Serum cell division cycle 42 reflects the development and progression of diabetic nephropathy in patients with diabetes mellitus

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Abstract. Cell division cycle 42 (CDC42) regulates podocyte apoptosis to take part in the development and progression of diabetic nephropathy (DN), but currently the clinical evidence is limited. The aim of the present study was to investigate the capability of serum CDC42 expression level to estimate the development and progression of DN in patients with diabetes mellitus (DM). Patients with type 2 DM (n=306) were enrolled and divided into normoalbuminuria (n=185), microalbuminuria (n=72) and macroalbuminuria (n=49) groups based on the urinary albumin-to-creatinine ratio. Serum CDC42 was measured in all subjects using enzyme-linked immunosorbent assay. The median (interquartile range) CDC42 in patients with DM was 0.461 (0.314-0.690) ng/ml (range, 0.087-1.728 ng/ml). CDC42 was positively associated with the estimated glomerular filtration rate (P<0.001), but negatively correlated with body mass index, systolic blood pressure, hemoglobin A1c, serum creatine, serum uric acid and C reactive protein (all P<0.050). CDC42 levels were lowest in the macroalbuminuria group, followed by the microalbuminuria group, and were highest in the normoalbuminuria group (P<0.001). CDC42 indicated that it was a favorable estimator for the presence of albuminuria [area under the curve (AUC), 0.792; 95% confidence interval (CI), 0.736-0.848] and macroalbuminuria (AUC, 0.845; 95% CI, 0.775-0.915). By analyses in four different multivariate logistic regression models, increased CDC42 was independently associated with the presence of microalbuminuria (all P<0.001), macroalbuminuria (most P<0.001) and microalbuminuria + macroalbuminuria (all P<0.001). Serum CDC42 level negatively correlated with microalbuminuria and macroalbuminuria in patients with DM, suggesting its ability for estimating the development and progression of DN.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder with the presence of hyperglycemia that is due to the impairment of insulin secretion, defective insulin action or both (1). The prevalence of DM has increased globally over the past decade, which is mainly due to the continuous rise in the incidence of type 2 DM (2). Diabetic nephropathy (DN) is one of the common complications in patients with DM (3,4). It is reported that 5.02 million patients with type 1 DM suffer from DN and 129.56 million patients with type 2 DM encounter DN in 2019 (5). Clinically, albuminuria is classic evidence for a DN diagnosis, with an aberrant level representing a decrease in renal function that is associated with DN progression (6-8). As DN is a main cause of end-stage kidney disease and increases the risk of mortality in patients with DM (5,6,9,10), finding biomarkers that reflect the albuminuria level to further estimate the development and progression of DN is important.

Cell division cycle 42 (CDC42), a member of the guanosine triphosphatases (GTPase) family, regulates blood lipids, inflammation, glycolysis and insulin secretion (11-13). It has been recognized as an essential regulator in DM in several studies (14-16). For example, a previous study indicated that CDC42 promotes insulin secretion via the Wnt/β-catenin pathway (14). Another study demonstrated that inhibition of CDC42/β-catenin signaling suppresses the glucose-stimulated insulin secretion, which leads to DM progression (15). A previous mouse model demonstrated that deletion of the CDC42 gene in pancreatic β cells attenuates the insulin expression through inhibiting the extracellular signal-regulated kinase 1/2 (ERK1/2)-neurogenic differentiation 1 (NeuroD1) signaling pathway (16).

Furthermore, studies have indicated that CDC42 participates in the incidence and progression of DN (17,18). For example, in a mouse model with DM decreased expression

levels and activity of CDC42 leads to podocyte apoptosis and proteinuria (17). Another study reported that CDC42 reduction under high glucose inhibits podocyte apoptosis and affects β-cell insulin secretion in a type 2 DM-induced DN mouse model (18). However, the clinical role of CDC42 for estimating the development and progression of DN in patients with DM is currently unknown.

