The impact of glycemic load on estimated glomerular filtration rate (eGFR) among people living with HIV (PWH) stratified by diabetes status

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Abstract

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Objectives

We sought to estimate the longitudinal impact of glycemic load on kidney function among people with HIV (PWH) receiving primary HIV care, stratified by diabetes status.

Methods

We used clinical data from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS), a multi-site cohort of adult PWH receiving healthcare in the United States. Kidney function was measured using estimated glomerular filtration rate (eGFR). Glycemic load was defined as five-year average daily glucose and calculated using a Bayesian hierarchical model that incorporated fasting/resting blood glucose and hemoglobin A1C. We used linear mixed models with random intercepts (with each participant considered as a cluster), stratified by diabetes status, and adjusted for age, sex, and diabetes medication prescription to estimate associations between glycemic load and kidney function.

Results

Our sample included 29,058 unique participants (mean of 8.7 observations per person) with 2,494 participants going from not having to having diabetes over the course of the study. Among 43,569 observations with diabetes, we found that each 10 mg/dL increase in past five-year average daily blood glucose was associated with a 0.29 (95%CI: 0.23, 0.34) mL/min/1.73m^2 increase in eGFR after adjusting for age, sex, and diabetes medication. Among 209,564 observations without diabetes, average daily glucose was not associated with eGFR after adjusting for sex and age. Age was associated with a -1.33 and -1.01 mL/min/1.73m^2 yearly decline in eGFR for observations with and without diabetes, respectively.

Conclusions

Glycemic load does not appear particularly predictive for kidney function, regardless of diabetes status, after adjusting for age and sex. Differences in kidney function between PWH with and without diabetes may instead be driven by steeper yearly kidney decline in PWH with diabetes

Preface:

There is a well-established link between chronic kidney disease (CKD) and diabetes mellitus (both Type 1 and Type 2) with diabetes being the number one reported cause of CKD in the United States. (1) It is estimated that around 50% of individuals with Type 2 diabetes (T2D) suffer from CKD (2) and roughly 24% of all CKD cases in the United States can be attributed to diabetes after adjustment for demographic factors. (3) The primary mechanism through which diabetes leads to CKD is hyperglycemia (i.e. high blood sugar) (4) and consequently, even pre-diabetes or impaired fasting glucose has also been associated with a modest increase in the relative risk of incident CKD. (5) While hyperglycemia is considered the general primary cause of kidney damage in diabetes, the exact mechanism of diabetic kidney damage is complex and multifactorial. Hyperglycemia can promote the metabolization of excess glucose to sorbitol (6), which causes cellular osmosis stress and oxidative damage to the microvascular structures in the kidneys. (4) Hyperglycemia also leads to increased chronic inflammation, which can further damage the renal tissue. (4) Over time, all of these factors can lead to glomerulosclerosis (i.e., scarring in the glomeruli), which results in a decreased ability for nephrons in the kidneys to effectively filter blood.

CKD in PWH

PWH have a markedly higher prevalence of CKD compared to individuals without HIV. A large study of over 250,000 individuals from the Community Health Applied Research Network (CHARN), a US-wide cohort of 19 hospital and primary care clinics, estimated a CKD prevalence of 14.3% among PWH and 5.9% for people without HIV after adjusting for demographic differences between PWH and the general population. (7) Despite the higher

prevalence of CKD among PWH compared to the general population, there are limited studies examining the generalizability of traditional CKD risk factors (e.g., diabetes status, hypertension, older age, etc.) among PWH specifically. (8) Furthermore, there are unique HIV-related risk factors for CKD. HIV has been shown to infect the renal epithelial cells, resulting in the rapid onset of proteinuria and focal segmental glomerulosclerosis, a process known as HIV-associated nephropathy (HIVAN). (9) HIVAN is very uncommon in PWH on effective antiretroviral therapy (ART) and as a result, cases of HIVAN have declined substantially in recent years. The development of CKD can also be linked to nephrotoxic ART medications, (10) though the use of tenofovir disoproxil fumarate (TDF), a widely used nephrotoxic ART medication, has decreased due to new formulations of tenofovir such as tenofovir alafenamide (TAF), which has been found to be substantially less nephrotoxic. (11, 12)

Diabetes in PWH

Some studies have indicated an increased risk of developing T2D (13, 14) among PWH, while other studies showing no independent association of HIV infection alone after adjustment for possible confounding factors. (15, 16) Proposed mechanisms for an independent association between HIV infection and T2D include growth hormone deficiency and the development of insulin resistance. (17) The crude rate of T2D is also possibly higher among PWH because of ART medications, which has been suggested as an independent risk factor for the development of T2D. (18, 19) Specifically, protease inhibitors have been linked to insulin resistance and reduced insulin secretion, while nucleoside reverse transcriptase inhibitors have been linked to metabolic abnormalities, though these links have not been rigorously proven. (17)

Measurement of Kidney Function

Kidney function is most commonly determined using estimated glomerular filtration rate (eGFR), which can be calculated from serum creatinine laboratory values, sex and age using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation or other equations. Creatinine may be influenced by variables other than kidney function such as diet, level of muscle mass, and conditions such as cirrhosis. As a result, eGFR is potentially overestimated in patients with cachexia and potentially underestimated in patients with high muscle mass. (20) The gold standard of measuring glomerular filtration rate (GFR) is an injection of inulin followed by urine collection every thirty minutes for 3-4 hours. GFR can also be measured by recording the clearance of other exogenous filtration markers such as iohexol. The GFR value found by these tests is referred to as measured GFR (mGFR). While mGFR is more accurate than eGFR, particularly in the earlier stages of kidney damage, it is more common for eGFR to be used in both healthcare and research settings since obtaining mGFR is significantly more costly and time-consuming. (21) While there are several validated formulas for calculating eGFR, the two main formulas include the MDRD (Modification of Diet in Renal Disease) equation (22) and the newer CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. (23)

