Red Wine Consumption Prevents Vascular Oxidative Stress Induced by a High-fat Meal in Healthy Volunteers

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Abstract: In order to investigate the effect of red wine on plasma lipid and oxidative stress parameters after a high-fat meal, fifteen healthy volunteers were studied: three days after a high-fat meal with 250 mL of water, they received the same meal with 250 mL of red wine. During both periods, serial blood samples were drawn before and 2, 4, and 8 hours after the meal to evaluate plasma lipids (cholesterol and triglycerides; retinyl palmitate), oxidative stress (D-ROM, and malondialdehyde) and antioxidant (total plasma antioxidant levels and uric acid) parameters. During the meal without wine, plasma lipid parameters increased significantly, whereas plasma total plasma antioxidant levels decreased, and a trend toward reduction of uric acid levels was seen). A similar trend in lipid parameters was observed after the meal with wine; no significant difference in individual lipid parameter trends after a meal with and without wine was observed. Wine ingestion induced higher total plasma antioxidant levels and uric acid; malondialdehyde levels remained constant after wine ingestion. Plasma D-ROM showed a significant postprandial increase in both experiments, but it was significantly lowered after wine ingestion. Our results give evidence of oxidative stress following a fat-rich meal in healthy subjects, suggesting that ingestion of red wine during a high-fat meal significantly reduces oxidative stress without inducing any significant modification in postprandial lipemia.

Key words: Postprandial lipemia, vascular oxidative stress, red wine, high-fat meal

Introduction

Oxidative stress is known to be involved in the pathogenesis of atherosclerosis and other vascular injuries [1–3]. Much has been reported in the literature about the potential role of antioxidant agents in the prevention of atherosclerosis, in addition to the evidence that several physiological and pathological situations might expose *in vivo* endothelial cells and plasma molecules to repeated oxidative stress that promotes atherosclerosis [4–9].

Recent epidemiological and intervention studies have attested that postprandial metabolic alterations, such as hyperlipidemia and hyperglycemia, represent a risk factor for cardiovascular diseases [10]. Further research has

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shown that postprandial glucose and lipid elevations are associated with a rate of oxidative stress that has the potential to damage blood vessels [11, 12].

Food intake leads, in both diabetics and nondiabetics, to a reduction in total radical-trapping antioxidant parameter (TRAP) and a relevant consumption of antioxidants, such as protein thiol groups, vitamin C, and uric acid, suggesting that oxidative stress, especially induced by a fat-enriched meal, can reduce natural antioxidant defenses [13–16]. The link between plasma level of chylomicrons (CM), their remnant forms, and the deposition of cholesterol in the arterial walls responsible for the development of typical atherosclerotic lesions, has attracted a broad interest in recent years [17–19].

Moderate consumption of beverages containing alcohol is associated with a lower mortality rate [20, 21], in particular the mortality due to ischemic heart disease (IHD), and is associated with the idea that an increased level of high-density lipoprotein (HDL) cholesterol may account for this protective effect [22]. The so-called French Paradox, the low IHD mortality rate observed in France despite a diet rich in saturated fat with consequent elevated cholesterol levels, has been explained in terms of red wine consumption [23, 24]. Red wine affects not only HDL plasma levels but also seems to influence plasma oxidation processes, reducing plasma low-density lipoprotein (LDL) susceptibility to lipid peroxidation [25–27].

Since oxidative stress, and particularly lipoprotein oxidation, has been assumed to play a crucial role in the pathogenesis of atherosclerosis [28], red wine consumption has drawn attention as a useful approach for preventing such disease [27, 29, 30].

Only few data are available on the *in vivo* effect of red wine on oxidative stress production and antioxidant levels during a meal [30–33]. Few data are also available on the acute effect of red wine ingestion on postprandial levels and clearance of both serum lipids and intestinally-derived lipoproteins.

