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Hemoglobin and Overt Nephropathy Complications in Type 1 Diabetes

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Diabetes is the most common cause of end stage renal disease (ESRD) (1,2). Approximately half of individuals with type 1 diabetes (T1D) will develop some degree of kidney disease and of those who progress to overt nephropathy approximately fifty percent will eventually progress to ESRD (1,3,4). Cardiovascular disease (CVD) and mortality are high in ESRD (5) and those with ESRD and diabetes fare worse than those with ESRD but without diabetes (6).

Risk factors for ESRD and coronary artery disease (CAD) in T1D are similar to those seen in the general population, and include hypertension, elevated lipid levels, and levels of proteinuria (7). Although improving blood pressure, lipid levels, and glycemic control may delay the progression to ESRD and CAD, they do not fully prevent these complications nor do they prevent early mortality in those with type 2 diabetes (T2D) and nephropathy.

Anemia is a known complication of chronic kidney disease and has been found to be more severe in those with diabetes related kidney disease and to occur at an earlier stage (8,9,10, 11). Furthermore, in individuals with T2D, hemoglobin (HGB) has been found to be a significant negative predictor of ESRD (7), while in a recent study of T1D, Thomas et al report that 52% of the patients with overt nephropathy were anemic, compared to only 11% of those with normal renal function, and that anemic individuals were twice as likely to have macrovascular disease. HGB may therefore be a powerful predictor of declining renal function and CAD. However, while a number of studies have shown that anemia (or low HGB) predicts progression to ESRD in diabetes (12,7), it is not clear whether anemia or a low HGB also predicts other major complications in this same population, e.g. mortality and CAD and, if so, whether it is independent of ESRD. Furthermore whether the standard WHO definition of anemia provides the best discrimination of risk isn't clear. A fuller understanding of these issues is critical as two recent trials have reported adverse outcomes when correcting anemia in renal failure patients (13,14).

Thus, to further investigate the association of anemia/HGB with the complications of overt nephropathy in T1D, we prospectively followed 175 individuals with childhood onset T1D and overt nephropathy from the Pittsburgh Epidemiology of Diabetes Complications Study cohort for twelve years. The specific objectives were to investigate the power of HGB, a marker of anemia, to predict ESRD, CAD, and mortality in individuals with T1D and overt nephropathy.

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Methods

The Pittsburgh Epidemiology of Diabetes Complications Study is a prospective study based on a well-defined cohort of adults with childhood-onset (<17 years old) T1D. There were 658 eligible subjects (325 women and 333 men) diagnosed between January 1, 1950, and May 30, 1980, who were first seen at baseline (1986 to 1988) and followed with examinations every two years. This report focuses on the 174 of these subjects, with a mean age and diabetes duration of 33.3 and 22.7 years, respectively, who either at baseline (n=140) or during follow-up (n=34) developed overt nephropathy as defined below.

Before attending each cycle of examinations, information was collected by questionnaire concerning demographic characteristics, medical history, and health care behaviors as previously described (15). At each cycle, both a standardized medical history and clinical examination were performed by a trained internist to document complications of diabetes.

Fasting blood samples were assayed for lipids, lipoproteins, glycosylated hemoglobin (HbA1), and HGB. High-density lipoprotein (HDL) cholesterol was determined by a heparin and manganese procedure, a modification of the Lipid Research Clinics method (16). Cholesterol was measured enzymatically, as were triglycerides. Low-density lipoprotein (LDL) cholesterol levels were calculated from measurements of the levels of total cholesterol, triglycerides, and HDL cholesterol. Anemia was defined as an HGB <13g/dl in men and HGB <12 g/dl in women, according to WHO guidelines (17). Glomerular filtration rate (GFR) was estimated using the four variable Modification of Diet in Renal Disease formula (18).

Stable glycosylated HbA1 was originally measured in saline-incubated samples by microcolumn cation exchange chromatography (Isolab, Akron, Ohio, USA). On October 26, 1987, the method was changed to high-performance liquid chromatography (Diamat, Bio-Rad Laboratories, Hercules, CA, USA). The two methods were highly correlated ($r = 0.95$; Diamat HbA1 = 0.18 ± 1.00 Isolab HbA1). The difference between the means of the two methods was 0.158% (normal range, 4.9% to 7.3% HbA1).

