Diabetes Ther (2021) 12:697–705
https://doi.org/10.1007/s13300-021-01003-3

ORIGINAL RESEARCH

Risk Factors for Albuminuria in Normotensive Older Adults with Type 2 Diabetes Mellitus and Normal Renal Function: A Cross-Sectional Study

Yingyi Zhou · Ke Chen · Xuan Du · Jiali Tang · Bimin Shi

Received: December 7, 2020 / Accepted: January 12, 2021 / Published online: January 29, 2021

ABSTRACT

Introduction: Diabetes mellitus (DM) is prevalent in developed and developing countries, including China. However, few studies have examined the potential risk factors for albuminuria in normotensive older adults with type 2 DM and normal renal function.

Methods: We recruited normotensive older adults (≥ 65 years) with type 2 DM and normal renal function from the First Affiliated Hospital of Soochow University from January to December 2019. We stratified participants according to their urine albumin to creatinine ratio (ACR) into the following groups: normal ACR (ACR1), microalbuminuria (ACR2), and macroalbuminuria (ACR3). Demographic characteristics, anthropometric parameters, and metabolic profiles were recorded. Creatinine clearance (Ccr) and homeostasis model assessment—insulin resistance (HOMA-IR) were calculated. Logistic regression was used to examine risk factors for albuminuria.

Results: A total of 250 older adults were enrolled during the study period, including 124, 82, and 44 with normal albuminuria, microalbuminuria, and macroalbuminuria, respectively. We found that an extended duration of DM (odds ratio [OR] 1.085, 95% confidence interval [CI] 1.012–1.164, $P = 0.022$), elevated systolic blood pressure (OR 1.049, 95%CI 1.018–1.081, $P < 0.01$), elevated glycated hemoglobin (OR 1.734, 95% CI 1.332–2.258, $P < 0.01$), low insulin (OR 0.871, 95% CI 0.804–0.944, $P < 0.01$), and low C-peptide (OR 0.365, 95% CI 0.239–0.588, $P < 0.01$) were independent risk factors for albuminuria.

Conclusion: Elevated blood pressure, low insulin, low C-peptide, and poor glycemic control were significant risk factors for albuminuria. These parameters may serve as early indicators for intervention.

Keywords: Albumin to creatinine ratio; Elderly; Hypertension; Insulin resistance; Renal function; Type 2 diabetes mellitus

Yingyi Zhou and Ke Chen have contributed equally to this study and should be considered as co-first authors.

Y. Zhou · X. Du · B. Shi (✉)
Endocrine Department, The First Affiliated Hospital of Soochow University, Suzhou, China
e-mail: Gtmake144523@163.com

K. Chen
Thoracic Surgery Department, The First Affiliated Hospital of Soochow University, Suzhou, China

J. Tang
Endocrine Department, Xishan Hospital, Wuxi, China

Key Summary Points
Why carry out this study?
Older adults with diabetes are at risk of developing complications such as diabetic kidney disease (DKD), but the risk factors for albuminuria among specific subpopulations in China remain unclear.
We aimed to identify risk factors for albuminuria in normotensive older Chinese adults with normal renal function.
We hypothesized that blood pressure and diabetes-related parameters were independent risk factors for albuminuria in normotensive older adults from China.
What was learned from the study?
We found that an extended duration of diabetes mellitus, elevated systolic blood pressure, low insulin, low C-peptide, and elevated glycated hemoglobin were independent risk factors for albuminuria.
The findings from this study may provide the epidemiologic basis for subsequent public health actions to ameliorate the rising incidence of DKD in older adults in China.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13560581.

INTRODUCTION

Diabetes mellitus (DM) is now a global public health issue [1]. The condition adversely affects approximately 11% of the Chinese population, and this percentage is expected to increase over time [2]. Another phenomenon that arouses public health concern in China is the aging of its population. In 2019, among 1.401 billion Chinese citizens, 176 million were ≥ 65 years of age [3]. According to the National Bureau of Statistics, elderly individuals account for 12.6% of the entire Chinese population. Its aging society puts pressure on the balance of medical insurance funds available in China [4]. Diabetic older adults are at risk of developing complications such as diabetic kidney disease (DKD), which adversely affects quality of life and overall survival [5]. The prevention and early diagnosis of DKD are extremely important in the management of older adults with DM [6]. It is not uncommon for clinicians to identify diabetic patients with albuminuria despite normal renal function and blood pressure (BP) [7]. In order to uncover risk factors for albuminuria among normotensive older adults with normal renal function in China, we enrolled patients from the endocrinology clinics of a single center for further analysis. We expect that the findings from this study will provide the epidemiologic basis for subsequent approaches to counteract the rising rate of DKD in older diabetic adults.

