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The analysis of risk factors for diabetic kidney disease progression: a single-centre and cross-sectional experiment in Shanghai

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ABSTRACT

Objective To identify the risk factors for diabetic kidney disease (DKD) development, especially the difference between patients with different courses.

Patients and methods 791 patients were considered to be eligible and were enrolled in the cross-sectional study from Shanghai Tongren Hospital Inpatient Department. 36 variables were initially screened by univariate analysis. The risk factors affecting progression of DKD were determined by logistics regression analysis. Subgroups were grouped according to the course of diabetes disease, and multivariate logistics regression analysis was performed to find out the different risk factors in two subgroups. Finally, the receiver operating characteristics curve is used to verify the result.

Results The logistic regression model indicated age (OR=1.020, p=0.017, 95% CI 1.004 to 1.040), systolic blood pressure (OR=1.013, p=0.006, 95% CI 1.004 to 1.022), waist circumference (OR=1.021, p=0.015, 95% CI 1.004 to 1.038), white blood cells (WBC, OR=1.185, p=0.001, 95% CI 1.085 to 1.295) and triglycerides (TG, OR=1.110, p=0.047, 95% CI 1.001 to 1.230) were risk factors for DKD, while free triiodothyronine (fT3, OR=0.711, p=0.011, 95% CI 0.547 to 0.926) was a protective factor for DKD in patients with type 2 diabetes mellitus (T2DM). Subgroup analysis revealed that in patients with a short duration of diabetes (<8 years), WBC (OR=1.306, p<0.001, 95% CI 1.157 to 1.475) and TG (OR=1.188, p=0.033, 95% CI 1.014 to 1.393) were risk factors for DKD,fT3 (OR=0.544, p=0.002, 95% CI 0.367 to 0.804) was a protective factor for DKD; whereas for patients with disease course more than 8 years, age (OR=1.026, Pp=0.012, 95%CI=95% CI[1.006– to 1.048]) was identified as the only risk factor for DKD and fT3 (OR=0.036, Pp=0.017, 95%CI=95% CI[0.439– to 0.922]) was a protective factor for DKD.

Conclusion The focus of attention should especially be on patients with a prolonged course of T2DM, and those with comorbid hypertension and hypertriglyceridaemia waist phenotype. More potential clinical indexes such as thyroid function and inflammatory indicators might be considered as early warning factors for DKD in T2DM. Women should pay attention to controlling inflammation and TGs, and men should strictly control blood pressure. Avoiding abdominal obesity in both men and women will bring great benefits.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study found related risk factors for diabetic kidney disease that need to be confirmed and supplemented in the next large-scale prospective study.
⇒ Due to the cross-sectional nature of this study, we could not identify the causal relationship between risk factors and diabetic nephropathy in a large sample.
⇒ The sample size of the data obtained is limited, and the data has a certain region, which is not representative.
⇒ Selection offset should be considered when interpreting the results of this study.
⇒ Exposure variables and outcome variables in the study coexist, and the time sequence between the exposure and the outcome cannot be judged.

INTRODUCTION

Diabetes has become a critical health concern worldwide owing to its high prevalence and related disability and mortality. A recent nationally representative epidemiological survey in China indicated that the overall prevalence of diabetes in mainland China in 2017 was 12.8% using the American Diabetes Association (ADA) diagnostic criteria and 11.2% using WHO criteria.[1 2] Type 2 diabetes mellitus (T2DM) and its complications have contributed tremendously to the burden of mortality and disability worldwide.[1]

Diabetic kidney disease (DKD) is one of the most important diabetic microvascular complications, affecting 40%–59.8% of patients with T2DM.[3 4] In China, the recent results of an epidemiological survey in 31 provinces and cities across the country from 2015 to 2017 showed the prevalence rate of T2DM. Although some progress has been made in reducing diabetes-related mortality and delaying the development of kidney disease from diabetes mellitus, the percentage of patients with DKD who progress to ESRD
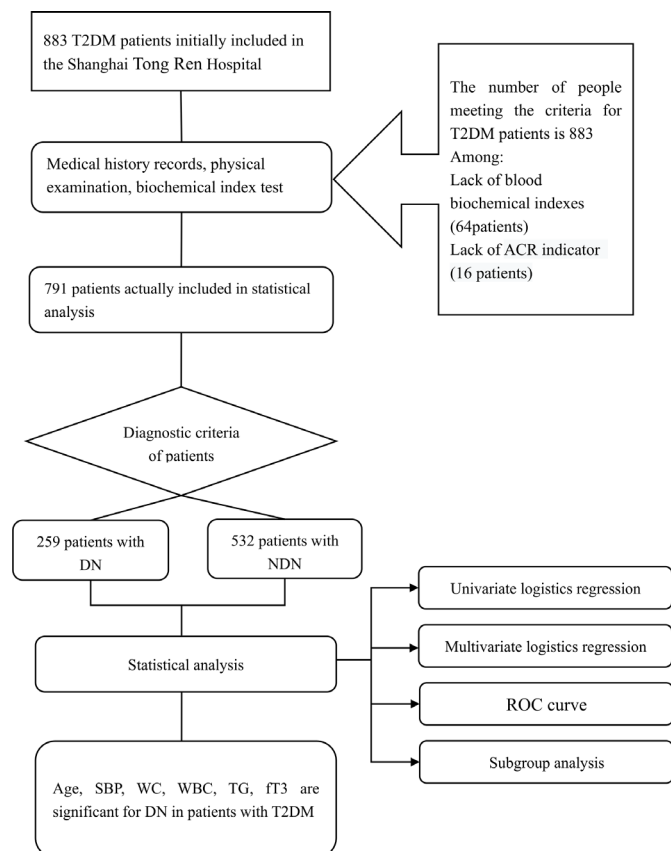
Figure 1 Logic flow plot of this study. Note: the logic flow plot shows the entire research process. fT3, free triiodothyronine; ROC, receiver operating characteristics; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglyceride; WBC, white blood cell; WC, waist circumference.