Therefore, the aim of the present study was to detect the serum CDC42 levels in patients with DM to investigate its use in estimating the development and progression of DN in these patients.

Materials and methods

Patients. During the period from February 2022 to November 2022, 306 patients with DM were consecutively enrolled in the present study. The enrollment criteria were: i) Diagnosed with type 2 DM according to the criteria of the American Diabetes Association (19); ii) ≥18 years old; and iii) had the willingness for participation and the collection of peripheral blood (PB). The exclusion criteria were: i) Had autoimmune systemic immune diseases; ii) had hematological disease; iii) had malignant disease; iv) had active infections; v) had other documented renal diseases; and vi) had a history of renal surgery. Clinicopathological characteristics of patients (including sex and age distribution) are included in Table I. The present study was approved by the Ethics Committee of Heilongjiang University of Chinese Medicine (Harbin, China; approval no. HZYLL202000302). Written informed consent was obtained from all patients.

Grouping. In the present study, patients were divided into three groups based on the urinary albumin-to-creatinine ratio (UACR): i) Normoalbuminuria, UACR <30 mg/g (n=185); ii) microalbuminuria, UACR of 30-300 mg/g (n=72); and iii) macroalbuminuria, UACR >300 mg/g (n=49).

Measurements. Characteristics of the patients were collected after enrollment, which included age, sex, body mass index (BMI), smoking status, DM duration, blood pressure, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), serum creatine (Scr), serum uric acid (SUA), lipid-related indexes and C reactive protein (CRP). Furthermore, the estimated glomerular filtration rate (eGFR) was calculated based on age and Scr according to the Chronic Kidney Disease Epidemiology Collaboration equation (20).

Additionally, PB samples of the patients were collected after enrollment, then the serum was isolated using a centrifuge for 10 min (2,054 x g, 4˚C). The serum CDC42 was measured using enzyme-linked immunosorbent assay (ELISA) using human CDC42 ELISA kits (cat. no. YJ908876; Shanghai Enzyme Link Biotechnology Co.) according to the manufacturer's protocols.

Statistical analysis. Data were processed using SPSS 26.0 (IBM Corp.). Normality was determined using the Kolmogorov-Smirnov test. Median values with interquartile range (IQR) were used to indicate non-normally distributed variables. Comparisons were made using the Wilcoxon rank sum, Kruskal-Wallis H rank sum and Chi-squared tests. The post hoc comparisons were achieved using the Bonferroni test. Correlations were assessed using Spearman's rank correlation test. Whether CDC42 could distinguish between different patients was assessed using receiver operating characteristic curves with area under the curve (AUC) and the Youden index (sensitivity plus specificity minus 1). Factors associated with microalbuminuria or macroalbuminuria were screened using logistic regression analyses with enter method. The model 1 included age and sex as factors, which were the most common confounders; the model 2 adjusted for factors included in model 1 and other factors including smoking status, DM duration, systolic blood pressure (SBP), and diastolic blood pressure (DBP); the model 3 adjusted for factors included in model 2 and other factors including FBG, HbA1c, triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and CRP; the model 4 adjusted for factors included in model 3 and other factors including Scr, eGFR, and SUA. P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics. The median age was 56.0 (IQR, 47.5-64.0), 57.5 (IQR, 51.3-64.0) and 63.0 (IQR, 55.5-68.5) years in the normoalbuminuria, microalbuminuria and macroalbuminuria groups, respectively (P<0.001). There were 79 (42.7%) female and 106 (57.3%) male patients in the normoalbuminuria group, 25 (34.7%) female and 47 (65.3%) male patients in the microalbuminuria group, and 16 (32.7%) female and 33 (67.3%) male patients in the macroalbuminuria group (P=0.295). The median DM duration was 11.0 (IQR, 7.5-15.0), 14.0 (IQR, 10.3-17.0) and 15.0 (IQR, 11.0-21.0) years in the normoalbuminuria, microalbuminuria and macroalbuminuria groups, respectively (P<0.001). Blood pressure indexes [including SBP and DBP] and blood biochemical indexes (including HbA1c, Scr, SUA and CRP) exhibited the highest levels in the macroalbuminuria group, followed by the microalbuminuria group, and the lowest levels in the normoalbuminuria group (all P<0.05). While eGFR was at its lowest in the macroalbuminuria group, followed by the microalbuminuria group, and highest in the normoalbuminuria group (P<0.001). The detailed information is presented in Table I.

