Consumption of High-Pressurized Vegetable Soup Increases Plasma Vitamin C and Decreases Oxidative Stress and Inflammatory Biomarkers in Healthy Humans[1]

Concepción Sánchez-Moreno,*† M. Pilar Cano,† Begoña de Ancos,† Lucía Plaza,† Begoña Olmedilla,** Fernando Granado,** and Antonio Martín*[2]

*Nutrition and Neurocognition Laboratory, Jean Mayer U.S. Department of Agriculture-Human Nutrition Research Center on Aging at Tufts University, Boston, MA; †Department of Plant Foods Science and Technology, Instituto del Frío-CSIC, Madrid, Spain; and **Unit of Vitamins, Section of Nutrition, Clínica Puerta de Hierro, Madrid, Spain

ABSTRACT Current evidence supports a significant association between fruit and vegetable intake and health. In this study, we assessed the effect of consuming a vegetable-soup "gazpacho" on vitamin C and biomarkers of oxidative stress and inflammation in a healthy human population. We also examined the association between vitamin C and F_2-isoprostanes (8-*epi*$PGF_{2\alpha}$), uric acid (UA), prostaglandin E_2 (PGE_2), monocyte chemotactic protein-1 (MCP-1), and the cytokines, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. Gazpacho is a Mediterranean dish defined as a ready-to-use vegetable soup, containing ~80% crude vegetables rich in vitamin C. Subjects (6 men, 6 women) enrolled in this study consumed 500 mL/d of gazpacho corresponding to an intake of 72 mg of vitamin C. On d 1, subjects consumed the gazpacho in one dose; from d 2 until the end of the study, d 14, 250 mL was consumed in the morning and 250 mL in the afternoon. Blood was collected before drinking the soup (baseline) and on d 7 and 14. Baseline plasma vitamin C concentrations did not differ between men and women ($P = 0.060$). Compared with baseline, the vitamin C concentration was significantly higher on d 7 and 14 of the intervention in both men and women ($P < 0.05$). Baseline plasma levels of UA and F_2-isoprostanes were higher ($P \leq 0.002$) in men than in women. The F_2-isoprostanes decreased on d 14 in men and women ($P \leq 0.041$), and UA decreased in men ($P = 0.028$). The concentrations of vitamin C and 8-*epi*$PGF_{2\alpha}$ were inversely correlated ($r = -0.585$, $P = 0.0002$). Plasma PGE_2 and MCP-1 concentrations decreased in men and women ($P \leq 0.05$) on d 14, but those of TNF-α, IL-1β, and IL-6 did not change. Consumption of the vegetable soup decreases oxidative stress and biomarkers of inflammation, which indicates that the protective effect of vegetables may extend beyond their antioxidant capacity. J. Nutr. 134: 3021–3025, 2004.

KEY WORDS: • *vegetable soup* • *vitamin C* • *F_2-isoprostanes* • *inflammation*

Increasing evidence indicates that fruit and vegetable consumption is associated with reduced risk of major diseases, including cardiovascular disease (CVD), stroke, cancer, and dementia (1–4). Current recommendations are that everyone should eat at least 5 portions of a variety of fruit and vegetables daily to reduce the risk of chronic diseases and possibly delay the onset of age-related problems (5–7).

Gazpacho is a typical Mediterranean dish that can be defined as a ready-to-use vegetable soup containing ~80% crude vegetables (tomato, cucumber, pepper), 2–10% olive oil, and other minor components (onion, garlic, wine vinegar, and sea salt) (8). The vegetables present in this soup are important components of the Mediterranean diet and constitute a simple way of ingesting generous amounts of vegetables.

Good nutrition is essential to good health; as a result, consumers are increasingly demanding healthy and nutritious products (9). Nonthermal processing techniques have been developed to meet consumer demands (10). Although high-pressure (HP)[3] technology alters some of the physicochemical properties, e.g., a higher glucose retardation index, water retention, or reduced extractability, it does not appear to affect the nutrient content (10,11). Interestingly, no study has examined the effect of regular consumption of vegetable soup on vitamin C, oxidative stress, and inflammatory biomarkers.

Vegetables contain many nutrients that contribute to re-

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[2] To whom correspondence should be addressed.
E-mail: antonio.martin@tufts.edu.