has not substantially declined.[5] Gembillo G et al reported that therapeutic inertiawas used to guide clinicians find the best way to improve the patient's quality of life and the best strategy to appropriately communicate pharmacological targets to achieve target glycaemia and delay or overcome DKD-related complications.[6] In addition, aggressive DKD in youth-onset type 2 diabetes should also receive great attention; it has a rising incidence, is genetically predisposed, is closely associated with obesity, hyperglycaemia, hyperlipidemia, insulin resistance, hypertension and inflammation, and represents a major worldwide burden.[7]

Several important clinical indicators have been discovered in research as independent risk factors that affect the incidence risk of DKD for patients with T2DM, such as disease course, body mass index (BMI), triglycerides (TGs), systolic blood pressure (SBP) and haemoglobin A1c (HbA1c).[8] That means DKD is related to certain factors such as poor glycaemic control, dyslipidaemia and hypertension in T2DM.[9] Relevant studies have reported that the course of T2DM has a great impact on the occurrence of DKD, and longer duration of diabetes has a higher likelihood of predicting DKD.[10 11] However, few studies have addressed the issue of whether there are

differences in the risk factors for the progression of DKD in patients with a duration of diabetes >10 years compared with those with a shorter duration of diabetes (<8 years). We suppose that the risk factors of DKD may be inconsistent under different courses of T2DM. Currently, the treatment of DKD is mainly to prevent or delay disease progression. Early detection and intervention of risk factors can reduce the progression of DKD. Hence, it is of great significance to focus on the risk factors of DKD at an early stage of T2DM.

In addition, More attention should be paid to the relationship between inflammation and DKD. More recently, the care time study have shown that the inflammatory burden of DKD is much greater than that of NDKD.[12] It has been reported that there are high concentrations of inflammatory cells in the glomeruli and tubulointerstitium of diabetic kidneys, as well as the overexpression of chemokines, cytokines and adhesion molecules, and inflammation has become a focus of DKD development.[13] We will also focus on the relationship between diabetic nephropathy and inflammation in this study.

We carried out the present study to investigate the risk factors of DKD in different courses of T2DM. Data analysis showed the differences between patients with a duration of diabetes >8 years and those with a short duration of diabetes (<8 years). Our study aims to provide theoretical and clinical basis for preventing and delaying the occurrence and development of DKD in patients with T2DM.

PATIENTS AND METHODS
Patient and public involvement
We conducted a cross-sectional survey at the Shanghai Tongren Hospital Inpatient Department. The patients participating in our study design were adults who were diagnosed with type 2 diabetes through medical records and diease history at Shanghai Tong Rren Hospital. All patients enrolled in our study gave informed consent to join this programme and signed the consent paper. We used data collected for patients with diabetes treated at the Endocrinology Department of this hospital from May 2020 to April 2021. The criteria defined by WHO in 1999 were used as the diagnostic criteria for diabetes.[14] The exclusion criteria of diabetic nephropathy were other types of diabetes and severe chronic diseases (advanced malignant tumour, cirrhosis, liver failure, myocardial infarction or severe heart failure).

A total of 883 patients were enrolled in this study. Among all participants, 64 were excluded due to incomplete data or abnormal values, and 16 lacked ACR indicators; finally, 791 participants were included in the analysis. A flow diagram of the study design is shown in figure 1. In this study, albumin-to-creatinine ratio(ACR) was used to define DKD; for a better definition of DKD in our population, repeated microalbuminuria measurements have been performed and analysed, and patients with ACR ≥30 mg/g were defined as patients with DKD. Renal biopsy is an essential tool to distinguish between

diabetes mellitus or underlying glomerulonephritis associated with renal involvement, and has great implications for the staging and diagnosis of diabetic nephropathy. Taking into account economic and practical factors, renal biopsy diagnosis cannot be performed for everyone. According to strict standards, hyperuricaemia is defined by male blood uric acid (UA) >420 umol/L and female blood UA >360 umol/L.

