RENAL FAILURE
2025, VOL. 47, NO. 1, 2483389
https://doi.org/10.1080/0886022X.2025.2483389

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CLINICAL STUDY

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Related factors for kidney disease and high chronic kidney disease progression risk in adult-onset type 1 diabetes mellitus patients from China: a multi-center cross-sectional study

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ABSTRACT

Background/Aim: Concerning the related factors for kidney disease and high chronic kidney disease (CKD) progression risk, there is still a lack of study in the adult-onset type 1 diabetes mellitus (T1DM) patients from China.

Methods: Four hundred and eighty-one adult-onset T1DM patients from the Guangdong T1DM translational medicine study were included. Logistic regression analysis (Forward: LR) was utilized to identify glycemic- and nonglycemic-related factors associated with moderate albuminuria, severe albuminuria, mildly reduced estimated glomerular filtration rate (eGFR), decreased eGFR, and high CKD progression risk, and to calculate the odds ratio (OR) and 95% confidence interval (CI).

Results: High CKD progression risk was positively associated with males (OR = 3.13, 95% *CI*:1.20−8.14, $p=0.019$), duration of T1DM (OR =1.13, 95% *CI*:1.05−1.21, $p<0.001$), triglyceride (OR =1.52, 95% CI:1.11−2.08, $p=0.008$), and systolic blood pressure (SBP) (OR =1.04, 95% CI:1.02−1.07, $p=0.001$), and negatively correlated with BMI (OR = 0.80, 95% CI:0.68−0.95, $p=0.011$). Meanwhile, moderate albuminuria, severe albuminuria, mildly reduced eGFR and decreased eGFR had different each of glycemic- and nonglycemic-related factors.

Conclusions: Hyperglycemia, hypertension, hyperuricemia, and BMI may be associated with different stages of kidney disease in adult-onset T1DM patients. Early-stage adult-onset T1DM patients with male, low BMI, prolonged diabetes duration, and comorbid hypertension and dyslipidemia should undergo a thorough evaluation of albuminuria and renal function to detect those at high CKD progression risk, who should be timely transferred to the nephrology specialty to receive professional treatment for kidney disease.

ARTICLE HISTORY
Received 22 June 2024
Revised 25 February 2025
Accepted 15 March 2025

KEYWORDS
Type 1 diabetes mellitus; adult-onset; diabetic nephropathy; progression risk; related factor

Introduction

Diabetic kidney disease (DKD) is a common microvascular complication of type 1 diabetes mellitus (T1DM), characterized by an increased risk of end-stage renal disease (ESRD) and cardiovascular disease (CVD) [1–3]. It is typically defined by albuminuria or a decline in estimated glomerular filtration rate (eGFR). In T1DM patients, the typical progression of DKD is that:1-early stage (hyperfiltration)-early rise in eGFR, compensation phase, 2-microalbuminuria-after the hyperfiltration phase, sign of early kidney damage, 3-Decline in eGFR-worsening kidney function, overt proteinuria [4–6]. Albuminuria and reduced eGFR were associated with ESRD, CVD, and mortality [2,7], while eGFR was still an independent and significant predictor after adjustment for conventional risk factors [7].

Various risk factors contribute to the development of DKD in adolescent-onset T1DM patients, such as hyperglycemia, hypertension, dyslipidemia, and obesity [8]. Besides glycemic, lipid, and blood pressure control, smoking, a modifiable risk factor [9,10], was also a significant risk factor for the

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development of DKD and adversely affect the progression of DKD in adolescent-onset T1DM patients [10,11]. For patients with T1DM, high risk of DKD progression imply a higher risk of greater eGFR decline and ESRD, and the American Diabetes Association (ADA) guidelines recommend that diabetes patients with high chronic kidney disease (CKD) progression risk should be referred to the Department of Nephrology for professional treatment [4]. To date, limited data have been reported on the factors associated with kidney disease and high CKD progression risk in adult-onset T1DM patients. Screening patients with the high risk of CKD progression in patients with early-stage adult-onset T1DM is essential for the early management of DKD and DKD progression.

Moreover, evidence suggests that kidney disease characteristics may vary among diabetes patients of different ethnicities [12–14]. At the same time, most new-onset T1DM cases in China were adult-onset, which differs from other countries [15]. Hence, further studies involving adult-onset T1DM patients from China are warranted to elucidate the glycemic and nonglycemic factors associated with kidney disease and high CKD progression risk. In this study, we utilized data from the Guangdong T1DM Translational Medicine (GTT) Study database to explore glycemic and nonglycemic factors associated with kidney disease and high CKD progression risk among adult-onset T1DM patients from China.

Methods

Patients selection and study design

The database system of the GTT Study was established in 16 tertiary hospitals throughout 12 cities in Guangdong, China. All centers prospectively collected clinical data on patients with T1DM who visited the participating hospitals, which had been described in our previous published articles [16,17]. Data were collected at patient enrollment and once a year thereafter. Trained, certified physicians and nurses conducted all measures according to the standardized protocols.

