

Research Article

Elevated Squamous Cell Carcinoma Antigen, Cytokeratin 19 Fragment, and Carcinoembryonic Antigen Levels in Diabetic Nephropathy

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Received 14 December 2016; Revised 16 May 2017; Accepted 28 May 2017; Published 4 July 2017

Academic Editor: Janaka Karalliedde

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Objective. We aimed to explore whether squamous cell carcinoma antigen (SCC), cytokeratin 19 fragment (Cyfra21-1), neuron-specific enolase (NSE), and carcinoembryonic antigen (CEA) are elevated in diabetic nephropathy (DN) and the association between urinary albumin-to-creatinine ratio (UACR) and tumor markers in diabetic patients. **Methods.** Nondialysis patients with diabetes ($n = 261$) and 90 healthy controls were enrolled. DN was defined as an UACR ≥ 30 mg/g in the absence of a urinary tract infection or other renal abnormalities. **Results.** Patients with DN had significantly higher serum SCC, Cyfra21-1, and CEA levels than those with normoalbuminuria and healthy controls. The rates of positive SCC, Cyfra21-1, and CEA significantly increased with increasing urinary albumin excretion (all P for trend < 0.001). In contrast, NSE was not affected by DN. SCC, Cyfra21-1, and CEA were significantly and positively correlated with UACR. In logistic regression, after multivariable adjustment, increased UACR was associated with increased odds ratio of elevated tumor marker levels (all P for trend < 0.05). **Conclusions.** Serum levels of SCC, Cyfra21-1, and CEA are markedly increased with increasing urinary albumin excretion, which affects the specificity for diagnosis for lung cancer. Appropriate interpretation of tumor markers in diabetic patients is mandatory to avoid unnecessary and even hazardous biopsies.

1. Introduction

Diabetes is one of the most common chronic diseases in nearly all countries [1]. The prevalence of diabetes continues to increase worldwide and is estimated at 11.6% in China [2–4]. Accumulating evidence has shown that diabetes is associated with an increased risk for cancer [5, 6]. Therefore, the American Diabetes Association and the American Cancer Society recommended that all diabetic patients should undergo appropriate cancer screenings [7].

Moreover, diabetic patients have been reported to be at increased risk for lung cancer [8], which is the most common cancer and the leading cause of cancer-related deaths worldwide [9]. Squamous cell carcinoma antigen (SCC), cytokeratin

19 fragment (Cyfra21-1), neuron-specific enolase (NSE), and carcinoembryonic antigen (CEA) are widely used for screening, early detection, monitoring therapy efficacy, and defining prognosis of lung cancer [10, 11]; however, several studies have also shown that serum tumor marker levels are elevated in patients with chronic kidney disease (CKD) [12–15]. Such false positive elevation of tumor markers in patients with CKD might cause misuse of these tumor markers and even lead to unnecessary subsequent clinical procedures.

Diabetic nephropathy (DN), which is defined as increased urinary albumin excretion in the absence of other renal diseases [16], has emerged as a leading cause of CKD globally [17]. According to the American Diabetes Association, DN can be categorized into stages of microalbuminuria

and macroalbuminuria based on the urinary albumin-to-creatinine ratio (UACR) [16, 18]. However, the effect of DN on serum tumor marker levels has not been studied. Moreover, in previous studies, CKD patients were divided into different groups according to their creatinine clearance rate (Ccr) [13, 14] or estimated glomerular filtration rate (eGFR) [15]. Of particular interest are the effects of different degrees of albumin excretion on these tumor markers in diabetic patients. Hence, we conducted this observational study to explore the association between UACR and these tumor marker levels in diabetic patients, in order to make better use of them in clinical practice.

