

Low-calorie cranberry juice supplementation reduces plasma oxidized LDL and cell adhesion molecule concentrations in men

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Elevated circulating concentrations of oxidized LDL (OxLDL) and cell adhesion molecules are considered to be relevant markers of oxidative stress and endothelial activation which are implicated in the development of CVD. On the other hand, it has been suggested that dietary flavonoid consumption may be cardioprotective through possible favourable impacts on LDL particle oxidation and endothelial activation. The present study was undertaken to determine the effect of the daily consumption of low-calorie cranberry juice cocktail on plasma OxLDL, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin concentrations in men. Thirty men (mean age 51 (SD 10) years) were recruited and asked to consume increasing daily doses of cranberry juice cocktail (125, 250 and 500 ml/d) over three successive periods of 4 weeks. Plasma OxLDL and adhesion molecule concentrations were measured by ELISA before and after each phase. We noted a significant decrease in plasma OxLDL concentrations following the intervention ($P < 0.0001$). We also found that plasma ICAM-1 ($P < 0.0001$) and VCAM-1 ($P < 0.05$) concentrations decreased significantly during the course of the study. In summary, the present results show that daily cranberry juice cocktail consumption is associated with decreases in plasma OxLDL, ICAM-1 and VCAM-1 concentrations in men.

Cranberry: Flavonoids: Oxidized LDL: Cardiovascular disease: ICAM-1: VCAM-1

CVD is the leading cause of death in North America¹ and it is well recognized that LDL-cholesterol is a major risk factor associated to CVD². However, not all CVD patients show high LDL-cholesterol concentrations and it has been shown that variations in the physical properties and composition of LDL particles such as LDL oxidation could explain, at least in part, the atherogenicity of LDL^{3,4} even in the absence of high LDL-cholesterol concentrations. As oxidized LDL (OxLDL) are not recognized by the LDL receptor but rather by scavenger receptors at the surface of sub-endothelial resident macrophages, LDL oxidation favours the unrestricted uptake of cholesterol, thereby leading to the formation of foam cells, which is the first step in the formation of the earliest atherosclerotic lesions known as fatty streaks².

Migration of monocytes from the bloodstream into the sub-endothelial space requires that cell adhesion molecules such as the intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin be expressed by endothelial cells. This process is referred to as endothelial activation². Interestingly, soluble forms of these different cell adhesion molecules can be measured in plasma probably as a result of the vascular endothelium breakdown,

and these concentrations have been shown to correlate with cardiovascular mortality⁵.

Numerous studies^{6–8} have shown that antioxidants and more specifically polyphenolic compounds can inhibit LDL oxidation, which in turn has been suggested to reduce OxLDL-induced expression of cell adhesion molecules by endothelial cells^{9,10}. Cranberry is a potent source of different antioxidant compounds such as flavonols, anthocyanidins, proanthocyanidins^{11,12}, as well as resveratrol¹³ and phenolic acids¹¹. Furthermore, cranberries also contain acetylsalicylic acid¹⁴ that possesses anti-inflammatory activity and that has been shown to decrease VCAM-1 expression *in vitro*¹⁵. The present study was therefore undertaken in order to examine the effect of consuming increasing doses of low-calorie cranberry juice cocktail (CJC) for a period of 12 weeks on plasma concentrations of OxLDL and cell adhesion molecules in men.

Material and methods

Subjects

Thirty-one healthy and sedentary men were recruited through the media to participate in a 12-week intervention.

Abbreviations: CJC, cranberry juice cocktail; ICAM-1, intercellular adhesion molecule-1; IκB, nuclear factor kappa B inhibitor; NF-κB, nuclear factor kappa B; OxLDL, oxidized LDL; PJ, cranberry-flavoured low-calorie placebo juice; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

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Inclusion and exclusion criteria are described in Table 1. Briefly, subjects had to have a waist circumference ≥ 90 cm, a fasting plasma LDL-cholesterol concentration between 3.0 and 5.0 mmol/l and absence of diabetes, CVD and renal, hepatic and endocrine disorders. A written consent was provided by each volunteer to participate in the study which was approved by the Medical Ethics Committee of Laval University (project no. 2003-131). During the course of the study, one subject dropped out of the project due to personal reasons not related to the intervention. Therefore, the data presented refer to the thirty men who completed the study.