This article presented the cross-sectional data collected between the June 2010 and December 2017 enrollment visit. All values of biochemical detection were from whole blood or serum collected at enrollment. For this analysis, we included patients diagnosed with T1DM, aged between 18 and 65 years at onset, and with a duration of diabetes exceeding one year. Subjects were excluded if they had one or more of the following situations: (1) diabetic ketoacidosis episode(s) within the past three months, (2) urinary tract infection, (3) glomerulonephritis hematuria, (4) acute kidney injury, (5) missing data on serum creatinine (SCr), or urinary albumin to creatinine ratio (ACR). Information on age, gender, diabetes duration, and medical history, including clinical characteristics at onset, medication, diabetes complication, and accompanying disease, were collected from medical records. The protocol and consent processes were approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (ID:[2010]2-36). Written informed consent was obtained from all subjects.

Definitions

The clinical diagnosis of T1DM was based on the ADA's descriptions of T1DM [18]. Patients enrolled in the GTT study were diagnosed with T1DM by an endocrinologist and characterized by insulin dependency shortly after diagnosis. In addition, they had to meet at least one of the following criteria: (1) symptoms of hyperglycemia at diagnosis, (2) a history of diabetic ketoacidosis or ketosis, (3) tested positive for T1DM associated autoantibodies, and (4) fasting and stimulated C-peptide levels <200pmol/L. After the initial diagnosis, we ensured that the patients would be followed up for no less than 18 months to confirm their insulin dependency to avoid misdiagnosis [15]. The adult-onset T1DM refers to the onset of T1DM at 18 years or older [19,20]. High glycated hemoglobin A1c (HbA1c) was defined by a value ≥7.0%. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, and/or diastolic blood pressure (DBP) ≥90 mmHg, and/or self-reported use of antihypertensive medications. Hyperuricemia was defined as serum uric acid (SUA) > 420 μmol/L [21,22]. Insulin resistance (IR) was estimated by the estimated glucose disposal rate (eGDR), which was an IR model of adult T1DM established by our previous research [23]. The lower the eGDR value, the more severe the IR.

Assessment of kidney disease and CKD progression risk stratification

According to Standards of Medical Care in Diabetes-2024 of the ADA, DKD was diagnosed [4]. The eGFR was estimated using the CKD epidemiology collaboration (CKD-EPI) equation (http://www.nkdep.nih.gov) [4]. The urinary ACR assessed urine albumin excretions in spot urine samples. Moderate albuminuria (microalbuminuria) was defined as urinary ACR between 30 and 300 mg/g, while severe albuminuria (macroalbuminuria) was defined as urinary ACR ≥ 300 mg/g [4]. Moderately reduced eGFR refers to 30 ≤ eGFR < 60 mL/min/1.73m^2 (the G3a and G3b stages) [24,25], decreased eGFR refers to eGFR < 60 mL/min/1.73m^2 (GFR categories G3a–G5) [25], and mildly reduced eGFR was defined as 60 ≤ eGFR < 90 mL/min/1.73m^2 [25]. CKD progression risk stratification was conducted according to the ADA and Kidney Disease: Improving Global Outcomes (KDIGO) guideline [4,25].

Sample size calculation

The equation, $n = Z_\alpha^2 \times P \times (1\text{-}P)/\delta^2$, was used to calculate the sample size of our research, $\alpha = 0.05$, $Z_\alpha = 1.96$, $\delta = 0.05$, and the proportion of DKD in early-stage adult-onset T1DM patients was 0.2, so the minimize sample of this research was 246. Accounting for the dropout rate of 0.2, a sample size of at least 308 cases was required to meet the criteria for adequate power (80%), and our sample size of 481 cases satisfied and exceeded the standard.

Statistical analysis

All statistical analyses were performed using IBM SPSS v.20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The skewed distribution of continuous variables was expressed as medians with interquartile ranges. Nonparametric tests, *Kruskal-Wallis* tests, were used to compare differences between group data for continuous data with a skewed distribution. Each category's number (n) and percentage (%) were calculated for categorical variables. The categorical variables were evaluated with a chi-square test or *Fisher* exact test.

Spearman's correlation analysis and stepwise multiple linear regression analysis assessed the correlations between urinary ACR and eGFR with other characteristics. Logistic regression analysis (Forward: LR) was conducted to ascertain the association of glycemic and nonglycemic-related factors with moderate albuminuria, severe albuminuria, mildly reduced eGFR, decreased eGFR, and high CKD progression risk and to calculate the odds ratio (OR) and 95% confidence interval (*CI*). A *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics and comparison of baseline covariates

1830 patients with T1DM were enrolled in the GTT study between June 2010 and December 2017. After selection, 481 patients with adult-onset T1DM were included in this analysis, finally (Shown in Figure 1). The characteristics of 481 patients are shown in Table 1. The median onset age was 28.5 [23.5, 35.3] years, and 47.2% (227/481) were male. The median duration of diabetes was 5.1 [2.8, 8.4] years, and the HbA1C level was 8.4 [7.1, 10.1]%. The median urinary ACR and eGFR were 11.5 [5.70, 23.0] mg/g and 111.9 [98.4, 122.6] ml/min/1.73m^2, respectively.

According to albuminuria status, 481 adult-onset T1DM patients were divided into three groups: the normoalbuminuria group had 378 (78.6%) patients, the moderate albuminuria (microalbuminuria) group had 85 (17.7%) patients, and the severe albuminuria (macroalbuminuria) group had 18 (3.7%) patients. The differences in diabetes mellitus (DM) duration, SBP, DBP, resting heart rate, TG, SUA, urinary ACR, SCr, eGFR, and proportion of hypertension, hyperuricemia, renin-angiotensin-aldosterone system (RAAS) inhibitors, and lipid-lowering agents were significant among the three groups, all $p < 0.05$. At the same time, there was no significant difference in gender, onset age, HbA1c, body mass index (BMI), height, weight, waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), lnGDR, and insulin requirement, all $p > 0.05$ (Shown in Table 1).