Several mathematical changes exist between the MDRD and CKD-EPI equations, but one of the key differences is the removal of Black race as a variable in the CKD-EPI equation, though age and sex remain in both equations. Age and sex are included in the equation to decrease measurement error from differing amounts of muscle mass, the primary non-kidney function related determinant of serum creatinine. By accounting for age and sex, the CKD-EPI equation isolates the effect of GFR on serum creatinine. (23) The CKD-EPI equation has been shown to be generally more reliable than the MDRD equation among PWH (24) and has been the

primary equation recommended by the Kidney Diseases Improving Global Outcomes (KDIGO) organization since 2012. (25)

In addition to creatinine, variations of the CKD-EPI equation have been developed to include cystatin-C, a protein that is also filtered by kidneys at a relatively constant rate. Though inclusion of both creatinine and cystatin-C have been shown to yield estimates with the least bias across different race/ethnicities (26), cystatin-C is not generally collected in primary care settings while routine creatinine measurement is part of routine care for PWH. (27)

Measurements of Glycemic Levels

Blood glucose level can have substantial variation throughout the day and is dependent on the timing of meals. Glycemic levels can also be measured by hemoglobin A1C (HbA1C), which interprets the amount of glycated hemoglobin available in the blood. Unlike blood glucose measurements, HbA1c has substantially less daily variability and is often considered an average of blood glucose levels over approximately three months. (28) While a fasting blood glucose of 126 mg/dL, random blood glucose of 200 mg/dL, *or* a HbA1c level of 6.5% or greater can all be diagnostic of T2D according to the American Diabetes Association, (29) HbA1c is currently considered the diagnostic gold standard. Techniques to measure HbA1c were widely standardized between 2000 to 2010, which increased its use and reliability. (30)

This study used a previously validated Bayesian hierarchical model from Crane et al. to calculate five-year average daily blood glucose. (31) A major benefit of this modeled average blood glucose is its ability to incorporate all available fasting blood glucose, random blood glucose, and HbA1c data for a patient into a single value. This is particularly important for this current study as participants often have a varied blend of available blood glucose and HbA1c

data due to the use of HbA1c increasing over the past 10 years. A drawback of Bayesian hierarchical models is that it can be computationally expensive to calculate for large data sets.

Glycemic Control and Kidney Function

It has been well-established that hyperglycemia (i.e., high blood glucose) among people with diabetes increases the risk of damage to multiple organ systems including the eyes, kidneys, nerves, and skin. Nevertheless, there is still debate on the benefits of standard glycemic control compared to intensive glycemic control. In intensive glycemic control, the common goal for HbA1C is 6.5% or lower, while in standard glycemic control the common goal for HbA1C is 8.5% or lower. (32) The benefit of intensive glycemic control for kidney outcomes is not fully understood. One meta-analysis found that while intensive glycemic control decreased the general risk of mortality from kidney failure, it did not significantly impact the progression to end-stage kidney disease in patients with more severe kidney damage. (33)

Nevertheless, prior literature does suggest an association between HbA1C levels and kidney function. A randomized controlled trial examining the impact of intensive glucose control in adult participants with T2D found that every 1% increase in HbA1C was associated with a 40% increased risk of a microvascular complication, which included new or worsening nephropathy or retinopathy. (34) A 2008 study from the Atherosclerosis Risk in Communities (ARIC) cohort showed that each 1% increase in HbA1C was associated with a 31% higher risk of CKD. (35) There is some evidence to suggest that poor glycemic control may also be an indicator for kidney damage progression for the people without diabetes. A longitudinal study in the Beijing Functional Community Cohort of adults without diabetes showed that the triglyceride-glucose index (TyG) was predictive of incident CKD over a median follow-up time

of almost four years. (36) Another large healthcare-based cohort study of >60,000 Japanese adults without diabetes or CKD at baseline receiving care at Aizawa Hospital Health Care Centre in Nagano, Japan found that each 1% increase of HbA1C was associated with 91% increase in risk of incident CKD, though there was no statistically significant association between fasting blood glucose and incident CKD. (37)

Age

In the general population, age is independently associated with a decline in eGFR of approximately 1 ml/min/1.73 m^2 per year even in healthy individuals. This has been attributed to a declining number of functioning nephrons and glomerulosclerosis caused by increased oxidative stress and inflammation as individuals age. (38, 39) Of note, the mechanisms underlying age-related kidney decline are thought to overlap with the mechanisms of hyperglycemia-related kidney decline. As a result, it can also be difficult to distinguish between normal aging changes and pathological changes in the kidney's structure. (40) Interestingly, human kidney biopsy and mouse studies have suggested that accelerated aging and cellular senescence are important mechanisms through which diabetic kidney damage occurs. (41, 42) In longitudinal epidemiologic studies of the general population, it has been shown that individuals with diabetes experience a steeper decline in kidney function over time, (43, 44, 45) with studies demonstrating differences in age-related decline in kidney function. In a cohort of people aged 20+ in Israel, participants with diabetes had an approximately a 0.15 ml/min/1.73 m^2 higher rate of yearly eGFR decline compared to participants without diabetes. (43) Other cohorts, including the ARIC cohort, which consists of randomly selected individuals aged 45-65 from the U.S. general population, (44) and a Canadian community-based cohort consisting of individuals older than 65 from the general population, (45) found that participants with diabetes had almost double

the rate of age-related kidney function decline compared to participants without diabetes. These significantly larger effect sizes compared to the Israeli cohort may be in part explained by the enrollment of older individuals in these two cohorts. Other factors that may accelerate the rate of age-related decline of kidney function include proteinuria, current smoking, and higher systolic blood pressure. (46)

