of the high total calories fed to their mothers, rather than the percentage of calories from fat.

Fatty liver disease is an increasingly important cause of liver failure. Recognition of the role of the prenatal environment in the genesis of fatty liver provides a potential intervention to prevent the disorder. By shedding new light on dietary contributors to adverse health conditions, this study can direct future research efforts toward developing strategies to preempt disease.

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## ◆ *Living Kidney Donors Have Similar Long-Term Survival and Quality of Life as the General Population*

Most kidney transplants involve organs from cadaveric donors; however, the demand for these organs far exceeds their supply. Therefore, some people opt to donate one of their two healthy kidneys, often to a sibling or other relative whose kidneys have failed. A recent study of nearly 3,700 people who donated kidneys between 1963 and 2007 found that people who choose to donate a kidney appear to have a normal life span, and that their risk of developing kidney failure is similar to that of the general population. Within a subset of donors who were studied more intensively, kidney function and high blood pressure were similar to the general population, and their quality-of-life was found to be excellent. Importantly, the researchers found no evidence of excess loss of kidney function over time in donors, some of whom donated kidneys twenty or more years ago.

Although the results of this study are good news for the participants, there are some important caveats. Potential kidney donors must meet strict selection criteria before they are allowed to donate. The relatively good health of the donors may explain at least part of the reason why their health and quality-of-life was found to be at least equal to, or better than, that of the general population. Additionally, in the past many volunteers donated a kidney at a relatively young age. In more recent times, however, the average age of donors has risen, and researchers and physicians will need to carefully monitor the health of these older volunteers. Additionally, participants in the current study were overwhelmingly Caucasian, and researchers do not know to what extent these findings can be extrapolated to kidney donors of other races and ethnicities. For example, African Americans have a much higher rate of diabetes, high blood pressure, and kidney failure than Caucasians, and it is possible they might be more likely to develop those conditions after donating a kidney. Further research will be necessary to better understand the long-term implications of kidney donation across a broad spectrum of the American population.

Nevertheless, the results of the current study indicate that there are few or no long-term detrimental health consequences for individuals who choose to donate a kidney. This finding may make potential donors more likely to donate a kidney, and have the consequence of increasing the supply of organs available for transplant.

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## ***New Insights into Blood Stem Cell Development with Implications for Tissue Regeneration***

Scientists have recently identified key factors which interact to regulate stem cell development and tissue regeneration. Therapies to regenerate diseased or injured organs will benefit from an in-depth knowledge of how stem cells and progenitor cells develop into complex tissues and organs. Previous research has implicated several factors in the regulation of blood (hematopoietic) stem cell formation and self-renewal. These include prostaglandin E2 (PGE2) and a series of factors known as the WNT signaling pathway. However, the exact mechanism by which these factors exert their effects on hematopoietic stem cells remained unknown.

Beginning with the zebrafish model system, investigators showed that PGE2 directly increased WNT pathway activity within embryonic blood stem cells, leading to the formation of greater numbers of these stem cells. Exploring the underlying mechanisms, the researchers found that PGE2 helps stabilize an important component of the WNT pathway. In addition to demonstrating the importance of these factors to embryonic blood stem cell development, the scientists investigated a potential role for PEG2 and the WNT pathway in adult animals. By studying zebrafish whose blood stem cells had been destroyed by irradiation, the researchers discovered that these factors also work together to promote regeneration of new blood stem cells in adult fish. Further studies revealed that PGE2 and WNT work together to promote formation of embryonic and adult blood stem cells in mice—evidence that these pathways also interact in mammals. Beyond blood cells, the PGE2/WNT interaction was also shown to be required for liver regeneration in both fish and mice. These results illuminate PGE2 and the WNT pathway as powerful regulators of cellular regeneration in the body. Future research efforts will delineate the feasibility of delivering appropriate levels of PGE2 to damaged tissues to promote WNT-dependent cellular regeneration in a precise and controlled manner to preempt further injury and restore health.

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## ◆ **Weight Loss in Overweight and Obese Women Reduces Urinary Incontinence**

Researchers have recently reported that weight loss reduces urinary incontinence in overweight and obese women. An estimated 13 million Americans, most of them women, suffer from urinary incontinence. Women usually experience either stress and/or urge urinary incontinence. “Stress” urinary incontinence is the leakage of small amounts of urine during physical activity, such as coughing, sneezing, and exercising. “Urge” urinary incontinence is the leakage of large amounts of urine at unexpected times, including during sleep. Many women who have the disorder suffer in silence due to embarrassment. Obesity is an established and modifiable risk factor for urinary incontinence, but conclusive evidence for a beneficial effect of weight loss on urinary incontinence has been lacking.

The NIDDK’s “Program to Reduce Incontinence by Diet and Exercise (PRIDE)” study recruited 338 obese and overweight women, who leaked urine at least 10 times per week, to determine whether a weight loss program could significantly reduce the frequency of urinary incontinence. The women were randomly assigned to one of two groups--one that participated in an intensive 6-month weight loss program of diet, exercise, and behavioral modification; or another that received information about diet and exercise, but no training to help them change their lifestyle. After 6 months, the investigators reported that women in the intensive group lost an average of 8 percent of their body weight (about 17 pounds) and reduced weekly urinary incontinence episodes by nearly one-half (47 percent). In contrast, women in the information-only group lost an average of 1.6 percent of body weight (about 3 pounds) and had 28 percent fewer episodes. Among women in the intensive treatment group, 41 percent achieved a clinically important reduction of at least 70 percent of weekly total incontinence episodes, whereas 22 percent of women in the information-only group achieved the same level of reduction. PRIDE provides high level evidence that a behavioral intervention reduces urinary incontinence in overweight and obese women thereby permitting patients and their health care providers to make better informed and personalized treatment decisions to improve this disorder.

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## ***New Genetic Risk Factors Identified for Ulcerative Colitis***

An international research group, including investigators from the NIDDK's IBD Genetics Consortium, has identified new genetic risk factors associated with ulcerative colitis (UC) through a genome-wide association study of over 1,000 people with UC compared to other individuals without the disease.

UC causes inflammation in the tissue lining the colon and rectum, which may result from abnormal immune responses within the intestines. Although UC shares some features with the other major form of IBD—Crohn's disease—other characteristics are distinct. Genome-wide association studies in recent years have identified genetic factors that contribute to each of these forms of IBD. These studies have been particularly fruitful in terms of uncovering genetic regions associated with Crohn's disease. In the current study, researchers intensified their efforts to identify additional genetic factors that increase susceptibility to UC.

To expand knowledge of genetic contributors to UC, researchers performed a genome-wide association study using DNA collected from individuals with or without UC who shared a similar ancestry, in order to minimize other genetic differences. With this method, they were able to identify chromosomal regions, as well as genes within some of those regions, that are associated with an increased risk of developing UC. Two chromosomal regions were linked for the first time to UC risk. Several genes located within or near these regions play a role in immune function and inflammation, and may contribute to disease susceptibility by altering these processes. Additional genetic factors previously implicated in UC and Crohn's disease, including the immune system gene *IL-23R*, were also confirmed in this analysis. However, many genetic factors that had proven important for Crohn's disease risk were not associated with susceptibility to UC, suggesting that the two forms of IBD have overlapping but unique genetic profiles.

The identification of genetic regions associated with increased susceptibility to UC has the potential to inform understanding of disease processes unique to this form of IBD. Additionally, this knowledge can provide targets for developing new, more personalized therapeutic and preemptive approaches to controlling this disease.

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