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Triglycerides and Renal Outcomes According to Albuminuria and in Consideration of Other Metabolic Syndrome Components in Diabetic US Veterans

John G. Rizk[a] Jui-Ting Hsiung[b, c] Yousif Arif[b] Leila Hashemi[e, f]
Keiichi Sumida[g] Csaba P. Kovesdy[g, h] Kamyar Kalantar-Zadeh[b, c, d]
Elani Streja[b, c]

[a]Department of Practice, Sciences, and Health Outcomes Research, University of Maryland School of Pharmacy, Baltimore, MD, USA; [b]Division of Nephrology and Hypertension, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine Medical Center, Orange, CA, USA; [c]Nephrology Section, Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA, USA; [d]Division of Nephrology and Hypertension, The Lundquist Institute, Harbor-UCLA Medical Center, Torrance, CA, USA; [e]Greater Los Angeles Healthcare System, Department of General Internal Medicine, Los Angeles, CA, USA; [f]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [g]University of Tennessee Health Science Center, Memphis, TN, USA; [h]Memphis VA Medical Center, Memphis, TN, USA

Keywords
Chronic kidney disease · Albuminuria · Renal outcomes · Triglycerides · Metabolic syndrome

Abstract

Introduction: Hypertriglyceridemia, a component of the metabolic syndrome, is a known independent predictor of albuminuria and chronic kidney disease (CKD) in the general population. Previous studies have shown that the relationship of triglycerides (TGs) with outcomes changes across stages of CKD. Our objective was to examine the association of TG independent of other metabolic syndrome components with renal outcomes in diabetic patients with or without CKD. ***Methods:*** This retrospective cohort study included diabetic US veteran patients with valid data on TGs, estimated glomerular filtration rate (eGFR), and albuminuria (urinary albumin/creatinine ratio) between fiscal years 2004 and 2006. Using Cox models adjusted for clinical characteristics and laboratory markers, we evaluated the relationship of TG with incident albuminuria (stratified by eGFR category) and based on eGFR (stratified by baseline albuminuria categories). To evaluate the relationship of TG with time to end-stage renal disease (ESRD), we stratified models by baseline CKD stage (eGFR category) and baseline albuminuria stage ascertained at time of TG measurement. ***Results:*** In a cohort of 138,675 diabetic veterans, the mean ± SD age was 65 ± 11 years old and included 3% females and 14% African Americans. The cohort also included 28% of patients with non-dialysis-dependent CKD (eGFR <60 mL/min/1.73 m^2), as well as 28% of patients with albuminuria (≥30 mg/g). The median (IQR) of serum TG was 148 (100, 222) mg/dL. We observed a slight positive linear association between TG and incident CKD after adjustment for Case-Mix and Laboratory variables among non-albuminuric and microalbuminuric patients.

karger@karger.com
www.karger.com/ajn

Correspondence to:
Elani Streja, estreja@hs.uci.edu

The relationship of high TG trended towards a higher risk of ESRD in CKD 3A non-albuminuric patients and in CKD 3A and 4/5 patients with microalbuminuria. ***Conclusion:*** In a large cohort, we have shown that elevated TGs are associated with all kidney outcomes tested independently of other metabolic syndrome components in diabetic patients with normal eGFR and normal albumin excretion rate, but the association is weaker in some groups of diabetic patients with preexisting renal complications.

Introduction

Approximately 40% of patients with type II diabetes develop diabetic kidney disease, the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the USA [1]. Whereas not all patients with type II diabetes develop CKD or ESRD, albuminuria (Alb), a main feature of diabetic kidney disease, can serve as a key factor associated with CKD and is a preferred method for kidney disease staging and management [2]. Microalbuminuria and macroalbuminuria are defined as having a urinary albumin/creatinine ratio (UACR) of 30–300 mg/g and >300 mg/g, respectively. Both are shown to be early factors associated with kidney and cardiovascular disease in the general population [3]. The exact mechanism of action is not completely understood; however, it is believed to be due to endothelial damage of the renal glomeruli [4].

Hypertriglyceridemia, a component of metabolic syndrome, is also a known independent risk factor for Alb and kidney disease in the general population [5, 6]. Compounding the situation further, hypertriglyceridemia is associated with obesity and insulin resistance, both of which contribute to the progression of kidney disease [7]. Previous studies have shown associations between each component of metabolic syndrome, including triglycerides (TGs), and renal outcomes, indicating the need to study this relationship in diabetic patients [6]. Studies evaluating the association between hypertriglyceridemia and Alb in patients with type II diabetes are scarce, while others have been conducted on patients with type I diabetes which is less associated with metabolic syndrome and insulin resistance. Additionally, studies on type II diabetes patients did not report microalbuminuria and macroalbuminuria values separately [8, 9].

In this study, we sought to examine the relationship of TGs with incident microalbuminuria and macroalbuminuria, separately, among patients with UACR <30 mg/g, with consideration for other metabolic syndrome components. In addition, we evaluate the association of serum TGs and time to ESRD or incident CKD among and across different stages of kidney function and Alb.