Index measurement method

The following participant characteristics were assessed: gender, region, age, disease course, body weight (kg), height (m), waist circumference (WC, cm), SBP and diastolic blood pressure (DBP) (SBP and DBP measurements (in mm Hg) were obtained using an automatic electronic blood pressure monitor (model high blood pressure (HBP)-9021; Omron Corp, Kyoto, Japan)). BMI was calculated according to weight and height; WC was measured by a standardised protocol. Biochemical indexes were collected to determine the associated factors, including fasting blood glucose, fasting insulin (FIN), fasting c-peptide (FCP), glycosylated HbA1c, haemoglobin (Hb), red blood cells (RBC), white blood cells (WBC), platelet, haematocrit (HCT), mean RBC volume (MCV), mean RBC haemoglobin (MCH), mean platelet volume (MPV), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), serum albumin, total cholesterol (TC), TG, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen (BUN), serum creatinine, UA, high-sensitivity C reactive protein (hs-CRP), free triiodothyronine (fT3), serum free thyroxine, hypersensitive thyroid stimulating hormone, parathyroid hormone, 25 hydroxyvitamin D (25VitD), procalcitonin (PCT), uric creatinine (Cr) and urinary microalbumin. Blood samples were collected through standardised processes and stored under standard conditions (refrigeration at 4°C) until sending to the laboratory of Tongren Hospital for measurement (within 2 hours of collection). An automatic biochemical analyser was used for biochemical testing (AU5800 clinical chemistry analyser; Beckman Coulter, Brea, California, USA). Urine biochemical indexes were analysed by urine test 500B (URIT, China).

Statistical analysis

Statistical analysis was performed using SPSS statistics software (V.25). Descriptive statistical analysis was performed on the data. The missing data were filled by the expectation maximisation algorithm method in SPSS. The data types in this study belong to measurement data, non-normally distributed measurement data and counting data. The measurement data are described by the mean and SD (x±s). For non-normally distributed measurement data, the median and quartiles (M (P25, P75)) are used. Data from demographics are expressed as frequencies and counts (%). First, 791 patients in our research were divided into two groups: the patients with DKD (DKD group) and those with NDKD. Next, we screened the suitable and effective risk factors for DKD by univariate logistics regression analysis. Then, the significant indicators were corrected by multivariate logistics regression analysis. Because the course of T2DM is closely related to the occurrence of DKD, subgroup analysis was conducted according to the median course of T2DM obtained from our data. Multivariate logistics regression analysis was performed to find out the differential risk factors. Receiver operating characteristics (ROC) curves were constructed by plotting sensitivity versus 1–specificity, and the areas under the ROC curves (AUCs) were calculated to determine the sensitivity and specificity of all the selected features. The research design, research object, research method and results are presented simply in a flow chart.

RESULTS

After handling the missing and abnormal values, a total of 791 patients with T2DM were finally obtained, including 475 men and 316 women (table 1). The mean age of the participants was 57.68±11.49 years. Of all the participants with T2DM in our analysis, 259 had DKD and 532 did not have DKD, and the prevalence of DKD in patients with T2DM was 32.74%. In the DKD group (n=259), 151 were men, accounting for 58%. The specific demographic and clinical characteristics are given in table 1. DKD in patients with T2DM is 32.74%. Considering the course of T2DM was analysed in the following subgroups, we did not include the course of disease indicators for logistic regression analysis. Thirty-six variables were initially screened by univariate analysis, as shown in table 2. Seventeen variables including age, SBP, WC, FIN, FCP, Hb, WBC, HCT, MCV, MCH, BUN, Cr, UA, TG, hs-CRP, fT3 and 25VitD were selected by univariate analysis. Then 17 factors with p<0.05 in univariate analysis were included in multivariate logistic regression analysis. Finally, using the statistical method of multivariate logistic regression analysis, the number of potential variables reduced from 17 to 6, including age, SBP, WC, WBC, TG and fT3. The results of multivariate logistic regression analysis showed that age (OR=1.020, p=0.017, 95% CI 1.004 to 1.040), SBP (OR=1.013, p=0.006, 95% CI 1.004 to 1.022), WC (OR=1.021, p=0.015, 95% CI 1.004 to 1.038), WBC (OR=1.185, p=0.001, 95% CI 1.085 to 1.295) and TG (OR=1.110, p=0.047, 95% CI 1.001 to 1.230) were risk factors for DKD, and fT3 (OR=0.711, p=0.011, 95% CI 0.547 to 0.926) was a protective factor for DKD in patients with T2DM (table 2). On this basis, in order to verify the test efficiency and accuracy of the regression model, the predicted probability p of 791 cases was taken as the ROC curve, and the AUC was 72% (figure 2).