METHODS

Study Participants

We screened adults ≥ 65 years of age with type 2 DM who presented for treatment at the endocrinology clinics of the First Affiliated Hospital of Soochow University during the period from January to December 2019. DM was diagnosed according to the diagnostic criteria put forth by the World Health Organization in 1999 [8]. We selected those with a creatinine clearance (Ccr) of 80–120 mL/min and no prior history of hypertension or treatment with an antihypertensive medication for inclusion in the study. Patients with the following characteristics were excluded: end-stage renal disease (ESRD) treated with chronic hemodialysis or peritoneal dialysis; severe infection; history of trauma, developing fracture, or a DM-related surgery such as limb amputation; edema,

pleural effusion, ascites, or congestive heart failure; diabetic ketoacidosis; treatment with cimetidine, glucocorticoid, or other medications that affect renal function; malignancy requiring chemotherapy or radiotherapy; or urinary tract infection. This study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (2017010), and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All enrollees provided written informed consent.

We stratified participants into the following groups according to their urine albumin to creatinine ratio (ACR) values (based on the guideline released by the American Diabetes Association (ADA) in 2010): normal albuminuria (ACR1), microalbuminuria (ACR2), and macroalbuminuria (ACR3) [9]. Those in the ACR1 group had urine ACR < 30 mg/g; those in the ACR2 group had ACR of 30–300 mg/g; those in the ACR3 group had ACR > 300 mg/g.

Study Procedures

The baseline clinical features recorded included age, gender, body height (BH), body weight (BW), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, and prior history of comorbidities. Body mass index (BMI) was calculated as BW divided by the square of BH (kg/m^2). Twenty milliliters of venous blood were collected after 12 h of fasting, and 5 mL of mid-stream urine was collected in the morning. Serum metabolic parameters, including glycated hemoglobin (HbA_{1c}), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), uric acid (UA), and creatinine (Cr) were measured using an automatic analyzer (Toshiba 7600, Japan). Fasting insulin (FINS) and fasting C-peptide (CP) were measured using a chemiluminescence analyzer (Tosoh AIA2000, Japan). HbA_{1c} levels were measured with high-performance liquid chromatography (Tosoh G8, Japan). Urine ACR was measured using an automatic chemiluminescence immunoassay (BioSystems A25, Spain). We calculated homeostasis model assessment—insulin resistance (HOMA-IR) using the following formula [10]: FINS × FPG/22.5. Ccr was estimated using the Cockcroft–Gault formula in mL/min (for males, [140 − age (years)] × BW (kg)/72 × Cr (mg/dL); for females, [140 − age (year)] × BW (kg)/85 × Cr (mg/dL)).

Statistical Analysis

We describe normally distributed variables as the mean ± standard deviation. Comparisons among groups were performed with one-way analysis of variance (ANOVA). We used multiple logistic regression analyses to identify risk factors for albuminuria (ACR2 or ACR3 status) among normotensive older adults with normal renal function. All statistical analyses were performed with SPSS 23.0, and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 250 older adults were enrolled in this study. Fifty percent of the study population was male ($n = 125$). Patient age ranged from 65 to 88 years. The ACR1 group included 124 patients (49.6%); the ACR2 group included 82 patients (32.8%); the ACR3 group included 44 patients (17.6%).

Comparison of Clinical Features and Metabolic Parameters Among ACR Groups

The results from comparisons of clinical features and metabolic parameters among ACR groups are provided in Table 1. There was no significant difference between groups in terms of age, gender, BMI, waist circumference, DBP, TG, HDL-C, UA, HOMA-IR, Cr, or Ccr. The ACR2 group had a significantly longer duration of DM than the ACR1 group, and the ACR3 group had a significantly longer duration of DM than the ACR1 group or the ACR2 group. SBP was significantly higher in the ACR2 group than in the ACR1 group, and significantly higher in the ACR3 group than in the ACR1 ($P < 0.01$)

Table 1 Comparison of clinical and laboratory features between the ACR1, ACR2, and ACR3 groups

