

Preventive effects of Daisaikoto on metabolic disorders in spontaneous obese type II diabetes mice

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Metabolic syndrome (MS) is one of the syndromes known as an underlying lifestyle-related diseases. Recently, the number of obese people keeps on increasing, and visceral fat accumulation has been reported as the most important risk factor for the development of MS. In this study, the effects of Daisaikoto, a Kampo preparation, on metabolic disorders were investigated using TSOD mice, an animal model of spontaneous obese type II diabetes.

Four-week-old TSOD mice that had not yet developed obesity and TSNO mice that do not develop metabolic disorders were given *ad libitum* powder feed containing Daisaikoto at a concentration of 1% or 3% for 2 months. After 2 months, the control TSOD mice developed various metabolic disorders such as marked obesity and visceral fat accumulation, increase of the blood glucose level, the insulin level, T-Cho level, TG level and LDL level, abnormal glucose tolerance, hypertension and neuropathy as distinct from the control TSNO mice. In the TSOD mice treated with Daisaikoto, the body weight gain and visceral fat accumulation were suppressed, and the abnormal glucose tolerance, elevation of blood pressure and peripheral neuropathy were also significantly suppressed. On the other hand, in TSNO mice, Daisaikoto showed no noteworthy impacts on most parameters. The above results suggested that Daisaikoto would be effective for the prevention against various symptoms of MS.

Key words Metabolic syndrome, metabolic disorders, Daisaikoto, TSOD mice, visceral fat, diabetic complication.

Introduction

Metabolic syndrome, a lifestyle-related disease, is defined by a disease state complicated by multiple metabolic diseases such as diabetes, hyperlipidemia and hypertension. Even when each individual component disease is mild, metabolic syndrome is known to be high risk, since visceral fat accumulation is linked with insulin resistance, leading to arteriosclerotic diseases such as cerebral infarction or myocardial infarction.^{1), 2)}

The causes of obesity in modern society are considered to include overeating, especially excessive ingestion of dietary fat, and insufficient exercise, and the number of people with obesity is increasing globally, especially in the advanced countries. The diagnostic criteria for metabolic syndrome have been established in Japan as well as in Western countries.³⁾ As mentioned above, metabolic syndrome is associated with a risk of inducing serious arteriosclerotic diseases, so it is important to prevent metabolic syndrome and to take early measures against this syndrome. Furthermore, it is important to establish therapeutic methods, including the establishment of exercise as a habit and improving lifestyle, that address metabolic syndrome. Lifestyle-related diseases can also be treated by Japanese Kampo medicine. Specifically, for the treatment of metabolic syndrome and obesity, Kampo preparations such as Daisaikoto, Saikokaryukotsuboreito, Tokakujokito, Daiobotanmpito,

Bofutsushosan, Tsudosan, Kumibinroto and Boigoto are used.⁴⁾ Daisaikoto is referred to for the Shokan-ron and Kinki-yoryaku, and is used for people who are relatively healthy but develop fullness, tenderness or discomfort of the hypochondrium and have a tendency toward constipation. Daisaikoto is believed to be effective against obesity, hypertension, diabetes and chronic constipation.⁵⁾

In this study, we investigated the preventive effect on metabolic syndrome-related symptoms of Daisaikoto, which has traditionally been used for the treatment of obesity, using an animal model of spontaneous obese Type II diabetes [TSOD (Tsumura, Suzuki, Obese, Diabetes) mice]⁶⁾⁻¹¹⁾ which is known to develop disease states similar to human metabolic syndrome.

Methodology

Experimental animals. We used male TSOD mice aged 3 weeks, and as control animals that did not develop metabolic disorders, male TSNO (Tsumura, Suzuki, Non-Obesity) mice⁷⁾ aged 3 weeks were obtained from the Institute for Animal Reproduction (Ibaragi Prefecture). The animals were kept in an animal room under the following conditions: room temperature of $23 \pm 2^\circ\text{C}$, relative humidity of $55 \pm 10\%$ and 12 hours of light per day. In the 1-week acclimation period, the animals were given *ad libitum* powder feed MF (Oriental Yeast Co., Ltd.) and water. Then, the powder feed was switched to the study feed

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glucose level was determined.

