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Traditional Chinese medicine body constitution predicts new-onset diabetic albuminuria in patients with type 2 diabetes

Taichung diabetic body constitution prospective cohort study

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Abstract

This prospective cohort study explored whether body constitution (BC) independently predicts new-onset albuminuria in persons with type 2 diabetes mellitus (T2DM) enrolled in the diabetes care management program (DCMP) of a medical center, providing evidence of integrating traditional Chinese medicine into DCMP for improving care quality. Persons with T2DM (n = 426) originally without albuminuria enrolled in DCMP were recruited in 2010 and were then followed up to 2015 for detecting new-onset albuminuria. The participants received urinalysis and blood test annually. Albuminuria was determined by an elevated urinary albumin/creatinine ratio (≥ 30 μg/mg), and poor glucose control was defined as Glycosylated hemoglobin above or equal to 7%. BC type (Yin deficiency, Yang deficiency, and phlegm stasis) was assessed using a well-validated body constitution questionnaire at baseline. Risk factors for albuminuria (sociodemographic factors, diabetes history, lifestyle behaviors, lipid profile, blood pressure, and kidney function) were also recorded. Hazard ratios (HR) of albuminuria for BC were estimated using multivariate Cox proportional hazards model. During the 4-year follow-up period, albuminuria occurred in 30.5% of participants (n = 130). The HR indicated that Yin deficiency was significantly associated with an increased risk of new-onset albuminuria in persons with T2DM and good glucose control after adjustment for other risk factors (HR = 2.09; 95% confidence interval = 1.05–4.17, P = .04), but not in those with poor glucose control. In persons with T2DM and poor glucose control, phlegm stasis was also significantly associated with a higher risk of albuminuria (2.26; 1.03–4.94, P = .04) after multivariate adjustment, but not in those with good glucose control. In addition to already-known risk factors, BC is an independent and significant factor associated with new-onset albuminuria in persons with T2DM. Our results imply Yin deficiency and phlegm stasis interacting with glucose control status may affect new-onset albuminuria in persons with T2DM.

Abbreviations: BC = body constitution, BCQ = body constitution questionnaire, BMI = body mass index, CAM = complementary and alternative medicine, CVD = cardiovascular disease, DBP = diastolic blood pressure, DCMP = diabetes care management program, DKD = diabetic kidney disease, ESRD = end-stage renal disease, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein-cholesterol, HRs = hazard ratios, LDL-C = low-density lipoprotein-cholesterol, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, TCM = traditional Chinese medicine, TDBCS = Taichung diabetic body constitution study, TG = triglyceride, UACR = urine albumin-to-creatinine ratio.

Keywords: albuminuria, body constitution, diabetic nephropathy, traditional Chinese medicine, type 2 diabetes mellitus

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

The global prevalence of diabetes mellitus has been rapidly rising during the past decades in both developed and developing countries.[1,2] The World Health Organization has reported that about 422 million people have diabetes, especially in middle- and low-income countries, and the number of deaths attributed to diabetes each year was 1.6 million in the whole world.[3] The International Diabetes Federation has also estimated that the population with diabetes will be 578 million by 2030 and projected to be around 700 million people by 2045 according to the global diabetes prevalence of 9.3% (463 million people) in 2019. The corresponding prevalence of diabetes will increase to 10.2% and 10.9% in 2030 and 2045, respectively.[4]

Albuminuria is a marker of kidney damage with increased excretion of urinary albumin, resulting from albumin leakage across the glomerular podocyte filtration barrier into the urine. Albuminuria has been associated with an increased risk of renal disease, cardiovascular disease (CVD), atherosclerosis, and all-cause and CVD mortality.[5–8] The possible underlying biological mechanism is endothelial dysfunction for albuminuria as a marker of generalized endothelial dysfunction, leading to accelerated atherosclerosis[9] and the increased risk of CVD.[10–12] It has also been reported to be associated with arterial stiffness, especially in persons with diabetes and hypertension.[13] A preferred method for detecting albuminuria is urinary albumin-creatinine ratio.

About 40% of people with diabetes will develop chronic kidney disease,[14] involving a great number of people who will develop end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in many countries.[15] Diabetic kidney disease (DKD) is typically characterized by persistent albuminuria, and albuminuria strongly predicts the progression of DKD.[16] Even early stages of DKD confer a substantial increase in the risk of CVD.[17,18] Thus, the therapeutic goal should be to prevent these earlier stages, not just ESRD.[16]

Traditional Chinese medicine (TCM), a widely used type of complementary and alternative medicine (CAM),[19–21] underlines the importance of personalized medicine using body constitution (BC) theory as foundation.[22–24] An individual's constitution status is formed by the state of Yin and Yang in his body. Yin and Yang deficiency BCs refer to the decrease of the material and energy level, respectively. The definition of Yin is the materials (including blood, body fluid, and essence like albumin) that perform physiological function, while Yang is the energy (including energy for digestion, heart contraction, and breathing) which maintains the physiological function. The Phlegm stasis is induced when the materials transported by the energy, like blood sugar and glycosylated hemoglobin (HbA1c), are impeded by external or environmental stimuli.[25]