2. Materials and Methods

2.1. Study Population. The study population consisted of 261 nondialysis type 2 diabetic patients with varying degrees of albumin excretion, who were inpatients of the Department of Endocrinology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine between October 2015 and June 2016. Patients who met the diagnosis for type 2 diabetes based on the American Diabetes Association 2014 criteria, and did not accept dialysis, are eligible for inclusion. After systematic physical and radiological examinations, patients with any sign of malignancy, pregnancy, nondiabetic kidney disease, urinary tract infection, heart failure, hepatocirrhosis, or liver failure were excluded. Patients were divided into three groups according to UACR: normoalbuminuria group (DM, UACR < 30 mg/g, $n = 96$), microalbuminuria group (DN1, UACR ≥ 30 to < 300 mg/g, $n = 88$), and macroalbuminuria group (DN2, UACR ≥ 300 mg/g, $n = 77$). Following a careful clinical examination, 90 healthy age- and sex-matched volunteers were enrolled as the control group. The study protocol was approved by the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. Written informed consent was obtained from all the participants.

2.2. Measurements. Detailed information regarding age, sex, medical history, and lifestyle-related risk factors were obtained by our clinical professionals. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes [2]. Current drinking was defined as alcohol intake more than once per month during the past 12 months [2]. Weight and height were measured using a balance beam and a vertical ruler in light clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure (BP) was measured using a mercury sphygmomanometer, with participants in a seated position after 5 min of rest. Two BP readings were obtained 1 min apart, and the mean was calculated. Hypertension was defined by systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or treatment with antihypertensive drugs.

Fasting venous blood and urine samples were collected from patients and controls in the morning and sent to clinical laboratories for measurement in time. SCC and CEA were measured using chemiluminescence immunoassays (Abbott

i2000SR, Longford, Ireland); Cyfra21-1 and NSE were measured by electrochemiluminescence immunoassays (Modular e601; Roche Diagnostics, Mannheim, Germany). Fasting plasma glucose (FPG) was measured using hexokinase methods. HbA1C was measured using high-performance liquid chromatography with the VARIANTII Hemoglobin Testing System (Bio-Red laboratories). eGFR was calculated using the Modification of Diet in Renal Disease formula: $eGFR \text{ (ml/min/1.73m}^2\text{)} = 186 \times (\text{serum creatinine} \times 0.011)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women})$ [19]. The cutoff values for each tumor marker were 1.5 ng/ml for SCC, 5 ng/ml for CEA, 17 ng/ml for NSE, and 3.3 ng/ml for CYFRA21-1. Measured values greater than or equal to the cutoff value were defined as positive.

Urinary albumin and creatinine were measured using the nephelometry and sarcosine oxidase method (BECKMAN COULTER AU5800, Japan). Before examination was conducted, the patients were instructed to avoid exercise for 1 h. UACR was calculated by dividing urinary albumin by urinary creatinine and expressed in mg/g. DN was defined as an UACR of ≥ 30 mg/g in the absence of urinary tract infection or other renal abnormalities [16, 20].

2.3. Statistical Analysis. We performed the statistical analysis using IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, NY, USA). Two-sided P values < 0.05 were considered significant. General characteristics were summarized as median with interquartile range (IQR) for continuous variables or as number with proportion for categorical variables. Kolmogorov-Smirnov tests and P-P plots were used to determine the normality of the data. To test for differences among the groups, Mann-Whitney U or Kruskal-Wallis tests were used for continuous variables with skewed distributions and Pearson chi-square tests for categorical variables. Spearman rank correlations with corresponding significance levels were evaluated to test the correlations between different variables.

Binary logistic regression analysis was conducted to determine the risk of elevated serum tumor marker levels for each category of UACR in diabetic patients, with normoalbuminuria (UACR < 30 mg/g) as the reference. Data were expressed as the odds ratio (OR) and 95% confidence intervals (CIs). Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, duration of diabetes, FPG, HbA1C, eGFR, current smoking, current drinking, hypertension, and use of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB).

3. Results

3.1. Clinical Characteristics of the Study Population. Baseline anthropometric and biochemical characteristics of the study population are summarized in Table 1. Among type 2 diabetic patients, 96 had normoalbuminuria, 88 had microalbuminuria, and 77 had macroalbuminuria. There were no significant differences in age and sex among the four groups. However, compared with the control group, diabetic patients with microalbuminuria and macroalbuminuria had significantly higher UACR, HbA1C, FPG, SBP, DBP, and BMI. These patients also had significantly lower eGFR. In addition,

TABLE 1: General characteristics of subjects included in the analysis.

