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Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with Type 2 diabetes mellitus

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Abstract

Background Oxidative stress and increased inflammation have been reported to be increased in subjects with diabetes and to be involved in the pathogenesis of cardiovascular complications after myocardial infarction (MI). It is well recognized that red wine has antioxidant and anti-inflammatory activities. We examined the effects of moderate red wine intake on echocardiographic parameters of functional cardiac outcome in addition to inflammatory cytokines and nitrotyrosine (oxidative stress marker), in subjects with diabetes after a first uncomplicated MI.

Methods One hundred and fifteen subjects with diabetes who had sustained a first non-fatal MI were randomized to receive a moderate daily amount of red wine (intervention group) or not (control group). Echocardiographic parameters of ventricular dys-synchrony, circulating levels of nitrotyrosine, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-18 (IL-18) and C-reactive protein (CRP) were investigated at baseline and 12 months after randomization.

Results After 1 year of diet intervention, concentrations of nitrotyrosine ($P < 0.01$), CRP ($P < 0.01$), TNF-α ($P < 0.01$), IL-6 ($P < 0.01$) and IL-18 ($P < 0.01$) were increased in the control group compared with the intervention group. In addition, myocardial performance index ($P < 0.02$) was higher, and transmitral Doppler flow ($P < 0.05$), pulmonary venous flow analysis ($P < 0.02$) and ejection fraction ($P < 0.05$) were lower in the control group, indicating ventricular dys-synchrony. The concentrations of nitrotyrosine, CRP, TNF-α and IL-6 were related to echocardiographic parameters of ventricular dys-synchrony.

Conclusions In subjects with diabetes, red wine consumption, taken with meals, significantly reduces oxidative stress and pro-inflammatory cytokines as well as improving cardiac function after MI. Moderate red wine intake with meals may have a beneficial effect in the prevention of cardiovascular complications after MI in subjects with diabetes.

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Keywords inflammation, myocardial infarction, oxidative stress, red wine

Abbreviations CRP, C-reactive protein; E/A ratio, early/late diastolic flow ratio; EF, ejection fraction; HOMA, homeostasis model assessment; IL-6, interleukin-6; IL-18, interleukin-18; IRT, Isovolumetric relaxation time; MI, myocardial infarction; MPI, myocardial performance index; NO, nitric oxide; TNF-α, tumour necrosis factor-α

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Introduction

Subjects with diabetes who sustain a non-fatal myocardial infarction (MI) have a more complicated course, including more frequent post-infarction angina, infarction extension, and congestive heart failure [1]. A growing body of evidence suggests that MI is associated with increased local and systemic inflammation in subjects with diabetes: increased inflammatory as well as oxidative processes seem likely mechanisms linking diabetes to poor cardiac outcome after MI [2,3].

Moderate red wine intake has been associated with a significant reduction in risk for MI, generally in non-diabetic populations [4]. Moderate intake of any type of alcoholic beverage appears to be beneficial, but some studies suggest that red wine confers additional health benefits [5]. Regular drinking of red wine has been suggested as the explanation for the 'French paradox', the relatively low incidence of coronary atherosclerosis in France as compared with other Western countries, despite the generally high intake of saturated fat in the French diet [6]. The chemical composition of red wine may contribute to its apparent benefit. A series of studies suggest that the polyphenolic compounds in red wine, such as flavonoids and resveratrol, may play an active role in limiting the initiation and progression of atherosclerosis [7,8]. Polyphenolic compounds appear to favourably maintain healthy blood vessels by reducing free-radical production as well as by promoting the formation of nitric oxide (NO), the key chemical relaxing factor that plays a pivotal role in the regulation of vascular tone and in the inhibition of adhesion of inflammatory cells to the vessel wall [9]. Whether or not red wine consumption has a similar association with CHD in individuals with diabetes after MI, however, has not been examined. A recent report noted an inverse association between alcohol consumption, including red wine, and CHD mortality in diabetic individuals [10]. The observations that several risk factors associated with poor outcome in subjects with diabetes during acute coronary syndrome, including inflammation [11], oxidative stress [12] and reduced NO availability [9], may be favourably affected by red wine likewise suggests the potential for particular cardiovascular benefits of moderate red wine use in this high-risk group. We therefore assessed whether moderate red wine intake is associated with a reduced risk for cardiovascular complications in subjects with diabetes who have had a non-fatal MI. Specifically, we examined the effects of moderate red wine intake, with meals, on echocardiographic parameters of functional cardiac outcome as well as inflammatory cytokines and nitrotyrosine, in subjects with diabetes after a first uncomplicated MI.