The aim of the present research is to investigate the short-term effect of the Italian red wine "Lambrusco" on postprandial lipid levels, oxidative stress, and total plasma antioxidants of healthy volunteers after a high-fat meal. To assess this effect, the impact of a single red wine dose on postprandial lipids (triglycerides, total cholesterol, and HDL cholesterol), CM markers (retinyl palmitate, RP), total plasma antioxidant capacity (ANTOX), urate (UA), lipid peroxidation (malondialdehyde, MDA), and reactive oxygen species (ROS) production were assayed.

Materials and Methods

Fifteen healthy, normocholesterolemic subjects (seven women, aged 37 ± 6 years; body mass index, BMI (kg/m^2) = 23.2 ± 1.7) were selected by the Geriatric Medical staff of the Estense Hospital in Modena, Italy. Informed consent was obtained in written form from each participant. No subjects presented a history of hypertension, diabetes mellitus, or tobacco smoking. None had hyperlipemia or were taking drugs at the time of the test. All subjects were nondrinkers/occasional drinkers (they consumed less than 15g ethanol occasionally). They had an *ad libitum* diet without any vitamin or antioxidant supplementation. Assessments began at 12:00 PM. Before the meal participants ingested nothing except water and rested in bed. Blood sample analyses were performed to detect serum lipids (HDL and total cholesterol, triglycerides), oxidative, and antioxidant parameter rates (see below).

Each volunteer, after a basal blood specimen, had a high-fat enriched meal (3766 J [900 calories], containing 50 g of fat, 14 g of saturated fat, 225 mg of cholesterol) according to Plotnick *et al* [34]. The meal consisted of an Egg McMuffin, Sausage McMuffin, two hash brown patties by McDonald's Corporation, and 60 000 U/m^2 of body surface of retinyl palmitate. During the meal all subjects drank 250 mL of water.

Blood sample analysis was performed for each person 2, 4, and 8 hours after eating. During this period participants had nothing except water and rested in bed.

Three days after the first sampling, the volunteers had the same meal drinking 250 mL of red wine. Serial blood specimens were drawn before and 2, 4, and 8 hours after eating to evaluate their plasma lipid profile (plasma total cholesterol and HDL-cholesterol, triglycerides, and retinyl palmitate), plasma oxidative stress, and antioxidant parameters.

Laboratory Assays

Plasma HDL- and total cholesterol (TC) and triglycerides (Tri) were measured enzymatically by an automated analyzer. MDA, as marker of lipid peroxidation [35], was evaluated by a highly sensitive HPLC method [36] with intra-assay and interassay coefficients of variation respectively of 4.5% and 5.8%. The uric acid level was assayed for the potential antioxidant effect of this compound by standard methods [37, 38].

Retinyl palmitate (RP) has been chosen as an indirect marker of chylomicrons (CM) and remnant chylomicrons (CMr), being incorporated within the CM core on packaging in the enterocyte and remaining in these particles until their removal by the liver. Even though the value of RP as a circulating marker of intestinally-derived lipopro-

teins to estimate postprandial CM and CMr levels in humans has been questioned [39–41], its value in accounting for lipemic patterns in response to meal ingestion has been recently confirmed [42]. RP was measured by a high-performance liquid chromatography (HPLC) method [39] with an intra-assay CV of 2.1% and inter-assay CV of 3.5% at 5 µg/mL.

Plasma total antioxidant capacity (ANTOX) was determined by spectrophotometric assay [43] using a specific commercial kit (Randox® laboratories, Ardmore, UK). Reactive oxygen species production (ROS) was assessed by a commercial kit (DIACRON D-ROM test®, Grosseto, Italy). The test evaluates hydroperoxides in terms of their oxidative capacity in biological samples D-ROM levels).

