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Case Report

Treatment of Patient with Diabetic Nephropathy using Chinese Prescription Kangen-karyu

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Abstract

Diabetic nephropathy is among the main causes of end-stage renal disease worldwide. The mainstay of diabetic nephropathy has been the management of hyperglycemia, blood pressure, and proteinuria using hypoglycemic agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. The utilization of traditional Chinese medicine to diabetic nephropathy has received increasing attention due to its wide availability, weak side-effects, and proven therapeutic mechanisms and benefits. In this paper, we report the case of a 54-year-old patient with a 10-year history of diabetes, who showed a marked improvement in diabetic nephropathy on the administration of 7.5 g of Kangen-karyu extract per day. After 6 months, estimated glomerular filtration rate had increased from 95.8 to 104.2 ml/min/1.73 m^2. Urinary protein and albumin levels decreased following administration. At that time, the somatic and subjective symptoms had partially disappeared. Herein, we present and discuss the evidence supporting the use and mechanism of Kangen-karyu extract against diabetic nephropathy based on the patient.

Keywords: Diabetic nephropathy; Traditional Chinese medicine; Kangen-karyu; Case report

1. Introduction

Diabetic nephropathy is one of the major microvascular complications of diabetes, and is among the main causes of end-stage renal disease worldwide [1]. Multiplication factors have been associated with the pathogenesis of diabetic nephropathy, including hyperglycemia-induced production of advanced glycation end products and reactive oxygen species [2]. A number of new therapies have been developed from experimental studies based on the pathogenic factors of diabetic nephropathy such as intensive glycemic control, precise hypertension control, renin-angiotensin-aldosterone system blockade, lifestyle modifications, including exercise and energy-restricted diet, and numerous novel agents [3], but the rate of end-stage renal disease due to diabetic nephropathy still remains high in spite of the widespread application of numerous therapeutic approaches focusing on the management of factors mentioned above [4-6]. Therefore, interventions are urgently required to effectively delay the progression of diabetic nephropathy.

Herbal medicines have gained significant importance over the last few decades, and the demand to use natural products for the treatment of diabetes is growing worldwide. However, the mechanisms of many plant species remain to be scientifically established, especially those with renoprotective effects [7]. Traditional Chinese medicine has also been used for a long time in the treatment of diabetes and its complications [8]. Traditional Chinese medicine has many advantages over conventional medical approaches for the prevention of diabetic complications because of reduced toxicity and/or side effects [9-11].

We have been investigating the multi-target therapeutic effects of traditional Chinese medicine for several human diseases using pre-clinical animal experiments. Kangen-karyu (Guan-Yuan-Ke-Li in Chinese), traditional Chinese herbal formula modified Kan-shin No. 2 (Guan-xin No. 2 in Chinese), was developed in Japan [12]. Kan-shin No. 2 was originally formulated in traditional Chinese medicine to cure blood stasis, and it has been used to treat thrombosis, myocardial infarction, and cerebral infarction in China [13]. Kangen-karyu is composed of six herbal formulas (Salviae Miltiorrhizae Radix, Cnidii Rhizoma, Paeoniae Radix, Carthami Flos, Aucklandiae Radix, and Cyperi Rhizoma, as shown in Table 1), and has been clinically used as a treatment for cardiovascular disorders, including angina pectoris and cerebrovascular diseases. Many studies demonstrated that Kangen-karyu exhibited favorable biological activity such as anti-aging effects, platelet aggregation inhibition, hypertension suppression, anti-dyslipidemia, aiding the recovery of learning and memory impairment induced by senescence, neuroprotection, and an anti-dementia effect in animal experiments [14-21]. Although studies have proposed the pharmacological functions of Kangen-karyu to treat various diseases, we previously reported evidence supporting its preventive and/or therapeutic potential against diabetes-induced renal damage using *db/db* mice, a type 2 diabetic animal model [22-25]. The results of our previous study provide important evidence that Kangen-karyu exerts a renoprotective effect against the development of diabetic nephropathy. They also provide scientific evidence to demonstrate the efficacy of traditional Chinese medicine at multi-system levels.

On the basis of the findings obtained from these fundamental studies, we administered Kangen-karyu to a diabetic nephropathy patient, and evaluated its treatment-based usefulness.

