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Does Tight Glycemic Control Slow the Progression of Chronic Kidney Disease?

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SECTION 1: Introduction

Approximately 15 percent of American adults (an estimated 37 million total) experience chronic kidney disease during their lifetime (Centers for Disease Control, 2021). Chronic kidney disease (CKD) is considered three or more months of decreased or damaged renal function defined as low glomerular filtration or albuminuria. CKD is progressive in nature and can turn into end stage renal disease (ESRD), which affects eight to nine percent of the United States population (Centers for Disease Control, 2021). Dialysis for those with end stage renal disease is estimated to cost $88,000 per year (Ferri, 2020), laying a heavy financial burden on patients.

The two most common known causes of ESRD are diabetes mellitus (43.2%) and hypertension (23%), both of which can be managed with a combination of lifestyle factors and medications (Ferri, 2020). With so many American adults being impacted with CKD and at risk for progression to ESRD, the primary goal of CKD treatment is to slow progression and sequelae. While providers manage medical regimes and monitor the disease progression in patients with CKD, the question arises, what can providers and patients do to slow the spread of their disease? With diabetes mellitus as one of the primary risk factors for ESRD, could tighter glycemic control slow the progression of CKD among patients with diabetes mellitus and CKD?

Problem Overview

Chronic renal disease is frequently a progressive decline that can result in buildup of nitrogenous waste products, metabolic acidosis, electrolyte abnormalities, anemia, bleeding, infection, hypertension, and hyperlipidemia (Ferri, 2020). These can result in patients being at increased risk for cardiovascular disease (even before decline to ESRD) than those without CKD

(Shama, Doley, & Das, 2018). Patients with diabetes mellitus are two to four times more likely to develop cardiovascular disease than a patient without diabetes (Ferri, 2020).

Despite the steady 15% of Americans who experience CKD during their lifetime, ESRD rates continue to rise. In 2018, the U.S. had one of the highest rates of ESRD in the world with 2,242 cases of ESRD per every million of the U.S. population. However, CKD is not isolated to the United States. Approximately 8-16% of the world's population has CKD (Chem, et al., 2021). These estimated 697-700 million patients worldwide are at an increased risk for disability and death. As a result, CKD is the 17th most common cause of global disability and the 12th most common cause of death (Shama, Doley, & Das, 2018).

ESRD can have devastating health impacts on patients, as many opt for dialysis and its high level of treatment burden. Not only is chronic renal disease linked to increased morbidity, cardiac-event related mortality, and increased hospitalizations, but patients with ESRD average six chronic medical conditions including anemia, electrolyte imbalances, fluid overload, bone mineral disorders, hypertension, and hyperparathyroidism (Al-mansouri et al., 2021). ESRD may also induce taxing symptoms such as pain, pruritus, fatigue, restless leg syndrome, depression, anxiety, constipation, anorexia, and nausea (Al-mansouri et al., 2021).

In addition to impacts on the individual health, disability, and increased death, CKD has staggering financial impacts. Medicare spending for American patients with CKD or ESRD comes in at over $120 billion dollars each year (Chem et al., 2021). This doesn't include lost wages as patients receive hemodialysis three times a week in outpatient centers, complicating their work schedules and diminishing their ability to work.

Despite the massive health and financial impacts of CKD, there is a need for increased screenings and referrals. In 2017, only 43.2% of Medicare patients who had hypertension and

diabetes were tested for albuminuria despite having the two most significant risk factors for renal disease (Saran et al., 2020). A nephrology referral is appropriate when eGFR declines more than 5 ml/min per 1.73 m^2 in one year or drops 25% or more from patient baseline (Ferri, 2020). However, a 2017 study showed that a third of patients with ESRD did not receive any nephrologist care prior to diagnosis (Saran et al., 2020). This highlights a gap in primary care. Primary care providers can provide education about the risk factors for renal function decline and refer when appropriate.

Diabetes mellitus is the leading cause of CKD globally (Shama, Doley, & Das, 2018) and its treatment has drawn considerable attention as an important component of CKD prevention and possible means of slowing progression. As many as 30% of patients with diabetes mellitus are diagnosed with diabetic nephropathy.

Definition of Terms

Chronic kidney disease (CKD) or **chronic renal disease**, as it is also termed, is defined as over three months of renal damage identified by either urine albumin of over 30 mg/g, elevated creatine, presence of hematuria, or by decreased renal function defined as **glomerular filtration rate** (GFR) of less than 60 ml/min per 1.73 m^2 (Ferri, 2020). GFR can be different in healthy individuals based on a variety of factors such as age, gender, protein intake, and even race-ethnicity, though the variations across ethnicities are not fully understood (Levey, 2021). Renal disease is staged using a numerical 1 through 5 system with 5 encompassing ESRD with the greatest amount of damage and the need to initiate dialysis or other forms of renal replacement. Stage 3 disease is uniquely divided into stage 3A and 3B. A GFR of under 15 ml/min per 1.73 m^2 is considered kidney failure.

Type 2 diabetes mellitus is defined as a condition of hyperglycemia often worsened by a variety of dietary, lifestyle, or autoimmune factors which causes an imbalance of glucagon and insulin levels, resulting in hyperglycemia and a multitude of other complications. This can be due to decreased insulin production or insulin resistance, a decreased response to insulin by the body's cells (Ferri, 2020). Diabetes mellitus (DM) is defined as a fasting glucose level equal to or over 126 mg/dl on two different occasions. It can also be diagnosed by an oral glucose tolerance test with levels of 200 mg/dl or more after a 75-gram glucose load. Lastly, it can be defined by a HbA1c of 6.5% or higher. **Normal fasting blood glucose** is considered less than 100 mg/dl (Ferri, 2020)

Hemoglobin A1c (HbA1c) has been used for over 30 years as a means of monitoring and identifying glycemic control. A HbA1c level reflects averages blood glucoses over the past 2 to 3 months. (Copur et al., 2020). A normal HbA1c is below 5.7%. Prediabetes is defined as 5.7-6.4% and diabetes is defined as 6.5% or above (Ferri, 2020). **Tight glycemic control** for the purpose of this research is defined as a HbA1c of 7.0% or less.

Albuminuria is the abnormal presence of protein in the urine, a sign of glomerular damage, and is commonly measured using the **albumin-to-creatine ratio (ACR).** An ACR of 30mg/g and above is considered abnormal. Albuminuria is often categorized as normal (less than 30mg/g), moderately increased (30 to 299 mg/g) and severely increased (300mg/g or more). Albuminuria is associated with primary renal disease, but can also be due to effects of hypertension, tobacco use, diabetes mellitus, and other factors (Levey & Inker, 2021).

Purpose Statement/PICO Question

Does tight glycemic control lower incidence of CKD and slow progression rates in patients? Should primary care providers treating patients with CKD and DM give extra attention

to glycemic control? Could more aggressive treatment strategies be associated with better outcomes? The purpose of this paper is to investigate the tie between glycemic control and renal disease progression. Are patients who maintain tight glycemic control at lower risk for progression of chronic renal disease?

Theoretical Framework

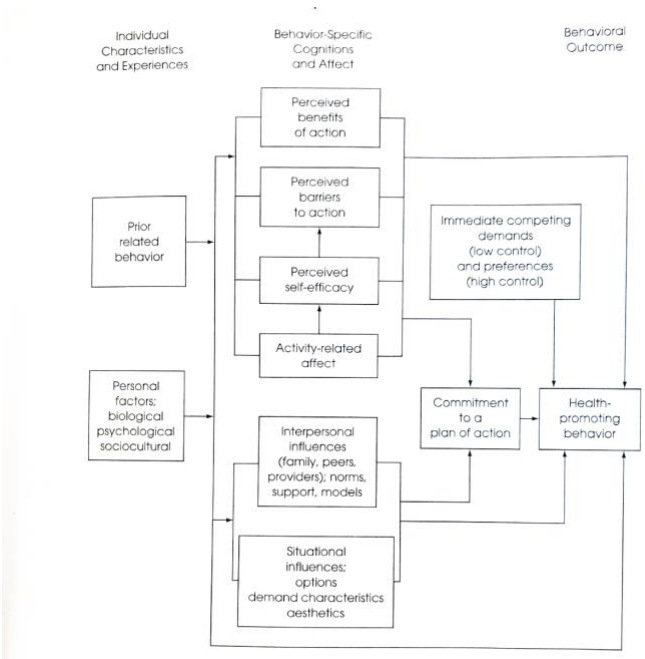
Using Nola Pender's Health Promotion Model as a theoretical framework, providers can work together with their patients to help them change behaviors to achieve a healthier lifestyle (Pender, Murdaught, & Parsons, 2011). This model focuses on individuals, their perceived benefits of action and how health care providers can encourage patients to make positive changes. If tighter glycemic control has impact on preventing CKD or slowing its decline, patients can see benefits associated with their changes in diabetic treatment.