Blood pressure was measured by a random-zero sphygmomanometer according to a standardized protocol [Hypertension Detection and Follow-Up] (19) after a 5-minute rest period. Blood pressure levels were analyzed, using the mean of the second and third readings.

Nephropathy status was determined based on consistent results from at least two of three timed urine collections (24-hour, overnight, timed samples during exam) and urine albumin excretion rate (AER). The adequacy of urine collection was determined by whether the total amount of creatinine excreted was appropriate for an individual's age, based on body size and gender. Urinary albumin was determined immuno-nephelometrically. Overt nephropathy was defined as an AER >200 μ g/min. ESRD was defined as being on dialysis or having received a kidney transplant. CAD was defined as myocardial infarction, ischemia (Minnesota Codes 1.1-1.3, 4.1-4.3, 5.1-5.3 and 7.1), or fatal CAD verified from death certificates, autopsy and/or medical records using standard criteria, revascularization, or Epidemiology of Diabetes Complications clinic diagnosed angina. A prevalent CAD case was defined as having known CAD before diagnosis of overt nephropathy. All deaths and hospitalized cardiovascular events were investigated by obtaining autopsy, coroner, or medical records. Deaths were classified by two physicians (TO, IF) according to Diabetes Epidemiology Research International (20) procedures. Supplementary data were obtained on some CVD hospitalized events. All procedures were approved by the Institutional Review Board of the University of Pittsburgh.

Continuous data were compared across groups by the Student's *t* test with serum creatinine, triglycerides, HDL cholesterol, and non-HDL cholesterol being log transformed prior to testing. Categorical data were compared across groups by chi-square tests. These analyses were

based on risk factors assessed at baseline, with baseline being defined as study baseline for prevalent overt nephropathy cases or the evaluation date during follow-up when overt nephropathy was determined for incident cases. Gender specific analyses, using tertiles of HGB and WHO defined anemia were also explored.

Univariate Cox proportional hazards models and the Kaplan-Meier method were used to explore the association of HGB with the outcomes of interest: ESRD, CAD, and mortality. Multivariable Cox proportional hazards regression analyses were conducted using the forward selection procedure to explore the relationship between HGB and the above mentioned outcomes. Covariates that were univariately significant were allowed to enter the model. Given the strong correlation of age and diabetes duration ($r=0.83$), both were not entered into the same model. To determine whether HGB's prediction of mortality was accounted for by those with ESRD having lower HGB, ESRD was a time-dependent ESRD covariate. The criterion for statistical significance was $P < 0.05$. Statistical analysis was conducted using SAS version 8.2 (Cary, North Carolina).

Results

Table 1 shows the characteristics at study entry (1986-1988) of the 658 study participants and the subcohort with baseline and subsequent overt nephropathy. Participants were followed for up to twelve years. Mean time to overt nephropathy was 4.1 years in the incident overt nephropathy population. Relative to the entire population, those with overt nephropathy at baseline or who subsequently developed overt nephropathy were older, of longer diabetes duration, had a worse lipid and hemodynamic profile, a higher AER (reflecting the selection criteria), and a lower HGB.

In those with overt nephropathy, HGB levels ranged from 9.2-18.8 g/dl. Overall, eleven percent were anemic. Of those who later progressed to ESRD or CAD, the prevalence of anemia at baseline was 15 and 11%, respectively. Fifty-nine (34%) subjects went on to develop ESRD and 59 (38%) of those free of CAD at baseline ($n=154$) progressed to CAD. There were a total of 39 deaths, with over half (61.5%) occurring in those with ESRD. The underlying cause of death was determined to be CVD in 47.5% of the cases, renal disease in 20%, acute complications in 2.5%, accident or suicide in 5%, infection in 17.5%, other-non diabetes in 2.5%, and other-diabetes in 2.5%. Of the 19 CVD deaths, 11 were due to myocardial infarction, 1 to chronic CAD, 2 to congestive heart failure, 4 to cerebral vascular accident, and 1 to peripheral vascular disease.

Data on HGB stability was limited as 18% had no further HGB values after baseline. 72% of participants remained within 1 std of their baseline value throughout follow-up, with 23% showing a fall of >1 std, and 5% a rise of >1 std. Of those with a fall of >1 std, 39.4% developed ESRD, 48.5% developed CAD, and 24.2% died, compared to 23.3 ($p=0.07$), 35.6 ($p=0.19$), and 15.5% ($p=0.25$) respectively in those remaining stable. The remaining analyses are limited to baseline overt nephropathy HGB values.

