High-cocoa polyphenol-rich chocolate improves blood pressure in patients with diabetes and hypertension

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Original Article

Abstract

BACKGROUND: The aim was to examine the effects of high-cocoa polyphenol-rich chocolate on lipid profiles, weight, blood pressure, glycemic control, and inflammation in individuals with Type 2 diabetes and hypertension.

METHODS: Sixty individuals [32 in dark chocolate group (DCG) and 28 in white chocolate group (WCG)] with Type 2 diabetes on stable medication were enrolled in a randomized, placebo-controlled double-blind study. Subjects were randomized to consume 25 g DCG or WCG for 8 weeks. Changes in weight, blood pressure, glycemic control, lipid profile, and high sensitive C-reactive protein (hsCRP) were measured at the beginning and end of the intervention. This clinical trial was registered at the Iranian registry of clinical trials.

RESULTS: In DCC group, compared with baseline, serum levels of Apo A-1 (P = 0.045) was increased and fasting blood sugar (FBS) (P = 0.027), hemoglobin A1c (HbA1c) (P = 0.025), Apo B (P = 0.012) and Log of hsCRP (P = 0.043) levels were decreased at the end of study. No changes were seen within the WCG in studied parameters. High polyphenol chocolate consumption compared to white chocolate resulted in significant decrease in of systolic (−5.93 ± 6.25 vs. −1.07 ± 7.97 mmHg, P = 0.004) and diastolic blood pressure (−6.4 ± 6.25 vs. 0.17 ± 7.9 mmHg, P = 0.002), FBS (−7.84 ± 19.15 vs. 4.00 ± 20.58 mg/dl, P = 0.019) over the course of 8 weeks of daily chocolate consumption neither weight nor body mass index and TG levels altered from baseline.

CONCLUSION: High polyphenol chocolate is effective in improving TG levels in hypertensive patients with diabetes and decreasing blood pressure and FBS without affecting weight, inflammatory markers, insulin resistance or glycemic control.

Keywords: Chocolate, Polyphenols, Type 2 Diabetes, Cardiovascular Risk, Lipid Profile, High Density Lipoprotein Cholesterol, Apolipoprotein

Introduction

The prevalence of Type 2 diabetes mellitus is rising worldwide, accompanied by an increasing risk of hypertension, cardiovascular disease, and mortality.[1] According to the result of the recent survey on the risk factor of chronic disorders in Iran, indicated that 7.8% of adult with age 25-64 years have Type 2 diabetes mellitus.[2] In diabetes, hypertension (defined as a blood pressure ≥ 140/90 mmHg) is a common comorbid condition affecting ~20-60% of diabetic patients, depending on obesity, ethnicity, and age. In observational studies, patients with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as nondiabetic patients with hypertension. Patients with diabetes and hypertension have also increased the risk of specific complications, including retinopathy and nephropathy.[3]

Intense pharmacologic treatment regimens are necessary, but often remain inadequate to prevent incidence and complications of Type 2 diabetes

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mellitus.[4] Observational studies have shown that physical activity, weight loss, and diet can prevent diabetes and its complications.[4]

Diet is a major lifestyle factor that can greatly influence the incidence and the progression of chronic diseases such as cancer, cardiovascular disease, and diabetes.[1] Recently, flavanols, a subgroup of plant-derived phytochemicals called flavonoids, have gained increasing attention, because epidemiological investigations revealed an inverse correlation between the dietary intake of flavanols and the mortality of cardiovascular disease,[5] and the incidence of diabetes.[6] In the context of human nutrition, flavanols are found in fruit, vegetables, tea and red wine and especially with high concentrations can be present in cocoa and cocoa products.[7] Dietary interventions with flavanol-containing cocoa products in humans indicate beneficial effects of flavanols on low-density lipoprotein oxidation,[8] platelet aggregation,[9] insulin sensitivity,[10] endothelial function and blood pressure.[11]

It has been hypothesized that flavonoid compounds found in foods, including epicatechin found in high-cocoa-solid chocolates, decrease the risk of death from coronary heart disease, cancer and stroke.[12] Short-term administration of dark chocolate was followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy subjects.[13] Therefore, we hypothesized that daily consumption of chocolate (25 g daily) containing polyphenol-rich; high-cocoa solids for 8 weeks would improve cardiovascular risk factors in patients with diabetes and hypertension.