In TCM clinical practice, treatments are individualized based on BC status to achieve the optimal treatment effect.[24,26,27] People that have a deviation from the normal BC state are variously prone to develop certain illnesses and differ in disease progression.[25,26] TCM practitioners used to adopt individualized plans such as exercise, sleep, diet and food properties, and living environment that are tailored to the individual's needs and goals, to adjust deviated BC for disease prevention and/or treatment.[28–30] The body constitution questionnaire (BCQ)[22,25,31,32] is a well-validated and useful tool for evaluating the Yin deficiency, Yang deficiency, and phlegm stasis BCs. Several clinical studies applied BCQ to discover the relationship between different BCs and disease, including diabetes,[33–36] breast cancer,[37] schizophrenia,[38] women with menopausal symptoms,[39] and perinatal women.[40,41] Among those prior studies focusing on persons with diabetes, 1 cross-sectional study revealed that the stasis and stagnation BC is associated with higher prevalence of peripheral arterial disease.[34] Another cross-sectional study found that Yin deficiency, Yang deficiency, and phlegm stasis BCs are closely related to a reduction in the health-related quality of life assessed by generic and diabetes-specific quality of life measures.[35] Another study reported a cross-sectional association between BC of Yang deficiency and diabetic retinopathy.[36] However, no longitudinal study to date has specifically explored the relationship of BCs and new-onset albuminuria, the early clinical hallmark of DKD, in persons with type 2 diabetes mellitus (T2DM).

HbA1c level has been treated as the gold standard of glycemic control in preventing diabetes-related microvascular and macrovascular complications.[42] Persons with different BC types are variously at risk of disease occurrence and disease progression. Thus, we are interested in whether HbA1c moderates the strength of the relationship between BC type and new-onset albuminuria. In this prospective cohort study, persons with T2DM had their BCs measured by BCQ and future new-onset albuminuria were prospectively assessed. We aimed to investigate whether BC can predict new-onset albuminuria alongside other already known traditional risk factors and whether the relationship BC type and new-onset albuminuria varied depending on the glucose control status as determined by HbA1c.

2. Methods

2.1. Study design and participants

This is a prospective, hospital-based cohort study based on the Taichung Diabetic Body Constitution Study (TDBCS). The flowchart of recruitment is shown in Figure 1. Baseline data collection was conducted from February 2010 to February 2011, and the endpoint was set at September 20, 2015. The original study population of TDBCS were 887 participants diagnosed with T2DM based on the American Diabetes Association criteria and recruited at the department of endocrinology and metabolism of an outpatient clinic of the Diabetes Health Promotion Center of Taichung Veterans General Hospital in Taichung, Taiwan. The exclusion criteria of the original TDBCS is those who cannot provide good data for BCQs, such those who are illiterate, alcoholic (that cannot provide good quality of data), or have a language barrier. After excluding those who had albuminuria at baseline, the total number of study subjects was 426. The study analysis included 426 participants with complete information. This prospective cohort study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (C10007), and each participant gave written informed consent.

All TDBCS participants underwent comprehensive health assessment at baseline to assess blood pressure of systolic blood pressure (SBP) and diastolic blood pressure (DBP), body measurements of body mass index and waist circumference, blood and urine tests, BCQs, diabetes history, and history of diseases and complications. After a 12 hours overnight fast, blood was drawn from an antecubital vein in the morning and was sent within 4 hours for analysis of HbA1c, fasting plasma glucose (FPG), creatinine, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG). A standardized questionnaire was designed to collect information, administered by an interviewer to record previous or current disease status, medication use, and lifestyle habits. Because these patients were under managed care, the follow-up visit was performed regularly every 3 to 6 months.

2.2. Body Constitution Measurement

BCQs were administered to all the participants, who self-reported their BC status on the same day for blood and urinary tests. One personnel collected the data and she had been trained to check through the questionnaire before leaving the respondent and clear up any discrepancies, ambiguities, or