Methods

Primary Study Population

The source population comprised patients who received at least one serum lipid measurement at any US Veterans Affairs (VA) medical center between fiscal years 2004 and 2006. The construction of LIPROVET (lipid profiles and management in veterans with CKD) has been previously described elsewhere [10]. Given the large sample size, nonintrusive nature, and patient anonymity, required written consent was waived. This study was approved by the Institutional Review Board of the Tibor Rubin VA Medical Center in Long Beach, CA.

For this study, we excluded patients for missing a serum TG measurement during the study period, with ESRD, missing an estimated glomerular filtration rate (eGFR) measurement prior to the TG measurement, invalid censoring information, missing data on metabolic syndrome components, being nondiabetic, and missing an UACR measurement prior to the TG measurement. The final study cohort included 138,675 diabetic patients with valid data on TG, eGFR, and UACR (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529414). We examined three outcomes: (I) time to ESRD, (II) time to incident CKD among 99,705 non-CKD patients, and (III) time to incident Alb among 100,129 Alb A1 patients.

Demographics and Clinical Measurements

Clinical records from the VA, Centers for Medicare and Medicaid Services (CMS), and the United States Renal Data System were combined for the ascertainment and measurement of demographic characteristics [10]. Data on select lipid, hypertension, and diabetes medication at the time of the TG measurement were obtained from VA and CMS databases only. Combined VA and CMS databases sourced data on chronic conditions using ICD-9 codes recorded within 2 years prior to the TG measurement. Data on indications of ever being a smoker or ever being an alcoholic were measured by the VA databases only [11]. Patients with either a recent comorbid diagnosis or medication prescription for diabetes were included in this cohort [12].

Data on laboratory measurements, including TG and eGFR, were only sourced from VA records. All low-density lipoprotein cholesterol values were calculated with the Martin-Hopkins equation, while all eGFR values were calculated with the CKD-EPI equation [13, 14]. Laboratory measurements of UACR or divided measurements of urine albumin and urine creatinine recorded on the same day were used in analyses. Measurements indicating urine protein or proteinuria were not included as UACR. eGFR values were used for CKD staging: non-CKD, 3A, 3B, and combined 4/5 (≥60, 45–<60, 30–<45, and <30 mL/min/1.73 m^2, respectively) [15]. UACR values were used for Alb staging as: Alb A1, A2, and A3 (<30, 30–300, and >300 mg/g, respectively) [16]. Metabolic syndrome components were defined by laboratory values, medications, or chronic conditions, as applicable (online suppl. Table 1) [17]. Measurements of waist circumference were

Table 1. Patient characteristics stratified by serum TG group

		Serum TGs (mg/dL)					
	Total	<80	80–<120	120–<160	160–<200	200–<240	≥240
N (%)	138,675	19,435 (14)	29,922 (22)	26,715 (19)	19,631 (14)	13,420 (10)	29,552 (21)
EGFR, mL/min/1.73 m^2	73 (58, 88)	75 (60, 90)	73 (58, 88)	72 (57, 87)	72 (57, 87)	72 (57, 88)	74 (58, 91)
eGFR category (%)							
G1/G2	72	75	72	71	70	71	72
G3a	18	16	18	19	19	19	17
G3b	8	7	8	9	9	9	9
G4/G5	2	1	2	2	2	2	2
Alb stage (%)							
A1	72	75	74	73	72	72	68
A2	24	22	23	23	24	24	27
A3	4	3	4	4	4	4	5
Age, years	65±11	67±11	67±11	66±11	66±10	65±10	62±10
Gender (% female)	3	2	2	3	3	3	3
Race (%)							
White	81	70	78	82	84	85	86
African American	14	26	18	14	11	10	8
Other	5	4	5	4	5	5	5
Hispanic ethnicity (%)	4	4	4	4	4	4	4
CCI	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Comorbid conditions (%)							
MI	7	6	8	8	8	8	7
CHF	12	12	13	13	12	12	11
PVD	12	12	13	13	12	12	11
Cerebrovascular disease	9	9	10	10	10	9	8
Dementia	2	2	2	1	2	2	1
COPD	17	16	17	17	17	17	17
Liver disease	3	3	3	3	3	2	3
Cancer	11	12	12	12	11	11	9
Anemia	7	7	7	7	7	7	7
Atrial fibrillation	7	7	7	7	7	6	6
Hypertension	85	82	85	85	85	85	85
ISHD	35	32	36	36	36	37	35
Depression	18	14	15	17	18	19	23
Substance abuse	4	5	4	4	4	4	5
Ever smoking	64	60	63	64	65	66	68
Ever alcoholism	15	17	15	15	14	14	14
Laboratory measurements							
Albumin, g/dL	4.0±0.4	3.9±0.4	4.0±0.4	4.0±0.4	4.1±0.4	4.1±0.4	4.1±0.4
ALP, U/L	70 (57, 87)	69 (56, 86)	70 (57, 86)	70 (57, 86)	70 (57, 86)	70 (57, 86)	72 (58, 89)
AST, U/L	22 (18, 27)	22 (18, 27)	22 (18, 27)	22 (18, 27)	22 (18, 27)	22 (18, 27)	23 (18, 29)
ALT, U/L	25 (18, 35)	22 (17, 32)	23 (17, 33)	24 (18, 34)	25 (18, 35)	25 (19, 36)	27 (20, 39)
Glucose, mg/dL	150.2±61.8	136.1±53.9	140.5±54.2	145.3±55.7	150.4±58.7	154.3±60.8	172.1±74.4
Hemoglobin A1c (%)	7.4±1.6	7.2±1.5	7.2±1.4	7.3±1.5	7.4±1.5	7.4±1.6	7.8±1.8
Hemoglobin, g/dL	14.1±1.6	13.7±1.6	13.9±1.6	14.1±1.6	14.3±1.6	14.3±1.6	14.4±1.6
WBC, x $10^3/mm^3$	7.3±2.7	6.8±2.5	7.2±2.7	7.3±2.7	7.5±2.9	7.5±2.3	7.6±2.6
SBP, mm Hg	136±19	135±19	136±19	136±19	136±19	136±19	137±19
DBP, mm Hg	74±11	72±11	73±11	73±11	74±11	74±11	75±11
BMI, kg/m^2	32±6	29±6	31±6	32±6	32±6	33±6	33±6
Lipid Panel, mg/dL							
TGs	148 (100, 222)	64 (54, 72)	100 (90, 110)	138 (129, 148)	178 (168, 188)	217 (208, 228)	321 (271, 416)
HDL	38 (33, 46)	46 (39, 56)	41 (35, 49)	39 (33, 45)	37 (32, 43)	36 (31, 42)	34 (30, 40)