Materials and Methods

This randomized, placebo-controlled, double-blind study was undertaken in the endocrinology and metabolism Institute of Tehran University of Medical Sciences, Iran, located at Firoozgar Hospital and the study was funded by the Tehran University of Medical Sciences. The study was approved by the Tehran University Ethics Committee, and written consent was obtained from all subjects prior to enrollment.

This study was conducted on 35-70 years old patients with diabetes and hypertension Type 2 referred to Firoozgar Hospital from March 2011 to February 2012. Sixty-eight subjects [4 in dark chocolate group (DCG) and 34 in white chocolate group (WCG)] with established Type 2 diabetes (age for DCG = 58.71 ± 9.07 and for WCG = 57.17± 7.86 years) were enrolled by blocked randomization

method. During the study 2 cases because of insulin use in DCG and 6 cases from WCG because of insulin use (n = 2) and other supplement consumption (n = 4) were excluded. Whom 60 patients (32 in DCG and 28 in WCG) completed the study. The mean diagnosis duration of diabetes was (mean ± standard deviation for DCG = 7.46 ± 4.62 and for WCG = 7.92 ± 3.92) months. Inclusion criteria were diagnosis of Type 2 diabetes based on the World Health Organization guidelines [fasting blood sugar (FBS) > 126 mg/dl or 2h BS > 200 mg/dl][14] and systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90.[15] Exclusion criteria included hemoglobin A1c (HbA1c) > 9.0%, treatment with insulin, any change in use of medication in the previous 2 months, having any kind of special diets such as vegetarian, lactation, pregnancy, congestive heart failure, malignancies, chronic kidney disease, severe cardiac arrhythmias and inflammation. All participants were either life-long nonsmokers or reported smoking abstinence of at least 5 years before study inclusion. All of the subject's chronic medications such as lipid reducing and blood pressure reducing drugs were maintained at stable doses for at least 2 months prior to the start of the study. The subjects were given chocolate bars containing either dark chocolate or white chocolate in the same package by blind person. The chocolates delivered as a monthly manner and compliance were assessed by asking for how many of the chocolate bars were used. Individual's adherence after 8 weeks intervention was determined by total chocolate number to consumed chocolate. The individuals with < 80% consumption were excluded. Subjects were advised not to consume any other chocolate during the period of the study. In addition, subjects were instructed to make no further changes to their diet, lifestyle, and physical activity. Flow of participants through each stage of the study is available in figure 1.

The chocolate for the study was provided by Farmand Co. The active product was high-polyphenol chocolate containing 83% cocoa solids compared with iso-caloric white chocolate, and was packaged to the same color and shape as high polyphenol chocolate. 25 g foil-wrapped bars were provided individually, and subjects were asked to consume one bar every day. Chocolate bars in the aluminum foil administered in dated, sequentially numbered, nontransparent boxes not labeled about content. Involved physicians and staff were unaware of the group assignment. Patients did not receive information regarding the chocolate and were instructed not to disclose their assigned group to

investigators. To avoid changes in body weight during the intervention, participants were carefully instructed how to make proportional reductions in energy from their habitual diet to substitute for that supplied by chocolates. This amount of dark chocolate would provide a total of 143 kcal daily, with 450 mg flavonoids in comparison with the same amount of calories without flavonoids in white chocolate.

Weight was measured in fasting state using calibrated weighing scales in light clothing and bare feet with nearest of 0.1 kg. Height was measured by un-stretched tape with the nearest of 0.5 cm without shoes and standing position near to the wall. Body mass index (BMI) was calculated as the weight (kg) divided by height (m²).

