Case Report

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Therapeutic potential of Chinese prescription Kangen-karyu for patient with lifestyle-induced metabolic syndrome

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SUMMARY We report a case of a 65-year-old patient with hypertension, dyslipidemia, type 2 diabetes, chronic kidney disease, and hyperuricemia, who showed an improvement in lifestyle-induced metabolic syndrome on the administration of 7.5 g of Kangen-karyu extract per day for 6 months. The levels of serum total cholesterol, low-density lipoprotein-cholesterol, and triglycerides were decreased. The systolic/diastolic blood pressure was decreased following administration. Other parameters such as estimated glomerular filtration rate, creatinine, uric acid, aspartate transaminase, alanine aminotransferase, γ-glutamyl transpeptidase, and creatine phosphokinase were improved by the administration of Kangen-karyu extract. At that time, the physical and subjective symptoms had partially disappeared. We present evidence supporting the use of Kangen-karyu extract against metabolic syndrome.

Keywords Chinese prescription, Kangen-karyu, lifestyle, metabolic syndrome, case report

1. Introduction

Lifestyle-induced metabolic disease is caused by an unhealthy lifestyle, which usually includes the combination of a poor diet, lack of exercise, environmental pollution, and excess stress. The most common causes of these lifestyle disorders are related to the diet – consuming unhealthy food uncontrolled eating, overconsumption of artificial sweeteners, processed foods, and junk foods. In addition, addictive habits like tobacco smoking, eating snacks, consumption of alcohol, irregular sleeping habits, stress, and modern-day urbanization have aggravated the situation. A subsequent milestone in the progression to metabolic disease is the development of metabolic syndrome, which is defined by having three or more of the following: increased waist circumference, high blood pressure, high triglycerides, low high-density lipoprotein (HDL)-cholesterol, and high fasting blood sugar. The final stage of this progression is the development of more severe metabolic disease such as diabetes, heart disease, obesity, fatty liver disease, and/or cancer (*1,2*).

In the treatment of metabolic syndrome, traditional Chinese medicine is an excellent example of alternative and complementary medicine with a long history, unique theory system, and variety of herbal remedies. Several randomized controlled trials have shown the curative effects of traditional Chinese medicine on metabolic syndrome, with some studies focusing on the independent components of metabolic syndrome (*3*). We chose Kangen-karyu (Guan-Yuan-Ke-Li in Chinese: a crude drug consisting of Salviae Miltiorrhizae Radix, Cnidii Rhizoma, Paeoniae Radix, Carthami Flos, Aucklandiae Radix, and Cyperi Rhizoma, as shown in Table 1), a traditional Chinese prescription modified from Kan-shin No. 2 (Guan-xin No. 2 in Chinese) (*4*). It showed beneficial effects to improve signs of high-fructose diet-induced metabolic syndrome, such as hyperglycemia, hyperlipidemia, and hypertension, through the reduction of triglyceride and cholesterol levels by the regulation of hepatic sterol regulatory element-binding protein-1 (SREBP-1) expression, and also exhibited protective effects against high-cholesterol diet-induced hypercholesterolemia in rats (*5,6*). We also reported the beneficial effect of Kangen-karyu on dyslipidemia in a mouse model of type 2 diabetes (*7*). As Kangen-karyu has been clinically used as a treatment for cardiovascular disease, including angina pectoris and cerebrovascular diseases (*8,9*), the results of our previous

Table 1. Composition of Kangen-karyu

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

study provide important evidence that this prescription ameliorates metabolic syndrome.

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

2. Case presentation

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 (Toyama, Japan). 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 65-year-old man with hypertension, dyslipidemia, type 2 diabetes, chronic kidney disease, and hyperuricemia was previously diagnosed with metabolic syndrome at Shinseikai Toyama Hospital. Subsequently, the patient modified his lifestyle and continued to receive existing treatments: an antihypertensive agent (micardis: 20 mg/day) and antilipidemic agent (livaro: 1 mg/day). However, he presented to our hospital on October 9, 2019, seeking to recover his functional level with herbal medicine. From the next day, Kangen-karyu extract (7.5 g/day) was administered three times a day before every meal until April 13, 2020.

Before Kangen-karyu extract administration, his initial anthopometric measurements included a body weight of 81.6 kg with a height of 173 cm, a body mass index (BMI) of 27.4 kg/m^2, and an abdominal circumference of 98.4 cm, which classified him as obese. His systolic/diastolic blood pressure was 130/86 mmHg (Table 2). Hemoglobin A1c (HbA1c) was 6.1%, showing poorly controlled blood glucose. The levels of serum lipids were as follows: total cholesterol: 216 mg/dL, low-density lipoprotein (LDL)-cholesterol: 118 mg/dL, HDL-cholesterol: 46 mg/dL, and triglycerides: 306 mg/dL, indicating hyperlipidemia (Table 3). In addition, the estimated glomerular filtration rate (eGFR) was 33.0 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation (*10*), and this corresponded to a serum creatinine level of 1.69 mg/dL. The serum uric acid level was 8.6 mg/dL, representing hyperuricemia derived from kidney disease.

