Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 474–479

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Albuminuric and non-albuminuric patterns of chronic kidney disease in type 2 diabetes

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ARTICLE INFO

Article history:
Received 22 September 2018
Accepted 2 November 2018

Keywords:
Diabetes
Diabetic nephropathy
Chronic kidney disease
Albuminuria
Glomerular filtration rate

ABSTRACT

A growing body of evidence supports a shift in the natural history of chronic kidney disease (CKD) in subjects with diabetes. Specifically, normoalbuminuric chronic kidney disease (NA-CKD), which is characterized by a decline in the glomerular filtration rate in the absence of a preceding or accompanying elevation of albuminuria, has become a widely prevalent variant of renal impairment in diabetes. Diabetic women and nonsmoking individuals with better glycemic control have a better chance of preserving normoalbuminuria, even in the case of declining renal function. The wide use of renin-angiotensin system blockers, advances in antihyperglycemic, antihypertensive, and hypolipidemic therapy, and smoking cessation are suspected to be responsible for an increasing proportion of NA-CKD among diabetic subjects with renal impairment. Significant differences in the sets of risk factors, renal morphology, comorbidity, and outcomes were found between the albuminuric and normoalbuminuric CKD patterns. NA-CKD, even if a more favorable option in terms of the risk of end-stage renal disease, is clearly associated with cardiovascular disease and its risk factors. The presence of NA-CKD in patients with diabetes increases the risk of myocardial infarction, stroke, and cardiovascular death. The study of the molecular pathways, clinical course, and outcomes of NA-CKD in diabetic subjects and the search for more specific diagnostic and treatment options are challenges for future research.

1. Introduction

In most developed countries, type 2 diabetes (T2D) is presently the leading cause of end-stage renal disease (ESRD). In countries with weaker economies, T2D is rapidly replacing communicable diseases as a leading cause of kidney failure [1]. At the same time, modern studies indicate not only the high worldwide prevalence of diabetic kidney disease (DKD) but also a change in its natural history. According to the classical paradigm, the clinical course of DKD is characterized by a progressive increase in albuminuria, followed by a decline in the glomerular filtration rate (GFR). In this paradigm, microalbuminuria is considered to be the equivalent of an early and potentially reversible stage of diabetic nephropathy. The data accumulating in recent years indicate a distinct shift in the clinical course of DKD due to the increase in the normoalbuminuric chronic kidney disease (NA-CKD) pattern. This trend is more evident in T2D subjects [2,3].

In this review we summarized data on epidemiology, pathology and pathogenesis, natural course and diagnosis of NA-CKD in patients with T2D. An in-depth literature search was conducted to identify studies that examined the prevalence and characteristics of NA-CKD in diabetic subjects. The eligible studies were searched from PubMed, Scopus and Web of Science up to 08 July 2018 using the terms “type 2 diabetes”, “albuminuria”, and “glomerular filtration rate”. We analyzed the data from cross-sectional and prospective studies reporting proportions of T2D individuals with increased urinal albumin excretion rate (AER) and decreased GFR. Specifically, the prevalence of diabetic individuals with elevated AER, eGFR less than 60 mL/min × 1.73 m^2 and NA-CKD were taken into consideration.

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https://doi.org/10.1016/j.dsx.2018.11.014
1871-4021/

2. Epidemiology: NA-CKD is an emerging pattern of renal impairment in diabetes

The contemporary traits of the natural history of DKD were identified in some epidemiological studies. The National Health and Nutrition Examination Surveys (NHANES) were conducted in the USA, with 6521 adult diabetic individuals included. Among them, the overall prevalence of CKD did not noticeably shift over time, from 28.4% in 1988–1994 to 26.2% in 2009–2014. However, the prevalence of albuminuria decreased from 20.8% to 15.9%, whereas the prevalence of reduced estimated glomerular filtration rate (eGFR) increased from 9.2% to 14.1%, and the prevalence of severely reduced eGFR (<30 mL/min × 1.73 m^2) increased from 1.0% to 2.7%. Significant heterogeneity in the temporal trend for albuminuria was noted by age ($p = 0.049$ for interaction) and race/ethnicity ($p = 0.007$ for interaction), with a decline in prevalence observed only among adults younger than 65 years and non-Hispanic whites. In contrast, no significant heterogeneity in the temporal trend for reduced eGFR was observed [4].

