# Culprits and cures for obesity may reside in our gut

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Obesity in the United States is reaching ever more alarming proportions, posing a severe menace to public health and exacerbating a crisis in health care costs both domestically and worldwide.

Now, Rosa Krajmalnik-Brown and fellow researchers at the Biodesign Institute at Arizona State University, in collaboration with Dr. John DiBaise and colleagues at the Mayo Clinic, Scottsdale, are looking into what may be a leading driver in body weight regulation—the diverse zoo of microorganisms inhabiting the human gut.

The team will explore the contributions of so-called gut microflora to the success or failure of two popular treatments for obesity, hopefully gaining new insight into how body weight is managed (or mismanaged) based on the demographics of these microorganisms. "We normally use microorganisms to solve environmental problems such as water clean-up and energy production," Krajmalnik-Brown says. "Now we are excited to have the opportunity to assess the contributions of our best collaborators, i.e., microorganisms, to human digestion and health."

The new study, supported by a 4 year, $1.7 million grant from the NIH, is part of a continuing collaboration between Biodesign and the Mayo Clinic. It began when John DiBaise, a gastroenterologist at Mayo, started to explore the underlying mechanisms leading to obesity and to contemplate possible alternatives to gastric bypass surgery—currently, one of the most effective treatments for morbid obesity.

DiBaise enlisted the help of Bruce Rittmann, director of Biodesign's Swette Center for Environmental Biotechnology—an expert on the use of microbial communities for human benefit, particularly in the areas of bioremediation and renewable bioenergy. Fellow researcher Krajmalnik-Brown, principle investigator for the new study, brings her detailed knowledge of microbial ecology to the table. She will apply modern high-throughput sequencing techniques to assess complex microbial communities in the guts of patients who have undergone gastric bypass surgery, comparing these with the microbial populations found in normal weight and obese subjects. Rittmann will develop a mathematical model which will integrate ecological and metabolic results gathered in the project.

The group had earlier speculated that the composition of microflora in the human gut may play a vital role in directing the way energy extracted from food is stored and expended.

Bacteria involved in fermentation, as well as methanogens belonging to the Archaea domain, seem to act syntrophically—that is, in a collaboration that accelerates efficient fermentation of polysaccharides and carbohydrates. Some of the fermentation products are absorbed via the intestinal wall and ultimately converted to fat. If left unchecked, such processes can contribute to obesity.

The crisis of obesity is acute, affecting some 4 million Americans. In the United States, the prevalence in adults has increased by over 75 percent since 1980. More than half of the U.S. population is currently overweight and 1 in 3 Americans qualify as clinically obese. Obesity-related illnesses kill about 300,000 Americans every year, many succumbing to diabetes, cardiovascular disease, cancer, and other obesity-associated maladies.

Currently, the most effective treatment for obesity is some form of bariatric surgery, in which a portion of the stomach and small intestine are bypassed, limiting the amount and type of food an individual can eat. In the case of morbid obesity, such surgeries are the only form of treatment that consistently achieve and maintain major weight loss, thereby decreasing the incidence of co-morbid afflictions and improving survival prospects and quality of life.

The two most successful variants of this surgery—known as the Roux-en-Y gastric bypass (RYGP) and laparoscopic adjustable band gastric bypass (LAGB)—will be evaluated in the current study. Having established in previous work that patients receiving these treatments display a unique composition of gut microbiota, the group will explore in depth how the dramatic microbial changes observed in post-surgery patients contribute to the success or failure of the procedure.

In order to evaluate the contribution of gut microbial communities for achieving and maintaining weight loss following gastric bypass, the new study has set 4 research goals: 1) Use high-throughput sequencing to identify fermenters that interact with a particular group of H2-consuming microorganisms; 2) Track and quantify the presence of luminal and mucosal H2-consuming microorganisms using quantitative PCR; 3) Track metabolic products and determine syntrophies and metabolic functions of the microorganisms associated with energy extraction; and 4) Integrate and interpret the results using an ecological approach through mathematical modeling.

Ultimately, new insights into the composition and dynamics of gut microbial communities, particularly the delicate syntrophy existing between fermenting Bacteria and methanogenic Archaea, will improve the accuracy of prognosis for those undergoing bariatric surgery. Further, such understanding may help identify individuals at risk of developing obesity, while opening the door to eventual, non-invasive therapies, based on management of gut microflora.

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