[3] Abbreviations used: CVD, cardiovascular disease; 8-*epi*$PGF_{2\alpha}$, 8-isoprostane; HP, high-pressure; IL, interleukin; MCP-1, monocyte chemotactic protein-1; PGE_2, prostaglandin E_2; TNF-α, tumor necrosis factor-α; UA, uric acid.

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ducing the risk of chronic disease, including folic acid, antioxidants, and fiber. Vitamin C is an important component of the protective effect provided by fruits and vegetables (1,12,13). The main contributors to daily vitamin C intake are vegetables and fruit juices (14). Tomato products are the third leading contributors of vitamin C in the U.S. diet (15). Gazpacho contains tomato and pepper as its main components, 2 foods that are rich in vitamin C (16). Because oxidative stress plays an important role in most disease processes and aging, the potential health benefits of fruits and vegetables were largely attributed to their potential antioxidant capacity (17). However, recent data indicate that the protective effect of fruits and vegetables may extend beyond this antioxidant capacity (18). To investigate the effect of vegetable soup on oxidative stress, we measured the levels of F_2-isoprostanes, which provide a meaningful estimation of oxidative stress status in vivo (1,19). One of the isoprostanes, 8-*epi* prostaglandin (PG)$F_{2\alpha}$, was shown to increase with age and chronic disease (20,21) and decrease after the consumption of isoflavones in soy and orange juice (13,22).

A positive association between serum uric acid (UA) and heart disease risk was reported (3,23,24). The death rate was higher in men and women in the upper quartile of UA concentration (23). A significant, graded, independent, and specific association between the level of serum UA and cardiovascular morbidity and mortality was reported. Uric acid may have a direct injurious effect on the endothelium, altering endothelial cell function and reducing readily available nitric oxide, which is relevant in the development of vascular dysfunction and cardiovascular risk.

PGE_2, produced during inflammation, is a potent inhibitor of T-cell activation and immune response (25). Monocyte chemotactic protein-1 (MCP-1) is expressed at high levels in atherosclerotic plaques (26). Given that systemic low-grade inflammatory activity has a strong prognostic value in CVD, some authors consider that circulating levels of cytokines such as tumor necrosis factor-α (TNF-α), and interleukin (IL)-6, would be appropriate markers with which to assess the anti-inflammatory effect of antioxidants in vivo (27). The association between circulating concentrations of antioxidants and biomarkers of inflammation has not been well described in human studies. Therefore, the objective of this study was to examine the effect of consuming vegetable soup on vitamin C and biomarkers of oxidative stress and inflammation.

SUBJECTS AND METHODS

Subjects. Healthy volunteers ($n = 12$; 6 men and 6 women) were enrolled in this study. Subjects were 22 ± 0.5 y old. The mean BMI was 22.5 ± 0.9 kg/m^2 and did not change during the study. Subjects maintained their usual lifestyles and diets during the study. They took no vitamin/mineral supplements or medications. Smokers and subjects with inflammatory disease or taking anti-inflammatory drugs were excluded from the study. None of the subjects were pregnant, lactating, or had any chronic illness. All study participants were in good health on the basis of a medical history, a physical examination, and normal results from clinical laboratory tests, including hematocrit (0.43 ± 0.01), plasma glucose (4.5 ± 0.1 mmol/L), triglycerides (0.7 ± 0.1 mmol/L), and cholesterol (4.3 ± 0.1 mmol/L). Subjects received oral and written information about the study and gave their written consent. The study was approved by the Clinic Research Ethics Committee of Hospital Universitario Clínica Puerta de Hierro, Madrid, Spain.

Study design. This study was an experimental study in which the subjects were asked to consume a prepared vegetable soup twice a day for 14 d. After a minimum of 12 h of fasting, blood was drawn before drinking the vegetable soup, defined as baseline (d 0). Blood samples were collected in heparin-coated tubes and centrifuged at 2000 × *g* for 15 min at 4°C. After plasma was collected, aliquots in triplicate were immediately mixed with an equal volume of cold 60 g/L metaphosphoric acid containing 1 mmol/L of the metal ion chelator diethylenetriaminepentaacetic acid, for vitamin C and UA analysis. The remaining plasma was stored at −80°C for analysis of 8-*epi*$PGF_{2\alpha}$, PGE_2, MCP-1, and the cytokines, TNF-α, IL-1β, and IL-6. Volunteers consumed 500 mL of HP vegetable soup on d 0, and continued to drink the vegetable soup at home, in 2 doses, 250 mL in the morning, and 250 mL in the afternoon, for 2 consecutive weeks. Blood samples were taken again during the intervention on d 7 and 14 of the study.