Pender's model identifies health care providers as key sources of influence that can help patients have increased or renewed commitment to healthy behaviors. The purpose of this paper is to identify if improved glycemic control could prevent renal decline, and thus additional disease and adverse outcomes. Pender's Health Promotion Model claims that people are more likely to be dedicated to a change in their behaviors if they can see how they will benefit from it.

A diagnosis of DM or CKD can be discouraging due to increased risk of adverse outcomes, cardiovascular disease, and mortality associated with both. Providers have a responsibility to help prevent disease and suffering through education, treatment, and shared decision making. Pender's model supports the patient and provider in their shared journey to improved health.

Figure 1.

Health Promotion Model



SECTION 2: Literature Review

Multiple literature searches contributed to this paper's findings. Using the Medline Complete database to search "renal failure or kidney failure or chronic renal failure" and "hemoglobin a1c or hba1c or glycosylated hemoglobin" for peer-reviewed articles written between 2016 and 2021, resulted in 408 academic articles. A repeated search using "chronic kidney disease or CKD" and "hemoglobin a1c or hba1c or glycosylated hemoglobin" filtered by peer-reviewed journals between 2016 and 2021, gave 93 results. A later search for "hemoglobin a1c or hba1c or glycosylated hemoglobin or glucose markers" and "ckd or chronic renal disease or renal failure or kidney disease or kidney failure" and limited to dates between 2017 and 2022 resulted in 153 peer-reviewed journal articles. A search for "glycemic control" and "kidney disease or chronic renal failure or ckd or esrd or renal insufficiency or kidney failure" between

January 2018 and January 2022 resulted in 26 peer-reviewed articles. The final search for "disease progression or exacerbation or deterioration" and "chronic kidney disease or ckd or esrd or renal insufficiency or kidney failure" and "hemoglobin a1c or hba1c or glycosylated hemoglobin" resulted in 175 peer-reviewed articles. There was a fair amount of article overlap between search findings. The included 20 articles were selected due to their emphasis on impact of glycemic control or findings related to renal disease incidence or progression. These 20 studies included participants from not only the United States, but also from Sweden, Malaysia, Saudi Arabia, China, and Taiwan. Most were retrospective cohort studies, but a few prospective trials and follow-up to prospective trials were identified. Several key themes arose from these 20 studies: risk factors for chronic kidney disease, progression and end-stage renal failure, the association between glucose control and renal disease, negative health outcomes, death, and lastly, the importance of multidisciplinary and wholistic care for patients with diabetes mellitus at risk for chronic kidney disease.

Presentation of Literature

Risk factors for chronic kidney disease

Who is the most at risk for CKD? Before uncovering possible prevention strategies, providers must know which patients to focus on. Burrows, et al. (2020), used a prospective design to identify those who are at high risk for CKD in an effort to promote better target future screenings. A 3-year community demonstration project named CKD Health Evaluation Risk Information Sharing (CHERISH) was set up to recruit 894 participants from eight US cities in four states. Inclusion criteria included presence of diabetes, hypertension, or age over 50 years. Participants were excluded if they were on dialysis or transplant recipients, had hemophilia, had chemotherapy treatment in past four weeks, or if they were on regular intravenous infusions.

Additional exclusions included the presence of variety of skin wounds (rash, burns, or dressings), edema, or other vein abnormalities (such as occlusions). The result was a racially diverse sample: 60% of sample was non-White. Findings compared the presence of possible risk factors (diabetes, hypertension, or age over 50 years) and CKD incidence in study population. Forty-three percent of the sample had diabetes. Nearly 85% had hypertension. The study found 34.9% of qualifying participants had CKD, approximately double the prevalence of CKD in the general US population. This demonstrated that even when accounting for other variables, they had identified a high-risk population. Compared to adults without DM or hypertension, patients with those risk factors were more likely to show faster disease progression.

Strengths of this study included the racially diverse sample, and simple inclusion criteria and study-set up. Weaknesses included the small sample size, the lack of general population representation (by only having DM, hypertension, or being 50 years old and up), and primarily only from urban settings within large cities. This study did not identify specifically any ties between HbA1c and CKD but demonstrated that those with diabetes or hypertension or both were more prone to CKD and faster disease progression. More research is needed to see if these risk factors hold true across both urban and rural settings, the general population, and with a more careful HbA1c measurements. Burrows et al (2020) focused primarily on risk factors for kidney disease and uncovered some risk factors for progression. Since a primary goal in the treatment of CKD is to prevent progression, providers should be aware of risk factors for faster decline.

Risk factors for chronic kidney disease and progression

Sui et al. (2020) sought to investigate what the most common risk factors for renal disease and progression are by doing a retrospective study out at Peking University hospital in

Beijing. It included 12,380 patients who had a new diagnosis of CKD (stages 1-4) between April 2010 and April 2015. Researchers excluded those who had diagnosis of acute kidney injury, renal stones, renal tumor, infection, or were on dialysis or renal replacement therapies. They compared cause of renal disease and disease progression over time. They found chronic glomerulonephritis (36.8%) to be the most common cause with hypertension (28.5%) and diabetic nephropathy (27.1%) following. In early stages of CKD, chronic glomerulonephritis was the most common (such as 57.7% stage 1), but it dropped down to 5.6% of chronic kidney disease stage 5 cases. In contrast, diabetic nephropathy incidence rose with the first three stages (16.5% of stage 1, 23.1% of stage 2, and 26.8% of stage 3), diminishing back to 10.8% for stage 4 and 22.8% for stage 5. Risks of renal progression were older age at diagnosis ($p = 0.001$), more comorbidities (such as hypertension, type 2 diabetes, coronary artery disease, CVA, or heart failure ($p < 0.01$), higher disease stage at diagnosis, and presence of diabetes mellitus type II. Strengths of this study included the huge sample size and the consistency of a single academic hospital as base. Weaknesses were that mortality data was not always available, longitudinal analysis of data was over minimum of six months, data was obtained from a single location and population, and in full disclosure, it was fully funded by AstraZeneca and contained multiple researchers that work for AstraZeneca. This study unveiled the possibility that since more early stages of disease onset may be related to chronic glomerulonephritis, it may not progress as frequently as diabetic nephropathy related renal disease. Additional research using HbA1c as a variable in a study of this size could be beneficial to determining if glycemic control was associated with declining function and if it was associated with risk of diabetic nephropathy. Overall, Sui et al. (2020) highlights the importance of being extra cautious in monitoring renal

progression among older patients, those with comorbid conditions, and those with diabetes mellitus.

Risk factors for CKD progression among patients with and without diabetes mellitus

Warren et al. (2018) also sought to identify those at highest risk for renal decline by monitoring eGFR decline over time comparing those with diabetes, those with pre-diabetes (termed "undiagnosed diabetes"), and those without diabetes. A prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study utilized 15,517 participants from four regions starting in 1987 and obtained creatine measurements over 26 years. Exclusion criteria included eGFR under 13 mL/min/1.73 m^2 and some ethnicities due to small sample size. Over multiple visits, they obtained creatine levels, HbA1c levels, *APOL1* genetic testing, and 1,5-anhydroglucitol levels (a newer marker associated with increased risk of CKD progression). They evaluated their findings with ANOVA for continuous variables and Pearson X^2 tests for categorical, as well as linear mixed methods evaluating eGFR and age over time. They explored commonly studied variables (age, gender, tobacco use, BMI, and SBP), but also included less-often studied factors such as family income and educational level. They found that prediabetes or diabetes at baseline was associated with higher rates of HTN and CAD, higher BMI, and lower income and education than those without diabetes. Age alone was associated in eGFR decline; however, disease progression was slowest among those without diabetes. Those with undiagnosed and diagnosed diabetes had steepest rates of decline even when adjusting for covariables ($P < 0.001$). Among those with diabetes, risk factors for steeper decline rates included systolic blood pressure (SBP) of 140 or higher, HbA1c of 7% or higher, being of Black ethnicity, and1,5-anhydroglucitol levels of <10 µg/ml. Strengths of this study include its massive sample size of 15,517 participants and its multiple locations across the U.S. It also spans the

1980s to 2010s and therefore precedes SGLT2 inhibitors and GLP1 antagonists. Weaknesses included the lack of other ethnicities (Hispanic, Asian, Arab, Indian, etc). They also only used baseline diagnosis and medication use data to determine category and variables. Warren et al. (2018) highlights the strong association of diabetes to the rate of disease progression. Providers may have the following question: what are modifiable risk factors in those with diabetes mellitus that are associated with lower renal functions?