Because the subjects in the DKD group studied here had a relatively shorter history of diabetes, we further assessed the DKD-related risk factors in the subgroups according to the course of diabetes. Subgroup analysis was conducted according to the median course of patients

Table 1   1 Demographic and clinical characteristics of patients with NDKD and DKD.

	NDKD (n=532)	DKD (n=259)	Total (n=791)
Sex			
Female	208 (39%)	108 (42%)	316 (40%)
Male	324 (61%)	151 (58%)	475 (60%)
Age (years)	60.00 (50 to 65)	62.00 (54 to 67)	61 (51 to 66)
DBP (mm Hg)	83.06±10.177	83.00±12.341	83.04±10.92
SBP (mm Hg)	133.21±16.286	137.57±20.503	134.64±17.88
BMI (kg/m^2)	25.25 (23.65 to 27.78)	26.02 (23.68 to 28.36)	25.59 (23.23 to 28.03)
WC (cm)	92 (85 to 100)	96 (89 to 102)	93.5 (87 to 100)
Course (years)	7.67 (7.08 to 8.33)	8.0 (7.42 to 8.5)	7.79 (7.25 to 8.33)
FBG (mmol/L)	6.8 (5.3 to 9.3)	6.8 (5.3 to 9.3)	6.8 (5.3 to 9.3)
FIN (pmol/L)	99 (63.55 to 148.2)	119.4 (76.4 to 169.6)	103.6 (68 to 155.3)
FCP (ng/mL)	0.37 (0.23 to 0.57)	0.41 (0.24 to 0.6)	0.38 (0.24 to 0.6)
HbA1c (%)	9 (7.6 to 9)	9.1 (7.8 to 10.8)	9 (7.6 to 10.7)
Hb (g/L)	138.69±15.83	134.95±16.6	137.46±16.17
RBC (10^{12}/L)	4.56±0.55	4.51±0.59	4.54±0.56
WBC (10^9/L)	6.15 (5.22 to 7.48)	6.75 (5.73 to 7.99)	6.35 (5.32 to 7.69)
PLT (10^9/L)	213 (177.25 to 248)	217(179 to 260)	215(178 to 251)
HCT (%)	40.2 (37.5 to 43.18)	39.3 (36 to 42.2)	40 (37.1 to 42.8)
MCV (fL)	88.5 (85.8 to 90.88)	87.8 (85.1 to 90.4)	88.2 (85.6 to 90.8)
MCH (pg)	30.5 (29.4 to 31.5)	30.1 (29.3 to 31.1)	30.4 (29.4 to 31.3)
MPV (fL)	10.6 (10.1 to 11.4)	10.8 (10 to 11.4)	10.7 (10.1 to 11.4)
ALT (U/L)	21(15 to 33)	20(14 to 30)	20(14 to 32)
AST (U/L)	19 (15 to 26)	19 (16 to 24)	19 (15 to 26)
ALP (U)	72 (57 to 85)	71 (59 to 87)	71 (58 to 85)
γ-GT (U)	24 (16 to 44)	38.7±62.39	25 (16 to 42)
ALB (G/L)	41 (39 to 44)	41 (38 to 44)	41 (39 to 44)
BUN (mg)	5.3 (4.4 to 6.4)	6 (4.7 to 7.5)	5.5 (4.5 to 6.8)
Cr (mg/dl)	57 (49 to 67)	62 (45 to 81)	57.6 (48 to 70)
UA (u/L)	324 (266 to 387)	356 (291 to 406)	333 (276 to 393)
TG (mmol/L)	1.38 (0.95,1.38)	1.63 (1.13 to 2.49)	1.45 (1.01 to 2.28)
TC (mmol/L)	4.45 (3.75,5.15)	4.55 (3.7 to 5.5)	4.5 (3.73 to 5.25)
HDL-C (mmol/L)	1.01 (0.86,1.19)	0.98 (0.84 to 1.17)	1 (0.85 to 1.19)
LDL-C (mmol/L)	2.92±1.07	2.88±1.16	2.91±1.1
hs-CRP (mg/L)	1.4 (0.7 to 2.7)	1.41 (0.7 to 3.35)	1.4 (0.7 to 2.9)
fT3 (pmol/L)	4.7 (4.3 to 5.1)	4.5 (4.1 to 4.9)	4.6 (4.3 to 5)
fT4 (nmol/L)	16.87 (15.2 to 16.9)	16.64 (15.37 to 18.43)	16.75 (15.27 to 18.62)
s-TSH (μIU/mL)	1.7 (1.14 to 2.43)	1.8 (1.22 to 2.67)	1.75 (1.13 to 2.51)
PTH (pmol/L)	2.94 (1.14 to 2.43)	2.92 (1.99 to 4.09)	2.93 (2.09 to 3.89)
25VitD (ng/ml)	16.53 (12.68 to 21.07)	15.25 (11.5 to 20.05)	16.25 (12.42 to 20.56)
PCT (ng/mL)	0.88 (0.5 to 1.98)	0.83 (0.5 to 1.92)	0.86 (0.5 to 1.95)
ACR (μmol/L)	13.85 (9.7 to 19.81)	97.7 (44.9 to 443.7)	19.6 (11.4 to 43.6)