According to eGFR, 481 adult-onset T1DM patients were divided into three groups: the normal eGFR group had 395 (82.1%) patients, the mildly reduced eGFR group had 71 (14.8%) patients, the decreased eGFR group had 15 (3.1%) patients. The differences in onset age, DM duration, HbA1c, BMI, SBP, TG, TC, SUA, lnGDR, urinary ACR, SCr, eGFR, and proportion of hypertension and hyperuricemia were significant among the three groups, all $p < 0.05$. At the same time, there was no significant difference in gender, height, weight, WC, HC, WHR, DBP, resting heart rate, LDL-c, insulin requirement, and proportion of RAAS inhibitors and lipid-lowering agents, all $p > 0.05$ (Shown in Table 2).

Chronic kidney disease progression risk stratification in 481 adult-onset T1DM patients

Among 481 adult-onset T1DM patients, the number of patients with G1, G2, G3a, G3b, G4, and G5 stages was 395,

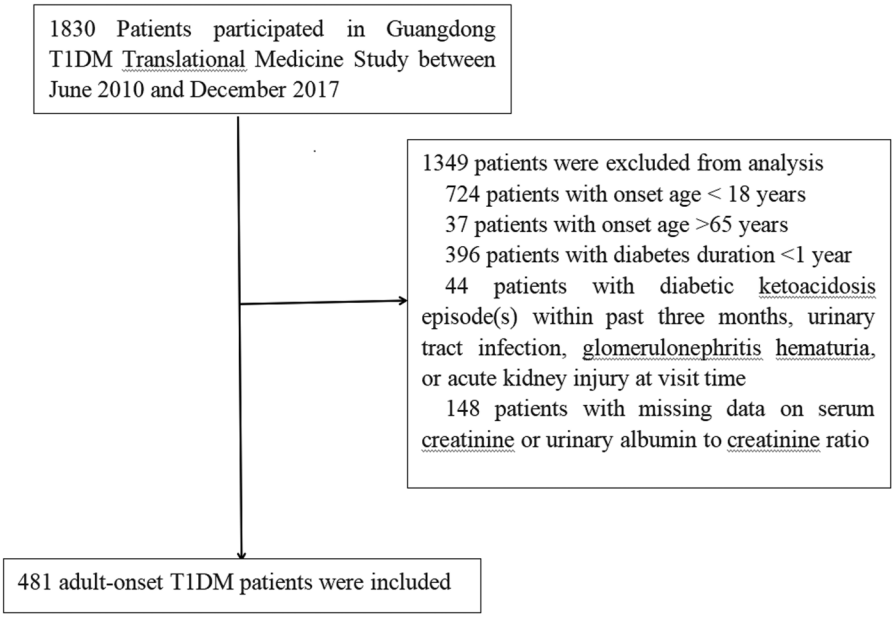

Figure 1. Flow chart of patient selection process. TIDM, type 1 diabets mellitus.

Table 1. Patient characteristics and comparison of covariates according to albuminuria subgroup.

