How do our kidneys influence our cardiovascular health?

The human body is a complex and interconnected system. In the **Human Translational Nephrology Lab** at the **University of Iowa**, USA, **Dr Diana Jalal** is investigating the links between the kidneys and the cardiovascular system. Patients with chronic kidney disease are at higher risk of developing cardiovascular disease, so Diana hopes to discover new therapies that will improve their health outcomes.

Dr Diana Jalal

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PROFILE

Field of research
Nephrology

Research project
Uncovering the links between chronic kidney disease (CKD) and cardiovascular disease (CVD)

Funders
US National Institutes of Health (NIH), Veterans Health Administration (VHA), American Heart Association (AHA)

Talk like a ...

nephrologist

Cardiovascular — relating to the heart and blood vessels

Cardiovascular disease (CVD) — a general term for any condition that affects the heart and/or blood vessels

Chronic kidney disease (CKD) — a condition in which the kidneys do not function properly

Diabetes — a disease characterised by unstable blood sugar levels, which can damage the kidneys and cardiovascular system

Dialysis — a medical treatment in which the blood is artificially filtered by a machine

Endothelial — relating to the cells that line the walls of blood vessels

Kidney — the organ that filters the blood

Nephrology — the branch of medicine that studies the kidneys

Placebo — a treatment that has no active properties, given to a control group during clinical trials

Translational research — research that applies lab-based findings to applications in humans

Vascular — relating to blood vessels

37 million people in the US live with some form of kidney disease, and over 800,000 of them suffer from kidney failure, also known as end-stage kidney disease. Chronic kidney disease (CKD) occurs when the kidneys become damaged and their function is reduced. It can lead to kidney failure which, if a patient does not receive dialysis or a kidney transplant, can be life-threatening. "The prevalence of CKD is increasing around the world. This has been linked to the rise in obesity, diabetes, high blood pressure and other cardiovascular risk factors," says Dr Diana Jalal, who leads the Human Translational Nephrology Lab at the University of Iowa. "Diabetes and high blood pressure are the most common causes of end-stage kidney disease."

Diana is interested in the links between the kidneys and the cardiovascular system. She believes that understanding these links could have a positive impact on health outcomes, as individuals with CKD have an increased risk of cardiovascular disease (CVD).

What do our kidneys do?

Kidneys are the body's filtration system. "They filter about 200 litres of fluid every day," says Diana. This is equivalent to more than a bathtub full of fluid being cycled through your kidneys! Our kidneys help us maintain healthy levels of water, minerals and salts in our blood, and they remove waste products from the body, which are excreted in urine. As the kidneys influence blood composition, impairment in kidney function can affect the cardiovascular system, which is responsible for transporting blood around the body.

What cardiovascular problems might people with CKD have?

The chemical nitric oxide plays an important role in the cardiovascular system, as it causes blood vessels to dilate (widen). "If nitric oxide availability is reduced, it leads to impaired dilation of the blood vessels, known as endothelial dysfunction,"

explains Diana. "Endothelial dysfunction is also caused by oxidative stress, which is when there is an imbalance between pro-oxidant and antioxidant substances (chemicals that promote or inhibit oxidation) in the body." Vascular stiffness occurs when blood vessels lose their elastic fibres and accumulate stiff fibres instead, causing the blood vessel walls to harden and forcing the heart to work harder to pump blood around the body.

People with CKD tend to have higher levels of endothelial dysfunction, oxidative stress and vascular stiffness. "While the exact mechanisms that lead to these conditions in people with CKD are not completely understood, it is believed that they contribute to the higher rates of CVD seen in these patients," says Diana.

The importance of translational research

"Translational research allows us to extend findings from lab-based research in cells and animals to clinical outcomes in humans," explains Diana. The Human Translational Nephrology Lab uses translational research to investigate the links between CKD and CVD and to translate these findings into therapies that will benefit patients. This may involve studying cultured cells to explore specific molecular pathways related to the diseases. The outcomes of these studies are then tested on animals, to investigate how the molecular pathways and diseases function in living organisms. Then, the team works with patients to explore CKD and CVD in humans. Sometimes, novel pathways are first identified in humans, then animal and cell models can be used to understand the mechanisms by which these may influence disease in humans.

"Cultured cells do not capture the complexities of human diseases," says Diana. "Animal models are more complex and have led to important discoveries regarding CKD; however, studying CKD in animals in the lab does not reflect all the factors at play in humans with CKD. Evaluating vascular measurements in patients with CKD allows us to better understand the factors that contribute to endothelial dysfunction." In this way, the team can explore the influence of CKD on CVD and test therapies that may reduce the risk of patients with CKD developing CVD.

