Effects of Concord grape juice on ambulatory blood pressure in prehypertension and stage 1 hypertension[1–3]

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ABSTRACT

Background: Consumption of flavonoid-containing foods may be useful for the management of hypertension.

Objective: We investigated whether 100% Concord grape juice lowers blood pressure in patients with prehypertension and stage 1 hypertension.

Design: We conducted a double-blind crossover study to compare the effects of grape juice (7 mL · kg^{-1} · d^{-1}) and matched placebo beverage on 24-h ambulatory blood pressure, stress-induced changes in blood pressure, and biochemical profile. Participants consumed each beverage for 8 wk with a 4-wk rest period between beverages. They ceased consumption of grapes and other flavonoid-containing beverages throughout the study.

Results: We enrolled 64 otherwise healthy patients taking no antihypertensive medications (31% women, 42% black, age 43 ± 12 y). Baseline mean (±SD) cuff blood pressure was 138 ± 7 (systolic)/82 ± 7 (diastolic) mm Hg. No effects on the primary endpoint of 24-h mean systolic blood pressure, diastolic blood pressure, or stress-induced changes in blood pressure were observed. A secondary endpoint was nocturnal dip in systolic pressure. At baseline, nocturnal pressure was 8.3 ± 7.1% lower at night than during daytime. The mean nocturnal dip increased 1.4 percentage points after grape juice and decreased 2.3 percentage points after placebo ($P = 0.005$). Fasting blood glucose was 91 ± 10 mg/dL at baseline for the entire cohort. Glucose decreased 2 mg/dL after consumption of grape juice and increased 1 mg/dL after consuming the placebo ($P = 0.03$).

Conclusions: We observed no effect of grape juice on ambulatory blood pressure in this cohort of relatively healthy individuals with modestly elevated blood pressure. Secondary analyses suggested favorable effects on nocturnal dip and glucose homeostasis that may merit further investigation. This trial was registered at clinicaltrials.gov as NCT00302809. *Am J Clin Nutr* 2010;92:1052–9.

INTRODUCTION

Hypertension affects >25% of the US adult population. There is considerable interest in dietary and other nonpharmacologic approaches to improve blood pressure control. Epidemiologic studies suggest that higher consumption of fruit and vegetables is associated with lower blood pressure and reduced cardiovascular mortality (1–3). In the well-controlled Dietary Approaches to Stop Hypertension (DASH) study, a low-fat diet rich in fruit and vegetables lowered blood pressure (4). Increased consumption of foods containing flavonoids has been proposed as a possible contributing mechanism for the benefits of the DASH diet.

Grapes are rich in flavonoids, and a body of work suggests that consumption of grapes and grape-containing products might lower blood pressure (5). In hypertensive animals, oral administration of red wine or grape extracts lowers blood pressure (6, 7). Mechanistic studies showed that grape flavonoids have favorable effects on endothelial function and inflammation that might reduce arterial stiffness and lower blood pressure (5). In population studies, wine consumption has been linked to lower blood pressure and reduced cardiovascular disease risk (8–10). Finally, a randomized intervention study showed a reduction in blood pressure after consumption of grape juice for 8 wk in 40 untreated hypertensive Korean men (11, 12).

The present study was designed to evaluate the effects of grape juice on blood pressure in otherwise healthy individuals with modest blood pressure elevation. It is conceivable that this population could benefit from a dietary intervention and avoid drug therapy. In contrast with the previous study by Park et al (11, 12), we sought to use more accurate 24-h ambulatory blood pressure monitoring as the primary endpoint (13) and to study a larger sample of both men and women. In addition to ambulatory blood pressure, we examined stress-induced changes in blood pressure and tested the hypothesis that grape juice would blunt the adverse effects of stress on blood pressure.

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SUBJECTS AND METHODS

Study subjects

We identified subjects for screening by advertising for individuals with mild or borderline blood pressure elevation who were taking no antihypertensive medications. All potential subjects provided written informed consent. All procedures were in accordance with the ethical standards of the Boston Medical Center Institutional Review Board.