To obtain information about dietary intake and to confidence none change calorie consumption in baseline and endpoint of study, participants were asked to 24 h record dietary intakes using 3 days

dietary records (one for weekend and 2 for week days) in the baseline and end of the study. Dietary intake data was processed using Nutritionist IV software (First Databank, San Bruno, Calif., USA) modified for Iranian food. International Physical Activity Questionnaire was used for evaluating physical activity levels before and after of the study. 10 ml fasting venous blood samples were separated by centrifugation at 3000 g and stored at -80 °C. Systolic and diastolic blood pressure was reported on average of two properly measured in the right or left arm supported at the heart level of seated position after 10 min of rest by a trained nurse using a mercury sphygmomanometer (Model Gamma G-7; Heine).[16] Fasting plasma glucose was measured by the glucose oxidize method (Pars Azmoon kit). HbA1c was measured by high-performance liquid chromatography method (Menarini Diagnostics, Florence, Italy). Insulin was measured by immunoradiometric assay (IRMA) method (Immunotech Co. Kit). Serum concentrations
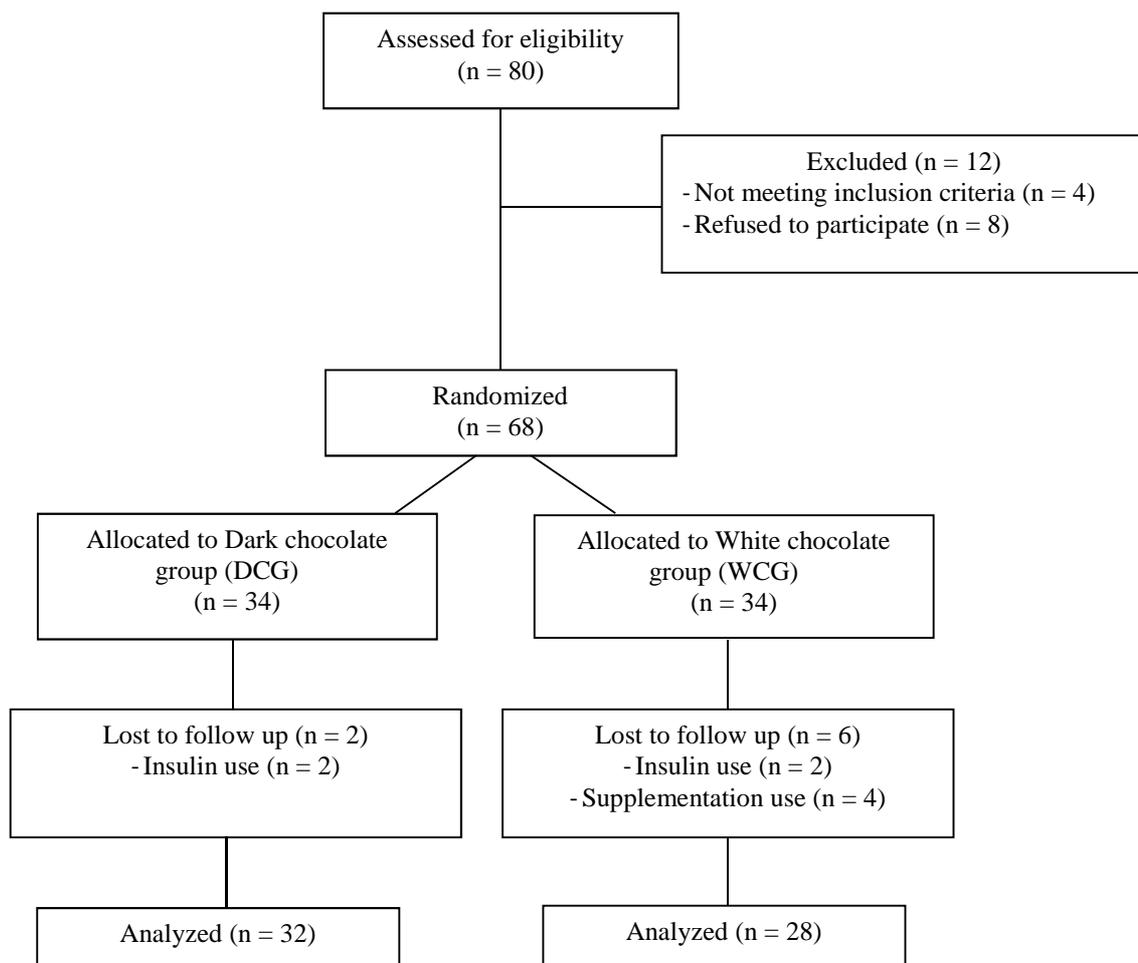
Figure 1. Study participants flow chart

