Add-on astragalus therapy for diabetic kidney disease: an open-label randomised controlled trial with responder regression analysis (abridged secondary publication)

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KEY MESSAGES

1. Add-on astragalus treatment for 48 weeks significantly improves kidney function in patients with stage 2 to 3 chronic diabetic kidney disease and macroalbuminuria.
2. The improvement occurs independently of blood pressure, blood glucose, and albuminuria control.

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Introduction

Diabetic kidney disease (DKD) is characterised by a progressive increase in albuminuria and/or a decline in renal function, as measured by glomerular filtration rate (GFR). DKD is the leading cause of end-stage kidney failure necessitating dialysis or transplantation. The pathogenesis of DKD is multifaceted. Conventional treatment strategies include control of blood pressure, blood glucose, and proteinuria. Traditional Chinese medicine (TCM) can further reduce the risk of end-stage kidney failure by 59%.[1] However, the effectiveness of TCM for DKD remains unclear.

Astragalus membranaceus, also known as huang-qi, is a frequently used TCM and dietary supplement for DKD. In a meta-analysis, astragalus more effectively improves renal clearance and reduces albuminuria than routine care; its effects are comparable to those of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[2] In vivo and in vitro evidence suggests that astragaloside IV, an active ingredient of astragalus, can ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis, and interstitial fibrosis by regulating the NF-κB and TGF-β_1 signalling pathways. We previously showed that patients with DKD who received astragalus had a greater likelihood of response. We aimed to evaluate the effect of an add-on astragalus-based TCM in patients with stage 2 to 3 DKD and macroalbuminuria.

Methods

The READY clinical trial recruited 118 patients aged 35 to 80 years from six outpatient clinics and the community who had type 2 diabetes diagnosed at least 5 years prior, repeated estimated GFR of 30 to 90 mL/min/1.73 m^2 over 3 months, and persistent macroalbuminuria confirmed by a urine-to-creatinine ratio (UACR) of ≥34 mg/mmol, and were treated with stable doses of anti-diabetic medication (eg, insulin and angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors) for 12 weeks. The participants were randomly assigned at a 1:1 ratio to receive either 48 weeks of add-on oral astragalus (<30 g/day) or standard medical care. The sample size was calculated based on the intention to control inflation factors for sample size estimation in subsequent studies.[3]

Primary outcomes were the slopes of changes in estimated GFR and UACR between baseline (week 0) and the treatment endpoint (week 48). Secondary outcomes included changes in blood pressure, biomarkers, and adverse events. Blood pressure was measured, and blood and urine samples were collected after an overnight fast (>8

hours). Biomarkers were assessed by an independent medical laboratory. Adverse events were recorded using a patient-completed questionnaire.

Outcomes were analysed using a mixed-effects regression model with an intention-to-treat approach. Hazard ratios for concomitant drug changes and major adverse events were estimated using a Cox proportional-hazards model, adjusted for baseline values of the corresponding outcome. Sensitivity analyses were conducted to test the robustness of the findings.

Results

In total, 118 patients with DKD were randomly assigned to receive either 48 weeks of add-on oral astragalus (n=56) or standard medical care (n=62). Baseline demographics were comparable between the two groups (Table). The mean age was 67.9 years, mean haemoglobin A1c was 7.0%, mean duration of diabetes was 13.4 years, mean estimated GFR was 58.0 mL/min/1.73 m^2, and mean UACR was 124.9 mg/mmol. The slope of estimated GFR decline was 4.58 mL/min/1.73 m^2 per year (95% confidence interval=1.53-7.63), with a smaller decline in astragalus-treated patients (-0.24±1.12 vs -4.16±1.07, P=0.003). Patients who received add-on astragalus had a 3.87 mL/min/1.73 m^2 (95% confidence interval=1.29-6.45) higher endpoint least-squares mean estimated GFR than the standard care controls (57.87 vs 54.00 mL/min/1.73 m^2, P=0.003). There was no significant change in UACR from baseline among astragalus-treated patients; the difference between groups was also not significant (Fig).

