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Research Article Open Access

Effects of *Bacillus* Natto Products on Blood Pressure in Patients with Lifestyle Diseases

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Abstract

The fermented soybean product natto is a popular traditional food in Japan and is considered a health supplement. To investigate the effect of supplements derived from natto on blood pressure in patients with lifestyle diseases, a cross-over, double-blind study was performed. The substances used were fermented soya (natto) extract and NKCP®, with main components of subtilisin NAT and bacillopeptidase F, respectively. A four-week course of NKCP® significantly decreased average systolic blood pressure from 130.9 to 120.5 mmHg (p=0.001) and diastolic blood pressure from 72.9 to 68.6 mmHg (p=0.024). However, after a four-week treatment with fermented soya (natto) extract, no significant changes in systolic or diastolic blood pressure were found (126.8 to 126.4 mmHg, and 70.9 to 68.3 mmHg, respectively). The difference in the effect on blood pressure between these two substances is considered as owing to the differences of the *in vitro* experimental results on blood fluidity. The use of dietary supplements, especially NKCP®, from natto provides additional blood pressure lowering effects in patients already receiving medical care.

Keywords: Functional food; Natto; Japanese food; Blood pressure; Lifestyle disease

Introduction

Hypertension (HT) is a serious global health problem that affects about 972 million adults and is attributed to 7.6 million excess deaths yearly [1,2]. In Japan, one in 5.6 persons suffers from HT [3]. HT is a cardiovascular and cerebrovascular risk factor and is related to the development of atherosclerosis and thrombosis. HT is characterized by endothelial dysfunction that frequently clusters with insulin-resistant disorders of metabolic homeostasis including obesity and type 2 diabetes [4,5]. Therefore, modern antihypertensive therapy focuses not only on blood pressure control but also on the favorable modification of known prognostic indices, such as endothelial and platelet dysfunction or coagulation and fibrinolytic abnormalities [6].

Recently, traditional Japanese foods have been the subject of increased attention because of Japan's lower prevalence of cardiovascular diseases than Western countries [7,8]. The fermented soybean product natto is a popular traditional food in Japan and is considered a health supplement because it contains a variety of peptides, amino acids, and vitamin B2. Although it is sticky and has a pungent smell of fermentation, it is widely accepted as a healthy and cheap food source in Japan. Some serine proteases with fibrinolytic activities have been purified from *Bacillus subtilis* var. *natto*. At the end of experimental growth, *Bacillus subtilis* var. *natto* produces several proteases including subtilisin NAT (nattokinase) and bacillopeptidase F [9-11]. The former is a main active component of fermented soya (natto) extract and the latter is that of NKCP®. Both substances are supplied as dietary supplements to help maintain blood fluidity. Although the anticoagulant and fibrinolytic effects of both substances have been compared *in vitro* [12], their differences in effect for blood pressure have not been investigated. Today, most adults suffer from lifestyle diseases and refer to doctors to receive medications if necessary. Some patients also take dietary supplements to enhance their blood pressure lowering effects or improve their complaints. Therefore, it is necessary to clarify the effects of dietary supplements on blood pressure in these patients.

The aim of this study is to investigate the effect of both fermented soya (natto) extract and NKCP®, derived from the traditional Japanese food natto, on blood pressure in patients with lifestyle diseases.

Materials and Methods

Participants

Patients who regularly visit the hospital or clinics with lifestyle diseases were considered eligible for this study. Lifestyle diseases include essential hypertension, type 2 diabetes or hyperlipidemia. Essential hypertension is defined as systolic blood pressure 140 mmHg or more and/or diastolic blood pressure 90 mmHg or more, as measured in the sitting position using a brachial sphygmomanometer. Hyperlipidemia is defined as low-density lipoprotein cholesterol (LDL-C) greater than 140 mg/dL, triglycerides (TG) greater than 150 mg/dL, or high-density lipoprotein cholesterol (HDL-C) less than 40 mg/mL. Type 2 diabetes was defined as fasting plasma glucose greater than 126 mg/dL, random plasma glucose greater than or equal to 200 mg/dL, or two-hour glucose in the oral glucose tolerance test greater than or equal to 200 mg/dL. We excluded patients with unstable angina, acute myocardial infarction, chronic obstructive pulmonary disease, renal insufficiency, acute liver disease, infectious disease, or any other serious life-threatening illness. Finally, 21 patients participated in this study. Of the 21 patients, 19 suffered from hypertension, 13 from hyperlipidemia, and 7 from type 2 diabetes. Twenty patients took concomitant medications: 13 patients took lipid-lowering agents, 6 took anti-diabetes drugs, and 18 took anti-hypertensive drugs. No changes in pharmacological regimens of patients were made during the course of the study.