Huang et al. (2020) sought to identify modifiable factors that were associated with decreased renal function using a seven-year observational cohort study. The research followed 320 patients at a multidisciplinary diabetes treatment center in Taiwan. Patients enrolled between January 2010 and December 2010 with diagnoses of both type II diabetes mellitus and CKD stage III. Participants were excluded who were under the age of 18, had a diagnosis of type I diabetes, acute renal injury, or severely elevated blood pressure over the last six months before the study enrollment. At reoccurring visits over the next seven years, data regarding blood pressure, cholesterol, LDL, HbA1c, and proteinuria were obtained. Study participants were also screened for diabetic retinopathy. Other variables explored included medication use, gender, length of time since diabetes diagnosis, BMI, and age. At the end of the seven years, 24.7% of patients had experienced a decline in their stage of renal disease and 5.4% had started dialysis. Factors positively associated with renal decline included female gender, lower eGFR at beginning of study, larger drop in eGFR over first two years of study, increased macroalbuminuria at onset, greater variability in SBP, proliferative diabetic retinopathy, and greater HbA1c variability. Greater HbA1c variability was ranked with a hazard score of 1.710 (95% CI, 1.033-2.832, $p = 0.019$). Factors associated with disease improvement were a higher eGFR at study's beginning, a smaller drop (or an increase) in eGFR over the first two years, less

glycemic variability, and SGLT2 inhibitor use. Strengths of this study include the seven years of follow-up and longer study period. Identifiable weaknesses are the lack of dietary information, exercise regime, and home blood-pressure information. This study does have a smaller sample size as only 96 patients experienced worsening renal function over the seven years. While it is impossible to draw causation from an observational study, it does reveal the possible importance of early glycemic control and the need to research GV in more depth. In addition to researching the risk factors for disease incidence and progression, understanding the risk factors for ESRD or the need for dialysis could help better position providers to help their patients with diabetes mellitus.

Risk factors for dialysis and end-stage renal disease

Kaewput et al. (2020) sought to identify risk factors associated with CKD decline and progression to stage V or dialysis necessity in patients with DM. Using a retrospective cohort design in Thailand, they identified 8,464 patients with type II DM who had utilized primary care services from Bangkok and university hospitals and clinics from January to December 2015 with eGFRs ranging from 15-59 ml/min/1.73m2. Patients were included in the study until they developed stage V renal disease, required dialysis, or until May 2018. Rates of renal decline were calculated and compared with a variety of factors including age, gender, duration of diabetes, HTN, dyslipidemia, CAD, CVA, smoking status, BMI, SBP, diastolic blood pressure, and baseline HbA1c among others. They found during an average follow-up period of 29 months, 4% of patients developed CKD stage V or required dialysis. They identified the following risk factors for CKD stage V and dialysis: increased duration of diabetes mellitus (HR 1.17 per 5-year increase, 95% CI, 10.1-1.35), increased SBP, albuminuria, and increased serum uric acid. While their multivariate analysis did identify increased baseline HbA1c as a risk factor

associated with a faster rate of annual eGFR decline (*p = 0.02)*, it was not as significant as other variables such as longer duration of type II diabetes mellitus (OR 1.20 per five year increase, 95% CI 1.07-1.33), as well as history of CAD, and increased SBP. Strengths of this study include its large sample size and the number of variables accounted for. Weaknesses include retrospective analysis, possible selection bias, and a predominantly female population (69.6% female), as well as inconsistencies across hospital labs' technology used to obtain creatine and urinary albumin values. Kaewput et al. (2020) demonstrates that HbA1c by itself may not be an adequate predictor of CKD progression and rate of decline. However, the number of years since a DM diagnosis is associated linearly with increased risk of not only ESRD and dialysis, but with a faster rate of renal decline. While Kaewput et al. did not find HbA1c to be a reliable predictor of CKD progression or decline, other researchers were also studying it.

Glycemic control and progression – HbA1c and CKD incidence & renal decline

Yasuno et al. (2020), demonstrated a significant relationship between diabetes and progression of CKD. Building on a hypothesis that higher HbA1c levels are associated with increased incidence and decline of CKD in their target population, they set out to study patients on Iki island, which has one of the highest rates of ESRD patients on dialysis in Japan. Using a retrospective cohort design to evaluate the records of The Iki Epidemiological Study of Atherosclerosis and CKD Project (ISSA-CKD), they evaluated 5,526 patients living in Iki City. Of the 5,526 patients, 953 had CKD at baseline. Inclusion criteria were patients undergoing annual health checkups in the city between 2008-2016. They excluded those who only came once or who didn't have their serum creatine checked. Dividing HbA1c into three categories (<7%, 7-9%, and >9%), they evaluated records for development or progression of CKD.

HbA1c had a linear association with the development and progression of CKD, even when other factors were controlled for (sex, age, presence of HTN, dyslipidemia, hyperuricemia, obesity, and smoking). Not only did those in the HbA1c of <7% category have the smallest risk of disease incidence, but they also had the smallest chance of progression even in the setting of a previous CKD diagnosis. The linear increase in risk of CKD with rising HbA1c was found across age categories regardless of diabetes diagnosis ($p = 0.553$). Some weaknesses of this study include its retrospective design, which makes it more prone to selection bias. Also, due to using one-time HbA1c measurements instead of trends over time, the study may not accurately trend blood sugar over a longer period. As a result, the association between HbA1c and CKD onset and progression could be even stronger than observed in the study. In conclusion, Yasuno et al. (2020) noted the significant association between high HbA1c levels and the risk of developing or progressing in CKD. This risk was consistent across multiple adult age categories. More studies are needed to trend multiple HbA1cs over time.

HbA1c Trajectories and impact on CKD progression

Low et al. (2019) studied HbA1cs over time to determine if HbA1c trajectories were associated with CKD progression. They utilized a prospective cohort design of 770 patients who attended a diabetes center at a Singapore hospital. The majority (58.5%) of their sample was male and over 50 years of age (70.6%). They included patients with at least two eGFR readings and three HbA1c levels, and a baseline eGFR of at least 15 mL/min per 1.75 m^2. They obtained data from 2002-2017 including additional variables such as HbA1c, BMI, duration of DM, tobacco use, SBP, low-density lipoprotein-cholesterol (LDL-C), urinary albumin creatine ratio (ACR), and medication use. They excluded those under the age 21; pregnant women; those with infections, cancer, or autoimmune diseases; and those with other causes of renal disease. HbA1c

linear trajectories were divided into four groups: stable, moderate stable, moderate-increasing, and high-decreasing. They measured for a primary outcome of CKD progression (a drop to a lower stage of renal disease along with a 25% or greater drop in eGFR). They found that 35.6% of their sample experienced renal decline over the course of their study. The near-optimal group had decreased risk of CKD compared with the other groups even when other variables were accounted for. The moderate-stable and moderate-increasing groups were found to be at an increased risk of renal decline. The high-decreasing group wasn't statistically significant after accounting for all variables, which may provide some hope for those working to improve their glycemic control—they may still have some ability to improve renal outcomes. Overall, Low et al. (2019) demonstrated that ideal stable glycemic control is associated with a lower risk of renal decline among patients with DM. Strengths of this study were that it assessed HbA1c trajectory independent of HbA1c baseline levels, providing additional light on the complete relationship between glycemic control over time and CKD. Weaknesses included the small sample size and the short duration of the study (average of 4.6 years per patient). While elevated or rising HbA1c is associated with renal decline, questions remain about HbA1c levels and mortality rates.