Characteristics	Overall $n=481$	Normoalbuminria $n=378$	Moderate albuminuria $n=85$	Severe albuminuria $n=18$	p- value
Male/Female	227/254	183/195	33/52	11/7	0.134
Onset age (years)	28.5 [23.5, 35.3]	28.7 [23.7, 35.3]	28.2 [22.6, 35.3]	27.9 [20.9, 33.0]	0.490
Duration of T1D (years)	5.1 [2.8, 8.4]	5.0 [2.8, 8.1]	5.1 [2.6, 10.1]	6.9[5.3,13.8]	0.04
HbA1c (%)	8.4 [7.1, 10.1]	8.4 [7.1, 10.1]	8.4 [7.2, 10.1]	8.8 [7.5, 10.7]	0.682
BMI (Kg/m^2)	20.7 [19.1, 22.6]	20.8 [19.2, 22.7]	20.4 [18.4, 22.4]	20.3 [18.4, 23.2]	0.339
Height (cm)	162.0 [156.8, 169.0]	162.0[157.0, 170.0]	160.0[156.0, 167.0]	164.5 [157.0, 168.3]	0.214
Weight (Kg)	55.0 [50.0, 60.5]	55.0 [50.0, 61.0]	52.0 [47.3, 60.0]	54.5 [45.5, 60.0]	0.148
WC (cm)	75.0 [70.0, 80.0]	75.0 [70.0, 80.0]	74.0 [70.0, 80.0]	73.0 [68.0, 79.3]	0.830
HC (cm)	89.0 [84.0, 93.0]	89.0 [85.0,93.0]	87.0 [83.0,92.0]	91.0 [85.0, 96.5]	0.072
Waist-hip ratio	0.85 [0.81, 0.90]	0.84 [0.81, 0.90]	0.85 [0.83, 0.90]	0.82 [0.76, 0.88]	0.064
Hypertension (Yes/No)	43/422	26/342	10/70	7/10	<0.001
SBP (mmHg)	113.0 [106.0, 124.0]	112.0 [106.0, 121.0]	116.5 [106.0, 130.0]	126.0 [109.0, 145.5]	0.026
DBP (mmHg)	71.0 [66.0, 80.0]	70.0 [66.0, 80.0]	73.0 [66.0, 80.0]	80.0 [73.5, 92.5]	0.010
Rest heart rate (bpm)	80.0 [74.0, 86.0]	80.0 [72.0, 85.0]	83.0 [78.0, 90.0]	85.0 [78.0, 89.0]	<0.001
TG (mmol/L)	0.93 [0.70, 1.31]	0.90 [0.68, 1.23]	1.06 [0.77, 1.35]	1.37 [1.07, 1.81]	0.001
TC (mmol/L)	4.63 [4.04, 5.32]	4.62 [4.04, 5.29]	4.65 [4.02, 5.23]	5.02 [4.46, 6.17]	0.093
LDL-c (mmol/L)	2.61 [2.13, 3.31]	2.60 [2.14, 3.34]	2.62 [2.02, 3.25]	2.69 [2.23, 3.90]	0.359
SUA (μmol/L)	273.0 [224.0, 335.0]	267.0 [222.0, 330.5]	276.0 [228.0, 337.0]	355.5 [255.3, 434.3]	0.032
Hyperuricemia (Yes/No)	30/383	18/307	7/65	5/11	<0.001
lnGDR (mg/min/kg)	1.63 [1.40, 1.83]	1.63 [1.42, 1.84]	1.63 [1.40, 1.85]	1.42 [1.13, 1.70]	0.074
Insulin requirement (IU/kg/d)	0.67 [0.53, 0.81]	0.67 [0.52, 0.81]	0.69 [0.56, 0.84]	0.59 [0.51, 0.70]	0.122
Urinary ACR (mg/g)	11.5 [5.70, 23.0]	8.5 [5.0, 14.2]	54.2 [37.1, 78.8]	392.2 [326.9, 601.1]	<0.001
SCr (μmol/L)	66.0 [55.0, 79.0]	66.0 [55.0, 77.0]	62.0 [52.0, 81.0]	92.5 [69.0, 169.5]	0.001
eGFR (ml/min/1.73m^2)	111.9 [98.4, 122.6]	112.0 [99.1, 122.4]	112.2 [96.4, 124.9]	83.9 [33.8, 113.1]	0.004
RAAS inhibitor [n(%)]	14 (2.9%)	5 (1.3%)	4 (4.7%)	5 (27.8%)	<0.001
Lipid lowering agents [n(%)]	19 (4.0%)	17 (4.5%)	0 (0%)	2 (11.1%)	0.023

Note: Data were medians (IQR) for skewed variables or numbers (proportions) for categorical variables.

Abbreviations: T1D, type 1 diabetes; HbA1c, glycated hemoglobin A1c; BMI, body mass index; WC, waist circumference; HC, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDLc, low-density lipoprotein cholesterol; SUA, serum uric acid; ln GDR, natural logarithm of the glucose disposal rate; ACR, albumin-creatinine ratio; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; RAAS, Renin-angiotensin-aldosterone System.

Table 2. Comparison of covariates according to eGFR subgroup.

Characteristics	Normal eGFR ($n=395$)	Mildly reduced eGFR ($n=71$)	Decreased eGFR($n=15$)	p- value
Male/Female	185/210	32/39	10/5	0.309
Onset age (years)	27.8 [23.0, 34.6]	30.7 [26.1, 41.8]	31.1 [29.9, 36.7]	0.002
Duration of T1D (years)	4.7 [2.6, 7.6]	9.2 [5.9, 14.3]	8.1 [3.7, 18.1]	<0.001
HbA1c (%)	8.5 [7.3, 10.4]	7.5 [6.8, 8.6]	7.7 [6.8, 9.9]	<0.001
BMI (Kg/m^2)	20.5 [19.0, 22.4]	21.8 [20.7, 23.3]	20.3 [17.4, 21.5]	<0.001
Height (cm)	162.0 [157.0, 169.0]	160.5 [155.0, 169.3]	166.0 [161.0, 169.0]	0.369
Weight (Kg)	54.0 [49.5, 60.0]	57.5 [50.0, 65.0]	55.0 [47.0, 60.0]	0.105
WC (cm)	74.0 [70.0, 80.0]	76.0 [71.0, 81.3]	76.0 [72.0, 78.0]	0.145
HC (cm)	88.0 [84.0, 92.3]	90.3 [87.0, 94.1]	87.0 [81.0, 95.0]	0.070
Waist-hip ratio	0.84 [0.81, 0.89]	0.86 [0.80, 0.90]	0.85 [0.80, 0.92]	0.840
Hypertension (Yes/No)	30/382	8/60	5/10	0.003
SBP (mmHg)	112.0 [105.0, 122.3]	120.0 [110.0, 130.0]	120.0 [103.0, 142.0]	0.020
DBP (mmHg)	70.5 [66.0, 80.0]	73.0 [65.8, 80.0]	78.0 [60.0, 86.0]	0.705
Rest heart rate (bpm)	80.0 [74.0, 86.0]	79.0 [71.0, 85.0]	81.0 [73.5, 93.3]	0.296
TG (mmol/L)	0.89 [0.66, 1.26]	1.08 [0.82, 1.39]	1.36 [1.16, 1.76]	<0.001
TC (mmol/L)	4.62 [4.03, 5.28]	5.07 [4.14, 6.13]	4.56 [4.35, 4.98]	0.028
LDL-c (mmol/L)	2.62 [2.13, 3.26]	2.79 [2.19, 3.85]	2.47 [1.91, 2.81]	0.143
SUA (μmol/L)	266.5 [222.0, 325.8]	292.0 [245.5, 376.5]	462.0 [326.8, 543.0]	<0.001
Hyperuricemia (Yes/No)	16/328	6/51	8/4	<0.001
lnGDR(mg/min/kg)	1.63 [1.38, 1.81]	1.76 [1.61, 1.91]	1.53 [1.27, 1.99]	<0.001
Insulin requirement (IU/kg/d)	0.68 [0.53, 0.81]	0.67 [0.51, 0.79]	0.64 [0.47, 0.72]	0.369
Urinary ACR (mg/g)	10.8 [5.7, 21.4]	18.8 [5.3, 30.9]	59.5 [7.1, 343.3]	0.002
SCr (μmol/L)	61.0 [53.0, 72.0]	87.0 [77.0, 98.0]	184.0 [153.0, 284.0]	<0.001
eGFR (mL/min/1.73m^2)	115.4 [106.9, 124.7]	82.0 [72.1, 85.9]	32.8 [22.5, 45.1]	<0.001
RAAS inhibitor [n(%)]	10 (2.5%)	2(2.8%)	2 (13.3%)	0.084
Lipid lowering agents [n(%)]	14 (3.5%)	4 (5.6%)	1 (6.7%)	0.388