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Study design

The substances used in the present study were fermented soya (natto) extract (100 mg/day, two times daily) and NKCP® (250 mg/day, two times daily). Each dose was the quantity recommended by each manufacturer. The fermented soya (natto) extract was made by Japan Bio Science Laboratory Co., Ltd. (Osaka, Japan); its active component is subtilisin NAT. The NKCP® was obtained from Daiwa Pharmaceutical Co., Ltd. (Tokyo, Japan) and its main component is bacillopeptidase F. The cross-over, double-blind study was performed at three facilities in Japan (Nagareyama Central Hospital, Ichihashi Clinic, and Hanzoumon Clinic). Cross-over application of one of the two substances for 4 weeks was performed in each patient. There was a 4-week washout period between the use of both substances. Therefore, the patient received one substance for 4 weeks, was observed for 4 weeks, and received another substance for 4 weeks. During the study, we instructed participants to continue their food intake patterns and lifestyles. Written informed consent was obtained from all patients before participating in the study. This study design was approved by the Shiba Palace Clinic Ethics Committee (Tokyo, Japan). One patient was excluded from the trial because of nausea and refusal to continue. There were no other adverse drug effects. Finally, the cross-over data of 20 patients were obtained.

Measurement of parameters

Body height and weight were measured in the morning before and after using the substance. Blood pressure was also measured in the right arm in the sitting position using a standard sphygmomanometer before and after substance administration. An average of three measurements was recorded for each patient. Patients were seated for at least 5 minutes before measurement. Blood samples for laboratory assays were obtained before and after substance treatment. Samples were obtained following overnight fasting. These samples were immediately coded so that investigators performing laboratory assays were blinded to subject identity or study sequence.

Statistical analysis

In comparing the values of laboratory data or blood pressure before and after using substances, the Wilcoxon Signed Rank test was used. Differences with a p-value less than 0.05 were considered significant.

Results

Laboratory findings

The average baseline values of complete blood count, biochemical analysis of protein, liver function, renal function, and electrolytes were normal after use of each substance. The laboratory findings for lifestyle diseases, coagulation, and fibrinolysis are shown in Table 1. The values of blood sugar before NKCP® and fermented soya (natto) extract use and the triglycerides before fermented soya (natto) extract use were higher than normal. Otherwise, values were within a normal range. When baseline values before using each substance were compared, no significant differences were found between the two groups.

Comparing values from before to after using NKCP® for 4 weeks, no significant differences were found except for adiponectin, LDL-cholesterol, and HbA1c (p=0.01, 0.04, 0.02, respectively). However, for these three items, values were within a normal range. For fermented soya (natto) extract use, no significant differences were found from before to after except for adiponectin, which had values that were within the normal range (p=0.001).

Blood pressure

Changes in blood pressure after using both substances are shown in Figure 1. For the comparison of baseline blood pressure (systolic and diastolic) in each substance, no significant differences were found (NKCP®: systolic 130.9 ± 4.2 mmHg, diastolic 72.9 ± 2.6 mmHg; fermented soya (natto) extracts: systolic 126.8 ± 3.8 mmHg, diastolic 70.9 ± 2.5 mmHg; p=0.25 in systolic, p=0.40 in diastolic).

A four-week course of NKCP® significantly decreased the average value of systolic blood pressure from 130.9 to 120.5 mmHg (p=0.001) and that of diastolic blood pressure from 72.9 to 68.6 mmHg (p=0.024). However, after a four-week course of fermented soya (natto) extract, no significant changes in either systolic or diastolic blood pressure were found (from 126.8 to 126.4 mmHg, and from 70.9 to 68.3 mmHg, respectively).