Serum CDC42 levels in patients with DM. The median serum CDC42 level was 0.461 (IQR, 0.314-0.690) ng/ml in patients with DM, ranging from 0.087 to 1.728 ng/ml. The distribution of serum CDC42 levels in patients with DM is presented in Fig. 1.

Correlation of serum CDC42 levels with clinical characteristics of patients with DM. Serum CDC42 levels were negatively correlated with BMI (P=0.020), SBP (P=0.016), HbA1c (P=0.027), Scr (P<0.001), SUA (P=0.001) and CRP (P<0.001). While serum CDC42 level was positively associated with eGFR (P<0.001). Additionally, serum CDC42 levels were not associated with other clinical characteristics, including age, sex, smoking status, DM duration, DBP, FBG, TG, TC, LDL-C or HDL-C (all P>0.05) in all patients with DM (Table II).

Table I. Comparison of demographic characteristics, disease features and biochemical indexes among normoalbuminuria, microalbuminuria and macroalbuminuria groups.

Characteristics	Normoalbuminuria (N=185)	Microalbuminuria (N=72)	Macroalbuminuria (N=49)	P-value
Median age (IQR), years	56.0 (47.5-64.0)	57.5 (51.3-64.0)	63.0 (55.5-68.5)	<0.001
Sex, n (%)				0.295
Female	79 (42.7)	25 (34.7)	16 (32.7)	
Male	106 (57.3)	47 (65.3)	33 (67.3)	
Median BMI (IQR), kg/m^2	24.6 (22.5-27.0)	25.6 (23.7-27.7)	25.3 (23.0-30.1)	0.124
Smoking status, n (%)				0.151
Never	141 (76.2)	47 (65.3)	33 (67.3)	
Former/current	44 (23.8)	25 (34.7)	16 (32.7)	
Median DM duration (IQR), years	11.0 (7.5-15.0)	14.0 (10.3-17.0)	15.0 (11.0-21.0)	<0.001
Median SBP (IQR), mmHg	129.0 (121.0-137.0)	131.0 (123.3-138.8)	136.0 (130.0-146.0)	0.001
Median DBP (IQR), mmHg	77.0 (71.0-85.0)	78.0 (71.3-88.8)	85.0 (72.5-93.5)	0.042
Median FBG (IQR), mmol/l	5.9 (4.9-8.0)	6.4 (5.3-8.0)	6.3 (5.4-8.8)	0.109
Median HbA1c (IQR), %	7.4 (6.5-8.1)	7.6 (6.9-8.6)	7.6 (6.8-8.8)	0.040
Median Scr (IQR), mg/dl	0.9 (0.8-1.0)	1.0 (0.9-1.3)	1.4 (1.1-1.8)	<0.001
Median eGFR (IQR), ml/min/1.73 m^2	82.0 (69.2-97.7)	72.6 (59.4-89.6)	52.8 (35.9-63.7)	<0.001
Median SUA (IQR), μmol/l	301.0 (259.0-351.5)	320.0 (278.0-382.0)	380.0 (322.0-451.5)	<0.001
Median TG (IQR), mmol/l	1.2 (0.7-1.7)	1.5 (0.9-2.2)	1.3 (0.6-2.2)	0.089
Median TC (IQR), mmol/l	4.3 (3.7-5.2)	4.9 (3.7-5.6)	4.5 (4.0-5.4)	0.156
Median LDL-C (IQR), mmol/l	2.9 (2.3-3.6)	3.2 (2.3-3.9)	3.1 (2.5-3.9)	0.213
Median HDL-C (IQR), mmol/l	1.0 (0.9-1.2)	1.1 (0.9-1.2)	1.0 (0.9-1.1)	0.634
Median CRP (IQR), mg/l	3.8 (2.8-5.8)	4.8 (3.4-7.0)	5.9 (2.8-10.5)	0.002

DM, diabetes mellitus; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Scr, serum creatine; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CRP, C reactive protein.