HbA1c level and risk of ESRD or death

Navaneethan et al. (2016) aimed to establish the association between HbA1c and ESRD and death in populations with both DM and CKD. They used a retrospective cohort design using data from an EMR-based CKD registry, mortality data from the Ohio Department of Health Mortality Files, and rates of ESRD from the US renal data system. Identifying 6,165 Ohio residents with diabetes who were on insulin or oral medication and also had CKD, they excluded those under 18 and those with ESRD (defined in their study as those requiring dialysis or who had received renal transplant). They then compared HbA1c (both as a category and as a

continuous variable) with mortality (both all-cause and cause-specific) and the development of ESRD requiring dialysis or continuous renal replacement therapy (CRRT). Over an average follow-up time of 2.3 years, 957 patients died and 205 were diagnosed with ESRD. There was a significant difference in incidence of ESRD across HbA1c levels ($p < 0.001$), even when accounting for 17 other factors including CKD stage, age, race, medications, smoking status, and BMI. HbA1c levels were independently associated with pre-ESRD mortality, but not linearly. Low HbA1cs (<6%) and high levels (>9%) were associated with a higher risk of mortality (compared with 6% to 6.9%). Twenty percent of deaths were related directly to diabetes with that percentage rising to 20% among those with HbA1c higher than nine. This research had two notable limitations: the retrospective design and the inconsistent periods spanning patient data (averaging 2.3 years). However, it did uniquely utilize the Ohio data for deaths allowing for more accurate mortality follow-up than other studies. While it supported this author's hypothesis that higher HbA1c levels are associated with worsening CKD and worse outcomes, it does not support the opposite. Lower HbA1cs were also associated with increased risk of death. These findings raise the concern that lower HbA1c levels may possibly be associated with a higher risk of death. Additional research such as tracking GV in relationship to all-cause death and closer monitoring for hypoglycemia in studies could further identify causes of this.

Intensive glycemic control – impact on renal outcomes

Mottl et al. (2018) worked to continue on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to see if participants monitored, for an extended period after the original trial, ended continued with same trends and associations with poor renal outcomes (measured as composite: albuminuria, a doubling in serum creatine, the need for dialysis, death, or a combination.) With consent from 8,601 willing participants of the original 10,139 from

across the United States and Canada from the ACCORD trial, they continued observation of those who participated in original interventions (tighter glycemic control, adding fenofibrate to simvastatin, and SBP control down to under 120 mmHg in patients with type II diabetes.) The original prospective trial included patients with type II diabetes diagnosis, a HbA1c of 7.5% or higher, and those age 40-79 if they had a history of cardiovascular disease. Patients ages 55 to 79 years old if they had atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two other risk factors for cardiovascular diseases (such as hypertension, obesity, or smoker). Those with BMI > 45 kg/m^2 and or creatine over 1.5 mg/dl were excluded. Participants were followed for an average of 7.7 years after the original study. One third reached the primary renal outcome. More intensive BP control was associated with a higher risk for composite renal outcomes (HR, 1.16, 95% CI, 1.05-1.23). Of note, a one hundred percent increase in serum creatine was the only renal outcome reached of the composite outcomes. Fenofibrate was more likely to be associated with a one hundred percent increase in serum creatine when compared to placebo (HR 2.0, 95% CI, 1.61-2.49). While during active treatment, the intensive glycemic control and normal glycemic groups had no difference in incidence of composite renal outcomes, but in the follow-up the negative renal outcomes were reduced in the intervention group (HR, 0.83, 95% CI, 0.71-0.97). Overall, it was determined in follow-up that possible renal harm could result from intense BP control or adding fibrate use to statin use. Additional research would be ideal to see if diet and exercise-improved BP came at the same risk of creatine doubling. Also, would repeating the glycemic study over a longer period result in the same outcomes?

HbA1c, while an effect tool for presenting a three-month average of glucose levels, has some limitations. It does not communicate if a patient's glucose control has been stable. GV can hide under an HbA1c. It is important to consider that while two patients in a study could have the

exact same HbA1c, they could have vastly different glycemic patterns during the day or night. GV is an important variable when considering the impact of glycemic levels and control on renal disease and decline.

Fasting blood glucose and disease progression

Jung (2021) compared average fasting blood glucose levels with renal outcomes in a retrospective cohort study from a national sample of 183,049 patients in Korea, of which 64,861 were on glucose-lower medications. It was hypothesized that lower average fasting glucoses could result in a slowing of renal disease. Renal outcomes were measured as a composite: doubling of serum creatine, ESRD, or death from CKD for primary composite outcomes. Secondary outcomes included the primary outcomes plus new-onset albuminuria, major cardiovascular events, and all-cause mortality. Patients were included if they were ages 40-70, and had participated in the national health screening survey between 2009-2010, if they had tested positive for albuminuria at least twice during the same window of time, and if they had diabetes mellitus (defined as fasting blood glucose of 126 or more or on prescription medication for diabetes) in the medication group – if on medication at least three months out of the year. Participants with a history of heart disease or stroke were excluded as well as those who passed away, developed coronary artery disease or cancer prior to obtaining baseline data for study. Patients had medical exams every other year with fasting blood glucose levels drawn after at least eight hours of fasting. For results, participants were divided into eight groups by average fasting glucose levels. Hazard ratios and Cox model with time-varying covariates was used for statistical analysis as well as spline regression analysis. Other variables explored included age, sex, albuminuria, antihypertensive medications, time of diabetes medication initiation, statin use,

family history of vascular disease, smoking history, alcohol consumption, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol level, income, and BMI. Over nine years of follow-up, 15.4% of those with albuminuria experienced a major renal composite outcome. The average glucose levels being treated for diabetes mellitus had a J-shaped Hazard ratio for the composite outcomes with risk of outcomes the lowest at glucose levels of 110-159 mg/dL. In the albuminuria population, the fasting glucose levels of 126-139 and 140-159 mg/dL were associated with decreased risk of composite outcomes. Glucose levels of 160-179 mg/dL were associated with increased risk compared to 110-125 mg/dL. Among patients with a decrease already in eGFR, glucose levels of 80-99 and 160-79 mg/dL were associated with increased risk of primary outcomes compared to 110-125 mg/dL. These findings could perhaps indicate that the ideal glucose levels for a patient with renal disease may be slightly higher than the levels needed to prevent the renal disease in the first place.

All-cause mortality was also evaluated, and levels of 160-179 mg/dL were associated with increased risk of mortality (compared to levels of 110-126 mg/dL) among those with albuminuria while 140-159 mg/dL were associated with increased risk among those with decreased eGFR. Untreated hyperglycemia was noted to have a linear association with composite renal outcomes while treated diabetes glucose levels had more of a J-shaped hazard ratio. Strengths of this study included its long-term outcomes, the large number of participants, and that it evaluated both eGFR and albuminuria. Weaknesses could include the lack of HbA1c data as fasting glucose levels alone won't provide the entire picture. Also data was only measured every two years for urine albumin and serum creatine which could miss key changes. Type I and II diabetics were not differentiated in this study. Study was also limited to those without cancer

of coronary artery disease which eliminates a key population of interest as patients with diabetes are at higher risk of cardiovascular disease.

Overall, one benefit of this study was the use of fasting blood glucose which shows a different part of the picture of glycemic control than HbA1c. While HbA1c considers the high spikes and impact of dietary intake during the day averaged over three months, fasting blood glucose shows more the pre-prandial levels and the long-acting insulin needs of each patient.