Note: Data were medians (IQR) for skewed variables or numbers (proportions) for categorical variables.

Abbreviations: T1D, type 1 diabetes; HbA1c, glycated hemoglobin A1c; BMI, body mass index; WC, waist circumference; HC, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid; ln GDR, natural logarithm of the glucose disposal rate; ACR, albumin-creatinine ratio; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; RAAS, Renin-angiotensin-aldosterone System.

71, 4, 5, 3, and 3, respectively, while with the A1, A2, and A3 stages was 378, 85, and 18, respectively. The patients with low CKD progression risk, moderately increased CKD progression, high CKD progression risk, and very high CKD progression risk were 372, 83, 17, and 9, respectively (Shown in Table 3).

Correlated factors for urinary ACR and eGFR in adult-onset T1DM patients

To analyze the factors associated with urinary ACR, the correlations between urinary ACR and other characteristics were assessed by Spearman's correlation analysis. Table 4 shows that urinary ACR positively correlates with the HbA1c, waist-hip ratio, SBP, DBP, resting heart rate, and TG and is negatively associated with lnGDR (all $p < 0.05$). After adjustment for those significant factors, stepwise multiple linear regression analysis showed that urinary ACR had an independent positive association with TG and SBP (both $p < 0.05$).

To analyze the factors associated with eGFR, the correlations between eGFR and other characteristics were assessed by Spearman's correlation analysis. Table 4 shows that eGFR is positively correlated with HbA1c and insulin requirement and negatively associated with age, duration of T1DM, BMI, SBP, TC, SUA, and lnGDR (all $p < 0.05$). After adjustment for those significant factors, stepwise multiple linear regression analysis showed that eGFR had an independent positive association with HbA1c, negative correlation with SUA, duration of T1DM, and onset age (all $p < 0.05$).

Table 3. Chronic kidney disease progression risk stratification in 481 adult-onset T1DM patients in China.

	A1 (n = 378)	A2 (n = 85)	A3 (n = 18)
G1 (n = 395)	321 (Low risk)	65 (Moderate risk)	9 (High risk)
G2 (n = 71)	51 (Low risk)	16 (Moderate risk)	4 (High risk)
G3a (n = 4)	2 (Moderate risk)	2 (High risk)	0 (Very high risk)
G3b (n = 5)	2 (High risk)	1 (Very high risk)	2 (Very high risk)
G4 (n = 3)	1 (Very high risk)	1 (Very high risk)	1 (Very high risk)
G5 (n = 3)	1 (Very high risk)	0 (Very high risk)	2 (Very high risk)

Note: T1DM, type 1 diabetes mellitus; G, GFR category (G1-G5); A, Albuminuria category (A1-A3).

Logistic regression analysis of independent related factors for kidney disease and high chronic kidney disease progression risk in adult-onset T1DM patients

The correlations between urinary ACR and other characteristics have been shown in Table 4. Binary multivariate logistic regression analysis (Forward: LR) was conducted to identify the independently related factors associated with moderate albuminuria in adult-onset T1DM patients, including the urinary ACR-correlated factors. Moderate albuminuria was set as the dependent variable, with normoalbuminuria as a reference, and the gender, onset age, duration of T1DM, and the urinary ACR correlated factors were set as covariates. Table 5 shows that in multivariate logistic regression analysis, moderate albuminuria had an independent positive correlation with SBP (OR:1.02, 95% *CI*: 1.01-1.04, $p = 0.005$) and resting heart rate (OR:1.04, 95% *CI*: 1.02-1.07, $p < 0.001$).

The correlations between urinary ACR and other characteristics have been shown in Table 4. The binary multivariate logistic regression analysis (Forward: LR) included these urinary ACR-correlated factors to identify the independently related factors with severe albuminuria in adult-onset T1DM patients. Severe albuminuria was set as the dependent variable, with non-macroalbuminuria as reference, the gender, onset age, duration of T1DM, and the urinary ACR correlated factors were selected as covariates. Table 5 shows that in logistic regression multivariate analysis, severe albuminuria had an independent positive correlation with SBP (OR:1.05, 95% *CI*: 1.03-1.08, $p < 0.001$).

