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Clinical Observation of Influence of Shibaweikeziliniaowan on Inflammatory Cytokines in Type 2 Diabetic Kidney Disease

Cong Peng[1], Wenchang Zhang[2], Lijun Dai[2], Deqing[2], Cirenlamu[2], Bianzhen[2]

[1]Wuhan No.1 Hospital, Wuhan 430022, Hubei, China

[2]Luozha Peoples Hospital, Luozha 851200, Tibet Autonomous Region, China

Abstract

Objective: To evaluate the impact of Shibaweikeziliniaowan on inflammatory cytokine profiles in patients with type 2 diabetic kidney disease (DKD). *Methods:* Sixty DKD patients were randomized equally into a control group (n=30) and a treatment group (n=30). Both cohorts received standard care and oral Dapagliflozin. The treatment group additionally received Shibaweikeziliniaowan. The intervention lasted eight weeks. Parameters measured pre- and post-treatment included urine microalbumin (mA1b), Urinary Albumin Creatinine Ratio (UACR), glycosylated hemoglobin A1c (HbA1c), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1). *Results:* Post-treatment, both groups exhibited significant reductions in mA1b, UACR, TNF-α, and IL-1 levels ($P < 0.05$, $P < 0.01$). Inter-group comparisons revealed statistically significant differences favoring the treatment group ($P < 0.05$). *Conclusion:* Shibaweikeziliniaowan demonstrates efficacy in lowering inflammatory cytokines, suggesting a renal protective role in DKD management.

Keywords

Type 2 diabetes mellitus (T2DM)
Diabetic kidney disease (DKD)
Shibaweikeziliniaowan
Inflammation
Tibetan medicine
Dapagliflozin

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1. Introduction

China harbors an estimated 129 million individuals with diabetes, with type 2 diabetes mellitus (T2DM) constituting over 90% of cases [1]. Diabetic kidney disease (DKD) represents a prevalent chronic microvascular complication of diabetes. In developed nations, DKD is the primary contributor to end-stage renal disease (ESRD) and a leading cause of mortality among diabetes (DM) patients [1–2]. The pathogenesis of DKD involves multiple factors. Growing evidence underscores the significant role of inflammatory processes in DKD initiation and progression [3]. Tibetan medicine, with a history exceeding two millennia, forms an integral part of traditional medical systems globally. Shibaweikeziliniaowan, a classical Tibetan formula documented for over four centuries in diabetes treatment. The study aimed to assess

the renal protective effects of Shibaweikeziliniaowan in type 2 diabetes mellitus (T2DM) patients with DKD and its influence on inflammatory cytokines TNF-α and IL-1.

2. Materials and methods

2.1. General information

Sixty patients diagnosed with T2DM and DKD were recruited from the outpatient and inpatient departments of Luozha People's Hospital (Tibet Autonomous Region) and Wuhan No.1 Hospital between March 2022 and October 2024. Using the parallel randomization method, participants were allocated 1:1 into a control group (n=30) and a treatment group (n=30). The control group comprised 15 males and 15 females, aged 39–79 years (mean 59.65±10.06), with diabetes duration ranging from 4 to 20 years (mean 9.85±4.56). The treatment group also included 15 males and 15 females, aged 48–77 years (mean 62.25±7.42), with a diabetes duration of 3–20 years (mean 9.75±4.01). Baseline characteristics, including sample size, gender distribution, age, and diabetes duration, showed no significant inter-group differences ($P > 0.05$), indicating comparability (**Table 1**).

2.2. Diagnostic criteria

The diagnosis adhered to the 1999 WHO criteria for diabetes and the 2020 Chinese Guidelines for Type 2 Diabetes Prevention and Treatment [4]. Inclusion required: confirmed T2DM history; exclusion of acute diabetic complications; persistent UACR ≥30 mg/g on different days; and/or documented eGFR decline; with other causes of renal impairment ruled out.

