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CORRESPONDENCE

Gender difference in the effects of cacao polyphenols on blood pressure and glucose/lipid metabolism in prediabetic subjects: a double-blinded, randomized, placebo-controlled crossover trial

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Several clinical studies have demonstrated the beneficial effects of cacao polyphenols in the prevention of cardiovascular disease [1]. One of the underlying mechanisms of such beneficial effects is the antioxidant effect of cacao [2]. Some studies have previously reported favorable effects of cacao supplements on parameters related to cardiovascular risk (i.e., vascular function parameters, blood pressure, and/or glucose metabolism) [3]. However, whether these favorable effects are significant, even in the early stage of elevated cardiovascular risk, remains to be clarified. Furthermore, gender differences in the risk of development of cardiovascular disease have also been well recognized [4], and recently, the contribution of oxidative stress to these differences has been reported [5]. However, gender differences regarding the favorable effects of cacao supplements on the risk of cardiovascular disorders have not yet been clarified.

The present study was conducted to examine the effects of a cacao-derived antioxidant supplement on the blood pressure, glucose/lipid metabolism, and vascular function parameters in subjects with early-stage abnormalities of glucose metabolism and to examine the gender differences in such effects using a double-blinded, randomized, placebo-controlled crossover design.

Prediabetic (glycated hemoglobin 5.8–6.5%) men and women aged 40–69 years who had not received any anti-diabetic treatment were recruited. The exclusion criteria for enrolment in the study consisted of a history of cardiovascular disease; malignant disease; other chronic diseases, including cardiovascular disease risk factors other than prediabetes (i.e., dyslipidemia, hypertension, and chronic kidney disease); body mass index ≥27.5/<18.5 kg/m^2; current smoking; heavy drinking; habitual use of antioxidant supplements; and allergy to milk/milk products/chocolate/cacao. Seventy volunteers were clinically screened by a physician, and 22 volunteers were enrolled in this study. Informed consent was obtained from all participants prior to the measurements. The study was conducted with the approval of the Ethics Guidelines Committee of Tokyo Medical University.

After enrolment, the subjects were randomly allocated to two groups (two orders of the intervention, from control to cacao and from cacao to control). Subjects took the cacao procyanidin supplement (83.3 ± 2.7 mg/day) in two divided doses (morning/evening 41.6 ± 1.4 mg/dose) or a placebo for 4 weeks. Each tablet contained 13.9 ± 2.7 mg procyanidins or 240 mg dextrin (placebo); therefore, 6 tablets/day were prescribed. A 2-week run-in period and a 3-week wash-out period were set between the cacao control (placebo) and cacao periods. Home blood pressure was monitored by tele-monitoring from the run-in period to the end of the study. Vascular functions and other cardiovascular risk factors were measured at the beginning and end of each intervention period. Control tablets were coated with dextrin. Experimental tablets contained the polyphenol extracts from the cacao bean. The amounts of procyanidins are represented as the epicatechin equivalent [6].

The mean age of the participants at baseline was 59.3 ± 7.1 years. All female participants were postmenopausal. In the total study population, no differences in any of the variables were observed between the cacao and control periods. In the subanalysis, the cacao supplement significantly reduced the office blood pressure and serum low-density lipoprotein levels and marginally reduced the homeostatic model assessment of insulin resistance and plasma insulin levels in women but not in men (Figs. 1 and 2). The cacao supplement had no effect on the vascular function [brachial–ankle pulse wave velocity,

