Original Paper

Annals of Nutrition & Metabolism

Ann Nutr Metab 2019;74:165–174
DOI: 10.1159/000497226

Received: April 19, 2018
Accepted: January 24, 2019
Published online: February 14, 2019

Raspberries Improve Postprandial Glucose and Acute and Chronic Inflammation in Adults with Type 2 Diabetes

Jace Schell[a] Nancy M. Betts[a] Timothy J. Lyons[b] Arpita Basu[c]

[a]Department of Nutritional Sciences, College of Human Sciences, Oklahoma State University, Stillwater, OK, USA; [b]Division of Endocrinology, Medical University of South Carolina, Charleston, SC, USA; [c]Department of Kinesiology and Nutrition Sciences, University of Nevada Las Vegas, Las Vegas, NV, USA

Keywords
Raspberries · Type 2 diabetes · Interleukin-6 · Glucose · Inflammation

Abstract
Background: Postprandial metabolic impairments in diabetes have been shown to play an important role in vascular complications. Dietary polyphenols and other bioactive compounds in berries have been shown to improve postprandial hyperglycemia and related metabolic impairments, but few clinical studies have been reported in diabetes. ***Objective:*** To examine the effects of daily dietary raspberries on postprandial and 4-week fasting glucose, lipids and biomarkers of inflammation in obese adults with type 2 diabetes. ***Design:*** This was a randomized crossover study with 2 different phases: a "postprandial phase" of acute raspberry supplementation (2 separate days at least 1 week apart), followed by a 1-week washout phase and then a 10-week "diet supplement phase", with and without raspberry supplementation periods of 4 weeks each, separated by 2-week washout phase. ***Results:*** The postprandial phase revealed significantly lower levels of serum glucose at 2 and 4 h postprandial after raspberry versus control phase. In addition, among the serum biomarkers of inflammation, interleukin (IL)-6 and high-sensitivity tumor necrosis factor alpha (hsTNF-α) were also lower at 4 h postprandial following raspberry versus control meal (all $p < 0.05$). Finally, postprandial serum triglycerides showed a decreasing trend at 4 h in the raspberry versus control phase. Four-week daily raspberry supplementation continued to show a significant lowering effects on IL-6 and hsTNF-α versus control phase (all $p < 0.05$); systolic blood pressure revealed a decreasing trend after 4-week of raspberry supplementation. No effects were noted on fasting glucose and lipids, C-reactive protein and arterial elasticity. ***Conclusions:*** Thus, dietary raspberries, which are low in calories and high in polyphenols and other nutrients may lower postprandial hyperglycemia and inflammation, and in general exert selected anti-inflammatory effects in adults with diabetes. These findings deserve further investigation.

Introduction

Accumulating research supports the role of dietary berries and their bioactive compounds in the prevention and management of chronic metabolic conditions,

KARGER

E-Mail karger@karger.com
www.karger.com/anm

Arpita Basu, PhD, RD
Department of Kinesiology and Nutrition Sciences
University of Nevada Las Vegas, 4505 S Maryland Parkway Box 453034
Las Vegas, NV 89154-3034 (USA)
E-Mail arpita.basu@unlv.edu

such as the metabolic syndrome, type 2 diabetes (T2D) and atherosclerotic cardiovascular diseases (CVD) [1–3]. Postprandial elevations of glucose and triglycerides (TGs), as well as biomarkers of oxidative damage and inflammation have been associated with increased risk for CVD [4–6]. Postprandial hyperglycemia, hypertriglyceridemia, and concomitant systemic inflammation have also been shown to elevate risks of vascular complications in T2D [7, 8]. It is known that dietary macro- and micronutrient intakes have profound influences on the extent of postprandial dysmetabolism in T2D. In general, meals high in fats and refined carbohydrates have been shown to exaggerate postprandial responses [9, 10], while micronutrients and fiber mitigate these postprandial effects [11, 12]. In this context, emerging evidence suggests a role for polyphenol-containing foods and beverages, especially dietary berries, grapes and wine polyphenols, in blunting adverse postprandial increments factors mediating vascular risk [13]. Such findings are promising, but further studies are needed on the effects of dietary berries and their bioactive compounds in the presence of a meal challenge and in the context of diabetes and associated metabolic abnormalities.

Among the commonly consumed berry fruits, blueberries, cranberries, and strawberries have been shown to improve postprandial metabolic stress to various degrees, but most of these studies have been conducted in nondiabetic adults with or without a meal challenge [14–16]. Thus, postprandial studies to address the role of berries in presence of a meal challenge need further investigation in adults with diabetes. We previously demonstrated the role of dried whole cranberries in reducing postprandial hyperglycemia, lipid peroxidation and inflammation in adults with T2D following a high-fat meal challenge [17]. Red raspberries are among the popular berries in the United States, and are not only high in fiber but also in phytochemicals, especially anthocyanins and ellagitannins, which account for most of their health effects [18]. No previous study has reported the effects of raspberries on postprandial metabolism following a high-fat meal in adults with diabetes.

In this randomized controlled trial, we examined the hypothesis that dietary raspberries improve postprandial metabolism following a high-fat fast-food style breakfast. We specifically examined the effects of raspberry supplementation on postprandial responses of serum glucose, lipids, vascular measures, and biomarkers of inflammation in adults who consumed a high-fat breakfast meal with or without the raspberries. We also examined the effects of short-term (4-week) daily raspberry supplementation on cardiometabolic profiles in the same group of adults.