A study of CKD in diabetic Pima Indians (Arizona, USA) showed a similar trend. In the first period of the study (1982–1988), 6.5% of 837 subjects with T2D had eGFR <60 mL/min × 1.73 m^2. Of these subjects, 83.3% had macroalbuminuria, whereas only 7.4% were microalbuminuric, and 9.3% of patients demonstrated normal urinary albumin-to-creatinine ratio (UACR). Among 1310 subjects in the second period of the study (2001–2006), the prevalence of reduced eGFR was similar (6.6%). Among those with reduced eGFR, normal UACR prevalence doubled to 17.2%, and microalbuminuria prevalence nearly tripled to 19.5%. At the same time, the prevalence of macroalbuminuria declined to 63.2%. The age- and sex-adjusted logarithm of the average UACR levels changed significantly over time in the study population ($p = 0.01$), more significantly in those with low eGFR ($p = 0.0003$). Twice as many subjects in the second period of the study received antihypertensive medicines, and 30% more received hypoglycemic medicines than did in the first period [5].

In the CRIC (Chronic Renal Insufficiency Cohort) study among 1980 US participants with diabetes and reduced GFR, a normal or mildly increased urinary albumin excretion rate (AER) was present in 28.4% of cases. Other participants demonstrated the albuminuric chronic kidney disease (A-CKD) pattern. Specifically, 27.5% of patients had microalbuminuria, 18.5% were macroalbuminuric (AER in the range of 300–999 mg/24 h), and 25.6% of participants demonstrated very high levels of AER [6].

A high prevalence of NA-CKD was observed in European diabetic populations also. The United Kingdom Prospective Diabetes Study (UKPDS) assessed the dynamics of the progression of CKD in subjects with T2D during the 15 years of the follow-up. Of 4006 patients with the requisite data, 1534 (38%) developed elevated albuminuria, 1132 (28%) showed renal impairment, and 557 (14%) individuals presented with both conditions. Of 1534 patients who developed albuminuria, 977 (64%) did not demonstrate renal impairment during the study, 372 (24%) progressed to renal impairment subsequent to albuminuria, and 12% showed renal impairment before albuminuria emergence. Of the 1132 patients who displayed renal impairment, 51% of subjects remained normoalbuminuric during follow-up, 16% developed albuminuria subsequent to renal impairment, and 33% developed albuminuria prior to a decline in renal function [7].

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) study, which included 10640 individuals with T2D, the UACR levels at baseline were in the normoalbuminuric, microalbuminuric, and macroalbuminuric range in 69%, 27%, and 4% of cases, respectively. The proportion of subjects with eGFR <60 mL/min/1.73 m^2 was 19%, while 0.4% of patients had eGFR <30 mL/min × 1.73 m^2. A total of 62% of patients with eGFR <60 mL/min × 1.73 m^2 were normoalbuminuric [8].

A similar trait was observed in the Italian multicenter Renal Insufficiency and Cardiovascular Events (RIACE) study, with 15773 T2D patients included. Among the individuals with a GFR of less than 60 mL/min × 1.73 m^2, 56.6% of subjects retained normal AER, 30.8% had microalbuminuria, and 12.6% were macroalbuminuric [9]. Among 11338 individuals with T2D and renal impairment (eGFR <60 mL/min × 1.73 m^2) enrolled in the Swedish National Diabetes Register, elevated AER was present in only 34.2% of patients [10]. In a cross-sectional study with a random sample of 2642 T2D patients in Spain, the prevalence of eGFR <60 mL/min × 1.73 m^2 was estimated to be 22.9%, and the prevalence of NA-CKD was 14.7% [11].

The National Evaluation of the Frequency of Renal impairment cO-existing with Noninsulin-dependent diabetes mellitus (NEFRON) survey collected data from 3893 individuals with T2D in Australia. In this study, 23.1% of subjects had eGFR <60 mL/min × 1.73 m^2, and 34.6% of participants had elevated UACR. An overlap of both a reduced eGFR and an elevated UACR was revealed in 10.4% of cases. In those with CKD, 27.3% had microalbuminuria, and 7.3% were macroalbuminuric. More than half (55%) of patients with eGFR <60 mL/min × 1.73 m^2 demonstrated normal AER [12].