The composition of the HP vegetable soup consumed by the participants was analyzed by reversed-phase HLPC (vitamin C and total carotenoids) with methods currently used in our laboratory (28), and by methods described in Official Method of Analysis of AOAC (energy, protein, carbohydrate, and fat) (29); the main components are reported in **Table 1**.

Vegetable soup preparation. The vegetable soup gazpacho was prepared with traditional methodology, using a domestic blender (Osterizer) to mix the following ingredients purchased in local supermarkets: tomatoes (*Lycopersicum esculentum* Mill., 50%), cucumber (*Cucumis sativus* L., short cucumber, 15%), green pepper (*Capsicum annuum* L., Italian pepper, 10%), onion (*Allium cepa* L., Onion Buti, 3%), garlic (*Allium sativum* L., white garlic, 0.8%), salt (0.8%), virgin olive oil (Carbonell, 2%), wine vinegar (Ibarra, Spain, 2%), sugar (0.05%), and water (16%).

Vegetable soup HP treatment. The vegetable soup was vacuum packed in plastic bags (Doypack) and then introduced into the pressure unit filled with pressure medium (water) to stabilize the soup using a HP treatment. HP treatment was performed in a hydrostatic pressure unit with a 2350-mL capacity, a maximum pressure of 500 MPa, and a potential maximum temperature of 95°C (Gec Alsthom ACB 900 HP, type ACIP 665). The conditions used in the HP treatment were 400 MPa at 40°C for 1 min, based on our previous studies (28). After treatment, the soup was kept at 4°C until the participants drank it; vitamin C remained stable.

Plasma assays

Vitamin C. Ascorbate was analyzed by paired-ion, reversed-phase HPLC coupled with electrochemical detection as previously described (30).

8-Isoprostane (8-epi$PGF_{2\alpha}$). We used an enzyme immunoassay kit (Cayman Chemical) to determine the concentration of 8-*epi*$PGF_{2\alpha}$ in plasma as previously described (13,30). The intra- and interassay variability CV were ≤10%.

Uric acid (UA). UA was analyzed by paired-ion, reversed-phase HPLC coupled with electrochemical detection, using the procedure described for vitamin C determination with the electrode potential of +0.6V but with the gain set at 1 μA as described previously (13,30).

Prostaglandin E_2 (PGE_2). PGE_2 was measured by a high sensitivity immunoassay kit (R&D Systems) based on a competitive binding technique. The method used was described extensively elsewhere (13,30,31). The intra- and interassay CV were ≤8%.

Monocyte chemotactic protein-1 (MCP-1). MCP-1 was measured by a quantitative sandwich enzyme immunoassay kit (R&D Systems). A monoclonal antibody specific for MCP-1 was precoated onto a microplate. Standards and samples were pipetted into the wells and any MCP-1 present was bound by the immobilized antibody.

TABLE 1

Composition of HP "gazpacho"[1]

Energy, *kJ/L*	1390 ± 36
Protein, *g/L*	6 ± 0.3
Carbohydrate, *g/L*	20 ± 7
Fat, *g/L*	25 ± 8
Vitamin C, *mg/L*	144 ± 9
Total carotenoids, *µg/L*	17,690 ± 1660

[1] Values are means ± SEM, $n = 6$.

After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for MCP-1 was added to the wells. After a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of MCP-1 bound in the initial step. The color development was stopped and the intensity of the color was measured. The intra- and interassay CV were ≤8%.

Cytokines. Theses assays employed a quantitative sandwich enzyme immunoassay kit (R&D Systems). A monoclonal antibody specific for TNF-α, IL-1β, or IL-6 was precoated onto a microplate. Standards and samples were pipetted into the wells and any TNF-α, IL-1β, or IL-6 present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for TNF-α, IL-1β, or IL-6 was added to the wells. After a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of TNF-α, IL-1β, or IL-6 bound in the initial step. The color development was stopped and the intensity of the color was measured. The intra- and interassay CV were ≤10%.

Statistical analysis. All values are presented as means ± SEM. The data were analyzed using repeated-measures ANOVA, and Tukey's tests or *t* tests. The gender × time interaction was used to test whether changes over time differed between men and women, and to describe the change over time and the mean difference between men and women. The analysis was performed using Systat 10 (SPSS). Correlations were determined by linear regressions or by Spearman's correlation as appropriate also using the Systat program. Differences were considered significant at $P < 0.05$.

