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CORRESPONDENCE

Modulation of blood pressure-lowering effects of dark chocolate according to an insulin sensitivity-randomized crossover study

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Dark chocolate (DC) may lower blood pressure (BP) by improving vascular function and insulin sensitivity (IS) [1]. However, the underlying mechanism remains unclear. Recently, home blood pressure (HBP) telemonitoring has been regarded as a sensitive and reliable method of evaluating hypertension [2], and day-to-day variability in HBP associated with vascular dysfunction has been reported as a predictor of cardiovascular disease (CVD) [3–5].

However, no previous study has comprehensively evaluated the effects of DC on HBP telemonitoring/HBP variability, vascular function, and IS. In addition, few studies have reported the effects of DC on BP among East Asian people, even though ethnic differences in glucose/insulin regulation have been suggested [6].

This study comprehensively evaluated the effect of DC consumption on HBP telemonitoring/HBP variability, vascular function, and IS. We also assessed the effect modification between DC consumption and IS in Japanese subjects.

We conducted a single-blinded, randomized, and controlled crossover study. Twenty apparently healthy middle-aged volunteers with a high normal BP or mild hypertension (130 mmHg ≤ office systolic BP (SBP) < 160 mmHg, 85 mmHg ≤ office diastolic BP (DBP) < 100 mmHg) without antihypertensive treatment were recruited. The exclusion criteria were chronic disease including CVD and its risk factors other than mild hypertension, obesity, current smoking habit, and premenopausal status. Informed consent was obtained from all the participants. The study was conducted with the approval of the Ethics Guidelines Committee of Tokyo Medical University. This trial was registered at http://www.umin.ac.jp/ as UMIN000028364.

The subjects consumed a total of 24 g/day of DC (total polyphenol: 540 mg) or white chocolate (total polyphenol: 0 mg) as a control for 4 weeks. The quantity of DC was determined based on previous studies [1]. The other nutrients contained in DC and white chocolate were almost the same. A 2-week run-in period and a 2-week wash-out period between the DC and control were provided. Vascular function and other CVD risk factors were measured at the beginning and end of each chocolate intervention period.

The HBP was measured twice in the morning using an OMRON HEM7251G device before breakfast. The mean HBP was calculated using the mean of the BP values obtained 5 days before the start and end of each intervention period. HBP variability was evaluated using the standard deviation and coefficient of variation of the mean HBP. Vascular function was evaluated by flow-mediated vasodilatation, brachial-ankle pulse wave velocity, radial augmentation index, and central BP. Markers of glucose/lipid metabolism, the renin–angiotensin–aldosterone system (plasma aldosterone/renin activity), and oxidative stress (serum 8-OHdG) were measured in fasting blood samples.

The effects of DC were assessed using a mixed analysis. A subgroup analysis to evaluate the potential effect modification between DC and the baseline IS (HOMA-IR; tertile) was performed.

The baseline characteristics prior to each chocolate intervention were not significantly different (Table 1). The overall compliance rate of each chocolate intervention was 99%. DC lowered the office DBP by 3.8 ± 1.2 mmHg ($P = 0.004$) but did not have any significant effects on other factors, including HBP variability, vascular function, markers of glucose/lipid metabolism, the renin–angiotensin–aldosterone system, and oxidative stress. On the other hand, in subjects with the lowest tertile of HOMA-IR, DC decreased the home SBP/

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Table 1 Baseline characteristics of the study subjects at the start of the study