Intervention

Upon entry into the study, subjects met with a dietitian and were instructed to maintain their usual nutritional habits throughout the entire intervention. Participants were subjected to a 4-week Run-In period which consisted of consuming 500 ml/d of a cranberry-flavoured low-calorie placebo juice (PJ). During the Run-In period, participants were instructed to reduce their alcohol consumption to a maximum of one drink/d (or < 15 g alcohol/d) and to refrain from consuming any vitamin, antioxidant or mineral supplements. This Run-In period was followed by three 4-week periods during which subjects successively consumed 125 ml (phase 1), 250 ml (phase 2) and 500 ml (phase 3) of CJC daily. These volumes were adjusted to 500 ml liquid/d by adding 375, 250 or 0 ml PJ/d for phases 1, 2 and 3 respectively. This was achieved in order to minimize the impact of incorporating increasing quantities of liquid in the daily diet of subjects and blind subjects from the level of treatment they were assigned to.

PJ and CJC were provided to the subjects in 125 ml ready-to-drink TetraBrik boxes from Tetra-Pak® (Richmond Hill, Ontario, Canada) that were packaged at Laval University. Both the PJ and CJC were kindly provided to us by Ocean Spray Cranberries Inc. who also monitored the packaging sessions to ensure adequate reconstitution and quality of both the PJ and CJC. A detailed description of the PJ and CJC that were used in the present study has been previously published¹⁶. In an effort to keep the subjects' sugar consumption to a minimum and limit possible detrimental changes in plasma TAG concentrations, we provided subjects with the

no added sugar version of Ocean Spray's Low-calorie CJC. Both the PJ and CJC were artificially sweetened with sucralose (Splenda®; McNeil Nutritionals LLC, Fort Washington, PA, USA). One box of 125 ml CJC or PJ contained 5.46 g of carbohydrates, and provided 91.3 kJ energy. A detailed description of both CJC and PJ is in Table 2.

Blood pressure and lipid measures

At each visit to the investigation unit, blood pressure was measured by a nurse with a manual sphygmomanometer with the subject in a supine position after a 5 min rest. Blood samples were obtained from the subjects' antecubital vein in the morning after a 12 h fast. Upon collection, cholesterol and TAG concentrations were determined in plasma by enzymatic methods using a Technicon RA-1000 analyser (Bayer Corporation Inc., Tarrytown, NY, USA) as previously described¹⁷. Plasma VLDL (density < 1.006 g/ml) were isolated by ultracentrifugation and the HDL fraction was obtained after precipitation of LDL from the infranatant (density > 1.006 g/ml) with heparin and MnCl_2 ¹⁸. The cholesterol and TAG contents of the infranatant fraction were measured before and after the precipitation step. LDL-cholesterol was obtained by subtracting the HDL-cholesterol concentration from the cholesterol content of the density > 1.006 g/ml fraction. Apolipoprotein (apo) B concentration was measured by nephelometry (Dade Behring, Mississauga, Ontario, Canada) in total plasma as well as in the density < 1.006 g/ml fraction (LDL-apo B). The lyophilized serum standards for apo B measurements were prepared at the Lipid Research Center of Laval University Medical Center and calibrated with reference standards obtained from the Centers for Disease Control (Atlanta, GA, USA). Commercial ELISA kits were used to determine plasma soluble forms of E-selectin, ICAM-1, VCAM-1 (R&D Systems, Minneapolis, MN, USA) as well as OxLDL (ALPCO Diagnostics, Windham, NH, USA) concentrations.

Table 2. Detailed description of the content of a portion (125 ml) of placebo juice (PJ) and low-calorie cranberry juice cocktail (CJC)† (Mean values and standard deviations for five determinations)

	PJ		CJC	
	Mean	SD	Mean	SD
Energy (kJ)	91.3		91.3	
Carbohydrates (g)	5.46	0.08	5.46	0.28
Ascorbic acid (mg)	32		32	
Total organic acids (g)	0.90	0.01	0.98	0.04
Total phenolics (mg)	39	0.09	100	6.50
Total anthocyanins (mg)	ND	ND	5.2	0.68
Cyanidin-3-galactoside	ND	ND	0.91	0.33
Cyanidin-3-glucoside	ND	ND	0.08	0.01
Cyanidin-3-arabinoside	ND	ND	1.3	0.26
Peonidin-3-galactoside	ND	ND	1.5	0.09
Peonidin-3-glucoside	ND	ND	0.24	0.01
Peonidin-3-arabinoside	ND	ND	1.2	0.09
Proanthocyanidins (mg)	ND	ND	74	5.21

ND, none determined.