Compared with standard care controls, patients who received add-on astragalus had significantly lower systolic blood pressure and gamma-glutamyl transferase levels (although not clinically significant) and significantly higher levels of haemoglobin and urate. Levels of serum potassium, serum lipids, and liver enzymes were comparable between the two groups, as were the rates of hospitalisation and specialist referral, and serum levels of TNF-alpha, TNF receptor 1, TNF receptor 2, MCP-1, VEGF, and TGF-beta1 levels, as well as the urine MCP-1-to-creatinine ratio.

Three (5.4%) serious adverse events occurred in the astragalus group: one spontaneous death, one hospitalisation for pancreatitis with acidosis and acute kidney injury, and one hospitalisation for dyspnoea. In the standard care group, seven (11.3%) serious adverse events occurred: one ischaemic stroke, one hospitalisation for laryngeal obstruction by foreign body, one hospitalisation for hyperkalaemia, one hospitalisation for dyspnoea, one hospitalisation for palpitation, one hospitalisation for injurious fall, and one hospitalisation for hypertension. The difference in the number of serious adverse events between the two groups was not significant.

There were no significant pairwise interactions of treatment effect with age, sex, baseline DKD stage, baseline UACR level, or TCM subgroups. However, a trend toward a better response was observed among patients who were older, had earlier-stage DKD, or exhibited a lower UACR level at baseline. These results remained robust in all sensitivity analyses.

Discussion

Patients with stage 2 to 3 DKD and macroalbuminuria who received add-on astragalus had a significantly higher estimated GFR after 48 weeks, compared with patients who received standard care. The demographics of our cohort were comparable to those of other major trials (eg, DAPA-CKD, CREDENCE). The annual estimated GFR decline (-3.60 to -4.16 mL/min/1.73 m^2 in sensitivity analyses) observed in our standard care controls was consistent with declines recorded in DAPA-CKD (-4 mL/min/1.73 m^2) and CREDENCE (-5 mL/min/1.73 m^2), as well as our previous trial (-4.06 to -4.67 mL/min/1.73 m^2). The estimated GFR decline after add-on astragalus ranged from 1.21 to -0.24 mL/min/1.73 m^2, which is equivalent to the natural estimated GFR decline observed in healthy ageing or general populations. The estimated treatment effect was 4.58 (range, 4.25-5.39) mL/min/1.73 m^2. This magnitude of treatment effect has been associated with a 30% to 80% decrease in subsequent all-cause mortality in other DKD cohorts.[4] Therefore, the effect of astragalus in stabilising kidney function appears to be clinically significant.

Although there was no significant difference in albuminuria change between the two groups, a previous study of atrasentan showed possible kidney protection independent of albuminuria reduction. Nevertheless, analyses of systemic and kidney-specific inflammation- and fibrosis-related biomarkers did not reveal any significant differences. We hypothesise that putative targets of astragalus in DKD could involve the TNF signalling pathway, the hormonal system, and the renin-angiotensin system. Further analyses, including a systematic proteomics analysis, are warranted to delineate the underlying mechanisms of action.

There was minimal attrition in the astragalus group. Most attrition in the standard care group was caused by reluctance to attend follow-up appointments without receiving study medication. Further studies and implementation strategies should consider more user-friendly form of medication (eg, granules, tablets, capsules), decentralised investigation tools (eg, digital monitoring and home-based sampling), and cross-over designs using waitlists or placebo controls.