Changes in amounts of visceral and subcutaneous fat.

At 0 week (age 4 weeks), 2 weeks (age 6 weeks), 4 weeks (age 8 weeks), 6 weeks (age 10 weeks) and 8 weeks (age 12 weeks) after initiation of the study drug, each mouse was anesthetized with Nembutal (50 mg/kg, i.p.) and fixed in an experimental X-ray CT instrument (LaTheta, Aloka Co., Ltd.) to determine the amount of visceral and subcutaneous fat by scanning from the ensiform cartilage to the sacral bone at intervals of 1.5 mm.

Blood pressure. Each mouse was fixed in a positioner THC-2 (Softron, Co., Ltd., Tokyo) while body temperature was maintained at 37°C, and blood pressure was determined in a non-invasive manner by inserting the tail up to its base into the tail cuff of a non-invasive blood pressure meter BP-98A (Softron, Co., Ltd., Tokyo).

Pain test. The foot pinch method as described by Suzuki, et al.¹²⁾ was used as a pain test. For this test, the proximal part of the tarsus in the metatarsal region of hind limb was pinched with an artery clip (BHO20R, pressure: 300 g, Bulldog Clamp, Johns Hopkins, Tokyo), and the time until the mouse bites the clip was determined as the latent reaction time. The mean latent reaction time from both hind limbs was calculated as the latent reaction time for each individual mouse.

Statistical processing. In each experiment, significant differences between the groups were examined using Dunnett's multiple comparison test.

Results and Discussion

Results:

Growth curve and feed intake. Figure 2 shows the growth curve up to 8 weeks after initiation of the study drug treatment (age 12 weeks).

The TSOD control group showed a larger body weight gain than the TSNO control group throughout the entire experimental period. Among the TSOD mice, the body weight gain was suppressed in the groups treated with Daisaikoto

compared with the control group from 6 weeks after treatment initiation, with a significant difference in the low-dose group at 7 weeks after treatment initiation (age 11 weeks). In the TSNO mice, all groups showed similar body weight changes with no inter-group difference.

There were no inter-group differences in changes in feed intake in either the TSOD mice or TSNO mice.

Blood biochemical tests. Table 2 shows the blood glucose levels, insulin levels, T-Cho levels, TG levels, HDL levels and LDL levels in each group of TSOD mice and TSNO mice determined at the completion of the experiment (age 12 weeks). The insulin level, T-Cho level, TG level, HDL level and LDL level were significantly higher in the TSOD control group than in the TSNO control group. The blood glucose level tended to be higher in the TSOD control group than in the TSNO control group.

On inter-group comparisons in the TSOD mice groups, the blood glucose level was significantly lower in the Daisaikoto low-dose group than in the control group, and tended to be lower in the high-dose group. The TG level

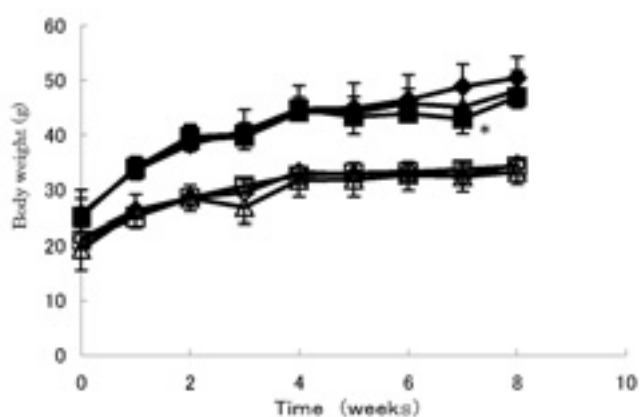


Figure 2 The effect of Daisaikoto on the body weight in mice. ◆:TSOD control, ■:TSOD Daisaikoto 1%, ▲:TSOD Daisaikoto 3%, ◇:TSNO control, □:TSNO Daisaikoto 1%, △: TSNO Daisaikoto 3%. Data represent the mean \pm S.D. of 5 to 6 animals. *: $p < 0.05$, Significantly different from the control group.