Univariate predictors of ESRD, CAD, and overall mortality are presented in Table 2. At the first time of known overt nephropathy, HGB was significantly lower in those who went on to ESRD, and in those who later died, while there was no significant difference in mean HGB levels in those who progressed to CAD compared to those who did not. Figures 1-3 shows the relationship of total HGB with ESRD, CAD, and mortality by sex-specific tertiles of HGB (Figure 1). Graphical examination revealed a similar relationship in both men and women for progression to ESRD, although absolute HGB levels were 2mg/L higher in men. However, there was no apparent relationship with CAD for men apart from a possible increased risk in the six men with anemia. A lower risk in the third tertile (>14 gm/L) for women was also

suggested. For mortality, there was an apparent linear declining risk in men, but for women the risk for mortality did not appear to decline until the third tertile. Statistical tests for an interaction between HGB and gender in CAD and mortality were not significant ($p=0.23$ and 0.43 for CAD and mortality, respectively).

Kaplan-Meier analyses (Figures 4-6) demonstrate the association of HGB, based on median split, with ESRD, CAD, and mortality after twelve years of follow-up. Univariate Cox proportional hazards modeling showed that HGB predicted ESRD (HR= 0.70, 0.61-0.80) and overall mortality (HR=0.84, 0.72-0.98), but not CAD (HR= 0.91, 0.79-1.0) after twelve years of follow-up. After adjustment for sex and other univariately significant covariates, HGB remained significantly predictive of ESRD (HR= 0.72, 0.61-0.85) but not overall mortality (HR= 0.92, 0.77-1.1). Table 2 presents the multivariable adjusted results of the association of HGB with ESRD, CAD, and mortality.

A key question is whether HGB predicts mortality after accounting for those with renal failure. When stratified by progression to ESRD, HGB was significantly inversely related to mortality in those free of ESRD after adjustment for sex and diabetes duration (HR=0.59, 0.39-0.89). We were unable to follow participants by HGB level from the time of known ESRD to determine whether HGB predicted mortality after accounting for renal failure. Including ESRD as a time dependent covariate, HGB significantly predicted overall mortality (HR=0.75, 0.59-0.93) (Table 3).

Discussion

Although the relationship of anemia with complications of kidney disease in both T2D and T1D has been investigated, its relationship in T1D has been limited to generally older individuals. Our study extends that of Thomas et al (11) by prospectively following a cohort of relatively young T1D individuals diagnosed before the age of 17. To our knowledge, we are the only study that has investigated this relationship in an exclusively childhood onset T1D population. This study demonstrates that in addition to predicting ESRD, HGB also predicts total mortality and mortality in those without subsequent ESRD in T1D individuals with overt nephropathy. Several important findings need to be highlighted.

First, the prevalence of anemia in this population was relatively low (11%); however, lower HGB still proved to be predictive of ESRD and of overall mortality after twelve years of follow-up. In contrast to our study, Thomas et al (11) found a prevalence of anemia of 52% in those with macroalbuminuria, approximately 5 times higher than that found in our population. Fischer et al (21) also found a high prevalence of anemia (26.3%) in patients with T1D. The different results could reflect differences in patient population. The subjects in both Thomas et al's and Fischer et al's studies were approximately 15 and 11 years older, respectively, than those in our study. This should not be overlooked as the prevalence of anemia increases with age (22). In addition, the subjects in that study were recruited from tertiary care clinics and could have had a higher prevalence of comorbidities associated with anemia. The majority of the participants in our study, which is a sub-study of the entire 658 individuals, already had overt nephropathy at study entry (1986-1988) and it is likely that baseline HGB, albeit in the normal range, already represents a fall in HGB and a decline to ESRD. In our study, only 22%, 15%, and 18% of the subjects who went on to develop ESRD, CAD, or to die, respectively, were anemic at baseline. Despite this low prevalence of anemia, lower HGB was able to predict ESRD and mortality after twelve years of follow-up, suggesting that at least in T1D with overt nephropathy, HGB level even in the clinically normal range, may be a powerful marker of declining kidney function and future complications. Indeed, the limited data that we did have suggested that change in HGB during follow-up was related to progression to ESRD.