Currently, the epidemiological data on the prevalence of NA-CKD from other parts of the world are limited. It was reported that among 1197 Japanese patients with T2D, the proportion of normal AER was 58%, while 42% of participants had microalbuminuria or macroalbuminuria. In the normoalbuminuria group, 223 (32%) cases showed CKD stage 3 or 4 [13].

The results of epidemiological and clinical studies estimating the prevalence of the signs of CKD in T2D subjects are summarized in Table 1. The data indicate that although the albuminuric pattern remains the most frequent variant of CKD in the general population of diabetic patients, those with NA-CKD make up a substantial proportion among T2D subjects with renal impairment.

3. Risk factors and renal pathology in albuminuric and non-albuminuric DKD: are there any differences?

The causes of the increasing prevalence of NA-CKD in patients with diabetes are not fully understood. Among others, the wide use of renin-angiotensin system blockers, advances in antihyperglycemic, antihypertensive, and hypolipidemic therapy, and smoking cessation are discussed [2,5,14]. New classes of antihyperglycemic agents, including GLP-1 analogs, DPP-4 inhibitors, and SGLT2 inhibitors, have demonstrated a distinct antialbuminuric effect in clinical trials [15–18]. It could be anticipated that the growing use of these drugs in clinical practice will contribute to a further increase in the proportion of NA-CKD among subjects with T2D and renal impairment.

Some studies have addressed the risk factors and comorbidity of two patterns of CKD in diabetic individuals. In the RIACE study, NA-CKD was more prevalent among women with T2D and was associated with cardiovascular disease [9]. It was demonstrated that among subjects with T2D and eGFR ≤30 mL/min × 1.73 m^2, women and nonsmoking individuals a have better chance of preserving normoalbuminuria. The subjects with reduced eGFR and normoalbuminuria, compared to those with A-CKD, demonstrated decreased levels of HbA1c [19]. In a Swedish 5-year prospective study, old age, high systolic blood pressure, and high triglycerides were independent predictors of both the development of albuminuria and renal impairment. Male sex, poor glycemic control (high HbA1c), low high-density lipoprotein cholesterol, and smoking showed an independent and significant association with

Table 1
The prevalence of CKD clinical manifestations in patients with diabetes.

Study, population	Years	N	Prevalence			Proportion of NA-CKD in patients with eGFR<60 mL/min × 1.73m^2, %	Ref.
			Elevated AER, %	eGFR<60 mL/min × 1.73m^2, %	NA-CKD, %		
National Health and Nutrition Examination Surveys (NHANES), USA	1988–1994	1431	20.8	9.2	7.6[a]	N/D	[4]
	2009–2014	2097	15.9	14.1	10.3[a]	N/D	
The study of CKD in diabetic Pima Indians, USA	1982–1988	837	47.4[a]	6.5	0.6	9.3	[5]
	2001–2006	1310	42.4[a]	6.6	1.1	17.2	
Chronic Renal Insufficiency Cohort (CRIC) Study, USA	2003–2008	1908	71.6	N/D	28.4	N/D	[6]
U.K. Prospective Diabetes Study (UKPDS), UK	1977–1997	4006	52.2[a]	42.2[a]	14.4[a]	50.8	[7]
Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation study (ADVANCE), Australasia, Asia, Europe and North America	2001–2008	10640	30.7[a]	19.1[a]	11.8	61.6[a]	[8]
The Renal Insufficiency and Cardiovascular Events (RIACE), Italy	2007–2008	15773	26.9[a]	17.1	9.4[a]	56.6	[9]
Study of NA-CKD in type 2 diabetic patients, Sweden	2003–2006	66065	23.9[a]	17.2[a]	10.2[a]	59.5[a]	[10]
CKD in the type 2 diabetic patients: of a Mediterranean area, GEDAPS 2007 Evaluation, Spain	2007	2642	19.5 (among 1478 patients)	22.9	14.7	71.1[a]	[11]
National evaluation of the frequency of renal impairment cO-existing with NIDDM (NEFRON), Australia	2005	3893	34.6	23.6	12.7	55.0	[12]
Study of CKD in diabetic patients in Japan	2008–2009	1197	43.7[a]	41.9	18.6	42.6[a]	[13]

AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NA-CKD, normoalbuminuric chronic kidney disease; N/D, No data available.
[a] The percentage is calculated from reported data.

the development of albuminuria but not with the decline in GRF. Female sex and high baseline creatinine levels were associated with an increased risk of renal impairment only [20]. In a cohort of Chinese T2D individuals, stratified into three groups with eGFR ≥90, 60–89 and 30–59 mL/min/1.73 m^2, the prevalence of diabetic retinopathy among these groups increased from 42.5%, 56.6%–66.7% in albuminuric subjects and from 29.4%, 33.0%–50.0% with no significant trend in patients with normal AER. Oppositely, the prevalence of low ankle-brachial index was gradually increased in normoalbuminuric subjects (17.5%, 22.6% and 44.4% in the groups with eGFR ≥90, 60–89 and 30–59 mL/min/1.73 m^2 respectively), but not in those with elevated albuminuria [21].

It was speculated that normoalbuminuric renal impairment represents a different pathway to the loss of renal function compared to that of an albuminuric one. The normoalbuminuric phenotype might be related to macroangiopathy instead of microangiopathy and/or be the consequence of repeated and/or unresolved episodes of acute kidney injury, even of a mild degree [3].

Some differences between A-CKD and NA-CKD were revealed by morphological investigations. It was demonstrated that normoalbuminuric type 1 diabetic subjects with GFR <90 mL/min × 1.73 m^2 have more evident glomerular involvement, as estimated by an increased width of the glomerular basement membrane and the volume of the mesangial matrix when compared to that of patients with normal AER and eGFR ≥90 mL/min × 1.73 m^2 [22]. Proteinuria in type 1 diabetic subjects is related to podocyte detachment [23]. Similarly, an increase in albuminuria in patients with T2D is associated with thickening of the basal membranes, mesangial expansion and podocyte damage [24,25]. At the same time, renal structural changes are more heterogeneous in T2D, while tubulointerstitial changes, arteriolosclerosis and global fibrosis of some glomeruli can predominate over the typical manifestations of glomerulopathy [26]. The morphology of NA-CKD in patients with T2D is poorly understood. When compared renal biopsy findings, associated with either normo-, micro-, or macroalbuminuria, in T2D subjects with eGFR and measured GFR of <60 mL/min/1.73 m^2, Ekinci E.I. et al. revealed typical glomerular changes mostly in patients with elevated albuminuria. At the same time, in those with NA-CKD, predominant interstitial and vascular changes were more frequent finds, which likely reflect greater contributions from aging, hypertension, and arteriosclerosis [27]. In Japanese people with T2D and the early stages of diabetic nephropathy (normoalbuminuria or microalbuminuria) the arteriolar hyalinosis score was positively correlated with AER and negatively correlated with GFR during 8.0 ± 3.5 years' follow-up [28].

The differences of molecular mechanisms of albuminuric and non-albuminuric patterns of DKD remain to be elucidated.

4. Natural course and outcomes of albuminuric and non-albuminuric DKD

Both increased albuminuria and reduced GFR are considered as predictors of ESRD and cardiovascular events in T2D subjects. In the ADVANCE study, during an average 4.3-year follow-up, 938 (8.8%) patients with T2D experienced a cardiovascular event, and 107 (1.0%) experienced a renal event. The multivariable-adjusted HR for cardiovascular events was 2.48 (95% CI 1.74–3.52) for every 10-fold increase in baseline UACR and 2.2 (95% CI 1.09–4.43) for every halving of baseline eGFR, after adjustment for regression dilution. There was no evidence of interaction between the effects of higher UACR and lower eGFR. Both the increase in UACR and the decrease in eGFR were independent predictors of nonfatal myocardial infarction, stroke, and cardiovascular death [8].

In cohort study of 4328 Japanese T2D individuals with median follow-up of 7 years, 419 renal events, 605 cardiovascular events and 236 deaths occurred. The UACR levels increased the risk and the adjusted hazard ratios for these three events. In addition to the effects of UACR levels, eGFR stages significantly increased the adjusted hazard ratios for renal events and all-cause mortality, especially in patients with macroalbuminuria [29].