RESULTS

There was no difference ($P = 0.060$) in baseline plasma vitamin C concentrations between men and women (**Table 2**). The plasma vitamin C concentration after drinking the HP vegetable soup increased in both men and women with no differences between d 7 and d 14 (Table 2). Plasma vitamin C concentrations increased by 26% in men ($P = 0.01$), and by 25% in women ($P = 0.017$) (Table 2 and **Fig. 1**).

Baseline plasma 8-*epi*$PGF_{2\alpha}$ levels were higher ($P = 0.002$) in men than in women (Table 2). An important finding of this study was the significant decrease in the plasma levels of 8-*epi*$PGF_{2\alpha}$ in men ($P = 0.041$) and women ($P = 0.011$) (Table 2). In agreement with previous studies, there was an inverse correlation between concentrations of vitamin C and 8-*epi*$PGF_{2\alpha}$ levels in both men and women at baseline and on d 7 and 14 ($r = -0.585$, $P = 0.0002$). There were positive correlations ($P \leq 0.0001$) between 8-*epi*-$PGF_{2\alpha}$ levels and UA ($r = 0.800$), PGE_2 ($r = 0.723$), and MCP-1 ($r = 0.709$) levels in both men and women at baseline and on d 14.

Baseline plasma UA concentration was lower ($P < 0.001$) in women than in men. UA concentrations on d 7 and 14 of the intervention tended to be lower in women ($P = 0.06$), and were lower in men on d 7 and 14 ($P \leq 0.028$) compared with baseline (Table 2). In general, there was an inverse association between UA concentrations with vitamin C ($r = -0.654$, $P < 0.0001$) at baseline and d 7 and 14. A positive correlation was also found between UA and PGE_2 concentrations ($r = 0.644$, $P = 0.0007$), and MCP-1 concentrations ($r = 0.576$, $P = 0.003$) in both men and women at baseline and on d 14.

Baseline plasma PGE_2 levels were higher ($P = 0.027$) in men than in women, but at the end of study, d 14 of intervention, plasma levels of PGE_2 decreased significantly in both men ($P = 0.041$) and women ($P = 0.031$) (Table 2). Interestingly, there was an inverse correlation between concentrations of vitamin C and levels of PGE_2 in both men and women at baseline and on d 14 ($r = -0.376$, $P = 0.070$). In addition, positive correlations between levels of PGE_2 and levels of MCP-1 ($r = 0.661$, $P = 0.0004$), and IL-6 levels ($r = 0.445$, $P = 0.029$) were found in both men and women at baseline and on d 14.

Baseline plasma MCP-1 levels were higher ($P = 0.013$) in men than in women. Interestingly, on d 14 of intervention, plasma levels of MCP-1 decreased significantly in both men ($P = 0.035$) and women ($P = 0.050$) (Table 2). Concentrations of vitamin C and levels of MCP-1 were inversely correlated in both men and women at baseline and on d 14 ($r = -0.625$, $P = 0.0011$).

Men and women did not differ ($P \leq 0.792$) in baseline plasma concentrations of TNFα, IL-1β, or IL-6 (Table 2), and the concentrations did not change during the study.

DISCUSSION

Consumption of the HP vegetable soup gazpacho was associated with an increased plasma concentration of vitamin C and

TABLE 2

Plasma vitamin C, 8-epiPGF$_{2\alpha}$, UA, PGE$_2$, MCP-1, TNF-α, IL-1β, and IL-6 concentrations in men and women at baseline and on d 7 and 14 of drinking HP "gazpacho" daily for 14 d[1]