Discussion

Blood pressure is strongly associated with age-specific mortality rates from stroke, almost as much as mortality rates from ischemic heart disease or other vascular causes [13]. Randomized trials have shown that the lowering of blood pressure can produce rapid reductions in vascular disease risk [14-18]. Furthermore, a 10 mmHg decrease in usual blood systolic blood pressure or 5 mmHg decrease in usual diastolic blood pressure is associated with a 40% lower risk of stroke death and 30% lower risk of death from ischemic heart disease or other vascular causes throughout middle age [13]. Therefore, for the prevention of fatal vascular diseases, the lowering blood pressure is required.

To reduce blood pressure, in addition to controlling macronutrient intake, antihypertensive medications are usually used. However,

	NKCP®			Fermented soya (natto) extract		
	Baseline	1 month	p-value	Baseline	1 month	p-value
Total cholesterol (mg/dL)	200.7 ± 7.0	195.7 ± 6.3	0.08	194.5 ± 5.1	194.7 ± 6.1	1.00
HDL cholesterol (mg/dL)	55.4 ± 2.8	53.4 ± 2.9	0.37	55.3 ± 2.7	57.6 ± 2.8	0.23
LDL cholesterol (mg/dL)	115.9 ± 5.6	111.5 ±5.4*	0.04	112.6 ± 5.0	111.2 ± 5.5	0.73
Triglyceride (mg/dL)	154.6 ± 14.7	183.4 ± 28.5	0.46	155.3 ± 22.9	142.8 ± 13.8	0.54
Blood sugar (mg/dL)	112.9 ± 10.1	114.9 ± 9.6	0.96	121.2 ± 11.6	107.1 ± 6.9	0.58
Hemoglobin A1c (%)	5.55 ± 0.1	5.62 ± 0.2*	0.02	5.59 ± 0.2	5.56 ± 0.2	0.22
Adiponectin (μg/mL)	11.6 ± 1.1	11.0 ± 1.0*	0.01	11.1 ± 1.0	11.8 ± 1.1**	0.001
D-dimer (μg/mL)	0.6 ± 0.03	0.6 ± 0.05	0.25	0.6 ± 0.02	0.6 ± 0.04	0.29
Total PAI-1 (ng/mL)	29.6 ± 3.1	30.5 ± 2.0	0.60	29.5 ± 2.9	24.3 ± 2.3	0.09

Values are represented as mean ± standard error (n=20).

Statistically significant (Wilcoxon *t*-test between baseline and 1 month): *p<0.05, **p<0.01.

Table 1: Changes in blood-test parameters after 1 month compared with baseline in volunteers treated with NKCP® or fermented soya (natto) extract.

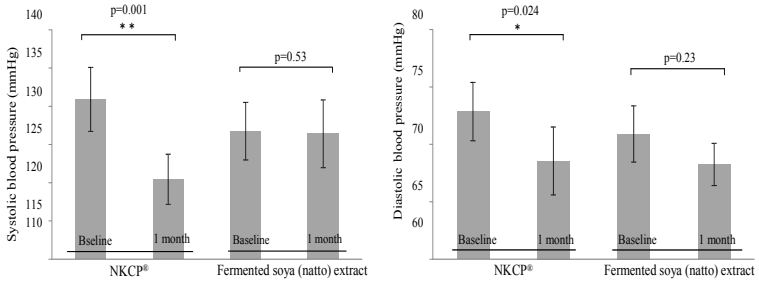

Figure 1: Changes in blood pressure after 1 month compared with baseline in volunteers treated with NKCP® or fermented soya (natto) extract. Vertical bar means ± standard error (n=20). Statistically significant (Wilcoxon t-test between baseline and 1 month): *p<0.05, **p<0.01.