Table 2 Effects of Daisaikoto on biochemical parameters of plasma.

| Biochemical parameters | TSOD Control | TSOD Daisaikoto 1% | TSOD Daisaikoto 3% | TSNO Control | TSNO Daisaikoto 1% | TSNO Daisaikoto 3% |
|------------------------|------------------|--------------------|--------------------|------------------|--------------------|--------------------|
| Glucose (mg/dL) | 221.9 \pm 64.9 | 141.6 \pm 11.5* | 174.9 \pm 26.1 | 193.1 \pm 21.9 | 195.6 \pm 45.7 | 186.1 \pm 30.6 |
| Insulin (ng/mL) | 11.9 \pm 14.0 | 11.9 \pm 0.7 | 8.3 \pm 8.1 | 0.5 \pm 0.3 | 0.4 \pm 0.5 | 0.6 \pm 0.3 |
| T-Cho (mg/dL) | 199.1 \pm 29.3 | 182.3 \pm 23.1 | 193.1 \pm 40.9 | 138.9 \pm 13.0 | 149.1 \pm 12.0 | 129.1 \pm 13.8 |
| TG (mg/dL) | 222.0 \pm 28.2 | 144.3 \pm 20.9** | 166.8 \pm 34.1* | 83.5 \pm 16.0 | 76.8 \pm 13.8 | 74.3 \pm 16.7 |
| LDL (mg/dL) | 20.4 \pm 7.0 | 13.9 \pm 6.2 | 16.2 \pm 5.2 | 7.8 \pm 1.5 | 7.7 \pm 2.2 | 6.5 \pm 1.8 |
| HDL (mg/dL) | 150.9 \pm 24.9 | 141.5 \pm 16.0 | 129.4 \pm 10.8 | 119.0 \pm 10.1 | 126.3 \pm 16.8 | 117.6 \pm 14.6 |

Data represent the mean \pm S.D. of 5 to 6 animals. *: $p < 0.05$, **: $p < 0.01$, Significantly different from the control group.

was significantly lower in both the low-dose group and high-dose group than in the control group. Daisaikoto tended to be associated with a dose-dependent reduction in insulin level, HDL level and LDL level. On the other hand, the T-Chol level did not show any Daisaikoto treatment-related changes.

In the TSNO mice, the treatment with Daisaikoto did not induce any changes in blood glucose level, insulin level, T-Chol level, TG level, HDL level or LDL level.

Glucose-tolerance test. The TSOD mice and TSNO mice were starved for one night and then administered oral glucose 2 g/kg each, and the time-course changes in blood glucose level were determined. The results are shown in Figure 3.

The blood glucose level after glucose loading was significantly higher in the TSOD control group than in the TSNO control group from 30 minutes to 180 minutes after glucose

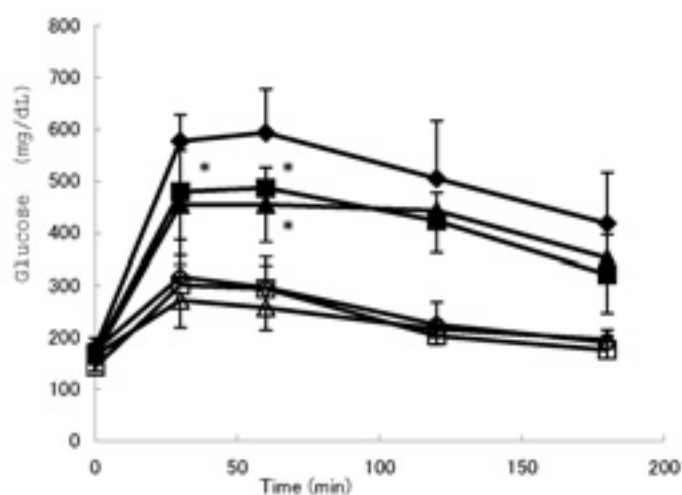


Figure 3 The effect of Daisaikoto on the plasma glucose level in the oral glucose tolerance test. ◆:TSOD control, ■:TSOD Daisaikoto 1%, ▲:TSOD Daisaikoto 3%, ◇:TSNO control, □:TSNO Daisaikoto 1%, △: TSNO Daisaikoto 3%. Data represent the mean \pm S.D. of 5 to 6 animals.