Table 1 (continued)

		Serum TGs (mg/dL)					
	Total	<80	80–<120	120–<160	160–<200	200–<240	≥240
Cholesterol	164 (142, 190)	147 (128, 169)	153 (134, 175)	160 (140, 183)	166 (146, 190)	172 (151, 197)	189 (164, 220)
LDL	96 (79, 117)	85 (69, 102)	91 (76, 110)	96 (79, 116)	100 (82, 120)	101 (85, 124)	105 (86, 129)
Medications (%)							
Statin	50	47	52	52	52	52	48
Ezetimibe	1	1	1	1	1	1	1
Non-statin	12	7	8	11	12	14	19
Fibrate	8	3	5	7	8	10	14
Niacin	3	3	3	3	3	4	4
Fish oil	0.3	0.2	0.2	0.3	0.3	0.5	0.6
Bile acid sequestrants	0.6	0.5	0.5	0.7	0.7	0.7	0.8
RAAS inhibitor	56	54	56	56	57	57	57

Data are presented as mean ± standard deviation, median (interquartile range), or percentage, as appropriate. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; ISHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PTSD, post-traumatic stress disorder; PVD, peripheral vascular sisease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; WBC, white blood cell count.

highly missing in the database and elevated body mass index (BMI) was used as a proxy measure.

Exposure and Outcome Assessment

The earliest TG measurements within the study period were categorized into the following: <80, 80–<120, 120–<160 (reference), 160–<200, 200–<240, and ≥240 mg/dL [10]. We then explored the relationship between TG and the following outcomes: ESRD with the receipt of renal replacement therapy, incident CKD, and incident Alb. Transition to ESRD was defined by the date of first service from United States Renal Data System records. Incident CKD among non-CKD patients was defined by having at least two eGFR values measured at least 90 days apart, where the eGFR was <60 mL/min/1.73 m^2 and never rose above this threshold over follow-up [15]. Incident Alb was similarly defined among Alb A1 patients using UACR measurements. Alb categories for outcomes included ≥30, 30–300, and >300 mg/g. Patients were followed from the date of their TG measurement and were censored for lost to follow-up, death, ESRD, December 31, 2014 (administrative), or incidence of CKD or Alb.

Statistical Analysis

Clinical characteristics for the cohort and stratified by TG group are presented in Table 1. Data are presented as mean ± standard deviation, median (interquartile range), or percentage.

We used Cox proportional hazards models to evaluate the association of TG and our renal outcomes. Analyses were stratified by both CKD (eGFR category) and Alb stage, as applicable. Levels of covariate adjustments were the following: (1) unadjusted, (2) age, (3) Case-Mix adjusted, which included age, gender, race, ethnicity, ever smoker, ever alcoholic, and the following comorbid conditions: Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disorder, dementia, liver disease, cancer, atrial fibrillation, hypertension, depression, ischemic heart disease, and prescription of statins, non-statins, and renin-angiotensin-aldosterone system inhibitors, (4) Case-Mix+Lab adjusted, which included the same variables as the Case-Mix model, as well as albumin, eGFR, logged UACR, BMI, hemoglobin A1c, and HDL. We performed tests of trend to evaluate the linear relationship between very low (<80 mg/dL) and very high (≥240 mg/dL) levels of TG and outcomes, across ordinal levels of CKD stage. In sensitivity analyses, we also examined the fold-change in UACR measured at baseline and 3 years among N = 79,413 Alb A1 patients with available data. Case-Mix+Lab-adjusted logistic regressions were performed to evaluate the odds of a fold-change >1.5 (vs. ≤1.5) and stratified by baseline CKD stage as another evaluation of changes in Alb.