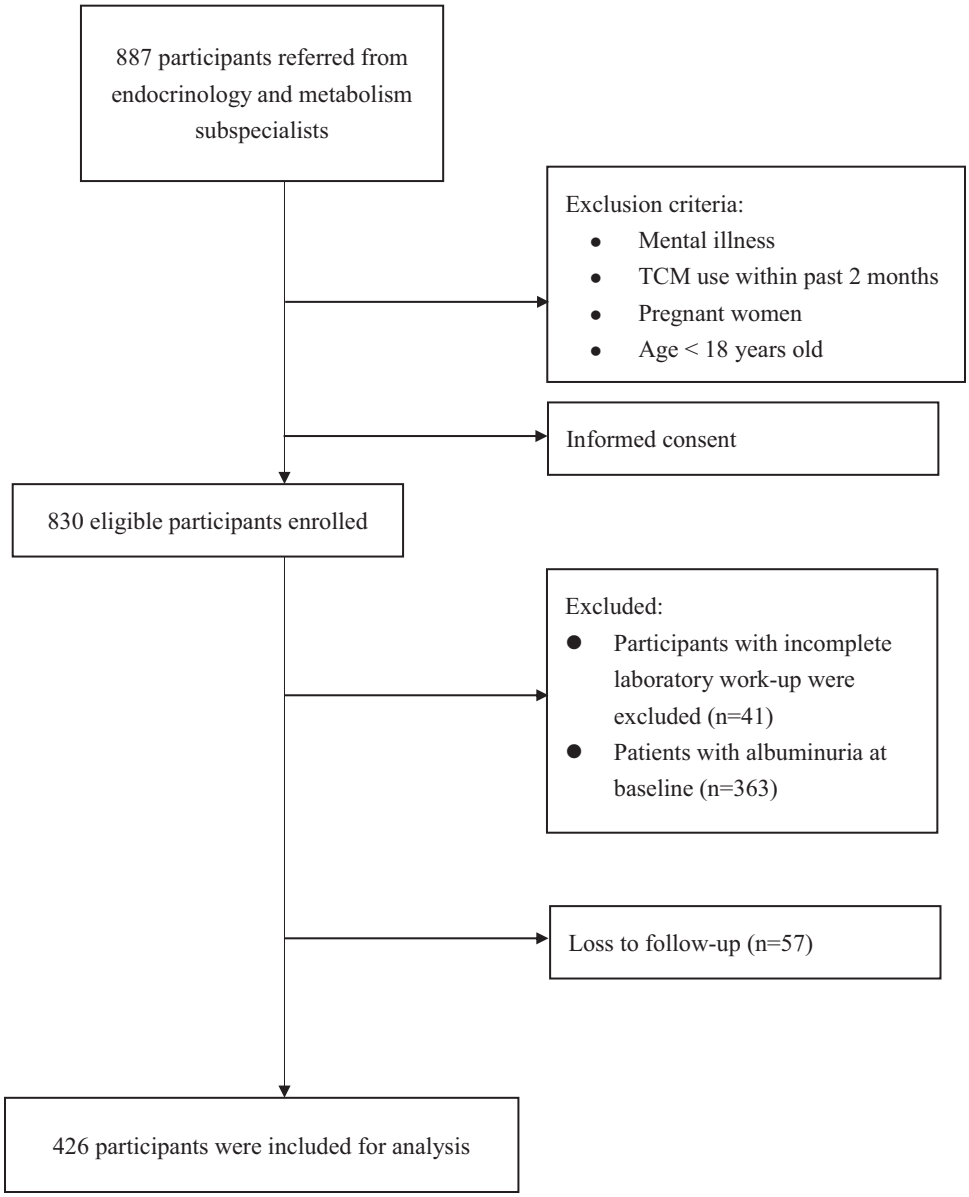

Figure 1. The flowchart of recruitment of the study subjects.

omissions to minimize the potential measurement bias. BCQ is well developed and validated.[22,25,32] Through a 2-stage Delphi process, 44 items of the BCQ were generated, with initial items being translated into colloquial questions. Each item in BCQ was tested for wording, sequencing, grammar correctness, and easy comprehension. The description of the 44 items of final version of BCQ was presented in Table S1, Supplemental Digital Content, http://links.lww.com/MD/I167. The number of BCQ items was reduced through the reliability evaluation of intraclass consistency.[22,25,32] Prior studies demonstrated that the BCQ had favorable factorial validity,[25] and the Cronbach's α of each constitution subscale ranged from 0.88 to 0.90.[25,31,32] The BCQ is a short questionnaire with 44 items on a 5-point Likert-type scale from 1 (never happened) to 5 (always happens), measuring 3 multi-item BC variables: Yang deficiency (19 items), Yin deficiency (19 items), and phlegm stasis (16 items) with some overlapped items belonging to these 3 scales. For each BC variable, the final score was derived by summing the score of each item belonging to each BC variable, ranging from 19 to 95 for Yang deficiency and Yin deficiency, and from 16 to 80 for phlegm stasis. A high score indicates a higher level of deviation from the constitution. The cutoff points for diagnosis for Yang deficiency, Yin deficiency, and phlegm stasis were 30.5, 29.5, and 26.5, respectively.[25,31,32]

2.3. Ascertainment of albuminuria

The primary outcome was albuminuria, with identified spot urine samples collected from each participant. All participants underwent similar blood and urinary tests again on each follow-up visit and anniversary visits as those performed during the baseline program. Urinary creatinine (enzymatic method) and albumin (immunoturbidimetry method) were measured by an auto-analyzer at Taichung Veterans General Hospital. Urine albumin-to-creatinine ratio (UACR) was calculated by the ratio of urinary albumin/creatinine. An elevated UACR ≥ 30 μg/mg was defined as the albuminuria,[43] a marker of increased urinary albumin excretion and kidney injury. The albuminuria incidence was based on urine tests during subsequent follow-up visits. The study cohort was then followed up from the entry (baseline) date to September 20,

Table 1

Baseline characteristics of study participants.