Methods

Participants

We recruited and enrolled adults with clinical diagnosis of T2D [19], and elevated waist circumference (>89 cm for women or >102 cm for men) in this randomized crossover study. Inclusion criteria were established and stable diabetes for at least 5 years but not on insulin therapy, absence of preexisting conditions, such as any type of cancer or coronary heart disease, abnormal liver, renal, or thyroid function, anemia, not taking antioxidants or fish oil supplements, and not currently enrolled in a weight-loss program. Exclusion criteria were currently smoking, and for women, pregnancy or lactation. The study protocol was approved by the Institutional Review Board at Oklahoma State University (OSU). This study was conducted in compliance with the Declaration of Helsinki, and all participants provided written informed consent. Study procedures were conducted in the Clinical Assessment Unit of the Department of Nutritional Sciences at OSU. This trial was registered at the clinicaltrials.gov (NCT03403582).

Study Design

This was a randomized crossover study with 2 different phases (Fig. 1): a "postprandial phase" of acute raspberry supplementation (2 separate days at least 1 week apart), followed by a 1-week washout phase and then a 10-week "diet supplement phase", with and without raspberry supplementation periods of 4 weeks each, separated by 2-week washout phase. Participants were asked to avoid alcohol and caffeine for 24 h as well as polyphenol-containing foods, such as other berries, tea, red wine, soy products, citrus juices, nuts, chocolate, and cocoa-containing products, or dietary supplements of these food extracts for 48 h before each study visit. Otherwise, participants were asked to maintain their usual diet, medications, and lifestyle during the entire course of the study. Habitual dietary intakes at baseline were assessed using a 3-day food record and data analyzed using Nutritionist Pro (version 3.2, 2007; Axxya Systems).

For the postprandial phase, each participant made 2 separate visits to the study site, arriving in a fasting state (i.e., after fasting 10–12 h). On each day of the study, blood draws, blood pressure, and vascular measurements were conducted in the fasting state (baseline), after which participants were administered a high-fat fast-food-style breakfast with or without raspberries. Breakfast was prepared at the clinic, and all participants underwent supervised consumption of the test meals. At 1, 2, and 4 h postprandial time points, starting from the time of completion of the breakfast meal intake, all measures were repeated.

Following the completion of the postprandial phase, participants underwent a 1-week washout phase, and were then randomized to consume raspberries or no raspberries for another 4 weeks on a daily basis while following their habitual diet and lifestyle patterns. Compliance was assessed during visits to the study site 3 days per week, and by return of unconsumed raspberries.

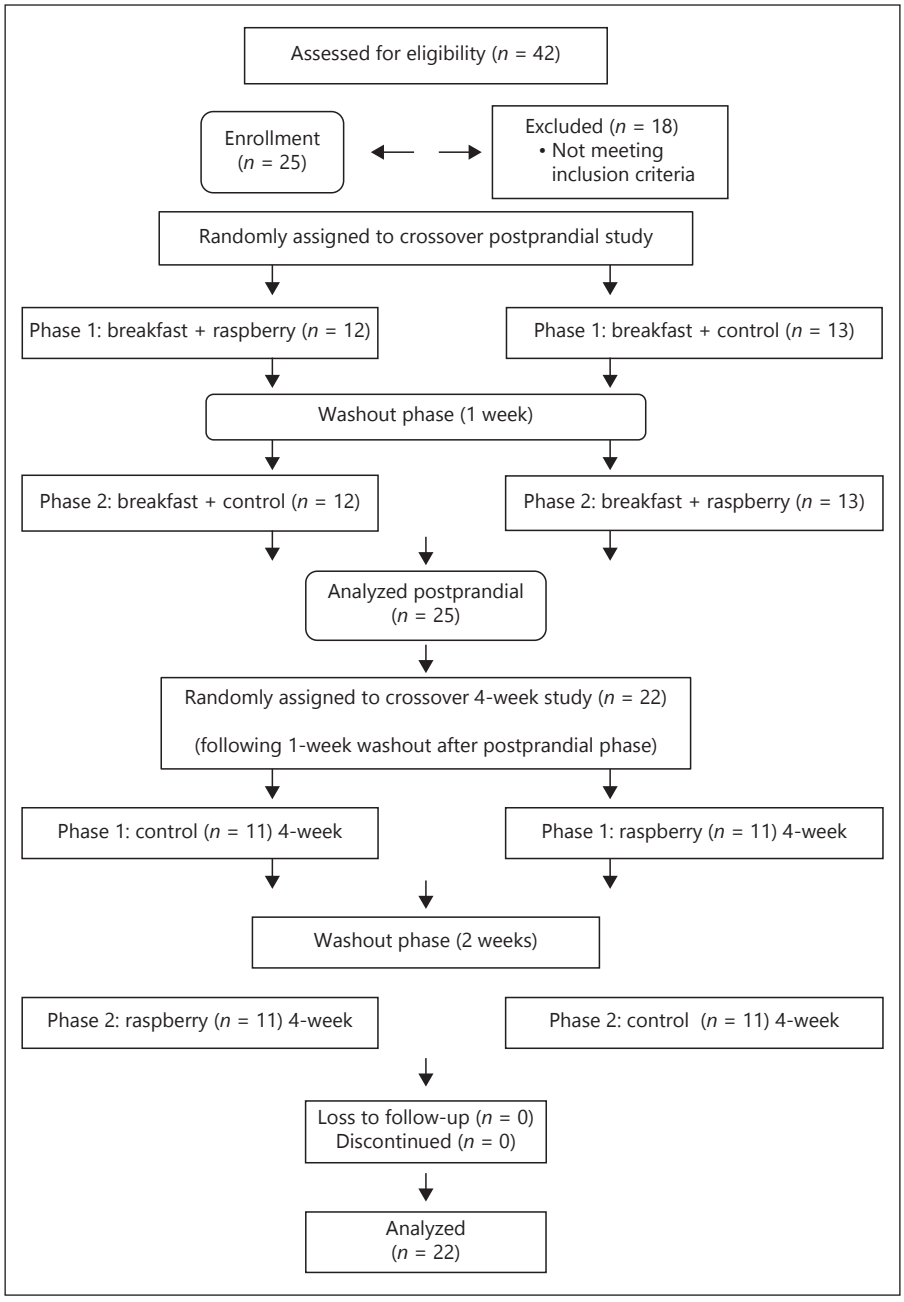

Fig. 1. Study design.