The correlations between eGFR and other characteristics have been shown in Table 4. The binary multivariate logistic regression analysis (Forward: LR) included these eGFR-correlated factors to identify the independently related factors with mildly reduced eGFR in adult-onset T1DM patients. Mildly reduced eGFR was set as the dependent variable, with

Table 4. The related factors of urinary ACR and eGFR in 481 adult-onset T1DM patients.

	Urinary ACR (mg/g)				eGFR (ml/min/1.73m^2)			
	Spearman's correlation analysis		Stepwise multiple linear regression		Spearman's correlation analysis		Stepwise multiple linear regression	
Parameter	r	*p*-value	β Coefficient ± SE	*p*-value	r	*p*-value	β Coefficient ± SE	*p*-value
Onset age (years)	−0.041	0.374			−0.409	<0.001	−0.86 ± 0.10	<0.001
Duration of T1DM (years)	0.072	0.114			−0.324	<0.001	−1.47 ± 0.17	<0.001
HbA1c (%)	0.118	0.01			0.296	<0.001	1.42 ± 0.38	<0.001
BMI (Kg/m^2)	−0.062	0.180			−0.179	<0.001		
Waist-hip-ratio	0.097	0.038			−0.024	0.614		
SBP (mmHg)	0.159	0.001	2.60 ± 0.88	0.003	−0.152	0.001		
DBP (mmHg)	0.141	0.002			−0.019	0.684		
Rest heart rate (bpm)	0.213	<0.001			0.051	0.276		
TG (mmol/L)	0.202	<0.001	22.50 ± 9.68	0.021	−0.057	0.213		
TC (mmol/L)	0.063	0.168			−0.133	0.003		
LDL-c (mmol/L)	0.035	0.444			−0.054	0.240		
SUA (μmol/L)	0.031	0.530			−0.292	<0.001	−0.08 ± 0.01	<0.001
Ln GDR (mg/min/kg)	−0.178	<0.001			−0.264	<0.001		
SCr (μmol/L)	−0.083	0.067			——	——		
eGFR (mL/min/1.73m^2)	0.031	0.504			——	——		
Urinary ACR (mg/g)	——	——			0.031	0.504		
Insulin requirement (IU/kg/d)	0.037	0.425			0.123	0.008		

Notes: ACR, albumin–creatinine ratio; T1DM, type 1 diabetes; HbA1c, glycated hemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid; ln GDR, natural logarithm of the glucose disposal rate; SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

Table 5. Logistic regression multivariate analysis (forward: LR) of independent related factors for kidney disease in 481 adult-onset T1DM patients.

	Moderate albuminuria		Severe albuminuria		Mildly reduced eGFR		Decreased eGFR	
Variable	OR (95% *CI*)	*p*	OR (95% *CI*)	*p*	OR (95% *CI*)	*p*	OR (95% *CI*)	*p*
SBP (mmHg)	1.02 (1.01 – 1.04)	0.005	1.05 (1.03 – 1.08)	<0.001	——	——	——	——
Resting heart rate (bpm)	1.04 (1.02 – 1.07)	<0.001	——	——	——	——	——	——
Onset age (years)	——	——	——	——	1.07 (1.04 – 1.11)	<0.001		
Duration of T1DM (years)	——	——	——	——	1.19 (1.12 – 1.25)	<0.001	1.16 (1.06 – 1.27)	0.001
HbA1c (%)	——	——	——	——	0.76 (0.63 – 0.90)	0.002	——	——
SUA (umol/L)	——	——	——	——	1.07 (1.003-1.01)	<0.001	1.013 (1.008-1.02)	<0.001
BMI (Kg/m^2)	——	——	——	——	——	——	0.72 (0.57 – 0.92)	0.010

Notes: When moderate albuminuria and severe albuminuria was set as the dependent variable, the gender, onset age, duration of T1DM, HbA1c, waist-hip ratio, SBP, DBP, resting heart rate, TG, and lnGDR were set as covariates.
When mildly reduced eGFR and decreased eGFR was set as the dependent variable, the gender, onset age, duration of T1DM, HbA1c, BMI, SBP, TC, SUA, lnGDR and insulin requirement were set as covariates.
Abbreviations: T1DM, type 1 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; SUA, serum uric acid; BMI, body mass index; eGFR, estimated glomerular filtration rate; ln GDR, natural logarithm of the glucose disposal rate.

Table 6. Logistic regression multivariate analysis (forward: LR) of independent related factors for high risk of CKD progression in 481 adult-onset T1DM patients.