	Yang deficiency (n = 426)			Yin deficiency (n = 426)			Phlegm stasis (n = 426)		
Variables	Yes (n = 46)	No (n = 380)	*P*-value	Yes (n = 118)	No (n = 308)	*P*-value	Yes (n = 57)	No (n = 369)	*P*-value
Age (yrs)	61.50 ± 17.20	62.39 ± 12.01	.7332	63.89 ± 14.73	61.69 ± 11.73	.1471	62.61 ± 16.18	62.25 ± 12.04	.8708
Female, n (%)	28 (60.87)	154 (40.53)	**.0084**	57 (48.31)	125 (40.58)	**.1494**	30 (52.63)	152 (41.19)	.1042
BMI (kg/m^2)	25.45 ± 3.83	25.36 ± 3.90	.8871	25.39 ± 3.42	25.37 ± 4.06	.9473	26.33 ± 4.39	25.23 ± 3.79	**.0450**
Waist (cm)	87.35 ± 10.00	88.42 ± 10.30	.5038	88.03 ± 9.50	88.41 ± 10.55	.7289	91.08 ± 10.92	87.88 ± 10.10	**.0280**
Lifestyle factors									
Smoke history, yes, n (%)	1 (2.17)	20 (5.26)	.7146†	5 (4.24)	16 (5.19)	.6829	3 (5.26)	18 (4.88)	.7516†
Alcohol history, yes, n (%)	0 (0.00)	15 (3.95)	.3879†	4 (3.39)	11 (3.57)	> .999†	1 (1.75)	14 (3.79)	.7043†
Exercise habits, yes, n (%)	38 (82.61)	308 (81.05)	.7986	94 (79.66)	252 (81.82)	.6099	43 (75.44)	303 (82.11)	.2298
Diabetic factors									
FBS (mg/dL)	138.30 ± 55.42	140.30 ± 37.19	.8166	139.30 ± 43.98	140.30 ± 37.69	.8325	137.20 ± 31.30	140.50 ± 40.62	.4805
HbA1c (%)	7.11 ± 1.28	7.55 ± 1.45	.0511	7.34 ± 1.41	7.56 ± 1.45	.1550	7.39 ± 1.40	7.52 ± 1.45	.5467
DMH (yr)	7.85 ± 7.97	8.44 ± 7.98	.6368	8.44 ± 7.82	8.35 ± 8.05	.9249	7.02 ± 6.23	8.59 ± 8.20	.0962
OHA use, yes, n (%)	42 (91.30)	363 (95.53)	.2660†	114 (96.61)	291 (94.48)	.3635	54 (94.74)	351 (95.12)	.7516†
Insulin usage, yes, n (%)	10 (21.74)	71 (18.68)	.6180	23 (19.49)	58 (18.83)	.8765	6 (10.53)	75 (20.33)	.0793
Lipid profile									
TC (mg/dL)	171.20 ± 32.41	172.80 ± 33.38	.7578	174.10 ± 31.75	172.10 ± 33.83	.5758	172.70 ± 31.38	172.70 ± 33.56	.9868
TG (mg/dL)	132.40 ± 70.43	136.20 ± 101.50	.7443	140.10 ± 98.56	134.10 ± 98.69	.5741	130.60 ± 111.80	136.60 ± 96.51	.6700
HDL (mg/dL)	53.46 ± 13.16	52.54 ± 14.73	.6870	51.86 ± 12.34	52.94 ± 15.33	.4508	53.47 ± 13.86	52.51 ± 14.68	.6422
LDL (mg/dL)	107.80 ± 27.15	103.00 ± 28.05	.2706	105.60 ± 28.58	102.70 ± 27.72	.3426	107.60 ± 28.96	102.90 ± 27.79	.2317
Blood pressure									
SBP (mm Hg)	129.00 ± 16.32	130.40 ± 14.19	.5247	131.10 ± 14.80	130.00 ± 14.28	.4533	130.50 ± 14.71	130.20 ± 14.39	.8819
DBP (mm Hg)	75.89 ± 8.67	77.07 ± 8.83	.3916	76.69 ± 9.09	77.04 ± 8.71	.7096	76.61 ± 9.27	76.99 ± 8.75	.7619
GPT (U/L)	26.89 ± 27.52	27.09 ± 20.50	.9624	23.93 ± 19.83	28.27 ± 21.79	.0597	29.60 ± 25.45	26.68 ± 20.63	.4123
Renal parameters									
Microalbumin	2.29 ± 4.51	2.29 ± 4.12	.9984	2.26 ± 3.65	2.30 ± 4.34	.9298	2.31 ± 4.17	2.29 ± 4.16	.9738
Serum Creatinine (mg/dL)	1.03 ± 0.30	1.02 ± 0.26	.6773	1.04 ± 0.28	1.01 ± 0.26	.2088	1.01 ± 0.25	1.02 ± 0.27	.7908
Urine Creatinine (mg/dL)	1.01 ± 0.30	1.10 ± 1.66	.3449	1.31 ± 2.96	1.01 ± 0.25	.2864	0.99 ± 0.25	1.11 ± 1.68	.2141
eGFR (mL/min)	73.96 ± 21.64	74.67 ± 18.58	.8097	71.62 ± 19.71	75.73 ± 18.50	.0445	74.93 ± 19.32	74.54 ± 18.87	.8874
Diabetic retinopathy, yes, n (%)	10 (21.74)	144 (37.89)	**.0312**	41 (34.75)	113 (36.69)	.7088	15 (26.32)	139 (37.67)	.0968
Foot neuropathy, yes, n (%)	8 (17.39)	33 (8.68)	.0664†	19 (16.10)	22 (7.14)	**.0050**	5 (8.77)	36 (9.76)	.8146
Number of comorbidity	3.07 ± 1.64	3.69 ± 1.81	**.0250**	3.72 ± 1.83	3.59 ± 1.79	.5076	3.30 ± 1.95	3.68 ± 1.78	.1393

Data were presented as mean ± standard deviation (SD) for continuous variables or number (%) for categorical variables.

P values were calculated using the Chi-square test or Fisher exact test.

† for categorical variable and *t*-test for continuous variable.

BMI = body mass index, FBS = fasting blood sugar, HbA1c = glycosylated hemoglobin, DMH = duration of diabetes mellitus, OHA = oral hypoglycemic agent, TC = total cholesterol, TG = triglyceride, HDL = high-density, lipoprotein, LDL = low-density lipoprotein, SBP = systolic blood pressure, DBP = diastolic blood pressure, GPT = glutamic pyruvic transaminase, eGFR = estimated glomerular filtration.

Table 2

The associations between body constitutions and albuminuria stratified by glucose control status.

