Kampo Medicine – Current Research

The Traditional Herbal Medicine Boiogito (Fang-Yi-Huang-Qi-Tang) Slows Postprandial Oxidation of Ingested Glucose Only in Women

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Main Messages

1. Highlights the gender specific effect of ingested glucose oxidation of traditional herbal medicine, *Boiogito* (BOT), which has been used to treat various metabolic diseases.
2. BOT decreased postprandial glucose oxidation only in women.
3. The gender difference in the effect of glucose oxidation may not be mediated by neither insulin nor incretion dependent pathway.

Areas of Uncertainty

1. Patients with metabolic syndrome and diabetes are needed to determine the precise effects of BOT on energy metabolisms and substrate oxidation rate.
2. The mechanism for gender difference should be identify precisely.
3. Substantial number of the patients and long term effect should be done in the double blind fashion, to confirm the further benefit of the BOT.

ABSTRACT

Objective: *Boiogito (BOT, Fang-Yi-Huang-Qi-Tang)* is a traditional herbal medicine and used to treat metabolic diseases in Asia, especially in women. We evaluated the gender specific effect of *BOT* on postprandial glucose and lipid metabolism with incretin axis.

Research Design and Methods: Age and BMI matched subjects (6 men and 5 women) were evaluated for 2 weeks *BOT* treatment on postprandial glucose, lipid metabolism and incretin axis on meal tolerance test with ^{13}C-glucose breath testing to measure glucose oxidation rate.

Results: *BOT* significantly decreased glucose oxidation rate only in women. Postprandial glucose, triglyceride, NEFA, RLP-c and active-GLP1 were not affected by *BOT* administration in either sex.

Conclusions: Traditional herb, *BOT* appears to decreased postprandial glucose oxidation only in women. The gender difference in the effect of glucose oxidation may not be mediated by neither insulin nor incretion dependent pathway.

(Japanese Clinical Trials Registry, No. UMIN000016493)

KEYWORDS: *Boiogito*, glucose metabolism, glucose oxidation, women

Introduction

Metabolic syndrome (MetS) is a cluster of diseases and disorders that increase the risk of developing cardiovascular diseases and diabetes mellitus. The prevalence of MetS is increasing in the populations of not only in obese Caucasian, but also in non-obese Asian, which has resulted in considerable medical and social problems.[1] Obesity is not a sole problems for MetS, while the body mass index (BMI) cut point for screening Asian Americans for prediabetes and diabetes likely to be lower than Caucasians.

Boiogito (BOT, Fang-Yi-Huang-Qi-Tang) is a common formulation in traditional herbal medicine in east Asian countries [5,8] and has been used to treat obesity, fatigue, hyperhidrosis, edema of lower extremities, oliguria, and arthralgia.[8] Shimada, et al. reported that *BOT* had a preventive effect on metabolic disorders in the Tsumura, Suzuki Obese

Diabetes (TSOD) mouse, a model of spontaneous obese type 2 diabetes. In addition to these, BOT is more often used in women than in man.[11] However, if any, few reports have examined how *BOT* improves whole body energy substrate metabolism in such conditions. Thus, we initially investigated the effects of *BOT*, particularly its effects on postprandial glucose and lipid metabolism to clarify the difference of gender

Methods

Subjects

Eleven healthy volunteers, sex (6 men and 5 women), age (36± 11.3 years) and BMI (21.5 ± 2.4) matched, were enrolled in the single center parallel designed trial. No participant had medical treatment, including diabetes mellitus and hyperlipidemia in the 6 months before the start of this study. The protocol of the study was approved by the Ethical Committee of Toho University School of Medicine (No. 21038), University Hospital Medical Information Network; UMIN Clinical Trials Registry, Number UMIN000016493.

Boiogito

BOT is a powdered, freeze-dried water extract and was purchased from Tsumura Co. Ltd. (Tokyo, Japan). According to the manufacturer's instructions, the standard daily dose of *BOT* for adults is 7.5g of powder, which comprises a mixture of 6 decocted medicinal herbs (g): *Sinomenium stem* (5.0), *Astragali radix* (5.0), *Atractylodis rhizoma* (3.0), *Glycyrrhizae radix* (1.5), *Zingiberis rhizoma* (1.0) and *Zizyphi fructus* (3.0). Participants were given *BOT* 3 times a day (2.5 g per dose) for 2 weeks.

Test meal (cookie test)

A test meal consisted of 30 pieces of solid test cookies, which in total consisted of 75g carbohydrate (85% flour starch, 15% maltose), 28.5g butterfat, 1.6g fiber, and 8.0g protein and contained 592 kcal (Neocookie; SARAYA Co.Ltd., Osaka, Japan).[3]

Laboratory testing

Venous blood was sampled from each participant using a conventional method every 30 min from 9:00 AM to 12:00 PM (7 times in total). Plasma concentrations of glucose, insulin, triglyceride, free fatty acid (FFA), active glucagon-like peptide-1(GLP-1) and remnant-like particle cholesterol (RLP-C) were measured.