Data are presented as n (%), mean±SD or median (IQR).
albumin-to-creatinine ratio(ACR) was used to define DKD;patients with ACR ≥30 mg/g were defined as patients with DKD; patients with ACR<30 mg/g were defined as patients with NDKD.diabetic kidney disease(DKD);non-diabetic kidney disease(NDKD)
ALB, serum albumin ; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine ; DBP, diastolic blood pressure; DKD, diabetic kidney disease; FBG, fasting blood glucose; FCP, fasting c-peptide; FIN, fasting insulin; fT3, free triiodothyronine; fT4, free thyroxine; Hb, haemoglobin; HbA1c, haemoglobin A1c; HCT, haematocrit ; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; MCH, mean RBC haemoglobin; MCV, mean RBC volume; MPV, mean platelet volume; NDKD, non-diabetic kidney diease; PCT, calcitonin original; PLT, platelet; PTH, parathyroid hormone; RBC, red blood cell ; SBP, systolic blood pressure; s-TSH, hypersensitive thyroid stimulating hormone; TC, total cholesterol; TG, triglycerides; UA, uric acid; 25VitD, 25 hydroxyvitamin D; WBC, white blood cells; WC, waist circumference; γ-GT, γ-glutamyl transpeptidase.

with DKD obtained from our data (8.0 years (7.42–8.5)). The prevalence rate of patients with DKD with disease course less than 8 years was 28.38%, and 38.53% for those with disease course more than 8 years. Multivariate logistic regression analysis was performed in two subgroups. The results showed that in patients whose diabetes course is

Table 2 Logistic regression analysis of DKD-related risk factors

| | Univariate logistics regression | | | | Multivariate logistics regression | | | |
| | 95% CI | | | | 95% CI | | | |
	β-coefficient	P value	OR	Lower-upper	β-coefficient	P value	OR	Lower-upper
Age	0.016	0.018	1.016	1.003 to 1.030	0.022	0.017	1.020	1.004 to 1.040
SBP	0.014	0.001	1.014	1.005 to 1.022	0.013	0.006	1.013	1.004 to 1.022
DBP	−4.88e-4	0.944	1.000	0.986 to 1.010				
BMI	0.036	0.052	1.036	0.100 to 1.074				
WC	0.025	<0.001	1.025	1.011 to 1.039	0.021	0.015	1.021	1.004 to 1.038
FBG	0.016	0.444	1.016	0.975 to 1.060				
HbA1c	0.043	0.200	1.044	0.977 to 1.116				
FIN	0.001	0.007	1.001	1.000 to 0.975	6.41e-4	0.136	1.001	0.100 to 1.001
FCP	0.783	0.002	2.187	1.328 to 3.602	0.280	0.366	1.330	0.717 to 2.468
Hb	−0.015	0.002	0.986	0.976 to 0.995	0.045	1.162	1.064	0.982 to 1.114
RBC	−0.175	0.791	0.839	0.643 to 1.100				
WBC	0.153	<0.001	1.166	1.079 to 1.260	0.170	0.001	1.185	1.085 to 1.295
HCT	−0.062	<0.001	0.940	0.908 to 0.972	0.205	0.065	0.814	0.655 to 1.013
PLT	0.200	0.203	1.002	0.999 to 1.004				
MCV	−0.043	0.010	0.958	0.927 to 0.990	0.022	0.716	1.022	0.909 to 1.148
MCH	−0.116	0.006	0.891	0.820 to 0.967	−0.215	0.195	0.807	0.584 to 1.116
MPV	0.027	0.345	1.028	0.971 to 1.087				
ALT	−0.002	0.347	0.998	0.992 to 1.003				
AST	5.16e-4	0.900	1.001	0.992 to 1.009				
ALP	0.004	0.138	1.004	0.999 to 1.009				
γ-GT	4.82e-4	0.740	1.000	0.998 to 1.003				
ALB	−0.022	0.193	0.978	0.947 to 1.010				
BUN	0.170	<0.001	1.185	1.101 to 1.275	0.103	0.053	1.109	0.999 to 1.231
Cr	0.013	<0.001	1.013	1.007 to 1.020	0.003	0.572	1.003	0.993 to 1.012
UA	0.003	<0.001	1.003	1.001 to 1.004	7.30e-4	0.482	1.001	0.999 to 1.003
TG	0.119	0.006	1.127	1.032 to 1.227	0.104	0.047	1.110	1.001 to 1.230
TC	0.091	0.115	1.095	0.978 to 1.227				
HDL-C	−0.135	0.583	0.874	0.540 to 1.414				
LDL-C	0.031	0.657	0.970	0.847 to 1.110				
hs-CRP	0.033	0.017	1.033	1.006 to 1.061	0.004	0.779	1.005	0.974 to 1.037
fT3	−0.492	<0.001	0.611	0.477 to 0.782	−0.340	0.011	0.711	0.547 to 0.926
fT4	−0.010	0.640	0.990	0.951 to 1.030				
TSH	0.071	0.091	1.074	0.989 to 1.166				
PTH	0.052	0.300	1.053	0.955 to 1.161				
25VitD	−0.038	0.002	0.963	0.940 to 0.986	−0.025	0.068	0.976	0.950 to 1.002
PCT	0.037	0.135	1.037	0.989 to 1.089				