*: $p < 0.05$, Significantly different from the control group.

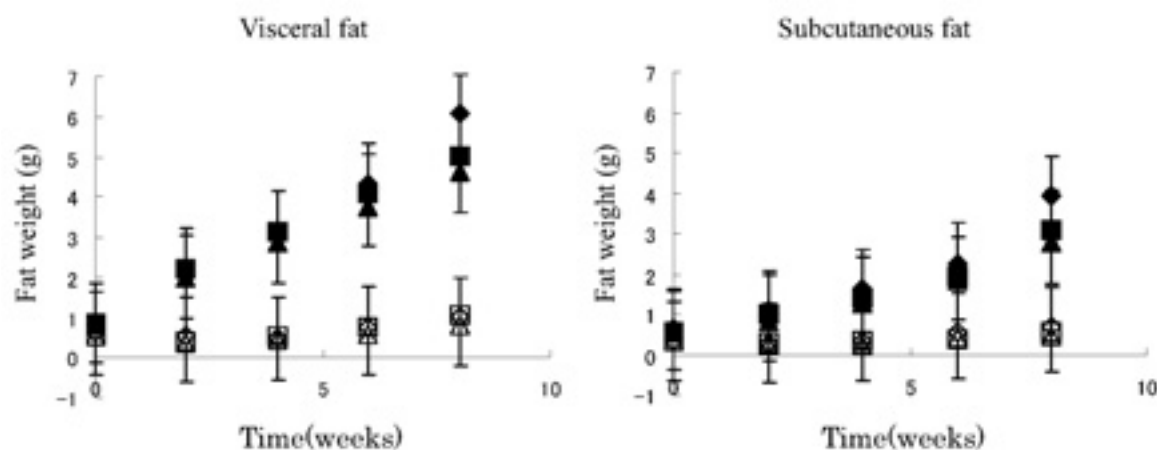


Figure 4 The effect of Daisaikoto on the accumulation of adipose tissue in mice. ◆:TSOD control, ■:TSOD Daisaikoto 1%, ▲:TSOD Daisaikoto 3%, ◇:TSNO control, □:TSNO Daisaikoto 1%, △: TSNO Daisaikoto 3%. Data represent the mean \pm S.D. of 5 animals.

loading, indicating the presence of abnormal glucose tolerance in the TSOD control group.

On inter-group comparisons in the TSOD mice, compared with the control group, the blood glucose level was significantly lower in the low-dose group at 30 minutes and at 60 minutes after glucose loading, and significantly lower in the high-dose group at 60 minutes after glucose loading, showing a general tendency for lower blood glucose in the Daisaikoto-treated groups.

On the other hand, in the TSNO mice, there were no marked differences in blood glucose levels after glucose loading between the control group and either group treated with Daisaikoto.

Changes in the amount of visceral and subcutaneous fat. Figure 4 shows changes in the amounts of visceral and subcutaneous fat from immediately before starting the study drug treatment to 2 weeks (age 6 weeks), 4 weeks (age 8 weeks), 6 weeks (age 10 weeks) and 8 weeks (age 12 weeks) after initiation of treatment with Daisaikoto in the TSOD mice and TSNO mice.

In the TSOD control group, the amount of visceral fat showed a rapid increase to about 7 times the baseline level and the amount of subcutaneous fat to about 6 times the baseline level after 8 weeks' treatment. On the other hand, in the TSNO control group, both the amount of visceral fat and the amount of subcutaneous fat had increased about 1.6 times from baseline after 8 weeks, this increase being far smaller than that in the TSOD control group. The amount of both visceral and subcutaneous fat in the TSOD control group was significantly higher than in the TSNO control group from 2 weeks after starting the experiment.

On inter-group comparisons in the TSOD mice, the amount of both visceral and subcutaneous fat tended to be lower in the groups treated with Daisaikoto than in the control group, and the difference became larger over time.