Meal Interventions

For the "post-prandial phase", the nutrient composition of the breakfast meals with and without raspberries is shown in Table 1. The fast-food-style breakfast meal consisted of 2 scrambled eggs, 2 tsp butter, hash brown potatoes (70 g), 2 buttermilk biscuits, and a sausage patty (57 g). For the raspberry supplement, 250 g frozen red raspberries were blended with 1 cup water to form a puree and consumed with the breakfast meal. The control meal had 85 g ripe banana to match the calorie (130 kcal) and carbohydrate content (30 g) of the raspberries. All breakfast meal ingredients were purchased from a local grocery store and prepared in the metabolic kitchen at the clinic each morning on the 2 trial days.

For the 4-week diet supplement phase, participants were provided with a daily dose of 250 g frozen red raspberries in insulated containers with instructions for storage and consumption. The participants were asked to consume the raspberries after thawing as a mid-afternoon snack and not with any other meal or snack, to avoid other dietary factors that may interfere with absorption of raspberry polyphenols and other bioactive compounds.

Anthropometrics and Vascular Measurements

Body weight, height, and waist circumference were measured at the screening visit prior to the postprandial phase, and at the beginning and end of each 4-week intervention period. At the

Table 1. Nutrient composition of breakfast meals

Nutrient	Control meal	Frozen red raspberry, (250 g) meal
Calories, kcal	974	974
Total fats, g	70	70
Carbohydrates, g	56	55
Proteins, g	31	31
Saturated fats, g	40	40
Monounsaturated fats, g	10	10
Polyunsaturated fats, g	20	20
Cholesterol, mg	465	465
Fiber, g	5.5	11.5
Total polyphenols, mg	–	343[1]
Anthocyanins, mg	–	225[2]
Total ellagic acid, mg	–	20
Total ellagitannins, mg	–	115

[1] GAE measured by the Folin-Ciocalteu method.
[2] Cyanidin-3-glucoside equivalents.
GAE, gallic acid equivalent.

same time-points, radial arterial waveforms with the subject supine were recorded for 30 s. The pressure transducer-amplifier system was connected to a specially designed device (Model CR-2000; Hypertension Diagnostics Inc.). These measures were performed at baseline and at 1, 2, and 4 h postprandially, as well as at the beginning and end of each 4-week supplementation period.

Biochemical Variables

On each study day of the postprandial phase, and at the beginning and end of each 4-week period in the diet supplementation phase, blood samples were sent to the Stillwater Medical Center Laboratory for analyses of serum glucose, insulin, lipid profiles (total cholesterol, TGs, LDL cholesterol, and HDL cholesterol) and high-sensitivity CRP. Analyses for glucose, insulin, and lipids were conducted using automated diagnostic equipment (Abbott Architect Instruments) by enzymatic colorimetric methods that used commercially available kits according to manufacturer's protocols. High-sensitivity CRP was assayed by ultrasensitive nephelometry (Dade Behring). Serum glycated hemoglobin was analyzed with the use of a DCA 2000+ Analyzer (Bayer). Insulin resistance was evaluated by homeostasis model assessment of insulin resistance and was calculated as follows: (insulin [mU/L] × glucose [mmol/L])/22.5. Among the serum biomarkers of inflammation, interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α) and plasminogen activator inhibitor-1 (PAI-1) were measured using commercially available ELISA kits (R&D Systems) according to the protocols of the manufacturer. The inter-assay coefficients of variations were 4.5, 6.4, 5.6, and 7.6% respectively.

Statistical Analysis

The objectives of the study were (a) to examine the effect of raspberry supplementation on postprandial glucose and lipids, and biomarkers of inflammation and arterial compliance following a high-fat meal, and (b) to assess the effects of a 4-week intake of raspberries on cardiometabolic variables in the same participants. Data are presented as means ± SEMs for serum biochemical variables, biomarkers of inflammation, blood pressure and measures of arterial compliance. Treatment effects of the test meal with or without raspberries on outcome variables were analyzed using a mixed model analysis of covariance using treatment and time point as repeated measures and baseline as a covariate. The area under the curve (AUC) for serum glucose was calculated for each subject and meal intervention using the trapezoid model. GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA) was used for graph plotting and calculation of AUC. A power calculation estimated that a sample size of 20 individuals would be sufficient to detect an SD difference in postprandial glucose with $\alpha = 0.05$ and $\beta = 0.80$. Data analyses were conducted with the use of IBM SPSS Statistics version 20.0 (IBM Corp.). Results corresponding to $p < 0.05$ are described as significant for the purposes of discussion.

Results

Baseline Features

As show in Figure 1, among the 42 participants screened, 25 qualified and were enrolled in the postprandial study. After a 1-week washout phase, participants were then randomized into the 10-week crossover study. Compliance was 100% among the 25 who enrolled participants in the postprandial study and the 22 who enrolled in the 10-week diet supplementation study. The baseline characteristics of the participants are shown in Table 2. All had T2D, were obese and on oral hypoglycemic agents: none was taking insulin. In general, they had elevated blood pressure, but serum lipids were generally within optimal levels at baseline.