Statistical analysis

Statistical data analysis was accomplished by means of SPSS Statistical Software package (SPSS, Chicago, II). The distribution of the various parameters within the population studied did not show a significant departure from normality with the Shapiro-Wilkes W test. Therefore repeated measures of analysis of variance (ANOVA) were performed to detect significant differences within the same and among different experiment data. The Spearman's r coefficient was applied to analyze correlation between continuous variables. All values are expressed as mean ± SD; in all statistical analyses a p value < 0.05 was held as significant.

Results

The baseline features of the volunteer group are displayed in Table I. Table II shows some characteristics of the wine used in the test. The behavior of the variables (mean values ± SD) during two different tests is illustrated in panels in Figures 1 and 2.

During the meal without wine, with respect to basal (fasting) values, plasma levels of triglycerides (F = 18.1, p = 0.01), RP (F = 20.6, p = 0.01), and total cholesterol (F = 7.8, p = 0.042) levels significantly increased (Fig. 1; panels I, II, and IV respectively), while those of plasma ANTOX (F = 9.8, p = 0.016) significantly decreased (Fig. 2, panel II). MDA levels significantly increased after the meal (F = 14.8, p = 0.001) (Fig. 2, panel III), and a trend toward reduction of uric acid levels (F = 6.11, p = 0.053) (Fig. 2, panel I) was observed.

Wine ingestion with the meal counterbalanced the decrease of ANTOX, inducing higher and significantly differing levels of total antioxidant plasma capacity (F = 10.2, p = 0.022) and uric acid (F = 10.02, p = 0.030) (Fig. 2, panel I and II) with respect to those observed after the meal with plain water; lipid parameters show a similarly significant increase to that observed after the meal with water with respect to basal values; nevertheless no significant variation in postprandial levels of triglycerides (F = 3.1, p = ns), RP (F = 2.1, p = ns), and total cholesterol (F = 2.8, p = ns) with respect to those obtained after plain water ingestion (Fig. 1, panels I, II, and IV respectively) was observed. MDA generation did not show a significant variation (F = 6.1, p = 0.058) and was significantly reduced after wine ingestion with respect to values observed after plain water ingestion (F = 8.7, p = 0.038) (Fig. 2, panel III). Plasma D-ROM production, expressed as a percentage of D-ROM with respect to the fasting conditions, shows a significant postprandial increase in both cases (F = 17.4, p = 0.01; F = 12.3, p = 0.012, respectively) although the hydroperoxide percentage increase (D-ROM) was always significantly lower after wine ingestion (p < 0.05 in all cases) (Fig. 3).

Table I: Basal Parameters of studied subjects (values are expressed as mean ± SD)

Parameter	
Albumin (g/dL)	4.1 ± 0.3
Total plasma protein (g/dL)	7.5 ± 0.4
Hemoglobin (g/dL)	14.8 ± 1.5
Lymphocyte count (n/mm^3)	2512 ± 452
PCR (mg/dL)	0.51 ± 0.5
VES (mm/h)	12.6 ± 3.1
Total cholesterol (mg/dL)	185 ± 26
Triglycerides (mg/dL)	80 ± 21
Creatinine clearance (mL/min)	92 ± 18

Table II: Wine Lambrusco Characteristics

Parameter	
Ethanol content (v/vv)	8.1 ± 0.2
Polyphenols total content* (mg/L)	11.6 ± 0.3
Total antioxidant power° (mmol/L)	29.8 ± 5.6
Urate (mg/dL)	traces

* HPLC [Methods in Enzymology (1999) 29: 113–121]
° measured by Randox® (UK) commercial kit

Discussion

The rise in postprandial oxidative stress has been proposed as a critical event in the pathogenesis of atherosclerosis in both diabetic and nondiabetic persons [11]. We have found a significant increase in plasma oxidative stress parame-