^{13}C-glucose breath test

^{13}C-glucose breath testing is non-invasive, simple method to detect dynamic alteration of metabolism.[2,7] Based on the previous researches, this test had been performed as done with other herbal medicine.[9] Briefly, on the day of the test, each participant took the last dose of *BOT* at 8:00 AM and ate the test meal between 8:30 and 8:45 AM, along with 200 ml of tap water containing 100mg of [1-^{13}C]-glucose (Otsuka Pharmaceutical Co. Ltd. Tokyo, Japan). Breath samples were collected every 10 min for 180 min, starting at 9:00 AM. Baseline (*i.e.*, without ^{13}C) breath samples were collected before 8:30 AM. Stable isotope ^{13}C enrichment in each sample was measured, and the glucose oxidation rate of each participant was calculated as previously described.[4] ^{13}C enrichment was measured as the tracer to tracee ratio and was expressed as Δ over baseline per mil (‰) using a non-dispersive infrared isotope spectrometry device (UBiT-IR 300; Otsuka Electronics Co.,Ltd., Osaka, Japan).

The results were converted to percentage $^{13}CO_2$ recovery in breath per hour (% dose/h) based on body surface area (BSA) and the assumed CO_2 production (VCO_2) as follows:

$$\%\ \text{dose/ hour} = \Delta‰ \times VCO_2 \times 0.01123 \times 10/\text{dose(mg)} \times \text{atom\% excess(APE)/molecular weight(MW)}$$

where MW is 46, VCO_2 is 300 (BSA mmol/hour, BSA(m^2) is $0.024265 \times \text{weight(kg)}^{0.5378} \times \text{height}^{0.3964}$ (cm), A (dose) is 80mg and APE is 99.5 atom%. Maximum concentration (C_{max}; %dose/ hour), time to maximum concentration (T_{max}; min), and area under the curve

(AUC) at each time point (%dose/ hour・min) were calculated. C_{max} and AUC reflect absorption of the labeled substrate.

Statistical analysis

The two way layout analysis of variance (ANOVA) was used to analyze the difference of the paired-data by sex and each time. After that, we calculate the Wilcoxon signed-rank test, to examine the statistical significance of any difference in measurements. All values are expressed as mean standard deviation (SD). A p value less than 0.05 was considered to indicate statistical significance.

Results

Eleven healthy volunteers (5 women and 6 men) participated in this study. The results of ^{13}C-glucose breath tests are shown in Fig. 1. The two way layout ANOVA was revealed the significant difference of the paired-data between baseline and after two weeks administration of *BOT* by sexes. *BOT* significantly decreased glucose oxidation from 20 to 170 min ($p<0.05$) only in women. No characteristic other than sex was associated with a significant difference in measurements.

Glucose, Insulin, serum active GLP-1, FFA, triglyceride (TG), RLP-C concentration were not statistically significant by *BOT* in either sex (Fig.2).