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How does Diana measure cardiovascular function?

Diana and her team use a range of methods to evaluate cardiovascular function in patients with CKD. To measure endothelial dysfunction, they place an inflatable cuff on the patient's forearm to cut off blood flow for a few minutes, then release the cuff, causing blood to rush into their arm. This should stimulate the release of nitric oxide, causing blood vessels to dilate. Using ultrasound technology, the researchers measure patients' blood vessel diameters. They have observed that blood vessels in patients with endothelial dysfunction dilate less than in patients without the condition.

"We measure vascular stiffness using the technique of arterial tonometry, which measures the speed at which blood vessel pulses travel from one point to another in the circulatory system," says Diana. In patients with stiffer blood vessels, the speed of travel increases.

The team also collects endothelial cell samples from patients to analyse their protein compositions. "We place a catheter into a vein in the arm, and then insert a thin wire to scrape off some cells from the blood vessel wall," says Diana. The cells are analysed to determine which proteins they contain, as protein expression is an important measure of whether cells are performing their specific function correctly.

Diana and her team use these methods to test the effectiveness of potential new therapies that might improve endothelial function and vascular stiffness in patients with CKD, hopefully preventing them from developing CVD.

What might improve cardiovascular health in patients with CKD?

Diana's team has recently finished two clinical trials investigating whether curcumin (a chemical found in turmeric) and resveratrol (a chemical found in red grapes) improve vascular function in patients with CKD. Patient's participating in the trials visited the Human Translational Nephrology Lab, where their blood pressure, endothelial function and vascular stiffness were measured before the study began. In each trial, participants were randomly assigned to receive either the therapy (curcumin or resveratrol) or a placebo. Participants then took their assigned drug for several months before returning to the lab for end-of-study measurements to assess whether their vascular function was influenced by consuming curcumin or resveratrol. The team is now in the process of evaluating the results of these trials to determine whether curcumin or resveratrol provide health benefits to patients with CKD, and whether they could be used as therapies.

Diana hopes that uncovering how kidney dysfunction leads to cardiovascular problems will result in new therapies, allowing patients with CKD to reduce their risk of developing CVD and live healthier lives.

About *nephrology*

Nephrology involves the study, diagnosis and management of kidney disease. Like many who work in medical research, Diana splits her time between treating patients and conducting research in the lab to learn more about the diseases she is treating.

What does Diana's dual role involve?

As a clinical nephrologist, Diana spends time with patients suffering from kidney conditions, both in hospital and in an outpatient clinic. In the hospital, she takes care of patients who have developed end-stage kidney disease and are dependent on dialysis, and she consults with other medical professionals to address patients' kidney-related problems. "In the clinic, I help CKD patients manage their blood pressure or diabetes, or counsel them about therapies to reduce their risk of developing CVD," she says. "Sometimes, I have to have difficult conversations with them about the need to start dialysis or to investigate kidney transplant options."

As a nephrology researcher, Diana coordinates her team in the Human Translational Nephrology Lab. "Most of the day-to-day research activities are carried out by members of my team, including Katharine Geasland (coordinator), Dr Mingyao Sun (post-doctoral fellow) and Colin Gimblet (doctoral student)," says Diana. "I meet with participants for our trials and answer their questions, but most of my time is spent analysing our data, writing manuscripts to summarise our results and submitting grant applications to get funding for new studies."

What are the rewards and challenges of nephrology?