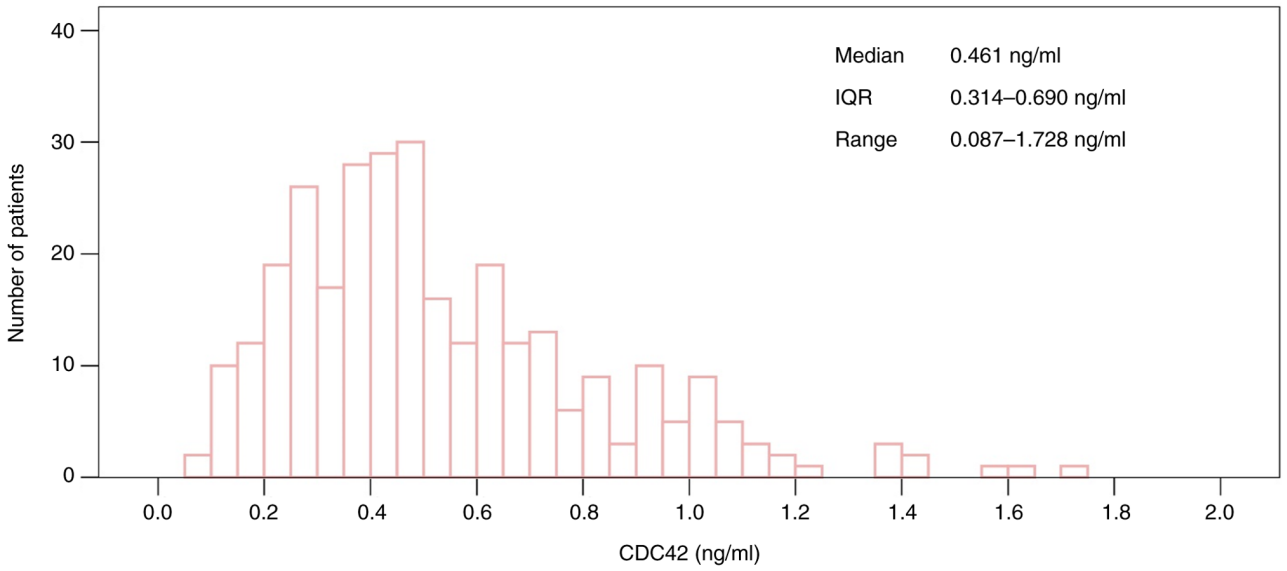


Figure 1. Distribution of serum CDC42 levels in patients with DM. CDC42, cell division cycle 42; DM, diabetes mellitus.

Serum CDC42 levels in normoalbuminuria, microalbuminuria and macroalbuminuria groups. Serum CDC42 level was lowest in the macroalbuminuria group (median, 0.245 ng/ml; IQR, 0.154-0.304 ng/ml), followed by the microalbuminuria group

Table II. Correlation of CDC42 with demographic characteristics, disease features and biochemical indexes in patients with DM.