Screening

We enrolled individuals with stage 1 hypertension (systolic blood pressure of 140–159 mm Hg or diastolic blood pressure of 90–99 mm Hg) and individuals in the upper range of prehypertension (systolic blood pressure of 130–139 mm Hg or diastolic blood pressure of 85–89 mm Hg) (13). After providing consent, potential subjects underwent 2 screening visits separated by 1 wk. At each visit, we measured brachial blood pressure 3 times (3 min between measurements) using an automatic physiologic recorder (Dinamap Pro Series 100; GE Health Care, Piscataway, NJ). Subjects rested in a semirecumbent position for $\geq$10 min before the first measurement. Subjects were eligible for inclusion in the study if the average of 3 systolic or diastolic pressure measurements was within the specified range at both screening visits. At the first visit, eligible subjects were interviewed to obtain a medical history and underwent measurement of height and weight. We excluded patients with a clinical history of coronary artery disease, stroke, diabetes mellitus, congestive cardiac failure, Raynaud syndrome, body mass index (in kg/m^2) $>$35, or use of antioxidant vitamins or estrogen replacement therapy within 4 wk. Pregnancy was excluded by using a urine pregnancy test at all study visits in premenopausal female subjects.

Dietary interventions and study design

After the first screening visit, potentially eligible subjects met with a nutritionist for dietary instruction. They were asked to stop all consumption of grape juice, wine, grape products, green or black tea, dark juices (eg, cranberry and pomegranate juice), and all dietary supplements for the duration of the study. Participants were instructed to maintain a diet that met the current recommendations for sodium intake ($<$2400 mg/d) (13). Subjects were educated about the calorie content of the study beverages and were instructed to consume the beverage in place of other juice or sugar-sweetened drinks or to cut 2 portions of carbohydrate-rich foods each day.

After qualifying at the second screening visit, subjects were enrolled into the study, which had a double-blind, placebo-controlled, crossover design. Subjects were randomly assigned by computer to receive 100% Concord grape juice first or placebo beverage first. There was a separate randomization for subjects with prehypertension or stage 1 hypertension to ensure balanced numbers of subjects within each group. The study beverages were supplied by the study sponsor (Welch Foods Inc, Concord, MA) and have been used in previous clinical studies (14–16). The 100% Concord grape juice contained 160 kcal, including 39 g natural sugar (52% fructose and 48% glucose) and 472.8 mg total polyphenols per 8 oz (240 mL). The Concord grape–flavored placebo beverage matched the flavor, color, calorie, and sugar profile of the juice, but did not contain any juice or polyphenolics. The amount of beverage consumed was individualized to 7 mL $\cdot$ kg^{-1} $\cdot$ d^{-1}. Thus, a 70-kg person would have consumed 490 mL/d containing 965 mg total polyphenols and $\approx$327 kcal. Each beverage was consumed for 8 wk with a 4-wk rest period between beverages. All subjects received both beverages. Participants were given a marked "sports bottle" and instructed to fill the bottle to the mark each day and consume about half the juice with breakfast and half with dinner.

Grape juice and the placebo beverage were coded, and the investigators and participants were blinded to the identity of the beverage until completion of data analysis. The beverages were maintained in 24-oz (710-mL) glass bottles at 4°C by a commercial storage company (Millbrook Cold Storage Inc, Somerville, MA) and delivered weekly to the participants by a delivery company experienced in clinical trials involving beverages (Inquil Solutions LLC, Melrose, MA). Subjects were asked to return the juice container caps after each beverage consumption period, and the average compliance was 86%. We completed a "per protocol" subgroup analysis for the participants with evidence of $\geq$75% compliance (n = 52).

Ambulatory blood pressure measurements

Subjects underwent 24-h ambulatory blood pressure monitoring before consuming the first beverage (model 90207; Spacelabs Medical, Issaquah, WA). The monitor was programmed to record blood pressure measurements 4 times per hour during the day and 2 times per hour at night. The mean systolic blood pressure during the entire 24-h monitoring period served as the primary endpoint of the study. Additional endpoints included 24-h mean diastolic blood pressure, heart rate, and pulse pressure. We also calculated the percentage decrease in systolic and diastolic blood pressure measured at night (2200 to 0600) compared with the daytime pressures (nocturnal dip). The ambulatory blood pressure recordings were repeated in an identical fashion before the second beverage consumption period and during the last 24 h of each beverage consumption period.

Other endpoints measured at all 4 study visits

In addition to 24-h ambulatory blood pressure measurements, we collected blood samples, measured "office blood pressure" by using the physiologic recorder, and assessed vascular function before and after each beverage period. Serum total cholesterol, triglycerides, HDL cholesterol, insulin, and glucose concentrations were analyzed on a commercial basis by Quest Diagnostics Inc (Cambridge, MA). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [(fasting insulin μIU/mL) $\times$ (fasting glucose mmol/L)]/22.5. C-reactive protein concentrations were measured on a commercial basis at Children's Hospital (Boston, MA) by using a high-sensitivity nephelometric method as previously described (17). Soluble CD40-ligand concentrations were measured at the University of Massachusetts Medical Center by using a commercially available enzyme-linked immunosorbent assay (Bender MedSystems GmbH, Vienna, Austria) as previously described (18).