of Triglyceride and total cholesterol were measured using the GPO-PAP kit and the CHOD-PAP kit, respectively (Pars Azmoon kit). High-density lipoprotein (HDL) cholesterol was measured by a direct colorimetric enzymatic method (Greiner). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. (TG levels of all patients were under 400 mg/dl). Apo-lipoproteins AI and B were measured by immunoturbidimetry method by using auto-analyzer Cobas (Pars Azmoon kit) and highly sensitive C-reactive protein (hsCRP) is measured by particle enhanced turbid metric immunoassay (Roche Products, Germany).

We used Kolmongrov-Smirnove test for normal distribution assessment of data. Normally distributed data within groups were compared using paired-samples t-test and between groups by independent-samples t-test. Log of non-normally distributed variables was used for changing their distribution to normal. Continues data are presented as mean ± standard deviation. Discrete variables are presented as n (%) and compared between two groups using chi-square test. Data adjusted for age, sex, energy intake and ANCOVA test used for comparing means between intervention groups. We used the SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA) for all the statistical analyzes. $P < 0.050$ was considered significant.

Results

As shown in table 1, baseline characteristics of the participants did not differ between DCG and WCG. At the baseline of the study, comparison of dietary intakes of energy, carbohydrate, protein, fat, fiber and micronutrients including vitamin C, vitamin E, vitamin A, selenium and zinc showed no significant differences between two groups. Also, within group differences of dietary intake were not significant. Thus, there is not confounder at the baseline (Table 2).

Table 1. Clinical baseline characteristics of the study population[*]

Variable	DCG (n = 32)	WCG (n = 28)	P
Age (year)	58.71 ± 9.07	57.17 ± 7.86	0.650
Weight (kg)	77.62 ± 11.40	76.58 ± 11.33	0.770
Gender			
Men (%)	37.50 (n = 12)	42.90 (n = 12)	0.200[†]
BMI (kg.m^2)	30.12 ± 4.18	29.42 ± 4.58	0.540
Duration of diabetes	7.46 ± 4.62	7.92 ± 3.92	0.360

P values refer to comparisons mean between groups (Independent t-test); [*] Data are means ± SD or percentage; [†] Chi-square test used for comparing; DCG: Dark chocolate group; WCG: White chocolate group; SD: Standard deviation; BMI: Body mass index

Table 2. Baseline and after intervention energy and selected nutrient intake of participants assigned to dark chocolate group (DCG) and white chocolate group (WCG)