	Hba1c<7% (n = 171)			Hba1c ≧ 7% (n = 255)		
	Albuminuria			Albuminuria		
	Yes (n = 48)	No (n = 123)	*P* value	Yes (n = 82)	No (n = 173)	*P* value
Yang deficiency						
No	42 (28.38)	106 (71.62)	.8200	74 (31.90)	158 (68.10)	.7774
Yes	6 (26.09)	17 (73.91)		8 (34.78)	15 (65.22)	
Yin deficiency						
No	27 (23.28)	89 (76.72)	**.0427**	61 (31.77)	131 (68.23)	.8178
Yes	21 (38.18)	34 (61.82)		21 (33.33)	42 (66.67)	
Phlegm stasis						
No	41 (28.47)	103 (71.53)	.7870	69 (30.67)	156 (69.33)	.1629
Yes	7 (25.93)	20 (74.07)		13 (43.33)	17 (56.67)	

P values were calculated using the 2-sided chi-square test.

2015, or until an albuminuria event, withdrawal from the study, or death.

2.4. Covariates

Covariates included the sociodemographic characteristics (age, gender, body mass index [BMI], and waist circumference), SBP and DBP, lifestyle behaviors (smoking history, alcohol drinking, and physical activity habits), and diabetes history (diabetes duration, oral hypoglycemia agent, and insulin usage) were obtained through personal interviews and assessment at the Diabetes Health Promotion Center of Taichung Veterans General Hospital. Biochemical markers such as HbA1c, FPG, serum glutamic-pyruvic transaminase, serum glutamic-oxalocetic transaminase, creatinine, hemoglobin, uric acid, total cholesterol, blood urea nitrogen, HDL-C, TG, and LDL-C were analyzed by a biochemical autoanalyzer (Hitachi Labospect 008, LST008, Hitachi High-Technologies Corporation Tokyo, Japan). The estimated glomerular filtration rate was derived using the following equation: 186 × serum creatinine – 1.154 × age – 0.203 × 1.212 (if Black) × 0.742 (if female).[44]

2.5. Statistical analysis

For descriptive analysis, continuous variables were presented as mean ± standard deviation, and categorical variables were presented as n (%). Two-sample *t*-tests were used to compare the continuous factors of the study subjects between who had and did not have the specific BC status at baseline, while chi-square tests were used to compare the categorical ones. Cumulative event risks stratified by BC status were calculated by the Kaplan–Meier method and compared using log-rank statistics.

Multivariable Cox's proportional hazards models were used to evaluate the association between BC status and the new-onset albuminuria to adjust for potential confounders, including gender, age, BMI, and waist circumference, smoking, alcohol drinking history, physical activity, FPG, HbA1c, DM duration, oral hypoglycemia agent, insulin use, TC, HDL-C, TG, LDL-C, GPT, SBP, DBP, comorbidity, and diabetic retinopathy. The assumption of proportional hazards was tested for the Cox models by the product term of BC status and survival time and the assumption was held. Adjusted hazard ratios (HRs) and their 95% confidence intervals were estimated. Interaction of glucose control with BC status was examined by adding product terms into the full Cox's model, and the likelihood ratio test was used to test for significance. Then, the joint associations of any 2 BC variables (Yang deficiency, Yin deficiency, and phlegm stasis) with albuminuria were explored by calculating HR and 95% confidence intervals after adjusting for age, sex, and multiple variables. The lowest likelihood of albuminuria was treated as reference group. The 2-sided *P* value < 0.05 was considered significant. All statistical analyses were executed under SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina).

3. Results

A total of 426 participants were included in the analysis, with 42.73% of women and mean age at baseline of 62.29 years old. During 1667.61 person-years of follow-up period with a mean (median) follow-up of 3.91 (4.81) years, 130 new-onset cases of albuminuria occurred (30.5%) with an incidence density of 77.96/1000 person-years. The characteristics of the study subjects stratified by Yang deficiency, Yin deficiency, and phlegm stasis status are presented in Table 1. Yang deficiency was associated with a higher proportion of women (*P* = .0084), a lower proportion of diabetic retinopathy (*P* = .0312), and a lower mean number of comorbidity (*P* = .0250); Yin deficiency was associated with a lower mean value of estimated glomerular filtration rate (*P* = .0445) and a higher proportion of foot neuropathy (*P* = .0050); and phlegm stasis was associated with higher mean values of BMI and waist (*P* = .0450 and 0.0280, respectively).

Table 2 presents the bivariate associations between BC status and new-onset albuminuria stratified by glucose control status because we detected significant interaction between glucose control and Yin deficiency (*P* = .0278) and borderline significant interaction between glucose control and phlegm stasis (*P* = .0549). Among those with good glucose control, the cumulative risk of new-onset albuminuria in persons with Yin deficiency was significantly higher than in those without Yin deficiency (38.18% vs 23.28%, *P* = .0427). The Kaplan–Meier cumulative risks for new-onset albuminuria showed persons with Yin deficiency are at borderline significantly higher risk (log rank *P* = .068) compared with those without Yin deficiency during a follow-up period of approximately 5 years (Fig. 2).