ALB, serum albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine ; DBP, diastolic blood pressure; DKD, diabetic kidney disease; FBG, fasting blood glucose; FCP, fasting c-peptide; FIN, fasting insulin; fT3, free triiodothyronine; fT4, free thyroxine; Hb, haemoglobin; HbA1c, haemoglobin A1c; HCT, haematocrit ; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; MCH, mean RBC haemoglobin; MCV, mean RBC volume; MPV, mean platelet volume; PCT, calcitonin original; PLT, platelet; PTH, parathyroid hormone; RBC, red blood cell ; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone; UA, uric acid; 25VitD, 25 hydroxyvitamin D; WBC, white blood cells; WC, waist circumference; γ-GT, γ-glutamyl transpeptidase.

less than 8 years, WBC (OR=1.306, p<0.001, 95% CI 1.157 to 1.475) and TG (OR=1.188, p=0.033) were risk factors for DKD, while fT3 (OR=0.544, p=0.022, 95% CI 0.367 to 0.804) was a protective factor for DKD. For those with longer course of T2DM, age (OR=1.026, p=0.012, 95% CI 1.006 to 1.048) was a risk factor for DKD, and fT3 (OR=0.036, p=0.017, 95% CI 0.439 to 0.922) was a protective factor for DKD (table 3). Subgroup analysis showed
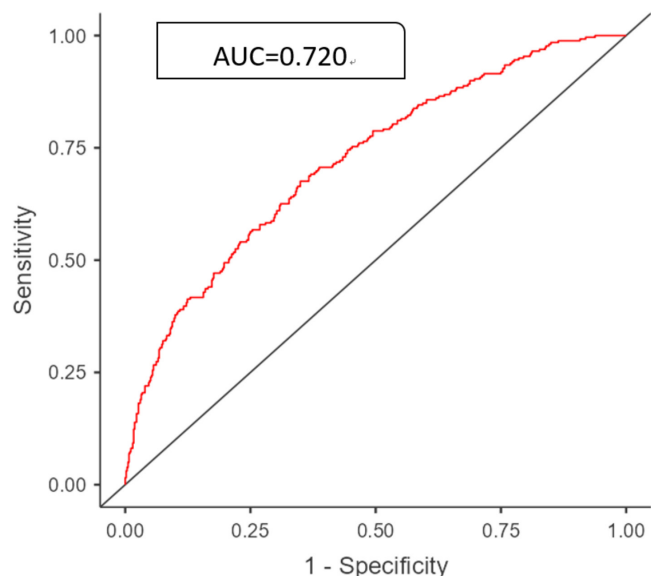
Figure 2 The pooled AUC of the ROC curve. Note: The y-axis indicates the true positive rate of risk prediction. The x-axis indicates the false-positive rate of risk prediction. The red line represents the performance of the regression model. AUC, area under the ROC curve; ROC, receiver operating characteristics.

that in female patients, WC (OR=1.026, p=0.030, 95% CI 1.002 to 1.049), WBC (OR=1.279, p=0.001, 95% CI 1.101 to 1.486) and TG (OR=1.553, p<0.001, 95% CI 1.234 to 1.955) are risk factors, and fT3 (OR=0.524, p=0.009, 95% CI 0.323 to 0.850) is a protective factor. As for male patients, age (OR=1.028, p=0.004, 95% CI 1.009 to 1.047), SBP (OR=1.015, p=0.014, 95% CI 1.003 to 1.026), WC (OR=1.025, p=0.017, 95% CI 1.004 to 1.047) are risk factors, and fT3 (OR=0.663, p=0.018, 95% CI 0.472 to 0.933) is a protective factor (table 4).