On the other hand, in the TSNO mice, there were no marked differences in visceral fat accumulation and subcutaneous fat accumulation between the control group and either group treated with Daisaikoto.

Blood pressure. Figure 5 shows systolic blood pressure (SBP) values in the TSOD mice and TSNO mice.

The SBP values in the TSOD control group were significantly higher than those in the TSNO control group.

On inter-group comparisons in the TSOD mice, the SBP values were lower in the groups treated with Daisaikoto than in the control group, with an apparent dose-response relationship, and a significant difference was seen between the high-dose group and the TSOD control group, with the values in the high-dose group comparable to those in the TSNO control group.

In the TSNO mice, there were no marked differences in SBP values between the control group and either group treated with Daisaikoto.

Pain test. Figure 6 shows the latent reaction time in the foot pinch test for the TSOD mice and TSNO mice. In this pain test, the latent reaction time was significantly longer in the TSOD control group than in the TSNO control group.

On inter-group comparisons in the TSOD mice, the latent reaction time decreased in the groups treated with Daisaikoto

compared with the control group in a dose-dependent manner. The latent reaction time was significantly shorter in the high-dose group, and the latent reaction time in the high-dose group was comparable to that in the TSNO control group.

On the other hand, in the TSNO mice, there were no marked differences in latent reaction time between the control group and either group treated with Daisaikoto.

Discussion:

Recently, quality of life has been improved in advanced countries, mostly due to sufficient food and well-developed transportation systems; however, the number of obese patients keeps on increasing. Visceral fat accumulation induces insulin resistance, abnormal glucose metabolism, abnormal lipid metabolism and hypertension, and even if these individual diseases are mild, the presence of more than one of these diseases in the same individual may induce development of metabolic syndrome, leading to arteriosclerosis or ischemic cardiovascular diseases. According to the interpretation of Kampo medicine by Keisetsu Ohtsuka¹³⁾ who is one of the authorities in this field, Daisaikoto is generally applied to those obese patients who have fullness, tenderness or discomfort in the hypochondrial or epigastric region and a tendency toward constipation, with the possible presence of diseases such as hypertension, cholecystitis, cholelithiasis, hepatitis, gastritis, asthma, obesity (adiposis) and chronic constipation. The wording used in this interpretation suggests that Daisaikoto can also be used for the collection of metabolic syndrome in modern society. As mentioned previously, in modern medicine, Daisaikoto is positioned as one of the Kampo preparations used for the treatment of metabolic syndrome and obesity, and the indications described in the package insert for Daisaikoto refer to the effects on obesity, hypertension, diabetes and chronic constipation in those people who remain relatively healthy but have fullness, tenderness or discomfort of the hypochondrium and a tendency toward constipation. There have already been papers published that report on basic pharmacological studies of Daisaikoto in obesity, hyperlipidemia, etc.¹⁴⁻¹⁷⁾

In this study, we focused on metabolic syndrome, one of many lifestyle-related diseases, and investigated the preventive effects of Daisaikoto on various symptoms of metabolic disorders using TSOD mice as an animal model developing the disease states seen in human metabolic syndrome. On conducting the experiments, the influences of Daisaikoto on TSNO mice that do not develop various symptoms of metabolic disorders were also investigated as control experiments. TSOD mice were established as a multi-gene obese Type-II diabetes model by selecting individual animals that developed obesity and diabetes from among ddY mice and repeating brother-sister inbreeding using the body weight and male urinary glucose level as indices. TSNO mice were established as a non-diseased model by selecting individual animals that did not develop obesity and diabetes from among ddY mice and repeating brother-sister inbreeding using lack of disease development as an index.