because of limitations and concerns like availability, cost, and adverse effects of antihypertensive medications, a proportion of the population, especially in Asia, has turned to complementary and alternative medicine [19,20]. Both substances used in this study were produced by fermentation with *Bacillus subtilis* var. *natto*. However, because the active components of subtilisin NAT and bacillopeptidase F are different, they cause different physiological effects. In this study, only NKCP® significantly decreased blood pressure after four weeks of use. Previously, to determine the effect of fermented soya (natto) extract on blood pressure for mild hypertension patients without medications, a randomized controlled trial was performed [21]. In that study, the average systolic blood pressure decreased 8.4 mmHg, while diastolic blood pressure decreased 4.8 mmHg after 4 weeks of fermented soya (natto) extract use. Because the participants of that study did not use antihypertensive medicines and did not suffer from diabetes mellitus, the patient populations are difficult to compare. However, because NKCP® had a greater hypotensive effect on both systolic and diastolic blood pressure than fermented soya (natto) extract, NKCP® may be effective for patients with mild hypertension without lifestyle diseases. Further research may clarify this point. Previously, fibrinolytic and antithrombotic effects of NKCP® have shown in both *in vitro* and *in vivo* studies. In the preliminary clinical trials of which NKCP® had been administered to healthy volunteers, shortening euglobulin lysis time of the human blood was observed [22]. Also, dose-dependent prolongation of both prothrombin time and active partial thromboplastin time were observed in rats with intra-duodenal administration of NKCP® [11]. These effects improve the blood fluidity and blood flow.

Therefore, an increase in blood fluidity by NKCP® is considered the most probable reason for decreasing blood pressure. More detail mechanisms of both NKCP® and fermented soya (natto) extract on human blood pressure are not entirely clear. In addition to Japanese traditional food, the efficacies of some Chinese medicines for treating hypertension have been suggested [20]. However, detail underlying mechanisms for blood pressure lowering effects have not fully understood. In future, in the field of complementary and alternative medicine including Japanese traditional food, blood pressure lowering mechanism might be clarified with modern science.

We assume that the difference in effect between these two substances is because of differences in the *in vitro* experimental results of blood fluidity. We previously compared the effects on blood coagulation and fibrinolysis of human blood by fermented soya (natto) extract and NKCP® [12]. We found that the NKCP®, with a main component of bacillopeptidase F, had a 2.5-fold greater fibrinolytic effect and over a 100-fold greater anticoagulant effect than fermented soya (natto) extract, with a main component of subtilisin NAT. Therefore, these differences contribute to more effective blood fluidity promotion by NKCP® and subsequent decrease in blood pressure. Because lifestyle diseases encourage atherosclerosis and thrombosis, the use of NKCP® contributes to both decreasing blood pressure and preventing coagulation and fibrinolytic abnormalities.

In the present study, participants suffered from lifestyle diseases so some blood chemistry items had abnormal values. However, because the patients were well-controlled with medical intervention and had no advanced thrombotic or vascular diseases, the clinical markers concerning blood coagulation and fibrinolysis were within normal ranges throughout the study. A four-week course of NKCP® significantly increased the values of HbA1c and decreased the value of adiponectin. A four-week course of fermented soya (natto) extract significantly increased the adiponectin value. However, because these values were within normal ranges and the changed values were small, we believe that these differences did not affect blood fluidity.

Our study has some limitations. First, sample size is small. To avoid drop outs of the participants, we conducted the trial with small number of patients with enough adherences. Second, we did not compare the blood pressure lowering effect in subjects who treated firstly with NKCP® (secondary with fermented soya extracts) and in those who treated firstly with fermented soya (natto) extracts (secondary with NKCP®). In this trial, for the baseline blood pressures in each substance, no significant differences were shown in both systolic and diastolic blood pressures. And, the observed duration was four weeks for each substance with a four weeks washout period in this trial. We considered that as the duration was not so long, the blood pressures were not markedly influenced by seasonable change. Furthermore, this study was performed as a cross-over, double-blind trial. Therefore, there is some scientific reliability. Third, participants were already referred to clinics or hospitals with lifestyle diseases and most of them have taken anti-hypertensive drugs. So, we could not observe single effects of the substances on blood pressure or compare the results with those of control subjects. However, as the aim of this study was to investigate the efficacy of both fermented soya (natto) extract and NKCP® on blood pressure in patients with well-controlled lifestyle diseases, this limitation does not affect the results of this study. To confirm the results of present study, further clinical trials with control subjects and enough numbers of participants might be needed.

Conclusion

For patients with lifestyle diseases, NKCP® alone significantly decreased both diastolic and systolic blood pressure. The use of dietary supplements from the Japanese traditional food natto provides additional hypotensive effects for patients receiving medical care.

NKCP® might avoid some premature death and disability due to cerebrovascular disease or stroke.

Conflicts of Interest

This study was financially supported by Daiwa Pharmaceutical Co., Ltd.

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