Group	Number (M/F)	Age (years)	Duration of DM (years)	BMI (kg/m^2)	Waist circumference (cm)	SBP (mmHg)	DBP (mmHg)	HBA1c (%)	FPG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
ACR1	124 (61/63)	69 ± 9	11.73 ± 5.54	24.65 ± 2.88	86.96 ± 9.42	127.2 ± 12.95	79.7 ± 11.04	7.20 ± 1.36	6.84 ± 1.17	1.07 ± 0.33	2.49 ± 1.02
ACR2	82 (40/42)	70 ± 7	13.48 ± 4.48[a]	25.69 ± 3.55	85.90 ± 8.46	131.4 ± 12.04[a]	81.6 ± 7.75	8.64 ± 1.95[b]	8.18 ± 2.53[b]	1.09 ± 0.23	2.61 ± 0.69
ACR3	44 (24/20)	72 ± 6	18.48 ± 4.65[b,d]	25.28 ± 3.02	87.25 ± 10.19	137.1 ± 11.04[b,c]	80.0 ± 7.66	11.47 ± 2.69[b,d]	10.4 ± 3.67[b,d]	1.03 ± 0.19	2.89 ± 0.73[a]

Group	Number (M/F)	Age (years)	TG (mmol/L)	TC (μmol/L)	UA (μmol/L)	FINS (μU/mL)	CP (ng/mL)	Cr (μmol/L)	Ccr (mL/min)	HOMA-IR
ACR1	124 (61/63)	69 ± 9	1.52 ± 0.60	4.22 ± 1.23	338.7 ± 96.91	14.51 ± 2.97	2.86 ± 0.87	59.47 ± 9.79	95.51 ± 10.62	1.07 ± 0.33
ACR2	82 (40/42)	70 ± 7	1.35 ± 0.44	4.63 ± 1.09	356.8 ± 81.42	12.70 ± 5.27[b]	2.15 ± 0.85[b]	57.26 ± 10.65	92.86 ± 11.53	1.09 ± 0.23
ACR3	44 (24/20)	72 ± 6	1.48 ± 0.43	5.35 ± 1.43[b,d]	368.2 ± 89.33	9.45 ± 7.47[b,d]	1.48 ± 0.64[b,d]	60.55 ± 9.05	91.44 ± 10.27	1.03 ± 0.19

ACR albumin-to-creatinine ratio, *BMI* body mass index, *Ccr* creatinine clearance, *CP* C-peptide, *Cr* creatinine, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *FINS* fasting insulin, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment—insulin resistance, *LDL-C* low-density lipoprotein cholesterol, *OR* odds ratio, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *UA* uric acid

[a] $P < 0.05$ compared with the ACR1 group; [b] $P < 0.01$ compared with the ACR1 group; [c] $P < 0.05$ compared with the ACR2 group; [d] $P < 0.01$ compared with the ACR2 group

and ACR2 groups (Table 1). FPG was significantly higher in the ACR2 group than in the ACR1 group, and significantly higher in the ACR3 group than in the ACR1 and ACR2 groups. LDL-C was significantly higher in the ACR3 group than in the ACR1 group. TC was significantly higher in the ACR3 group than in the ACR1 and ACR2 groups. FINS and CP were significantly lower in the ACR2 group than in the ACR1 group ($P < 0.01$), and significantly lower in the ACR3 group than in the ACR1 ($P < 0.01$) and ACR2 ($P < 0.01$) groups.

Multiple Logistic Regression for Risk Factors for Positive ACR

We subsequently performed multiple logistic regression with ACR2 or ACR3 as the dependent variable, incorporating SBP, HbA1c, FPG, LDL-C, TC, FINS, CP, and the duration of type 2 DM into the analysis. We found that a longer duration of DM (odds ratio [OR] 1.085, 95% confidence interval [CI] 1.012–1.164; $P = 0.022$), higher SBP (OR 1.049, 95% CI 1.018–1.081; $P < 0.01$), lower FINS (OR 0.871, 95% CI 0.804–0.944; $P < 0.01$), lower CP (OR 0.365, 95% CI 0.239–0.588; $P < 0.01$), and higher HbA_{1c} (OR 1.734, 95% CI 1.332–2.258; $P < 0.01$) were independent risk factors for albuminuria in this population of normotensive older adults with normal renal function (Table 2).

DISCUSSION

In the current study, we discovered important risk factors for albuminuria in a cohort of healthy Chinese older adults with DM. The risk factors identified included BP, insulin/C-peptide, and glycemic control status. The identification of these risk factors, which have only rarely been addressed in developing countries, is expected to facilitate the selection of important preventive and therapeutic targets for those with DM.