Methods

Study population

The study is a randomized secondary prevention trial to test whether moderate alcohol consumption with meals may reduce risk factors of cardiovascular disease complications after a first and recent (< 2 months) MI in subjects with diabetes. Eligible patients were survivors of a first acute MI as diagnosed by a cardiologist at any of the four recruiting hospitals in the catchment area (Napoli, Benevento and Campobasso) between 2001 and 2004. All patients were assessed by cardiologists according to the World Health Organization criteria for MI, which require typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the electrocardiogram [13]. Patients with the following conditions were not enrolled: cardiac surgery or angioplasty during the past 6 months; non-ischaemic cardiomyopathy; implanted pacemaker; or permanent tachyarrhythmias; non-cardiac diseases such as inflammatory disorders, malignancy, or infection; patients who drank no alcohol. Eligible patients were < 70 years old, were clinically stable, and had no medical or social conditions that would limit their ability to participate in a dietary trial. The study protocol was approved by the institutional ethics committee for human subjects. Written informed consent was obtained from all patients.

Randomization

After clinical stabilization, the patients were randomized in an unblinded one-to-one fashion to receive either dietary advice according to the Mediterranean diet, with red wine intake of one 118-ml (4-oz) glass of wine each day [alcohol: 11.0 g: (intervention group)], or no red wine or other alcohol consumption (control group). Treatment was started within 36 ± 12 days of MI. Patients were seen at 1, 3, 6, 9 and 12-months. At baseline and 12 months after enrolment, patients underwent follow-up, including echocardiography.

Dietary advice

In the intervention group, the mean recommended daily caloric intake was 8372 kJ (2000 kcal). The recommended composition of the dietary regimen was: carbohydrates 178 g, proteins 73 g, saturated fat 9 g, monounsaturated fat 17 g, polyunsaturated fat 8 g, sodium 1.1 g, potassium 3 g, calcium 0.5 g, phosphorus 1.2 g, fibre 25 g. This regimen was very similar to the Mediterranean-style Step I diet. All patients were encouraged to take physical activity (at least 1-h walk three times a week). The control group followed similar dietary advice without red wine or alcohol intake, thus the only difference between the intervention and control groups was the red wine intake. All patients were examined every third month. At the first session, a thorough interview lasting for at least 1 h was performed. Every patient was asked to describe their intake of foods and beverages for the past 24 h, and dietary advice was adjusted individually and repeated every third month. The patients were asked at every visit to prepare a written 4-day diary of foods and beverages consumed. They were asked not to weigh the foods but to describe in ordinary words the size of the single ingredients (e.g. a small, medium, or large apple) or size of portions of food; in addition, they were asked to describe in detail fat percentages, especially in dairy produce and minced meat. Also, the patients were asked to note their hot meals. The food diaries were returned to the study nurse, who reviewed the contents; in case of

doubt, the diary was returned to the patient with appropriate clarifying questions. Analysis of the polyphenol profiles of the red wine (Castel San Lorenzo DOC, Barbera, 2000) was carried out by SEA Laboratories, Rome, Italy. The amount of polyphenols was 1792 mg/l.

Echocardiography

All patients underwent two-dimensional and Doppler echocardiography before starting the intervention. Myocardial synchronization was assessed by diastolic filling time, mitral regurgitation time [the ratio of velocity time intervals of mitral early (E) and late (A) diastolic flows, E/A ratio], pulmonary vein flow analysis (PVFs/PVFd ratio), the effective ejection time (EF), right ventricular relaxation time (RV-RT_m) and myocardial performance index (MPI). Doppler velocities and time intervals were measured from mitral inflow and left ventricular outflow recordings. Isovolumetric relaxation time (IRT) was the time interval from cessation of left ventricular outflow to onset of mitral inflow, ejection time (ET) was the time interval from the onset and cessation of left ventricular outflow, and mitral early diastolic (E) flow deceleration time (EDT) was the time interval between the peak E velocity and the end of the early diastolic flow. Isovolumetric contracting time (ICT) was calculated by subtracting ET and IRT from the total systolic time interval. The ratio of velocity time intervals (vti) of mitral early (E) and late (A) diastolic flows (Evti/Avti) was calculated. MPI was calculated by using the formula MPI = (IRT + ICT)/ET. The function of right ventricle (RV-RT_m) was evaluated by Doppler tissue imaging (DTI) of the right ventricular tricuspid anulus.