The results of a nationwide observational study from the Swedish National Diabetes Register (66065 patients with T2D, with a follow-up of 5.7 years) confirm the notion that both albuminuria and renal impairment are independent risk factors for cardiovascular outcomes and mortality in T2D. During follow-up, a total of 10% of patients experienced a cardiovascular event, and 3.7% of those were fatal. Increasing levels of albuminuria and renal impairment were independently associated with an increased risk of cardiovascular events and all-cause mortality. In normoalbuminuric patients, a reduction in renal function was an important predictor of cardiovascular events and all-cause mortality. Glycemic control (high HbA1c), smoking, and hyperlipidemia had important effects on the risk of cardiovascular events in patients with albuminuria, while high blood pressure, but not glycemic control, had an effect in patients with normoalbuminuric renal impairment [10].

It is well known that progression of albuminuria and the rate of renal decline in T2D are highly heterogeneous. While most subjects with DKD show a slow decrease in kidney function, some patients develop a rapid decline in GFR, up to ESRD. In Joslin Kidney study with 1181 T2D patients enrolled, fast decline in the renal function ($\geq$5 mL/min $\times$ 1.73 m^2 per year) was revealed in 7% of patients with normal AER, 15% of those with microalbuminuria and 51% of patients with proteinuria. The decrease in eGFR >10 mL/min $\times$ 1.73 m^2 per year was observed in 1%, 3% and 21% of patients with normoalbuminuria, microalbuminuria and proteinuria respectively [30]. In the JDNCS nationwide observational study of 456 Japanese patients with T2D and clinically suspected diabetic nephropathy followed for a median of 4.2 years, remission of macroalbuminuria to normo-/microalbuminuria at 1 and 2 years was associated with a lower incidence of ESRD than no remission; however, it was not a determinant for ESRD independently of initial eGFR and initial protein-to-creatinine ratio [31].

One could assume that NA-CKD is a more favorable pattern than CKD which proceeds with albuminuria. In the FinnDiane study, the presence of NA-CKD in patients with type 1 diabetes did not significantly increase the risk of ESRD. During the 13-year follow-up, ESRD developed in 0.3% of patients with normal AER and GFR at baseline, in 1.3% of participants with NA-CKD, in 13.9% of patients with isolated albuminuria, and in 63% of patients with a combination of elevated AER and reduced GFR ($p < 0.001$). NA-CKD did not increase the risk of albuminuria (hazard ratio [HR] 2.0 [95% CI 0.9–4.4]) or ESRD (HR 6.4 [0.8–53.0]) but did increase the risk of cardiovascular events (HR 2.0 [1.4–3.5]) and all-cause mortality (HR 2.4 [1.4–3.9]). However, the highest risk of cardiovascular and renal end points was observed in the patients with albuminuria [32].

Likewise, in the recent CRIC study, NA-CKD was associated with a much lower risk of ESRD, CKD progression, or rapid decline in eGFR compared with the A-CKD pattern. Among 515 diabetic participants with normal/mildly increased AER at baseline, only 26 (5%) progressed to ESRD during a median follow-up of 6.3 years, and only 5% of ESRD events occurred in people with normoalbuminuric decreased renal function at baseline. Among those with baseline moderately increased ($n = 498$) and severely increased albuminuria ($n = 800$), 21.7% and 56.1% progressed to ESRD, respectively. Baseline AER was strongly and positively associated with a crude incidence of ESRD and CKD progression. The much lower rates of ESRD in those without albuminuria were consistent across a range of important subgroups (defined according to type of diabetes, age, sex, race/ethnicity, eGFR, and use of renin-angiotensin system blockers) [6].

Thus, the A-CKD and NA-CKD patterns demonstrate significant differences in their natural history and outcomes. The NA-CKD, even if a more favorable option in terms of the risk of ESRD, is clearly associated with cardiovascular disease and its risk factors.

5. Albuminuric and non-albuminuric patterns of DKD: current challenges and perspectives

As we accept the fact that NA-CKD has become a common pattern, a set of clinically important challenges should be addressed. At present, we require information about molecular pathways that determine different variants of DKD. The outcomes and concordance of the two CKD patterns with other diabetic complications and associated conditions necessitate further research. The differences in the set of risk factors and natural history of NA-CKD in diverse ethnic populations should be explored as well.