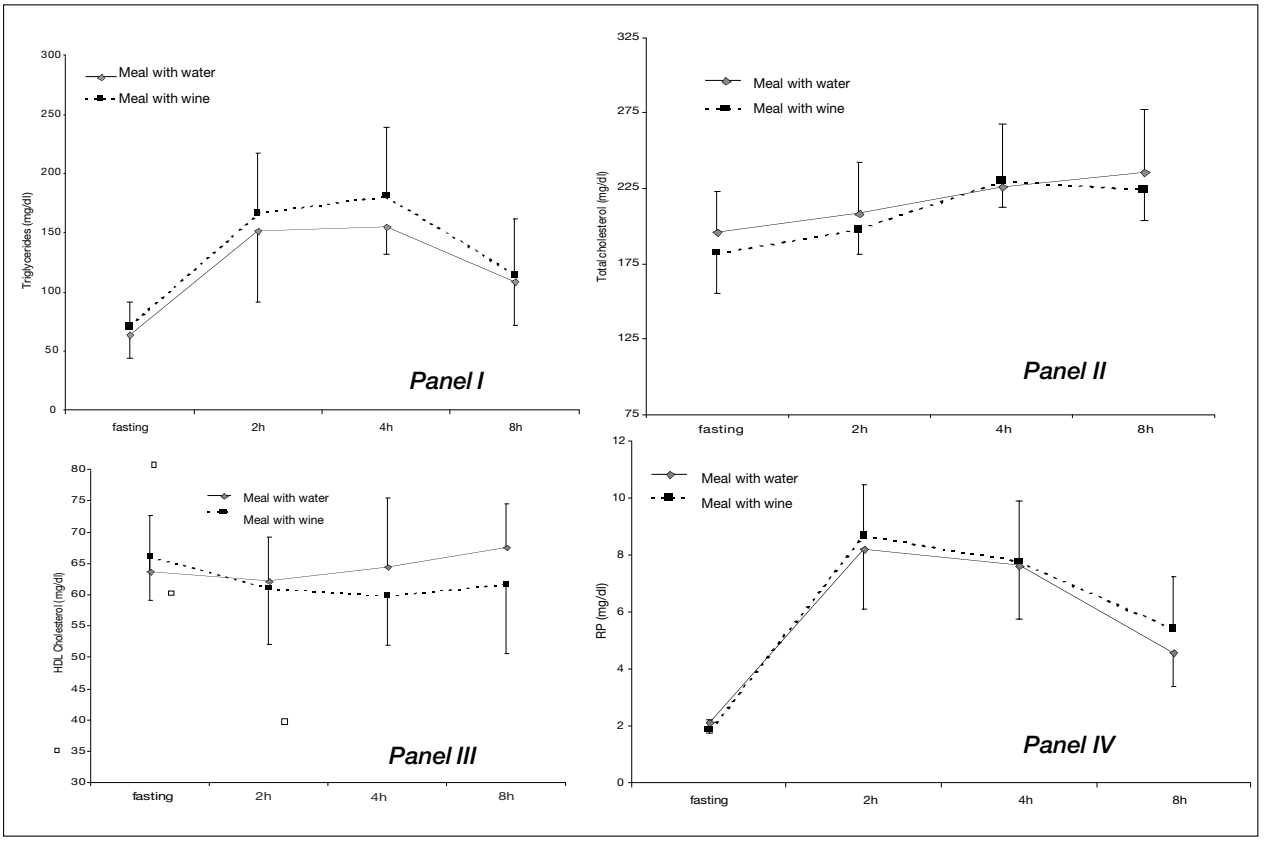

Figure 1: Lipid parameters (mean ± SD) (triglycerides, Panel I; Total cholesterol, Panel II; HDL-cholesterol, Panel III; Retinyl palmitate (RP), Panel IV) trend after the meal with water or wine ingestion. No significant differences (ANOVA for repeated measures) were observed between mean levels reached during the two experiments.