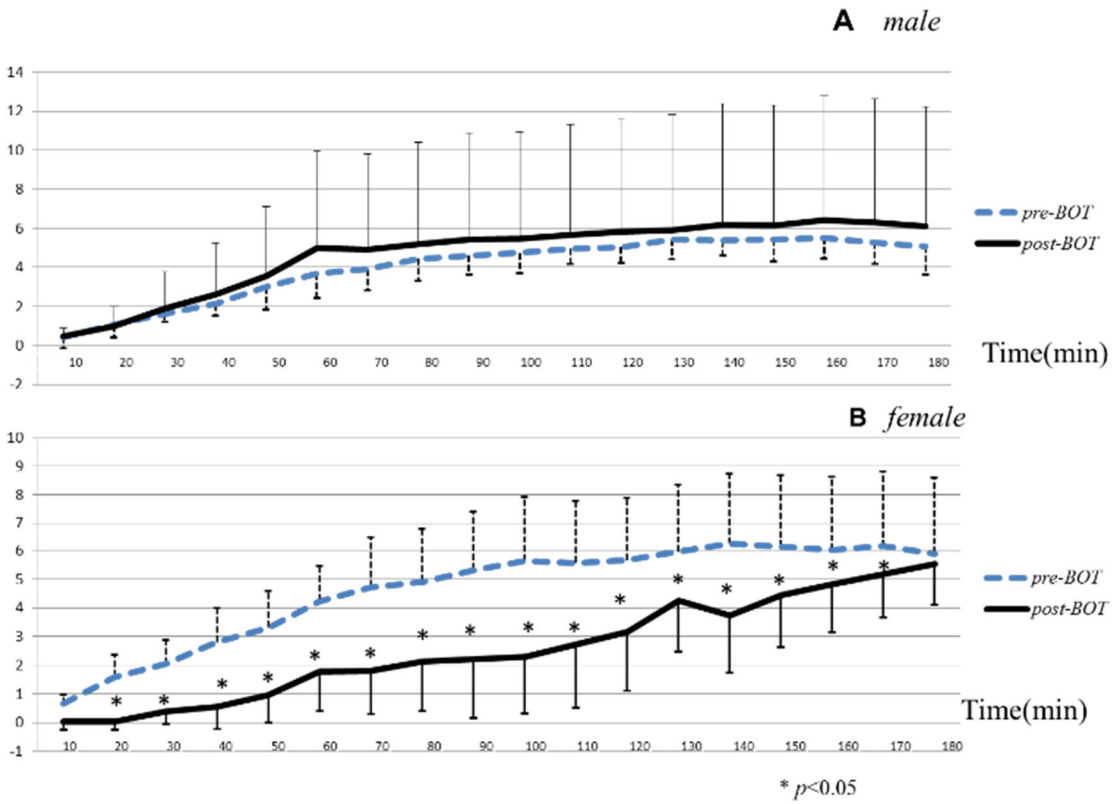

Figure legends

Postprandial ^{13}C-glucose breath test as measured by 13C-glucose oxidation rate (% dose / hour), in male (A) and female (B). Dotted line and solid line indicate pre- and post- *Boiogito* (*BOT*) values, respectively. *BOT* significantly decrease glucose oxidation in female, but not in male from 20 to 170 min ($p<0.05$). Values are mean ± SD.

Discussion

This is the first report to study the effect of herbal medicine, BOT, on postprandial dynamic alternation on energy substrate metabolism. We evaluated glucose oxidation with ^{13}C-glucose breath testing which is non-invasive method. In the present study, two weeks' *BOT* ingestion induced decrease postprandial ^{13}C-glucose oxidation in women. However, postprandial blood glucose, insulin and active GLP-1 concentration was not altered by *BOT* in both men and women.

BOT has been used to treat a number of conditions in obese people for more than two millenniums and traditionally suggested that it improves obesity among women. If *BOT* delays glycolysis without changing total energy expenditure, the body would instead obtain energy by lipid oxidation. Such lipid consumption decreases fat stores, thus reducing obesity, albeit serum TG, FFA and RLP-c level did not significantly change in this trial. This might be considered either by enhanced rates of lipid turnover or reduced glucose absorption by intestine.

Hoo et al. isolated the effective fraction from *Astragali radix*, a principal ingredient of *BOT*, and reported that it alleviates glucose intolerance, insulin resistance and hypertriglyceridemia in *db/db* diabetic mice[4].

It is widely believed that *BOT* is an effective treatment for obesity in middle-aged women, which slows postprandial glucose oxidation rate somewhat observed in the present study. Sex differences in lipid and glucose metabolism has recently been investigated. Lipid oxidation tends to be suppressed lower in female than in male with oral fructose ingestion[7]. Besides, it is known that female has sex-specific mechanism relevant in nutritional change, might be the effect of fibroblast growth factor 21 (FGF 21)[6]. BOT may also share the sex-specific difference in fuel energy metabolism.

Although the present findings were preliminary data, this study suggests that the herbal formulation *BOT* decreased postprandial glucose oxidation rate, which is independent on neither insulin nor GLP-1-incretin pathways, in healthy women. Further studies of patients with metabolic syndrome and diabetes are needed to determine the precise effects of *BOT* on energy metabolisms and substrate oxidation rate.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests Statement

All authors have no competing financial interests to declare.

Contributorship Statement

K.T, H.U, K.N., T.N., K.S., T.H., and Y.U. contributed to the research and reviewed and edited the manuscript. K.T. contributed to the research, data analysis and interpretation, discussion, and writing of the manuscript. H.U. contributed research, data analysis and interpretation , discussion, and writing the manuscript. K.N. contributed research, data analysis and interpretation , discussion, and writing the manuscript. T.N. contributed to the protocol, data generation, discussion and writing the manuscript. K.S contributed to the protocol, data generation, discussion and writing the manuscript. T.H. contributed to the research, data analysis and interpretation, and writing and editing of the manuscript. Y.U. contributed to the research, data analysis and interpretation, and writing and editing of the manuscript. K.T. and H.U. are guarantor of this work, had full access to all the data and takes responsibility for the accuracy of the data and the analysis.

Data sharing statement No additional data are available.

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