Postprandial Biochemical and Vascular Profiles

As shown in Table 3, postprandial supplementation of raspberries versus control conditions, following a high-fat breakfast meal, resulted in a significantly lower postprandial blood glucose, but not insulin at 2 and 4 h time points ($p < 0.05$). The mean AUC (0–240 min) of serum glucose responses was also significantly lower following raspberry supplementation (0.58 vs. 0.88 at 2 h, and 0.52 vs. 0.78 at 4 h; both $p < 0.05$). Among the postprandial lipid profiles, TGs tended to be lower at 4 h following raspberry versus control phase, while no changes were noted in postprandial serum total, LDL, and HDL-cholesterol levels. Among the biomarkers of inflammation, raspberry supplementation was associated with significant decreases in serum IL-6 and high-sensitivity tumor necrosis factor alpha (hs-TNFalpha) levels at 4 h postprandial, while CRP, IL-1β, and PAI-1 levels did not differ from control. Finally, we did not observe any change

Table 2. Baseline characteristics of the study participants

Variable	Value[1]
Number	25
Age, years	54±4.2
Gender, male/female	5/20
Weight, kg	104±11
BMI, kg/m^2	35.3±2.0
Waist circumference, inches	45±1.8
Serum glucose, mg/dL	142±11
Serum insulin, mU/L	15.8±2.6
Insulin resistance (HOMA-IR)	3.5±0.9
Serum HbA_{1c}, %	8.4±0.6
Serum total cholesterol, mg/dL	192±11
Serum LDL cholesterol, mg/dL	115±11
Serum HDL cholesterol, mg/dL	45±2.5
Serum TGs, mg/dL	162±15
Serum hs-CRP, mg/L	5.3±1.2
Systolic BP, mm Hg	151±5.5
Diastolic BP, mm Hg	94±3.0
SAEI, mL/mm Hg × 100	5.6±3.6
LAEI, mL/mm Hg × 10	17±7.4
Medication/supplement use	
Insulin	0 (0)
Oral hypoglycemic agents	15 (60)
Statins/fibrates	5 (20)
CCBs	3 (12)
ACEIs/ARBs	10 (40)
Aspirin	6 (24)
Multivitamins/minerals	6 (24)
Botanical supplements	2 (8)

[1] Mean ± SEMs for continuous variables; number (%) for non-continuous variables.

BP, blood pressure; ACEIs/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCBs, calcium channel blockers; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; TGs, triglycerides; LAEI, large artery elasticity index; SAEI, small artery elasticity index; BMI, body mass index.

in systolic and diastolic blood pressure, or in small and large artery elasticity throughout the postprandial period in either condition.

Four-Week Feeding of Raspberries on Biochemical and Vascular Profiles

Table 4 shows the fasting biochemical and vascular profiles after 4 weeks of daily raspberry versus no raspberry feeding when adjusted for baseline values as covariates. Daily raspberry supplementation for 4 weeks was associated with significant decreases in serum IL-6 and hs-TNFα levels, while CRP, IL-1β and PAI-1 levels were not affected. Interestingly, no differences were noted in fasting glucose and TGs, as well as liver function tests between the 2 phases at 4 weeks. Among the markers of vascular function, we observed a decreasing trend in systolic blood pressure at 4 weeks of raspberry supplementation versus controls.

Dietary Intakes

As shown in Table 5, dietary intakes of macro- and micronutrients calculated on the basis of 3-day food records were not significantly different between the raspberry and control phases of the 4-week intervention. In general, we observed the habitual intake of dietary nutrients to be high in total fats, and moderate in proteins and carbohydrates, and low in fiber and Vitamin E. These intakes did not differ significantly throughout the study.

Discussion

This is the first study to examine the postprandial effects of red raspberry supplementation following a high-fat fast food style meal challenge in adults with established T2D. Overall, red raspberries lowered postprandial blood glucose at 2 and 4 h versus control condition, and tended to lower serum TGs, especially after 4 h. In addition, raspberry consumption was associated with significantly lower biomarkers of inflammation, particularly IL-6 and TNF-α. These findings were generally supported in our 4-week supplementation study: raspberry supplementation was associated with a significantly lower serum-IL-6 and TNF-α, and a trend toward lower systolic blood pressure. On the other hand, fasting serum glucose and TGs were not affected by raspberries at 4 weeks. Taken together, these findings provide further evidence on the benefits of red raspberries, and by extension, other polyphenol containing foods, in improving postprandial excursions in blood glucose and inflammation that contribute to the burden of atherosclerotic CVD in diabetes. In addition, the dose of red raspberries administered in our study was readily consumed by the participants without discomfort, and thus, our findings hold practical relevance in the nutritional management of T2D.

Berries have been reported to improve postprandial hyperglycemia in studies of healthy volunteers and in a few studies of participants with T2D. In a postprandial study reported by Törrönen et al. [20] different types of berries, such as strawberries, bilberries, lingonberries, red raspberries, cloudberries, chokeberries, cranberries, and blackcurrants were associated with differential effects on

Table 3. Postprandial changes in metabolic and vascular profiles following raspberry intervention with a high-fat meal challenge in adults with T2D in a crossover study (n = 25)