ters after a fat-rich meal (Fig. 2): a post-prandial lipids increase (triglycerides and total cholesterol) is associated with a concurrent increase of lipid peroxides, as determined by MDA or D-ROM plasmatic production. According to previous reports, these data support the evidence that red wine ingestion during a meal increases plasma antioxidants [33]. In healthy subjects, red wine content seems also able to counterbalance the oxidative effect of meal ingestion, confirming that red wine's protective role is related to its antioxidant properties. Such a beneficial effect has been related to red wine consumption independently of its effect on postprandial lipemia. Our results did not in fact show a significant difference in postprandial hyperlipemia during the different stages of the experimental procedure in the fat-rich meal with or without red wine, suggesting that red wine ingestion has no short-term effect on intestinally, meal-generated, potentially atherogenic lipoproteins (CM) and on plasma lipid levels (Fig. 1). It is to be remarked that lipid levels were higher after the meal with wine, even if not reaching statistical significance, with respect to values reached after the meal with water: this result may depend also on the relative low ethanol content of our wine (see below) with respect to the concurrent high lipid content of the meal. A similar explanation may account for the poor effect on HDL levels. Alcohol intake may influence HDL levels (increase), nevertheless this increase is observed for continuous and significant consumption (habitual drinkers), whereas our patients were "occasional drinkers" [44].

Plasma urate elevation contributes to the plasma antioxidant status, in addition to wine urate content. In any case, poor UA content was detected in Lambrusco wine samples (Table II). Ethanol intake may enhance UA synthesis via urate metabolism and renal handling [45], nevertheless it is unlikely that the effect on UA depends on the acute effect of ethanol on urate metabolism, since Lambrusco has a low ethanol content (about 8 v/v, that is about 16 g of alcohol intake for 250 mL of wine intake); moreover, the effect of a single alcohol intake does not seem to be able to significantly increase urate levels in nondrinkers or occasional drinkers [46]. The increase in urate levels observed after wine ingestion may instead represent the