Glycemic variability – impact on eGFR decline

Low et al. (2017) investigated the possible impact of GV on the decline of eGFR in patients with type 2 diabetes mellitus. Utilizing a retrospective design, they utilized data from 1,628 qualifying patients at the Diabetes Centre at Khoo Teck Puat Hospital in Singapore between 2002-2014. They included those with a diagnosis of type II diabetes. They excluded anyone who didn't have at least two years of follow up or who was pregnant, under 21 years of age, or had a diagnosis of cancer, autoimmune disease, urinary tract infection, polycystic renal disease, hematuria, or glomerulonephritis. HbA1c was used both as an average for each patient and as a coefficient of variation. Over an average of 5.5 years of follow-up, 28.7% patients experienced renal decline. Risk factors associated with increased renal decline included: longer duration of diabetes mellitus, older age, higher SBP, LDL-C. Increased average GV (measured as mean coefficient of variation) was significantly higher in those with eGFR decline than those without (13% vs 9.6%, $p < 0.001$). Increased GV was positively associated with female gender, increased years since diabetes type II diagnosis, poor glycemic control at early visits, albuminuria, and using an renin-angiotensin system inhibitor ($p < 0.05$ for all). Increased GV was associated with increased risk of renal decline even after adjusting for average HbA1c. There were no significant connections noted between average HbA1c and eGFR decline (*p*

>0.05). Strengths of this study included not only the vast range of eGFRs within the population but also the large cohort size and ethnic diversity. Weaknesses of Low et al. (2017)'s research could include the lack of consistent time intervals between HbA1c measurements as well as the possibility that the renal disease may have caused the symptoms/other problems. Could the renal disease have impacted the glycemic variability? Could the duration of diabetes have caused decline? Future research with a prospective study with regular HbA1c intervals and measurements of daily GV (as opposed to comparing HbA1c) might shed more light.

Glycemic variability – impact on all-cause mortality in patients with ESRD on dialysis

Glycemic variability was later pursued by Shi, Liu, Yu, & Han (2020). They sought to compare glycemic irregularity and all-cause mortality in diabetic patients on hemodialysis. While previous studies tracked HbA1c, Shi, Liu, Yu, & Han realized that though multiple patients could have the same HbA1C, they might have glycemic variability. Perhaps it might better explain adverse outcomes than HbA1C levels alone. They recruited 1,230 patients ages 18-80 on dialysis for more than three months, who had maintained a steady hemoglobin level for the past three months. Participants used a GlucoDay device to measure GV five times a day. They also charted exercise, time of meals, and medication scheduling for an average of 2.4 years. They found that the group with the highest coefficient of variation (CV) also had the highest rates of death. The highest CV group quarter was associated significantly with the highest risk of all-cause mortality (HR 1.934, 95% CI 2.448-3.583, $p < 0.001$). This was despite controlling for age, sex, tobacco used, cardiovascular disease, medications, hypoglycemia, and other lab work differences. They suspected that the association between high levels of GV and increased risk of overall mortality could be due to hypoglycemia or possibly due to previous research that a high GV results in more oxidative stress than in sustained high blood glucose levels alone.

Regardless, the detailed tracking of glycemic levels in this study gives strength. Weaknesses included possible selection bias (patients all recruited from the same HD center.) The study is also observational. There was limited data on diabetes medications – which may have played a part in glycemic variability. Repeating this study in a population with diabetes, but without previous diagnosis of CKD and trending over time, while tracking medications more carefully could aid in building a stronger understanding of the impact of GV in preventing the onset of chronic kidney disease. Does decreased variability in glucose levels provide equal benefit compared with having a low HbA1c level? More research is needed.

Incidence and causes of glycemic variability in ESRD patients.

Yusof Khan et al. (2021) hypothesized that greater amounts of GV would be found in patients with DM on dialysis when compared with non-diabetic patients on dialysis. Researchers studied 150 patients undergoing hemodialysis (93 with DM and 57 without) across five dialysis centers in Malaysia. Inclusion criteria included patients on dialysis over 18 years of age with relatively constant hemoglobin levels over the past three months and no recent medication adjustments. All patients were on morning dialysis shifts to have a consistent glucose sampling time. Exclusion criteria included type I diabetics, patients with hospitalization in past three months, blood loss, cancer, inflammatory state, or hemoglobinopathy. Patients self-monitored and reported blood glucoses from home in addition to the following measurements on dialysis days: fasting levels, pre-dialysis, each hour during dialysis. At home, patients measured fasting, pre-prandial and post-prandial measurements for all three daily meals. Patients were encouraged to eat their normal intake of food and document each meal. Researchers chose standard deviation (SD) and percentage of coefficient (% CV) to measure GV. The chi-squared test and independent-sample *t* test were used for univariate analysis. Average HbA1c in the diabetic

population was 7.4%. The patients with DM showed higher levels of GV. Risk factors for increased GV noted were presence of diabetes, older age. HbA1c, ferritin, LDL, and triglyceride levels were associated with higher levels of GV as well. Interestingly, there was no association between the types of medications patients were on and their GV levels. Twelve percent of study participants without DM were noted to have more GV than target rates. Thirty-three percent of those with DM were found to have GV above recommended rates. Researchers also noted that dialysis patients were at higher risk for hypoglycemia due to glucose-free dialysate which is used in Malaysia. HbA1c between eight and ten percent was associated with increased GV among study participants. Limitations of this study include that it used self-monitoring of glucose levels instead of continuous monitoring. It also did not regular dietary intake of patients to show patterns after normal patient dietary choices. Researchers recommended regular glucose monitoring in patients on dialysis especially those with DM, of older age, with elevated lipids, or HbA1c.

Additional research found explores glucose levels and outcomes outside chronic kidney disease or decline. Outcomes studied include risk of acute kidney injury, contrast-induced nephropathy, or even longevity of renal transplant survival. These can provide additional light on the possible pros and cons of glucose control.

Glycemic control and risk of acute kidney injury

Xu et al. (2020) conducted an observational study of a U.S. and Sweden-based cohorts seeking to establish the tie between glycemic control and risk of acute kidney injury. They hypothesized that increased HbA1c was associated with increased risk of acute kidney injury. They used data from 22,877 U.S.-based patients in mostly rural Pennsylvania that utilized Geisinger health care system and 12,157 patients who used Stockholm health care system. They

included those over 18 years old, with diagnosis of type 2 diabetes, and a diagnosis of CKD stage III through V. They excluded patients who were missing information such as age, gender, or if on dialysis. They excluded health care visits that involved diuretics or heart failure admissions. Interestingly, at baseline, the U.S. cohort had higher average HbA1cs and lower use of insulin than the Swedish cohort. HgA1c baselines and time-dependent HbA1cs were compared to outcomes (measured as acute renal injury – a creatine elevation of 0.3 mg/dl or more over seven days for any reason, onset of dialysis, or mortality). Other variables explored included age, gender, lab results, medications, and race (only included in U.S. cohort as illegal to gather in Sweden). Over an average of 3.1 years of follow up (U.S) and 2.3 years (Sweden), they found that when compared to HbA1c of 6%-6.9%, higher HbA1cs were associated with increased risk of AKI. In the U. S. group, HbA1c at or over 9% was associated with 29% higher risk of AKI (HR 1.29, 95% CI, 1.18-1.41). In the Swedish group, low and high HbA1c levels were associated with an increased risk of AKI. Using categorical analysis, HbA1c over 9% was associated significantly with increased risk of AKI. Both higher and lower HbA1c groups were associated with increased risk of death. Baseline of 9% or higher positively associated with increased risk of death in both cohorts. Benefits of this trial include its large sample size and using participants from two countries with two different health care systems. Weaknesses include missing information and inconsistent time frames between rechecked HbA1cs.

HbA1c and post-coronary arteriogram renal complications

Zhang et al. (2021) also investigated the relationship between pre-procedure HbA1c and post procedure renal complications, specifically among patients with diabetes. Researchers sought to discover if HbA1c levels pre procedure are associated with incidence of contrast-induced nephropathy (CIN) post coronary arteriogram with or without percutaneous intervention.

In this prospective trial, 670 patients undergoing coronary arteriogram were monitored at the 24 and 72-hour marks post procedure for rising serum creatine. Pre procedure, baseline serum creatine and HbA1c levels were obtained, and participants received 12 hours of IV hydration, aspirin, and clopidogrel. Those excluded included those with ST-elevated myocardial infarction, recipients of contrast dye in the past two weeks beforehand, and those with decreased left ventricular ejection fraction (LVEF), malignancy, infection, fever, hypotension, or other conditions that affect HbA1c (pregnancy, uremia, blood transfusions, hemolytic anemia, and hemoglobinopathy). Contrast-induced nephropathy was defined as a 25% increase in serum creatine. Patients were divided by HbA1c into five groups. Even when accounting for other variables, they found that higher HbA1c was still positively associated with increased risk of CIN and that specifically, it was a significant association between HbA1c of 9.5-11% and >11% and incidence of CIN ($p < 0.0001$). There was no significant association between those with HbA1c under 9.5% and CIN incidence.