Plasma analyses

Routine analyses samples were drawn after fasting at randomization and every third month. Serum concentrations of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-18 (IL-18), as well as nitrotyrosine levels, were determined in duplicate using a highly sensitive, quantitative sandwich enzyme assay (Santa Cruz Biotechnology, Santa Cruz, CA, USA; R & D Systems, Minneapolis, MN, USA). High-sensitivity C-reactive protein (CRP) was assayed by immunonephelometry on a Behring Nephelometer 2 (Dade Behring, Marburg, Germany). In our laboratory, the median (interquartile range) for these values in a group of 50 healthy participants of both sexes (n = 25 for each) were as follows: IL-6, 2.0 pg/ml (0.3–5.2 pg/ml); TNF-α, 1.7 pg/ml (0.5–4.2 pg/ml); and IL-18, 119 pg/ml (50–175 pg/ml). Nitrotyrosine was determined because this modified amino acid is a product of free-radical (O^{2-}) interaction with NO. The interaction of O^{2-} with NO is very rapid and leads to inactivation of NO and production of the potent oxidant peroxynitrite. Detection of nitrotyrosine is strongly suggestive of increased generation of peroxynitrite [14]. Assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono, Italy). Insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the following formula: fasting plasma glucose (mmol/l) × fasting serum insulin (μU/ml) divided by 25.

Statistical analysis

Data are presented as group mean ± SD. One-way ANOVA was used to compare baseline data, followed by Scheffé's test for pairwise comparisons. We compared data using a Wilcoxon test for IL-6, TNF-α, IL-18, HOMA score and triglycerides. Multiple comparisons were made with ANOVA followed by post-hoc analysis (Student–Newmann–Keuls test) to locate the significant difference indicated with ANOVA. Linear regression and correlation were used to assess relationships between variables. A value of $P < 0.05$ was considered significant. All calculations were made on an IBM PC computer (SPSS Inc., Chicago, IL, USA; version 12.01).

Results

Patients characteristics

A total of 131 patients were enrolled in the study, 93 patients (71%) during hospitalization for MI. Sixty-eight patients were randomized to the Mediterranean diet with red wine (intervention group), and 63 to the Mediterranean diet without red wine or other alcohol consumption. Five patients were excluded from the study, three because of withdrawal of consent and two because of lack of compliance. Three patients had ultrasound scanning images that could not be analysed. A further eight patients died during the study period. Thus, 115 patients completed the study. The demographic and clinical baseline data are given in Table 1. There was no difference in age, smoking status, and fasting glucose, insulin, HbA_{1c}, cholesterol or triglyceride levels. The troponin I levels during myocardial infarction were also similar. The use of anti-ischaemic agents, angiotensin-converting enzyme inhibitors and the angiotensin 2 receptor (AT2) antagonist did not differ between groups at randomization or during follow-up. There was no difference in the use of β-blockers and long-acting nitrates, calcium-antagonists, vitamins, and angiotensin-converting enzyme inhibitors at 12 months of follow-up. Both groups were > 80% compliant with statin treatment. All patients were treated with insulin. At randomization, there was no difference in the alcohol intake between groups.

Dietary intervention

After 12 months, the intake of fruit and vegetables was similar in both groups. However, we found a similar intake of fatty fish, red meat, and contents of polyunsaturated fatty acids between the groups. Main dietary kJ recorded after 12 months follow-up was not significantly different between the groups [control group 8163 kJ (1950 kcal); intervention group 8581 kJ (2050 kcal)]. There was no difference in weight loss between the groups, all patients lost at least 2% of their initial body weight with a mean decrease of 2.8 ± 1.5 kg (Table 2). In the control group,