Variable	Fasting	1 h	2 h	4 h
Serum glucose, mg/dL				
Control	143±16	178±19	206±16	187±12
Raspberry	134±11	154±13	172±21*	154±10*
Serum insulin, mU/L				
Control	14.4±1.6	25.4±3.6	35.6±1.6	26.4±2.6
Raspberry	15.3±3.2	28.6±2.2	38.2±3.2	21.1±3.2
Serum TG, mg/dL				
Control	158±13	171±11	185±13	167±13
Raspberry	148±21	166±25	173±21	152±21#
Serum TC, mg/dL				
Control	187±11	178±11	184±10	179±10
Raspberry	207±9	205±8	194±9	191±11
Serum LDL-C, mg/dL				
Control	111±11	104±11	98±13	104±10
Raspberry	108±9	106±9	103±7	98±12
Serum HDL-C, mg/dL				
Control	43±2.8	45±2.7	44±3.2	42±2.5
Raspberry	44±4.4	40±4.5	39±4.3	40±3.8
CRP, mg/L				
Control	5.3±1.2	5.4±1.2	5.0±1.2	5.2±1.2
Raspberry	4.9±3.2	4.8±3.2	5.1±3.2	4.8±2.2
IL-6, pg/mL				
Control	8.8±5.2	14.3±7.2	27.4±7.8	28.8±8.2
Raspberry	10.5±6.1	11.6±6.5	15.2±5.5	11.6±7.1*
IL-1β, pg/mL				
Control	18.8±7.2	21.7±5.2	25.8±7.5	22.6±4.8
Raspberry	21.5±6.1	19.4±4.5	18.7±6.6	23.2±8.1
hsTNF-α, pg/mL				
Control	4.7±1.5	9.7±1.5	14.7±6.5	18.7±7.5
Raspberry	6.3±2.5	7.3±3.5	7.8±5.5	9.3±6.5*
PAI-1, ng/mL				
Control	6.5±3.2	7.2±3.1	6.8±4.2	6.6±3.5
Raspberry	5.1±2.5	5.5±1.5	4.7±2.7	5.4±2.8
Systolic BP, mm Hg				
Control	153±6	150±7	155±6	149±8
Raspberry	148±5	144±4	142±7	138±3
Diastolic BP, mm Hg				
Control	91±3	90±4	85±3	87±2
Raspberry	85±3	88±5	82±3	84±4
LAEI, mL/mm Hg × 10				
Control	18±6.4	21±5.4	19±6.5	18±3.4
Raspberry	21±4.4	20±4.1	23±3.4	24±2.4
SAEI, mL/mm Hg × 100				
Control	5.5±3.6	4.4±3.6	4.7±2.6	5.3±2.6
Raspberry	5.1±2.1	5.4±2.1	5.3±2.3	5.0±2.3

* $p < 0.05$ versus control; # $p < 0.1$ versus control.

BP, blood pressure; hsTNF-α, high sensitivity tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; LAEI, large artery elasticity index; PAI-1, plasminogen activator inhibitor-1; SAEI, small artery elasticity index; TG, triglycerides; T2D, type 2 diabetes; CRP, C-reactive protein.

Table 4. Biochemical and vascular profiles at the end of 4 weeks of raspberry supplementation following a habitual diet (n = 22/group)

Variables	Baseline	Raspberry 4-week	Washout	Control 4-week
Glucose, mg/dL	137±16	130±11	134±9	141±10
TGs, mg/dL	155±12	149±10	145±9	151±11
CRP, mg/L	5.1±1.2	4.8±0.9	5.3±1.2	5.5±2.2
IL-6, pg/mL	12.5±6.6	7.2±5.5*	8.5±4.1	10.5±6.5
IL-1β, pg/mL	15.8±7.6	20.5±6.4	23.7±5.3	27.7±7.4
hsTNF-α, pg/mL	5.5±1.5	3.2±2.1*	4.4±2.5	5.3±3.3
PAI-1, ng/mL	7.5±3.2	5.6±2.6	6.8±2.9	7.4±3.4
ALT (U/L)	45.3±4.3	39.1±3.3	42.3±4.3	40.3±3.6
AST (U/L)	33.2±2.2	30.3±4.2	29.4±1.2	33.6±3.4
Systolic BP, mm Hg	151±5	144±7#	146±6	154±7
Diastolic BP, mm Hg	89±3	84±5	85±3	88±6
LAEI, mL/mm Hg × 10	21±6.4	18±4.3	19±3.4	22±5.4
SAEI, mL/mm Hg × 100	5.3±2.6	4.7±2.4	4.9±2.4	5.5±2.8

* $p < 0.05$ versus control.
# $p < 0.1$ versus control.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; hsTNF-α, high sensitivity tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; LAEI, large artery elasticity index; PAI-1, plasminogen activator inhibitor-1; SAEI, small artery elasticity index; TG, triglycerides; CRP, C-reactive protein; TGs, triglycerides.

Table 5. Dietary nutrient intakes in a 10-week crossover trial in obese adults with T2D (n = 22/group)

Nutrients	Baseline	Raspberry 4-week	Washout	Control 4-week
Calories, kcal	2,018±183	2,504±441	2,000±184	1,922±203
Carbohydrates, g	218±16	303±46	211±20	218±29
Fats, g	92±12	94±21	87±13	78±11
Proteins, g	92±11	107±19	96±10	76±7
Saturated fats, g	31±4	33±6	29±3	28±3
MUFA, g	17±4	22±6	17±4	13±3
PUFA, g	8±2	12±3	7±1.5	6±2
Fiber, g	21±2	23±3	18±2	22±3
Vitamin C, mg	47±9	61±17	48±9	55±28
Vitamin E, mg	8±2	11±2	7±1	9±2
Beta-carotene, μg	614±203	790±214	680±243	688±306

Values are means ± SEMs.
MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; T2D, type 2 diabetes.