Other Major Factors Impacting Kidney Function

After diabetes, the second leading cause of CKD in the US is uncontrolled hypertension, which can cause narrowing of blood vessels in the kidneys and lead to decreased blood flow. (47) This narrowing is caused by pathogenic changes in the renin–angiotensin–aldosterone system, which regulates blood volume in the body. Much like the pathogenesis of diabetic kidney disease, these processes lead to inflammation and oxidative stress, which can cause glomerulosclerosis over time. (48) There is a high degree of comorbidity between hypertension and T2D with up to 75% of individuals with diabetes also having hypertension (48). While it is not possible to conduct randomized controlled trials on this topic, sophisticated observational studies suggest that diabetes is a direct cause of hypertension. (49) Obesity is another significant contributor to CKD. While obesity is strongly linked to both hypertension and T2D, it has also been shown to be an independent risk factor for CKD. Obesity can cause inflammation through increased leptin secretion from fat tissue, which can also lead to glomerulosclerosis over time. (50)

Objective

Since there is limited literature investigating the generalizability of traditional CKD risk factors among PWH, the present study aims to examine the impact of glycemic control on kidney function among people living with HIV in care with stratification for diabetes status.

Manuscript

Introduction

The general relationship between diabetes and chronic kidney disease (CKD) has been well established with diabetes being one of the leading causes of CKD in the United States. (1) While the exact mechanism of kidney damage from diabetes is complex, it is believed that poor glycemic control can damage the renal microvascular structures over time and cause kidney inflammation and fibrosis. (51, 52) Furthermore, prior literature suggests that there is an association between pre-diabetes and chronic kidney disease even after controlling for traditional risk factors, though the association appears to be modest. (5)

The prevalence of CKD is markedly higher among PWH. Using data from Community Health Applied Research Network clinic locations that included both PWH and those without HIV, researchers found that PWH had significantly higher odds (adjusted odds ratio (OR): 4.75, 95% CI: 4.23-5.34) of a CKD diagnosis compared to people without HIV. (7) Despite the increased prevalence of CKD, there have been limited studies on the generalizability of CKD risk factors among PWH. Developing a better understanding of the factors that influence kidney function decline among PWH is essential as PWH are at risk for accelerated aging, leading to higher rates of age-related health problems, such as CKD, compared to age-matched individuals without HIV. (53) Furthermore, clinically significant kidney damage could possibly lead to a reduction in ART regimen options that are available for an individual. The primary objective of

this study is to analyze the effect of glycemic control on the rate of kidney decline in people living with HIV (PWH), stratified by diabetes status.

Methods

Study Population

This study utilized data from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort, a multi-site cohort of adult PWH in care in the United States. In total, 9 of 10 sites that had clinical data available at the time of analysis were included, including Case Western Reserve University, Fenway Institute/Harvard University, Johns Hopkins University, University of Alabama at Birmingham, University of North Carolina, University of California San Diego, University of California San Francisco, University of Washington, and Vanderbilt University. CNICS participants include PWH receiving primary HIV care from healthcare organizations affiliated with sites and at regular intervals. CNICS receives de-identified clinical (laboratory, diagnosis, and prescribing) data on PWH from participating healthcare facilities. (54)

All CNICS participants with at least one measure of creatinine collected from 2015 or later were included in the analysis. Participants from whom “Intersex” was listed as their birth sex (n=2) were excluded as the CKD-EPI Equation was validated only for individuals assigned as male or female at birth. Only creatinine data collected within the study period of January 2015 to March 2023 were included. Fasting blood glucose, resting (i.e. random) blood glucose, and HbA1C values collected before January 2015 were included if they were within an observation’s time-period of interest (the five years prior to the index date for a particular observation, see

detailed description of model below). CNICS sites received Institutional Review Board approval for the CNICS study protocol, which includes guidelines for the use of de-identified clinical data.

CNICS Operational Diabetes Definition

PWH were classified as having diabetes if at least one of the following three criteria were met: 1) a hemoglobin A1C (HbA1C) test result of 6.5% or greater at least once, 2) a prescription for diabetes-related medication (e.g., metformin, semaglutide) ***and*** a recorded diagnosis of diabetes, or 3) a prescription for diabetes-specific medication (e.g., insulin, sulfonylureas). As we used longitudinal data, some PWH transitioned from not having diabetes to having diabetes over the course of the study (see Figure 1). In our models, diagnosis of diabetes was treated as an absorbing state, therefore once classified as having diabetes, PWH were always considered to have diabetes.

Exposure and Outcome of Interest

The primary outcome of interest was estimated glomerular filtration rate (eGFR) in mL/min/1.73m^2, calculated using the 2021 CKD-EPI formula using creatinine, sex, and age. (55) While there are different formulas to calculate eGFR from creatinine, research has shown that the CKD-EPI formula is generally more accurate for PWH. (24) Since many participants had multiple creatinine values in a given year, and people with more severe CKD tended to have more measures annually, we randomly selected a maximum of two creatinine laboratory values per individual per calendar year by grouping together all creatinine values from a particular person in a particular calendar year and using the *slice_sample* function from the *dplyr* package in R, which relies on pseudo-random number generation, to select two random values. (56) All non-numeric creatinine laboratory values (e.g. not reported, “lab error”) were removed before selection, along with all values of zero. Therefore, participants could have zero (had no reported

creatinine data in a calendar year), one (had only one reported creatinine laboratory value), or two creatinine laboratory values per calendar year. By only selecting a maximum of two creatinine laboratory values per year, we minimized the impact of a cluster of outliers, such as individuals with transitory or acute kidney injury who are likely to have many reported creatinine laboratory values within a short time frame. While it is possible for an outlier to be selected for a particular individual, the impact of selecting an outlier is minimized across the entire sample. Each selected creatinine value constituted an observation, and the report date of selected creatinine value was considered the index date of that observation.

