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ADVANCES IN NEPHROLOGY

Weill Cornell Medicine

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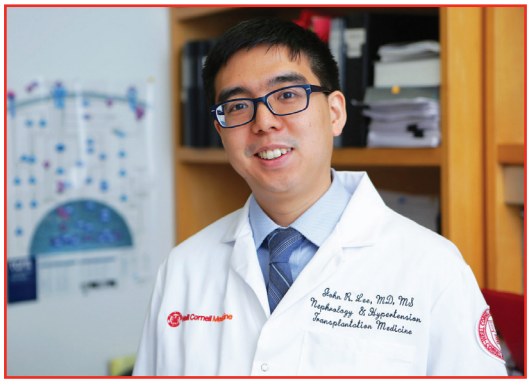
Gut Reaction: The Microbiome and Kidney Transplantation

Many studies today suggest that the trillions of microorganisms that live in our bodies play a crucial role in human health. Indeed, the human gut contains an intestinal community of microbiota that play a significant role in host metabolism, physiology, nutrition, and immune function.

Among the researchers who seek to unravel the relationships between perturbations in the microbiome and several disease states is **John R. Lee, MD,** a physician scientist in the Division of Nephrology and Hypertension at NewYork-Presbyterian/Weill Cornell Medical Center. Dr. Lee's investigations span the areas of infectious diseases, gastroenterology, nephrology, and transplant surgery.

Dr. Lee was inspired to care for kidney transplant recipients and pursue research while under the mentorship of **Manikkam Suthanthiran, MD,** Stanton Griffis Distinguished Professor in Medicine, Weill Cornell Medicine, and Chief, Division of Nephrology and Hypertension, NewYork-Presbyterian/Weill Cornell, and **Eric G. Pamer, MD,** Enid A. Haupt Chair in Clinical Investigation, and Head, Division of Subspecialty Medicine, Memorial Sloan Kettering Cancer Center. Dr. Suthanthiran is a pioneer in the development of noninvasive urinary biomarkers for evaluating acute rejection in kidney transplantation. Dr. Pamer is a pioneer in investigating innate and adaptive immune responses to infection with a focus on the role of the gut microbiota in preventing infections.



Dr. John R. Lee

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Using Technology to Improve Dietary Adherence in Chronic Kidney Disease

In order to slow the progression of chronic kidney disease (CDK), a key element of care is dietary restriction – easier said than done, according to **Maya K. Rao, MD,** Director of the Chronic Kidney Disease Program in the Division of Nephrology at NewYork-Presbyterian/Columbia University Medical Center. "We don't have that many medicines that slow the progression. But we do know that diet is important; recent research has shown that diets high in sodium and potassium for individuals with advanced kidney disease are associated with progression, morbidity, and mortality," says Dr. Rao. "However, the recommended diet for patients with pre-dialysis chronic kidney disease – which can include low sodium, low potassium, and low phosphorous – is very complex and patients have a hard time adhering to it."

> "Our goal was to first figure out what the barriers are for patients in following a kidney diet and then to use technology to create something that will help them adhere to it."
>
> — Dr. Maya K. Rao

The many dietary restrictions often leave patients bewildered and frustrated, notes Dr. Rao. They are being asked to adhere to and negotiate multiple restrictions, and compliance is almost immediately undermined by the anticipated burden of organizing a meticulous, measurement-guided diet.

"Many patients have diabetes, and they're told to follow a diabetic diet as well. So you're talking

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NewYork-Presbyterian Nephrology ranks #4 in the nation.

Gut Reaction: The Microbiome and Kidney Transplantation

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In 2014, Dr. Lee and his colleagues undertook a pilot study that identified significant alterations in gut microbiota following kidney transplantation. "I thought it would be very intriguing to study changes in the gut microbiome in relation to complications in kidney transplant recipients," says Dr. Lee, who conducted the study as a National Institute of Health KL2 Scholar awarded by the Weill Cornell Clinical and Translational Science Center.

The pilot study provided insight into the importance of gut microbiota in terms of post-transplant complications. The researchers analyzed the bacterial composition of serial stool samples from 26 kidney transplant patients using a novel technique called 16S rRNA deep sequencing. "From pre-transplantation to post-transplantation, the fecal abundance of Proteobacteria increased," notes Dr. Lee. "Proteobacteria are comprised of a group of gram-negative bacteria, many of which are known to cause diseases in humans."

The research team further reported that transplant recipients who developed diarrhea early after transplantation had less microbial diversity and had a lower abundance of *Bacteroides, Ruminococcus, Coprococcus,* and *Dorea* than recipients who did not develop diarrhea, suggesting that diarrhea may be associated with a lack of beneficial bacteria.

"Post-transplant diarrhea is actually a common complication following kidney transplantation," says Dr. Lee. "In many cases we don't know why. Many transplant physicians will attribute the diarrhea to the immunosuppressive medications and will lower their immunosuppressive medication dosages. But this strategy can put the kidney at risk for rejection. Our data suggest that diarrhea may be a state of lower commensal bacteria. So a potential therapy could include a probiotic to treat the diarrhea rather than reducing immunosuppressive medications."