† Other ingredients included in PJ and CJC are filtered water, cranberry juice concentrate (CJC only), fructose, pectin, sodium citrate, ascorbic acid, sucralose and acesulfame-K.

Table 1. Exclusion and inclusion criteria of the study

Inclusion criteria	
Men between 18 and 70 years of age	
BMI ≥ 25 and ≤ 35 kg/m ²	
Waist circumference ≥ 90 cm	
LDL-cholesterol between 3.0 and 5.0 mmol/l	
No use of medication known to affect lipid metabolism or possess anti-inflammatory effect	
Exclusion criteria	
Alcohol consumption > 15 g alcohol/d	
Chronic use of supplements (vitamins, minerals or flavonoids)	
Chronic diseases: CHD, diabetes, etc.	
Dyslipidaemia secondary to renal insufficiency, hypothyroidism or others	
Smoking (one or more cigarettes/d)	

Statistical analyses

Data are presented as means and standard deviations unless stated otherwise. Treatment effect and changes between CJC doses on the different variables were determined using the MIXED model procedure for repeated measures. When needed, covariance matrix structures were treated for compound symmetry, order 1 autoregressive or Huynh-Feldt. Associations between changes in variables were quantified with Spearman correlation coefficients. Changes in men with (*n* 9) or without (*n* 21) the metabolic syndrome were tested for significance using Student's paired *t*-tests. All analyses were performed with the SAS statistical package version 8.2 (SAS Institute, Cary, NC, USA) and *P* ≤ 0.05 was considered significant.

Results

Subjects' physical and metabolic characteristics upon their entry into the study are presented in Table 3. As shown in Fig. 1, the intervention yielded a decrease in plasma OxLDL (*P* < 0.001), which reached significance from baseline after the 250 ml/d (−5.5 (SD 27.1) %, *P* < 0.05) and 500 ml/d (−20.7 (SD 21.1) %, *P* < 0.001) phases. As reported and discussed in a previous publication by our group¹⁶, the intervention yielded a significant increase in plasma HDL-cholesterol (*P* = 0.0010) concentration but failed to significantly affect circulating TAG (*P* = 0.0553) as well as levels of total cholesterol (*P* = 0.85) and LDL-cholesterol (*P* = 0.52) (Table 4).

The effects of consuming increasing daily doses of CJC on plasma cell adhesion molecule concentrations are illustrated in Fig. 2. We found that both soluble VCAM-1 (sVCAM-1; *P* < 0.05) and soluble ICAM-1 (sICAM-1; *P* < 0.0001) were decreased following the intervention, reductions reaching significance compared to baseline values after consumption of the 500 ml/d CJC dose for both sVCAM-1 (−6.4 (SD 11.5) %, *P* < 0.01) and sICAM-1 (−7.5 (SD 15.4) %, *P* = 0.001). There was no effect of the intervention on plasma E-selectin concentrations (*P* = 0.66).

Table 3. Baseline physical and metabolic characteristics of the thirty men

Variable	Mean	SD	25th to 75th percentiles
Age (years)	51	10	46–60
Weight (kg)	85.0	11.8	78.1–89.2
BMI (kg/m ²)	27.8	3.2	25.7–28.8
Waist circumference (cm)	97.9	6.4	92.5–100
Waist/hip ratio	0.95	0.04	0.92–0.99
Cholesterol (mmol/l)	5.97	0.85	5.45–6.51
TAG (mmol/l)	1.64	0.76	1.31–1.75
LDL-cholesterol (mmol/l)	4.06	0.70	3.64–4.58
HDL-cholesterol (mmol/l)	1.24	0.26	1.06–1.32
Cholesterol/HDL-cholesterol	4.97	1.18	3.96–5.86
Apolipoprotein B (g/l)	1.19	0.23	1.05–1.29
Oxidized LDL (U/l)	61.3	20.7	45.7–70.2
Soluble E-selectin (ng/ml)	43.1	18.5	28.7–59.7
sICAM-1 (ng/ml)	191.4	59.3	134.8–227.5
sVCAM-1 (ng/ml)	425	61	385–480

sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

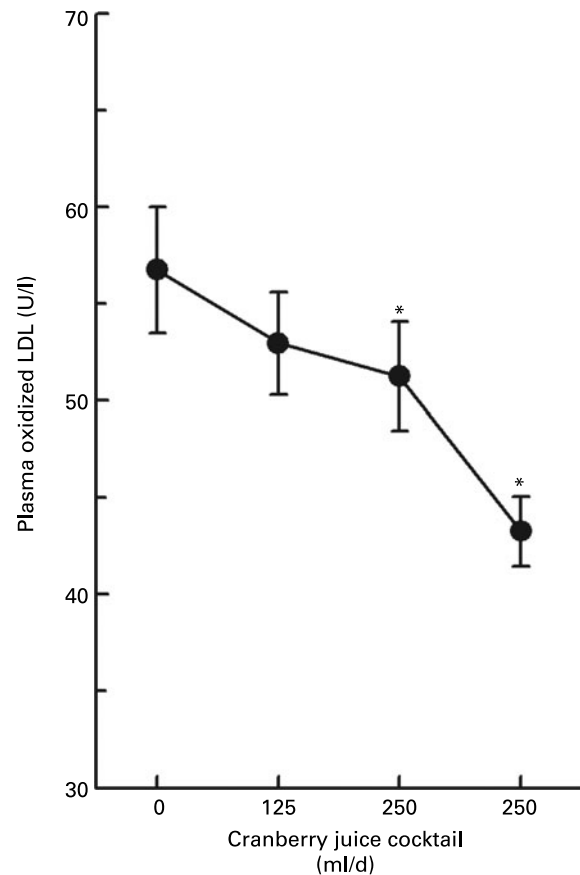


Fig. 1. Changes in plasma oxidized LDL (*P* < 0.0001 across doses) concentrations during the intervention. Values are means with their standard errors depicted by vertical bars. Mean values were significantly different from baseline (0 ml CJC/d): **P* < 0.05.

In an effort to characterize the relationships between the responses in plasma sVCAM-1, sICAM-1, soluble E-selectin and OxLDL concentration (0–500 ml CJC/d), we computed Spearman correlation coefficients between these variables. As shown in Fig. 3, we found a positive correlation between change in sVCAM-1 and OxLDL concentrations (*r* 0.62, *P* < 0.005) but an inverse association between sICAM-1 and OxLDL concentrations (*r* −0.40, *P* < 0.05).

We also examined the impact of being characterized by the metabolic syndrome, according to the National Cholesterol Education Program Adult Treatment Panel III guidelines¹⁹, on the responses of OxLDL and adhesion molecules to the intervention. As shown in Fig. 4, we found that consuming low-calorie CJC for a period of 12 weeks significantly reduced plasma OxLDL and sICAM-1 concentration in both men with and without the metabolic syndrome. However, circulating sVCAM-1 were significantly lower at the end of the intervention only in men without the metabolic syndrome. We found no effect of the presence of the metabolic syndrome on the response of plasma soluble E-selectin concentrations to the intervention (data not shown).

As shown in Table 4, a significant variation was noted in systolic blood pressure (*P* across doses < 0.05) during the intervention which was accounted for by a significant decrease between the 125 and 500 ml CJC/d (−7 (SD 12) mmHg,

Table 4. Changes in lipids, blood pressure and heart beat during the intervention