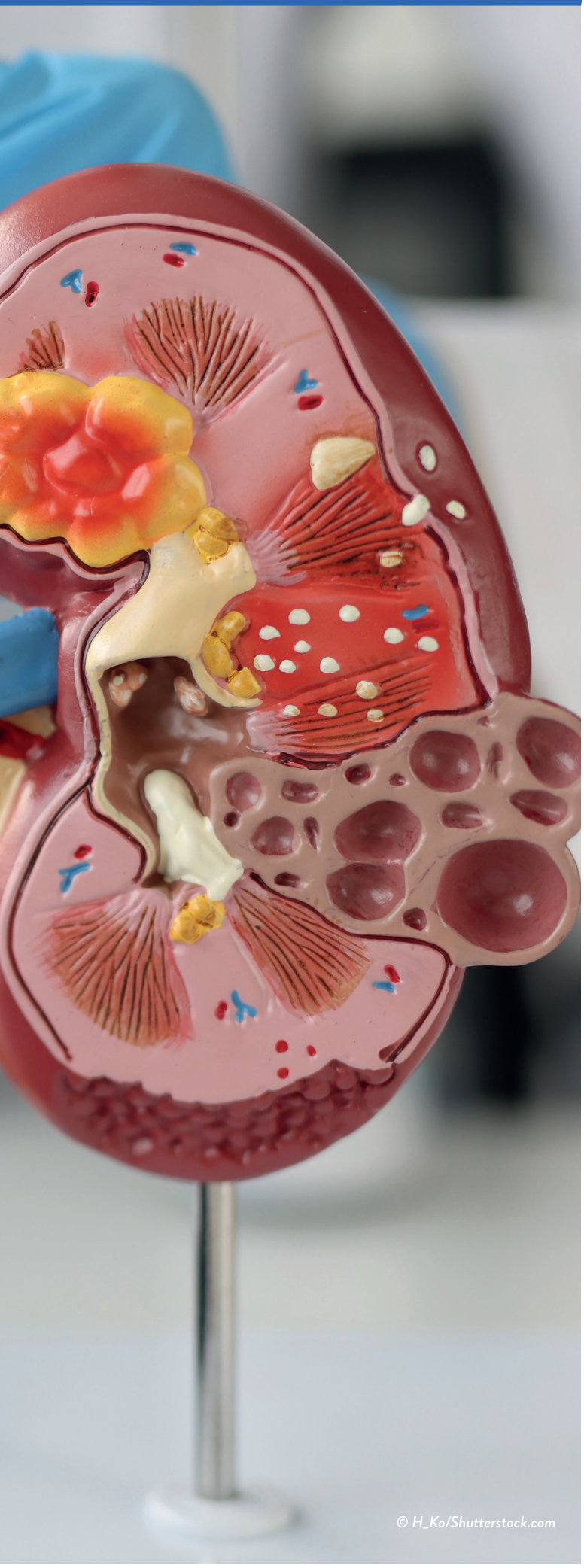
"I have always enjoyed the fact that my career allows me to form long-lasting bonds with patients and their families," says Diana. "It is extremely rewarding to see patients in whom we are able to maintain stable kidney function, as it shows that what we are doing makes a difference to their health." However, end-stage kidney disease can be fatal, and Diana's hardest days are when one of her dialysis patients dies. But, as she explains, even the challenging aspects of the job are worthwhile and important. "It is difficult when a patient reaches the stage when they need dialysis or a kidney transplant, but I find it a privilege to hold their hand through the tough times."

Pathway from school to *nephrology*

- At school, Diana recommends securing a strong foundation in STEM subjects, particularly biology and chemistry.
- At university, degrees in medicine, biomedical science, biology or nursing could all lead to a clinical or research career in nephrology.

Explore careers in *nephrology*

- This article explains the many roles that nephrologists fulfil for patients: www.healthline.com/health/what-is-a-nephrologist
- The National Kidney Foundation (www.kidney.org) has a wealth of resources about nephrology and kidney disease, including a podcast about life as a nephrologist: www.kidney.org/podcasts/life-as-a-nephrologist
- The International Society of Nephrology (www.theisn.org) hosts an online 'academy', which provides a wide range of nephrology resources, including webinars, courses and podcasts: academy.theisn.org
- Diana's department, the Division of Nephrology at the University of Iowa (www.medicine.uiowa.edu/internalmedicine/nephrology) offers opportunities for students to shadow clinicians and volunteer in research labs: www.uihealthcare.org/job-shadows



Meet *Diana*

At school, I really enjoyed math and chemistry. Ironically, biology was my least favourite STEM subject in high school, and it wasn't until college that I developed an appreciation for biology.

Growing up, my dad had a significant influence on my dreams to become a scientist. He worked for a large pharmaceutical company in the Middle East, and I used to enjoy visiting him at work and being in the lab across from his office. My dad was always happy when discussing science, and he derived great pleasure from contributing to the betterment of people's lives. He influenced me to want to do the same.

> ***When I discovered the opportunity to work as both a clinical and research nephrologist, it seemed natural for me to follow this path.***

As I grew older, I realised I wanted to pursue a career in medicine. While studying at the University of Jordan, I was inspired to focus on nephrology by the kidney patients I worked with. Most memorably, I met a young woman who had developed kidney failure and whose husband had donated a kidney to her. She later named her two children after the nephrologist who treated her. Several years later, this nephrologist became my father-in-law!

My early love of the lab returned when I moved to the US for further nephrology training. When I discovered the opportunity to work as both a clinical and research nephrologist, it seemed natural for me to follow this path.

When I'm not working, I enjoy spending time with my family and friends. I like cycling with my husband, hanging out with my kids and running with my friends.

Diana's *top tips*

1. Work hard.

2. Don't be afraid to venture outside your comfort zone.

3. Be bold, but stay true to your values.