Diet ingredient	Intervention group	Before (mean ± SD)	After (mean ± SD)	Mean difference (mean ± SD)	P
Energy (Calories)	DCG	1880.80 ± 495.93	1844.72 ± 51.18	-36.290 ± 327.33	0.120
	WCG	1981.01 ± 504.61	1923.03 ± 468.72	-57.980 ± 364.88	
Carbohydrate (g)	DCG	255.60 ± 72.58	253.20 ± 76.15	-2.400 ± 66.34	0.430
	WCG	264.45 ± 81.50	258.87 ± 76.60	-5.570 ± 84.67	
Protein (g)	DCG	81.33 ± 26.46	78.47 ± 26.63	-2.860 ± 19.12	0.320
	WCG	90.10 ± 40.14	81.28 ± 21.01	-8.820 ± 43.26	
Fat (g)	DCG	62.48 ± 24.95	60.69 ± 21.95	-1.780 ± 23.56	0.560
	WCG	69.75 ± 27.17	66.85 ± 25.82	-2.900 ± 34.86	
Fiber (g)	DCG	12.21 ± 5.92	13.32 ± 5.82	1.110 ± 7.68	0.540
	WCG	14.90 ± 11.71	15.02 ± 6.19	2.640 ± 14.04	
Vitamin A (micro g)	DCG	945.27 ± 742.54	980.10 ± 704.38	34.830 ± 695.50	0.430
	WCG	1067.98 ± 800.76	1022.31 ± 709.27	-45.670 ± 840.37	
Vitamin C (mg)	DCG	87.59 ± 83.30	93.57 ± 85.47	5.980 ± 114.69	0.320
	WCG	92.65 ± 73.37	87.02 ± 85.71	-5.620 ± 14.01	
Vitamin E (mg)	DCG	33.07 ± 63.19	29.82 ± 57.34	-3.240 ± 78.19	0.410
	WCG	43.13 ± 84.22	43.03 ± 82.74	-0.090±123.27	
Zinc (mg)	DCG	7.89 ± 4.06	7.78 ± 2.98	-0.100 ± 3.69	0.320
	WCG	9.26 ± 4.66	8.39 ± 3.03	-0.870 ± 5.91	
Selenium (mg)	DCG	0.10 ± 0.05	0.10 ± 0.05	0.004 ± 0.06	0.340
	WCG	0.11 ± 0.05	0.12 ± 0.05	0.008 ± 0.08	

P values refer to comparisons mean difference between intervention groups (Independent t-test); SD: Standard deviation; DCG: Dark chocolate group; WCG: White chocolate group

Table 3 shows the fasting plasma glucose concentrations, HbA1c, serum lipids and other biochemical variables and the corresponding differences of these variables for the WCG and DCG. Compared to baseline, consumption of dark chocolate resulted in a significant decrease in fasting blood glucose (FBG) (-7.84 ± 19.15 mg/dl, P = 0.027), diastolic blood pressure (-5.93 ± 6.25 mmHg, P = 0.001), systolic blood pressure (-6.4 ± 6.25 mmHg, P = 0.001), HbA1c (-0.14 ± 0.34%, P = 0.025), Apolipoprotein B (-4.46 ± 9.44 mg/dl, P = 0.012) and hsCRP levels (-7.88 ± 17.98 nm/l, P = 0.043) and significant increase in Apo-lipoprotein A-1 level (4.56 ± 12.36 mg/dl, P = 0.045) in DCG. Despite major changes in mentioned variables, no such effects were observed in the WCG. Comparison of the two intervention groups showed that dark chocolate intake resulted in significant decrease in diastolic blood pressure (-5.93 ± 6.25 vs. -1.07 ± 7.97 mmHg, P = 0.002), systolic blood pressure (-6.4 ± 6.25 vs. 0.17 ± 7.99 mmHg, P = 0.004), FBS (-7.84 ± 19.15 vs. 4.00 ± 20.58 mg/dl, P = 0.019) compared to white chocolate consumption. We did not observe any significant effect of dark chocolate consumption on fasting insulin, HbA1c, triglyceride, LDL-cholesterol, HDL-cholesterol, Apo-lipoproteins AI and Apo-lipoproteins B levels comparing to white chocolate consumption.

Discussion

Cocoa has been claimed to protect the vascular endothelium by augmenting nitric oxide (NO) availability and thereby improving Endothelium-dependent vasorelaxation.[17] The results of our study showed that high cocoa chocolate consumption decreased blood pressure among diabetic patients. We did not observe any significant effect of dark chocolate intake on serum triglyceride, FBG, fasting insulin, HbA1c, Apo-lipoprotein B, hsCRP and Apo-lipoprotein A-1 level compared to the WCG. Also, dark chocolate consumption did not affect triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol levels in comparing with WCG.