We found HGB to be predictive of ESRD in our population, a finding consistent with other studies (12,7). Because the majority of erythropoietin is produced by the kidney's peritubular fibroblasts (9), impairment in kidney function would result in decreased production of red blood cells. Therefore, anemia could be a marker of declining kidney function, rather than a causative factor. In our population, 63% of those anemic at study baseline had a GFR of less than 60mL/m; however, most individuals (73%) with low GFR were not anemic. After adjusting for kidney function, HGB remained associated with ESRD; therefore, it appears that the association of HGB with ESRD is additional to that of declining renal function. It is possible that low levels of HGB may aggravate underlying CAD, which in turn may accelerate progression to ESRD (7). Alternatively, low HGB could reflect abnormalities in tubular function that are in addition to low glomerular filtration.

Anemia has been shown to be a risk factor for CVD events in the general population (23) and in those with chronic kidney disease. In patients with chronic kidney disease, Levin et al (24) found hemoglobin to be linearly related to left ventricular growth. For each half gram decrease in hemoglobin, there was a 32% increase in left ventricular growth. Jurkovitz et al (5) in the ARIC study found that those with both high creatinine and anemia had a threefold increased risk of coronary heart disease, compared to no increased risk in those without anemia.

In contrast to the epidemiologic studies, trial results have not found that aggressive treatment of anemia with normalization of HGB prevents CVD. Two recent trials have suggested that mortality is increased with complete correction of anemia. The CREATE trial, a randomized trial of epoetin in individuals with stage 3-4 chronic kidney disease and mild to moderate anemia (HGB 11-12.5 g/dl) were randomized to either a HGB target of 13-15 or 10.5-11.5. The investigators found that more aggressive treatment of anemia in chronic kidney disease did not slow the progression of left ventricular hypertrophy (14). There was also a trend toward increased kidney disease and mortality. The CHOIR study was recently stopped by the data safety monitoring board when it was found that treatment to a HGB of 13.5 (vs. 11.3) was associated with a higher risk of events, i.e. a composite of CVD and mortality, though there was not a statistical difference in mortality alone (13). However, it is important to point out that in both of the above studies the control group was treated to current recommended National Kidney Foundation Kidney Disease Outcomes Quality Initiative targets (25). More severe anemia may increase the risk of CVD. The values of HGB in our population were within the normal range and although associated with increased ESRD and mortality risk, these trials indicate that therapeutic increasing levels of HGB is not of benefit and may actually be harmful. Whether this is related to specific effects of the medications or that anemia is not a mediator but a marker of outcomes is unclear.

Anemia has been consistently shown to be associated with increased mortality in epidemiologic analyses. Almed et al (26) in the Studies of Left Ventricular Dysfunction trial found that lower hematocrit and kidney function were risk factors for overall mortality. The investigators found a significant interaction between hematocrit and GFR on overall mortality, such that risk for mortality was higher in those with both lower hematocrit and lower GFR than by either factor alone. In contrast, in our population, HGB was predictive of mortality in those never progressing to ESRD, but was only predictive of overall mortality after accounting for those with ESRD by inclusion of a time-dependent covariate for ESRD. This suggests a diminished association with mortality in those with ESRD, perhaps due to competing risk factors.

The mechanism whereby anemia may increase the risk of mortality in overt nephropathy has yet to be determined. Certainly increasing morbidity from CAD (27) is a possible mechanism. In individuals with heart disease, those with anemia have worse outcomes (28). In Lindenfeld's (22) meta-analysis of studies of anemia and heart failure, common in chronic kidney disease, anemia was associated with mortality in 12 out of 13 of the studies. The relationship between

hematocrit or HGB was linear in six of the studies. In the Women's Ischemia Syndrome Evaluation, women with anemia had greater CVD mortality and all-cause mortality (27), although there was no difference in the severity of CAD nor was ejection fraction significantly related to HGB. However, anemic women did have higher levels of inflammatory markers. Therefore, it is possible that the relationship of anemia with mortality is related to other confounders, such as inflammation. Autonomic neuropathy is another possible mechanism. Bosman et al (29) found a higher prevalence of sympathetic dysfunction and postural hypotension in anemic individuals with T1D nephropathy compared to those with T1D nephropathy without anemia. In the Epidemiology of Diabetes Complications study, of which the population reported on in this study is a subcohort, autonomic neuropathy, which was found to predict declining hematocrit levels in those with overt nephropathy (30), was predictive of overall mortality (31).