Table 3 shows the crude and multivariate-adjusted HRs of new-onset albuminuria for BC status stratified by glucose control status because we detected a significant interaction of Yin deficiency (*p* for interaction = 0.0278).and glucose control and a borderline significant interaction glucose control and Phlegm stasis (*p* for interaction = 0.0549). After multivariate adjustment, among those with good glucose control, persons with Yin deficiency were more likely to have new-onset albuminuria compared with those without Yin deficiency (HR and 95% CI: 2.09 [1.05, 4.17], *P* = .0360). Among those with poor glucose control, phlegm stasis was associated with an increased risk of new-onset albuminuria (2.26 [1.03–4.94], *P* = .0410). We further examined the joint effects of combined 2 body constitutions stratified by glucose control status. Among persons with

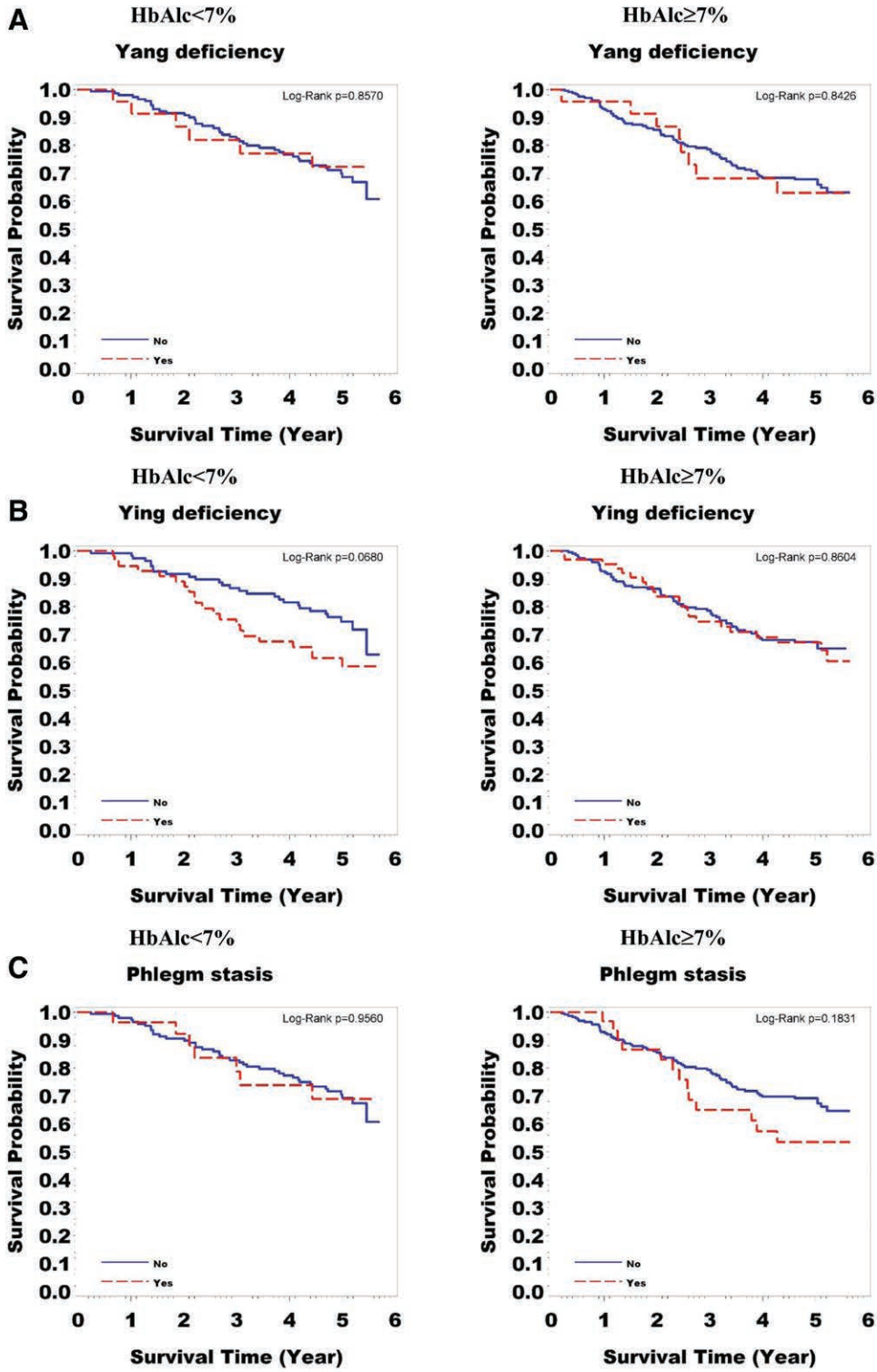

Figure 2. Kaplan-Meier survival curves of albuminuria for Yang deficiency (a), Yin deficiency (b), and Phlegm stasis (c) stratified by glucose control status.

poor glucose control, persons without Yin deficiency but with phlegm stasis were more likely to develop albuminuria (4.20 [1.13-15.55], P = .031) (Table 4).

4. Discussion

In the prospective cohort study, we considered traditional risk factors for new-onset albuminuria, including BMI, waist circumference, HbA1c, blood pressure, lipid profiles, diabetes duration, smoking, alcohol drinking, physical activity, oral hypoglycemia agent, and insulin use, and we found that Yin deficiency and phlegm stasis interacted with poor glucose control on incident albuminuria. Among those with good glucose control, persons with T2DM who had Yin deficiency were about 2 times more likely to develop albuminuria, whereas among those with poor glucose control, persons with T2DM who had Phlegm stasis were 2.26 times more likely to have new-onset albuminuria. In addition, we found persons with poor glucose control who

Table 3

The multivariate-adjusted hazard ratios of body constitutions stratified by glucose control status.