	Men			Women		
	Baseline	d 7	d 14	Baseline	d 7	d 14
Vitamin C,[2] *μmol/L*	44.4 ± 1.1	54.2 ± 1.7	56.1 ± 1.8	51.1 ± 1.3	63.9 ± 2.0	63.7 ± 1.8
8-*epi*$PGE_{2\alpha}$,[3] *ng/L*	195.1 ± 11.6	155.2 ± 16.9	141.5 ± 13.2	137.3 ± 8.3*	114.7 ± 8.6*	98.2 ± 7.9*
UA,[4] *μmol/L*	420.2 ± 21.0	357.0 ± 8.3	362.4 ± 9.2	276.5 ± 11.1*	248.7 ± 13.2*	253.2 ± 10.7*
PGE_2,[5] *ng/L*	321.8 ± 21.2	ND[6]	256.0 ± 18.3	236.4 ± 25.3*	ND	161.5 ± 15.6*
MCP-1,[7] *ng/L*	618.6 ± 45.5	ND	465.4 ± 43.6	440.0 ± 37.3*	ND	321.5 ± 41.0*
TNF-α, *ng/L*	5.5 ± 1.7	ND	5.8 ± 1.9	4.1 ± 1.2	ND	3.9 ± 1.1
IL-1β, *ng/L*	0.9 ± 0.2	ND	1.1 ± 0.2	0.8 ± 0.1	ND	0.6 ± 0.1
IL-6, *ng/L*	0.37 ± 0.09	ND	0.29 ± 0.08	0.20 ± 0.03	ND	0.12 ± 0.05

[1] Values are means ± SEM, $n = 6$. * Different from men at that time, $P < 0.05$.
[2] Higher than baseline for men and women at d 7 and 14 (time effect), $P < 0.05$, based on repeated-measures ANOVA (Tukey's test).
[3] Lower than baseline for men and women at d 14 (time effect), $P < 0.05$, based on repeated-measures ANOVA (Tukey's test).
[4] Lower than baseline for men at d 7 and 14 (time effect), $P < 0.05$, based on repeated-measures ANOVA (Tukey's test).
[5] Lower than baseline for men and women at d 14 (time effect), $P < 0.05$, based on a Student's *t* test.
[6] ND, not determined.
[7] Lower than baseline for men and women at d 14 (time effect), $P < 0.05$, based on a Student's *t* test.

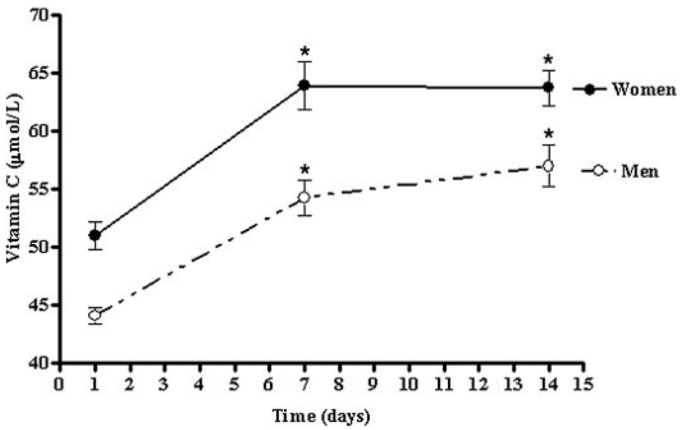

FIGURE 1 Plasma vitamin C concentrations in men and women at baseline and after 7 and 14 d of consuming gazpacho. Values are means ± SEM, $n = 6$. Means for both genders at d 7 and 14 were greater than at d 0, $P < 0.05$.

decreased biomarkers of inflammation in both women and men. There was an inverse correlation between concentrations of plasma vitamin C and concentrations of 8-*epi*PGF$_{2\alpha}$, UA, PGE$_2$, and MCP-1, suggesting that vitamin C may play a critical role in reducing the formation of compounds produced by random oxidation of phospholipids by oxygen radicals involved in the development of oxidative processes and inflammation.

Vitamin C plays an important role in several biological processes that might affect chronic disease risk, including free radical scavenging, collagen and hormone synthesis, hemostasis, and protection of lipid membranes. Because humans cannot synthesize vitamin C, it must be acquired from the diet. In a previous study (13), we showed that consuming 2 glasses of orange juice (500 mL) increased plasma vitamin C significantly. In this study, consumption of HP vegetable soup increased plasma vitamin C by 26% in men and 25% in women. The soup is rich in several nutrients, in addition to vitamin C; however, the role played by the vitamin C in oxidative stress and inflammatory biomarkers is upheld by the strong correlations between plasma vitamin C concentrations and biomarkers of oxidation and inflammation. It is possible that other nutrients present in the soup may have synergistically contributed to these effects. For example, the plasma concentration of carotenoids also increased (data not shown).

More than 80% of the vitamin C in Western diets comes from foods of vegetable/fruit origin, chiefly citrus fruits. Because diets rich in fruits and vegetables are protective against cancer, it was hypothesized that antioxidants in fruits and vegetables may be responsible for these effects (32). In a study by Broekmans and colleagues (33), daily intake of a mixture of fruits and vegetables (500 g) for 4 wk was associated with a 64% increase in vitamin C concentration. In our study, vitamin C increased 25%, whereas F$_2$-isoprostanes decreased 28%, and PGE$_2$ and MCP-1 26% (Table 2).