Table 1 Clinical characteristics of the study patients

	Intervention (n = 57)	Control (n = 58)
Age (years)	36.5 ± 4.6	35.1 ± 5.1
Body mass index (kg/m^2)	28.6 ± 2.1	27.6 ± 1.5
Waist–hip ratio	0.72 ± 0.07	0.73 ± 0.04
Systolic blood pressure (mmHg)	125 ± 5.9	123 ± 5.1
Diastolic blood pressure (mmHg)	84 ± 3.8	83 ± 3.5
Fasting glucose (mmol/l)	7.5 ± 0.5	7.7 ± 0.4
Fasting insulin (μU/ml)	12.5 ± 3.2	12.1 ± 2.3
HbA_{1c} (%)	7.2 ± 1.3	7.3 ± 1.5
HOMA	3.3 ± 0.4	3.2 ± 0.2
Total cholesterol (mmol/l)	6.7 ± 0.4	6.8 ± 0.6
High-density lipoprotein cholesterol (mmol/l)	1.22 ± 0.3	1.24 ± 0.3
Triglyceride (mmol/l)	2.52 ± 0.6	2.56 ± 0.3
TNF-α (pg/ml)	5.8 ± 1.5	5.5 ± 0.7
IL-6 (pg/ml)	4.2 ± 0.9	4.4 ± 0.5
IL-18 (pg/ml)	227 ± 27.4	229 ± 25.8
C-reactive protein (mg/l)	3.4 ± 0.7	3.3 ± 0.3
Nitrotyrosine (μM)	0.55 ± 0.06	0.53 ± 0.04
LVM/BSA (g/m^2)	84.1 ± 11	82.2 ± 10
LVM/h^2 (g/m^2)	60.4 ± 8	58.3 ± 8
Fractional shortening (%)	36 ± 3	37 ± 6
LVIDD (mm)	42.7 ± 5.1	41.1 ± 4.9
Infarct segment length (%)	35 ± 2.2	36 ± 3.2
Interventriculum septum (mm)	10.9 ± 1.6	9.8 ± 1.1
Left ventricular posterior wall (mm)	10.1 ± 1.3	9.5 ± 1.8
Mitral deceleration (ms)	156 ± 13	155 ± 19
E/A ratio	0.9 ± 0.2	0.9 ± 0.3
Myocardial performance index	0.57 ± 0.08	0.58 ± 0.04
PVFs/PVFd ratio	1.41 ± 0.08	1.42 ± 0.5
RV-RT_m (ms)	42.4 ± 5	10.3 ± 4
Ejection fraction (%)	51 ± 7	52 ± 11

LVM/BSA, left ventricular mass index/body surface area; LVM/h^2, left ventricular mass index/height^2; LVIDD, left ventricular internal diastolic diameter; E/A ratio, the ratio of velocity time intervals of mitral early (E) and late (A) diastolic flows; PVF, pulmonary vein flow; RV-RT_m, right ventricular relaxation time.
Data are presented as group mean (SD). There were no statistically significant differences between intervention and control groups at baseline.

analysis of the food diaries did not show any evidence of alcohol intake.

Echocardiographic parameters

Echocardiographic/Doppler measurements are presented in Table 1. At baseline, there was no difference in infarct segment length (P = 0.10), wall motion scores (P = 0.11), ejection fraction (P = 0.15), MPI (P = 0.12), transmitral Doppler flow (P = 0.16) and pulmonary venous flow analysis (P = 0.12), between the groups. After dietary intervention, MPI was higher (P < 0.02), and transmitral Doppler flow (P < 0.05) and pulmonary venous flow lower (P < 0.02) in the control group compared with the intervention group (Fig. 1; Table 2).

Laboratory analysis

At baseline, there was no difference in fasting glucose and insulin concentrations. HOMA scores, serum lipid and blood pressure levels were similar in the two groups (Table 1). Serum TNF-α, IL-6, IL-18, nitrotyrosine and CRP levels were similar in the two groups (Table 1). After 12 months, a significant decrease in blood glucose levels, total cholesterol and low-density lipoprotein cholesterol levels, as well in blood pressure and heart rate, was seen in both groups (P < 0.001 for the reduction in both groups) (Table 2). In the 115 patients who completed the study, a significant increase in high-density lipoprotein cholesterol level was observed only in the intervention group (P < 0.02), whereas triglyceride levels remained unchanged in both groups (Table 2). In the intervention group, liver function tests did not change (data not shown). Compared with the intervention group, the control group had lower insulin concentrations and HOMA scores. In the control group, serum TNF-α (P < 0.01), IL-6 (P < 0.01), IL-18 (P < 0.01), CRP (P < 0.01) and nitrotyrosine levels (P < 0.01) were higher than in the intervention group (Fig. 2, Table 2).