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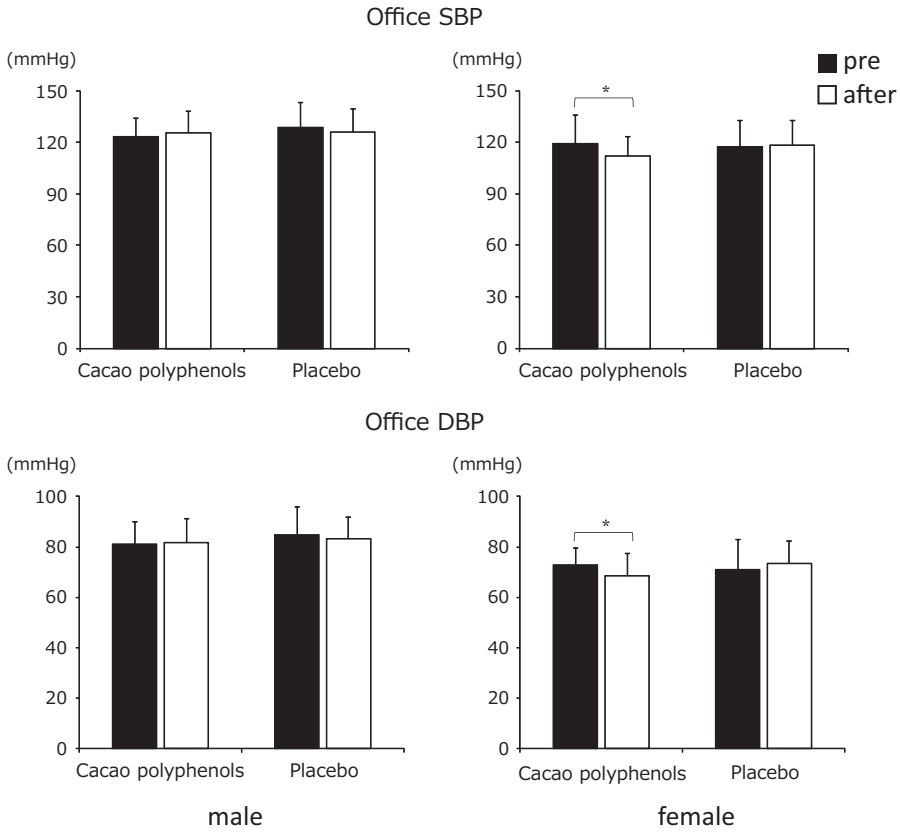

Fig. 1 Effects of cacao polyphenols and the placebo on the HOMA-IR and serum LDL cholesterol. HOMA-IR homeostatic model assessment of insulin resistance, LDL low-density lipoprotein. *$p < 0.05$ vs. baseline

radial augmentation index, flow-mediated vasodilatation, and reactive hyperemia peripheral arterial tonometry (RH-PAT)] in either men or women.

The present study only focused on prediabetic subjects because oxidative stress is thought to play pivotal roles in the development of abnormalities related to cardiovascular diseases in these subjects [7]. However, in the overall study population including men and women, we could not confirm any beneficial effects of the cacao-derived antioxidant supplement on the risk factors of cardiovascular disease.

However, gender-related differences in the degree of oxidative stress are known [5]. Recently, du Plooy et al. reported that higher total glutathione levels may act as a counter-regulatory mechanism to protect against the oxidative vascular damage caused by endothelin-1 in black women [8]. Under physiological conditions, females appear to be less susceptible to oxidative stress. This may be due to the antioxidant properties of estrogen [5]. A subanalysis of the present study demonstrated the beneficial effects of a cacao-derived antioxidant supplement on the risk factors of cardiovascular disease. However, the supplement exerted no effect on endothelial function. Therefore, in the postmenopausal state, oxidative stress might have no direct adverse effect on vascular function.

According to an experimental study, in the estrogen-deficient state, oxidative stress causes insulin resistance via reduction of the expression of antioxidant enzymes such as superoxide dismutase (SOD1) and glutathione peroxidase (GPX1), as well as via increases in the pro-oxidative enzyme NADPH oxidase (NOX4) and mitogen-activated protein kinases extracellular signal–regulated kinase 1/2 and p38 [9]. Apart from these cellular mechanisms of insulin resistance, abnormal blood flow in the peripheral tissues is also an important factor that affects insulin resistance [10]. However, the cacao-derived antioxidant supplement in this study had no effect on endothelial function, including in the peripheral arteries, as assessed by RH-PAT. Thus these cellular mechanisms may play pivotal roles in the development of insulin resistance in prediabetic postmenopausal women.