Our study had several limitations. First, it

TABLE. Patient characteristics at baseline

Variable	All patients (n=118)*	Add-on astragalus (n=56)*	Standard care (n=62)*	P value
Age, y	67.9±7.8	67.2±7.9	68.5±7.8	0.380
Female	43 (36.4)	20 (35.7)	23 (37.1)	0.876
Body mass index, kg/m^2	28.0±4.3	28.1±4.3	27.9±4.3	0.774
Haemoglobin A1c, %	7.0±1.0	7.1±0.9	7.0±1.1	0.753
History of diabetes, y	13.4±7.2	14.1±8.4	12.8±6.0	0.348
Smoking history				0.418
Non-smoker	76 (64.4)	33 (58.9)	43 (69.4)	
Ex-smoker	22 (18.6)	13 (23.2)	9 (14.5)	
Current smoker	20 (17.0)	10 (17.9)	10 (16.1)	
Smoking duration, y	12.0±18.9	14.1±19.7	10.0±18.1	0.236
Blood pressure, mmHg				
Systolic	152.1±19.0	153.3±20.8	151.1±17.3	0.538
Diastolic	77.0±10.0	76.4±10.6	77.5±9.4	0.548
Estimated glomerular filtration rate, mL/min/1.73 m^2	58.0±17.5	57.2±16.6	58.7±18.4	0.624
Urine albumin-to-creatinine ratio, mg/mmol	124.9±2.2	133.7±2.3	117.4±2.0	0.369
Urine albumin-to-creatinine ratio, mg/g	1105.3±19.5	1183.2±20.4	1038.9±17.7	0.369
Cholesterol, mmol/L				
Triglyceride	1.8±0.0	2.0±1.2	1.7±0.9	0.151
High-density lipoprotein	1.1±0.3	1.1±0.3	1.1±0.2	0.798
Low-density lipoprotein	2.5±0.7	2.5±0.6	2.5±0.7	0.904
Haemoglobin, g/dL	13.1±1.6	12.9±1.6	13.2±1.6	0.265
Serum potassium, mmol/L	4.6±0.4	4.6±0.4	4.6±0.4	0.943
Comorbidity				
Diabetic retinopathy	79 (67.0)	36 (64.3)	43 (69.4)	0.559
Coronary artery disease	5 (4.2)	1 (1.8)	4 (6.5)	0.209
History of stroke	7 (5.9)	5 (8.9)	2 (3.2)	0.190
Known peripheral artery disease	2 (1.7)	2 (3.6)	0	0.133
Congestive heart failure	0	0	0	-
Concomitant medication				
Angiotensin-converting enzyme inhibitors	52 (44.1)	21 (37.5)	31 (50)	0.172
Angiotensin receptor blockers	66 (55.9)	35 (62.5)	31 (50)	0.172
Maximally tolerated dose of the above drugs	103 (87.3)	50 (89.3)	53 (85.5)	0.536
Beta-blocker	49 (41.5)	20 (35.7)	29 (46.8)	0.223
Diuretic	15 (12.7)	7 (12.5)	8 (12.9)	0.948
Calcium channel blocker	99 (83.9)	46 (82.1)	53 (85.5)	0.622
Statin	92 (78.0)	46 (82.1)	46 (74.2)	0.298
Aspirin	16 (13.6)	7 (12.5)	9 (14.5)	0.749
Metformin	106 (89.8)	52 (92.9)	54 (87.1)	0.301
Sulfonylurea	68 (57.6)	28 (50.0)	40 (64.5)	0.111
Insulin	22 (18.6)	12 (21.4)	10 (16.1)	0.460
SGLT2i	15 (12.7)	8 (14.3)	7 (11.3)	0.626
DPP-4i	37 (31.4)	16 (28.6)	21 (33.9)	0.536
GLP-1 RA	4 (3.4)	4 (7.1)	0	0.032