Strengths of this study included the prospective design and the consistent timeframe of measurements taken both pre and post procedure, as well as consistency of pre-op preparation, intravenous hydration and medications. Weaknesses include the many exclusions that include common cardiac disease co-morbidities such as decreased LVEF (45% and below). Authors also recognized the limits of using HgA1c to measure glycemic control as it cannot measure day to day variability or sudden changes in glycemic control. Further research repeating this study and involving those with lower LVEF and other exclusion groups might prove beneficial.

Donor HbA1c and renal transplant survival rates

Bendersky et al (2019) explored if elevated donor HbA1c affected renal transplant survival rates using a sample of 1,518 transplants studied from the Network for Organ

Sharing/Organ Procurement and Organ Transplant Network's standard transplant analysis Research (STAR file). This study included transplants from 2018 donors with diabetes. It excluded transplants with missing donor HbA1c levels and with missing survival timeframes.

By dividing donor HbA1c levels into less than 6.5% and equal to or greater than 6.5%, they compared the survival times of their renal grafts. They explored variables such as donor age, ethnicity, BMI, and medical history. They also sought to account for other variables such as recipient age, sex, ethnicity, medical conditions, presence of diabetes, and time spent waiting on transplant list. The 1-year survival rate for grafts was 92.9% for those from donors with HbA1c <6.5 but 89.7% for those at or above 6.5 percent. Increasing linear risk of transplant failure over one year was also noted in rising HbA1c levels up to ten percent. The study had few donors with HbA1c levels over ten percent.

While strengthened by its large sample size, concerning weaknesses remain. Some grafts were excluded from study as donor HbA1c wasn't always available. Additionally, levels were not always measured the same amount of time from grafting. While not directly comparing HbA1c with CKD progression, monitoring the association between donor HbA1c and renal graft survival could lead to valuable insights on the impact of HbA1c on renal disease. Authors purposed matching higher HbA1c donors with recipients with lower estimated survival rates. Future research could include lengthening the study to see if the linear trend is true over more than a year. Also it would be ideal if researchers could monitor HbA1c over an extended time prior to renal transplant donation. This is often impossible to obtain in post-mortem donors but could perhaps be possible in living donors. Additional research would be needed.

Importance of multidisciplinary care in patients with diabetes mellitus and CKD

Low et al. (2019) studied the outcomes of patients with diabetes mellitus and CKD stages III through IV who utilized multidisciplinary care compared with those who only see endocrinologists. They hypothesized that a multidisciplinary care approach could improve renal outcomes in patients with diabetes mellitus. Using a nested case-control prospective trial design, they enlisted 837 patients (67.3% Chinese, 26.7% Malay) and divided them into two groups – one which utilized regular joint nephrology and endocrinologist care, including access to a pharmacist, social worker, dietician, and advance practice nurse (APN), and the other which utilized only endocrine care between November 2001 and March 2016. Exclusions helped eliminate those with CKD stage V, cancer, a short life expectancy, or the inability to change lifestyle factors due to psychosocial or financial reasons or difficulty. Goals of care in the intervention group included obtaining an HbA1c of 6.5-8% depending on age and comorbidities, SBP of 130 or less, LDL-C levels of under 2.6 mmol/L, and avoiding complications (such as electrolyte imbalances, hypoglycemia, etc.), and technology available to participants in the intervention group included ambulatory BP monitoring and continuous glucose monitoring. Over an average of three years of follow up, 240 patients declined to stage V renal disease (28.7% of intervention group compared with 45.8% of the control group). Additionally, the intervention group experienced a significant reduction in HbA1c from initial levels (P <0.001). The Cox regression model demonstrated 45% lower hazard ratio of decline to CKD stage 5 among intervention group than in the control group (P = 0.004) even after adjusting for the many variables explored. Risk factors identified for CKD progression to stage V included: elevated LDL-C, CKD stages III to IV, increasing ACR, and HbA1c CV tertile 3. Strengths included the control group and prospective design. Weaknesses include that those with financial difficulty

were not included, sampling times varied between two groups, and the possibility of errors in eGFR calculation.

Jiamjariyapon et al. (2017) worked to evaluate the impact of a multidisciplinary team on CKD outcomes in the rural regions of Thailand. They hypothesized that implantation of a multidisciplinary team including village health volunteers could slow the progression of CKD among local villagers. They used a randomized controlled trial with cluster groupings. They enlisted 442 participants with CKD stages III or IV from two districts of the Kamphang Phet province in western Thailand. They excluded those with severe cardiovascular disease, obstructions of the kidneys or urethras, HIV, pregnancy, cancer, red blood cells or white blood cells in the urine, or urine protein creatinine ratios of over 3.5 g/g (nephrotic range). These 442 patients were divided into two groups: a control group and an intervention cohort. The intervention group received visits from a multidisciplinary team of nurses, pharmacists, a nutritionist, physical therapist, and both paid and volunteer community health workers. These teams provided educational programing including appropriate CKD diet and medication information, as well as visiting patients in their homes. These visits were scheduled six to eight weeks after each hospital encounter and included monitoring medication compliance, assisting with blood pressure monitoring, and promoting regular exercise. The control group received standard clinical care and medication prescriptions as well as group education at the hospital during visits. The control group did not receive visits from the multidisciplinary group. Patients from both groups were seen initially and then every three months for two years. Of note, 98.6% of the control group and 92% of the intervention group had an educational background of elementary school or lower. Results tracked were eGFR over time calculated using a creatine-based CKD EPI equation and other lab work including HbA1c and 24-hour urine and normalized

Protein Nitrogen Appearance (nPNA) as well as serum bicarbonate, and LDL. medications used to treat patient's diabetes, hypertension, and for coronary artery disease were also taken into consideration. After an average of 24 months of follow up, researchers found a mean difference in eGFR among the intervention group was 2.74 ml/min/1.13m^2 lower than in the control group (95% CI 0.60 – 4.50, $p = 0.009$). The average rate of eGFR progression per year was 2.0 ml/mi/1.73 m^2 in the control and 0.09 ml/min/1.73 m^2 per year in the intervention group. Interestingly, the intervention group also experienced improved serum bicarbonate, 24-hours urine nPNA, 24-hour urine sodium, HbA1c, and triglyceride levels compared with the control group. There were no significant differences in SBP between groups.

Strengths of this study included the multi-disciplinary approach, utilization of community resources, especially in Thailand where there is approximately one nephrologist for every 15,000 CKD patients (Jiamjariyapon et al, 2017). Weaknesses included that a cluster randomized trial was used instead of a double-blinded randomized control trial. Also, differences in baseline values across groups could affect decline. Also, measurements were averaged over time, when more frequent lab work may have been more accurate. Ultimately Jiamjariyapon et al. (2017) demonstrated that a multi-disciplinary and community approach could slow renal disease more notably than hospital and clinic programs alone. This is especially true in areas such as rural Thailand without adequate access to specialty providers. Providers in rural regions need to consider the positive impact multi-disciplinary and community teams can make for CKD patients.

Another study from Thailand by Cha'on et al. (2020) sought to follow the establishment of a quality improvement project named Chronic Kidney Disease Prevention in Northeast Thailand (CKDNET). Goals included surveillance, screening, diagnosis, and treatment. This

program was designed to identify risk factors for kidney disease, measure the burden of CKD in northeast Thailand, and come up with a cost-effect care model. The six strategies of CKDNET include establishment of a registry of patients with CKD in Thailand, development of CKD models, provide patients access to CKD care, improve patient compliance, monitor for cost-effectiveness, and community prevention. The screening program was initiated in 2017 and soon spread from its initial sub district to across the province. Participants were included if local, over eighteen years old, without fever, and if they hadn't experienced amputation or weight loss (10% or more) in the past 12 weeks. These participants were screened using fasting blood samples, urine collection to measure albumin/creatinine ratios, and renal ultrasounds to rule out structural abnormalities. Along with screenings, community CKD prevention programs were developed to promote education on sodium intake reduction. Apps for increasing water intake "H2O for life" and CKD app Kidney Khon Kaen named after the region which allows guided management for patients and education while tracking participants. Education programs were introduced into the school systems by teachers to reach students. Education was also provided by team members to primary health care providers to remind them to screen those at high risk for CKD (elderly patients or those with DM or HTN). Compliance programs were run by case managers and nurse trainings were implemented to help them become case managers to give more informed care to those with CKD.