	Hba1c<7% (n = 171)			Hba1c ≧ 7% (n = 255)		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Yang deficiency						
Unadjusted	0.92	(0.39–2.18)	.8571	1.08	(0.52–2.24)	.8426
Adjusted	1.56	(0.49–4.94)	.4529	1.14	(0.46–2.81)	.7733
Yin deficiency						
Unadjusted	1.69	(0.96–2.99)	.0711	1.05	(0.64–1.72)	.8589
Adjusted	2.09	(1.05–4.17)	**.0360**	0.62	(0.32–1.21)	.1622
Phlegm stasis						
Unadjusted	1.02	(0.46–2.28)	.9556	1.49	(0.83–2.70)	.1860
Adjusted	0.38	(0.12–1.21)	.1018	2.26	(1.03–4.94)	**.0410**

Adjusted for BC, sociodemographic characteristics, lifestyle behaviors, diabetic factors, blood pressure, Lipid profile, GPT, comorbidity and diabetic retinopathy.

Analysis by Cox proportional hazard models.

Sociodemographic characteristics: gender, age, BMI, and waist circumference. Lifestyle behaviors: smoke and alcohol drinking history and physical activity. Diabetic factors: FPG, HbA1c, DM duration, oral hypoglycemia agent, and insulin use. Blood pressure: SBP and DBP. Lipid profile: TC, TG, HDL, and LDL.

Model is considered for interaction terms of HbA1c and Yin deficiency; HbA1c and Phlegm stasis. The *P*-values of interaction term between HbA1c and Yin deficiency was 0.0278 and HbA1c and Phlegm stasis was 0.0549 on albuminuria.

Table 4

The joint effects of combined two body constitutions stratified by glucose control status.

	Hba1c<7% (n = 171)			Hba1c ≧ 7% (n = 255)		
	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
No Yang deficiency and no Yin deficiency	1.80	(0.21–15.18)	.588	1.00	(Ref.)	
Yang deficiency but no Yin deficiency	1.00	(Ref.)		--	--	.987
No Yang deficiency but Yin deficiency	2.71	(0.32–22.77)	.359	0.75	(0.39–1.43)	.381
Yang deficiency + Yin deficiency	3.03	(0.32–29.14)	.337	1.17	(0.54–2.52)	.690
No Yang deficiency and no Phlegm stasis	2.47	(0.55–11.08)	.238	1.00	(Ref.)	
Yang deficiency but no Phlegm stasis	1.76	(0.14–22.70)	.664	1.03	(0.36–2.92)	.959
No Yang deficiency but Phlegm stasis	1.00	(Ref.)		1.87	(0.89–3.96)	.100
Yang deficiency + Phlegm stasis	2.84	(0.49–16.60)	.247	1.38	(0.47–4.05)	.555
No Yin deficiency and no Phlegm stasis	1.00	(Ref.)		1.43	(0.72–2.84)	.304
Yin deficiency but no Phlegm stasis	1.86	(0.89–3.87)	.097	1.00	(Ref.)	
No Yin deficiency but Phlegm stasis	--	--	.989	4.20	(1.14–15.55)	**.031**
Yin deficiency + Phlegm stasis	1.07	(0.43–2.65)	.887	1.97	(0.75–5.15)	.168

Adjusted for BC, sociodemographic characteristics, lifestyle behaviors, diabetic factors, blood pressure, Lipid profile, GPT, comorbidity and diabetic retinopathy.

Analysis by Cox proportional hazard models.

Sociodemographic characteristics: gender, age, BMI, and waist circumference. Lifestyle behaviors: smoke and alcohol drinking history and physical activity. Diabetic factors: FPG, HbA1c, DM duration, oral hypoglycemia agent, and insulin use. Blood pressure: SBP and DBP. Lipid profile: TC, TG, HDL, and LDL.

--: not estimable due to no event in the combined 2 body constitution.

didn't have Yin deficiency but had phlegm stasis were about 4 times more likely to develop albuminuria.

Persons with the presence of protein albumin in the urine, that is the early stages of DKD, are at increased risk of death, which may result from the associated cardiovascular disease burden directly or indirectly.[45,46] Microalbuminuria is the earliest clinical hallmark of DKD, and UACR has been shown to be the independent predictor of cardiovascular mortality and renal events in patients with T2DM.[47] Distinguishing persons with T2DM who are at higher risk of albuminuria occurrence is crucial for the prevention of DKD[48,49] and vast efforts have been devoted to recognizing the risk factors for albuminuria.[50–55] Prior studies' evidence indicates that HbA1c, SBP, retinopathy, duration of diabetes, kidney function, body height, and smoking were all independent risk factors of albumuria.[50–52] After these already-known risk factors are taken into consideration, the present study's results add to the emerging concept that BC confers additional risk of new-onset albuminuria in persons with T2DM.