Characteristics	CDC42 (ng/ml), median (IQR)	*r*/*Z* value	P-value
Age, years[a]	-	-0.092	0.108
BMI, kg/m^{2}[a]	-	-0.133	0.020
DM duration, years[a]	-	-0.111	0.053
SBP, mmHg[a]	-	-0.138	0.016
DBP, mmHg[a]	-	-0.103	0.073
FBG, mmol/l[a]	-	-0.098	0.085
HbA1c, %[a]	-	-0.127	0.027
Scr, mg/dl[a]	-	-0.329	<0.001
eGFR, ml/min/1.73 m^{2}[a]	-	0.305	<0.001
SUA, μmol/l[a]	-	-0.190	0.001
TG, mmol/l[a]	-	-0.097	0.090
TC, mmol/l[a]	-	-0.102	0.076
LDL-C, mmol/l[a]	-	-0.112	0.051
HDL-C, mmol/l[a]	-	0.023	0.684
CRP, mg/l[a]	-	-0.213	<0.001
Sex[b]		-0.828	0.407
Female	0.459 (0.357-0.716)		
Male	0.463 (0.297-0.680)		
Smoking status[b]		-1.220	0.222
Never	0.477 (0.336-0.702)		
Former/current	0.431 (0.273-0.675)		

[a]Continuous variables are shown using Spearman's rank correlation test by *r* value and P-value; [b]categorical variables are shown using Wilcoxon rank sum test by median value, IQR, *Z* value, and P value; -, values are not available for showing. CDC42, cell division cycle 42; DM, diabetes mellitus; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Scr, serum creatine; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CRP, C reactive protein.

(median, 0.372 ng/ml; IQR, 0.264-0.562 ng/ml) and highest in the normoalbuminuria group (median, 0.545 ng/ml; IQR, 0.435-0.794 ng/ml) (P<0.001). Two-group comparison revealed that the serum CDC42 level was increased in the normoalbuminuria group vs. microalbuminuria group (P<0.001), in the normoalbuminuria group vs. macroalbuminuria group (P<0.001) and in the microalbuminuria group vs. macroalbuminuria group (P=0.001) (Fig. 2). In addition, serum CDC42 levels indicated a value to distinguish albuminuria (microalbuminuria + macroalbuminuria) from normoalbuminuria [AUC, 0.792; 95% confidence interval (CI), 0.736-0.848], with the optimal cutoff value of 0.3 ng/ml among seven values (0.2-0.8 ng/ml) (sensitivity, 0.521; specificity, 0.968; Youden index, 0.488) (Fig. 3A). Furthermore, serum CDC42 levels revealed a favorable capability for differentiating macroalbuminuria from normoalbuminuria + microalbuminuria (AUC, 0.845; 95% CI, 0.775-0.915), with the optimal cutoff value of 0.3 ng/ml among seven values (sensitivity, 0.755; specificity, 0.875; Youden index, 0.631) (Fig. 3B).

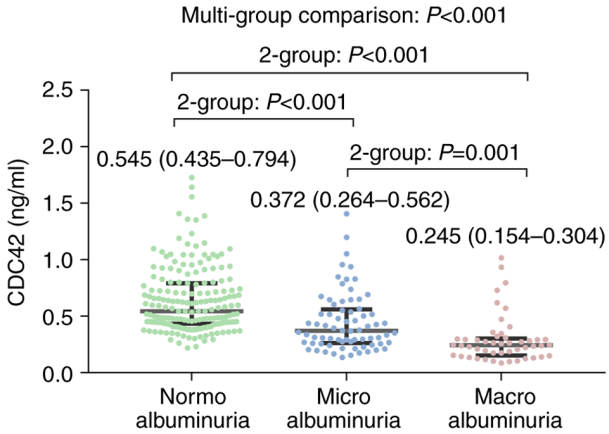
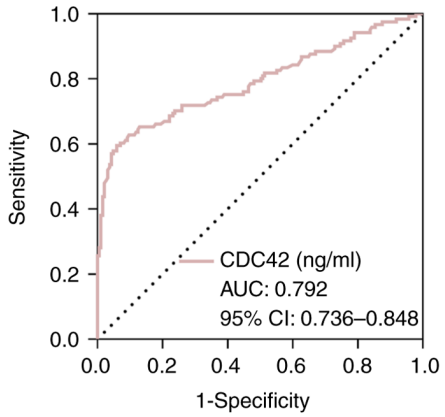


Figure 2. Serum CDC42 levels were varied among patients with DM and normoalbuminuria, microalbuminuria and macroalbuminuria groups. CDC42, cell division cycle 42; DM, diabetes mellitus.