Parameters	Control group	DM group	DN1 group	DN2 group
N (male/female)	90 (45/45)	96 (47/49)	88 (44/44)	77 (39/38)
UACR, mg/g	6.16 (4.91–7.96)	10.22 (6.76–14.07)*	69.09 (42.10–136.47)* [†]	796.80 (477.78–1874.10)* ^{†§}
Age, yrs	63 (56–69)	63 (57–69)	64 (56–70)	63 (56–70)
Duration of diabetes, yrs	—	10 (6–16)	12 (8–16)	13 (9–18)
BMI, kg/m ²	23.51 (22.09–25.51)	24.00 (21.84–27.17)*	24.66 (22.98–27.60)*	24.80 (23.15–27.80)*
eGFR, ml/min/1.73m ²	116.62 (100.71–136.27)	107.17 (92.23–125.11)*	102.28 (85.56–120.36)*	68.82 (45.12–87.16)* ^{†§}
FPG, mmol/l	5.30 (5.00–5.50)	7.50 (6.30–8.60)*	7.60 (6.40–9.10)*	7.90 (6.50–9.20)*
HbA1C, %	5.30 (5.10–5.50)	7.40 (6.50–8.20)*	8.00 (7.10–9.20)* [†]	8.10 (7.10–9.30)* [†]
SBP, mmHg	120.0 (111.0–130.0)	130.0 (120.0–132.0)*	130.0 (120.0–140.0)* [†]	136.0 (130.0–146.0)* ^{†§}
DBP, mmHg	75.0 (69.0–80.0)	80.0 (73.0–80.0)*	80.0 (75.0–80.0)*	80.0 (75.5–84.0)*
Hypertension, %	—	21.9	31.8	42.9 [†]
Use of ACEI/ARB, %	—	24.0	37.5 [†]	44.2 [†]
Current smoker, %	16.7	17.7	26.1	36.4* [†]
Current drinker, %	8.9	10.4	14.8	26.0* [†]

Data are summarized as median (interquartile range) for continuous variables or as number with proportion for categorical variables. DM: diabetes mellitus with normoalbuminuria; DN1: diabetes mellitus with microalbuminuria; DN2: diabetes mellitus with macroalbuminuria; UACR: urinary albumin to creatinine ratio; BMI: body mass index; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HbA1C: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers. * $P < 0.05$ versus control group; [†] $P < 0.05$ versus DM group; [§] $P < 0.05$ versus DN1 group.

TABLE 2: Serum tumor marker levels in diabetic patients and controls.

Tumor markers	Control group	DM group	DN1 group	DN2 group
N	90	96	88	77
SCC	0.50 (0.10–0.90)	0.60 (0.20–0.90)	0.80 (0.40–1.10)* [†]	1.25 (0.58–1.80)* ^{†§}
Cyfra21-1	1.70 (1.28–2.15)	2.20 (1.80–3.28)*	2.95 (2.10–3.90)* [†]	3.50 (2.60–4.50)* ^{†§}
NSE	6.32 (5.72–7.35)	6.42 (5.46–7.26)	6.53 (5.04–8.65)	6.77 (5.67–8.75)
CEA	1.67 (1.12–2.57)	2.02 (1.46–3.11)	2.71 (1.86–4.02)* [†]	3.43 (2.43–4.89)* [†]

Data are summarized as median (interquartile range) for continuous variables. DM: diabetes mellitus with normoalbuminuria; DN1: diabetes mellitus with microalbuminuria; DN2: diabetes mellitus with macroalbuminuria; SCC: squamous cell carcinoma antigen; Cyfra21-1: cytokeratin 19 fragment antigen 21-1; NSE: neuron specific enolase; CEA: carcinoembryonic antigen. * $P < 0.05$ versus control group; [†] $P < 0.05$ versus DM group; [§] $P < 0.05$ versus DN1 group.

diabetic patients with macroalbuminuria had significantly higher UACR than those in the other groups, while FPG and BMI were not significantly different among the three diabetic groups.