Across the world, traditional medicine is either the mainstay of health care delivery or serves as a complement to it, and the World Health Organization had published traditional medicine strategy 2014 to 2023, which aimed to promote the traditional medicine contribution to the people-centered health care. Many people with diabetes turn to CAM for self-treatment. Of United States diabetic adults, 26.2% reported using some form of CAM in the past year,[56] and the pooled global prevalence of CAM use among adults with diabetes was 51%.[57] TCM, an import part of CAM, is commonly used in the world, and the use of TCM in the United States and Europe is growing.[20] There are several studies revealed that TCM herbal formula could attenuate deterioration of albuminuria in T2DM patients,[58] benefit in DKD treatment,[59] and the use of TCM is associated with lower end-stage renal disease and mortality rates among patients with DKD.[60,61] However, there is no study reported how the DKD is developed form the TCM perspective and no study focused on the prevention of diabetic albuminuria, the earliest clinical hallmark of DKD. BC is a distinct characteristic of a person and is influenced by the genetic composition, psychological condition, ontogeny, and environment.[33,62] Since BC affects an individual's vulnerability and the progression of disease, applying the longitudinal research model to investigate the impact of BC on specific stage of certain disease could provide the significant evaluation and information for disease prevention and health promotion.[63,64] This is the first longitudinal, prospective cohort study which explored how BC affect the T2DM patients in the progression of new-onset diabetic albuminuria, which could provide the

important information for personalized DKD prevention and treatment strategy in T2DM clinical care.

The results of our previous cross-sectional study suggest that patients with T2DM who have both Yang deficiency and Phlegm stasis BCs are associated with a 3fold risk for albuminuria.[36] This longitudinal study further followed up the cohort population for a mean (median) follow-up period of 3.91 (4.81) years, and the results imply phlegm stasis and Yin deficiency interacting with glucose control status may affect new-onset albuminuria in persons with T2DM. The difference in the findings of cross-sectional study and longitudinal study can be explained by the following TCM theories. First, based on TCM theory, when the energy flow is stagnant, it would result in the formation of watery phlegm or static blood,[4–6] then the individual would develop Phlegm stasis BC. Persons with T2DM and poor glucose control, means the sugar (Yin) transported by the energy (Yang) becomes more stagnant, hence, the Phlegm stasis BC would be formed and would cause vascular endothelial dysfunction[65] and vessel obstructions,[34] which would aggravate the impeded energy flow. This vicious cycle can lead to the diabetic complications, including albuminuria, atherosclerosis, and cardiovascular disease, etc. Second, inflammatory processes seem to play an important role in the development of diabetes and its late complications.[66,67] In persons with T2DM and good glucose control, the Yin deficiency BC is presented as an obvious material decrease. In TCM theory, the Yin deficiency would lead to excess heat and worsen the inflammation process, hence, the herbs with the effect of nourish Yin are usually used to treat the diabetes.[67] Last, as the time goes by, the inflammation process (in Yin deficiency BC) and phlegm and static blood formed in the vessels (in Phlegm stasis BC), both conditions will lead to the diabetic nephropathy as new-onset albuminuira occurred. In TCM theory, diabetic nephropathy is referred to as an intrinsically deficient but extrinsically excessive syndrome.[68] The more the leakage of the material of the body occurred (including albumin), the more intrinsically deficient it became; and without the body materials, the energy (Yang) could not work properly, then the Yang-deficiency and Phlegm stasis conditions would be more severe. Therefore, the transition of BC type is the possible explanation for the differences in the findings between cross-sectional study and longitudinal study.

Albuminuria is a reversible state, leading to the vast efforts devoted to modifying its potential risk factors for albuminuria prevention, yet the global incidence of ESRD in patient with T2DM continues to rise.[15,69–71] On the basis of TCM clinical practice, the deviation of BC can be corrected by TCM herbal treatment, which may be used as an intervention for albuminuria prevention. However, further research is needed to demonstrate that TCM herbal treatment correction in BC deviation leads to lower albuminuria incidence.

This study has several strengths. First, to the best of our knowledge, this is the first prospective study to evaluate the temporal association between BC status and new-onset albuminuria and BC in persons with T2DM. Second, our study used a standardized and validated instrument to measure BC status, which minimized the potential measurement error. Third, the HRs revealed strong associations with a value of 2.09 for Yin deficiency in persons with good glucose control and 2.26 for phlegm stasis in persons with poor glucose control. A strong association indicates a greater magnitude of the increased albuminuria risk observed; this indicates a reduced likelihood that the relationship is due merely to the effect of some unsuspected or uncontrolled confounding variable.

This study has a number of limitations. First, our statistical approach considered baseline BC only and did not take time-varying BC into account because of unavailability of data. Second, a potential selection bias may exist because this is a hospital-based study and all participants were recruited from a medical center. The proportions of persons with T2DM and multi-comorbidities, poorer glucose control, and longer diabetes duration in the medical center may be higher than those treated in other clinical settings. Our study's findings may not be generalizable to populations with T2DM in other clinical settings. However, our results can be generalizable to a population with T2DM with similar disease characteristics as ours. Third, although this study assessed the joint effects of combined 2 body constitutions, the effects of some combination classes cannot be estimated due to small sample size. Future studies with a larger sample size are warranted to assess the joint effects of these body constitutions. Lastly, this prospective cohort study collected as many potential confounding variables as possible to minimize the possibility of a confounding effect, but unmeasured confounders may still exist because our study was an observational 1. To provide the randomization approach to control for unmeasured confounders, a future study that uses Mendelian randomization analysis to rule out reverse causality may be needed.

This study demonstrates BC in TCM is associated with risk of new-onset albuminuria. On the basis of TCM theory, BC is a modifiable factor, which can be adjusted by lifestyle behavior interventions and TCM treatments. Our study provides evidence that deviation from normal BC interacting with glucose control status may affect the development of albuminuria in persons with T2DM. The use of BCQ as a screening tool can help identify patients with T2DM at high risk of developing albuminuria and enable useful clinical decisions to be made.

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