Associated factors for albuminuria. Serum CDC42 levels (P<0.001) and eGFR (P<0.001) were negatively associated with albuminuria, while age (P<0.001), BMI (P=0.021), DM duration (P<0.001), SBP (P=0.004), DBP (P=0.031), HbA1c (P=0.004), Scr (P<0.001), SUA (P<0.001), TG (P=0.017) and CRP (P=0.001) were positively correlated with albuminuria. Furthermore, serum CDC42 levels (P<0.001) and eGFR (P<0.001) had a negative association with macroalbuminuria, whereas age (P<0.001), BMI (P=0.025), DM duration (P<0.001), SBP (P<0.001), DBP (P=0.020), HbA1c (P=0.035), Scr (P<0.001), SUA (P<0.001) and CRP (P=0.001) had a

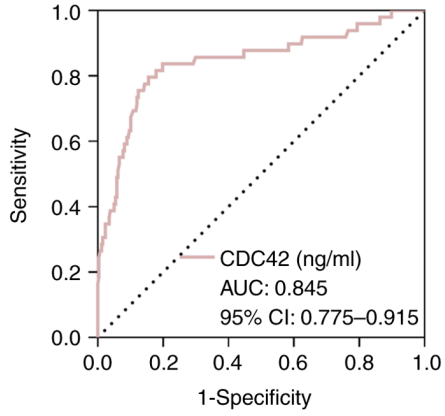
A



Presence of albuminuria (microalbuminuria+macroalbuminuria)

CDC42 cutoff value	Sensitivity	Specificity	Youden index
0.2 ng/ml	0.198	1.000	0.198
0.3 ng/ml	0.521	0.968	0.488
0.4 ng/ml	0.661	0.816	0.477
0.5 ng/ml	0.752	0.557	0.309
0.6 ng/ml	0.818	0.449	0.267
0.7 ng/ml	0.884	0.324	0.209
0.8 ng/ml	0.917	0.232	0.150

B



Presence of macroalbuminuria

CDC42 cutoff value	Sensitivity	Specificity	Youden index
0.2 ng/ml	0.347	0.973	0.320
0.3 ng/ml	0.755	0.875	0.631
0.4 ng/ml	0.837	0.716	0.553
0.5 ng/ml	0.878	0.494	0.372
0.6 ng/ml	0.898	0.389	0.287
0.7 ng/ml	0.918	0.272	0.191
0.8 ng/ml	0.959	0.198	0.158

Figure 3. Serum CDC42 levels indicated a value to estimate the presence of albuminuria and macroalbuminuria in patients with DM. (A) ROC curve of serum CDC42 levels for differentiating albuminuria from normoalbuminuria in patients with DM. (B) ROC curve of serum CDC42 levels for distinguishing macroalbuminuria from normoalbuminuria + microalbuminuria in patients with DM. ROC, receiver operating characteristic; CDC42, cell division cycle 42; DM, diabetes mellitus.

positive correlation with macroalbuminuria (Table SI). To further investigate the predictive value of serum CDC42 levels for the presence of albuminuria, four multivariate logistic models were established. The four models elucidated that serum CDC42 levels were independently negatively associated with the presence of microalbuminuria (vs. normoalbuminuria) (all P<0.001), macroalbuminuria (vs. normoalbuminuria) (most P<0.001), microalbuminuria or macroalbuminuria (vs. normoalbuminuria) (all P<0.001) and macroalbuminuria (vs. normoalbuminuria or microalbuminuria) (all P<0.001). The detailed information is listed in Table III.