3.2. Positive Rates and Serum Tumor Marker Levels. Serum tumor marker levels in the three diabetic groups and the healthy controls are shown in Table 2. Diabetic patients with microalbuminuria or macroalbuminuria had significantly higher serum SCC, Cyfra21-1, and CEA levels than those in the DM group and the control group. Moreover, diabetic patients with macroalbuminuria had significantly higher serum SCC and Cyfra21-1 levels than those in the other three groups. Meanwhile, the Cyfra21-1 levels in the three diabetic groups were significantly higher than those in the control group. By contrast, the four groups had comparable serum NSE levels.

The positive rates for SCC, Cyfra21-1, and CEA significantly increased with increasing urinary albumin excretion (all P for trend < 0.001 ; Figure 1).

3.3. Correlations of Serum Tumor Marker Levels with the Urinary Albumin to Creatinine Ratio and Other Parameters in Diabetic Patients. Correlation results are presented in Table 3. SCC ($r = 0.336$), Cyfra21-1 ($r = 0.299$), and CEA ($r = 0.348$) were significantly and positively correlated with UACR. Significant negative correlations of eGFR with SCC, Cyfra21-1, and CEA were also observed. In addition, Cyfra21-1 was also significantly and positively correlated with age, duration of diabetes, and FPG. Significant positive correlations of CEA with duration of diabetes, FPG, and HbA1C were also observed. There were no associations of NSE with UACR and eGFR.

3.4. Association of UACR with Elevated Serum Tumor Marker Levels in Diabetic Patients. The binary logistic regression analyses (Table 4) showed that the risk of elevated SCC, Cyfra21-1, and CEA levels increased across the UACR categories (P for trend < 0.05 in every model). In an unadjusted model, compared with diabetic patients with normoalbuminuria, the ORs for positive SCC, Cyfra21-1, and CEA rates

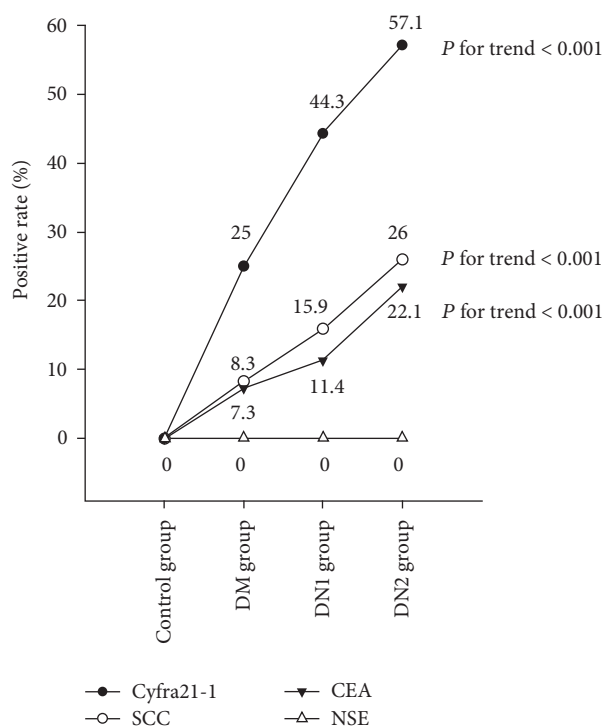


FIGURE 1: Positive rates of serum Cyfra21-1, SCC, CEA, and NSE levels in diabetic patients and healthy controls. DM: diabetes mellitus with normoalbuminuria; DN1: diabetes mellitus with microalbuminuria; DN2: diabetes mellitus with macroalbuminuria; SCC: squamous cell carcinoma antigen; Cyfra21-1: cytokeratin 19 fragment antigen 21-1; NSE: neuron-specific enolase; CEA: carcinoembryonic antigen.

TABLE 3: Spearman correlation coefficients between serum tumor markers and measured parameters.