The presence of DM has gradually assumed increasing importance as a major public health threat in China because of the associated complications, especially DKD [11, 12]. The pathologic manifestations of diabetic nephropathy initially involve renal glomeruli and tubules. They result in glomerular epithelial hypertrophy and tubular and glomerular basement membrane thickening, and culminate in interstitial fibrosis and glomerulosclerosis [13]. Renal function worsens over time in patients with DKD, and even the most optimal approach to glycemic control becomes ineffective as renal function deteriorates [14]. This scenario occurs irrespective of age, and older adults may be particularly vulnerable to the development of DKD due to the impairment of organ reserves and the presence of other comorbidities. Older patients with DKD tend to have a poorer quality of life and lower survival than those without [15]. The emergence of DKD also places older adults at risk of incurring a financial burden [16]. Earlier diagnosis and management are

Table 2 Risk factors for ACR2 or ACR3

Variable	*B*	Standard error	Wald	OR (95% CI)	*P* value
Duration of DM	0.082	0.036	5.250	1.085 (1.012–1.164)	0.022
SBP	0.048	0.015	9.614	1.049 (1.018–1.081)	< 0.01
FINS	0.218	0.124	3.089	0.871 (0.804–0.944)	< 0.01
CP	0.090	0.216	21.638	0.365 (0.239–0.588)	< 0.01
HbA1c	0.550	0.135	16.715	1.734 (1.332–2.258)	< 0.01

ACR albumin-to-creatinine ratio, *CP* C-peptide, *DM* diabetes mellitus, *FINS* fasting insulin, *HbA1c* glycated hemoglobin, *OR* odds ratio, *SBP* systolic blood pressure

important strategies for mitigating these adverse influences in patients with DKD.

Microalbuminuria has been identified as an early marker of DKD [17], but the accuracy of using microalbuminuria to predict DKD and the stability of microalbuminuria measurements have always been controversial, as urinary microalbumin levels are affected by numerous factors, such as diet and exercise [18–20]. Urinary output may affect urinary ACR, but the endogenous production of creatinine is relatively stable. Checking urine microalbumin levels is an integral part of reaching a diagnosis of DKD [21]. When patients have normal renal function and BP, the presence of microalbuminuria can help clinicians identify minor renal injuries earlier. In such cases, targeted management may retard or even reverse the course of albuminuria.

In this study, we showed that those with albuminuria had a significantly longer duration of DM, higher SBP, TC, and LDL-C, and poorer glycemic control than those without albuminuria (Table 1). The appearance of positive urine ACR is closely correlated with the clinical course of type 2 DM. We therefore explored significant risk factors for albuminuria in older adults with type 2 DM. In a 12-year study that investigated these issues in India [22], the authors found that the duration of DM and a diagnosis of hypertension were significantly associated with the development of DKD. In that study, 44.1% of the diabetic patients who initially did not have albuminuria were found to have subsequently developed albuminuria within approximately 11 years. We similarly revealed that SBP was an independent risk factor for albuminuria among normotensive older adults with DM (Table 2). It is likely that the rise in SBP is accompanied by increased expression of angiotensin-converting enzyme 2 (ACE2), leading to renal microvascular injury [23, 24]. While the older adults in our study did not have hypertension, their mean SBP levels were close to 140 mmHg. Such levels of SBP are known to cause subtle injuries to the kidney. In addition, prior studies showed that dyslipidemia may lead to glucosaminoglycan conjugation of the basement membrane, which causes lipid peroxidation and interstitial inflammation [25, 26]. LDL-C can bind to the LDL receptor on the mesangial cell membrane, causing damage to mesangial cells and podocytes, aggravating proteinuria, and driving the progression of glomerular and interstitial fibrosis [27]. In this study, we further showed that glycemic control indices (HbA1c, FPG, FINS, and CP) were significantly poorer in the ACR3 group than in the ACR1 and ACR2 groups, and most of the glycemic control indices investigated were independent risk factors for albuminuria (Table 2). Hyperglycemia can be toxic to vascular endothelial cells and is associated with increased levels of advanced glycated end products within endothelial cells [28]. Advanced glycated end products are toxic molecules that can inhibit the synthesis of DNA [29], resulting in cellular injury and accelerating apoptosis. Moreover, the oxidation of glucose in endothelial cells is accompanied by the generation of reactive oxygen species, which lead to oxidative injury and the development of proteinuria [22, 30]. Insulin plays an important role in maintaining the physiologic function of the vascular endothelium, and normal insulin levels facilitate proper endothelial function [31]. However, suboptimal insulin levels may fail to exert a hypoglycemic effect and lead to hyperglycemic endothelial toxicity [32]. Hyperglycemia increases the production of glycated protein, and the risk of incident albuminuria increases with HbA1c level [33].