Data on clinical characteristics, smoking, and alcoholism were missing for <0.4%, 3%, and 15% of the cohort, respectively, and were imputed using a missing category. Albumin, hemoglobin A1c, and HDL were missing for 30%, 18%, 0.4% of the cohort, respectively, and were imputed by means. All analyses were performed using SAS Enterprise Guide (7.1) (Cary, NC).

Results

In a cohort of 138,675 diabetic veterans, the mean ± SD was 65 ± 11 years old and included 3% females and 14%

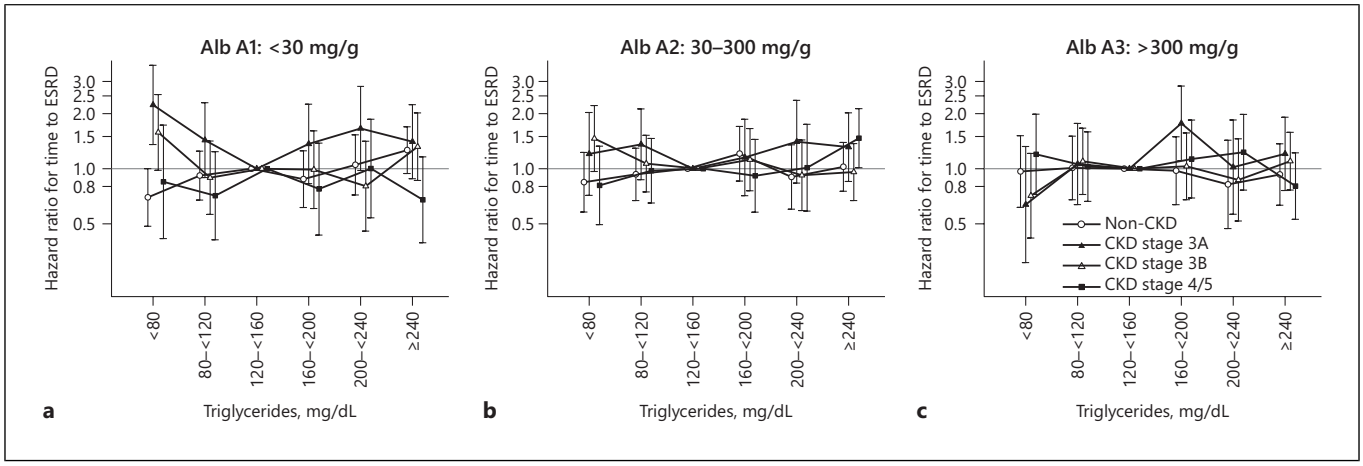

Fig. 1. Association of serum TGs and time to ESRD in Case-Mix+Lab adjustment across stages of CKD and Alb: (**a**) A1, (**b**) A2, and (**c**) A3. Case-Mix+Lab: age, gender, race, ethnicity, ever smoking, ever alcoholic, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, atrial fibrillation, hypertension, depression and ischemic heart disease, prescription of statins, non-statins, and RAASi, and albumin, eGFR, logged UACR, BMI, HgbA1c, and HDL. RAASi, renin-angiotensin-aldosterone system inhibitors; HgbA1c, hemoglobin A1c.

African Americans (Table 1). The cohort also included 28% of patients with nondialysis-dependent CKD, as well as 28% of patients with Alb (≥30 mg/g). The median (IQR) of serum TG was 148 (100, 222) mg/dL. The patients with elevated TG were more likely to be younger, white, depressed, a smoker, obese, and be prescribed a non-statin. Yet, these patients were also less likely to have had cancer and be an alcoholic. Similarly, we also stratified clinical characteristics by Alb stage (online suppl. Table 2). Patients with the highest level of Alb were less likely to be white but have a higher prevalence of chronic conditions including cardiovascular disease subtypes.

Serum TGs and Time to ESRD Stratified by CKD (eGFR Category) and Alb Stages

We observed 3,219 veterans who transition to ESRD over a follow-up of 9.6 (7.2, 10.0) years, resulting in a crude rate of 2.82 (2.72, 2.91) events per 1,000 person-years (online suppl. Table 3A). In unadjusted analyses, patients with Alb A1 and non-CKD had a linear relationship between TG and transition to ESRD, while this relationship was U-shaped for those with CKD stage 3A–3B. Additional adjustments for Case-Mix and Lab covariates reflected a similar pattern for Alb A1 patients (Fig. 1a; online suppl. Table 4A). Compared to the reference TG 120–<160 mg/dL, the positive relationship between TG ≥240 mg/dL and risk of ESRD transition diminished across CKD stage, where the relationship was attenuated for CKD stage 4/5 patients (p trend = 0.047). In Alb A1 patients, low TG <80 mg/dL were associated with a lower risk of ESRD transition in non-CKD patients, yet a higher risk in CKD stage 3A–3B patients.