2.3. Treatment methods

Control group: Received standard diabetes management encompassing patient education, dietary guidance, exercise prescription, and glucose-lowering medication. Comorbidities were addressed with appropriate pharmacotherapy. Additionally, Dapagliflozin tablets (produced by AstraZeneca Pharmaceutical Co. Ltd., National Drug Approval Number J20170040) were administered orally (10 mg once daily in the morning).

Treatment group: Received the same standard management and Dapagliflozin as the control group, plus oral Shibaweikeziliniaowan (produced by Tibet Ganlu Tibetan Medicine Co. Ltd., National Drug Approval Number Z54020076). The dosage was 3 pills twice daily (morning and evening) with warm water.

The treatment duration for both groups was 8 weeks (equivalent to two consecutive 4-week courses).

2.4. Observation indicators

Parameters assessed pre- and post-treatment in both groups included: weight (WT), waist circumference (WC), body mass index (BMI), fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), glycated hemoglobin (HbA1c), urinary microalbumin (mA1b), urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR, calculated using the MDRD formula), serum tumor necrosis factor alpha (TNF-α) (quantified by enzyme-linked immunosorbent assay, ELISA), and serum IL-1 (quantified by ELISA).

2.5. Statistical analysis

Data are presented as [Mean ± SD (mean ± standard deviation)] mean ± standard deviation. Experimental data are expressed as [Mean ± SD (mean ± standard deviation)]. SPSS 16.0 software was utilized for statistical analysis. Between-group comparisons for continuous variables employed independent samples t-tests, while within-group changes used paired t-tests. Categorical data were analyzed using Chi-square (x^2) tests. Statistical significance was defined as $P < 0.05$.

Table 1. Comparison of general data between the two groups of patients (mean ± SD)

Group	Case	Gender		Age (year)	Duration of diabetes (year)
		Male	Female		
Control	30	15	15	59.65±10.06	9.85±4.56
Treatment	30	15	15	62.25±7.42▲	9.75±4.01▲

Note: Compare with control group: ▲$P > 0.05$, ■$P < 0.05$, ●$P < 0.01$

3. Results

3.1. Comparison of changes in the general conditions of the two groups of patients before and after treatment

Baseline WT, WC, and BMI showed no significant difference between groups ($P > 0.05$). Post-treatment, both groups demonstrated significant reductions in these parameters compared to baseline ($P < 0.01$). However, no statistically significant difference was observed between the two groups post-treatment ($P > 0.05$) (**Table 2**).

3.2. Comparison of changes in blood glucose (BG) and glycosylated hemoglobin (HbA1c) levels between the two groups before and after treatment

Baseline FPG, PPG, and HbA1c levels were comparable between groups ($P > 0.05$). After 8 weeks, both groups achieved significant reductions in all glycemic parameters compared to baseline ($P < 0.01$). Nevertheless, the magnitude of improvement did not differ significantly between the control and treatment groups ($P > 0.05$) (**Table 3**).

3.3. Comparison of changes in albuminuria levels between the two groups before and after treatment

Baseline mA1b and UACR levels were similar between groups ($P > 0.05$). Treatment led to significant decreases in both mA1b and UACR within each group ($P < 0.01$). Crucially, the reduction in mAlb and UACR was significantly greater in the treatment group compared to the control group ($P < 0.05$) (**Table 4**).