The search for diagnostic markers of NA-CKD and predictors of its development is of practical importance. Taking into account the results of morphological evaluations, the markers of tubular and interstitial involvement could be useful for the diagnostics of NA-CKD. In this regard, additional markers of renal injury, such as serum and urinary neutrophil gelatinase-associated lipocalin, chitinase-3-like protein 1, cystatin C, and plasma growth differentiation factor 15, have been proposed to unmask early renal dysfunction in DKD [33,34]. As renal function declines, the increase in plasma concentrations of fibrogenic and inflammatory mediators, including TGF-β, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-6, TNF-α, macrophage colony-stimulating factor (M-CSF), macrophage inflammatory protein 1α (MIP-1α), C-reactive protein, and urinary type IV collagen excretion, could be revealed in individuals with T2D [35–37]. Regretfully, the diagnostic value of some of the mentioned markers is limited by their low specificity to renal pathology.

It would be very beneficial to identify predictors of the loss of renal function in a situation where albuminuria remains normal. Evidently, GFR itself may be important prognostic indicator. The results of retrospective observational study of 2533 T2D patients have shown that one-year eGFR decline >7.5% is a good predictor of prognosis of renal failure [38]. Some new markers of renal function decline were identified in recent prospective studies. It was demonstrated that nonalbumin protein-to-creatinine ratio is a reliable predictor of the development and progression of CKD in patients with T2D [39]. Besides, some inflammatory markers are considered as candidates for CKD prediction. Specifically, it was shown that higher circulating TNF-α soluble receptors (sTNFR1 and sTNFR2) are associated with DKD and predicts incident cardiovascular disease and mortality independently of microalbuminuria and kidney function in subjects with T2D [40]. The high-sensitivity C-reactive protein and retinol-binding protein 4, a marker of tubular damage, turned out to be independent predictors of eGFR decline in T2D patients [41]. Some regulatory substances are considered as biomarkers of renal function decline. Thus, circulating fibroblast growth factor 21 levels predict progressive kidney disease in T2D subjects with eGFR $\geq$60 mL/min/1.73 m^2 and normoalbuminuria [42]. A decreased plasma α-klotho is another predictor of eGFR decline in this cohort of patients [43].

In recent years, the applicability of “omix” technologies and system-biological approaches for monitoring and predicting of CKD has been tested [44]. It was shown that the plasma protein panel, identified using systems biology approaches and including chitinase-3-like protein 1, growth hormone 1, hepatocyte growth

factor, matrix metalloproteases 2, 7, 8, and 3, tyrosine kinase, and tumor necrosis factor receptor α, combined with clinical variables, enhances the prediction of renal function loss over a wide range of baseline eGFR values in patients with T2D and CKD [45]. The analysis of the spectrum of urine proteins in 2672 patients with CKD, including 2044 subjects with diabetes, showed the advantages of a urine proteome before albuminuria as a predictor of decreased renal function in patients with baseline GFR >70 mL/min × 1.73 m^2. In contrast, in patients with more severe CKD (GFR <50 mL/min × 1.73 m^2), albuminuria was a more reliable prognostic marker [46].

At present, there are no specific guidelines for the management of patients with NA-CKD. Clinical heterogeneity of the course of CKD in diabetes should be considered when planning the design and interpretation of the results of clinical trials on new medicines in the field.

6. Conclusion

A growing body of evidence supports a transformation of the clinical course of CKD in T2D. At present, NA-CKD, which is characterized by a decline in GFR in the absence of AER elevation, has become a prevalent variant of DKD. The NA-CKD pattern, even if a more favorable option in terms of ESRD, is clearly associated with cardiovascular disease and its risk factors.

Conflicts of interest

None of the authors have any conflict of interests in the manuscript.

List of abbreviations

A-CKD	albuminuric chronic kidney disease
AER	albumin excretion rate
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DKD	diabetic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
MDRD	Modification of Diet in Renal Disease
NA-CKD	normoalbuminuric chronic kidney disease
T2D	type 2 diabetes
UACR	urinary albumin-to-creatinine ratio

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