Variables	Daily cranberry juice cocktail consumption								P across doses
	0 ml		125 ml		250 ml		500 ml		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total cholesterol (mmol/l)	5.84	0.76	5.90	0.68	5.86	0.75	5.82	0.82	0.8476
LDL-cholesterol (mmol/l)	4.03	0.64	4.10	0.60	4.04	0.67	3.97	0.73	0.5246
HDL-cholesterol (mmol/l)	1.19	0.04	1.23	0.04	1.28*	0.04	1.28*	0.04	0.0010
apo B (g/l)	1.16	0.20	1.19	0.17	1.16	0.18	1.18	0.20	0.2362
TAG (mmol/l)	1.57	0.48	1.43	0.45	1.44	0.48	1.49	0.66	0.0553
Systolic blood pressure (mmHg)	110	13	114	14	111	13	107*	10	0.0311
Diastolic blood pressure (mmHg)	73	9	75	8	73	9	71	8	0.2881
Heart beat (beats/min)	67	8	68	8	68	9	67	8	0.9041

Mean values were significantly different from those of the 0 ml group: * $P < 0.05$.

$P = 0.0036$) doses. On the other hand, we noted no significant change in diastolic blood pressure or heart beat in response to the 12-week intervention (Table 3).

Finally, we examined the relationships between changes in systolic blood pressure and plasma cell adhesion molecule concentrations following the intervention. A significant association was noted between change in plasma VCAM-1 concentrations and systolic blood pressure ($r = 0.42$, $P < 0.05$). However, no correlation was noted between changes in systolic blood pressure and circulating ICAM-1 ($P = 0.51$) or E-selectin ($P = 0.87$) concentrations.

Discussion

In the present study, we report that consumption of increasing doses of low-calorie CJC on a daily basis for a period of 12 weeks is associated with reductions in plasma OxLDL as well as sICAM-1 and sVCAM-1 concentrations but has no effect on circulating E-selectin concentrations in men. It is, to our knowledge, the first time that low-calorie CJC supplementation has been associated with reductions in plasma cell adhesion molecule concentrations in man. In this sense, the present observations tend to give further support to the cardioprotective potential of cranberries that has been already suggested²⁰.

The significant reduction in plasma OxLDL concentrations with consumption of CJC observed in the present study is in agreement with results from previous investigations having shown that cranberry antioxidants decrease metal ion-induced LDL oxidation *in vitro*^{6,7} and with a previous study from our group in which we observed a decrease in OxLDL concentration following a 2-week CJC supplementation in men²¹. Consumption of other fruit juices rich in flavonoids such as grape²² and pomegranate²³, which share similarities with cranberries in regards to their polyphenolic content, has also been shown to reduce plasma OxLDL concentrations.

Although, plasma LDL-cholesterol concentrations and LDL oxidation are closely related²⁴, the reduction in circulating OxLDL concentrations we report herein cannot be explained by changes in LDL-cholesterol concentrations as these remained stable throughout the entire intervention, as previously reported¹⁶. Furthermore, it has been shown that small dense LDL particles are more susceptible to oxidation²⁵. Although LDL size was not measured in the present study, we

have previously shown that a 2-week CJC supplementation was not associated with any significant variation in LDL size despite a reduction in plasma OxLDL concentrations²¹. In addition, there was no change in the LDL-*apo B*/LDL-cholesterol ratio, a crude marker of LDL density, during the current intervention. This suggests that LDL size may not be a major contributor to the decrease in OxLDL observed in the present study. We believe that the reduction of plasma OxLDL concentrations in response to low-calorie CJC supplementation is likely to be attributable to polyphenolic compounds of the cranberries as they exert a potent antioxidant activity^{26,27} and have been shown to prevent *in vitro* LDL oxidation^{6,7}. On the other hand, it may be argued that consuming low-calorie CJC may have affected the total antioxidant capacity of the subjects through increases and/or preservation of endogenous antioxidant defences. However, evidence against such changes have been recently provided with data indicating that CJC supplementation for 2 weeks had no effect on fasting blood glutathione peroxidase, catalase and superoxide dismutase activities nor on fasting circulating glutathione concentrations²⁸. However, the possibility of improvements in these parameters over the course of the 12-week low-calorie CJC supplementation such as the one we report herein cannot be excluded.