In Alb A2 patients, we observed an attenuated relationship between low TG <80 mg/dL and time to ESRD after adjustment for Case-Mix and Lab covariates (Fig. 1b; online suppl. Table 4B). Likewise, we observed a U-shaped relationship with TG in CKD stage 3A patients only. The elevated risk with TG ≥240 mg/dL was observed in patients with CKD 3A and 4/5. Both non-CKD and CKD stage 3B patients with TG ≥240 mg/dL had a null risk with ESRD. Finally, patients with Alb A3 had a higher crude rate of transition to ESRD, yet relationships were less clear in this group. The relationship of low TG trended toward a lower risk of ESRD among CKD stage 3A and 3B patients compared to the reference (Fig. 1c; online suppl. Table 4C). However, Alb A3 patients with elevated TG did not have a clear pattern in risk of ESRD across CKD stages (p trend = 0.73). Notably, patients with both Alb A3 and CKD stage 3A and TG 160–<200 mg/dL had a higher adjusted risk of ESRD compared to the reference.

Serum TGs and Time to Incident CKD in Non-CKD Patients Stratified by Alb Stage

Among the 99,705 patients with non-CKD, we observed a crude rate of 26.7 (26.4, 27.1) incident CKD events per 1,000 person-years over follow-up (online suppl. Table 3B). In age-adjusted analyses, we observed a slight positive linear relationship between TG and time to

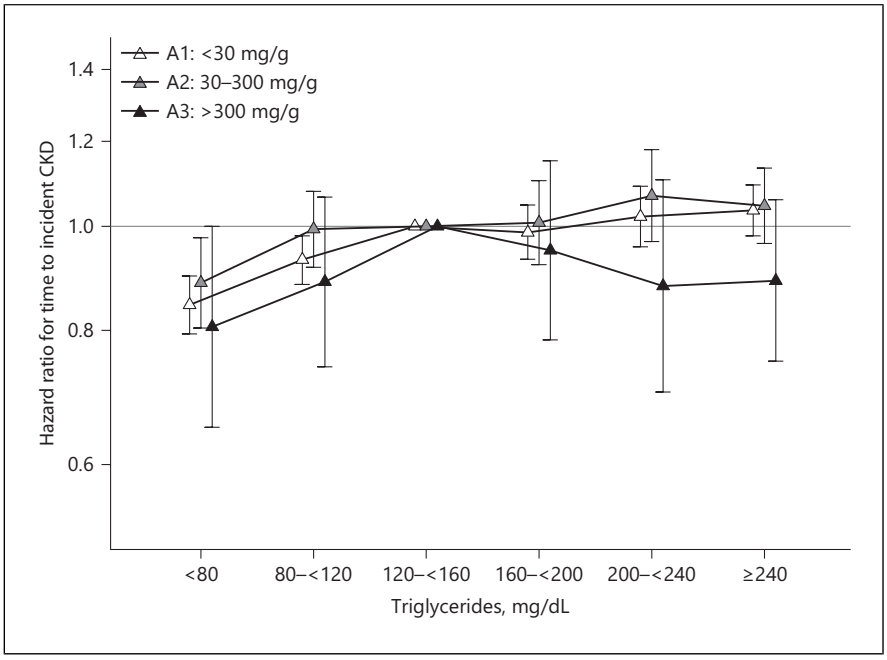

Fig. 2. Association of serum TGs and time to incident CKD in Case-Mix+Lab adjustment among Non-CKD patients and across Alb stages. Case-Mix+Lab: age, gender, race, ethnicity, ever smoking, ever alcoholic, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, atrial fibrillation, hypertension, depression and ischemic heart disease, prescription of statins, non-statins, and RAASi, and albumin, eGFR, logged UACR, BMI, HgbA1c, and HDL. RAASi, renin-angiotensin-aldosterone system inhibitors; HgbA1c, hemoglobin A1c.

incident CKD in Alb A1 and A2 patients, where those with high TG had a higher risk (online suppl. Table 5). Conversely, patients with Alb A3 yet elevated TG had a lower risk of incident CKD in age-adjusted analyses. These relationships were similar yet attenuated after further adjustment for Case-Mix and Lab covariates (Fig. 2). Patients with low TG had a lower risk of incident CKD across all Alb stages, while the high risk for incident CKD and elevated TG was attenuated for Alb A1 and A2 patients. Patients with Alb A3 trended toward a lower risk of incident CKD for all TG levels.