There are several limitations of this study. First of all, this was an epidemiological study and as such, results are based on observational data. We cannot rule out that other unmeasured factors may be confounding the associations. For example, the majority of the participants had overt nephropathy at study inception; therefore, we could not control for the true duration of overt nephropathy nor could we measure HGB at true overt nephropathy diagnosis. Other factors related to the duration of overt nephropathy may also be confounding the relationship of HGB with outcomes of interest in this study. As the majority of the participants already had overt nephropathy at study entry (1986-1988) it is likely that this data suggests that HGB, albeit in the normal range, is already falling in this group and reflects the beginning of the decline to renal failure. Unfortunately, this data set does not allow us to address this, i.e. prediction before overt nephropathy. Additionally, as an observational study, it could not be determined whether HGB plays an etiologic role in ESRD, CAD, or mortality, or whether it is simply a function of declining kidney function and therefore in the biological pathway between kidney disease and these outcomes. However, we controlled for kidney function by using AER and estimated GFR as markers of kidney function in multivariable analyses. Randomized controlled clinical trials may provide more robust answers to these questions. Results from ongoing trials such as the TREAT trial may provide further light on the role of HGB and the correction of anemia in the association of complications in diabetes.

To our knowledge, this is the first study to prospectively examine the role of HGB on outcomes of childhood onset T1D complicated by overt nephropathy. Our results suggest that low HGB, even in the normal range, is predictive of progression to ESRD and mortality even after accounting for those with ESRD in a population with T1D and overt nephropathy. Close monitoring of declining HGB levels in patients with diabetes may be an important part of monitoring the progression toward renal complications. Further studies may help to determine if correction of HGB may help to delay progression to or ameliorate complications in those suffering from this disease.

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Acronyms List

T1D, Type 1 diabetes
T2D, Type 2 diabetes
CAD, Coronary artery disease
AER, Albumin excretion rate
HGB, Hemoglobin
GFR, Glomerular filtration rate

HDL, High density lipoprotein cholesterol
 LDL, Low density lipoprotein cholesterol
 HbA1, Glycosylated hemoglobin
 CVD, Cardiovascular disease
 ESRD, End Stage Renal Disease
 TREAT, Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin alfa) Therapy
 CREATE, Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta ARIC
 Atherosclerosis Risk in Communities
 CHOIR, Correction of Hemoglobin and Outcomes in Renal Insufficiency

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Figure 1.

Percentage that progressed to End Stage Renal Disease by Hemoglobin Category. Hemoglobin ranges in men: anemia: <13g/dl, tertile 1: <15.2 g/dl, tertile 2: 15.2-16.39 g/dl, tertile 3: $\geq$ 16.4 g/dl. Hemoglobin ranges in women: anemia: <12 g/dl, tertile 1: <13.1 g/dl, tertile 2: 13.1-14.09 g/dl, tertile 3: $\geq$ 14.1 g/dl.

Figure 2.

Percentage that progressed to Coronary Artery Disease by Hemoglobin Category. Hemoglobin ranges in men: anemia: <13g/dl, tertile 1: <15.3 g/dl, tertile 2: 15.3-16.39 g/dl, tertile 3: ≥ 16.4 g/dl. Hemoglobin ranges in women: anemia: <12 g/dl, tertile 1: <13.3 g/dl, tertile 2: 13.3-14.09 g/dl, tertile 3: ≥ 14.1 g/dl.

Figure 3.

Percentage that Died by Hemoglobin Category. Hemoglobin ranges in men: anemia: <13g/dl, tertile 1: <15.2 g/dl, tertile 2: 15.2-16.39 g/dl, tertile 3: ≥ 16.4 g/dl. Hemoglobin ranges in women: anemia: <12 g/dl, tertile 1: <13.1 g/dl, tertile 2: 13.1-14.09 g/dl, tertile 3: ≥ 14.1 g/dl.

Figure 4. Survival curves for end-stage renal disease for baseline hemoglobin above or at/below gender-specific median (13.75 g/L in women and 15.85 in men), $p < 0.0001$

Figure 5.
Survival curves for cardiovascular disease for baseline hemoglobin above or at/below gender-specific median (13.75 g/L in women and 15.85 in men), $p=0.01$

Figure 6.