Patients with DM typically receive lifelong treatment in outpatient clinics, and older adults with DKD frequently go unnoticed during the subtle early manifestations of the disease [34]. This is particularly problematic for those without a history of hypertension and with normal renal function, because clinicians may consider them to be at lower risk of DKD. Compared to those with hypertension or impaired renal function, few DM patients without a history of hypertension and with normal renal function undergo urine ACR measurement. Based on our findings, we suggest that clinicians should pay attention to SBP, FPG, HbA1c, and FINS levels in normotensive older adults with type 2 DM and normal renal function. If abnormalities involving any of the above parameters are noted, urine ACR should be checked to exclude the presence of DKD. For those with a long duration

of DM, urine ACR should also be checked to exclude DKD.

This study has some limitations. The sample size for this cross-sectional study was moderate at best because of funding issues. We collected mostly metabolic parameters, but there could be other potential confounding factors that we did not measure. Large studies that investigate more comprehensive panels of variables are needed to validate our findings.

CONCLUSIONS

Based on a cohort of healthy Chinese older adults with DM, we revealed that BP, insulin/C-peptide, and glycemic control status were significant predictors of albuminuria presence. Results from this study suggest that among older adults with DM, those with high BP, low insulin, low C-peptide, and poor glycemic control are predisposed to albuminuria development or even progression. Our findings shed light on how to select subpopulations of older adults with DM for albuminuria screening in order to improve their outcomes.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Funding. No funding or sponsorship was received for this study or the publication of this article. The Rapid Service Fee was funded by the authors.

Medical Writing and/or Editorial Assistance. The manuscript received editorial assistance from Dr. Rachel Davis at Medjaden Bioscience Limited (funded by the authors).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. YZ: A. Study design/planning; B. Data collection/entry; C. Data analysis/statistics; D. Data interpretation; E. Preparation of manuscript; F. Literature analysis/search. KC: B. Data collection/entry; E. Preparation of manuscript. XD: C. Data analysis/statistics; E. Preparation of manuscript. JT: E. Preparation of manuscript. BS: A. Study design/planning; F. Literature analysis/search; G. Funds collection.

Disclosures. Yingyi Zhou, Ke Chen, Xuan Du, Jiali Tang, and Bimin Shi declare that they have no conflict of interest.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (2017010), and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All enrollees provided the written informed consent.