An experimental study reported that estrogen prevents elevation of the blood pressure caused by increased oxidative stress [11]. The results of the present study indicate that the cacao-derived antioxidant supplement reduced blood pressure in postmenopausal women and suggested that oxidative stress may have a causal role in the elevation of blood pressure in these female subjects. In the present study, the supplement did not affect the endothelial function or other vascular function parameters that are thought to participate in changes in blood pressure. Therefore, one of the plausible mechanisms of blood pressure reduction by this supplement in menopausal women is that it might counteract the mechanisms involved in insulin-related elevation of blood pressure, such as increases in renal sodium reabsorption and/or sympathetic nervous activity.

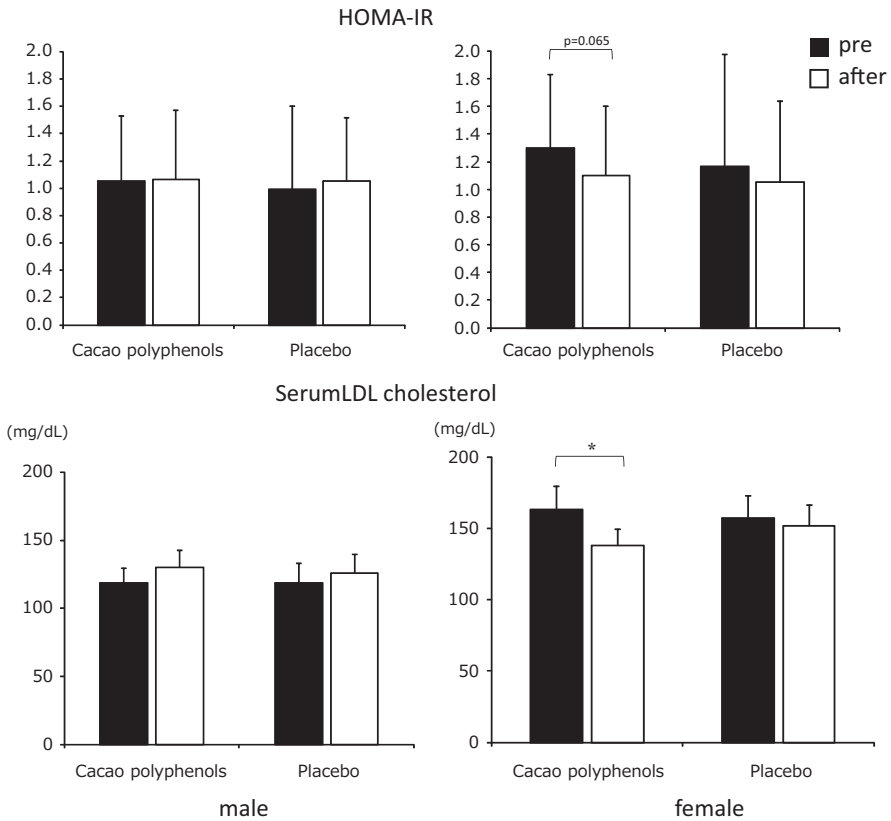

Fig. 2 Effects of cacao polyphenols and the placebo on office blood pressure. SBP systolic blood pressure, DBP diastolic blood pressure. *$p <$ 0.05 vs. baseline

These results suggest that oxidative stress may increase the risk of blood pressure elevation and induce abnormalities in glucose/lipid metabolism in postmenopausal women with prediabetes but not in prediabetic men. The cacao-derived antioxidant supplement may exert preventive effects on the development of hypertension, diabetes mellitus, and dyslipidemia, especially in postmenopausal women.

Compliance with ethical standards

Conflict of interest KS, HT, and AY received a research grant for this study from Meiji Co., Ltd. The other authors declare that they have no conflict of interest.

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