The low cardiovascular mortality observed in Kuna Indians has been hypothesized to be consequences of high consumption of cocoa-rich beverages.[18] Studies showed that flavanols, subclass of flavonoids is richly represented in natural cocoa beans, increased NO production in cultured human vascular endothelial cells[19] and improved NO depended endothelium vaso relaxation in finger and brachial arteries of healthy humans.[20] Because insulin

sensitivity is dependent on NO availability, we hypothesized that dark chocolate containing polyphenols in addition to the decreasing effect on blood pressure, it might improve insulin sensitivity.[21]

To best of our knowledge, our study was the first study done on the diabetic patients with hypertension. Results of our study showed that feeding of high-polyphenol chocolate for 8 weeks decreased systolic and diastolic blood pressure. A previous report from a prospective study showed a significant inverse relationship between total flavonoid intake and coronary heart disease mortality over a 5 years follow-up period in elderly men.[22] Similarly, the Stockholm Heart Epidemiology Program, assessing the long-term chocolate effects among patients with established coronary heart disease, showed that chocolate consumption had a strong inverse association with cardiac mortality.[23]

Previous studies have suggested that polyphenols could show lipid-lowering effects through different mechanisms including; slowing triacylglycerol absorption via pancreatic lipase inhibitors, increasing fecal excretion of cholesterol,[24] decreasing of hepatic B100 secretion[25] and activation of AMP-activated protein kinase.[26]

The common lipid abnormality in diabetes mellitus is change in plasma triglyceride levels which certainly contribute to the development of cardiovascular disease.[27]

In insulin-deficient diabetic rats, lipoprotein lipase is not activated and hypertriglyceridemia was happened, Mokhtar Ruzaidi et al.[28] Suggested that the chocolate extract increased insulin secretion and hypotriglyceridemic effect of chocolate extract is due to an increase in insulin secretion.

In the agreement to our study, results of Mellor et al. showed that high polyphenol chocolate did not have a significant effect on TG level compared with low polyphenol in diabetic patients.[29]

In other study, daily consumption of dark chocolate did not show a significant effect on TG compared with consumption of white chocolate in healthy subjects.[17] It seems that the dark chocolate has not hypotriglyceridemic impact in diabetic patients and this effect also was not observed in healthy subjects. Inconsistent with our findings, two other studies[13,17] did not observe the effect of chocolate consumption on lipid profiles. In our study, lipid profiles of subjects did not change adversely following the intervention. Thus, the stearic acid in cocoa butter may be an explanation for neuter the beneficial effects of chocolate consumption.

Table 3. Biochemical and anthropometric measurements and mean differences ± standard deviation (SD) at baseline and after the intervention period

	DCG (n = 32)				WCG (n = 28)				P**
	Before	After	Differences	P*	Before	After	Differences	P*	
Diastolic blood pressure (mmHg)	85.15 ± 8.56	79.21 ± 8.89	-5.93 ± 6.25	0.001	86.96 ± 8.08	87.14 ± 8.09	-1.07 ± 7.97	0.920	0.002
Systolic blood pressure (mmHg)	137.03 ± 10.61	130.62 ± 11.19	-6.40 ± 6.25	0.001	137.32 ± 8.55	136.25 ± 8.34	0.17 ± 7.99	0.470	0.004
FBS (mg/dl)	138.06 ± 26.99	130.21 ± 23.67	-7.84 ± 19.15	0.027	134.89 ± 34.46	138.89 ± 30.04	4.00 ± 20.58	0.312	0.019
Fasting insulin	9.77 ± 6.29	9.36 ± 4.70	-0.40 ± 4.68	0.625	10.37 ± 4.63	11.45 ± 5.98	1.04 ± 6.19	0.572	0.141
HbA1c (%)	7.24 ± 1.02	7.10 ± 0.83	-0.14 ± 0.34	0.025	7.55 ± 0.94	7.45 ± 1.19	-0.10 ± 0.78	0.504	0.552
Triglyceride (mg/dl)	118.84 ± 46.02	112.37 ± 41.65	-6.46 ± 19.91	0.110	140.57 ± 47.94	143.57 ± 44.07	3.00 ± 17.82	0.331	0.055
Total cholesterol (mg/dl)	155.65 ± 35.23	153.15 ± 31.35	-2.50 ± 15.55	0.370	158.64 ± 40.33	152.42 ± 37.49	-6.21 ± 19.49	0.103	0.454
LDL cholesterol (mg/dl)	90.59 ± 29.31	87.53 ± 22.44	-3.06 ± 20.56	0.406	95.03 ± 38.75	94.35 ± 35.02	-0.67 ± 9.52	0.709	0.340
HDL cholesterol (mg/dl)	41.87 ± 8.73	42.21 ± 9.17	0.34 ± 7.66	0.802	38.53 ± 9.24	38.57 ± 8.00	0.03 ± 4.63	0.968	0.414
Apo-lipoproteins AI (mg/dl)	149.81 ± 17.89	154.37 ± 16.02	4.56 ± 12.36	0.045	152.14 ± 25.61	150.46 ± 25.56	-1.67 ± 12.19	0.472	0.060
Apo-lipoproteins B (mg/dl)	86.53 ± 20.11	82.06 ± 17.94	-4.46 ± 9.44	0.012	87.96 ± 23.79	85.46 ± 21.05	-2.50 ± 11.70	0.268	0.354
hsCRP (nm/l)	26.71 ± 34.66	18.82 ± 23.72	-7.88 ± 17.98	0.043	18.59 ± 20.70	17.21 ± 15.53	-1.38 ± 14.90	0.831	0.276