With regard to vascular testing, we assessed stiffness of the central aorta by determining carotid-femoral pulse wave velocity at each visit by applanation tonometry (Sphygmacor; AtCor

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Medical USA, Itasca, IL). Vasodilator function was measured in the fingertip by using digital pulse amplitude tonometry (Endo-PAT 2000R; Itamar Medical Ltd, Caesarea, Israel) as previously described (19). The increase in pulse amplitude in the fingertip during reactive hyperemia depends on nitric oxide and is impaired in patients with metabolic risk factors (20).

Stress testing

We investigated the effects of beverage consumption on stress-induced changes in blood pressure by using 2 established psychological tests and the cold pressure test (21). Subjects were asked to perform a video game challenge (Breakout by Atari Inc, Sunnyvale, CA) that involved moving a cursor to keep a ball from "falling" off the bottom of the video screen and a star-tracing task that involved looking in a mirror and tracing a star pattern. These tasks have been shown to be frustrating and require significant mental concentration. Each psychological test was performed for 3 min. There was a 10-min rest period between the tasks, and the order of task performance was randomized (video game first or star-tracing task first). Baseline blood pressure was measured before the beginning of the tasks and was subsequently repeated once every minute during task performance. After completion of the psychological tests and a 10-min rest period, we conducted the cold pressor test. This thermal pain test involved each subject immersing one hand in a basin of ice water for 45 s. Blood pressure was measured after completion of the cold pressor test. Because it was possible that participants would become familiar with the psychological tasks and experience less stress after repeated performance, we administered the tasks on only 2 occasions (after each beverage), rather than on 4 occasions (before and after each beverage).

Statistical analysis

All analyses were performed with SAS 9.1 (SAS Institute Inc, Cary, NC). We compared the clinical characteristics of the placebo-first and grape juice-first groups using the unpaired *t* test or chi-square test for continuous and categorical variables, respectively. We evaluated the effect of beverage consumption on blood pressures, biochemical markers, and vascular function measures by using a general linear model for correlated data with PROC MIXED, an unstructured covariance matrix, and standard restricted maximum likelihood estimation. C-reactive protein and CD40 ligand were assessed after log-transformation because they lacked a normal distribution. We considered the effect of grape juice to be different from placebo if the treatment (grape juice or placebo) by follow-up (before beverage or after beverage) interaction had a P value <0.05. We adjusted for potential carryover by including in the model the 3-factor interaction: treatment by follow-up by treatment period (first beverage or second beverage). We completed prespecified analyses that included the subgroups of subjects with prehypertension ($n = 38$), stage 1 hypertension ($n = 26$), and evidence of good compliance ($n = 52$). Data are presented as means ± SDs.

The primary endpoint was a mean systolic blood pressure measured with a 24-h ambulatory blood pressure monitor. By using data from the DASH study (provided by Thomas Moore), we calculated that a sample size of 64 subjects would provide >90% power to detect a treatment effect of 5 mm Hg (22).

RESULTS

Study subjects

As outlined in **Figure 1**, 228 individuals underwent screening, and 145 were excluded. The most common reasons for exclusion were failure to meet the blood pressure criteria ($n = 95$), a body mass index >35 ($n = 12$), and participant decision after learning the details of study design ($n = 25$). Participants often qualified on the initial screening visit, but had blood pressure below the entry cutoff on the follow-up screening visit. Of the 83 randomly assigned subjects, 46 had prehypertension and 37 had stage 1 hypertension. Nineteen subjects withdrew or were terminated from the study, mostly by patient preference. One subject withdrew while drinking grape juice after developing diarrhea that may have been related to the study intervention.

The clinical characteristics of the 64 subjects who completed the study are shown in **Table 1**. The participants had an average age of 43 ± 12 y, were overweight, and were predominantly male. A relatively high proportion of subjects were black (42%). The grape juice–first and placebo-first groups were balanced in regard to clinical characteristics and baseline biochemical profiles. The average cuff blood pressure was 141 ± 7 (systolic)/84 ± 8 (diastolic) mm Hg at the first screening visit and 138 ± 7 (systolic)/82 ± 7 (diastolic) mm Hg at the beginning of the study for the entire group.