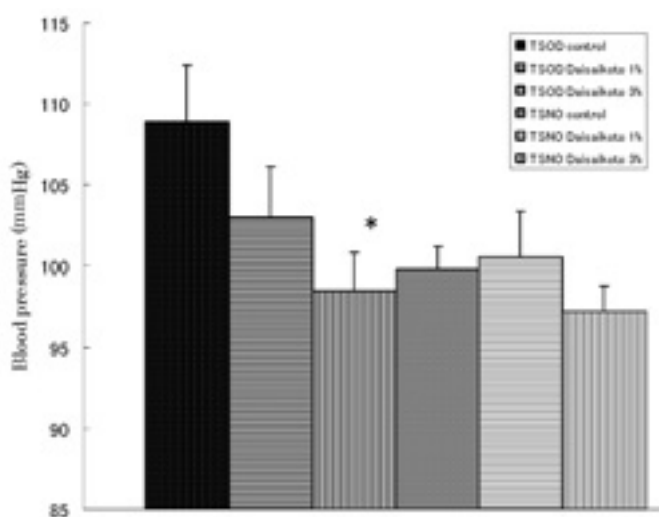


Figure 5 The effect of Daisaikoto on blood pressure in mice. Data represent the mean \pm S.D. of 5 to 6 animals. *: $p < 0.05$, Significantly different from the control group.

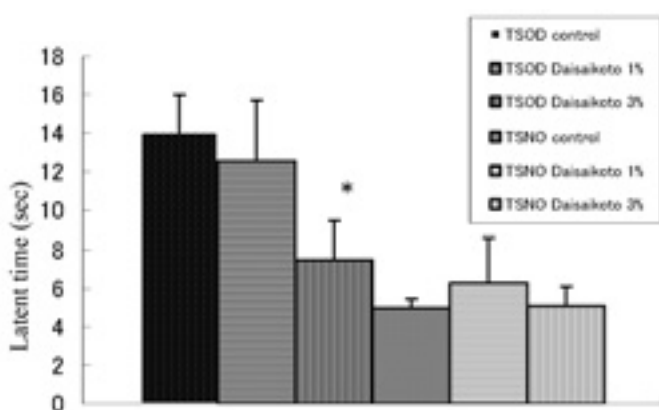


Figure 6 The effect of Daisaikoto on the peripheral neuropathy. Data represent the mean \pm S.D. of 5 to 6 animals. *: $p < 0.05$, Significantly different from the control group.

First, the validity of TSOD mice as a model for metabolic syndrome was evaluated. Compared with the TSNO control group, the TSOD control group showed significantly higher body weight gain and significantly higher visceral/subcutaneous fat accumulation throughout the experimental period (from age 4 weeks to age 12 weeks) and developed marked obesity. On analysis of the ratio of visceral fat to subcutaneous fat using CT image analysis, it was revealed that visceral fat accumulation is dominant and that the obesity type is visceral fat-accumulating. Additionally, plasma biochemical tests conducted at the age of 12 weeks showed that the insulin level, T-Cho level, TG level and LDL level were all significantly higher in the TSOD control group than in the TSNO control group, and also that the blood glucose level tended to be higher in the TSOD control group, suggesting that major symptoms of metabolic syndrome had developed. On the other hand, the HDL level was similarly higher in the TSOD control group, and this was the sole parameter that was inconsistent with the context of the risk factors leading to metabolic syndrome in TSOD mice. One previous paper has stated that rodents originally show high HDL concentrations and many animal models of obesity show an increase in HDL concentration due to the absence of CETP (cholesterol ester transfer protein) and that any animals hardly develop arteriosclerotic diseases.¹⁰⁾ Looking at blood pressure, the SBP was significantly higher in the TSOD control group than in the TSNO control group, suggesting a hypertensive state in the TSOD control group. Furthermore, on the glucose-tolerance test, abnormal glucose tolerance was observed in the TSOD control group. In accordance with the fact that patients with advanced metabolic syndrome develop peripheral neuropathy as a diabetic complication, it has been reported that TSOD mice develop impairments of hind limb movement with increasing age.¹⁰⁾ To examine this, a pain test was performed in this study, and the pain transduction reaction was determined using, as an index, latent reaction time on pain stimulation to the hind limb with a pinch. The latent reaction time was found to be significantly longer in the TSOD control group than in the TSNO control group, so it was confirmed that the TSOD control group developed neuropathy. From the above results, we judged that TSOD mice would develop similar symptoms of the human metabolic syndrome, as has been shown to occur in studies in other animal models which we have previously reported on^{7), 10), 18)} and would be suitable for use in the evaluation of drug effects on metabolic syndrome. At the age of 4 weeks, the body weight, amount of visceral fat and the amount of subcutaneous fat are comparable between TSOD mice and TSNO mice, suggesting that the symptoms of metabolic disorders have not yet developed at this age, so we subsequently investigated the preventive effects of Daisaikoto on various symptoms of metabolic disorders using animals aged 4 weeks.

