

Approximately 29.1 million people in the US have diabetes, accounting for nearly 10% of the population [1]. Despite the huge impact of this disease, the intricate details of how diabetes progresses to more serious health issues are not well understood. One of the major complications caused by the effects diabetes is chronic kidney disease (CKD). In order to create a better understanding of how diabetes affects the kidneys, I am proposing a research project to mathematically model the chemical reactions within a significant cell of the kidney due to diabetes.

Diabetes is characterized by hyperglycemic conditions, or elevated levels of glucose in the blood. The kidney is the main filtration unit of the body; as such any adjustments to the blood supply affect kidney function. Filtration within the kidney occurs in the fundamental filtration unit of the kidney called the glomerulus. The podocyte cells within the glomerulus play a significant role in many mechanisms that can lead to CKD [2]. The progression of diabetes is closely linked with the decrease of podocytes within a glomerulus. In a non-diabetic state, the podocyte number remains relatively stable, while in a diabetic state the podocyte number fluctuates and decreases (Figure 1). The death of podocytes begins a chain reaction of failure within each glomerulus, ultimately leading to dysfunction of the kidney altogether. For the significant role of podocyte cells in the progression of diabetes to CKD, I aim to isolate the types of podocyte damage and identify the chemical reactions induced by diabetes that lead to such damage. In doing this, I propose to answer the question: How do chemicals within the kidney alter podocyte function?

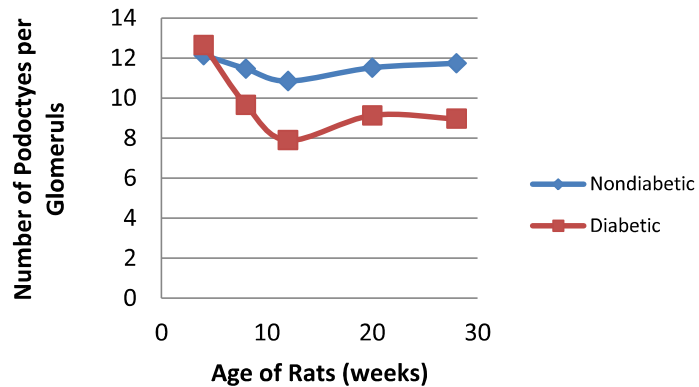


Figure 1: Number of podocytes per glomerulus in nondiabetic and type II diabetic rats. Data interpreted from literature. [3]

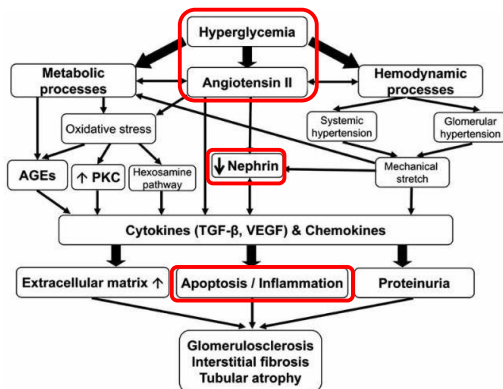


Figure 2: Flowchart of key chemicals linked to podocyte and kidney malfunction. [4]

Within the past year, I have studied the podocytes as well as the significant chemicals involved in glucose metabolism within the podocytes. The Wentz grant will allow me to continue this research and make strides in understanding and treating this widespread disease.

I plan to answer this question by utilizing mathematical modeling, meaning I will derive ordinary differential equations based on published data to describe the time-dependent concentrations of different significant chemicals affecting the death of podocyte cells. Two key chemicals I aim to include in these equations are Angiotensin II and Nephhrin, as they have been connected to both podocyte malfunction, in the form of programmed cell death, or apoptosis, as well as hyperglycemic conditions (Figure 2). I will then utilize a software program to solve these ordinary differential equations.

With the Wentz grant, I aim to shed light on an area of diabetes that has yet to be clarified—more specifically, how chemicals linked to diabetes lead to podocyte malfunction.

References: [1] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014. U.S. Department of Health and Human Services 2014. [2] López-Novoa, J.M., Martínez-Salgado, C., Rodríguez-Peña, A.B., López Hernández, F.J. Common Pathophysiological Mechanisms of Chronic Kidney Disease: Therapeutic Perspectives. *Pharmacology & Therapeutics* 2010;128:61-81. [3] Susztak, K. Glucose-Induced Reactive Oxygen Species Cause Apoptosis of Podocytes and Podocyte Depletion at the Onset of Diabetic Nephropathy. *Diabetes* 2006;55:225-33. [4] Ziyadeh, F.N., Wolf, G. Pathogenesis of the Podocytopathy and Proteinuria in Diabetic Glomerulopathy. *Current Diabetes Reviews* 2008; 4:39-45.