DISCUSSION

The increasing prevalence of diabetes around the world and changes in clinical practice have influenced the epidemiology of chronic kidney disease (CKD) in recent years. In many countries, diabetes is responsible for over 40% of new cases of end-stage renal disease (ESRD), surpassing other complications to become the single leading driver of incident kidney failure.[15] The results of this study show that the prevalence of DKD in patients with T2DM at the Shanghai Tongren Hospital is 32.74%.

Overall, there were five significant risk factors and one protective factor for the whole disease course and age group, including age, SBP, WC, WBC, TG and fT3, which was not completely consistent with previous studies.[16] A cross-sectional study reported risk factors for DKD included poor glycaemic control, older age and longer duration of diabetes mellitus.[17] SBP is one of the main diagnostic indicators of hypertension. It has been pointed out that SBP is positively associated with the development of diabetic nephropathy in individuals with T2DM,[18] suggesting that hypertension is a risk factor for DKD.[8] These findings highlight the view that prevention of hypertension, especially SBP has been an attractive therapeutic target in T2DM. With regards to abdominal obesity, it has been considered a risk factor for diabetic complications and has a close connection with DKD. Various obesity-related indices were significantly associated with albuminuria and advanced kidney disease in patients;[19] WC was also associated with DKD in Asian persons with T2DM.[20] The association between WC and DKD that we found in our case group is in line with the finding reported from seven communities in Shanghai, China, in 2018.[21 22] The hypertriglyceridaemia waist (HW) phenotype is represented by the simultaneous presence of elevated TG levels and increased WC. TG has an important role in the progression of kidney disease in patients with diabetes.[23 24] Several lines of evidence have linked the HW phenotype to early diabetic nephropathy. It was observed that the HW phenotype was associated with elevated urine microalbumin (UMA) and early diabetic nephropathy in patients with T2DM.[25] Our study also shows that both WC and TG are risk factors for diabetic nephropathy, which is consistent with existing studies.[26 27]

Another important issue that has been addressed in our study, the risk factors for the progression of DKD in patients with a duration of diabetes >8 years were different

Table 3 Logistic regression analysis in subgroups according to the course of diabetes

| | <8 years | | | | ≥8 years | | | |
| | 95% CI | | | | 95% CI | | | |
	β-coefficient	P value	OR	Lower-upper	β-coefficient	P value	OR	Lower-upper
Age	0.019	0.127	1.019	0.995 to 1.043	0.026	0.012	1.026	1.006 to 1.048
SBP	0.012	0.062	1.012	0.999 to 1.025	0.011	0.094	1.011	0.998 to 1.023
WC	0.034	0.081	1.034	0.996 to 1.074	0.022	0.138	1.023	0.993 to 1.053
WBC	0.267	<0.001	1.306	1.157 to 1.475	0.062	0.306	1.064	0.945 to 1.199
TG	0.172	0.033	1.188	1.014 to 1.393	0.105	0.079	1.110	0.988 to 0.248
fT3	−0.609	0.002	0.544	0.367 to 0.804	−0.452	0.017	0.036	0.439 to 0.922

fT3, free triiodothyronine; SBP, systolic blood pressure; TG, triglycerides; WBC, white blood cells; WC, waist circumference.

Table 4	Logistic regression analysis in subgroups according to gender						
	Female				Male		
	95% CI				95% CI		
	β-coefficient	P value	OR	Lower-upper	β-coefficient	P value	OR	Lower-upper
Age	0.018	0.193	1.0183	0.991 to 0.818	0.028	0.004	1.028	1.009 to 1.047
SBP	0.005	0.459	1.0055	0.991 to 1.020	0.015	0.014	1.015	1.003 to 1.026
WC	0.025	0.030	1.0255	1.002 to 1.049	0.025	0.017	1.025	1.004 to 1.047
WBC	0.246	0.001	1.2793	1.101 to 1.486	0.089	0.096	1.093	0.984 to 1.215
TG	0.440	<0.001	1.5531	1.234 to 1.955	0.049	0.348	1.050	0.948 to 1.163
fT3	−0.646	0.009	0.5239	0.323 to 0.850	−0.410	0.018	0.663	0.472 to 0.933

fT3, free triiodothyronine; SBP, systolic blood pressure; TG, triglycerides; WBC, white blood cells; WC, waist circumference.