The primary exposure of interest was long-term glycemic burden, operationalized as five-year average daily glucose levels derived from a hierarchical Bayesian model previously described and validated by Crane et al. (31) This model incorporated all available fasting glucose, resting glucose, and HbA1C laboratory results for an individual for the five years preceding the sampling date for creatinine. Using the creatinine sampling date as an anchor for calculating five-year average glucose provided a notable advantage as it allowed for the integration of HbA1C and fasting/resting blood glucose data while also accounting for the greater variability of fasting/resting blood glucose values compared to HbA1C values. Furthermore, since the model used data from a relatively long timeframe, outliers in blood glucose are effectively “flattened”. This model relied on the premise that the average blood glucose for an individual on a particular day varies randomly around a personalized mean (that can change for a specific individual from one creatinine sampling time to the next). The model also included a subpopulation-level mean average daily blood glucose stratified by age and diabetes status.

This model combines the information about an individual's personalized distribution of average daily blood glucose with information from the population-level distribution for the individual's age and diabetes status by considering the sub-population level distribution as the statistical prior. The end result is that for individuals with less blood glucose-related data, the population-level distribution is weighted more heavily than the personalized distribution. In this way, the model allowed for more stable estimates for individuals with sparse data. This technique is referred to as borrowing strength and is commonly associated with hierarchical Bayesian models. (57)

Covariates

Our covariates of interest were sex, age, any diabetes medication prescription, race/ethnicity, and diabetes status. Weight was included only as a descriptive variable to characterize our cohort. While exact collection dates were available for laboratory results, only the birth year of participants was available, so age was approximated by assuming a birth date of June 30th for each participant and estimating age at the date of the visit or sample collection date. June 30th was chosen to reduce measurement error as it falls in the middle of the year. Weight data came from in-clinic measurements of weight during routine appointments. A participant was classified as "prescribed diabetes medication" from the start date of their first diabetes medication prescription (including both diabetes-specific and diabetes-related medication) and remains permanently classified as "taking diabetes medication" in the analysis.

Statistical Analysis

We used descriptive statistics (mean, median, IQR, percent) to summarize the baseline characteristics of our cohort and the characteristics of all observations contributed by participants. Observations were classified by the diabetes status of the individual at the time of

creatinine sample collection. To account for irregular follow-up across the cohort and nonindependence of multiple observations from the same participant, we utilized linear mixed models (LMM) with random intercepts, fixed slopes, and an exchangeable covariance structures with clustering by participant. (72) Our primary analysis was stratified by diabetes status at the time of sampling for the creatinine measure. Since participants could transition from being classified as not having diabetes to having diabetes, eGFR measures from creatinine taken at different times from the same participant may appear in both strata of our analysis. For each stratum, we conducted an unadjusted model with average five-year daily glucose as the only predictor of eGFR and a model that adjusted for birth sex and age centered at 40. For the stratum consisting of observations with diabetes, we completed an additional model that included birth sex, age centered at 40, and the prescription of any diabetes medication as covariates. The prescription of any diabetes medication was considered a binary variable with participants categorized as having been prescribed diabetes medication after the start date of their earliest available diabetes medication prescription.

To further test for an interaction between diabetes status and age, we conducted a sensitivity analysis that included all observations regardless of diabetes status and controlled for birth sex, age centered at 40, diabetes status at the time of creatinine sampling, five-year average daily glucose, and an interaction term between age and diabetes status. All observations have the associated birth year and birth sex of the participant, so there were no missing data. All analyses were conducted using R (version 4.2.2), with the LMM fitted using the *lme4* package. (60)

Results

Cohort Characteristics

In total there were 253,140 creatinine-derived eGFR observations from 29,058 unique participants with a mean follow up time of 4.56 (± (SD): 2.8) years. The mean age at baseline for all participants was 44.6 (± 12.3) and 18.4% (n = 5,356) of all participants were female. (See Table 1a) At baseline, 90.0% (N=26,154) of participants did not have diabetes, but over the course of the study period, 8.5% (N=2494) met our defined diabetes criteria for a total of 18.5% (5403) of participants classified as having diabetes by the end of the study period. PWH with diabetes at baseline had a similar number of follow-up observations (mean: 8.9 ± 4.4) compared to PWH without diabetes at baseline (mean: 7.0 ± 4.0).

Over the course of the study, approximately 17% of all eGFR observations came from participants classified as having diabetes at the time of creatinine sample collection. There was a total of 43,574 observations when PWH had diabetes and 209,612 when PWH did not have diabetes. The mean of the five-year average daily glucose for observations without diabetes was 95.1 (± 10.3), which was significantly lower than the mean for observations with diabetes (150.0 ± 49.2). The mean weight for observations without diabetes was slightly lower (81.0 ± 18.9) than the mean weight for observations with diabetes (91.1 ± 24.0). (See Table 1b)

Model Results

In the unadjusted model consisting of observations without diabetes, each increase of 10 mg/dL of average daily glucose was associated with a -1.59 (95% CI: -1.68, -1.50) mL/min/1.73m^2 decrease in eGFR. After adjusting for age (centered at 40) and sex, the association between average daily glucose and eGFR for this group was attenuated and became non-significant (0.01, 95% CI: -0.08, 0.09). For observations with diabetes, the unadjusted model showed that each increase of 10 mg/dL of average daily glucose was associated with a 0.08 (95% CI: 0.02, 0.13) increase in eGFR. After adjusting for sex and age, this association remained

relatively unchanged (0.27, 95% CI: 0.21, 0.32). Among observations with diabetes, being prescribed diabetes medications was associated with a statistically significant but small decrease in eGFR (-1.06, 95% CI: -1.68, -0.43). (Table 2)

