

## Efficacy of Chinese prescription Kangen-karyu for patient with metabolic syndrome

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**SUMMARY** Metabolic syndrome is a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus. The risk factors include hypertension, dyslipidemia, hyperglycemia, and central obesity. Various diagnostic criteria have been proposed by different organizations over the past decade. The utilization of traditional Chinese medicine to treat metabolic syndrome has received increasing attention due to its wide availability. In this paper, we report the case of a 68-year-old patient with hypertension, hypercholesterolemia, borderline diabetes, and obesity, who showed an improvement in metabolic syndrome on the administration of 7.5 g of Kangen-karyu extract per day. After 6 months, the levels of serum total cholesterol, low-density lipoprotein-cholesterol, triglycerides, hemoglobin A1c were decreased. The abdominal circumference and body weight were decreased following administration. At that time, the somatic and subjective symptoms had partially disappeared. Herein, we present and discuss the evidence supporting the use of Kangen-karyu extract against metabolic syndrome.

**Keywords** Metabolic syndrome, traditional Chinese medicine, Kangen-karyu, case report

### 1. Introduction

Metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease and diabetes. These factors include dysglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol levels, and obesity (particularly central adiposity). Metabolic syndrome is now both a public health and clinical problem. In the public health arena, more attention must be given to modification of lifestyles of the general public of all nations to reduce obesity and increase physical activity. Although therapeutic lifestyle modification is first-line therapy for the metabolic syndrome and thus deserves initial attention, drug therapy may be necessary in many patients to achieve recommended goals (1-3).

Major pharmacological interventions include management of dyslipidemia with statins, decreasing prothrombotic risk with antiplatelet drugs, and the use of insulin sensitizers to decrease the risk of diabetes. There is no single drug therapy for metabolic syndrome and currently available pharmacotherapy and associated comorbidities necessitate prolonged use of multiple medications, which is challenging for patients due to

polypharmacy and reduced compliance (2). Thus, there is growing interest in the use of natural products to reduce the risk and progression of metabolic syndrome.

Kangen-karyu (Guan-Yuan-Ke-Li), a crude drug developed from a traditional Chinese prescription consisting of six herbs (*Salviae Miltiorrhizae Radix*, *Cnidii Rhizoma*, *Paeoniae Radix*, *Carthami Flos*, *Aucklandiae Radix*, and *Cyperii Rhizoma*, shown in Table 1), has been clinically used as a treatment for cardiovascular diseases, such as angina pectoris and cerebrovascular diseases. Kangen-karyu shows biological activity, such as an anti-aging effect, the inhibition of platelet aggregation, hypotensive effect, and the recovery of learning and memory impairment induced by senescence (4-7). In our previous studies, Kangen-karyu showed favorable ameliorative effects on signs of fructose-induced metabolic syndrome, such as hyperglycemia, hyperlipidemia, and hypertension, through the reduction of triglyceride and cholesterol levels with the regulation of hepatic sterol regulatory element-binding protein-1 (SREBP-1) expression, and also exhibited protective effects against diet-induced hypercholesterolemia in rats (8,9). We also reported the beneficial effect of Kangen-karyu on dyslipidemia in

**Table 1. Composition of Kangen-karyu**

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

a mouse model of type 2 diabetes (10). These results suggest that Kangen-karyu can ameliorate metabolic syndrome.

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

## 2. Case report

This study was conducted according to the ethical guidelines for epidemiological research set by the Japanese Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour, and Welfare. Ethical approval was obtained from the Clinical Research Ethics Committees of Shinseikai Toyama Hospital. Written informed consent was obtained from the patient at the time of enrollment for the collection of clinical information and biosamples for archival and research purposes. A 68-year-old man with hypertension, hypercholesterolemia, and borderline diabetes was previously diagnosed with metabolic syndrome at Shinseikai Toyama Hospital (Toyama, Japan). From December 2017, the patient subsequently modified his lifestyle and continued to receive existing treatments: antihypertensive agents (amlodin: 5 mg/day, azilva: 20 mg/day), an antilipidemic agent (lipitor: 5 mg/day), and agents for reflux esophagitis (takepron: 30 mg/day, gasmotin: 15 mg/day). However, he presented to our hospital on February 13, 2019, seeking to recover his functional level with herbal medicine. Kangen-karyu extract (7.5 g/day) was administered three times a day until August 30, 2019.

Before Kangen-karyu extract administration, his initial anthropometric measurements included a body weight of 82.6 kg with a height of 165 cm, a body mass index (BMI) of 30.3 kg/m<sup>2</sup>, and an abdominal circumference of 105.8 cm which classified him as obese. His systolic/diastolic blood pressure was 133/85 mmHg (Table 2). Hemoglobin A1c (HbA1c) was 7.3%, showing poorly controlled blood glucose. The levels of serum lipids were as follows: total cholesterol: 230 mg/dL, low-density lipoprotein (LDL)-cholesterol: 142 mg/dL, LDL-cholesterol/high-density lipoprotein (HDL)-cholesterol: 2.3, and triglycerides: 353 mg/dL, indicating metabolic syndrome (Table 3).

Assessment of somatic and subjective symptoms

involved completing a series of questionnaires at the beginning and end of the study. The symptom checklist included the following symptoms: dizziness and palpitation, stiff shoulders 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, mottled 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. At the same time, the tongue was evaluated based on factors such as the color, coating, and sublingual vein.