Consumption of grape juice for 14 d was associated with decreases in plasma sICAM-1, an effect that was attributed to polyphenolic grapes²⁹. The present results are supportive of the effect of polyphenols on ICAM-1 production. Interestingly, similarities exist in the polyphenol content of grapes and cranberries. Both have been characterized as potent sources of quercetin, myricetin and resveratrol^{27,30}, which have been identified as strong antioxidants²⁷. In contrast, other polyphenol-rich foods like tea have shown equivocal results on their effects on circulating adhesion molecule concentrations^{31–33}. Differences in the design of these studies but mostly in the type of flavonoids found in tea compared to cranberries are likely to explain the discrepancies between these previous observations and the present results.

The most extensively characterized pathway for cell adhesion molecule production involves the activation of NF- κ B. Briefly, stimulation of a phosphorylation cascade will ultimately lead to the cleavage of the nuclear factor kappa B (NF- κ B) inhibitor (I κ B)/NF- κ B complex and nuclear translocation of NF- κ B where it will be able to regulate the

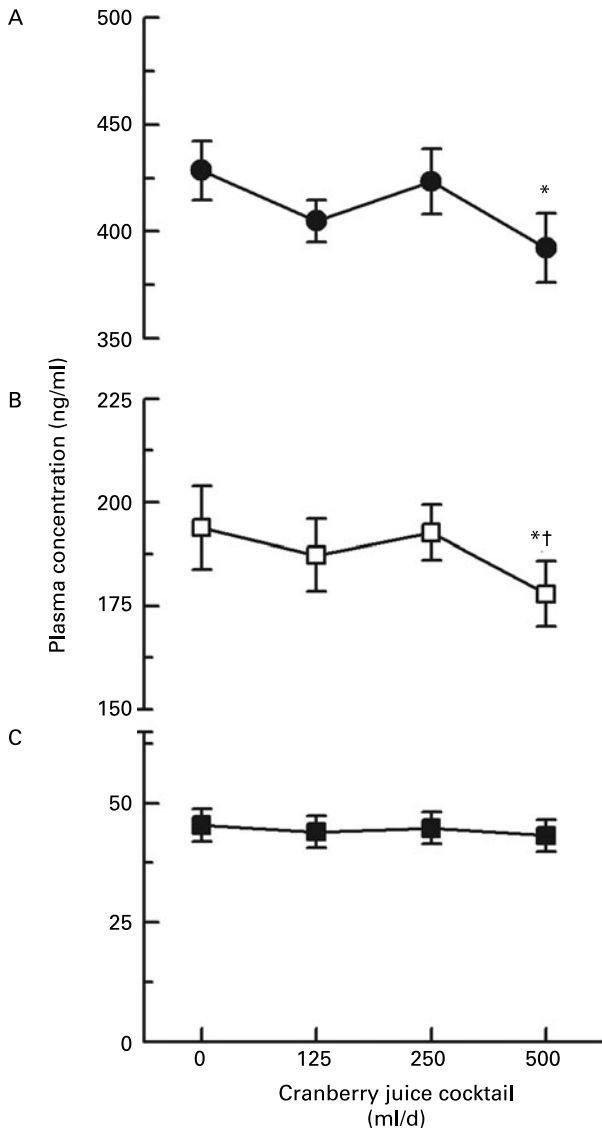


Fig. 2. Changes in plasma soluble vascular cell adhesion molecule-1 (A; $P < 0.05$ across doses), intercellular adhesion molecule-1 (B; $P = 0.0001$) and soluble E-selectin (C; $P = 0.66$) concentrations during the intervention. Values are means with their standard errors depicted by vertical bars. Mean values were significantly different from baseline (0 ml CJC/d): * $P < 0.05$. Mean values were significantly different from week 8 (250 ml CJC/d): † $P < 0.05$.

transcription of numerous genes such as ICAM-1 and VCAM-1³. Many stimuli have been identified to activate the $\text{I}\kappa\text{B}/\text{NF-}\kappa\text{B}$ pathway including many inflammatory mediators and OxLDL³. The present observations are somewhat supportive of the OxLDL-induced production of sVCAM-1 as the change in plasma OxLDL concentration following the intervention was positively correlated to the change in circulating sVCAM-1. Unfortunately, NF- κB activation was not assessed in the current study and thus our hypothesis remains to be ascertained.