Table 2. Comparison of changes in general conditions of the two groups of patients before and after treatment (mean ± SD)

Group		Wt (kg)	WC (cm)	BMI
Control (n = 30)	before	81.53±8.46	94.39±9.25	26.47±2.62
	after	79.17±8.59°	92.16±8.96°	24.31±1.88°
Treatment (n = 30)	before	82.09±8.92$^{\blacktriangle}$	94.83±10.05$^{\blacktriangle}$	26.78±2.67$^{\blacktriangle}$
	after	78.32±7.48$^{\blacktriangle\circ}$	91.84±9.38$^{\blacktriangle\circ}$	24.03±1.74$^{\blacktriangle\circ}$

Note: Compare with control group: $^{\blacktriangle}P > 0.05$, $^{\blacksquare}P < 0.05$, $^{\bullet}P < 0.01$; Compare with before treatment: $^{\triangle}P > 0.05$, $^{\square}P < 0.05$, $^{\circ}P < 0.01$

Table 3. Comparison of changes in BG and HbA1c levels between the two groups of patients before and after treatment (mean ± SD)

Group		FPG (mmol/L)	PPG (mmol/L)	HbA1c (%)
Control (*n* = 30)	before	12.67±4.95	18.47±9.12	9.35±1.48
	after	6.98±1.83°	9.14±3.08°	7.07±0.92°
Treatment (*n* = 30)	before	13.16±5.45$^{\blacktriangle}$	19.15±9.36$^{\blacktriangle}$	9.51±1.63$^{\blacktriangle}$
	after	6.75±1.49$^{\blacktriangle\circ}$	8.84±2.73$^{\blacktriangle\circ}$	6.95±0.88$^{\blacktriangle\circ}$

Note: Compare with control group: $^{\blacktriangle}P > 0.05$, $^{\blacksquare}P < 0.05$, $^{\bullet}P < 0.01$; Compare with before treatment: $^{\triangle}P > 0.05$, $^{\square}P < 0.05$, $^{\circ}P < 0.01$

Table 4. Comparison of changes in albuminuria levels between the two groups of patients before and after treatment (mean ± SD)

Group		mA1b (mg/L)	UACR (mg/g)	eGFR (mL·min^{-1}· (1.73m²)$^{-1}$)
Control (n = 30)	before	134.81±50.23	89.46±27.32	91.31±28.25
	after	76.41±29.35°	47.43±22.53°	94.96±31.17$^{\triangle}$
Treatment (n = 30)	before	137.26±46.87$^{\blacktriangle}$	92.15±31.93$^{\blacktriangle}$	86.57±29.46$^{\blacktriangle}$
	after	59.38±27.49$^{\circ\blacksquare}$	36.87±15.18$^{\circ\blacksquare}$	93.24±26.48$^{\triangle\blacktriangle}$

Note: Compare with control group: $^{\blacktriangle}P > 0.05$, $^{\blacksquare}P < 0.05$, $^{\bullet}P < 0.01$; Compare with before treatment: $^{\triangle}P > 0.05$, $^{\square}P < 0.05$, $^{\circ}P < 0.01$

3.4. Comparison of changes in TNF-α and IL-1 levels between the two groups before and after treatment

Baseline TNF-α and IL-1 concentrations showed no inter-group difference ($P > 0.05$). Post-treatment, both TNF-α and IL-1 decreased significantly in both groups relative to baseline levels ($P < 0.01$). Importantly, the treatment group exhibited a significantly greater reduction in both TNF-α and IL-1 levels compared to the control group ($P < 0.01$) (**Table 5**).

Table 5. Comparison of changes in TNF-α and IL-1 levels between the two groups of patients before and after treatment (mean ± SD)

Group		TNF-α(ng/L)	IL-1 (ng/L)
Control (n = 30)	before	8.97±2.53	15.78±2.97
	after	6.96±1.25°	11.34±2.17°
Treatment (n = 30)	before	9.17±2.34$^{\blacktriangle}$	16.82±3.14$^{\blacktriangle}$
	after	5.84±0.92$^{\circ\bullet}$	9.36±2.52$^{\circ\bullet}$

Note: Compare with Control group: $^{\blacktriangle}P > 0.05$, $^{\blacksquare}P < 0.05$, $^{\bullet}P < 0.01$; Compare with before treatment: $^{\triangle}P > 0.05$, $^{\square}P < 0.05$, $^{\circ}P < 0.01$

3.5. Safety observation

No significant adverse events were reported in either group. All participants tolerated the treatments well and completed the study; no withdrawals occurred due to adverse reactions. Pre- and post-treatment assessments (complete blood count, urinalysis, stool analysis, liver/kidney function tests, electrocardiogram) indicated that all monitored parameters remained within normal ranges throughout the study period for both groups, with no clinically significant abnormalities detected.