Survival curves for mortality for baseline hemoglobin above or at/below gender-specific median (13.75 g/L in women and 15.85 in men), $p=0.003$

Table 1

Characteristics of the 658 Epidemiology of Diabetes Complications Study Participants at Study Entry (1986-1988) by Baseline and Subsequent Renal Status. Data are n (%), mean (SD), or median (IQR)

Characteristic	Total Population (658)	ON Free (n=430)	Prevalent ON (n=140)	Incident ON (n=34)
Male, n (%)	333 (50.6)	209 (48.6)	74 (52.9)	18 (52.9)
Age (years)	27.6 (7.9)	26 (7.8)	30.9 (6.3)	28.8 (7.7)
Duration (years)	19.4 (7.5)	18.0 (7.3)	22.7 (6.6)	18.5 (8.1)
Hgb (g/dl)	15.1 (1.7)	15.3 (1.5)	14.5 (2.1)	15.1 (1.6)
HbA1c (%)	10.4 (1.8)	10.1 (1.7)	10.6 (1.9)	11.2 (2.3)
Body mass index (kg/m ²)	23.5 (3.2)	23.4 (3.3)	22.7 (6.6)	23.7 (3.8)
AER (μ/min)	16.5 (7.5-186.6)	9.8 (6.2-20.0)	974.6 (406.6-1871.9)	45.8 (11.9-92.9)
Serum creatinine (mg/dL)	0.9 (0.7-1.1)	0.8 (0.7-1.0)	1.0 (0.9-1.4)	0.9 (0.6-1.0)
SBP (mm Hg)	113.8 (16.0)	109.1 (11.0)	123.6 (16.5)	111.6 (11.9)
DBP (mm Hg)	72.9 (11.1)	70.0 (8.9)	79.8 (11.9)	71.7 (9.5)
HDLc (mg/dL)	53.8 (12.3)	54.8 (11.8)	52.3 (13.1)	53.7 (12.9)
nonHDLc (mg/dL)	116.2 (35.0)	125.2 (32.5)	165.5 (52.0)	145.7 (38.7)

Missing data on 54 individuals due to prevalent ESRD at baseline or missing data.

Table 2
Baseline Predictors of ESRD, CAD, and Overall Mortality (Mean (SE) or N (%)) in those with ON (n=174)

Risk Factor	Incident ESRD		Incident CAD		Overall Mortality	
Anemia (%)	Yes (59)	No (115)	Yes (59)	No (95)	Yes (39)	No (135)
	13 (22) [†]	6 (5)	9 (15)	7 (7)	7 (18)	12 (9)
Diabetes duration (yrs)	24.7 ± 0.8 [§]	22.1 ± 0.6	26.8 ± 0.8 [‡]	19.8 ± 0.6	26.5 ± 0.8 [‡]	22.0 ± 0.6
Hemoglobin (g/dl)	13.7 ± 0.3 [‡]	15.0 ± 0.2	14.5 ± 0.3	14.8 ± 0.2	14.0 ± 0.3 [*]	14.8 ± 0.2
Men	14.0 ± 0.3 [‡]	16.0 ± 0.2	15.3 ± 0.3	15.9 ± 0.2	15.0 ± 0.4	15.7 ± 0.2
Women	12.6 ± 0.3 [‡]	14.0 ± 0.2	13.2 ± 0.4	13.8 ± 0.2	12.7 ± 0.3	13.7 ± 0.2
Body mass Index (kg/m ²)	23.9 ± 0.4	24.1 ± 0.3	24.5 ± 0.4	23.7 ± 0.3	24.4 ± 0.5	23.9 ± 0.3
Systolic BP (mm Hg)	131.1 ± 2.3 [‡]	119.3 ± 1.3	126.9 ± 2.3 [*]	119.0 ± 1.6	132.3 ± 2.8 [§]	120.6 ± 1.3
Diastolic BP (mm Hg)	82.6 ± 1.4 [§]	77.3 ± 1.1	81.0 ± 1.6	77.1 ± 1.2	82.5 ± 1.7	78.1 ± 1.0
Serum Creatinine (mg/dL) ^{**}	1.9 ± 0.1 [‡]	1.0 ± 0.4	1.4 ± 0.1 [*]	1.1 ± 0.1	1.0 ± 0.2 [‡]	1.2 ± 0.1
Glomerular filtration rate (mL/min/1.73 m ²)	54.3 ± 4.4 [‡]	100.2 ± 5.4	75.6 ± 5.1 [*]	94.3 ± 6.5	57.8 ± 5.4 [‡]	92.4 ± 4.9
Albumin Excretion Rate (μ/min) ^{**}	2073.4 ± 259 [‡]	696.8 ± 74	1329 ± 224	959 ± 129	2044.3 ± 264 [‡]	913.2 ± 113
Total cholesterol (mg/dL) ^{**}	242.1 ± 9.5 [‡]	206.4 ± 3.4	222.2 ± 6.6	214.4 ± 5.7	237.7 ± 9.9 [§]	213.4 ± 4.4
Triglycerides (mg/dL) ^{**}	181.0 [‡] ± 18.2	129.9 ± 9.7	145.1 ± 12.5	147.3 ± 14.5	200.3 ± 20.9 [§]	131.3 ± 22.2
HDL cholesterol (mg/dL) ^{**}	49.6 [§] ± 1.4	54.5 ± 1.4	50.3 ± 1.7	54.5 ± 1.4	47.9 ± 1.6 [§]	54.3 ± 1.2
Non-HDL cholesterol (mg/dL) ^{**}	192.6 ± 9.5 [‡]	151.9 ± 3.4	171.9 ± 6.5	159.9 ± 5.8	189.8 ± 9.7 [§]	159.0 ± 4.4
Glycosylated HGB (%) ^{**}	10.8 ± 0.3	10.8 ± 0.2	10.5 ± 0.2	11.0 ± 0.2	11.3 ± 0.3	10.7 ± 0.2
Sex (% male)	30 (51)	60 (52)	37 (63) [*]	44 (46)	20 (50)	71 (53)
Ever smoker (%) ^{***}	26 (44)	58 (50)	33 (56)	39 (41)	26 (65) [*]	59 (44)
ACE inhibitor use	9 (16)	11 (10)	8 (14)	8 (9)	5 (13)	15 (12)