Older age was associated with lower eGFR regardless of diabetes status, although the effect of older age was stronger among the stratum of observations with diabetes (Table 2). For each one-year increase in age, observations without diabetes experienced a -1.01 mL/min/1.73m^2 decrease in eGFR (coefficient: -1.01, 95% CI: -1.02, -0.99), while observations with diabetes experienced -1.32 (95% CI: -1.36, -1.27) decrease in eGFR. In both models, male sex was associated with higher eGFR compared to female sex. This effect was slightly accentuated for observations in the stratum with diabetes (4.94, 95% CI: 3.42, 6.46) compared to observations in the stratum without diabetes (2.26, 95%: 1.70, 2.82). In adjusted models, we found that the intercept was relatively similar between the stratum of observations without diabetes (intercept: 92.59, 95% CI: 91.62, 93.57) and the stratum of observations with diabetes (intercept: 87.88, 95% CI: 86.26, 89.49). Since the age variable was centered at 40, this suggests that observations with and without diabetes have relatively similar eGFR values at age 40, but due to the sharper age-related decline in kidney function, those with diabetes experience clinically significant kidney damage (defined as an eGFR of 60 mL/min/1.73m^2 or less) almost an entire decade earlier (late 60s as opposed to late 70s) compared to those without diabetes. (See Figure 2)

Sensitivity Analysis

To further investigate the interaction between age and diabetes status, we examined a non-stratified model, which included an interaction term between diabetes and age. Corroborating the results in the stratified model, we found that the interaction term between

diabetes and age was statistically significant in the expected direction with the presence of diabetes associated with a steeper decline in eGFR for increasing age. (see Table 3)

Discussion

In this study of 253,140 observations from 29,058 PWH in care in the US, we found that the association between five-year average daily glucose and kidney function was statistically significant, but modest among PWH with diabetes in both unadjusted and adjusted models. Furthermore, five-year average daily glucose was not associated with kidney function among PWH without diabetes after adjusting for age and sex. While those with diabetes have higher glucose levels on average compared to those without diabetes as expected, our findings suggest that averaged glucose is not particularly predictive of future kidney function decline, however, having diabetes appears predictive of age-related decline.

In the context of existing literature, these findings are somewhat unexpected as prior studies have shown an association between hyperglycemia and higher risk of CKD in both the general population and among PWH specifically. For example, a study conducted using data from the ARIC cohort found that each 1% increase in HbA1C was associated with a 31% increased risk of incident CKD in their sample, which consisted of individuals from the general population in four locations across the US. (35) Another study conducted by Investigators using data from the Veterans Aging Cohort Study found that participants with comorbid diabetes and HIV were more likely to progress to an eGFR below 45 ml/min/1.73m^2 compared to participants with only HIV. (61) Furthermore, the mechanism of action through which hyperglycemia damages the kidney, as described previously in this paper, has been well-documented.

It is important to note that we do not believe that our findings indicate that diabetes is not associated with kidney function or that hyperglycemia does not damage the kidneys. After we found a more modest association between five-year average daily blood glucose and eGFR than predicted a priori, we conducted secondary analyses that looked at the long-term trajectory of eGFR, stratified by diabetes status, over years of life. We found that our data quite clearly demonstrates that participants with diabetes have drastically different outcomes for kidney function over time. Participants with diabetes experienced approximately 0.30 mL/min/1.73m^2 greater decline in eGFR per year compared to participants without diabetes. Since age-related kidney function decline has been shown to follow a linear pattern regardless of diabetes status, (44) we can extrapolate a general age-related trajectory from our model. This trajectory suggests that, on average, individuals with diabetes experience Stage 3 CKD almost an entire decade before individuals without diabetes (i.e. in their mid 60s as opposed to mid 70s). (See Figure 2)

This appears to be driven by a significantly steeper yearly decline in eGFR among those with diabetes compared to those without diabetes. Even after controlling for the prescription of diabetes medication among participants with diabetes and five-year average daily glucose, this significantly steeper yearly decline in eGFR among participants with diabetes persisted. This suggests that glycemic control alone is not enough to ameliorate the deleterious effects of diabetes on kidney function and that additional interventions targeting kidney function may be necessary for PWH with comorbid diabetes. Moreover, these findings highlight the critical importance of diabetes prevention among PWH. While a decline in kidney function is a natural consequence of the aging process, clinically significant CKD predominantly impacts those older than 70 and data from the National Health and Nutrition Examination Survey (NHANES) show that most individuals with CKD in the US are older than 70. (74) This fact highlights the

significance of the differential age-related decline in kidney function by diabetes status observed; it was notable even by the age of 50. Given that kidney damage is irreversible and progressive, more rapid decline in kidney function at earlier ages could result in significant excess morbidity and mortality for PWH with diabetes.

While our findings may not have demonstrated as extreme of a decline as predicted a prior, they are not completely divergent from the literature. For example, a study, from the previously described ARIC cohort, that looked at the trajectory of eGFR decline among participants with and without diabetes found no statistically significant difference in mean annual eGFR change between individuals with a baseline HbA1C less than 7 and those with a baseline HbA1C between 7-9. (44) There are a limited number of papers that look at glycemic load specifically as an exposure variable of interest on kidney function among PWH. Our study fills this gap in the literature by providing evidence that averaged glucose has a statistically significant but modest impact on eGFR and is therefore less predictive of kidney decline than having diabetes. Moreover, few other studies have looked at the impact of the interaction between age and diabetes on kidney function among PWH specifically. While studies among the general population have also found that people with diabetes had a greater decline in age-related kidney function compared to people without diabetes, our study shows that the findings of these other studies can be extended to PWH. (43, 44, 45). Indeed, when compared to a study of the general population that also included adults of all ages (43), our study actually found a stronger effect size of diabetes on age-related kidney function decline among PWH.