compared with those with a short duration of diabetes (<8 years). First, our results of subgroup analysis showed that TG was still a significant risk factor in patients with a duration of diabetes <8 years. This is similar to the results of previous studies, suggesting that for people with a short course of T2DM doctors should pay more attention to the treatment of hypertriglyceridaemia. Second, we surprisingly found that WBC was another risk factor for DKD. WBC is an important indicator of inflammation. It has been reported that with the progression of DKD, the total number of WBCs, monocytes and neutrophils in peripheral blood were increased. WBC (r=0.194, p=0.014) was independently and significantly associated with DKD.[28] Microvascular complications of T2DM are associated with increased WBC count.[29] Other studies have demonstrated that increased levels of several proteins including monocyte chemotactic protein-1 (MCP-1), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), interleukin (IL) 6 and interleukin-1α (IL-1α) are detected as early as CKD stage 1–2 prior to significant kidney impairment, and several mediators decrease after stage 3–4 including IL-6, macrophage inflammatory protein (MIP)-1β and interleukin-1 receptor antagonist (IL-1RA).[30] Therefore, in the early stages of diabetes, the classic markers of inflammation (such as WBC) may warn of diabetic nephropathy. Third, HbA1c was not found to be a significant risk factor of DKD in our study, which was inconsistent with the results in the study by Hu *et al*.[8] This result might partly be explained by glycaemic intervention, as well as relatively high levels of HbA1c in our study population. Therefore, our results emphasise the importance of lipid-lowering treatment, and that we should pay more attention to inflammation during the early stage follow-up.

It is worth noting that fT3 (OR=0.036, p=0.017, 95% CI 0.439 to 0.922) was a protective factor for DKD both in patients with long duration of T2DM and those with short disease course, while the protective effectiveness gradually decreases during the prolongation of the disease course (<8 years, OR=0.544, p=0.002, 95% CI 0.367 to 0.804; >8 years, OR=0.036, p=0.017, 95% CI 0.439 to 0.922). Studies have shown that the prevalence of DKD decreased gradually as the quartiles of fT3 levels increased; fT3 (p<0.05) levels exhibited a potentially significant association with DKD in patients with T2DM.[31] Low serum fT3 levels have been shown to be associated with endothelial dysfunction as assessed by flow-mediated dilation in patients with chronic kidney disease.[32] A study indicated that decreased fT3 might imply the risk and useful predictors for DKD.[33] Previous research has reported that patients with low fT3 levels are more likely develop DKD than those with high fT3 levels, whereas an appropriate increase of fT3 could reduce endothelial injury and protect the kidney.[34] fT3 would enhance lipid metabolism, thus enhancing energy consumption, and protect the kidney from the mechanism of glucose and lipid metabolism. A study shows that thyroid hormone-thyroid hormone receptor axis alterations are critically involved in DKD-associated podocyte pathology, and they identify thyroid hormone receptor alpha 1 (TRα1) as a key regulator of the pathogenesis of DKD.[35] Thyroid dysfunction is associated with associated disturbances in glucose metabolism, and slightly higher fT3 may be beneficial when glucose metabolism is high.[36] Our results suggested that ensuring normal thyroid function in the early stages of T2DM might reduce the prevalence of DKD. Through early detection and improvement of relative risk factors of DKD during clinical management, it might reduce the incidence of DKD, as well as improve the quality of life for patients with diabetes.

This study found that the risk factors of inflammation and TGs in women with DKD are more harmful, while the control of blood pressure in men is of great significance for delaying disease progression. These differences may be related to female sex hormone, sex genes interaction.[37] Avoiding abdominal obesity in both men and women will bring great benefits; studies have shown that the progression of kidney disease is not only closely related to BMI and WC, but also more closely related to the visceral adiposity index.[38] More related research is expected to be studied.

LIMITATIONS OF THIS STUDY

Although we attempted to find out all the DKD risk factors and analyse them as accurately as possible, there were still some limitations in our study. First, there is a selection

bias in the population studied, because the patients with T2DM were collected from the inpatient department of Shanghai Tongren Hospital. The sample size of the data obtained is limited, and the data have a certain region, which is not representative. Second, because of the cross-sectional design of this study, we could not identify the causal relationship between risk factors and diabetic nephropathy. Third, ACR was obtained on the basis of single measurements without repeated tests. Although multiple variables were adjusted, other confounding factors (diet, medications and family history of CKD, etc) existed. Finally, further exploration of risk factors for diabetic nephropathy needs to be confirmed and supplemented in the next large prospective study.

CONCLUSION

In this retrospective observational study, the prevalence of DKD in hospitalised individuals with T2DM was 32.74%. Age, SBP, WC, WBC and TG are risk factors for DKD while fT3 is a protective factor for DKD in patients with T2DM. More attention should especially be focused on patients with a prolonged course of T2DM, or those with comorbid hypertension and HW phenotype. Especially in patients with disease course less than 8 years, TG intervention might be of great significance to the process of DKD. More potential clinical indexes such as thyroid function and inflammatory indicators might be considered as early warning factors for DKD. Women should pay attention to controlling inflammation and TGs, and men should focus on blood pressure. Avoiding abdominal obesity in both men and women will bring great benefits. These observations in our study may help to identify patients at greatest risk of disease progression and aid its prevention.

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