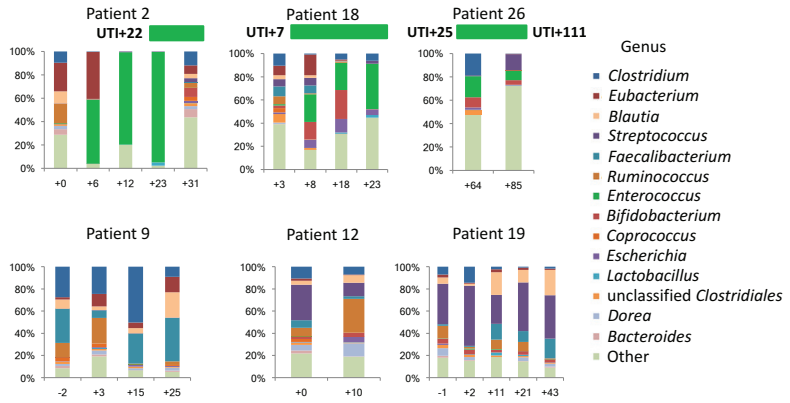
The researchers also looked at urinary tract infections, which are the most common bacterial infection in this population. They report that the relative abundance of pathogenic bacteria in the gut precedes and/or is associated with urinary tract infection by the pathogenic bacteria.

"Our findings offer insights toward a potentially new fundamental understanding of urinary tract infection development," says Dr. Lee. "If gut microbiota is linked to development of bacterial infections, treatment options may include fecal transplantation or probiotics. Fecal transplantation so far is an established treatment for recurrent *Clostridium difficile* infections. Our data suggests that fecal transplants for other infectious complications, for example, recurrent multidrug resistant infections, may prove beneficial."

Achieving Therapeutic Tacrolimus Levels

Establishing therapeutic levels of tacrolimus, one of the most common immunosuppressive drugs in organ transplant recipients, can be challenging because of variability in drug absorption, metabolism, and disposition from patient to patient. To better understand tacrolimus dosing, Dr. Lee and his colleagues also investigated the relationship between the gut microbiota and tacrolimus dosing requirements in adult kidney transplant recipients.

Enterococcus Fecal Abundance and Enterococcus Fecal Urinary Tract Infections in Allograft Recipients



The six sets of bar graphs represent six of the 26 kidney transplant recipients studied; patients 2, 18, and 26 developed Enterococcus UTI and patients 9, 12, and 19 are three of the 23 patients who did not develop Enterococcus UTI. Each bar represents the relative composition of bacteria in the stool sample from each patient. The x axis indicates the day of specimen collection from the transplantation event as the day of reference (day 0); the y axis indicates the relative bacterial percentage corresponding to each taxon. The timing or day of the Enterococcus UTI is indicated by the horizontal bar in green above the bar graphs. (Source: Transplantation*, October 15, 2014)*

"In 2012, over 90 percent of kidney transplant recipients were maintained on calcineurin inhibitors with the majority being treated with tacrolimus," says Dr. Lee. "Tacrolimus has a narrow therapeutic index, with sub-therapeutic levels leading to immune rejection and supra-therapeutic levels leading to nephrotoxicity and neurotoxicity. Further complicating this is the difficulty in predicting initial tacrolimus dosing to maintain therapeutic trough levels."

One major variability in organ transplantation is that patients will eventually require different doses of tacrolimus as indicated by blood levels. "Some patients will need a lot and some will need less," says Dr. Lee. "It turns out that in looking at the bacteria in the gut, there may actually be certain bacteria that are associated with an increased amount of dosing. In the future we may be able to profile the bacteria in the gut and predict how much dosing of tacrolimus is needed. We then may be able to monitor patients using this profile to understand how much they may need going forward and provide more personalized medicine." Dr. Lee is now planning to conduct a validation study of the initial findings described herein. He is currently funded by a K23 career development award from the National Institute of Allergy and Infectious Diseases.

Reference Articles

Lee JR, Muthukumar T, Dadhania D, Taur Y, Jenq RR, Toussaint NC, Ling L, Pamer E, Suthanthiran M. Gut microbiota and tacrolimus dosing in kidney transplantation. *PLoS One.* 2015 Mar 27;10(3):e0122399.

Lee JR, Muthukumar T, Dadhania D, Toussaint NC, Ling L, Pamer E, Suthanthiran M. Gut microbial community structure and complications after kidney transplantation: A pilot study. *Transplantation.* 2014 Oct 15;98(7):697-705.

For More Information

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Using Technology to Improve Dietary Adherence in Chronic Kidney Disease *(continued from page 1)*

Dr. Maya K. Rao

about a lot of information that at times conflicts with each other," says Dr. Rao. "They may be able to eat one thing on one diet, but are not supposed to eat that on another diet. They get the feeling that there's nothing they can eat and end up not following it because it's too complicated.