A significant strength of our study is the large sample size of PWH in comparison to most other studies looking at kidney function changes among PWH, which had sample sizes mostly smaller than 5000 participants. (12, 62, 63, 64, 65, 66) This large sample, in combination with

our high-quality longitudinal data, allows for a high degree of precision in our age effect estimate. Furthermore, our sample is geographically and demographically diverse, which makes it less likely that our results predominantly reflect an unusual population at a single site. Another strength of our study is that even participants without diabetes have routine creatinine laboratory testing as regularly monitoring kidney function is the standard of care for PWH due to the nephrotoxic potential of certain ART medications and the risk of HIVAN. This enables us to reduce the systematic bias resulting from primarily including individuals with some indication to receive routine creatinine labs.

While our study had several strengths, as with all observational studies, there are some limitations. One limitation is that our models did not distinguish between the different potential causal pathways through which hyperglycemia can impact kidney function. (see Figure 3) Since the primary objective of the present study was to explore the general pathway from hyperglycemia to CKD stratified by diabetes, we did not control for hypertension and obesity. These two conditions are possibly mediators to some degree in the potential causal pathway between hyperglycemia and CKD, thus adjusting for these conditions could induce overadjustment bias. (73) Another limitation is that diabetes status is treated as a binary variable in our analysis, but studies looking at the changes in glucose metabolism in individuals prior to being diagnosed with T2D suggests that the development of T2D often occurs over an extended time frame. (58, 59) This suggests that observations categorized as not having diabetes may have altered glucose metabolisms more resembling those of observations with diabetes than not. Therefore, the differences in kidney function changes between those with and without diabetes may be attenuated in our results. Additionally, our models do not account for diabetic hyperfiltration, which can occur in a subset of individuals with both Type 1 and 2 diabetes. (70)

Finally, another limitation is our model does not control for health behaviors (e.g. diet, physical activity, smoking), a history of acute kidney injury, or a history of recurrent kidney infections.

Conclusion

Our study consisting of a large cohort of PWH in care in the US provides evidence that averaged glucose is less predictive of kidney function decline than diabetes status. However, we found that participants with diabetes have significantly worse kidney function at older ages compared to their age and sex matched peers. This difference appears to be driven by a significantly faster yearly decline in kidney function among participants with diabetes. These findings are highly suggestive that the impact of diabetes and hyperglycemia on kidney function is not fully captured by typical measurements of blood glucose. Ultimately, our findings highlight the importance of closely monitoring kidney function, even among PWH with well-controlled diabetes.

Figure 1: Diabetes status flow chart with initial number of participants in both categories

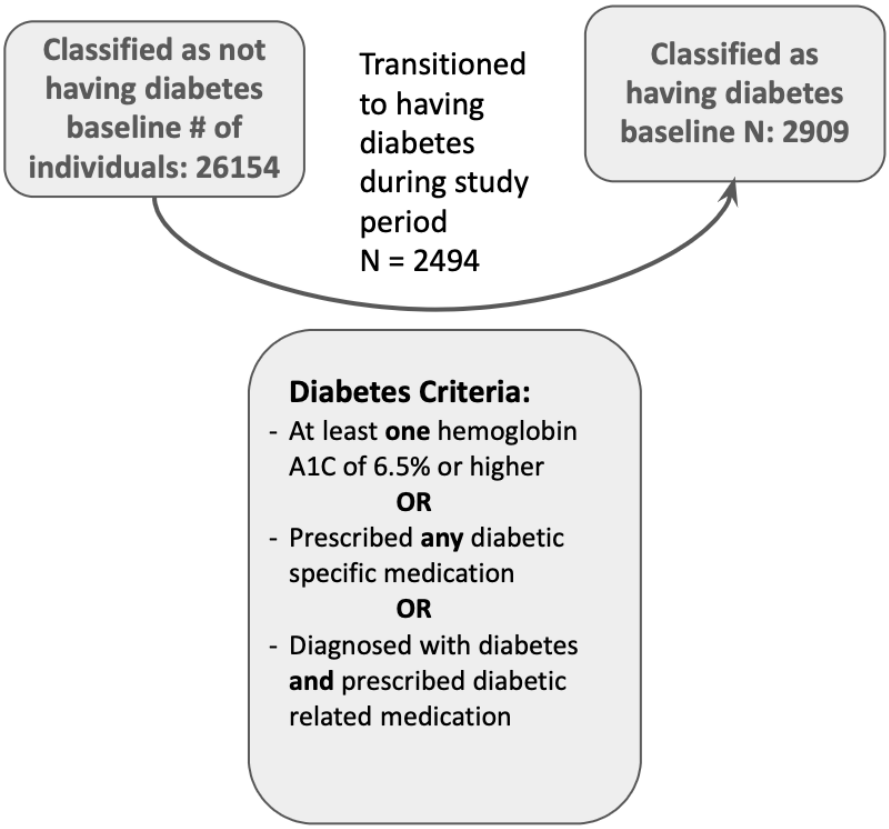


Table 1a: Characteristics of individual patients

	N (%)[1] Mean (± SD) *Median (IRQ)*
Unique patients	29,058
Age at baseline (years)	44.6 (±12.3)
Female	5,356 (18.4%)
Race	
White	11,529 (39.6)
Black	12,044 (41.4)
Hispanic	3,959 (13.6)
Other/Unknown	1,526 (5.2)
HbA1C at baseline %[2]	5.7 (±1.3) *5.0 (5.1-5.8)*
Weight at baseline (kg)[3]	82.8 (±19.8) *80.0 (69.4-92.9)*
Five-year average daily glucose at baseline (mg/dL)	100.46 (±28.7) 94.51 (*87.5-102.8)*
Follow-up time (days)	1665.0 (±1027.3)
Number of follow-up observations	8.7 (±5.0)