Serum TGs and Time to Incident Alb in Alb A1 Patients Stratified by CKD Stage

Finally, in 100,129 patients with Alb A1, we observed a crude rate of 21.1 (20.7, 21.4) incident Alb ≥30 mg/g per 1,000 person-years (online suppl. Table 3). In unadjusted analyses, we observed a linear relationship between TG and time to incident Alb ≥30 mg/g in non-CKD, CKD stage 3A–3B patients, while the relationship for patients with CKD stage 4/5 was less clear (online suppl. Table 6). Case-Mix and Lab adjustment identified a flat relationship between TG and incident Alb ≥30 mg/g for lower CKD stages (Fig. 3a). Moreover, we observed a more pronounced U-shaped relationship with TG among CKD stage 4/5 patients, albeit with large confidence intervals. In CKD stage 4/5 patients, TG <80 and ≥240 mg/dL were associated with a 1.35 and 1.25 times risk compared to the reference group. We observed a noticeable upward trend between high TG and incident Alb in increasing CKD stages (p trend <0.0001). Across levels of adjustment, the relationships with TG and incident Alb 30–300 mg/g were similar (online suppl. Fig. 2).

Finally, we explored the relationship between TG and incident Alb >300 mg/g. We observed a far lower crude rate of 1.95 (1.85, 2.04) events per 1,000 person-years. Like previous analyses, the relationship between TG and incident Alb >300 mg/g in non-CKD patients was linear after adjustment for Case-Mix and Lab covariates (Fig. 3b; online suppl. Table 7). The relationship for CKD stage 3A and 3B patients was somewhat attenuated; however, we observed a higher risk of Alb >300 mg/g with high TG. The HR (95% CI) for TG ≥240 mg/dL for CKD stage 3A and 3B was 1.41 (0.98, 2.21) and 1.73 (1.09, 2.74), respectively. We were unable to sufficiently evaluate this relationship among CKD stage 4/5 patients given low power yet also observed a similar increasing trend with advancing CKD stages (p trend <0.0001).

Sensitivity Analyses

Among 79,413 patients with baseline Alb A1 and a subsequent UACR measurement within 3 years of the start of the study, we calculated a fold-change to characterize the difference in UACR levels relative to a patient's baseline value. For Alb A1 patients, the odds ratio of an elevated fold >1.5 demonstrated a similar relationship to our incident Alb analyses (online suppl.

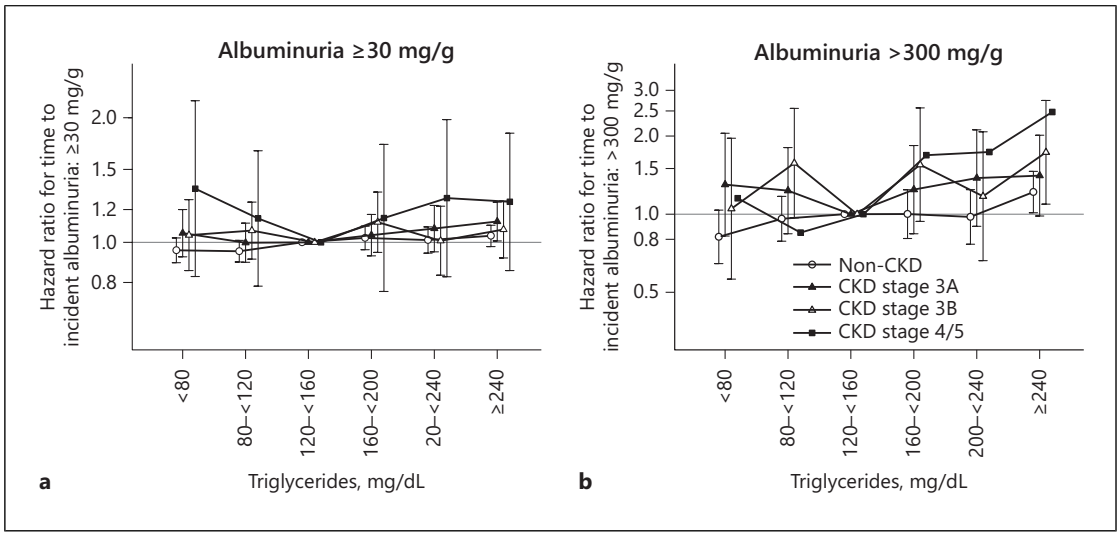

Fig. 3. Association of serum TGs and time to incident Alb of ≥30 mg/g (**a**) and >300 mg/g (**b**) in Case-Mix+Lab adjustment among Alb A1 patients. Case-Mix+Lab: age, gender, race, ethnicity, ever smoking, ever alcoholic, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, atrial fibrillation, hypertension, depression and ischemic heart disease, prescription of statins, non-statins, and RAASi, and albumin, eGFR, logged UACR, BMI, HgbA1c, and HDL. RAASi, renin-angiotensin-aldosterone system inhibitors; HgbA1c, hemoglobin A1c.