After the intervention period, the decline in serum TNF-α, IL-6, CRP and nitrotyrosine levels correlated with the changes in EF, RV-RT_m, E/A ratio, PVFs/PVFd ratio and MPI

Table 2 Parameters changes after dietary intervention in study population

	Intervention group	Control group	*P*
Body mass index (kg/m^2)	–2.8 ± 1.1	–2.7 ± 1.5	NS
Waist–hip ratio	–0.04 ± 0.01	–0.03 ± 0.01	NS
Systolic blood pressure (mmHg)	–2.1 ± 0.5	–2.2 ± 0.4	NS
Diastolic blood pressure (mmHg)	–1.5 ± 0.2	–1.6 ± 0.3	NS
Fasting glucose (mmol/l)	–1.2 ± 0.4	–1.3 ± 0.3	NS
Fasting insulin (μU/ml)	–3.8 ± 1.5	–2.0 ± 1.1	< 0.05
HbA_{1c} (%)	–1.1 ± 0.6	–1.2 ± 0.7	NS
HOMA	–1.2 ± 0.9	–0.9 ± 0.3	< 0.05
Total cholesterol (mmol/l)	–1.8 ± 0.4	–1.7 ± 0.5	NS
High-density lipoprotein cholesterol (mmol/l)	1.8 ± 0.7	0.9 ± 0.2	< 0.05
Triglyceride (mmol/l)	–0.9 ± 0.1	–0.8 ± 0.1	NS
IL-18 (pg/ml)	–61.7 ± 5.1	–28.2 ± 3.8	< 0.05
LVM/BSA (g/m^2)	–15 ± 2.3	–6 ± 1.2	< 0.05
LVM/h^2 (g/m^2)	–13 ± 3.1	–5 ± 1.1	< 0.05
Fractional shortening (%)	5 ± 1.0	6 ± 1.6	NS
Interventricular serptum (mm)	0.1 ± 0.07	0.3 ± 0.09	NS
LVPW (mm)	0.1 ± 0.06	0.2 ± 0.01	NS
PVFs/PVFd ratio	0.19 ± 0.02	0.7 ± 0.01	< 0.05
RV-RT_m (ms)	–21 ± 4	–9 ± 5	< 0.05

LVM/BSA, left ventricular mass index/body surface area; LVM/h^2, left ventricular mass index/height^2; PVF, pulmonary vein flow; RV-RT_m, right ventricular relaxation time.
Data are presented as group mean (SD). There were no statistically significant differences between intervention and control groups at baseline.