^{*} p<0.05

[§] p<0.01

[‡] p<0.001

[‡] p<0.0001

^{**} Naturally logarithmically transformed before testing

Having smoked at least 100 cigarettes in a lifetime

Table 3
Adjusted Predictors of ESRD, CAD, and Mortality, HR (95% C.I.)

Risk Factor	ESRD	CAD	Mortality	Mortality (Adjusted for ESRD)
Sex (female)	0.50, 0.27,0.90 [*]	0.69, 0.36,1.3	1.1, 0.51-2.5	0.73, 0.34,1.6
Hemoglobin (g/dL)	0.72, 0.61,0.85 [†]	0.94, 0.80, 1.1	0.92, 0.77, 1.1	0.75, 0.59,0.93
Diabetes Duration (years)		1.1, 1.1, 1.1 [‡]	1.1, 1.0, 1.1 [*]	1.1, 1.0-1.1
GFR (mL/min/1.73 m ²)	0.97, 0.96,0.98 [‡]			0.98, 0.96,0.99
Log-AER (μ/min)	1.3, 1.0, 1.6 [*]		1.6, 1.2, 2.3 [§]	1.6, 1.1,2.3
Log-Triglycerides (mg/dL)	2.7, 1.6, 4.4 [‡]		2.4, 1.3-4.2 [§]	2.9, 1.6,5.4
SBP (mm Hg)				
DBP (mm Hg)				
Ever Smoker ^{***}			2.1, 1.0-4.3 [*]	2.3, 1.4,4.9
ESRD-to-death Follow- up time				0.70, 0.59,0.83

ESRD model allowed for the following variables: sex, diabetes duration, HGB, GFR (glomerular filtration rate), log-albumin excretion rate (AER), log-total cholesterol, log-triglycerides, SBP (systolic blood pressure), and DBP (diastolic blood pressure), and ever smoker. CAD model allowed for the following: sex, diabetes duration, HGB, SBP, DBP, Log-HDL, GFR, estimated glucose disposal rate, and ever smoker. Mortality model allowed for the following variables: sex, diabetes duration, HGB, GFR, log-AER, log-total cholesterol, log-triglycerides, SBP, and Ever smoker. Mortality model adjusted for ESRD allowed for the following variables: sex, diabetes duration, HGB, GFR, SBP, log-total cholesterol, log-triglycerides, log-albumin excretion rate, and ESRD-to-death follow-up time.

*
p<0.05

§
p<0.01

†
p<0.001

‡
p<0.0001

**
(Natural) Logarithmically transformed

Having smoked at least 100 cigarettes in a lifetime