Fig. 3). Non-CKD and CKD stage 3A–3B patients demonstrated a flat relationship between TG and an elevated fold-change, where non-CKD and CKD stage 3A patients had higher odds. While the relationship among CKD stage 4/5 patients was largely attenuated, it similarly trended toward higher odds of an elevated UACR change.

Discussion

The main finding of our study is that in patients with diabetes, normal eGFR, and normal albumin excretion, TGs are positively associated with the time to proteinuria, onset of CKD defined as eGFR <60 mL/min/1.73 m^2, and ESRD and that this relationship can be extended to some of the patients with CKD. In our previous study using data from the same cohort, higher TGs have also been identified as a risk factor for deterioration of eGFR and shortened time to renal replacement therapy [18]. However, the present study in patients with diabetes further defines the association by also examining albumin excretion data and shows this association seems to be limited to patients with normal baseline eGFR and albumin excretion rate and certain groups of patients with microalbuminuria and advanced CKD.

Our study on US veterans with diabetes confirms the findings from the general population where hypertriglyceridemia as a component of the metabolic syndrome has been shown to be independently associated with incident Alb. This was reported in Chinese [19], Korean [20], Japanese [21], Italian [22], and Native American [23] populations. The Chinese medical literature describes a risk factor for kidney disease and cardiovascular outcomes labeled "hypertriglyceridemic waist," emphasizing the role of hypertriglyceridemia within the features of metabolic syndrome [24].

Type II diabetes studies have shown a similar association, but most of the studies did not separate microalbuminuria from proteinuria. In the Italian Association of Clinical Diabetologists Study [9], which aimed to look at predictors of individual components of diabetic kidney disease and their relationship with traditional risk factors, for every 10 mg/dL higher TG level, the risk of increased albumin excretion was 1% higher. Similarly, the increase in risk was reported to be 12% per mmol in the Swedish National Diabetes Register [8] and 10% per mmol in a Finnish study [25]. In a single-center study in Asian patients, the association was reported to be 39% higher per mmol [26], suggesting a stronger relationship in Asian patients. In another study, the time to onset of microalbuminuria was higher if more than 50% of TG levels were above 150 mg/dL [27]. Similar studies were

reported in patients with type I diabetes, where, as opposed to type II diabetes, metabolic syndrome and insulin resistance are not the main features of the disease [28, 29].

In our study, we separated microalbuminuria onset from proteinuria onset and we used time to onset as a measure of the effect. There was a shorter time to onset of proteinuria, while microalbuminuria was not associated with elevated TGs. This was true for all stages of CKD. In our study, we also reported that in patients without CKD (defined by eGFR ≥60 mL/min/1.72 m^2) at baseline, low TGs were associated with a lower risk of development of proteinuria but not microalbuminuria. Patients with diabetes and decreased eGFR have two distinct phenotypes: albuminuric and non-albuminuric [30]. The albuminuric diabetic nephropathy is more rapidly progressing [31], and increases in UACR over time in this group are associated with subsequent decline of eGFR [32]. The transition from non-albuminuric to albuminuric phenotype is insufficiently studied. In our study, 22.7% of the CKD patients with non-albuminuric phenotype at baseline developed UACR >30 mg/g. We believe that this group of patients who switched phenotype will need to be studied in observational studies and possibly targeted for TG-lowering therapies in randomized clinical trials.

Microalbuminuria is associated with an inflammatory process [33], thus reflecting a range of inflammatory states such as metabolic syndrome (e.g., hypertension, hyperlipidemia, obesity, insulin resistance), infections, or rheumatologic diseases [33]. The content of TGs in the blood is largely influenced by dietary carbohydrate content and obesity [34]. Patients with a diet high in carbohydrates also tend to have higher levels of inflammation either through diet alone, being obese, or poor glycemic control, which are all related to a pro-inflammatory state. Hypertriglyceridemia may be a proxy of high inflammation, where hyperglyceridemia may be mediating the relationship between inflammation and renal outcomes. Unfortunately, data are limited in that reliable information on inflammatory markers to conduct mediation analyses were not available, but future studies should study this important research question.

We also reported that for the onset of CKD, low TGs are associated with a lower risk of the outcome irrespective of UACR, while high TGs are associated with a higher risk of the outcome in patients with normal UACR or with microalbuminuria but not with proteinuria. The relationship between triglyceride level and time to onset of CKD in the former groups is inverse. An increase in risk of CKD with elevation of TGs was reported in the Swedish National Diabetes Register with 20% increased risk per mmol TG concentration [8]. Other studies reported the association between incidence of CKD and hypertriglyceridemia but with no decrease with increasing albumin excretion rate [9, 33]. In the Italian Association of Clinical Diabetologists Study [9], every 10 mg/dL higher TG level, the risk of decreased eGFR (<60 mL/min/1.73 m^2) was 2% in patients with normal albumin excretion rate and 3% in patients with increased albumin excretion rate. Moreover, the Renal Insufficiency And Cardiovascular Events Study [35] reported that in patients with type II diabetes, higher TG concentration is associated with a progressive increase in the risk of CKD and that the relationship was stronger with increasing severity of Alb. In a small Japanese study, Kitaoka et al. [36] reported post-meal triglyceridemia was associated with higher odds of nephropathy progression (similar to our cohort defined as changes in UACR) in multivariable adjusted models among 161 patients with normoalbuminuria (67.7%), microalbuminuria (28%), or macroalbuminuria (4.3%).