* Data are presented as mean ± standard deviation or No. (%) of patients

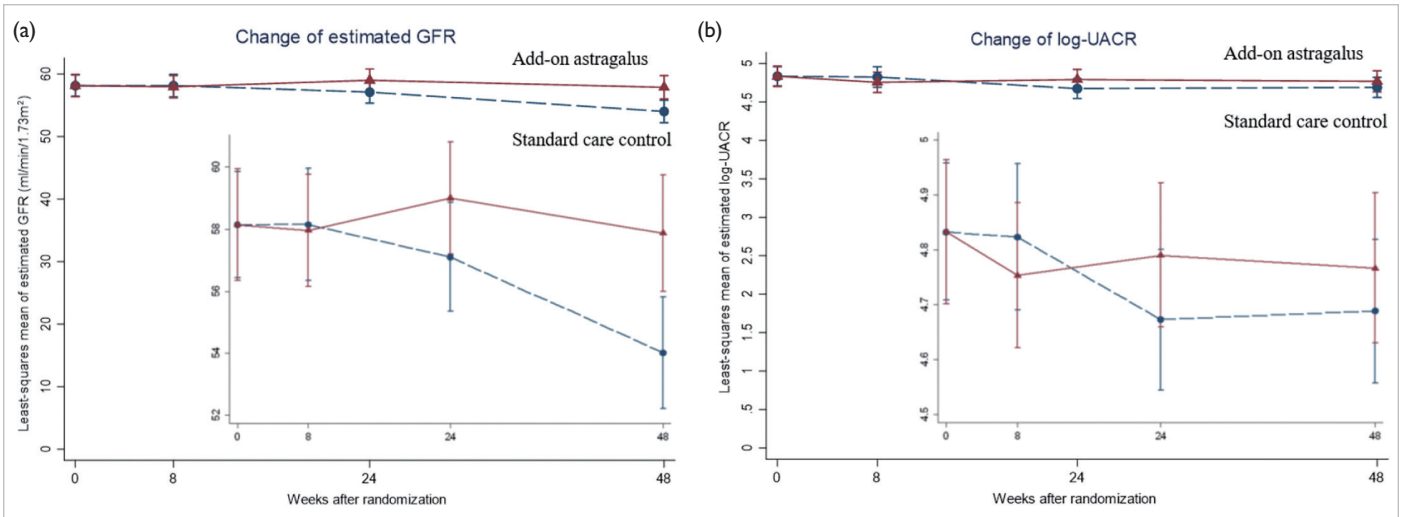

FIG. (a) The mixed-effects regression model with an intention-to-treat approach shows that the slope of estimated glomerular filtration rate (GFR) decline was 4.58 mL/min/1.73 m^2 per year (95% confidence interval=1.53-7.63), with a smaller decline in astragalus-treated patients (-0.24±1.12 vs -4.16±1.07, P=0.003). (b) There is no significant change in the urine albumin-to-creatinine ratio (UACR) from baseline among astragalus-treated patients, and the difference between the two groups was not significant

was not double-blind placebo-controlled because placebos are not routinely used in pragmatic trials and do not exert favourable clinical effect on continuous laboratory outcomes.[5] To minimise potential placebo effects, we assessed objective primary outcomes to reduce detection bias, adjusted for blood pressure control in sensitivity analyses, and analysed the intention-to-treat population via data tracking and sensitivity analyses on censoring criteria to decrease attrition bias. Second, our study had a relatively small sample size and short duration due to limited funding. We recruited patients with stage 2 to 3 DKD and macroalbuminuria who represent a more homogenous group with faster disease progression and are therefore more likely to benefit from add-on astragalus treatment. Nevertheless, large-scale trials are needed to determine the long-term effectiveness of astragalus treatment beyond 48 weeks.

Conclusion

Add-on astragalus treatment for 48 weeks significantly improved kidney function and thus could be a useful strategy in the multidisciplinary management of DKD. We recommend the inclusion of TCM for DKD in the public health system.

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Disclosure

The results of this research have been previously published in:

1. Chan KW, Kwong ASK, Tsui PN, et al. Add-on astragalus in type 2 diabetes and chronic kidney disease: a multi-center, assessor-blind, randomized controlled trial. Phytomedicine 2024;130:155457.

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