The results of the screening program were astonishing. An astonishing twenty-five percent of 2,000 region participants screened were identified to have CKD. Diabetes and hypertension were found to be the largest regional risk factors for disease. Widespread CKD awareness campaigns were used in areas with higher levels of literacy. A salt-reduction campaign was effective to reduce the salt content in 8.7% of university eateries. The CKDNET

care model when compared to the conventional care model in Thailand was found to be not only cost effective, but also effective to slow down the progression of CKD to ESRD in one in four patients. Limitations of this program included that the region had a higher level of CKD which could limit cost-effectiveness if applied to other regions with less incidence of CKD. Also the CKD registry developed does depend on hospital data which doesn't fully include all community data. Ultimately Cha'on et al. (2020) followed the development of a multi-goal program that demonstrated ability to slow down progression of renal disease in a high-risk area through screening, surveillance, and comprehensive care. While application of findings to a United States population might look slightly different, this program does demonstrate the impact of early screening, close surveillance, and community health interventions including promotions for patient education and screening websites and apps. Providers working in high-risk rural populations with limited access to specialty care should consider benefits of community health interventions to slow the progression of renal disease.

Importance of wholistic care in patients with diabetes mellitus

Michishita et al. (2017) sought to determine the combined effect of glycemic control and regular exercise on rates of CKD development in middle-aged and older men. Using a retrospective design, they recruited 303 males in Japan who had been part of a previous study. Surveys asked if they exercised at least two times per week for a minimum of 30 minutes of exercise and/or if they walked for at least an hour each day. This group excluded any with history of cardiovascular disease, strokes, renal disease, or dialysis. Initial bloodwork and medical records for was obtained for each, then they were monitored for six years. Participants were divided into four groups: reported regular exercise with high glucose levels, low levels of exercise with high glucose levels, regular exercise with normal glucose tolerance (NGT), and

those with low levels of exercise with NGT. After six years, CKD was noted in 32 men (10.6% of study participants). The percentage of those who exercised were significant lower in the CKD group than those in the non-CKD group ($p < 0.05$). CKD developed at the highest rate among those who had poor glucose tolerance and exercised irregularly compared with those in the other three groups including those who did exercise regularly with hyperglycemia (log-rank test: $p = 0.004$). Even when adjusting for other variables such as age, BMI, medications, smoking, and alcohol consumption, hyperglycemic group was associated with increased risk of CKD (HR = 5.89, 95% CI = 1.87-16.63, $p = 0.003$). This highlights the positive combined impact that regular exercise and good glycemic control can have on decreasing incidence of CKD in the male population. Weaknesses include the limited population who may be at increased risk for CKD to start with, no females included, and it excluded those with many diseases who may better reflect the general population. Strengths included the longer follow-up period of 6 years. While the importance of regular exercise and tight glycemic control are clear, more questions remain regarding application to the general population.

Summary of Literature

SECTION 3: Discussion and Synthesis

Identifying patients at risk for CKD is an important part of primary care and can help increase screenings in appropriate populations. Burrows et al. (2020) identified diabetes and hypertension as well as age over 50 as risk factors for renal disease development and progression. Sui et al. (2020) went into more detail and noted chronic glomerulonephritis as the most common cause of early-stage disease but only 5.6% of ESRD cases. Hypertension and diabetic nephropathy were identified as the most common causes of late and end stage renal disease. These findings agree with Center for Disease Control's (CDC) noted risk factors of diabetes and high blood pressure. Though CDC also identifies heart disease, family history of CKD, and obesity as notable risk factors with diabetes and hypertension being the two areas of greatest prevention focus.

When a population at-risk is identified, screening is implemented and identifies those with CKD. Once identified, a provider's focus turns to goals of slowing renal decline and progression of renal disease. Warren et al. (2018) sough to identify who was at highest risk for renal decline by monitoring eGFR in those with pre-diabetes, diabetes, and without it. Warren et al. (2018) identified pre-diabetes and diabetes as risk factors for renal decline as well as steepest rates of decline among those with systolic blood pressures of 140 mm Hg or higher, HbA1c of 7% or higher, non-White ethnicity, and 1,5-anhydroglucitol of under ten. Huang et al. (2020) followed renal function in participants in Taiwan over seven years and identified the following factors as positively associated with renal decline: female gender, length of time since diabetes diagnosis, SBP variability, diabetic retinopathy, lower renal function at study's beginning, and

greater HbA1c variability. HbA1c variability is of increased interest as it is a modifiable risk factor (along with SBP variability).

Risk factors for progression to end stage renal disease and dialysis identified by Kaeput et al. (2020) in a Thai population had some overlap with risk factors identified by Warren et al. (2018) and Huang et al. (2020): increased duration of diabetes, elevated SBP, and increased baseline HbA1c. Two risk factors for ESRD in this Thai population that were not identified in other studies were albuminuria and increased serum uric acid. This is most likely because other studies were looking to identify factors for progression rather than for ESRD.

As a modifiable risk factor associated with incidence and progression of renal disease, diabetes mellitus and glucose levels (whether high or variable) deserves some attention. Intensive blood glucose control comes with an increased risk of hypoglycemia and providers need to know if the benefits in renal disease prevention are beneficial before exposing their patients to possible risks. Yasuno et al. (2020) demonstrated a significant link between diabetes and progression of CKD in Japanese patients. They identified a significant linear association between HbA1c and development and progression of CKD even when accounting for other risk factors. HbA1c does have some limitations. It is an average of approximately the last 3-months of glucose levels and does not reflect the day-to-day highs and lows a patient may be experiencing.

Low et al. (2019) studied HbA1c trajectories over time among primarily male patients with a majority over fifty years of age to see if there was a possible impact on CKD progression. They found that the moderate stable trajectories and moderate increasing trajectories were at increased risk for CKD. They concluded that stable glycemic control was associated with decreased risk of renal decline. Navaneethan et al. (2016) identified a significant association in

their U.S. population between low HbA1cs (<6%) and high HbA1c (>9%) and increased risk of mortality. They also observed a direct correlation between rising HbA1c levels and ESRD incidence.

Jung (2021) found that untreated hyperglycemia was noted to have a linear association with composite renal outcomes such as doubling of serum creatine, ESRD, or death from CKD while treated diabetes glucose levels had more of a J-shaped hazard ratio. This shows that over aggressive glucose control among those with diabetes mellitus comes with some increased risks as well.

Mottle et al. (2020) noted that over an average of 7.7 years, intensive glycemic control resulted in a reduced incidence of composite renal outcomes (presence of albuminuria, doubling in serum creatinine, need for dialysis, or death) while in contrast targeting SBP of under 120 mmHg was associated with increased incidence of composite renal outcomes.

Mottl et al. (2020) sought to break down the impact of GV in an ethnically diverse population in Singapore using HbA1c both as an average and as a coefficient of variation. They identified risk factors for renal decline as longer duration of diabetes mellitus, increasing age, elevated SBP, and higher LDL-C. They determined that increased variability was significantly higher in those with eGFR decline than those without. Yusof Khan et al. (2021) found the following risk factors for increased GV in patients with ESRD on dialysis: older age, DM, high HbA1c, elevated lipids, and abnormal ferritin and albumin levels.

Studies comparing HbA1c with renal outcomes are restricted by the limits of HbA1c itself. HbA1c is an average and not reflective of GV over time. Most of the research found was retrospective and often based on HbA1c. Shi, Liu, Yu, & Han (2020) however took a more prospective approach and utilized GlucoDay devices to measure GV five times a day monitoring

for all-cause mortality rates in patients with diabetes mellitus on dialysis. They found the group with the highest amount of GV was significantly associated with the highest risk of all-cause mortality of all groups.

While the focus is often on chronic renal disease, glycemic control has impacts on acute renal complications. Zhang et al. (2021) studied the relationship between pre-coronary arteriogram HbA1c and post-procedure rates of contrast induced nephropathy among patients with diabetes. Elevated pre-procedure HbA1c of 9.5-11% was positively associated with increased risk for contrast-induced nephropathy, indicating that glycemic control could have an impact on even acute renal conditions and decrease the kidney's abilities to process contrast dye without complication.