Effects of beverage consumption on biochemical markers and body weight

The effect of beverage consumption on the biochemical markers and body weight is shown in **Table 2**. No effects on serum lipids, C-reactive protein, soluble CD40 ligand, or body weight were observed. Fasting serum glucose was 2 mg/dL lower after 8 wk of grape juice consumption and was 1 mg/dL higher after 8 wk of placebo consumption ($P = 0.03$). No differences in the effect of either beverage on fasting insulin concentration or HOMA-IR were observed.

In the subgroup analyses (data not shown), a similar favorable effect of grape juice consumption was observed on serum glucose concentrations in the subgroups with prehypertension ($n = 38$; $P = 0.03$) and with good compliance ($n = 52$; $P = 0.03$). No effect was observed in the subgroup with stage 1 hypertension.

Effects of beverage consumption on blood pressure

The effects of beverage consumption on ambulatory blood pressure and office blood pressure are shown in **Table 3**. No significant difference in the effect of grape juice compared with that of placebo on mean systolic blood pressure by 24-h ambulatory monitor was observed. No effects on diastolic blood pressure, heart rate, or office blood pressure were observed. In the subgroup analyses (data not shown), no significant effects of beverage consumption on the primary endpoint of ambulatory systolic blood pressure in the prehypertension subgroup ($n = 38$; $P = 0.47$) or in the stage 1 hypertension subgroup ($n = 26$; $P = 0.92$) were observed. Furthermore, no effects on ambulatory diastolic pressure or office blood pressure were observed in the participants in the prehypertension or stage 1 hypertension subgroups, and no effects on any blood pressure variable were observed in the subgroup with good compliance.

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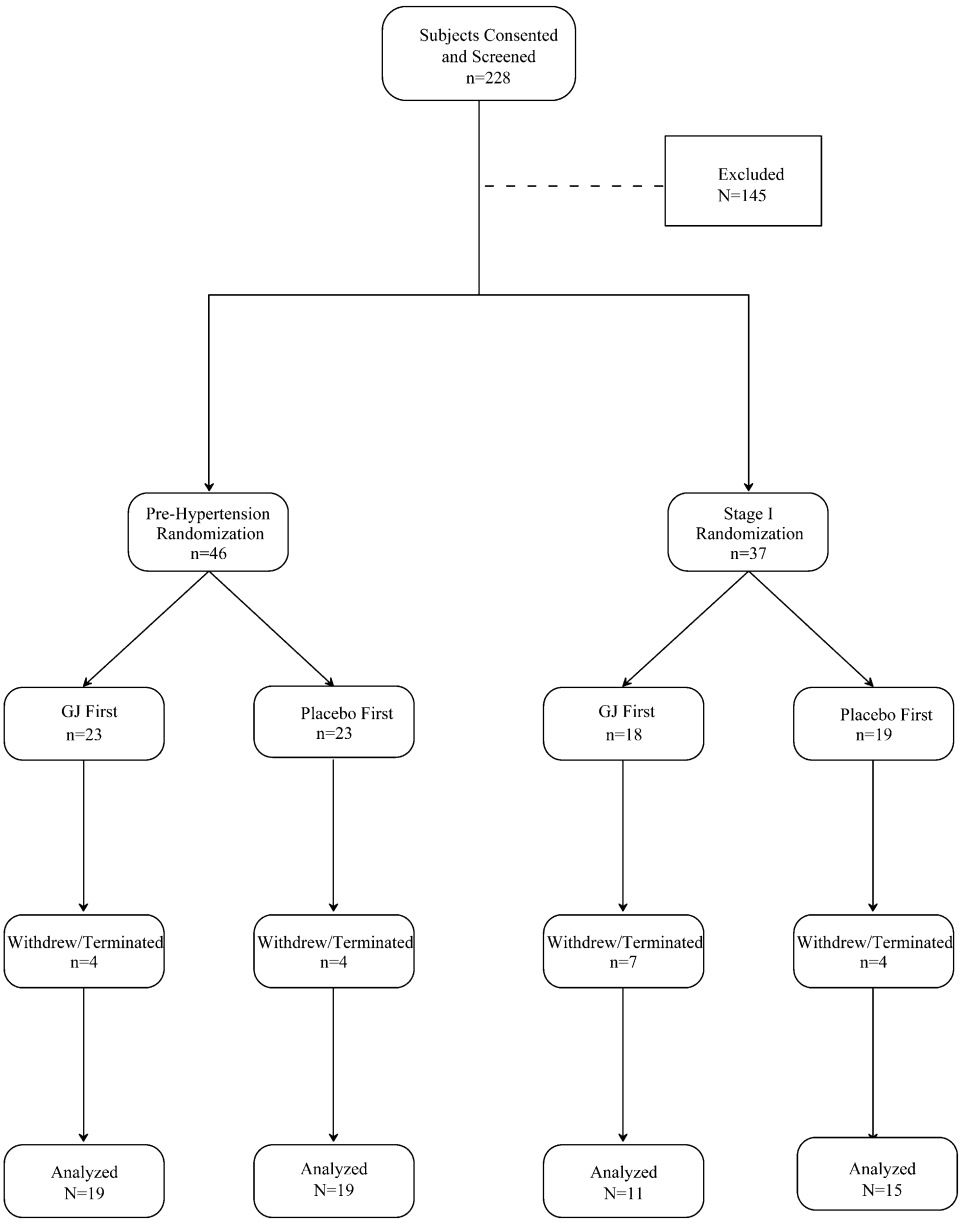

FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. GJ, grape juice.

The nocturnal dip in systolic blood pressure increased by 1.4 percentage points after grape juice and decreased by 2.3 percentage points after placebo ($P = 0.005$), which reflected a favorable effect of grape juice. A significant difference in the effects of the 2 beverages on the nocturnal dip in diastolic blood pressure ($P = 0.03$) was also observed. In the subgroup analysis (data not shown), the effect of grape juice also differed from the effect of placebo on the nocturnal dip in systolic blood pressure in subjects with prehypertension ($n = 38$; $P = 0.04$), stage 1 hypertension ($n = 26$; $P = 0.04$), and good compliance ($n = 52$; $P = 0.04$).

Effect of beverage consumption on blood pressure reactivity

The effects of beverage consumption on the blood pressure responses to the 2 psychological stress tasks and the cold pressor test are displayed in **Table 4**. Compared with baseline, each stress test was associated with a significant change in systolic blood pressure, with increases in blood pressure during the star-tracing and cold pressor tests ($P < 0.001$ for both). Unexpectedly, the video game led to a net decrease in systolic blood pressure ($P = 0.02$). Beverage consumption had no effect on the blood pressure responses to the stress tasks for the group as a whole.

In the subgroup of participants with prehypertension, the video game decreased systolic blood pressure from 130 ± 9 to 126 ± 11 mm Hg after consumption of grape juice and increased systolic blood pressure from 129 ± 9 to 132 ± 13 mm Hg after consumption of placebo. The differential effect of beverage consumption on blood pressure response was statistically significant ($n = 38$; $P = 0.02$). In the subgroup of participants with good compliance, the cold pressor increased blood pressure from 133 ± 12 to 137 ± 14 mm Hg after grape juice and from 132 ± 11 to 140 ± 16 after placebo. The differential effect of beverage

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TABLE 1
Baseline characteristics (first screening visit)[1]

Characteristic	Grape juice first (n = 30)	Placebo first (n = 34)	P^2
Age (y)	41 ± 13[3]	44 ± 11	0.44
Male sex [n (%)]	19 (63)	25 (74)	0.38
Black race [n (%)]	13 (43)	14 (41)	0.86
History of hypertension [n (%)]	10 (33)	5 (15)	0.08
Smoking [n (%)]	11 (37)	15 (44)	0.55
Family history of CAD [n (%)]	3 (10)	1 (3)	0.24
Waist (inches)[4]	36 ± 4.8	37 ± 5.4	0.34
BMI (kg/m^2)	28 ± 3.8	28 ± 3.9	0.63
Creatinine (mg/dL)	0.94 ± 0.17	0.91 ± 0.17	0.45

[1] CAD, coronary artery disease.
[2] P for unpaired t test or chi-square test for continuous and categorical variables, respectively.
[3] Mean ± SD (all such values).
[4] One inch = 2.54 cm.

was also statistically significant (n = 52; P = 0.03). No other significant effects of beverage consumption on the other stress-induced changes in blood pressure were observed in the subgroups (data not shown).

Vascular function

The effects of beverage consumption on vascular function are shown in **Table 5**. As shown, no effects of grape juice or placebo beverage were observed on carotid-femoral or carotid-radial pulse wave velocity—measures of stiffness of the central aorta and upper extremity conduit arteries, respectively. Also, no effects of the 2 beverages on the hyperemic increase in pulse amplitude in the finger tip, as measured by digital pulse amplitude tonometry, were observed. No significant effects of beverage on vascular function were observed in any of the prespecified subgroups (data not shown).