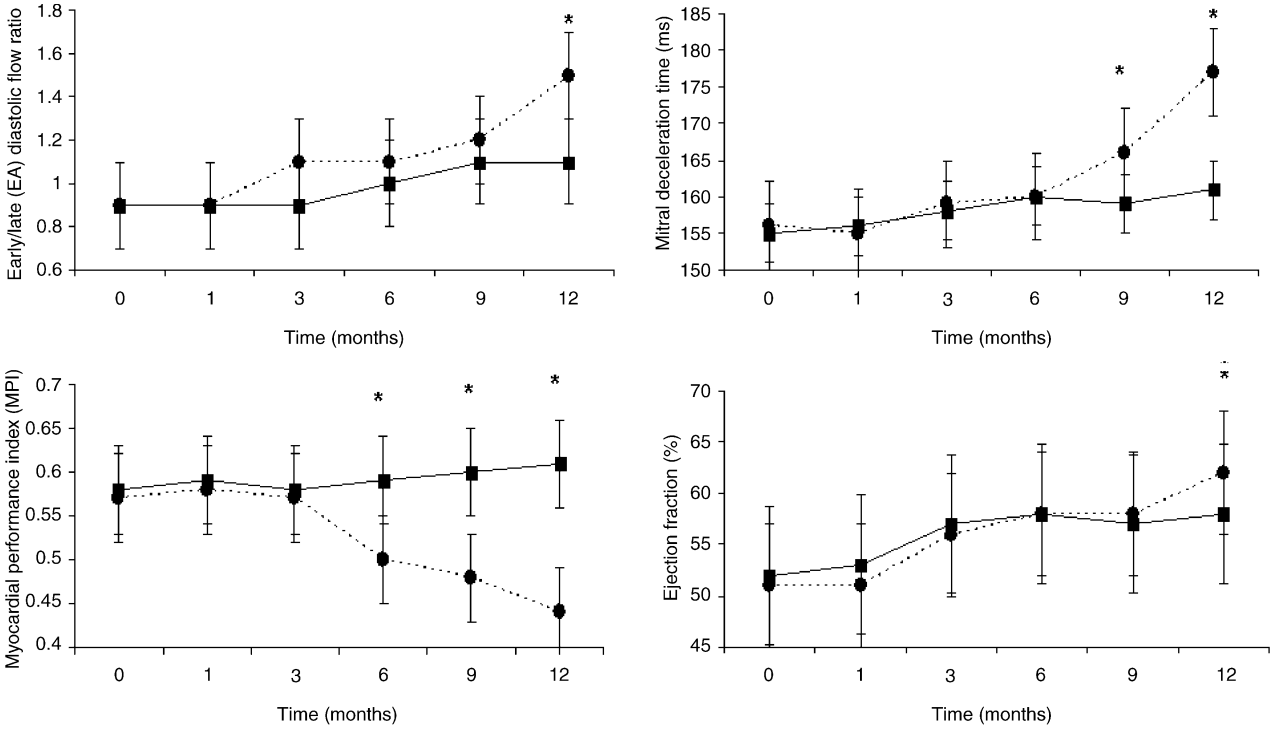

Figure 1 Echocardiographic parameters in study population (●, intervention group; ■, control group). *$P < 0.05$.

(Table 3). To assess the independent association of changes in echocardiographic parameters of cardiac function with changes in serum nitrotyrosine, IL-6, TNF-α and CRP levels, a multivariate analysis was performed, in which MPI was the dependent variables and IL-6, TNF-α and CRP levels were the independent variables. The model explained 75% of the variability in the change of MPI, nitrotyrosine, IL-6, TNF-α and CRP concentrations.

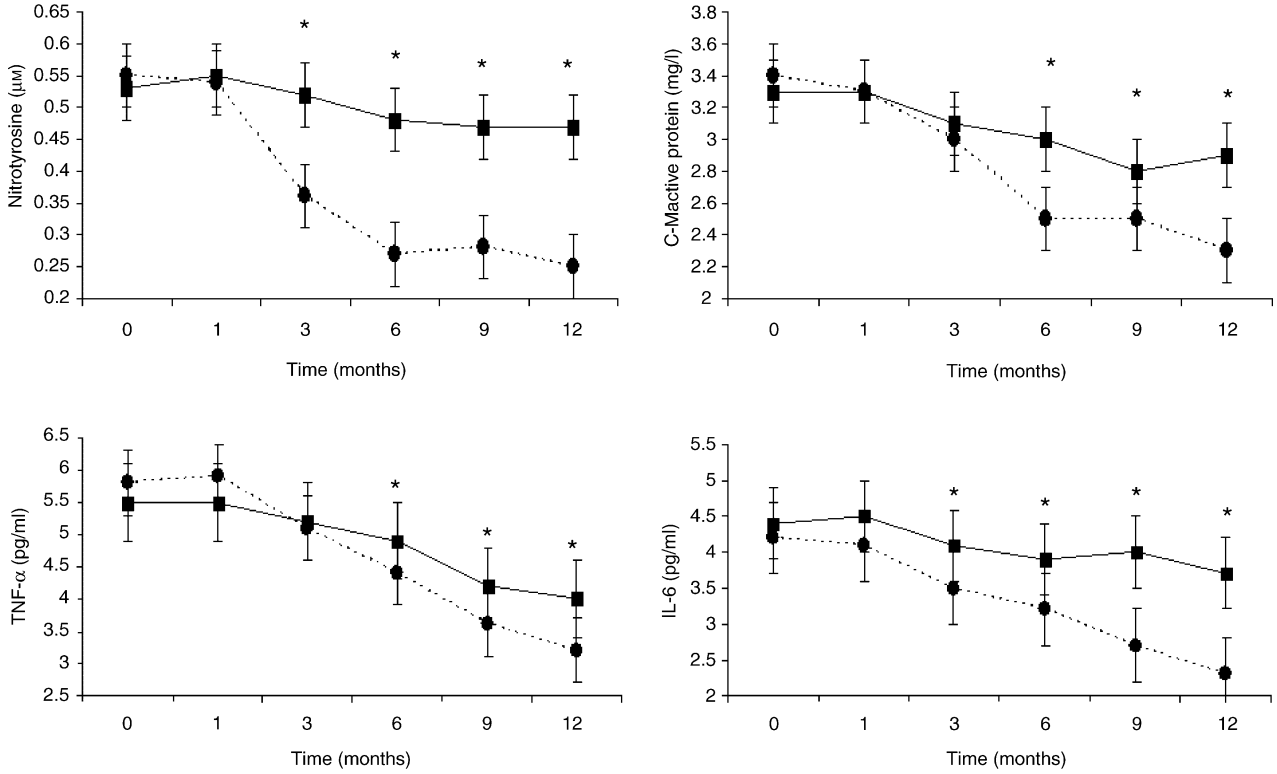

Figure 2 Cytokine and nitrotyrosine levels in study population (●, intervention group; ■, control group). *$P < 0.05$.