Discussion

There have been a small number of studies demonstrating the dysregulation of CDC42 in patients with metabolic disorders (21,22). For example, a previous study indicated that the PB CDC42 mRNA was decreased in patients with obesity-associated metabolic syndrome compared with healthy controls (21). Another study demonstrated that CDC42 levels were increased in obesity-associated asthma patients compared with normal-weight asthma patients (22). Diabetes is also a chronic metabolic disease, but currently, to the best of our knowledge, no study has indicated CDC42 levels in patients with DM. The present study quantified serum CDC42 levels and revealed the median was 0.461 ng/ml (IQR, 0.314-0.690 ng/ml) in patients with DM; range, 0.087 to 1.728 ng/ml. Compared with healthy controls in one previous study (median, 0.668 ng/ml; IQR, 0.507-0.841 ng/ml) (23), the serum CDC42 levels were reduced in patients with DM in the present study. However, the comparison of CDC42 levels between patients with DM and healthy controls required further verification. Additionally, the present study also revealed that serum CDC42 levels were negatively associated with the microalbuminuria and macroalbuminuria in patients with DM. The possible explanation could be that decreased CDC42 inhibited actin cytoskeleton rearrangement of podocyte to impair podocyte and induce podocyte apoptosis, while the podocyte was essential for differentiation of glomerular epithelial cells and the structure and function of the glomerular filtration barrier (24,25). In addition, podocyte was exposed to plasminogen due to the impaired glomerular filtration barrier, resulting in further injury to kidney mediated by oxidative stress (24-27). Additionally, the present study also indicated that the optimal cutoff value of serum CDC42 for identifying albuminuria and macroalbuminuria in patients with DM might be 0.3 ng/ml, while its utilization needed further validation.

Table III. Four different multivariate logistic regression models for analyzing the correlation of CDC42 with the presence of microalbuminuria, macroalbuminuria and microalbuminuria + macroalbuminuria in patients with DM.

	Model 1		Model 2					
Characteristics	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Presence of microalbuminuria and macroalbuminuria								
Normoalbuminuria	Ref.		Ref.		Ref.		Ref.	
Microalbuminuria	<0.001	0.042 (0.010-0.172)	<0.001	0.045 (0.011-0.188)	<0.001	0.055 (0.013-0.237)	<0.001	0.050 (0.010-0.257)
Macroalbuminuria	<0.001	<0.001 (<0.001-0.001)	<0.001	<0.001 (<0.001-0.003)	<0.001	<0.001 (<0.001-0.004)	0.007	<0.001 (<0.001-0.044)
Presence of microalbuminuria or macroalbuminuria								
Normoalbuminuria	Ref.		Ref.		Ref.		Ref.	
Microalbuminuria or macroalbuminuria	<0.001	0.017 (0.005-0.058)	<0.001	0.019 (0.005-0.069)	<0.001	0.023 (0.006-0.087)	<0.001	0.037 (0.008-0.169)
Presence of macroalbuminuria								
Normoalbuminuria or microalbuminuria	Ref.		Ref.				Ref.	
Macroalbuminuria	<0.001	0.001 (<0.001-0.008)	<0.001	0.001 (<0.001-0.016)	<0.001	0.001 (<0.001-0.019)	<0.001	0.006 (<0.001-0.094)

Model 1, adjusted for age, sex; Model 2, adjusted for age, sex, BMI, smoking status, DM duration, SBP, DBP; Model 3, adjusted for age, sex, BMI, smoking status, DM duration, SBP, DBP, FBG, HbA1c, TG, TC, LDL-C, HDL-C, CRP; Model 4, adjusted for age, sex, BMI, smoking status, DM duration, SBP, DBP, FBG, HbA1c, Scr, eGFR, SUA, TG, TC, LDL-C, HDL-C, CRP. CDC42, cell division cycle 42; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; Scr, serum creatine; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CRP, C reactive protein; ref, reference.