postprandial glucose and insulin levels in healthy nondiabetic women. In their study, only strawberries decreased postprandial glucose, and the berry mixture consisting of strawberries, bilberries, cranberries and blackcurrants decreased postprandial glucose as well as insulin in response to white bread or rye bread, while red raspberries did not exert any notable effects. The study did not report effects on postprandial lipids and other surrogate markers of CVD [20]. These responses may be explained by the different polyphenol composition and amounts of digestible carbohydrates in different berries, as well as the macronutrient composition of the control meal. Beneficial effects of strawberries in counteracting postprandial inflammation and insulinemia at dietary achievable doses were also noted in overweight adults, as well as in those with elevated serum TG levels following a high carbohy-

drate moderate fat meal [14, 21]. In comparison to other berries, especially blueberries, strawberries and dried cranberries, red raspberries are lower in total caloric content, and a rich source of fiber and several categories of polyphenols [18]. Our findings can be explained by reported mechanistic data showing the role of red raspberry polyphenols, such as anthocyanins and ellagitannins in activating cellular glucose transporters, inhibiting α-glucosidase activity and increasing insulin sensitivity, thereby improving glycemic profiles [22–24]. These findings deserve further investigation in larger clinical studies of T2D using red raspberries along with habitual meals that vary in macronutrient composition.

In our study, red raspberries decreased postprandial biomarkers of inflammation following a high-fat breakfast, as well as inflammatory markers in the fasting state at 4 weeks of red raspberry supplementation on a habitual diet. Inflammation underlies many vascular complications in diabetes and contributes to atherosclerotic CVD [25]. Fruit polyphenols, especially those found in berries, grapes and oranges have demonstrated anti-inflammatory effects in several acute and chronic feeding studies as reviewed by Joseph et al. [26]. In this review, several postprandial studies involving fruit and wine polyphenols with or without meal challenge were shown to decrease postprandial inflammation, such as by decreasing CRP, IL-6, IL-1β, TNF-α, PAI-1 and adhesion molecules in mostly healthy, overweight but non-diabetic adults [26]. These biomarkers were also shown to be decreased in long-term feeding studies of berries and other fruits, such as grapes and pomegranates mostly in obese or pre-diabetic adults [26]. This review reports no studies using red raspberries which is an important gap addressed by the present study. Our observations on the anti-inflammatory effects of red raspberries, especially on systemic IL-6 and TNF-α in adults with T2D can be explained by reported mechanistic studies showing raspberry-derived ellagitannins in decreasing TNF-α-induced nuclear factor-kappab activation in a rat model of gastric inflammation [27], and of red raspberry-derived anthocyanin extracts in decreasing inflammation in murine macrophages [28]. Cytokines, such as IL-6 and TNF-α, play an important role in insulin resistance and the subsequent complications of T2D, and IL-6 has been shown to be predictive of diabetes risks in cohort studies [29, 30]. In a recently reported systematic review on the magnitude of changes in inflammatory markers in healthy adults, researchers examined 5 most commonly measured inflammatory markers in postprandial studies as follows: CRP, IL-6, -1β, -8, and TNF-α. Among these 5 biomarkers, the review highlights IL-6 to be the most responsive to postprandial meal composition in healthy participants [31]. Our postprandial observations following acute raspberry supplementation conform to these previous findings, and provide further evidence on the meal modulation of cytokines in context of diabetes. Keeping in view the critical role of acute and chronic inflammation in T2D and atherosclerotic CVD, our findings demonstrate selected anti-inflammatory effects of commonly available fruits, such as red raspberries, which prove their relevance in diabetes management.

Few clinical studies have been reported on the effects of black and red raspberries on diabetes or metabolic syndrome-related biomarkers. Black raspberry extracts have been shown to be beneficial in adults with the metabolic syndrome, and have been specifically shown to decrease blood glucose and lipids as well as vascular inflammation in pre-diabetic subjects, and also decrease systolic blood pressure in adults with hypertension [32–34]. The raspberry doses used in these 8 or 12-week studies were quite high and in most cases not dietary achievable in fresh fruit equivalents. Our daily dose of 250 g frozen red raspberries for 4 weeks showed a decreasing trend in systolic blood pressure, and conform to large cohort studies supporting habitual consumption of whole berries at lower intakes than doses supplemented in clinical studies are subsequently associated with decreased risks of hypertension [35, 36]. These effects of red raspberries in T2D are promising and deserve further investigation in larger trials.

Our study has some limitations that must be considered in the interpretation of our findings. First, we have a small sample size of adults with T2D and lack non-diabetic controls which limit generalizability to larger populations. Our chronic feeding study was of short duration, and we measured selected biomarkers of vascular inflammation, but did not measure biomarkers of oxidative stress that are also modulated in postprandial high-fat feeding and contribute to atherosclerotic CVD. Finally, our postprandial study only examined effects of red raspberries following a high-fat meal, and we did not include meals with varying amounts of other nutrients, such as meals high in complex carbohydrates or proteins that are habitually consumed and often recommended in T2D for glycemic control. These remain the scope for future investigation.

In conclusion, our study findings support our hypothesis as we found red raspberries to significantly improve postprandial hyperglycemia and selected markers of inflammation, as well as show a decreasing trend in

postprandial TGs following a fast food style meal challenge. Keeping in view the high prevalence of high-calorie and high-fat fast food and convenience food consumption in the United States and other countries [37, 38], and their detrimental effects on cardio-metabolic risks [38–40], our findings are of practical importance in ameliorating their adverse postprandial effects through dietary raspberry supplementation. We noted lesser significant effects of our 4-week red raspberry feeding, which showed no effects on fasting glucose and lipids but continued to lower selected biomarkers of inflammation and revealed a lowering trend in systolic blood pressure. These effects of red raspberries were observed at dietary achievable levels, and thus our findings support the inclusion of red raspberries as part of a healthy diet in the management of diabetes and its vascular complications.