	SCC	CA211	CEA
Age, yrs	0.061	0.132*	0.023
BMI, kg/m ²	0.046	0.076	0.050
Duration of diabetes	0.051	0.255***	0.150*
FPG, mmol/l	0.061	0.146*	0.247**
HbA1C, %	0.076	0.134	0.234**
UACR	0.336***	0.299***	0.348**
eGFR, ml/min/1.73m ²	-0.195**	-0.249***	-0.142*

Data were Spearman correlation coefficients. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. BMI: body mass index; FPG: fasting plasma glucose; HbA1C: glycated hemoglobin; UACR: urinary albumin to creatinine ratio; eGFR: estimated glomerular filtration rate. SCC: squamous cell carcinoma antigen; Cyfra21-1: cytokeratin 19 fragment antigen 21-1; CEA: carcinoembryonic antigen.

in patients with macroalbuminuria were 2.584 (95% CI 1.313, 5.083; $P < 0.001$), 4.000 (95% CI 2.097, 7.630; $P < 0.001$), and 2.783 (95% CI 1.356, 5.800; $P < 0.01$), respectively (Table 4, model 1). After adjusting for age, sex, BMI, duration of diabetes, FPG, HbA1C, eGFR, current smoking, current drinking, hypertension, and use of ACEI/ARB, ORs for elevated SCC, Cyfra21-1, and CEA levels were slightly attenuated but remained significant (Table 4, model 2).

4. Discussion

The present study showed that the serum levels of three tumor markers for lung cancer (SCC, Cyfra21-1, and CEA) were elevated in type 2 diabetic patients, especially those with DN. In addition, the positive rates for the three tumor markers gradually and markedly increased with increasing urinary albumin excretion. Binary logistic regression analyses indicated that UACR was an independent risk factor for elevated tumor markers in diabetic patients. In contrast, NSE was not affected by DN. To the best of our knowledge, this is the first study to explore the association between different degrees of albumin excretion and serum tumor marker levels in patients with type 2 diabetes.

Diabetes has been associated with an increased risk of lung cancer, which is now the most common cancer and the leading cause of cancer death worldwide [8, 9]. Serum SCC, Cyfra21-1, NSE, and CEA levels are now widely used to increase the diagnostic specificity for screening, early detection, monitoring therapy efficacy, and defining prognosis of lung cancer [11, 21]. However, accumulating evidence has shown that these tumor marker levels are elevated in patients with CKD [12–15]. Nomura et al. [13] reported significantly elevated serum SCC, Cyfra21-1, and CEA levels in patients with chronic renal failure, whereas NSE was not affected. Arik et al. [12] also reported increased serum SCC levels in nondialysis uremic patients.

However, few studies have explored the association between DN and tumor markers. Kashiwabara et al. [22] reported that serum Cyfra21-1 levels were higher in patients with DN than those in diabetic patients with normal renal function and healthy controls, which concurred with our results. Notably, this study was conducted 18 years ago and the definition of DN was based on abnormal urinary IgG-to-creatinine ratio (>1.1 mg/g). In the present analysis, we used UACR to define and categorize DN according to the American Diabetes Association criteria, which adds new and further evidence to the previous studies.

What is the possible underlying mechanism for the observed associations between serum tumor marker levels and UACR in diabetic patients? As pointed out previously, tumor marker levels may be modified by several tumor-independent physiological or pathological statuses that increase the synthesis (such as inflammation) and reduce its elimination (such as kidney or liver failure) [23]. First, albuminuria is a potent stimulus of mitochondrial dysfunction, inducing tubular injury and tubulointerstitial inflammation through oxidative stress [24]. In addition, urinary albumin excretion causes tubular lesions through activation of the HSP70-TLR4 axis in DN [25]. The tubular damage caused by albuminuria would lead to impaired excretion of these tumor markers. Second, many tumor markers are metabolized in the kidney [26]. Elevated levels of several tumor markers can be frequently detected in patients with impaired kidney function because their renal function is retarded [23]. Indeed, eGFR gradually decreased with increasing UACR in our study population, which could also be an important mechanism of the false positive elevations.

TABLE 4: Associations of urinary albumin-to-creatinine ratio with tumor marker status (positive or negative) in diabetic patients.