On inter-group comparisons of body weight gain in the TSOD mice, almost no marked differences were seen in the Daisaikoto-treated groups compared with the control group until 4 weeks after the start of Daisaikoto treatment, but thereafter a tendency toward suppression of body weight

gain started appearing in the Daisaikoto-treated groups, and a significant suppression was seen in the low-dose group after 7-week treatment (age 11 weeks). On analysis of the amount of body fat using X-ray CT examination, Daisaikoto was found to be associated with a tendency toward suppression of visceral/subcutaneous fat accumulation from 4 weeks after starting treatment, and this effect was dose-dependent. As part of the diagnosis criteria for metabolic syndrome, visceral fat accumulation is regarded as being particularly important^{4), 19), 20)} rather than mere body weight gain, but the body weight changes associated with Daisaikoto were parallel to the changes in the amount of visceral fat and the amount of subcutaneous fat. Since the suppressive effect of Daisaikoto on visceral fat accumulation became more marked over time, it is expected that positive effects of Daisaikoto in metabolic disorders based on visceral fat accumulation will increase with increasing duration of treatment. Ohminami et al.^{16), 17)} reported that Daisaikoto exhibited a suppressive effect on body fat accumulation in mice with gold thioglucose-induced obesity and that oral administration of Daisaikoto for 10 days to rats loaded with peroxidized corn oil showed a marked suppression of intestinal absorption of neutral fat. These results suggest that the mechanism by which Daisaikoto acts to suppress accumulation of adipose cells is due, at least in part, to suppression of intestinal absorption of dietary fat.

In this study using TSOD mice, the blood glucose level was significantly lower in the low-dose group and tended to be lower in the high-dose group than in the control group, and the insulin level tended to be lower in a dose-dependent manner. On the glucose-tolerance test, the elevation in blood glucose level after glucose loading was suppressed in the Daisaikoto-treated groups and the improvement in glucose tolerance was confirmed in the Daisaikoto-treated groups. On the other hand, in TSNO mice, the baseline blood glucose levels as well as the blood glucose levels after glucose loading were not changed by Daisaikoto treatment. Goto et al.¹⁵⁾ used rats with experimental cyproheptadine-induced diabetes and reported that Daisaikoto suppressed hyperglycemia, improved glucose tolerance and tended to increase insulin secretion in glucose-tolerance tests. In our study, the results related to the effect of Daisaikoto on insulin level differed from the report of Goto et al.¹⁵⁾ It is known that in metabolic syndrome, visceral fat accumulation induces insulin resistance, and elevation of blood glucose levels leads to excessive secretion of insulin, resulting in hyperinsulinemia.²¹⁾ Since the TSOD mice used in this study develop hyperinsulinemia,⁷⁾ it is partly speculated that Daisaikoto treatment-induced suppression of visceral fat accumulation prevented aggravation of insulin resistance and resulted in the decreased insulin level. The suppression of hyperglycemia and improvement in glucose tolerance seen with Daisaikoto in this study were partly considered to be due to the prevention of metabolic disorders aggravation, including alleviation of insulin resistance.

Concerning the effects of Daisaikoto on serum lipid levels, the TG level was significantly lower and LDL level was lower in the TSOD mice treated with Daisaikoto than in the

control TSOD mice. But, the T-cho level showed no change and the HDL level tended to be lower with Daisaikoto treatment. Yamada et al.²²⁾ reported that serum total cholesterol levels tended to decrease and that serum triglyceride levels significantly decreased in cholesterol-loaded rabbits when Daisaikoto was administered orally for 6 to 9 months, and they speculated that these effects could be attributed to the significant suppression of fat absorption, especially neutral fat absorption, and improvement in lipid metabolism. Ohminami et al.^{17),23)} reported that oral administration of Daisaikoto for 10 days to rats loaded with peroxidized corn oil did not decrease the total cholesterol level but significantly suppressed elevation of neutral lipid levels, and they observed marked suppression of neutral fat absorption with Daisaikoto in the investigation of intestinal fat absorption. Also Goto et al.¹⁵⁾ reported that Daisaikoto improved lipid metabolism in an experimental diabetes model. These facts suggest that the significant decrease in neutral lipid levels in the TSOD mice treated with Daisaikoto that was seen in this study is a result of suppressing intestinal absorption of dietary neutral fat and improving lipid metabolism.