DCG: Dark chocolate group; WCG: White chocolate group; FBS: Fasting blood glucose; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; hsCRP: Highly sensitive C-reactive protein; Data adjusted for age, sex, energy intake; * Values refer to variation from week 0 to week 8 within groups (Paired t-test); ** Values refer to comparisons between groups with adjusting for age, sex, energy intake (ANCOVA test)

Unlike some proposed mechanisms for glucose lowering effect of polyphenols including; synthesis of glucose transporter isoform 1 and activation of phosphatidylinositol 3-kinase,[17] the results of our study indicate that dark chocolate with 450 mg of polyphenols is not effective on improvement of FBG, insulin and HbA1c levels in hypertensive diabetic subjects. Similarly, Mellor et al. did not observe a significant effect of polyphenols-rich chocolate consumption on fasting glucose, and insulin levels.[29]

In other study, daily consumption of dark chocolate (6.3 g) for 18 weeks, did not demonstrate significant improvement in glucose and insulin levels.

In contrast to our findings, consumption of flavones (902 mg) for 12 weeks resulted in a decrease of insulin resistance in overweight and obese subjects.[30] Together, regarding these findings, we suggest that a higher dose of polyphenols with longer duration may result in a reduction of glucose and insulin.

To the best of our knowledge, there are few data about anti-inflammatory property of DCG. We examined the effect of cocoa consumption on hsCRP as an inflammatory marker.

In our study, despite significant decrease of hsCRP within DCG, we did not observe a significant difference between dark and WCGs. Similar to our findings, the study by Mathur et al. showed that cocoa consumption (36.9 g of dark chocolate bar and 30.95 g of cocoa powder drink) for 6 wk did not affect hsCRP level.[31]

There were a few limitations in the present study. First, serum polyphenols concentrations were not measured at the baseline and end point that may affect the results in both groups. In addition, our study design has not the possibility to double blinding, and patients were aware of the intervention grouping kind. Another limitation might be the financial restrictions that unpowered the follow-up time and more biochemical assessments such as polyphenol levels, that may need more time and investigation to show maximum results on changes in principle outcomes measured. Moreover, monitoring adherence to the intervention monthly may be another limitation in the present study; a close supervision of all participants has to be carried out through personal contact daily or weekly. Finally, we find that may be better this study conducted again with one more group as placebo to compare with previous groups (DCG and WCG) to provide better controlling.

Conclusion

Consuming high-polyphenol chocolate and not white chocolate over an 8 weeks period improved cardiovascular risk indices by decreasing systolic and diastolic blood pressure in patients with diabetes and hypertension without a detrimental effect on triglyceride, weight, insulin resistance, BMI. Our study clearly establishes improvements of blood pressure after regular consumption of flavanol-containing cocoa in patients with Type 2 diabetes, highlighting the potential of flavanol-containing diets, and underscoring their potential health care benefit for reducing the risk of cardiovascular events in diabetic patients.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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