Characteristic	Mean ± SD
Age (year)	53.8 ± 4.4
Female (*n*, %)	9 (45%)
BMI (kg/m^2)	24.6 ± 0.4
Office SBP (mmHg)	126 ± 9
Office DBP (mmHg)	85 ± 7
Office HR (bpm)	68 ± 13
Home SBP (mmHg)	134 ± 9
SD of home SBP	7.4 ± 4.1
CV of home SBP	5.5 ± 3.0
Home DBP (mmHg)	87 ± 8
SD of home DBP	6.0 ± 3.5
CV of home DBP	6.9 ± 3.8
Home HR (bpm)	71 ± 13
FMD (%)	6.0 ± 2.3
baPWV (cm/s)	1407 ± 180
rAI (%)	87.3 ± 8.1
CBP (mmHg)	148 ± 12
Fasting glucose (mg/dl)	103 ± 11
Serum insulin (μU/ml)	5.44 ± 2.62
HOMA-IR	1.40 ± 0.71
LDL cholesterol (mg/dl)	129 ± 30
HDL cholesterol (mg/dl)	57 ± 15
Triglycerides (mg/dl)	145 ± 100
Plasma Aldosterone (pg/ml)	156 ± 64
Plasma renin activity (ng/ml/h)	0.98 ± 0.69
Serum 8-OHDG (ng/ml)	0.22 ± 0.12
Total energy consumption (kcal/day)	1943 ± 444
Carbohydrate (g/day)	242 ± 63
Fat (g/day)	55 ± 16
Protein (g/day)	65 ± 17
Na (mg/day)	4332 ± 1216
K (mg/day)	2336 ± 627
Alcohol (g/day)	27 ± 34
Exercise (Mets/day)	6.5 ± 10.3

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SD* standard deviation, *CV* coefficient of variation, *FMD* flow-mediated dilation, *baPWV* brachial pulse wave velocity, *rAI* radial augmentation index, *CBP* central systolic blood pressure, *HOM-IR* homeostatic model assessment of insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *8-OHDG* 8-hydroxy-2′-deoxyguanosine

DBP (home SBP: −11.9 ± 3.2 mmHg, home DBP: −8.1 ± 2.2 mmHg, both $P < 0.05$; interaction $P < 0.05$) but did not affect HBP variability or other factors (Table 2).

In this study, DC lowered the office DBP but did not have any significant effects on other factors overall. On the other hand, the effect modification between DC and IS was statistically significant with a decrease in home SBP/DBP in subjects with normal IS.

To the best of our knowledge, our study is the first to comprehensively evaluate the effect of DC on HBP telemonitoring, HBP variability, vascular function, and other CVD risk factors.

Our results are partly consistent with some previous studies. A recent meta-analysis of RCTs reported a reduction in DBP, but not SBP, after the chronic intake of a cocoa product [1]. In addition, a Cochran review revealed a greater BP-lowering effect of cocoa in persons younger than 45 years and in those with an initial SBP higher than 140 mmHg [7]. Compared with this review, the mean age of our study participants was older, and the mean SBP was lower. Therefore, the BP-lowering effects of DC consumption might have been attenuated in our study participants.

We may also need to consider ethnic differences in insulin regulation, since East Asian populations reportedly have lower insulin secretion levels and higher IS than Caucasian and African populations [6, 8]. One study from Italy reported BP-lowering effects of DC in hypertensive patients with impaired glucose tolerance [9]. Thus, it might be shortsighted to conclude that only subjects with a normal IS will benefit from DC in the Japanese population, since not many studies have evaluated the effects of DC among Japanese people. In fact, one previous study suggested the BP-lowering effects of cacao polyphenol in the Japanese prediabetic women [10].

Regarding HBP variability, no impairment by DC consumption was observed. Our results suggested that the potential cardioprotective effects of DC might not be due to the modulation of HBP variability.

Our study has several strengths, including the use of telemonitoring HBP to obtain precise HBP measurements and comprehensive evaluation of CVD risk factors. Nevertheless, this study also had several limitations. First, a potential carryover effect between each chocolate intervention may exist. However, the 2-week wash-out period might be enough to remove any carryover effects. Second, the sample size in the subgroup analysis was not large enough to evaluate the effects of DC. However, DC consumption reduced not only the HBP but also the office BP among subjects with normal IS, and this consistency supports the robustness of our findings. Nonetheless, additional studies with large sample sizes are needed.

A common amount of DC may have a beneficial effect on BP without affecting vascular function in subjects with normal IS, but these beneficial effects may be blunted in subjects with impaired IS. Further studies are needed to confirm or refute this finding.