Concerning hypertension, which has been adopted as one of the diagnostic criteria for metabolic syndrome, a dose-dependent antihypertensive effect of Daisaikoto was observed. Regarding the mechanism of onset of hypertension in metabolic syndrome, insulin resistance due to visceral fat accumulation, hyperinsulinemia, sympathetic nerve activity and adipocyte secretion of adipocytokines are known to be involved.²⁴⁾ As mentioned previously, it was recognized in this study that the Daisaikoto treatment was associated with dose-dependent suppression of visceral fat accumulation and prevention of hyperinsulinemia, and the antihypertensive effect was partly considered to be due to these effects. Although the suppressive effect on visceral fat accumulation was slight even in the high-dose group compared with the TSNO control group, elevation of blood pressure could be prevented, giving blood pressure that was comparable to that in the TSNO control group. Yoshida et al.²⁵⁾ reported that a 5 % decrease in body weight can markedly decrease the morbidity of obesity-related hypertension, and the suppression of body weight gain and suppression of visceral fat accumulation achieved by the Daisaikoto treatment in this study are considered to have been enough to prevent the onset of hypertension. The pain test was performed for the purpose of investigating the effect of Daisaikoto treatment on diabetic peripheral neuropathy. In this pain test, the prolonged latent reaction time was shortened in a dose-dependent manner by Daisaikoto treatment, suggesting that Daisaikoto would exert a preventive effect on peripheral neuropathy.

In the TSNO mice used in this study as a non-diseased model, no marked changes were observed in any parameters except for mild diarrhea noted only in the high-dose group. This fact suggests that Daisaikoto exerts a preventive effect on each of various symptoms of metabolic disorders (obesity, visceral fat accumulation, hyperglycemia, abnormal lipid metabolism, hypertension, peripheral neuropathy) but has no direct influence on the non-diseased body, namely

the healthy body.

Conclusion

The above results suggest that Daisaikoto may prevent various metabolic disorders such as abnormal lipid metabolism, hyperglycemia, hyperinsulinemia, hypertension and peripheral neuropathy, and Daisaikoto is considered to be one of valuable drugs for the prevention of various symptoms of metabolic syndrome.

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Japanese abstract

メタボリックシンドローム (MS) は、生活習慣病の基礎病態として特に注目されている症候群の一つである。近年、肥満人口は増加の一途をたどっているが、内臓脂肪の蓄積は MS の病態基盤として最も重要な危険因子であることが報告されている。本研究においては、MS 類似病態を発症する肥満性 2 型糖尿病モデル動物である TSOD マウスを用い、諸代謝性疾患に対する漢方薬大柴胡湯の効果を検討した。肥満が未発症の 4 週齢 TSOD マウスおよび代謝性疾患を発症しない TSNO マウスに大柴胡湯を 1% および 3% 混和させた粉末飼料を 2 ヶ月間自由摂取させた。その結果、普通食摂餌 TSOD マウスは、試験開始後より普通食摂餌 TSNO マウスに比べ著しい肥満および内臓脂肪の蓄積、血糖値、インスリン値、T-Cho 値、TG 値および LDL 値の上昇、耐糖能異常などを発症し、さらに高血圧および末梢神経障害が認められた。TSOD マウスにおいて、大柴胡湯は投与後期より体重増加や内臓脂肪の蓄積等に対して低下作用を与え、さらに、耐糖能異常、血圧の上昇や末梢神経障害を有意に抑制した。以上より、MS 諸症状に対する大柴胡湯の有用性が示唆された。

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