[1] % is out of number of unique patients (29,058)

[2] Closest recorded HbA1C occurring after and within 2 years of baseline date (missingness of 49.2%)

[3] Closest recorded weight occurring after and within 2 year of baseline date (missingness of 11.8%)

Table 1b: Patient characteristics by observations

	People without diabetes observations (n = 209,612)[1] N (%) Mean (± SD) *Median (IRQ)*	**People with diabetes observations** (n = 43,574)[1] N (%) Mean (± SD) *Median (IRQ)*
Unique patients (N)[2]	26,154	5,403
Age (years)	48.0 (±12.4)	56.2 (±10.4)
Female	39,282 (18.7)	12,244 (28.1)
Race		
White	84,171 (40.2)	13,102 (30.1)
Black	87,796 (41.9)	23,945 (55.0)
Hispanic	27,638 (13.2)	4,999 (11.5)
Other/Unknown	9,961 (4.8)	1,528 (3.5)
Treated with any diabetes medication	N/A	38,137 (87.5)
HbA1C %	5.9 (±2.0) *5.6 (5.2-6.1)*	7.5 (±2.9) *6.9 (6.1-8.3)*
Five-year average daily glucose (mg/dL)	95.1 (±10.3) *94.7 (88.7-100.8)*	150 (±49.2) *136.7 (114.5-150.4)*
Weight (kg)	81.0 (±18.9) *78.7 (63.3-81.0)*	91.1 (±24.0) *87.5 (74.4-104.2)*

[1]A single individual may contribute to observations in multiple categories (ex: an individual may go from not having diabetes to having diabetes)

[2]Patients may change categories (see Figure 1) so an individual may be considered a unique patient for different categories and N will not sum to total number of unique patients in entire sample

Table 2a: Unadjusted and adjusted mixed linear model results for estimated eGFR[1] (mL/min/1.73m^2) for observations without diabetes status[2]

Observations without diabetes only (# of obs = 209,612)			
	Coefficient [95% CI]		
	Unadjusted model	Adjusted model[3]	Age-only model
Intercept	103.17 (102.27, 104.07)	92.59 (91.62, 93.57)	94.57 (94.34, 94.80)
Five-year average daily glucose (per 10 mg/dL)	-1.59 (-1.68, -1.50)	0.01 (-0.08, 0.09)	----------
Age centered at 40 (year)	----------	-1.01 (-1.02, -0.99)	-1.01 (-1.02, -1.00)
Male sex	----------	2.26 (1.70, 2.82)	----------

Table 2b: Unadjusted and adjusted mixed linear model results for estimated eGFR[1] (mL/min/1.73m^2) for observations with diabetes status[2]

Observations with diabetes (# of obs = 43,574)				
	Coefficient [95% CI], p-value			
	Unadjusted model	Adjusted model[3]	Adjusted model[4]	Age-only model
Intercept	73.79 (72.73, 74.86)	87.88 (86.26, 89.49)	88.29 (86.66, 89.92)	95.05 (94.09, 96.01)
Five-year average daily glucose (per 10 mg/dL)	0.08 (0.02, 0.13)	0.27 (0.21, 0.32)	0.29 (0.23, 0.34)	----------
Age centered at 40 (year)	----------	-1.33 (-1.38, -1.29)	-1.32 (-1.36, -1.27)	-1.30 (-1.35, -1.26)
Male sex	----------	4.98 (3.46, 6.50)	4.94 (3.42, 6.46)	----------
Use of any diabetes medication	----------	----------	-1.06 (-1.68, -0.43)	----------

[1] Calculated by CKD-EPI formula for creatinine
[2] Calibrated with random intercepts and fixed slopes with each individual as a cluster
[3] Adjusted for age centered at 40 and birth sex
[4] Adjusted for age centered at 40, birth sex, and use of diabetes medication

Table 3: Mixed linear model results for estimated eGFR[1] (mL/min/1.73m^2) for entire sample

All observations (# of obs = 137262)	
	Coefficient [95% CI], p-value
	Adjusted model[1]
Intercept	90.63 (89.99, 91.27)
Five-year average daily glucose (per 10 mg/dL)	0.16 (0.12, 0.20)
Age centered at 40 (year)	-1.06 (-1.07, -1.04)
Male sex	2.84 (2.29, 3.38)
Classified as having diabetes	-1.39 (-1.83, -0.95)
Age*Diabetes classification	-0.03 (-0.04, -0.01)

[1] Adjusted for five-year average daily glucose, age, sex, diabetes status, and interaction between age and diabetes status

Figure 2: Comparison of the rate of age-related decline in kidney function as measured by eGFR between observations diagnosed with diabetes and observations not diagnosed with diabetes