Common Name	**Botanical Name**	**Family Name**
Salviae Miltiorrhizae Radix	*Salvia miltiorrhiza* BUNGE	Labiatae
Cnidii Rhizoma	*Cnidium officinale* MAKINO	Umbelliferae
Paeoniae Radix	*Paeonia lactiflora* PALLAS	Paeoniaceae
Carthami Flos	*Carthamus tinctorius* L.	Compositae
Aucklandiae Radix	*Aucklandia lappa* DCNE.	Compositae
Cyperi Rhizoma	*Cyperus rotundus* L.	Cyperaceae

Table 1: Composition of Kangen-karyu.

2. Case Presentation

A 54-year-old woman (weight, 90.0 kg; height, 164.2 cm) with diabetes mellitus, hypertension, dyslipidemia, and diabetic nephropathy presented at Shinseikai Toyama Hospital (Toyama, Japan). She was previously diagnosed with type 2 diabetes at another hospital, but had not received oral hypoglycemic agents from 2008 until 2016. Her hemoglobin A1c (HbA1c) levels were subsequently found to be poorly controlled and therefore insulin injection therapy was recommended. The patient subsequently modified her lifestyle and continues to take this medication. However, in March 2018, diabetic nephropathy corresponding to stage 2 chronic kidney disease (CKD) was detected in a routine medical checkup. She presented at our hospital on April 6, 2018, seeking to recover her functional level with herbal medicine.

At present, HbA1c was 7.6%, showing poorly controlled blood glucose. The estimated glomerular filtration rate (eGFR) was 95.8 ml/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation [26], and this corresponded to a serum creatinine level of 0.51 mg/dl. The urinary protein and albumin levels were 103 and 35.7 mg/g creatinine, respectively, indicating stage 2 CKD (Table 2).

Parameter	**Pre**	**Post**
HbA1c (%)	7.6	7.5
Serum creatinine (mg/dl)	0.51	0.46
eGFR (ml/min/1.73 m^2)	95.8	104.2
Urinary protein (mg/g creatinine)	103	26
Urinary albumin (mg/g creatinine)	35.7	11.3

Table 2: Laboratory data on administration of Kangen-karyu for 6 months.

Assessment of somatic and subjective symptoms involved completing a series of questionnaires at the beginning and the end of the study. The symptom checklist included the following symptoms: dizziness and palpitation, stiff shoulder and headache, coldness of the limbs and fatigability, mental stress, sleeping disorder, tension of the stomach and abdomen, pain, numbness of the waist and body, dark circles around eyes and lip symptoms, stains on face, aza skin, and tongue symptoms. The change in each symptom was assessed with a 3-point rating scale: "marked improvement" was 5 points, "improvement" was 4 points, and "slight improvement" was 2 points. The assessment of global improvement rating of subjective symptoms simply involved the addition of points.

The patient continued to receive existing treatments: hypoglycemic agents (metformin: 750 mg/day, ipragliflozin: 50 mg/day), an antihypertensive agent (termisartan: 20 mg/day), antilipidemic agent (atrovastatin: 5 mg/day), and antacid-laxative (magnesium oxide: 990 mg/day). In addition, Kangen-karyu extract (7.5 g/day) was administered three times a day until October 15, 2018.

During the administration of Kangen-karyu extract, regular tests were performed to assess its effect on diabetic nephropathy. As shown in Table 2, eGFR was subsequently increased from 95.8 to 104.2 ml/min/1.73 m^2 at the 6-month follow-up. The urinary protein level decreased from 103 to 26 mg/g creatinine. Urinary albumin excretion also fell to 11.3 mg/g creatinine. Other parameters such as HbA1c, creatinine, and systolic and diastolic blood pressures showed slight differences in treatment with Kangen-karyu extract during the follow-up period (Table 2). At that time, the somatic and subjective symptoms such as stiff shoulder, headache, coldness of the limbs, and fatigability had disappeared. After 6 months, the score using the questionnaire had decreased from 45 to 35 at follow-up. There was, however, no significant change in the physical characteristics on the administration of Kangen-karyu, as shown in Table 3.