Table 2 Difference between effect of daily dark chocolate and white chocolate consumption on markers according to the tertiles of HOMA-IR at baseline

	Difference between effect of dark chocolate and white chocolate				
	The lowest tertile of HOMA-IR ($N = 7$, HOMA-IR:0.3–1.0)		The highest tertile of HOMA-IR ($N = 7$, HOMA-IR:1.8–3.1)		
	Difference (SE)	*P* value	Difference (SE)	*P* value	Interaction *P*
BMI (kg/m^2)	−0.47 (0.26)	0.145	0.09 (0.13)	0.545	–
Office SBP (mmHg)	−8.1 (3.4)	0.079	3.4 (3.1)	0.338	0.007
Office DBP (mmHg)	−6.0 (2.7)	0.053	−4.3 (2.4)	0.103	0.015
Office HR (bpm)	2.4 (2.8)	0.407	4.3 (2.9)	0.211	–
Home SBP (mmHg)	−11.9 (3.2)	0.021	4.7 (3.1)	0.159	0.009
SD of home SBP	0.2 (1.0)	0.842	−5.7 (2.8)	0.074	–
CV of home SBP	0.6 (0.7)	0.409	−4.5 (2.0)	0.052	–
Home DBP (mmHg)	−8.1 (2.2)	0.022	5.4 (3.0)	0.106	0.054
SD of home DBP	−1.9 (2.0)	0.388	−4.7 (2.6)	0.102	–
CV of home DBP	−1.3 (2.3)	0.581	−5.6 (3.0)	0.095	–
Home HR (bpm)	−0.6 (3.6)	0.875	−1.3 (2.9)	0.686	–
FMD (%)	−0.19 (1.28)	0.890	−2.27 (1.65)	0.204	–
baPWV (cm/s)	29 (39)	0.471	−134 (30)	0.012	–
rAI (%)	−4.3 (3.2)	0.201	3.2 (3.7)	0.443	–
CBP (mmHg)	−12.6 (7.4)	0.125	−10.3 (5.2)	0.119	–
HOMA-IR	−0.23 (0.19)	0.269	−0.36 (0.63)	0.583	–
Fasting glucose (mg/dl)	1.6 (2.8)	0.578	2.1 (3.6)	0.597	–
Serum insulin (μU/ml)	−0.81 (0.71)	0.283	−0.70 (2.76)	0.804	–
HDL cholesterol (mg/dl)	−3.1 (2.1)	0.221	0.6 (3.6)	0.876	–
LDL cholesterol (mg/dl)	0.2 (8.0)	0.981	10.6 (4.2)	0.065	–
Triglycerides (mg/dl)	31 (23)	0.252	−54 (43)	0.284	–
Plasma renin activity (ng/ml/h)	−0.09 (0.15)	0.567	−0.38 (0.56)	0.513	–
Plasma Aldosterone (pg/ml)	−1.2 (28.3)	0.969	−23.2 (49.7)	0.651	–
Serum 8-OHDG (ng/ml)	0.05 (0.05)	0.346	0.05 (0.13)	0.7223	–

The treatment effects (effects of dark chocolate consumption) were calculated as the changes in each value at the beginning and the end of each intervention period, and random subject-effect models of the restricted maximum likelihood (REML) analyses for linear mixed models were applied. The treatment was set as fixed effect and the subjects were set as a random effect. The interaction *P* was also assessed to evaluate the effect modification by evaluating a cross-product term of treatments and HOMA-IR

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SD* standard deviation, *CV* coefficient of variation, *FMD* flow-mediated dilation, *baPWV* brachial pulse wave velocity, *rAI* radial augmentation index, *CBP* central systolic blood pressure, *HOM-IR* homeostatic model assessment of insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *8-OHDG* 8-hydroxy-2′-deoxyguanosine

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Compliance with ethical standards

Conflict of interest CM obtained a research grant for this study from Morinaga & Co. Ltd., Japan. HI and MK serve as members of Morinaga & Co., Ltd.

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