Of all the essential nutrients, vitamin C has generated the greatest interest for its potential influence on immune function and its in vivo antioxidant protective function as an aqueous phase peroxyl and oxygen radical scavenger (34). Numerous biomarkers of oxidative damage were proposed, including biomarkers for DNA damage, proteins, and lipids (35–37). The F$_2$-isoprostanes are products of free radical–catalyzed lipid peroxidation of arachidonic acid (38). They are formed in situ, esterified to phospholipids, and subsequently released by phospholipases into the plasma, where they can be measured (39). Changes in F$_2$-isoprostane levels in urine or plasma were associated with health status and different pathological processes (40). Some studies investigated the effects of antioxidant supplements on levels of F$_2$-isoprostane (41–43); however, very few studies examined the effect of dietary interventions (13,22). Recent reports indicated that the consumption of tomato-based products might be associated with a reduced risk of CVD (44), and decreased LDL oxidizability and urinary excretion of 8-iso-PGF$_{2\alpha}$ (45). In our study, after daily consumption of a vegetable soup, plasma 8-*epi*PGF$_{2\alpha}$ concentrations were significantly reduced and inversely associated with vitamin C (Table 2).

Several mechanisms, including increased platelet adhesiveness and platelet lysis, vascular endothelial cell injury, formation of free radicals, and oxidative stress appear to be involved in the association between high serum UA and cardiovascular mortality (46). After subjects consumed the soup daily for 14 d, UA was reduced by 18% in men and 8% in women (Table 2), and was inversely associated with plasma vitamin C concentrations. The lower reduction in UA concentrations in women compared with men may be attributable to the higher vitamin C concentration in women than in men throughout the study. Another finding of this study was the positive correlation between UA and 8-*epi*PGF$_{2\alpha}$ concentrations, suggesting a possible contribution of both compounds to vascular injury.

Prostaglandins play a major role as mediators of the inflammatory response. PGE$_2$ is a key regulator of inflammation and has a profound effect on tumorigenesis (25). PGE$_2$ increases significantly after cerebrovascular events and is positively associated with the severity and clinical outcome of stroke (30,47). Interestingly, PGE$_2$ concentrations decreased in men and women at the end of the intervention (Table 2). It is possible that this decrease in PGE$_2$ was mediated by the improved nutrient status, including plasma ascorbate, tocopherol, and carotenoids after the intervention.

A considerable number of studies have examined the role of chemokines, most notably MCP-1, in the initial stages of plaque formation. MCP-1 is expressed at high levels in atherosclerotic plaques (48). Consumption of the vegetable soup affected MCP-1 concentrations, which were lower in both men and women at the end of the intervention (Table 2). Plasma concentrations of MCP-1, 8-*epi*PGF$_{2\alpha}$, and PGE$_2$ were higher in men than in women at baseline and throughout the study, which may concur with the gender differences in CVD reported in other studies (49,50).

The in vivo decrease in oxidative stress and inflammatory status observed in this study, associated with increased plasma vitamin C concentration, provides new evidence for the beneficial effects of eating vegetables. This is one of the very few studies examining the effects of dietary intervention, rather than supplements, on circulating levels of antioxidants and inflammatory biomarkers in a healthy human population.

Some limitations of this study should be acknowledged. Perhaps the most important of these is the small number of subjects enrolled in the study. However, the relatively small variability in the various analyses (intra- and interassay) performed contributed to the significant effects observed in some of the biomarkers assessed after consumption of the vegetable soup. Because this was a healthy population, the main objective of the study was to assess the effect of consuming vegetable in the form of a vegetable soup on concentrations of vitamin C and biomarkers of oxidative stress and inflammation.

In conclusion, consumption of gazpacho (500 mL/d) increased plasma vitamin C and decreased 8-*epi*PGF$_{2\alpha}$, PGE$_2$, and MCP-1. Vitamin C was significantly and inversely correlated with 8-*epi*PGF$_{2\alpha}$, UA, PGE_2, and MCP-1, whereas 8-*epi*PGF$_{2\alpha}$ was positively correlated with UA, PGE_2, and MCP-1. The data strongly suggest that increasing vegetable consumption could improve human health.

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