On the other hand, the contribution of OxLDL to the reduction in plasma sICAM-1 concentrations following the intervention is not so clear as we found an inverse relationship between the decrease in circulating OxLDL and sICAM-1 concentrations. Although statistically significant, the physiological relevance of that relationship remains to be better understood. Results

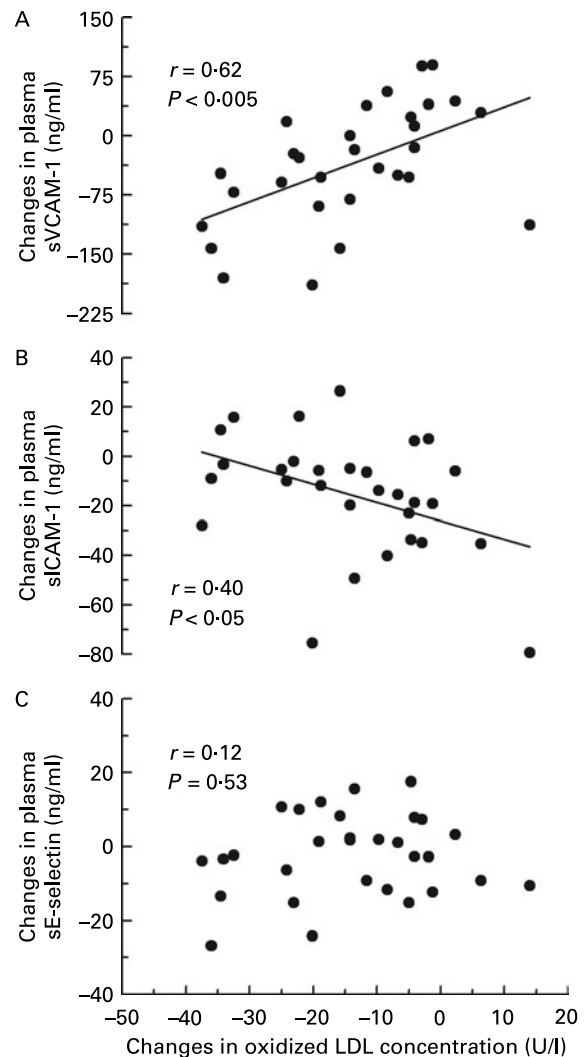


Fig. 3. Associations between changes in plasma oxidized LDL and soluble vascular cell adhesion molecule-1 (sVCAM-1; A), soluble intercellular adhesion molecule-1 (sICAM-1; B) as well as soluble E-selectin (sE-selectin; C) concentrations over the course of the entire intervention.

from *in vitro* studies suggest that molecules like quercetin^{34,35}, resveratrol^{36,37}, proanthocyanidin³⁸, anthocyanidin³⁹, hydroxycinnamic acid³⁹ and acetylsalicylic acid^{40,41} have all been shown to prevent TNF- α -induced expression of VCAM-1 and/or ICAM-1 through their inhibition of NF- κB activation. Because cranberries are rich in quercetin, it is likely that the 12-week low-calorie CJC supplementation may have lowered plasma sICAM-1 through a direct effect of the increase in flavonoid intake.

Abdominal obesity is associated with a cluster of metabolic alterations including hypertriglyceridaemia, low HDL-cholesterol and impaired glucose–insulin homeostasis that has been defined as the metabolic syndrome⁴². Furthermore, the metabolic syndrome *per se* is now recognized as a risk factor of cardiovascular events⁴³. It is therefore relevant to develop strategies aimed at improving the metabolic condition of abdominally obese individuals that could reduce their CVD risk. In the present study, we found that consuming low-calorie CJC for a period of 12 weeks significantly reduced