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

Parameter	Pre	Post
Body weight (kg)	81.6	81.7
Height (cm)	173	173
BMI (kg/m^2)	27.4	27.2
Abdominal circumference (cm)	98.4	98.0
Systolic blood pressure (mmHg)	130	126
Diastolic blood pressure (mmHg)	86	70

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

Parameter	Pre	Post
HbA1c (%)	6.1	6.5
Total cholesterol (mg/dL)	216	197
LDL-cholesterol (mg/dL)	118	108
HDL-cholesterol (mg/dL)	46	46
LDL-cholesterol/HDL-cholesterol	2.6	2.3
Triglycerides (mg/dL)	306	224
Uric acid (mg/dL)	8.6	7.7
Urea nitrogen (mg/dL)	21.7	20.8
Creatinine (mg/dL)	1.69	1.46
eGFR (mL/min/1.73 m^2)	33.0	38.7
AST (U/L)	26	18
ALT (U/L)	42	25
ALP (U/L)	215	202
LDH (U/L)	154	148
γ-GTP (U/L)	168	76
CPK (U/L)	197	112

The patient was an alcoholic, and alcohol consumption was assessed by questioning. The patient was asked about their average frequency (days per month) and amount (in mL) of alcoholic beverages ingested on a typical occasion or during a typical day, and categorized as a heavy consumer (≥ 30 g alcohol/day) according to the average daily alcohol consumption proposed by Agarwal (*11*). At that time, enzymes related to the hepatobiliary system and myocardial infarction were determined to assess their effects on the relationship between alcohol consumption and metabolic syndrome. Alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), and creatine phosphokinase (CPK) were found to be poorly controlled. There were, however, no significant changes in the activities of aspartate transaminase (AST), alkaline phosphatase (ALP), or lactate dehydrogenase (LDH) (Table 3).

Assessment of somatic and subjective symptoms involved completing a series of questionaries at the beginning and end of the study. The symptom checklist included the following: 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 the eyes and lip symptoms, stains on the 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.

During the administration of Kangen-karyu extract, a physical examination was performed to evaluate its effect on metabolic syndrome. As shown in Table 2, BMI and abdominal circumference showed no changes on administration of the Kangen-karyu extract, but the systolic/diastolic blood pressure was decreased from 130/86 to 126/70 mmHg. The total cholesterol level had decreased from 216 to 197 mg/dL at the 6-month follow-up. The elevated levels of LDL-cholesterol and LDL-cholesterol/HDL-cholesterol were slightly reduced on treatment with Kangen-karyu extract during the follow-up period. Oral administration of Kangen-karyu extract significantly reduced the increased triglyceride level. Other parameters such as eGFR, creatinine, uric acid, AST, ALT, γ-GTP, and CPK were improved by the administration of Kangen-karyu extract, as shown in Table 3. At that time, somatic and subjective symptoms such as cold limbs, fatigue, insomnia, tension in the stomach and abdomen, gas in the bowels, pain and numbness of the lower back, pale complexion, and stains had improved. After 6 months, the score using the questionnaire had decreased from 46 to 36 at the follow-up. There was a slight improvement in the tongue coating on the administration of Kangen-karyu.

3. Discussion

Metabolic syndrome is defined as a disease state complicated by multiple metabolic diseases such as hyperlipidemia, hypertension, and diabetes. Even when each individual component disease is mild, the risk of metabolic syndrome is high. Over the past decade, different organizations have proposed various diagnostic criteria. The use of traditional Chinese medicine for the treatment of metabolic syndrome is becoming increasingly common due to its wide availability. Traditional Chinese prescriptions have received much attention as potential sources of novel therapeutic agents due to their multiple beneficial effects and absence of toxic and/or side effects (*12*).

We chose Kangen-karyu extract for the following reasons. Firstly, it has been clinically used as a treatment for cardiovascular diseases (*8,9*). Secondly, Kangen-karyu has received much attention as a source of new therapeutic agents based on pre-clinical animal experiments related to various human diseases (*5-7,13-18*). To add to these findings, we reported experimental evidence supporting its preventive and/or therapeutic potential against metabolic syndrome. 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 (*6*). 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. The levels of serum total cholesterol, LDL-cholesterol, and triglycerides were decreased. The systolic/diastolic blood pressure was decreased compared with non-administration. At that time, the somatic and subjective symptoms had partially disappeared. Herein, we present a therapeutic option of Kangen-karyu based on metabolic parameters.

Although the mechanism underlying the development of the metabolic syndrome is not understood fully, it has been proposed that metabolic syndrome appears as a result of the reciprocal action of several environmental factors. In particular, alcohol consumption is one of the most prevalent habits in the general population (*19*). The beneficial effect of regular, light to moderate alcohol consumption on the development of coronary artery disease can be explained by several factors, including increase HDL-cholesterol and the balance between blood coagulation and fibrinolysis (*20,21*). The harmful effects of heavy alcohol consumption are due to an increase in plasma triacylglycerol and increased blood pressure (*22,23*). Each of these factors is a component of metabolic syndrome. Therefore, it is of interest to evaluate the overall associations of alcohol consumption with the development of metabolic syndrome. In the present case, the levels of serum total cholesterol, LDL-cholesterol, and triglycerides improved following the administration of Kangen-karyu extract. The blood pressure decreased compared with non-administration. In addition, interesting findings were obtained with regard to enzymes related to the hepatobiliary system and myocardial infarction: the levels of AST, ALT, γ-GTP, and CPK decreased compared with non-administration. Although the association of alcohol consumption with metabolic syndrome is complex and controversial, as both protective and detrimental effects have been reported (*19,24*), we report evidence to support the use of Kangen-karyu as an adjunctive therapy for a patient with lifestyle-induced metabolic syndrome. Kangen-karyu exhibits good efficacy in the treatment of lifestyle-induced metabolic syndrome.

Treatment for metabolic syndrome involves the management of a cluster of chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, and obesity. However, traditional Chinese medicine has received much attention as a source of multi-target strategies due to its multiple beneficial effects and absence of toxic and/or side effects. We have been

investigating the multi-target therapeutic effects of Kangen-karyu on patients with metabolic syndrome. 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.

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