	Urinary albumin-to-creatinine ratio			P for trend
	<30	30–299	≥300	
SCC positive				
Model 1	Ref.	1.023 (0.506–2.067)	2.584 (1.313–5.083)***	0.002
Model 2	Ref.	1.113 (0.815–3.569)	2.552 (1.297–5.021)**	0.003
Cyfra21-1 positive				
Model 1	Ref.	2.388 (1.278–4.460)**	4.000 (2.097–7.630)***	<0.001
Model 2	Ref.	1.952 (1.010–3.774)*	2.443 (1.054–5.664)*	0.026
CEA positive				
Model 1	Ref.	0.996 (0.362–1.748)	2.783 (1.336–5.800)**	0.006
Model 2	Ref.	1.275 (0.440–3.691)	2.299 (1.077–4.907)*	0.035

Data were odds ratio (95% confidence interval). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. SCC: squamous cell carcinoma antigen; Cyfra21-1: cytokeratin 19 fragment antigen 21-1; CEA: carcinoembryonic antigen. Model 1 was unadjusted. Model 2 included terms for age, sex, BMI, duration of diabetes, FPG, HbA1C, eGFR current smoking and current drinking, hypertension, and use of ACEI/ARB. SCC positive was defined as serum SCC level ≥ 1.5 ng/ml; Cyfra21-1 positive was defined as serum Cyfra21-1 level ≥ 3.3 ng/ml; CEA positive was defined as serum CEA level ≥ 5.0 ng/ml.

One interesting finding from the present study was that SCC, Cyfra21-1, and CEA levels were elevated even in the normoalbuminuric diabetic patients, with positive rates of 8.3%, 25.0%, and 7.3%, respectively. Previous studies have demonstrated that glomerular and tubular lesions occur early in diabetic patients in the absence of microalbuminuria [27–29]. Moreover, Surendar et al. [30] also found that cystatin C, an early indicator of renal impairment, was elevated even in patients with impaired glucose tolerance. Owing to the limited knowledge in this field, further investigation is warranted.

Taking into account the increased incidence of diabetes and DN, our study is of clinical importance. The cut-off values for SCC, Cyfra21-1, and CEA obtained from a normal population are not applicable to diabetic patients, especially those with DN. UACR is an important factor to be considered for prevention of diagnostic errors derived from false positive results. Considering NSE is not affected by DN, it may serve as a useful tool in the screening and early detection of lung cancer in diabetic patients.

Our study had some strengths. First, this study is the first to investigate the associations between UACR and tumor marker levels in diabetic patients. Second, strict quality control of the data is guaranteed by the fact that all information including potential confounders are collected by clinical professionals. However, our study also has some limitations. First, owing to the cross-sectional design, causal relationships between UACR and tumor marker levels could not be determined. Second, our sample size was relatively small. Further prospective and longitudinal studies with larger sample size and long-term follow-up are warranted. Third, among the 10 newly diagnosed diabetic patients, we used a single random measurement of UACR to diagnose DN rather than three measurements. However, recent data suggest that single urinary albumin measurements are accurate in predicting nephropathy [31] and have been used previously by other investigators [32].

5. Conclusion

In conclusion, serum SCC, Cyfra21-1, and CEA levels gradually and markedly increase with increasing urinary albumin

excretion in diabetic patients. This affects the specificity for screening, early detection, monitoring therapy efficacy, and defining prognosis of lung cancer unless higher cutoff values are used. Appropriate interpretation of tumor markers in diabetic patients is mandatory to avoid unnecessary and even hazardous biopsies.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

Authors' Contributions

Hao Lu and Jue Zhang designed the research; Jianzhong Chen, Feng Tao, Bin Zhang, Qingguang Chen, Yan Qiu, Qian Luo, Yanna Gen, and Jiali Meng conducted the research; Jianzhong Chen analyzed the data; Jianzhong Chen and Feng Tao wrote the manuscript. All the authors read and approved the final manuscript. Jianzhong Chen and Feng Tao contributed equally to this manuscript.