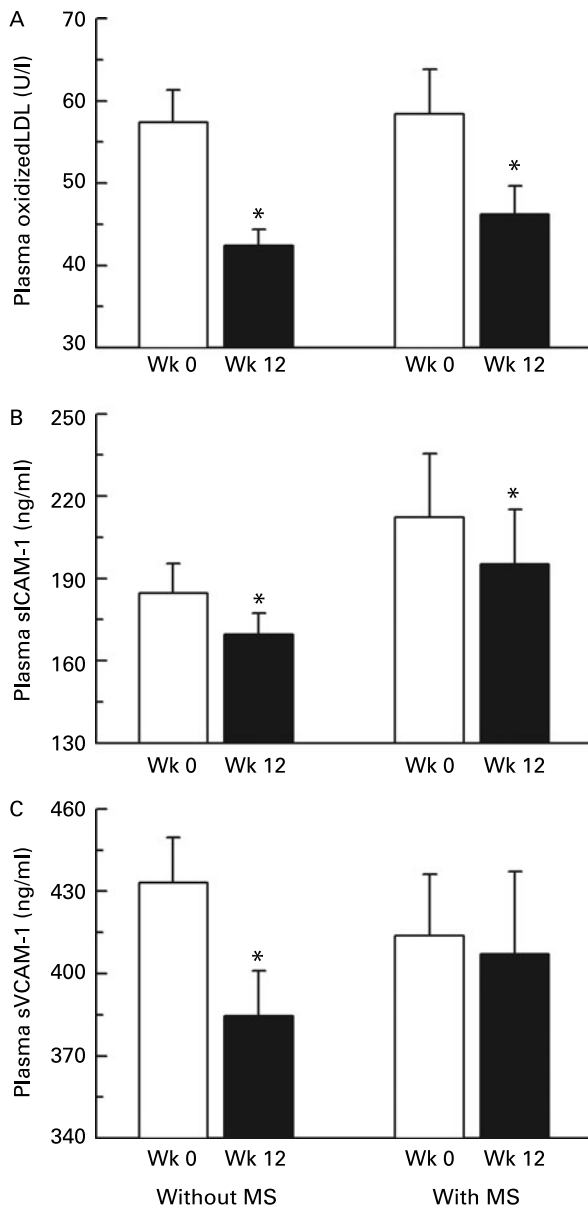


Fig. 4. Changes in plasma oxidized LDL (A), soluble intercellular adhesion molecule-1 (sICAM-1; B) and vascular cell adhesion molecule-1 (sVCAM-1; C) concentrations in response to the intervention in men with or without the metabolic syndrome (MS). Values are means with their standard errors depicted by vertical bars. Mean values were significantly different from week 0 (Wk 0): * $P < 0.05$.

plasma OxLDL and sICAM-1 concentrations in both men with and without the metabolic syndrome. However, our intervention yielded a significant reduction of sVCAM-1 concentrations only in subjects without the metabolic syndrome.

High blood pressure is an important risk factor for CVD¹⁹. In the present study, we noted a slight significant decrease in systolic blood pressure over the course of the intervention. We found no effect of drinking low-calorie CJC on a daily basis on diastolic blood pressure. Previous studies with fruit juice have also reported a blood pressure-lowering effect. Indeed, pomegranate⁴⁴, Concord grape juice⁴⁵ and sweetie juice (mix of grapefruit and pumelo)⁴⁶ in man as well as grape

juice with wine vinegar in rats⁴⁷ have all been shown to lower blood pressure. Among possible mechanisms underlying the hypotensive effect of these beverages, inhibition of the activity of the angiotensin-converting enzyme has been suggested as most likely. On the other hand, dark chocolate, a food also rich in flavonoids, has been reported to increase resting brachial artery diameter⁴⁸ which is concordant with a blood pressure-lowering effect. Neither angiotensin-converting enzyme activity nor brachial artery diameter were measured in the present study and the decrease in systolic blood pressure emergent herein remains unexplained.

One important drawback of the present study is that we are not able to clearly assess whether the favourable changes in plasma OxLDL, ICAM-1 and VCAM-1 concentrations we noted were the result of increasing doses of CJC or duration of the intervention. Furthermore, although a similar study design has been previously used in numerous studies^{16,21,49–53}, the absence of a placebo control group is also unfortunate and surely imposes a limit to the present study. These issues are presently under investigation in our laboratory.

In summary, results of the present study show that a 12-week supplementation with low-calorie CJC reduces plasma OxLDL concentrations in men. Furthermore, to our knowledge, the present study is the first to show that consuming low-calorie CJC leads to a decrease in circulating sICAM-1 and sVCAM-1 concentrations in man. Although further research is needed to warrant our observations, the present study reinforces the notion that consuming fruits and vegetables, or their derived products, can have significant benefits on the CVD risk profile.

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