Variable	β Coefficient	S.E	WALD	OR (95% *CI*)	*p*
Male	1.139	0.488	5.452	3.13 (1.20 – 8.14)	0.019
Duration of T1DM (years)	0.120	0.034	12.338	1.13 (1.05 – 1.21)	<0.001
BMI (Kg/m^2)	−0.219	0.086	6.474	0.80 (0.68 – 0.95)	0.011
TG (mmol/L)	0.422	0.160	6.964	1.52 (1.11 – 2.08)	0.008
SBP (mmHg)	0.040	0.012	10.764	1.04 (1.02 – 1.07)	0.001

Notes: High risk and very high risk of CKD progression was set as the dependent variable, with low risk and moderate risk of CKD as reference, the gender, onset age, duration of T1DM, HbA1c, BMI, SBP, DBP, TG, and TC were set as covariates.
Abbreviations: CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol.

patients with normal eGFR as the reference, the gender and eGFR correlated factors were selected as covariates. Table 5 shows that in multivariate logistic regression analysis, mildly reduced eGFR had an independent positive correlation with onset age (OR:1.07, 95% *CI*: 1.04-1.11, $p<0.001$), duration of T1DM (OR:1.19, 95% *CI*: 1.12-1.25, $p<0.001$), and SUA (OR:1.007, 95% *CI*: 1.003-1.01, $p<0.001$), negatively correlation with HbA1c (OR:0.76, 95% *CI*: 0.65-0.90, $p=0.002$).

The correlations between eGFR and other characteristics have been shown in Table 4. The binary multivariate logistic regression analysis (Forward: LR) included these eGFR-correlated factors to identify the independently related with decreased eGFR in adult-onset T1DM patients. Decreased eGFR was set as the dependent variable, with patients with eGFR ≥ 60 mL/min/1.73m^2 as a reference, the gender and eGFR correlated factors were selected as covariates. Table 5 shows that in multivariate logistic regression analysis, decreased eGFR had an independent positive correlation with the duration of T1DM (OR:1.16, 95% *CI*: 1.06-1.27, $p=0.001$) and SUA (OR:1.013, 95% *CI*: 1.008-1.02, $p<0.001$), negatively correlation with BMI (OR:0.72, 95% *CI*: 0.57-0.92, $p=0.010$).

High risk and very high risk of CKD progression were set as the dependent variable, with low risk and moderate risk of CKD as a reference, the gender, onset age, duration of T1DM, HbA1c, BMI, TG, LDL-c, SBP, and DBP were set as covariates. The binary logistic regression multivariate analysis (Forward: LR) showed that high risk of CKD progression was positively associated with male (OR:3.13, 95% *CI*: 1.20 – 8.14, $p=0.019$), duration of T1DM (OR:1.13, 95% *CI*: 1.05-1.21, $p<0.001$), TG (OR:1.52, 95% *CI*: 1.11-2.08, $p=0.008$), and SBP (OR:1.04, 95% *CI*:1.02-1.07, $p=0.001$), and negatively correlated with BMI (OR:0.80, 95% *CI*:0.68-0.95, $p=0.011$) (Shown in Table 6).

Discussion

This study targeted the adult-onset T1DM cohort, representing a significant proportion of the overall T1DM population. Previous studies predominantly focused on DKD in adolescent-onset T1DM patients, with limited attention directed toward adult-onset T1DM patients [4]. This study firstly revealed the prevalence of moderate albuminuria, severe albuminuria, mildly reduced eGFR, decreased eGFR, and high and very high risk of CKD progression was 17.7%, 3.7%, 14.8%, 3.1%, and 5.4%, respectively in adult-onset T1DM patients with a median duration of diabetes 5.1 years. Previous studies showed that DKD affects over 25% of youth and adolescents with T1DM of >10 years duration [26,27]. Recent studies showed that the prevalence of DKD in Indian adult-onset T1MD patients with DM duration ≤5 years was 23.8%, higher than that in adolescent-onset T1DM patients [28], but had no data on the prevalence of moderate albuminuria, severe albuminuria, mildly reduced eGFR, decreased eGFR, and high risk of CKD progression. Our results showed that the prevalence of albuminuria was 21.4%, similar to the previous study [28]. These results indicated that it was essential to early screen the DKD and evaluate the CKD progression risk in adult-onset T1DM patients.

Our research also analyzed factors related to moderate albuminuria, severe albuminuria, mildly reduced eGFR, and

decreased eGFR based on a survey utilizing multi-center data from patients with early-stage adult-onset T1DM in China. The results showed that urinary ACR and eGFR were correlated with hyperglycemia, hypertension, dyslipidemia, and lnGDR. Both moderate albuminuria and severe albuminuria exhibited independent positive correlations with hypertension. Conversely, mildly reduced eGFR and decreased eGFR demonstrated independent correlations with hyperglycemia and hyperuricemia, with decreased eGFR also negatively correlated with BMI. Risk factors of DKD in adult-onset T1DM patients are poorly defined. Multiple risk factors contributed to the development of DKD in adolescent-onset T1DM patients, including hyperglycemia, hypertension, dyslipidemia, and overweight [8]. There needs to be more studies on the factors associated with kidney disease in adult-onset T1DM patients, primarily early-stage patients. Our study showed that kidney disease in adult-onset T1DM patients was also correlated with hyperglycemia, hypertension, hyperuricemia, dyslipidemia, and BMI, but hyperglycemia, hypertension, hyperuricemia, and BMI were associated with different stages of kidney disease. These factors are hypothesized to contribute to CKD progression across different stages of DKD. Among the related factors of DKD, hyperuricemia was a controversial influencing factor. Some studies indicated that SUA level is positively associated with DKD [29,30], but some studies showed no causal link between SUA level and the occurrence of DKD [31–33]. Whether hyperuricemia plays a crucial role in the pathogenesis of DKD in adult-onset T1DM patients still needs further investigation.