Acknowledgments

This study was supported by the Ministry of Science and Technology in China (2014AA022304); Construction for Shanghai Key Laboratory of Traditional Chinese Clinical Medicine (14DZ2273200); Three-Year Action Plan for Shanghai Traditional Chinese Medicine Development (ZY3-CCCX-2-1003). The authors thank all the team members from the Department of Clinical Laboratory and Department of Endocrinology and Metabolism of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. The authors would like to thank Editage (www.editage.cn) for the English language editing.

References

- [1] D. R. Whiting, L. Guariguata, C. Weil, and J. Shaw, "IDF diabetes atlas: global estimates of the prevalence of diabetes

- for 2011 and 2030," *Diabetes Research and Clinical Practice*, vol. 94, pp. 311–321, 2011.
- [2] Y. Xu, L. Wang, J. He et al., "Prevalence and control of diabetes in Chinese adults," *Journal of the American Medical Association*, vol. 310, pp. 948–959, 2013.
 - [3] E. Selvin, C. M. Parrinello, D. B. Sacks, and J. Coresh, "Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010," *Annals of Internal Medicine*, vol. 160, pp. 517–525, 2014.
 - [4] G. Danaei, M. M. Finucane, Y. Lu et al., "National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants," *Lancet (London, England)*, vol. 378, pp. 31–40, 2011.
 - [5] H. Noto, A. Goto, T. Tsujimoto, K. Osame, and M. Noda, "Latest insights into the risk of cancer in diabetes," *Journal of Diabetes Investigation*, vol. 4, pp. 225–232, 2013.
 - [6] B. B. Barone, H. C. Yeh, C. F. Snyder et al., "Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 300, pp. 2754–2764, 2008.
 - [7] E. Giovannucci, D. M. Harlan, M. C. Archer et al., "Diabetes and cancer: a consensus report," *Diabetes Care*, vol. 33, pp. 1674–1685, 2010.
 - [8] B. Carstensen, D. R. Witte, and S. Friis, "Cancer occurrence in Danish diabetic patients: duration and insulin effects," *Diabetologia*, vol. 55, pp. 948–958, 2012.
 - [9] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, "Global cancer statistics, 2012," *CA: A Cancer Journal for Clinicians*, vol. 65, pp. 87–108, 2015.
 - [10] J. Schneider, "Tumor markers in detection of lung cancer," *Advances in Clinical Chemistry*, vol. 42, pp. 1–41, 2006.
 - [11] F. Chen, X. Y. Wang, X. H. Han, H. Wang, and J. Qi, "Diagnostic value of Cyfra21-1, SCC and CEA for differentiation of early-stage NSCLC from benign lung disease," *International Journal of Clinical and Experimental Medicine*, vol. 8, pp. 11295–11300, 2015.
 - [12] N. Arik, B. Adam, T. Akpolat, K. Hasil, and S. Tabak, "Serum tumour markers in renal failure," *International Urology and Nephrology*, vol. 28, pp. 601–604, 1996.
 - [13] F. Nomura, A. Koyama, M. Ishijima, S. Takano, M. Narita, and T. Nakai, "Serum levels of five tumor markers for lung cancer in patients with chronic renal failure," *Oncology Reports*, vol. 5, pp. 389–392, 1998.
 - [14] Y. Xiaofang, Z. Yue, X. Xialian, and Y. Zhibin, "Serum tumour markers in patients with chronic kidney disease," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 67, pp. 661–667, 2007.
 - [15] H. L. Tong, Z. N. Dong, X. Y. Wen, J. Gao, B. Wang, and Y. P. Tian, "Impact of chronic kidney disease on serum tumor markers concentrations," *Chinese Medical Journal*, vol. 126, pp. 274–279, 2013.
 - [16] J. L. Gross, M. J. de Azevedo, S. P. Silveiro, L. H. Canani, M. L. Caramori, and T. Zelmanovitz, "Diabetic nephropathy: diagnosis, prevention, and treatment," *Diabetes Care*, vol. 28, pp. 164–176, 2005.