Bendersky et al. (2019) took research another step further hypothesizing that renal donor HbA1c would impact transplant failure rates in a recipient. Findings indicated that elevated donor HbA1c was directly correlated (up to HbA1c of 10%) with increased risk of transplant failure. Few donors with HbA1cs over 10% were candidates to donate.

Glycemic control should be a strong focus of primary care providers seeking to prevent and slow the progression of chronic renal disease in their diabetic population. Can multidisciplinary care make a difference for these patients at high risk? Low et al. (2019)'s prospective trial for patients with CKD stages 3 or 4 and diabetes mellitus showed that multidisciplinary care was associated with a significant decline in HbA1c from baseline as well as a lower risk of declining to CKD stage 5 compared with endocrine-only group. Jiamjariyapon et al. (2017) demonstrated that a multi-disciplinary approach companied with volunteer community teams could slow renal disease progression more notably than hospital and clinic programs alone. Cha'on et al. (2020) discussed a community health program that promoted CKD

screening, education of providers and nurses, and uncovered a region where population was at especially high risk for CLD. Through community education and enrollment in CKD surveillance and treatment programs, CKD progression was slowed in 25% of participants. Providers should consider community health and screening interventions to help aid in slowing progression of CKD.

Michishita et al. (2020) in Japan highlighted with a prospective trial that glycemic control and regular exercise in middle-age and older patients, primarily males, was associated with lower rates of chronic renal disease development compared with study participants exercising regularly but with hyperglycemia.

Providers are called to both prevent and treat disease and chronic renal disease is no exception. As studies demonstrate that tight glycemic control dose indeed decrease the risk of kidney disease onset and progression, providers have the responsibility to share with their patients the benefits of lifestyle and pharmaceutical interventions to prevent and slow disease progression. As research demonstrates the value of a multidisciplinary team approach, providers can encourage their patients to follow up on consults to endocrinology and nephrology when indicated. Glycemic control can indeed decrease incidence, delay progression, and help prevent sequelae of CKD in patients with diabetes mellitus. This merits a change in how primary care providers approach conversations surrounding CKD in their patients with diabetes. More emphasis on prevention should accompany the recommended yearly urine albumin to creatine ratio checks. If patients understand that they can be an active force for CKD prevention by focusing on glycemic control, they may work together with their providers to improve outcomes.

Implications for Advanced Nursing Practice

The advanced practice nurse (APN) is a prime candidate to work with patients to improve renal outcomes by improving glycemic control. Nearly one in three American adults visit an APN or physician assistant (PA) at least once a year, and nearly half of American patients with diabetes see an APN or PA for some part of their care (Jackson et al., 2018). APNs can provide effective care to their diabetic patients. One study of 368,481 patients with diabetes mellitus in the U.S. Department of Veterans Affairs (VA) health care system compared diabetes care outcomes (average HbA1c, SBP, and LDL-C) between those treated by physicians, Pas, and NPs. They found no clinically significant difference in diabetes outcomes or the control of those outcomes between patients treated by physician, NP, or PA primary care providers. This still held true when only evaluating medically complex patients including those on insulin or with poorer health status (Jackson et al., 2018). As effective members of the primary care team, APNs can make in impact in diabetes care that could potentially result in decreased CKD incidence and improved outcomes. This becomes increasingly relevant as the U.S. faces an increasing shortage of primary care and specialty providers.

The Association of American Medical Colleges has highlighted an estimated worsening shortage of physicians of between 37,800 and 124,000 providers by 2034 leaving gaps in both primary care and specialty care (AAMC, 2021). While the U.S. population is estimated to grow over 10% by then, population of those age sixty-five years old and above is estimated to grow over 42%. Physician specialties and providers that care for aging adults and diseases older adults are at higher risk because CKD may only continue to grow. The APN can make a difference by helping to provide quality care to patients who have or are at risk for chronic kidney disease both

in the primary care and in specialty settings such as endocrinology and nephrology. What helps an APN provide effective care according to patients?

A qualitative study by du Pon et al. (2019) of twenty patients with type II DM in the Netherlands undergoing treatment by practice nurses revealed factors that help patients to feel actively involved in their diabetes care. In the Netherlands, NPs are called Advanced Practice Nurses and have an MSN degree in advance practice. These practice nurses in the study were responsible for routine diabetes consultations, physical examinations, glucose checks, lab tests, and discussing results with patients. They also also discuss well-being, hypoglycemia or hyperglycemia issues, medication adherence, and offer lifestyle counseling with patients and thus provide care similar to a general practitioner. Four factors identified as helpful to encourage active participation in care for patients with diabetes were: building a trusting relationship with their nurse providers, having adequate time in their appointment, the chance to intentionally prepare for their visit, and having their spouse present during their appointment. While collected from a limited sample size, this can highlight some application to APNs looking to decrease CKD incidence and slow progression by encouraging better glycemic control. APNs can positively impact their patient's perception of their own active participation in their diabetes control by providing adequate time, allowing family or a significant other to attend when patient desires, and most of all building a trusting relationship and a safe place for questions.

This is in line with Nola Pender's Health Promotion Model (Pender, Murdaught, & Parsons, 2011). The APN can work together with his or her patient to help them see the benefit of improved glucose control including preventing the incidence of and slowing the progression of chronic kidney disease. These perceived benefits can encourage them to change behaviors and work closely with their APN to work together towards shared health goals.

Recommendations for Future Research

Missing gaps in research include the need for more prospective trials, increased utilization of continuous glucose monitoring, comparison of continuous readings and HbA1c, and studies on the impact of dietary interventions on incidence of and progression of CKD in patients with DM.

Prospective trials are often expensive as extensive testing is necessary to demonstrate impact on renal disease incidence and progression. However, they are necessary to show cause and effect. Retrospective studies can draw associations between glycemic control and hazard risks for CKD, but limits remain when trying to prove causation.

Continuous glucose monitors provide researchers with an accurate means to measure glucose levels and trends over time in patients with DM at risk for CKD. Shi et al. (2020) demonstrated with GlucoDay devices that GV was associated with increased mortality rates in patients with DM on dialysis. This technology could specifically be studied on those with DM without CKD and monitor regular glucose measurements to compare with HbA1 levels. These careful measurements could provide more data about who develops CKD or who with CKD experiences a decline. This could guide preventative efforts more accurately than average HbA1c alone.

HbA1c alone is not enough to provide a complete picture. By combining measurements from continuous blood glucose monitoring (fasting, pre-prandial, and post-prandial glucose levels) and HbA1cs, researchers could paint a full picture of the impact of glycemic control and variation on CKD. This research would be expensive but could prevent CKD and progression for an untold number of patients worldwide in the future.

This researcher's recommendations for future study would be a prospective cohort study comparing continuous glucose readings over two years in patients with DM to evaluate the relationship between daily glucose trends, average daily glucose levels, HbA1c, and fasting glucose levels with incidence of and progression of CKD. As such a study would be quite expensive to undertake, so funding might be solicited from CKD foundations or a company that makes continuous glucose monitors might be willing to donate monitors for the study. This study would also be consistent with Pender's Health Promotion Model as it would shed more light on patients' perceived benefits of action which can help bring about new changes (Pender, Murdaught, & Parsons, 2011).

Another gap in research is the lack of studies on American community health initiatives to decrease incidence and progression of CKD. Researchers and teams in Thailand (Cha'on, et al., 2020; Jiamjariyapon et al., 2017) promoted interventions in rural and small communities that may also benefit more urban communities in the United States. Future research could include following community health outcomes and enrolling volunteers to promote awareness of CKD and education for prevention.

Conclusion

There is a statistically significant association between poor glycemic control and the incidence of CKD as well as the rate of renal function decline in CKD. Improved glycemic control is one means to decrease the risk of renal disease, ESRD, and mortality. Tight glycemic control defined as a HbA1c less than 7% may be too restrictive for patients in late stages of CKD. Individualized goals are needed to avoid hypoglycemia and increased risk of death.

Primary care providers are well-positioned to screen at-risk patients for CKD and utilize their influence and education to share practical recommendations for increased glycemic control

with patients. A team approach could slow the wave of CKD falling upon an estimated 37 million Americans (Centers for Disease Control, 2021). Nurse practitioners are in a prime position to initiate CKD screening, surveillance, and interventions to slow renal decline.

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