Our research also assessed the related factors of high CKD progression risk, which received increasing attention. The results showed that the high risk of CKD progression was positively associated with males, duration of T1DM, TG, and SBP, and negatively correlated with BMI. ADA guidelines recommend that diabetes patients with the high risk of CKD progression should be referred to the Department of Nephrology [4]. However, few studies investigated the risk factors for high CKD progression risk patients in early-stage adult-onset T1DM patients. Previous studies showed that the male sex predicted faster progression to kidney failure [34]. In the CKD cohort, women had a lower risk of CKD progression and death compared with men [35]. Potential explanations for differences in CKD progression risk between men and women include the protective effect of endogenous estrogens and/or the harmful effects of testosterone, sex differences in nitric oxide metabolism, and the differential effect of sex on lifestyle and traditional risk factors [35–37]. A recent predictive model for CKD progression in diabetic patients showed that diabetes duration, cardiovascular risk factors, and dyslipidemia contributed to CKD progression [38]. Still, this model did not include the BMI. Our results showed that male gender, low BMI, T1DM duration, hypertension, and dyslipidemia correlated with high CKD progression risk, which is consistent with previous studies. Only BMI was still a controversial factor for CKD progression. While some studies have affirmed that high BMI contributes to CKD development and hastens its progression in non-diabetic individuals [39–42], its impact on patients with underlying diseases remains uncertain. Some studies showed BMI was negatively correlated with ESRD in diabetes patients [43], while higher BMI in ESRD patients had better survival [44]. Our results confirmed low BMI was positively linked with high CKD progression risk in T1DM patients, which may be correlated with malnutrition-inflammation-atherosclerosis (MIA) syndrome [45], or with increased DNA oxidative damage during weight loss led to kidney toxicity [46].

Till now, ADA guidelines recommend that urinary ACR and eGFR should be assessed in T1DM patients with a duration of ≥5 years regardless of treatment, and the risk of CKD progression according to eGFR and albuminuria should be also assessed [4]. Up to now, there has been no data on the risk factors of DKD and high CKD progression risk of early-stage adult-onset T1DM patients in other countries. There's not enough evidence to recommend how to screen DKD and high CKD progression risk in early-stage adult-onset T1DM patients in the world. Considering the hazards of DKD, based on our findings, we recommend that in adult-onset T1DM patients worldwide with one of the following characteristics: male, low BMI, dyslipidemia, and hypertension, regardless of DM duration, urinary ACR and eGFR should be closely evaluated to screen DKD and high risk of CKD progression.

Though evidence and recommendations that diabetes patients with moderate albuminuria and severe albuminuria should be treated with RAAS blockers have been established a long time [4], only 4.7% and 27.8% of patients were treated with RAAS blockers among those with moderate albuminuria and severe albuminuria in our study, respectively. This situation may be related to the lack of knowledge of endocrinologists about DKD [47]. The T1DM patients with moderate albuminuria and severe albuminuria may be timely transferred to the Department of Nephrology.

A notable strength of our study is its pioneering analysis of factors associated with moderate albuminuria, severe albuminuria, mildly reduced eGFR, decreased eGFR, and high CKD progression risk utilizing multi-center data from patients with early-stage adult-onset T1DM in China. Our research may be helpful for the early management of DKD and DKD progression, and our findings also confirm existing literature, and help the adult-onset T1DM patients from China. However, this research had several limitations. First, our study is a cross-sectional study and had a relatively small number of positive events. Thus, we could not further discuss the contribution of the related factors to kidney disease and high CKD progression risk. We could not get a causal relationship between related factors with kidney disease and high CKD progression risk. Second, our study did not exclude confounding factors, such as diet, physical activity, nutrition, inflammation, and smoking for CKD progression. Third, the results were limited to the Chinese adult-onset T1DM patients who visited tertiary hospitals, whether our research findings suit other groups remains uncertain.

In conclusion, hyperglycemia, hypertension, hyperuricemia, and BMI are associated with different stages of kidney disease in early-stage adult-onset T1DM patients. Early-stage

adult-onset T1DM patients with male, low BMI, long T1DM duration, and accompanied with hypertension and dyslipidemia should be closely evaluated urinary ACR and renal function to detect patients at high risk of CKD progression and timely be transferred to nephrology specialty to improve the renal prognosis.

Acknowledgements

We thank all the doctors, nurses, technicians, and patients for their dedication to this study in the 16 participating hospitals.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol and consent processes were approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (ID: [2010]2-36). Written informed consent was obtained from all subjects.

Authors' contributions

JJ, WJH, and LL were primarily responsible for the study design, data collection, interpretation, and manuscript writing. SHL, JHY, and YD contributed to data analysis and critical revision of the manuscript. XYZ, WR, and DZY contributed to the discussion and edited the manuscript. LL, WJH and JJ contributed to data collection and the discussion. WR, KXT, and DZY contributed to the study design, interpretation of data analyses, discussion, and critical revision of the manuscript. All authors read and approved the final manuscript.

Disclosure statement

On behalf of all authors, the corresponding author states that there is no conflict of interest to disclose.

Funding

This study was supported by the Strategic Pilot Science and Technology Project of the Chinese Academy of Sciences (grant XDB 38010100), the Chinese National Natural Science Foundation (grant 82100822), and the Chinese National Natural Science Foundation (grant 82100857).

Data availability statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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