4. Discussion

Recent landmark cardiovascular and renal outcome trials have established that sodium-glucose cotransporter-2 inhibitors (SGLT2is), including Dapagliflozin, confer significant cardiorenal protection by reducing risks of adverse cardiovascular and renal events [5–8]. Dapagliflozin can lower UACR and has the effects of delaying the progression of heart and kidney diseases and protecting the heart and kidney organs. The 2023 ADA guidelines advocate SGLT2i as preferred agents for T2DM patients with CKD or high cardiorenal risk to mitigate ESRD risk, and for patients with diabetes and heart and kidney diseases or those at risk of heart and kidney diseases, SGLT2i should be the preferred choice. Therefore, the authors selected dapagliflozin tablets as one of the main treatment drugs in this study.

The Shibaweikeziliniaowan is composed of Chebulae Fructus, Safflower, Round Cardamom, Zhaxun Paste, Folium Symplocos, Sticklac, Tibetan Madder, Emblic Leafflower Fruit, Turmeric, Barberry Bark, Puncturevine Caltrop Fruit, Gold Mica, Chinese Juniper Resin, Small Umbrella Saxifrage, Baxiaga, Sword Bean, Bear Bile Powder, Artificial Cow Bezoar, etc. It has the effects of benefiting the kidney and consolidating essence, and diuresis. It is used for kidney diseases, pain in the waist and kidney, frequent urination, turbid urine, diabetes, premature ejaculation, etc. It is a traditional classic Tibetan medicine for treating diabetes [9]. Animal experiments have shown that the Shibaweikeziliniaowan can reduce urinary protein and has protective effects on the kidneys of diabetic rats [10]. Some studies have found that the Shibaweikeziliniaowan can effectively control blood sugar levels and reduce adverse reactions [11–13]. The findings (consistent with limited sample size considerations) showed no significant additive effect of Shibaweikeziliniaowan on HbA1c reduction beyond Dapagliflozin.

Microalbuminuria serves as an early marker of kidney damage and also an indicator of mortality risk and progression of DKD. Renal biopsy pathological examination is the gold standard for diagnosing DKD, but it is not recommended for routine use. Clinically, random urine UACR measurement is generally recommended. An increase in UACR is closely related to decreased eGFR, cardiovascular events, and increased mortality risk. The study demonstrates that adjunctive Shibaweikeziliniaowan therapy significantly reduces mA1b and UACR levels in DKD patients compared to Dapagliflozin alone ($P < 0.05$), indicating a specific benefit in ameliorating albuminuria and potentially preserving renal function.

The complex pathogenesis of DKD involves significant contributions from inflammation [14]. Hyperglycemia promotes protein glycation, stimulating macrophage release of TNF-α and IL-1. TNF-α

exacerbates oxidative stress and glomerular permeability, impairing the filtration barrier and reducing GFR [15]. IL-1 can increase the permeability of endothelial cells, change the renal hemodynamic state, stimulate the proliferation of glomerular mesangial cells and fibroblasts, and participate in the occurrence and development of DKD [16].

The key finding is that Shibaweikeziliniaowan significantly suppresses circulating levels of TNF-α and IL-1 in DKD patients, with reductions markedly exceeding those seen with Dapagliflozin monotherapy ($P < 0.01$). This potent anti-inflammatory effect of Shibaweikeziliniaowan likely constitutes a key mechanism underpinning its observed benefits in reducing albuminuria and protecting renal function in DKD.

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Disclosure statement

The authors declare no conflict of interest.

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