DISCUSSION

In this randomized, double-blind, placebo-controlled, crossover study, consumption of Concord grape juice for 8 wk had no effect on the primary endpoint, ie, mean systolic blood pressure measured by 24-h ambulatory monitor. The subjects were otherwise healthy, were taking no antihypertensive medications, and had a mean baseline blood pressure in the prehypertension range (138/82 mm Hg). The subjects consumed a relatively large amount of grape juice (nearly 500 mL/d for a 70-kg person), and the study had >90% power to detect a decrease of 5 mm Hg. Thus, it is unlikely that an achievable and clinically meaningful antihypertensive effect of grape juice in this cohort was missed. Grape juice consumption had no effect on many secondary endpoints, including diastolic blood pressure, office blood pressure, stress-induced increases in blood pressure, vascular function, arterial stiffness, or blood markers of inflammation and platelet activity.

Although the study was negative for the primary endpoint, we did observe several potentially beneficial effects of Concord grape juice consumption compared with placebo. First, consumption of grape juice was associated with a modest enhancement of the normal nocturnal dip in blood pressure. Second, it is interesting that there was a modest, but significant, decrease in fasting blood glucose after consumption of grape juice, despite concerns that the additional 327 kcal/d for a 70-kg person might have adverse effects. Finally, grape juice had beneficial effects in several prespecified subgroup analyses, including beneficial effects of grape juice consumption on the stress blood pressure responses in participants with prehypertension and the group with good compliance.

The findings of our study differ from the prior study in Korean men with hypertension. In that study, consumption of a smaller amount of grape juice (5.5 mL · kg^{-1} · d^{-1}) for 8 wk was associated with a 7.2-mm Hg reduction in systolic blood pressure compared with a 3.5-mm Hg reduction with placebo (11). Grape juice consumption also reduced oxidative damage to lymphocyte DNA and improved plasma radical scavenging capacity (12). These apparently discrepant findings likely reflect differences in the study population. It was observed in the DASH study that individuals with a higher blood pressure had a larger response to the dietary intervention (4), and the participants in the Korean study had higher blood pressure at baseline (≈150/95 mm Hg) than did the participants in the present study (138/82 mm Hg). It also is possible that the different results reflect methodologic differences between studies. The present study may be more reliable because we used 24-h ambulatory monitoring rather

TABLE 2
Effects of beverage consumption on biochemical profile and weight[1]

Variable	Sample size	Before grape juice	After grape juice	Before placebo	After placebo	P^2
Total cholesterol (mg/dL)	63	187 ± 34[3]	189 ± 32	189 ± 37	193 ± 37	0.41
LDL (mg/dL)	63	114 ± 31	114 ± 29	114 ± 33	117 ± 33	0.27
HDL (mg/dL)	63	54 ± 15	54 ± 15	55 ± 18	54 ± 16	0.68
Triglyceride (mg/dL)	63	93 ± 53	104 ± 70	101 ± 78	105 ± 66	0.54
Glucose (mg/dL)	64	91 ± 10	89 ± 11	90 ± 11	91 ± 13	0.03
Insulin (mU/L)	52	6.2 ± 5.0	6.0 ± 5.4	6.7 ± 6.2	7.9 ± 13.0	0.46
HOMA-IR	52	1.4 ± 1.2	1.4 ± 1.3	1.5 ± 1.5	2.0 ± 3.8	0.31
C-reactive protein (mg/L)	59	1.1 (0.4, 2.5)[4]	0.8 (0.4, 2.5)	1.2 (0.6, 2.9)	1.4 (0.6, 4.0)	0.61
Soluble CD40 ligand (mg/mL)	58	1.0 (0.4, 3.5)	1.0 (0.4, 3.6)	0.9 (0.5, 3.2)	1.0 (0.6, 3.9)	0.58
Weight (kg)	64	85 ± 15	85 ± 15	85 ± 16	85 ± 16	0.82

[1] HOMA-IR, homeostasis model assessment of insulin resistance.
[2] P for treatment by follow-up interaction as determined by using a general linear model for correlated data with PROC MIXED, an unstructured covariance matrix, and standard restricted maximum likelihood estimation in SAS (SAS Institute Inc, Cary, NC).
[3] Mean ± SD (all such values).
[4] Median; first and third quartile cutoffs in parentheses (all such values).