Table 3 Relationships between the changes of nitrotyrosine and pro-inflammatory cytokines with echocardiographic parameters in intervention group

	Nitrotyrosine	TNF-α	IL-6	IL-18	CRP
TNF-α*	0.20†	–	–	–	–
IL-6*	0.32‡	0.08	–	–	–
IL-18*	0.21†	0.11	0.22†	–	–
C-reactive protein*	0.27†	0.10	0.10	0.12	–
HOMA	0.30‡	0.19†	0.19†	0.24†	0.18†
Ejection fraction	–0.21†	–0.18†	–0.31‡	–0.15	–0.24‡
E/A ratio	–0.19†	–0.32‡	–0.32‡	–0.10	–0.22‡
Myocardial performance index	0.27†	0.45§	0.21†	0.12	0.39‡
PVFs/PVFd, ratio	–0.22†	–0.27‡	–0.31‡	–0.16	–0.20‡
RV-RT_m	0.21†	0.19†	0.32‡	0.08	0.19†

*Log-transformed; †$P < 0.05$; ‡$P < 0.02$; §$P < 0.01$.
PVF, pulmonary vein flow; RV-RT_m, right ventricular relaxation time.
Data are presented as group mean (SD).

Discussion

To the best of our knowledge, there have been no studies investigating the effects of moderate red wine intake on oxidative stress, inflammatory markers, and functional cardiac outcome in patients with a recent MI. The main findings of our study demonstrate that moderate consumption of red wine with meals was associated with a significant reductions in oxidative stress and inflammatory reaction and improvement of cardiac function in middle-aged diabetic survivors of a recent MI. In our study, heart function, assessed by echocardiographic parameters of cardiac synchronization, improved significantly in the intervention group. In particular, moderate red wine intake resulted in significant improvement of dys-synchrony between right and left ventricular contraction and relaxation. The lower MPI values, which measure both systolic and diastolic parameters of ventricular function [15], indicate better functional outcome after MI in patients randomized to receive red wine. Moreover, the increased diastolic filling time, the reduction of mitral regurgitation, and the increased effective ejection time in the intervention group suggest that red wine intake may improve cardiac synchronization after MI. Studies have identified dys-synchrony between right and left ventricular contraction and relaxation as an independent predictor of heart failure and cardiac mortality in patients with heart failure and cardiac ischaemic diseases [16]. Thus,

the improvement of cardiac function suggests that moderate red wine intake may reduce cardiovascular complications after MI in subjects with diabetes.

Diabetes mellitus is characterized by a high incidence of cardiovascular complications after MI, such as heart failure and extension of infarct size [1], and oxidative stress has been recognized as a major pathophysiological link between cardiovascular complications and diabetes after MI [2,17]. However, an increase of inflammatory cytokines may also contribute to the development of cardiovascular complications after MI, and a close relationship between oxidative stress and a pro-inflammatory state has been demonstrated in both diabetic [2] and non-diabetic patients [18]. Lower mortality as a result of coronary heart disease is associated with moderate consumption of red wine [6]. The cardiovascular benefits of moderate wine consumption have been thought to stem, at least partly, from antioxidant activities of red wine [19]. A recent report suggested that red wine increases the antioxidant power of plasma in humans [20]. Since that study, several authors have published results confirming that the consumption of moderate amounts of red wine elicits a prompt, although temporary, rise of plasma antioxidative defences [21]. Consequently, it has been suggested that this property may provide a clue to the role of certain wines in the so-called 'French paradox' [6]. This hypothesis has also been supported by a number of studies suggesting that moderate consumption of red wine may be more effective than consumption of other alcoholic beverages in decreasing the risk of coronary heart disease mortality [22]. Other studies and reviews have failed to show a beneficial effect for red wine, however, and hence it could be concluded that other lifestyle factors such as diet, exercise, socioeconomic status, or pattern of alcohol consumption may have played a role in reducing the rate of atherosclerosis in wine drinkers.