Findings from the present study demonstrated that increased serum CDC42 levels were correlated with increased eGFR in patients with DM, suggesting its positive association with renal function. The probable explanation could be: The formation and function of glomerular filtration barrier relied on the actin-based cytoskeleton podocyte, which was positively regulated by CDC42 (28). Moreover, CDC42 promoted the development of kidney tubules through regulating epithelial cell polarity, lumen formation and the actin cytoskeleton, leading to the promoted function of tubular function (26). Meanwhile, CDC42 could positively regulate the formation and function tubular cilia to inhibit tubular cell apoptosis and fibrosis, leading to impaired tubular function (29). According to the aforementioned positive regulation of CDC42 on glomerular and tubular function, elevated serum CDC42 levels could promote the renal function in patients with DM. Additionally, the present study also observed the negative correlation of serum CDC42 levels with several indexes, including BMI, SBP, HbA1c, Scr, SUA and CRP, in patients with DM. The possible reasons could be: First, CDC42 is involved in cholesterol metabolism through regulating cytoskeleton, therefore, impacting BMI (30). Second, CDC42 participated in insulin secretion to affect blood glucose concentration and its decrement led to increased HbA1c (11,13). Third, CDC42 could negatively regulate glucose as aforementioned, and the latter influenced SBP (31). Fourth, as CDC42 was negatively associated with glucose (as aforementioned) and SUA was affected by glycemia, CDC42 was negatively associated with SUA (32). Fifth, CDC42 was associated with renal injury, which might result in increased Scr (26,28). Finally, CDC42 was correlated with T cell activation and inflammatory factor and suppressed immune response, affecting CRP (33). Thus, serum CDC42 levels were negatively correlated with these clinical characteristics in patients with DM.

Sustained diabetes-associated metabolic and hemodynamic perturbations can induce renal inflammation and drive renal damage, eventually leading to renal fibrosis (34). Renal outcomes are worse in patients with DM and albuminuria compared with normoalbuminuria; meanwhile, patients with DN and higher levels of albuminuria exhibit worse prognosis (35,36). Apart from previous studies in mice with DM (17,18,26,37), the present study confirmed that serum CDC42 levels were independently negatively correlated

with the presence of microalbuminuria and macroalbuminuria in patients with DM, suggesting it could estimate the attenuated severity of DN. One possible reason could be that the low level of CDC42 under the high glucose conditions induced podocyte apoptosis, which resulted in unstable kidney barrier function in glomeruli and contributed to protein loss, accelerating the development and progression of DN (17,24,25,38,39). Another possible reason could be that the deficiency of CDC42 promoted renal tubular epithelial cell-induced inflammation through regulating cytoskeletal function, impacting albumin absorption and aggravating DN (11,26,40). Thus, the increased serum CDC42 levels reflected the attenuated severity of DN, which might be a therapeutic strategy for predicting DN in patients with DM. In addition, considering that urinary albumin detection was a simple measurement for DN diagnosis. Albuminuria was one of the most common clinical characteristics of DN, but it was only a symptom. It was considered that the detection of more biomarkers might help to understand the pathogenesis of DN. Especially that CDC42 could regulate podocyte apoptosis to take part in the development and progression of DN.

However, the present study had a number of limitations. First, the present study was a single-center study, which might result in selective bias. Furthermore, the present study only detected serum CDC42 levels in patients with DM at the enrollment, and its level at multiple time points in the long term as well as the corresponding value for predicting the development and progression DN in patients with DM remained unclear. Third, the present study found the negative correlation of serum CDC42 level with the presence of microalbuminuria and macroalbuminuria, but not DN risk, which required further exploration. Finally, the present study estimated development and progression of DN through microalbuminuria and macroalbuminuria in patients with DM; however, the results needed to be further validated in patients who were pathologically diagnosed as DN.

In conclusion, serum CDC42 levels were independently negatively associated with the presence of albuminuria in patients with DM, which may be a useful biomarker for estimating the development and progression of DN in these patients.

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Availability of data and materials

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

Authors' contributions

HY, JM and NZ designed the study. YG and WZ collected the data. HY, JM, WZ and NZ analyzed the data. HY, JM and WZ drafted the manuscript. YG and NZ revised the manuscript. JM and NZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Heilongjiang University of Chinese Medicine (Harbin, China; approval no. HZYLL202000302). Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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