"Current dietary counseling is not effective," says Dr. Rao. "We give patients multiple hand-outs of recommendations and expect them to be able to put it all together. In addition, there is a lot of math involved. For example, we recommend a patient have no more than 2,000 milligrams of potassium in a day and expect a patient to calculate their potassium intake, accounting for serving size. It becomes impossible."

In an effort to address this nutritional dilemma, Dr. Rao undertook a project that harnesses technology to help patients make dietary changes. "Our goal was to first figure out what the barriers are for patients in following a kidney diet and then to use technology to create something that will help them adhere to it," she says.

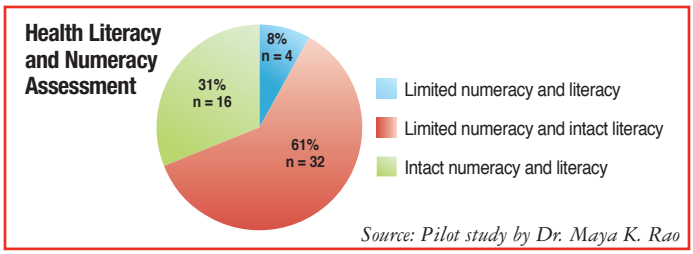
With support from a grant from the Irving Institute for Clinical and Translational Research at Columbia, Dr. Rao and her colleagues launched a cross-sectional study among English and Spanish-speaking patients with stage 4 and 5 CKD, many who live in the Dominican community surrounding the Hospital, are older, and for whom English is their second language.

Patients provide answers to a series of questions about the foods they eat, including how often and how much in the course of a week or more. Specifically, they complete a five-part analysis designed to evaluate possible barriers to dietary adherence, including assessment of health literacy and numeracy, a food frequency questionnaire, and a knowledge assessment of foods high in potassium and phosphorus. The researchers hypothesized a number of barriers to diet compliance would exist, including:

- Limited health literacy and numeracy
- Multiple prescribed modifications based on an individual's clinical picture
- Need for adjustment as the disease progresses
- Limited self-management skills
- Poor educational tools
- Limited access to nutritionists

A telling and integral aspect of Dr. Rao's study focuses on patient health literacy and numeracy. "What we found so far is that only 30 percent of the group has intact health literacy and numeracy," she says. "Seventy percent of the cohort has either limited health literacy or limited numeracy – or both. We started to see how ineffective nutrition counseling can be and that technology could be extremely useful."

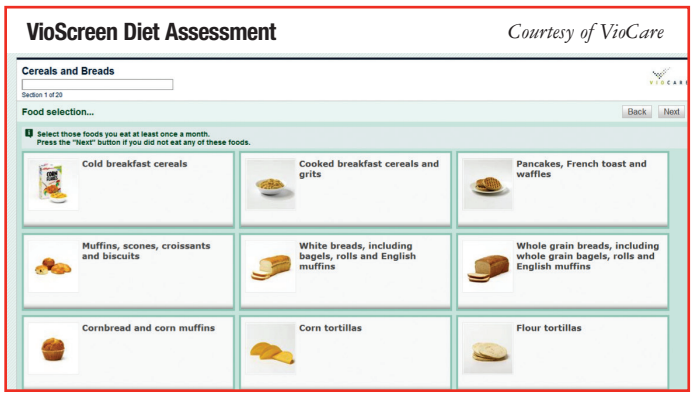
Although these results were based on only 55 of the eventual 100 participants of this first preliminary study, it nonetheless points toward factors that may make it difficult for a person



Source: Pilot study by Dr. Maya K. Rao

challenged by advanced kidney disease to take control of their very specific nutritional requirements.

Dr. Rao has been working with a healthcare technology company that has developed web-based dietary analysis software that provides the equivalent of 90 days of nutrition tracking in 20 minutes. This cloud-based, self-administered questionnaire collects data on an individual's dietary behavior and food use patterns, estimates nutrient intake, and delivers detailed dietary analysis data and reports. From any computer or tablet, the patient can answer eating behavior questions about foods, frequencies, and portion sizes.



"The digital survey avoids any dependence on volume measurements," says Dr. Rao. "The program interprets the nutritional values of a patient's actual dietary intake. Our immediate goal is to create a tool that can be used in the office by a physician, a practitioner, or a nutritionist that gives patients very tailored recommendations and focuses on nutrients important in kidney disease, including sodium, potassium, and phosphorus content. The prescription will include reasonable food replacements to make the diet easier to follow."

Patients with advanced kidney disease are generally seen every two or three months. "Repetitive use will allow us to provide patients with nutritional oversight with some frequency and to give feedback on any changes they've made to their diet," she adds.

Dr. Rao envisions patients being able to fill out the questionnaire on their own in the waiting room prior to their appointment. "This is personalized medicine – it's not about giving patients a generic diet that they can't follow, but it's figuring out what they're eating, what they like to eat, and how we can work with them so that they can follow a prescribed diet. Providing them with a good quality of life, slowing down the disease progression, and lengthening the delay before dialysis are really our goals."

For More Information

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