Lipotoxicity can contribute to kidney disease by inducing glomerulosclerosis, tubulointerstitial injury, and cellular lipid loading in both glomeruli and tubules [37]. Increased glomerular uptake of circulating lipids and tubular reabsorption of albumin-bound fatty acids result in increased deposition of TGs in the renal parenchymal cells. These lipids undergo chemical modification, leading to the formation of metabolites and free radicals that are damaging to the endothelium of renal microvessels [38, 39]. This can trigger the transforming growth factor expression in human glomerular epithelial cells, resulting in the accumulation of abnormal lipid and, eventually, glomerulosclerosis [40]. Previous studies have shown that the impact of TGs on CKD is evident only in CKD stage 3 but not in CKD stage 4 and 5 [41], suggesting that intervention in correcting hypertriglyceridemia in patients with CKD should be performed as early as possible.

There are several limitations to these analyses. First, we excluded a large proportion of diabetic patients who were without a valid UACR measurement within the VA. The presence of diabetes is a clinical indication for UACR collection, and thus this select population may be representative of diabetic veteran patients who are more regular users of the VA medical system and under closer specialized VA care. Given the observational nature of this study, our analyses may be subjected to residual confounding such as diet and other adiposity-related factors. Our study population largely comprised males versus females (97.0 vs. 3.0%, respectively), which may limit generalizability to female patients, who may have differences in lipid metabolism and renal disease development

or progression due to sex hormones, sex chromosomes, sex hormone and sex chromosome interactions, or other genetic and epigenetic factors [42, 43]. Finally, while waist circumference is a standard measurement for metabolic syndrome, only 49 patients had available data, and so we used BMI ≥30 kg/m^2 as a surrogate marker [44]. Previous studies, however, reported a strong correlation between BMI and waist circumference (rho = 0.78) [45].

Yet, strengths of this study include the large number of diabetic veteran patients, with sufficient data to evaluate strata of CKD and Alb. Furthermore, the covariate rich datasets of the VA and CMS allowed for the detailed measurements of medication and laboratory data. Moreover, we required a strict definition in the evaluation of incident CKD and Alb to more conservatively identify renal outcomes.

Conclusion

In a large cohort, we have shown that elevated TGs are associated with all kidney outcomes in patients with normal eGFR and normal albumin excretion rate, but the association is weaker in patients with preexisting microvascular renal complications. Interventions addressing TG lowering have been shown to delay the onset or worsening of kidney outcomes for fenofibrate [46–48], niacin [49], and omega 3 fatty acids [50–52]. Clinical evidence has indicated that agents such as SGLT2 inhibitors (glucosuria effects) [53], thiazolidinediones, and some DPP-4 inhibitors can reduce the risk of development or worsening of Alb through a range of anti-inflammatory mechanisms and their effect on other conditions (e.g., obesity) that can have profound impact on the kidneys [53, 54]. Clinical trials should be conducted in patients with diabetes before the onset of microvascular complications to test the hypothesis that targeting TG concentration may prevent the development of kidney outcomes, which in turn are predictors of cardiovascular outcomes.

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Opinions expressed in this presentation are those of the authors and do not represent the official opinion of the US Department of Veterans Affairs or the US Government.

Statement of Ethics

This study was approved by the Institutional Review Board of the Tibor Rubin VA Medical Center of Long Beach, CA (decision reference number: 1406), which waived the requirement of informed consent because of the anonymous characteristics of the data.

Conflict of Interest Statement

K.K.Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, AstraZeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition & Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma. C.P.K. received honoraria from Abbott, Akebia, Astra Zeneca, Bayer, Boehringer Ingelheim, CSL Behring, CSL Vifor, Cara Therapeutics, GSK, Rockwell, Takeda and Tricida. Other authors do not have a conflict of interest. Results have been presented at the virtual 2020 American Society of Nephrology Kidney Week.

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Author Contributions

Conception and design: Elani Streja, John Rizk, and Kamyar Kalantar-Zadeh. Analysis and Interpretation of the data: Elani Streja, John Rizk, Jui-Ting Hsiung, and Yousif Arif. Writing – original draft, writing – review and editing, revision for intellectual content, and final approval of the version to be published: John G. Rizk, Jui-Ting Hsiung, Yousif Arif, Leila Hashemi, Keiichi Sumida, Csaba P. Kovesdy, Kamyar Kalantar-Zadeh, and Elani Streja. All authors agree to be accountable for all aspects of the work and meet the criteria for authorship as per the ICMJE criteria.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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