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TABLE 3
Effect of beverage consumption on ambulatory and office blood pressure

Variable	Sample size	Before grape juice	After grape juice	Before placebo	After placebo	P^1
24-h Ambulatory blood pressure						
Systolic blood pressure (mm Hg)	64	124 ± 11[2]	122 ± 10	124 ± 12	124 ± 10	0.67
Diastolic blood pressure (mm Hg)	64	77 ± 8	76 ± 7	78 ± 9	77 ± 8	0.90
Pulse pressure (mm Hg)	64	47 ± 7	46 ± 7	47 ± 8	47 ± 7	0.35
Heart rate (beats/min)	64	76 ± 10	76 ± 12	76 ± 10	76 ± 12	0.53
Nocturnal dip in systolic blood pressure (%)	63	6.8 ± 7.4	8.2 ± 7.4	9.9 ± 7.1	7.6 ± 8.3	0.005
Nocturnal dip in diastolic blood pressure (%)	63	9.9 ± 9.8	11.4 ± 8.6	13.0 ± 8.7	11.1 ± 9.7	0.03
Office blood pressure (mm Hg)						
Systolic blood pressure	63	133 ± 12	132 ± 12	133 ± 11	132 ± 10	0.76
Diastolic blood pressure	64	80 ± 10	79 ± 10	80 ± 8	78 ± 8	0.32

[1] P for treatment by follow-up interaction as determined by using a general linear model for correlated data with PROC MIXED, an unstructured covariance matrix, and standard restricted maximum likelihood estimation in SAS (SAS Institute Inc, Cary, NC).
[2] Mean ± SD (all such values).

than office blood pressure measurements. Furthermore, the present study had a much larger sample size, with 64 participants receiving both beverages in a crossover study, whereas the study by Park et al randomly assigned separate groups of 19 and 21 men to treatment with grape juice and placebo, respectively (11). Nevertheless, it remains possible that grape juice may have a beneficial effect in untreated individuals with more elevated blood pressure.

Many studies have reported antihypertensive effects after treatment with other foods and beverages that are rich in flavonoids. For example, several studies have reported a blood pressure–lowering effect of high-polyphenol dark chocolate in patients with hypertension (23, 24). Pomegranate juice has also been reported to lower blood pressure in hypertensive patients (25). In general, the studies showing beneficial effects of polyphenol-rich foods and beverages were completed in patients with hypertension. On the other hand, a study of patients with prehypertension showed no benefit of dark chocolate (26), a finding consistent with the present study.

An interesting finding of our study was the decrease in fasting blood glucose observed after grape juice consumption. This result is consistent with a prior study that demonstrated a reduction in fasting blood glucose, insulin, and hemoglobin A_{1C} after consumption of grape juice, wine, or dealcoholized wine (27). Favorable effects of chocolate (24) and tea (28, 29) on insulin sensitivity have also been reported. Such findings could indicate increased insulin sensitivity or insulin release. The mechanisms accounting for improved insulin sensitivity or release after consumption of grape-derived polyphenols and other dietary sources of these bioactive compounds remain incompletely understood. However, experimental studies suggest that these compounds may improve insulin signaling via the PI3 kinase-Akt pathway and activate sirtuin-1 and AMP kinase (30, 31).

Another effect of grape juice consumption in the present study was the increase in the nocturnal dip in blood pressure. Large-scale studies have shown that a greater degree of nocturnal dip is associated with lower mortality after adjustment for other risk factors (32). Failure to dip >10% is associated with worse cardiovascular outcome and is more common in black individuals (33). It is interesting that there was a large proportion of black individuals in the present study (42%) and that, on average, the study cohort was in the "nondipper" range (mean nocturnal decrease: 8.3%). The dip in blood pressure at night has been attributed to the inhibition of the sympathetic nervous system activity, and studies suggest that failure to dip reflects excessive sympathetic activity (34). Further study will be needed to confirm our finding that grape juice consumption increased nocturnal dipping and to elucidate the mechanism of the effect.