Parameter	**Pre**	**Post**
Body weight (kg)	90	89.6
Soft lean mass (SLM) (kg)	48.6	48.3
Skeletal muscle mass (SMM) (kg)	28.4	27.8
Body fat mass (BFM) (kg)	38.4	38.3
Body mass index (BMI) (kg/m^2)	33.4	33.2
Percent body fat (PBF) (%)	42.7	42.8
Visceral fat area (VFA) (cm^2)	179	181
Systolic blood pressure (mmHg)	113	122
Diastolic blood pressure (mmHg)	74	66

Table 3: Physical characteristics on administration of Kangen-karyu for 6 months.

3. Discussion

Diabetic nephropathy is a clinical syndrome characterized by the outbreaks of persistent albuminuria that should be confirmed on at least two occasions separated by 3-6 months, with a continuous decline in GFR, and increased arterial blood pressure. Microalbuminuria is considered the first sign indicating the onset of diabetic nephropathy [27]. The stages of CKD are mainly based on measured or eGFR. There are five stages, but the kidney function is normal in stage 1 and minimally reduced in stage 2 [26, 28, 29]. Treatment of diabetic nephropathy should be devised based on the clinical stage of the disease process. In the present case, the patient's eGFR corresponded to stage 2 CKD, which was indicative of chronic renal failure. In spite of favorable glycemic control, blood pressure management, and lipid management, there was no improvement in the disease status. Therefore, the patient gave her consent to experimentally receive herbal medication to improve her condition.

We chose Kangen-karyu extract for the following reasons. Kangen-karyu was developed by the modification of herbal constituents of Kan-shin No. 2 in Japan [12]. It has been clinically used as a treatment for cardiovascular diseases. Kangen-karyu has received much attention as a source of new therapeutic agents based on pre-clinical animal experiments related to various human diseases [14-21]. To add to these findings, we reported evidence supporting its preventive and/or therapeutic potential against diabetes-induced renal damage [22-25]. The administration of Kangen-karyu reduced the increased serum glucose level in type 2 diabetic mice, and decreased the elevated oxidative and inflammatory biomarkers in the serum and kidney. The increased serum creatinine and urea nitrogen levels, which reflect renal dysfunction, and renal structural changes, representing glomerular enlargement, were significantly improved by Kangen-karyu administration. The results of our previous study suggest that Kangen-karyu improves diabetes-induced renal damage through pleiotropic effects on the development of diabetic nephropathy.

Diabetic nephropathy is among the main causes of end-stage renal disease [30]. Multiple factors such as metabolic and hemodynamic alterations, oxidative stress, activation of the renin-angiotensin system, and inflammation may interdepend on various levels, causing a progressive nephropathy [31]. In the present case, there was an improvement in diabetic nephropathy following the administration of Kangen-karyu extract for 6 months, although we cannot come to a conclusion on the pathway that was affected. Most notably, urinary protein and albumin levels were recovered by Kangen-karyu administration for 6 months to near-normal levels. eGFR increased to 104.2 ml/min/1.73 m^2 within the normal range. In addition, the score using the questionnaire was decreased during the follow-up. Herein, we present a therapeutic option of Kangen-karyu in the early phase of diabetic nephropathy.

Because of the short follow-up period, administration of Kangen-karyu extract cannot be assured of the long-term effects of this patient on progressive nephropathy. However, this case provides strong evidence to support the administration of Kangen-karyu extract as a therapeutic agent to prevent the progression of diabetic nephropathy and improve the renal function, especially in the early stages of the disease.

Most traditional Chinese medicine treatments are formulated to contain a mixture of herbs to enhance the curative efficacy and also reduce the side-effects; it is relatively difficult to identify a single component of the formula that is the primary reason for the effectiveness of therapy against diabetic nephropathy. In summary, traditional Chinese medicine is widely applicable and good efficacy in the treatment of diabetic nephropathy.

4. Conclusion

We report evidence of use as an adjunctive therapy for Kangen-karyu in a patient with diabetic nephropathy corresponding to stage 2. Kangen-karyu exhibits good efficacy in the treatment of diabetic nephropathy.

Conflict of Interest

The authors declare that they have no competing interests.

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