 - [17] R. Gupta and A. Misra, "Epidemiology of microvascular complications of diabetes in south Asians and comparison with other ethnicities," *Journal of Diabetes*, 2016.
 - [18] M. E. Molitch, R. A. DeFronzo, M. J. Franz, W. F. Keane, C. E. Mogensen, and H. H. Parving, "Diabetic nephropathy," *Diabetes Care*, vol. 26, Supplement 1, pp. S94–S98, 2003.
 - [19] X. Lv, W. Sun, X. Huang et al., "Association of serum fetuin-A levels with the risk of albuminuria in middle-aged and elderly Chinese," *The Journal of Clinical Endocrinology and Metabolism*, vol. 101, pp. 1235–1242, 2016.
 - [20] J. Wu, X. Li, Y. Tao, Y. Wang, and Y. Peng, "Free triiodothyronine levels are associated with diabetic nephropathy in euthyroid patients with type 2 diabetes," *International Journal of Endocrinology*, vol. 2015, p. 204893, 2015.
 - [21] D. W. Yang, Y. Zhang, Q. Y. Hong et al., "Role of a serum-based biomarker panel in the early diagnosis of lung cancer for a cohort of high-risk patients," *Cancer*, vol. 121, Supplement 17, pp. 3113–3121, 2015.
 - [22] K. Kashiwabara, K. Kishi, H. Nakamura et al., "Mechanism of increased serum cytokeratin 19 fragment levels in patients with diabetic nephropathy as a model of chronic renal failure," *Internal Medicine (Tokyo, Japan)*, vol. 37, pp. 917–921, 1998.
 - [23] G. Coppolino and D. Bolognani, "Tumour markers and kidney function: a systematic review," *BioMed Research International*, vol. 2014, Article ID 647541, 9 pages, 2014.
 - [24] D. Liu, M. Xu, L. H. Ding et al., "Activation of the Nlrp3 inflammasome by mitochondrial reactive oxygen species: a novel mechanism of albumin-induced tubulointerstitial inflammation," *The International Journal of Biochemistry & Cell Biology*, vol. 57, pp. 7–19, 2014.
 - [25] H. F. Jheng, P. J. Tsai, Y. L. Chuang et al., "Albumin stimulates renal tubular inflammation through an HSP70-TLR4 axis in mice with early diabetic nephropathy," *Disease Models & Mechanisms*, vol. 8, pp. 1311–1321, 2015.
 - [26] J. Trape, X. Filella, M. Alsina-Donadeu, L. Juan-Pereira, A. Bosch-Ferrer, and R. Rigo-Bonnin, "Increased plasma concentrations of tumour markers in the absence of neoplasia," *Clinical Chemistry and Laboratory Medicine*, vol. 49, pp. 1605–1620, 2011.
 - [27] T. Narita, H. Sasaki, M. Hosoba et al., "Parallel increase in urinary excretion rates of immunoglobulin G, ceruloplasmin, transferrin, and orosomucoid in normoalbuminuric type 2 diabetic patients," *Diabetes Care*, vol. 27, pp. 1176–1181, 2004.
 - [28] W. J. Fu, S. L. Xiong, Y. G. Fang et al., "Urinary tubular biomarkers in short-term type 2 diabetes mellitus patients: a cross-sectional study," *Endocrine*, vol. 41, pp. 82–88, 2012.
 - [29] C. Gluhovschi, G. Gluhovschi, L. Petrica et al., "Urinary biomarkers in the assessment of early diabetic nephropathy," *Journal of Diabetes Research*, vol. 2016, Article ID 4626125, 13 pages, 2016.
 - [30] J. Surendar, S. Anuradha, B. Ashley et al., "Cystatin C and cystatin glomerular filtration rate as markers of early renal disease in Asian Indian subjects with glucose intolerance (CURES-32)," *Metabolic Syndrome and Related Disorders*, vol. 7, pp. 419–425, 2009.
 - [31] G. Pugliese, A. Solini, C. Fondelli et al., "Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the renal insufficiency and cardiovascular events (RIACE) study," *Nephrology, Dialysis, Transplantation*, vol. 26, pp. 3950–3954, 2011.
 - [32] A. A. Tahrani, A. Ali, N. T. Raymond et al., "Obstructive sleep apnea and diabetic nephropathy: a cohort study," *Diabetes Care*, vol. 36, pp. 3718–3725, 2013.