In predefined subgroup analyses, we observed favorable effects of grape juice consumption on changes in blood pressure induced by psychological stress and the cold pressor test. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, blood pressure response induced by the video game challenge, star-tracing task, or the cold pressor test predicted incident hypertension in 4202 normotensive subjects (21). In that study, stress testing was performed between 1987 and 1988, and the video game challenge produced an increase in blood pressure of 9–10 mm Hg. In our study, the video game challenge had a neutral to blood pressure–lowering effect, possibly reflecting greater familiarity of our cohort with video games. In the subgroup with confirmed compliance, it was interesting that the blood pressure response to the cold pressor test was reduced by 50% after grape juice consumption; however, because they represent only subgroup analyses, these findings should be interpreted with caution. Confirmation is required before firm conclusions can be drawn about a protective effect of grape

TABLE 4
Stress-induced changes in blood pressure (n = 64)[1]

Variable	After grape juice	After placebo	P^2
Systolic blood pressure (mm Hg)			
Before stress	132 ± 12[3]	132 ± 10	—
Video game	130 ± 14	131 ± 13	0.17
Star tracing	134 ± 14	136 ± 15	0.51
Cold pressor test	137 ± 17	139 ± 16	0.20
Diastolic blood pressure (mm Hg)			
Before stress	79 ± 10	78 ± 8	—
Video game	80 ± 10	78 ± 9	0.08
Star tracing	83 ± 12	81 ± 11	0.19
Cold pressor test	81 ± 12	81 ± 11	0.71

[1] Each stress stimulus was associated with a significant change in systolic blood pressure compared with before stress ($P < 0.05$).
[2] P for treatment by follow-up interaction as determined by using a general linear model for correlated data with PROC MIXED, an unstructured covariance matrix, and standard restricted maximum likelihood estimation in SAS (SAS Institute Inc, Cary, NC).
[3] Mean ± SD (all such values).

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TABLE 5
Effects of beverage consumption on vascular function[1]

Variable	Sample size	Before grape juice	After grape juice	Before placebo	After placebo	P^2
Carotid-femoral PWV (m/s)	47	7.1 ± 1.4[3]	7.1 ± 1.4	7.3 ± 2.0	7.4 ± 1.5	0.92
Carotid-radial PWV (m/s)	62	8.1 ± 1.4	8.1 ± 1.5	8.4 ± 1.8	8.3 ± 1.9	0.82
ln PAT ratio	56	0.44 ± 0.32	0.35 ± 0.40	0.42 ± 0.40	0.35 ± 0.41	0.64

[1] PWV, pulse wave velocity; PAT, pulse amplitude tonometry.
[2] *P* for treatment by follow-up interaction as determined by using a general linear model for correlated data with PROC MIXED, an unstructured covariance matrix, and standard restricted maximum likelihood estimation in SAS (SAS Institute Inc, Cary, NC).
[3] Mean ± SD (all such values).

juice. These results and our observations about nocturnal dipping are consistent with the premise that grape juice might have modest favorable effects on sympathetic nervous system–induced changes in blood pressure.

Prior studies in experimental models and in sicker populations have shown beneficial effects of grape juice consumption on other aspects of vascular function and inflammation. As we recently reviewed, grape products improve endothelial function, inhibit platelet aggregation, and reduce inflammation (5, 14, 15). Possibly because of the modest blood pressure elevation and generally healthy study cohort, we observed no benefits of grape juice consumption on arterial stiffness assessed as pulse wave velocity (35) or on endothelial function in the fingertip as measured by peripheral arterial tonometry (20). We also observed no effect on C-reactive protein or soluble CD40 ligand—markers of inflammation and platelet activation.

Our study had several limitations. As mentioned, the cohort had only a modestly elevated blood pressure. Although much larger than the prior grape juice study, the sample size was modest compared with other studies showing favorable effects of dietary interventions on blood pressure. We had a high rate of screen failures, which reflected the difficulty in identifying individuals with elevated blood pressure who were not taking antihypertensive medications. Furthermore, we had a 23% withdrawal rate, largely reflecting the subjects' unwillingness to continue consuming a large volume of beverage on a daily basis. We did not record alcohol consumption, which could have influenced blood pressure. Finally, our study involved withholding grape products and other foods containing polyphenols. This aspect of the study design might explain the apparent worsening of some endpoints during consumption of the placebo beverage and reflect a lack of steady state in regard to flavonoid status. The study limitations were balanced by the placebo-controlled crossover study design and the use of 24-h ambulatory blood pressure monitoring to accurately measure changes in blood pressure.

In conclusion, we observed no effect of Concord grape juice consumption on ambulatory mean blood pressure in a group of otherwise healthy individuals taking no antihypertensive medications, with prehypertension, and with stage 1 hypertension. We also observed no effect on stress-induced increases in blood pressure, vascular function, or markers of inflammation. Interestingly, we observed modest, but potentially favorable, effects of grape juice on fasting blood glucose and the nocturnal dip in blood pressure. Further studies are needed to confirm these latter findings and identify the responsible mechanisms.

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