Acknowledgment

We thank the National Processed Raspberry Council for supporting the study. Also, supported by the Jim and Lynne Williams Endowed funds at OSU.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

1 Cassidy A, Bertoia M, Chiuve S, Flint A, Forman J, Rimm EB: Habitual intake of anthocyanins and flavanones and risk of cardiovascular disease in men. Am J Clin Nutr 2016; 104:587–594.

2 Jacques PF, Cassidy A, Rogers G, Peterson JJ, Meigs JB, Dwyer JT: Higher dietary flavonol intake is associated with lower incidence of type 2 diabetes. J Nutr 2013;143:1474–1480.

3 Cassidy A, Rogers G, Peterson JJ, Dwyer JT, Lin H, Jacques PF: Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults. Am J Clin Nutr 2015;102:172–181.

4 Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, Anfossi G, Trovati M: Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diabetes Care 2011;34:2237–2243.

5 Aslam M, Aggarwal S, Sharma KK, Galav V, Madhu SV: Postprandial hypertriglyceridemia predicts development of insulin resistance glucose intolerance and type 2 diabetes. PLoS One 2016;11:e0145730.

6 Dror E, Dalmas E, Meier DT, Wueest S, Thévenet J, Thienel C, Timper K, Nordmann TM, Traub S, Schulze F, Item F, Vallois D, Pattou F, Kerr-Conte J, Lavallard V, Berney T, Thorens B, Konrad D, Böni-Schnetzler M, Donath MY: Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation. Nat Immunol 2017;18:283–292.

7 Onat A, Can G, Çiçek G, Ayhan E, Doğan Y, Kaya H: Fasting, non-fasting glucose and HDL dysfunction in risk of pre-diabetes, diabetes, and coronary disease in non-diabetic adults. Acta Diabetol 2013;50:519–528.

8 Leon-Acuña A, Alcala-Diaz JF, Delgado-Lista J, Torres-Peña JD, Lopez-Moreno J, Camargo A, Garcia-Rios A, Marin C, Gomez-Delgado F, Caballero J, Van-Ommen B, Malagon MM, Perez-Martinez P, Lopez-Miranda J: Hepatic insulin resistance both in prediabetic and diabetic patients determines postprandial lipoprotein metabolism: from the CORDIOPREV study. Cardiovasc Diabetol 2016;15:68.

9 Christiansen E, Schnider S, Palmvig B, Tauber-Lassen E, Pedersen O: Intake of a diet high in trans monounsaturated fatty acids or saturated fatty acids. Effects on postprandial insulinemia and glycemia in obese patients with NIDDM. Diabetes Care 1997;20:881–887.

10 Dandona P, Ghanim H, Abuaysheh S, Green K, Batra M, Dhindsa S, Makdissi A, Patel R, Chaudhuri A: Decreased insulin secretion and incretin concentrations and increased glucagon concentrations after a high-fat meal when compared with a high-fruit and -fiber meal. Am J Physiol Endocrinol Metab 2015; 308:E185–E191.

11 Silva FM, Kramer CK, Crispim D, Azevedo MJ: A high-glycemic index, low-fiber breakfast affects the postprandial plasma glucose, insulin, and ghrelin responses of patients with type 2 diabetes in a randomized clinical trial. J Nutr 2015;145:736–741.

12 Peluso I, Villano DV, Roberts SA, Cesqui E, Raguzzini A, Borges G, Crozier A, Catasta G, Toti E, Serafini M: Consumption of mixed fruit-juice drink and vitamin C reduces postprandial stress induced by a high fat meal in healthy overweight subjects. Curr Pharm Des 2014;20:1020–1024.

13 Burton-Freeman B: Postprandial metabolic events and fruit-derived phenolics: a review of the science. Br J Nutr 2010;104(suppl 3):S1–S14.

14 Burton-Freeman B, Linares A, Hyson D, Kappagoda T: Strawberry modulates LDL oxidation and postprandial lipemia in response to high-fat meal in overweight hyperlipidemic men and women. J Am Coll Nutr 2010;29: 46–54.

15 Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N: Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. J Food Sci 2008;73:H241–H245.

16 Ono-Moore KD, Snodgrass RG, Huang S, Singh S, Freytag TL, Burnett DJ, Bonnel EL, Woodhouse LR, Zunino SJ, Peerson JM, Lee JY, Rutledge JC, Hwang DH: Postprandial inflammatory responses and free fatty acids in plasma of adults who consumed a moderately high-fat breakfast with and without blueberry powder in a randomized placebo-controlled trial. J Nutr 2016;146: 1411–1419.

17 Schell J, Betts NM, Foster M, Scofield RH, Basu A: Cranberries improve postprandial glucose excursions in type 2 diabetes. Food Funct 2017;8:3083–3090.

18 Burton-Freeman BM, Sandhu AK, Edirisinghe I: Red raspberries and their bioactive polyphenols: cardiometabolic and neuronal health links. Adv Nutr 2016;7:44–65.

19 Marathe PH, Gao HX, Close KL: American diabetes association standards of medical care in diabetes 2017. J Diabetes 2017;9:320–324.

20 Törrönen R, Kolehmainen M, Sarkkinen E, Poutanen K, Mykkänen H, Niskanen L: Berries reduce postprandial insulin responses to wheat and rye breads in healthy women. J Nutr 2013;143:430–436.

21 Edirisinghe I, Banaszewski K, Cappozzo J, Sandhya K, Ellis CL, Tadapaneni R, Kappagoda CT, Burton-Freeman BM: Strawberry anthocyanin and its association with postprandial inflammation and insulin. Br J Nutr 2011;106:913–922.