However, support for a more pronounced cardioprotective effect for red wine as compared with other alcoholic beverages first emerged from the Copenhagen City Heart Study, in which 13 285 men and women were observed for 12 years [23]. The results from this study suggested that patients who drank wine had half the risk of dying from coronary heart disease or stroke as those who never drank wine. Those who drank beer and spirits did not experience this advantage. The additional benefit of red wine is supported further by an analysis of 13 studies involving 209 418 participants. This analysis showed a 32% risk reduction of atherosclerotic disease with red wine intake, which was greater than the 22% risk reduction for beer consumption [5]. Red wine has been suggested to be cardioprotective via various mechanisms such as its antioxidant activity and effects to increase NO availability [9]. Our findings support the hypothesis that the reduced O^{2-} production and increased NO availability by red wine intake may be an important mechanism for protection of the ischaemic heart in subjects with diabetes. The observation that red wine intake was associated with lower nitrotyrosine levels indicates reduced generation of the potent oxidant peroxynitrite, produced by the interaction of O^{2-} with NO that leads to inactivation of NO. The peroxynitrite anion is cytotoxic because it inhibits mitochondrial electron transport, oxidizes sulfydryl groups in protein, initiates lipid peroxidation without the requirement for transition metals, and nitrates amino acids such as tyrosine, which affects many signal transduction pathways such as the inflammation pathway [24]. There is considerable evidence demonstrating the anti-inflammatory properties of red wine, including inhibition of reactive oxygen species in neutrophils, monocytes and macrophages [25]. The release of various cytokines from macrophages and lymphocytes has been shown to be inhibited by red wine [26].

Because polyphenolic compounds exhibit antioxidant and anti-inflammatory properties, we hypothesized that red wine would prevent oxidant-dependent inflammatory responses in myocardial ischaemia and improve heart function. Consistent with this interpretation, we also found that synchrony between right and left ventricular contraction and relaxation positively correlated with changes in nitrotyrosine, a good marker of peroxynitrite formation [14] and pro-inflammatory cytokine levels in subjects with diabetes after MI randomized to moderate red wine intake. As we excluded any associated conditions by through clinical and laboratory investigations, it is reasonable to hypothesize that in the clinical setting any changes in cardiac function can be interpreted as a consequence of red wine intake itself. In support of this, red wine intake may reduce the inflammatory process, and thus improve cardiac contractile function [27]. During the past decade, TNF-α and IL-1β have been shown to be present in the sera of septic patients and responsible for most, if not all, of the reversible cardiac depression often seen with this syndrome [28]. Interest in these findings has been amplified by reports of elevated circulating as well as intracardiac TNF-α levels in patients with heart failure [29]. Accordingly, we found that patients randomized to diet without red wine intake had higher circulating levels of TNF-α, IL-6, IL-18 and CRP and impaired cardiac function as compared with patients randomized to diet with red wine intake. Furthermore, it might be speculated that the favourable effect of red wine intake on cardiac function might also be because of its ability to decrease circulating TNF-α, IL-6, IL-18 and CRP. Interestingly enough, the concentrations of TNF-α, IL-6 and CRP were positively related to myocardial performance index and right ventricular relaxation time and negatively related to transmitral Doppler flow, pulmonary venous flow analysis and ejection fraction. All of these observations suggest that cytokines might be partly responsible for dys-synchrony between right and left ventricular contraction and relaxation observed in subjects with diabetes randomized to diet without red wine intake after MI. Recent research has begun to clarify some of the intracellular signalling mechanisms that contribute to cardiac myocyte contractile dysfunction. IL-6 has been shown to rapidly suppress voltage-dependent Ca^{2+} current ($I_{Ca\text{-}L}$) in adult rat ventricular myocytes [30]. Consistent with these data, higher concentrations of recombinant human TNF-α have been

shown [31] to result in rapid and reversible declines in contractile function of isolated hamster papillary muscles or of adult guinea pig and rabbit ventricular myocytes.

A direct effect of alcohol should not be excluded. It is now well recognized that a moderate alcohol intake has a favourable effect on cardiovascular disease in subjects with diabetes [10]. However, it should be stressed that red wine consumption causes a decrease in oxidative stress [9] and inflammatory cytokines [11] independently of the alcohol content of the wine. It has been suggested that polyphenols contained in red wine may account for these protective effects.

In conclusion, our study supports previous work showing that MI is associated with increased oxidative stress and inflammation in subjects with diabetes. In addition, we have demonstrated that red wine ingestion reverses these changes. Thus, moderate red wine intake may provide another safe method for down-regulating oxidative stress and inflammation in subjects with diabetes, and thus reduce cardiovascular complications after MI.

Competing interests

None declared.

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