The patient continued to receive antihypertensive agents, the antilipidemic agent, and agents for reflux esophagitis. In addition, Kangen-karyu extract (7.5 g/day) was administered three times a day until August 30, 2019.

During the administration of Kangen-karyu extract, physical tests were performed to assess its effect on metabolic syndrome. As shown in Table 2, BMI and abdominal circumference showed slight decreases on treatment with Kangen-karyu extract. The total cholesterol level decreased from 230 to 178 mg/dL at the 6-month follow-up. The elevated level of LDL-cholesterol also reduced from 142 to 91 mg/dL. In addition, oral administration of Kangen-karyu extract reduced the increased serum triglyceride and HbA1c levels. Other parameters such as hepatic and renal function parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea nitrogen, and creatinine] were not affected by the administration of Kangen-karyu extract, as shown in Table 3. At that time, the somatic and subjective symptoms such as stiff shoulders, headache, feeling heavy in the head, and mottled skin had improved. After 6 months, the score using the questionnaire had decreased from 51 to 41 at follow-up. There was a slight improvement in the tongue coating on the administration of Kangen-karyu.

## 3. Discussion

The first formalized definition of metabolic syndrome was proposed in 1998 by a consultation group on the

**Table 2. Physical characteristics on administration of Kangen-karyu for 6 months**

Parameter	Pre	Post
Body weight (kg)	82.6	80.6
Height (cm)	165	165
BMI (kg/m <sup>2</sup> )	30.3	29.6
Abdominal circumference (cm)	105.8	101.8
Systolic blood pressure (mmHg)	133	131
Diastolic blood pressure (mmHg)	85	83

**Table 3. Laboratory data on administration of Kangen-karyu for 6 months**

Parameter	Pre	Post
HbA1c (%)	7.3	6.6
Total cholesterol (mg/dL)	230	178
LDL-cholesterol (mg/dL)	142	91
LDL-cholesterol/HDL-cholesterol	2.3	1.7
Triglycerides (mg/dL)	353	269
AST (U/L)	15	12
ALT (U/L)	19	18
Urea nitrogen (mg/dL)	13.5	14.7
Creatinine (mg/dL)	0.54	0.60

definition of diabetes for the World Health Organization (WHO) (11). This group emphasized insulin resistance as the major underlying risk factor and the necessity of evidence of insulin resistance for diagnosis. A diagnosis of the syndrome based on the WHO could thus be made on the basis of several markers of insulin resistance plus 2 additional risk factors, including obesity, hypertension, a high triglyceride level, reduced high-density lipoprotein cholesterol level, or microalbuminuria. Subsequently, various criteria have been put forward by the International Diabetes Federation, WHO, and other diabetic societies throughout the world (12). Japanese criteria of metabolic syndrome were established in 2005, and the definition is as follows: if a man has a waist circumference > 85 cm (in the case of a woman, > 90 cm) in addition to two or more of the following: lipid abnormality [high triglyceride level (> 150 mg/dL) and/or HDL-cholesterol level (< 40 mg/dL)], elevated blood pressure [systolic blood pressure (> 130 mmHg) and/or diastolic blood pressure (> 85 mmHg)], and elevated blood glucose [fasting blood glucose (> 110 mg/dL)] (13). In the present case, the patient fulfilled the criteria for metabolic syndrome. In spite of favorable blood lipid and blood pressure management, there was no improvement in the disease status. Therefore, the patient gave his consent to experimentally receive herbal medication to improve his 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 (14). 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 (4-6,8-10,15-17). To add to these findings, we reported evidence supporting its preventive and/or therapeutic potential against metabolic syndrome (9). The administration of Kangen-karyu significantly improved high-fructose-induced metabolic syndrome such as hyperglycemia, hyperlipidemia, and hypertension through the reductions of triglyceride and cholesterol contents with the regulation of hepatic SREBP-1 and the nuclear factor-kappa B signaling pathway. The results of our previous study suggest that Kangen-karyu may play a protective role against metabolic syndrome.

In the present case, there was an improvement in metabolic syndrome following the administration of Kangen-karyu extract for 6 months. Most notably, the levels of serum total cholesterol, LDL-cholesterol, triglycerides, and HbA1c improved following the administration of Kangen-karyu extract. The abdominal circumference and body weight decreased compared with non-administration (from 105.8 to 101.8 cm; from 82.6 to 80.6 kg, respectively). In addition, the score using the questionnaire was decreased during the follow-up. Herein, we present a therapeutic option of Kangen-karyu based on metabolic parameters.

Treatment for metabolic syndrome involves the management of a cluster of chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, and obesity. There is no single treatment for patients with metabolic syndrome. However, traditional Chinese medicine has received much attention as a source of multi-target strategies due to their multiple beneficial effects and absence of toxic and/or side effects. We have been investigating the multi-target therapeutic effects of Kangen-karyu, one of our major interests among traditional Chinese medicine agents, on patients with metabolic disease. The present case provides strong evidence to support the administration of Kangen-karyu extract as a therapeutic agent to prevent the progression of metabolic syndrome.

We report evidence to support the use of Kangen-karyu as an adjunctive therapy for a patient with metabolic syndrome. Kangen-karyu exhibits good efficacy in the treatment of metabolic syndrome.

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