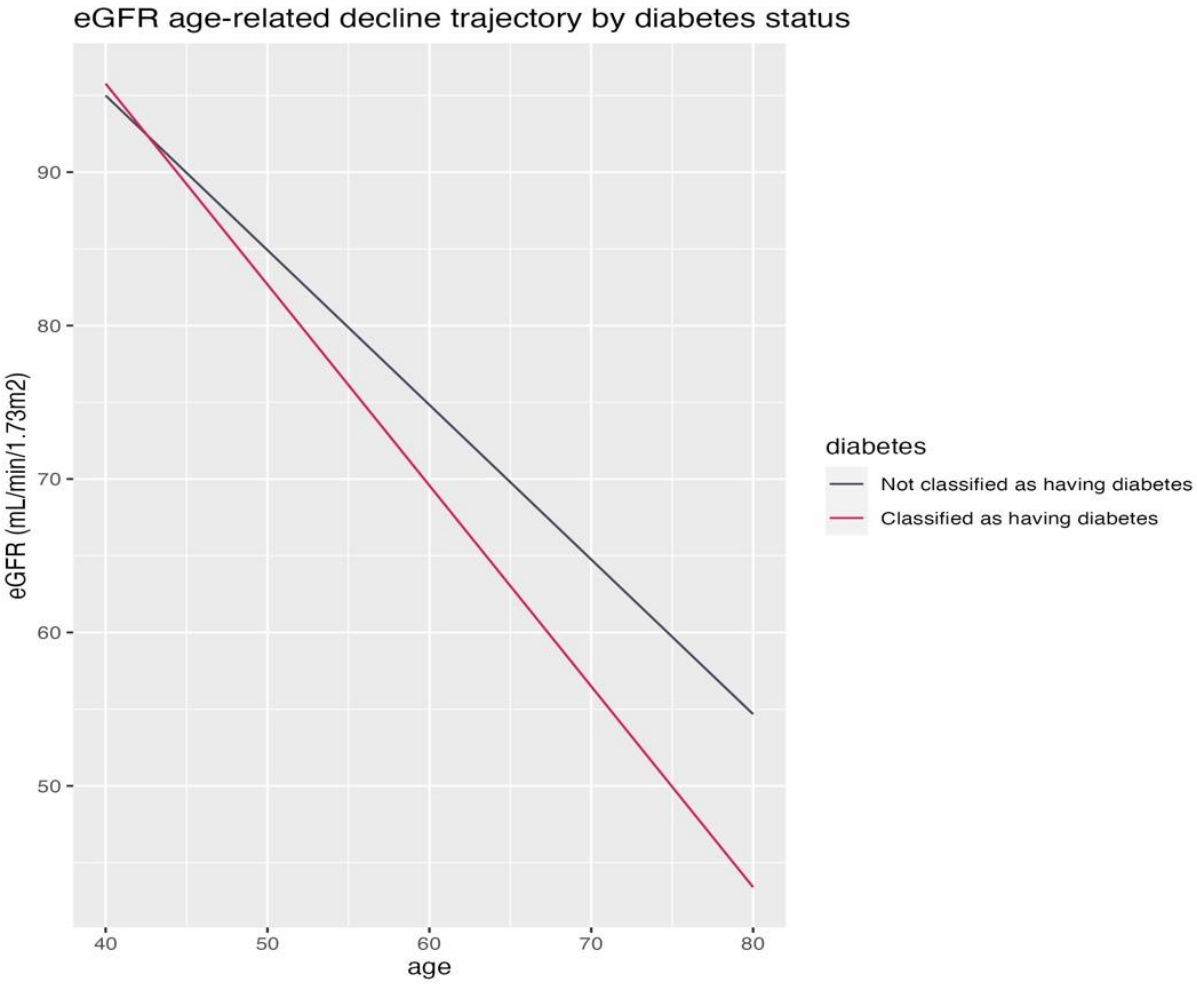
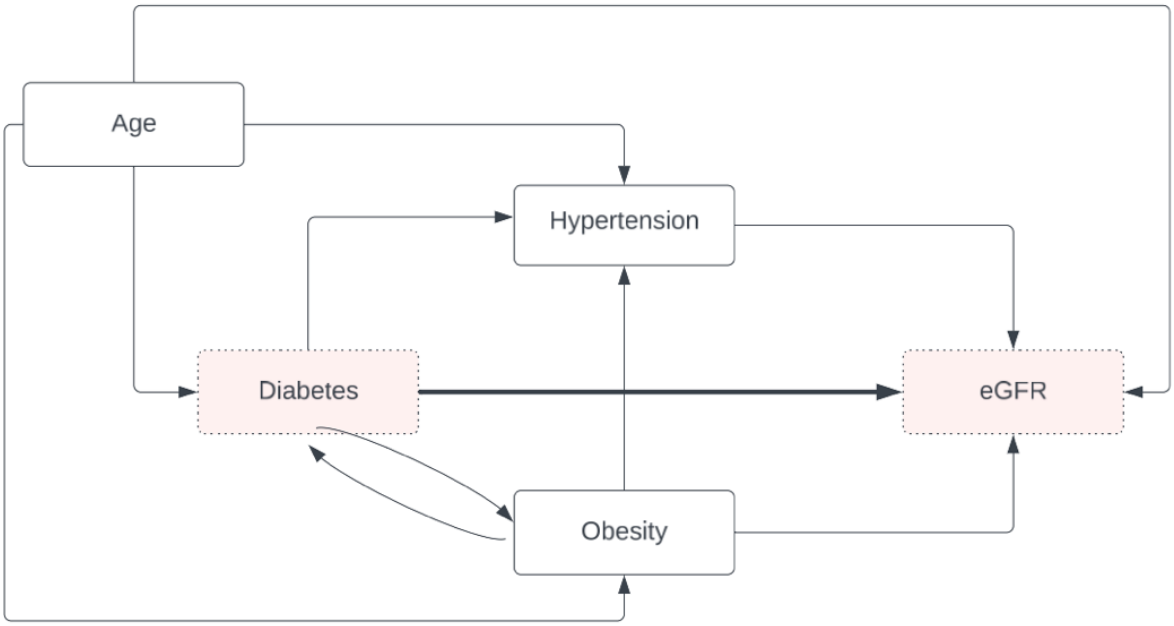


Figure 3: Chart depicting relationship between diabetes and eGFR with major known related variables that may be mediators or confounders



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