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

REFERENCES

1. Congress IDF. Shaping the future of diabetes. Diabetes Res Clin Pract. 2017;2017(126):317–9.
2. Ma RCW. Epidemiology of diabetes and diabetic complications in China. Diabetologia. 2018;61: 1249–60.
3. Zimmet P, Shi Z, El-Osta A, Ji L. Author Correction: Epidemic T2DM, early development and epigenetics: implications of the Chinese Famine. Nat Rev Endocrinol. 2019;15:312.
4. Qiu X, Zhao T, Kong Y, Chen F. Influence of population aging on balance of medical insurance funds in China. Int J Health Plan Manage. 2020;35: 152–61.
5. Molitch ME, Adler AI, Flyvbjerg A, et al. Diabetic kidney disease: a clinical update from kidney disease: improving global outcomes. Kidney Int. 2015;87:20–30.
6. Abdelhafiz AH. Diabetic kidney disease in older people with type 2 diabetes mellitus: improving prevention and treatment options. Drugs Aging. 2020;37:567–84.
7. Singh D, Simoni J, Wesson DE. Albuminuria in primary hypertension is associated with tubulointerstitial injury even in subjects with normal renal function. J Investig Med. 2006;54:S311–2.
8. Rossi G. Diagnosis and classification of diabetes mellitus. Recenti Prog Med. 2010;101:274–6.
9. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care. 2010;33(Suppl 1):S11-61.
10. Eslam M, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Use of HOMA-IR in hepatitis C. J Viral Hepat. 2011;18:675–84.
11. Yang L, Chu TK, Lian J, et al. Risk factors of chronic kidney diseases in Chinese adults with type 2 diabetes. Sci Rep. 2018;8:14686.
12. Hu H, Sawhney M, Shi L, et al. A systematic review of the direct economic burden of type 2 diabetes in China. Diabetes Ther. 2015;6:7–16.
13. Qi C, Mao X, Zhang Z, Wu H. Classification and differential diagnosis of diabetic nephropathy. J Diabetes Res. 2017;2017:8637138.
14. Osman WM, Jelinek HF, Tay GK, et al. Clinical and genetic associations of renal function and diabetic kidney disease in the United Arab Emirates: a cross-sectional study. BMJ Open. 2018;8:e020759.
15. Cid Ruzafa J, Paczkowski R, Boye KS, et al. Estimated glomerular filtration rate progression in UK primary care patients with type 2 diabetes and diabetic kidney disease: a retrospective cohort study. Int J Clin Pract. 2015;69:871–82.
16. White S, Chadban S. Diabetic kidney disease in Australia: current burden and future projections. Nephrology (Carlton). 2014;19:450–8.
17. Agha A, Amer W, Anwar E, Bashir K. Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: a randomized controlled trial. Saudi J Kidney Dis Transpl. 2009;20:429–35.
18. Aziz KM. Correlation of urine biomarkers: microalbuminuria and spot urine protein among diabetic patients. Application of spot urine protein in diabetic kidney disease, nephropathy, proteinuria estimation, diagnosing and monitoring. Recent Pat Endocr Metab Immune Drug Discov. 2015;9: 121–33.
19. Cizmecioglu FM, Noyes K, Bath L, Kelnar C. Audit of microalbumin excretion in children with type I diabetes. J Clin Res Pediatr Endocrinol. 2009;1: 136–43.
20. Zhang J, Yin Y, Chen L, et al. Short-term high-salt diet increases corin level to regulate the salt-water balance in humans and rodents. Am J Hypertens. 2018;31:253–60.
21. Brondani LA, Soares AA, Recamonde-Mendoza M, et al. Urinary peptidomics and bioinformatics for the detection of diabetic kidney disease. Sci Rep. 2020;10:1242.
22. Luis-Rodriguez D, Martinez-Castelao A, Gorriz JL, De-Alvaro F, Navarro-Gonzalez JF. Pathophysiological role and therapeutic implications of inflammation in diabetic nephropathy. World J Diabetes. 2012;3:7–18.
23. Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 is a key modulator of the renin-angiotensin system in cardiovascular and renal disease. Curr Opin Nephrol Hypertens. 2011;20: 62–8.
24. Mizuiri S, Hemmi H, Arita M, et al. Expression of ACE and ACE2 in individuals with diabetic kidney disease and healthy controls. Am J Kidney Dis. 2008;51:613–23.
25. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu X, Wang Z. Lipid accumulation and chronic kidney disease. Nutrients. 2019;11:722.
26. Gowd V, Gurukar A, Chilkunda ND. Glycosaminoglycan remodeling during diabetes and the role of

dietary factors in their modulation. World J Diabetes. 2016;7:67–73.

27. Zhang Y, Ma KL, Liu J, et al. Dysregulation of low-density lipoprotein receptor contributes to podocyte injuries in diabetic nephropathy. Am J Physiol Endocrinol Metab. 2015;308:E1140–8.

28. Xue M, Qian Q, Adaikalakoteswari A, Rabbani N, Babaei-Jadidi R, Thornalley PJ. Activation of NF-E2-related factor-2 reverses biochemical dysfunction of endothelial cells induced by hyperglycemia linked to vascular disease. Diabetes. 2008;57:2809–17.

29. Zhu W, Yuan Y, Liao G, et al. Mesenchymal stem cells ameliorate hyperglycemia-induced endothelial injury through modulation of mitophagy. Cell Death Dis. 2018;9:837.

30. Fakhruddin S, Alanazi W, Jackson KE. Diabetes-induced reactive oxygen species: mechanism of their generation and role in renal injury. J Diabetes Res. 2017;2017:8379327.

31. Lteif A, Vaishnava P, Baron AD, Mather KJ. Endothelin limits insulin action in obese/insulin-resistant humans. Diabetes. 2007;56:728–34.

32. Fadini GP, Albiero M, Vigili De Kreutzenberg S, Avogaro A. Hypoglycemia affects the changes in endothelial progenitor cell levels during insulin therapy in type 2 diabetic patients. J Endocrinol Invest. 2015;38:733–8.

33. Ren H, Wu C, Shao Y, Liu S, Zhou Y, Wang Q. Correlation between serum miR-154-5p and urinary albumin excretion rates in patients with type 2 diabetes mellitus: a cross-sectional cohort study. Front Med. 2020;14:642–50.

34. Harris S, Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Long-term efficacy and safety of canagliflozin (CANA) in older patients with type 2 diabetes mellitus (T2DM) over 104 weeks. Can J Diabetes. 2014;38:S44.