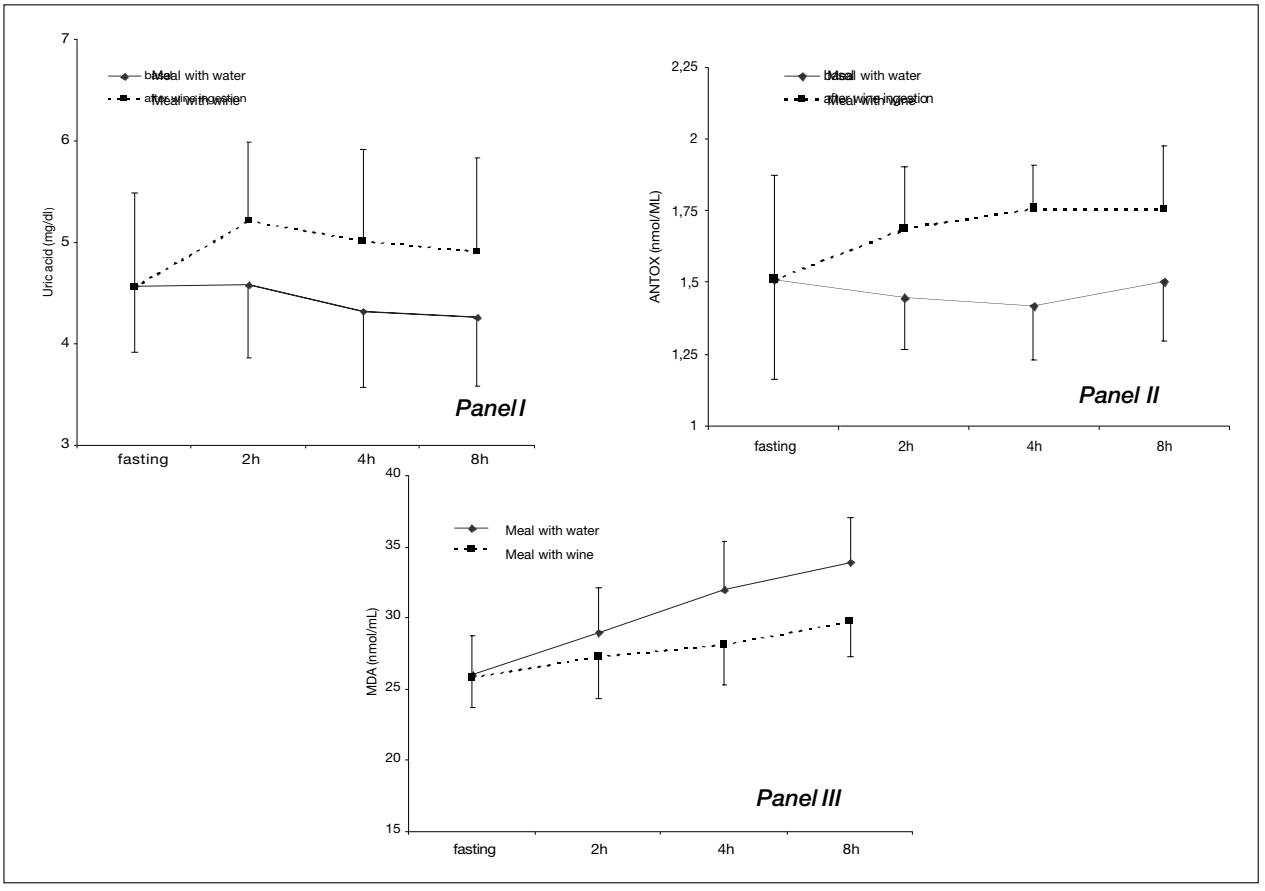

Figure 2: Plasma Uric Acid (Panel I), total antioxidant capacity (ANTOX, Panel II), and malondialdehyde (MDA) levels after the meal with water and wine ingestion (values are expressed as mean ± SD). UA and ANTOX mean levels were significantly higher and MDA significantly lower at 2, 4, and 8 hours ($p<0.05$ in all cases) after wine ingestion.

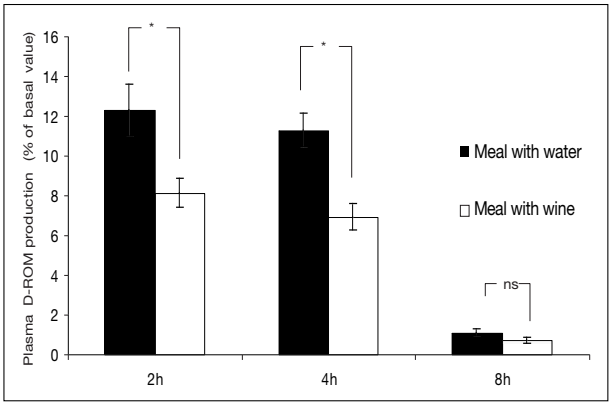

Figure 3: Plasma oxygen radical production [expressed as D-ROM % increase at 2, 4, and 8 hours from the meal out of the basal value) (mean ± SD)] after the meal with water and with wine. % increase was always lower than after wine ingestion. *$p < 0.01$, ns= not significant.
Basal absolute values (first vs second experiment) were 311 ± 112 vs. 286 ± 81, Carr Units; p = ns.

result of decreased urate oxidative modification and may serve as an indirect marker of antioxidant protection by wine content. Also the observation of significantly lower peroxide levels in plasma, as measured both by MDA and D-ROM, mainly expresses a lower lipid and protein oxidation after wine ingestion, excluding the peroxides that may be present in the meal. In conclusion, even taking into account the small number of the studied sample, our results give evidence of oxidative stress following a fat-rich meal in healthy subjects and suggest that moderate intake of red wine, with its relatively high content of polyphenols and poor content of alcohol during a high-fat meal, prevents or significantly reduces oxidative stress without inducing any significant modification in postprandial lipemia. These data point toward a new approach toward prevention of oxidative stress and related diseases.

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