For decades, doctors have known that diabetics with mismanaged glucose levels are more likely to suffer from periodontal disease and non-healing wounds, but they didn’t know why or how to manage the problem. These unanswered questions motivated Dr. Dana Graves, Vice Dean for Scholarship and Research, Director of the Doctor of Science in Dentistry Program, and Professor in the Department of Periodontics at Penn Dental Medicine, to bring clarity to this field of research, which has the potential to improve quality of life for the 30 million Americans living with diabetes.

“The harm that severe periodontal disease and non-healing wounds inflict on diabetes patients is astonishing,” Dr. Graves explains. “It was alarming that the roots of these destructive conditions were going unexamined from a research perspective.”

MAKING NEW CONNECTIONS

At Penn Dental Medicine, Dr. Graves has honed in on the cellular mechanisms underlying periodontitis and wound healing in diabetics, uncovering a path to alleviating the painful consequences of the disease in patients who will not, or cannot, properly control it.

To understand the biological connection between diabetes and periodontal disease, Dr. Graves compared the oral microbiomes of diabetic mice and healthy mice. Before the diabetic mice developed hyperglycemia, or high blood sugar levels, he noticed that the bacteria composition of the two groups’ microbiomes were similar. Once the diabetic mice became hyperglycemic, however, the bacteria in their microbiome became less diverse than that of their littermates. This change resulted in increased inflammation and greater risk of developing periodontitis.

“In poorly controlled diabetes, there is greater inflammation of the gums,” says Graves. “You have a cycle where diabetes causes inflammation that changes the bacteria in the mouth, which causes more inflammation, which makes people with diabetes have a higher risk of periodontal disease.”

Next, to confirm that diabetes is indeed the factor that causes these shifts in the oral microbiome and triggers the onset of periodontal disease, Dr. Graves transferred bacteria from diabetic mice to healthy mice, resulting in the rapid bone loss and severe inflammation associated with diabetes-derived periodontitis.

Between 15 and 30 percent of dental patients have periodontitis, and diabetics with high glucose levels are three times as likely to develop the disease. Dr. Graves’ research on the bacterial changes caused by diabetes has the potential to improve treatment options for people with periodontitis, diabetes, and both.

Dr. Dana Graves advances understanding of the dangerous impact of mismanaged diabetes
LIFE-CHANGING SOLUTIONS

In addition to the pain and tooth loss associated with periodontal disease, diabetics with mismanaged glucose levels face the possibility of another very serious complication: chronic wounds. Diabetes dramatically slows the wound healing response, allowing a biofilm to form that prevents wounds from healing. The issue is so serious that it leads to amputations in adults more than any other cause.

“You think about someone who has a cut or a scrape and you assume that treatment costs 30 cents, the price of a bandage,” says Dr. Graves. “For a diabetic, it is an entirely different story. The treatment of a diabetic wound can cost anywhere from $30,000 to $60,000.”

Dr. Graves and his team identified a critical molecule that helps explain why diabetics suffer from this problem, pinpointing a target for therapies that could help boost healing. In the lab, he created small wounds on the tongues of normal mice and diabetic mice under anesthesia. As expected, the diabetic mice healed more slowly than the normal mice. He then bred Foxo1, a protein that facilitates wound healing in non-diabetic patients, out of the diabetic mice. Surprisingly, the healing process was improved significantly, demonstrating that this protein has the opposite effect in diabetic mice compared to normal mice.

“In terms of a wound-healing response, it looks like Foxo1 might be one of the central regulators that are affected by the diabetic condition,” Dr. Graves says. “By gaining a better understanding of the mechanisms behind these chronic wounds, we are moving closer to less invasive and less costly treatment options for diabetics with chronic wounds.”

A PLACE PRIMED FOR PROGRESS

Dr. Graves noted that working at Penn Dental Medicine, where spending time in both the lab and hands-on with patients is encouraged, has propelled him to take a closer look at these previously unexplained cellular functions.

“There is a synergy between research and clinical work that benefits both components of the job,” Dr. Graves explains. “As a practicing periodontist, having a research background pushes you not to take what you see at face value, but to dig into the evidence. Likewise, questions that arise in the clinic lead me to pursue different paths in the lab.”

He adds that his work, and Penn Dental Medicine’s capacity to attract star talent, have benefited tremendously from donor support.

“Penn creates a dynamic environment that is different from most other institutions,” Dr. Graves says. “The university demands excellence, and for this reason, you are surrounded by highly accomplished researchers. Donor support has helped to attract the best researchers and clinicians, raised our NIH ratings, and enabled us to triple the number of publications we produce. It inspires you to push forward and raise the bar.”

MORE INFORMATION

For more information on how to support the research of Dr. Graves, contact Elizabeth Ketterlinus, Senior Associate Dean for Development & Alumni Relations, ekett@upenn.edu, 215-898-3328.