22 Rasouli H, Hosseini-Ghazvini SM, Adibi H, Khodarahmi R: Differential α-amylase/α-glucosidase inhibitory activities of plant-derived phenolic compounds: a virtual screening perspective for the treatment of obesity and diabetes. Food Funct 2017;8:1942–1954.
23 Bellesia A, Verzelloni E, Tagliazucchi D: Pomegranate ellagitannins inhibit α-glucosidase activity in vitro and reduce starch digestibility under simulated gastro-intestinal conditions. Int J Food Sci Nutr 2015;66:85–92.
24 Hidalgo J, Teuber S, Morera FJ, Ojeda C, Flores CA, Hidalgo MA, Núñez L, Villalobos C, Burgos RA: Delphinidin Reduces Glucose Uptake in Mice Jejunal Tissue and Human Intestinal Cells Lines through FFA1/GPR40. Int J Mol Sci 2017;18:pii: E750.
25 Shi C, Men L, Yu C, Yao J, Bai R, Yang Y, Sun L, Sun G, Song G, Zhang Y, Xing Q, Du J: Atherosclerosis associated with dynamic inflammation changes after multifactorial intervention in short-duration type 2 diabetes: a randomized, controlled, 10-year follow-up trial. J Diabetes Complications 2017;31:1286–1292.
26 Joseph SV, Edirisinghe I, Burton-Freeman BM: Fruit polyphenols: a review of anti-inflammatory effects in humans. Crit Rev Food Sci Nutr 2016;56:419–444.
27 Sangiovanni E, Vrhovsek U, Rossoni G, Colombo E, Brunelli C, Brembati L, Trivulzio S, Gasperotti M, Mattivi F, Bosisio E, Dell'Agli M: Ellagitannins from Rubus berries for the control of gastric inflammation: in vitro and in vivo studies. PLoS One 2013;8:e71762.
28 Li L, Wang L, Wu Z, Yao L, Wu Y, Huang L, Liu K, Zhou X, Gou D: Anthocyanin-rich fractions from red raspberries attenuate inflammation in both RAW264.7 macrophages and a mouse model of colitis. Sci Rep 2014;4:6234.
29 Koloverou E, Panagiotakos DB, Georgousopoulou EN, Chrysohoou C, Tousoulis D, Stefanadis C, Pitsavos C; ATTICA Study Group: Single and combined effects of inflammatory markers on 10 year diabetes incidence: the mediating role of adiposity-Results from the ATTICA cohort study. Diabetes Metab Res Rev 2017;34.
30 Klüppelholz B, Thorand B, Koenig W, de Las Heras Gala T, Meisinger C, Huth C, Giani G, Franks PW, Roden M, Rathmann W, Peters A, Herder C: Association of subclinical inflammation with deterioration of glycaemia before the diagnosis of type 2 diabetes: the KORA S4/F4 study. Diabetologia 2015;58:2269–2277.
31 Emerson SR, Kurti SP, Harms CA, Haub MD, Melgarejo T, Logan C, Rosenkranz SK: Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: a systematic review. Adv Nutr 2017;8:213–225.
32 An JH, Kim DL, Lee TB, Kim KJ, Kim SH, Kim NH, Kim HY, Choi DS, Kim SG: Effect of rubus occidentalis extract on metabolic parameters in subjects with prediabetes: a proof-of-concept, randomized, double-blind, placebo-controlled clinical trial. Phytother Res 2016;30:1634–1640.
33 Jeong HS, Hong SJ, Lee TB, Kwon JW, Jeong JT, Joo HJ, Park JH, Ahn CM, Yu CW, Lim DS: Effects of black raspberry on lipid profiles and vascular endothelial function in patients with metabolic syndrome. Phytother Res 2014;28:1492–1498.
34 Jeong HS, Hong SJ, Cho JY, Lee TB, Kwon JW, Joo HJ, Park JH, Yu CW, Lim DS: Effects of rubus occidentalis extract on blood pressure in patients with prehypertension: Randomized, double-blinded, placebo-controlled clinical trial. Nutrition 2016;32:461–467.
35 Jennings A, Welch AA, Fairweather-Tait SJ, Kay C, Minihane AM, Chowienczyk P, Jiang B, Cecelja M, Spector T, Macgregor A, Cassidy A: Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. Am J Clin Nutr 2012;96:781–788.
36 Cassidy A, O'Reilly ÉJ, Kay C, Sampson L, Franz M, Forman JP, Curhan G, Rimm EB: Habitual intake of flavonoid subclasses and incident hypertension in adults. Am J Clin Nutr 2011;93:338–347.
37 Min J, Jahns L, Xue H, Kandiah J, Wang Y: Americans' perceptions about fast food and how they associate with its consumption and obesity risk. Adv Nutr 2018;5:590–601.
38 Braithwaite I, Stewart AW, Hancox RJ, Beasley R, Murphy R, Mitchell EA; ISAAC Phase Three Study Group; ISAAC Phase Three Study Group: Fast-food consumption and body mass index in children and adolescents: an international cross-sectional study. BMJ Open 2014;4:e005813.
39 Devaraj S, Wang-Polagruto J, Polagruto J, Keen CL, Jialal I: High-fat, energy-dense, fast-food-style breakfast results in an increase in oxidative stress in metabolic syndrome. Metabolism 2008;57:867–870.
40 Ursini F, Zamburlini A, Cazzolato G, Maiorino M, Bon GB, Sevanian A: Postprandial plasma lipid hydroperoxides: a possible link between diet and atherosclerosis. Free Radic Biol Med 1998;25:250–252.