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Polyphenolics and fat absorption

S Pal^{1*}, M Naissides¹ and J Mamo¹

¹Department of Nutrition, Dietetics and Food Sciences, Curtin University, Perth Western Australia, Australia

OBJECTIVES: To elucidate whether the acute consumption of red wine polyphenolic compounds regulates lipid and lipoprotein metabolism in dyslipidemic postmenopausal women.

DESIGN: Eight dyslipidemic postmenopausal women each consumed a mixed meal accompanied by either water, dealcoholized red wine or alcoholic red wine on three separate visits, in a random order, 2 weeks apart. One fasting and six hourly postmeal blood samples were taken and analyzed for plasma apolipoprotein B48 (apoB48; specific marker of chylomicrons (CM) and their remnants (CMR)); total-, LDL- and HDL-cholesterol; triglycerides (TAG); insulin and glucose at each time point.

RESULTS: There was a decrease in postprandial apoB48 levels after alcoholic and nonalcoholic red wine consumption compared to water.

CONCLUSION: Red wine attenuates postprandial CM and CMR levels in plasma, possibly by delaying the absorption of dietary fat, as suggested by a decrease in plasma apoB48 levels. The reduction of postprandial lipoproteins in circulation after red wine consumption may partly explain the low cardiovascular mortality rates among the French.

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Keywords: cardiovascular disease; lipoproteins; polyphenolics; red wine; lipids

Introduction

Over half of all Australians are classified as overweight or obese, and this is increasing by ~1% of the population per year. Overweight and obesity carries with it significantly higher risks for developing diabetes, hypertension, stroke and coronary artery disease (CAD). Epidemiological evidence suggests that moderate consumption of wine as part of a 'healthy lifestyle' program may positively enhance cardiovascular health, obesity and diabetes.^{1,2} Epidemiological studies indicate that moderate consumption of red wine (1–2 drinks/day) lowers the risk of cardiovascular disease, with alcohol drunk as wine having a stronger inverse relationship with CAD incidence compared to alcohol intake alone. The polyphenols found in red wine are resveratrol, the flavonoids, catechin, epicatechin, quercetin and phenolic acids, such as gallic acid. Some of these phenolic compounds are also present in other beverages, fruits and vegetables. Polyphenolics have been shown in numerous studies to have

antiatherogenic properties.^{3,4} Polyphenolics have also been shown to increase the metabolic rate and increase fat oxidation in humans, implicating a potential use of these compounds as an antiobesity treatment.^{5,6} However, the exact mechanisms by which 'red wine phenolics' benefit the cardiovascular system in humans remain unclear.

There is both insufficient and paradoxical evidence, which do not allow us to confidently promote wine consumption as part of a healthy heart lifestyle program. Wine, or rather alcohol, is calorie sparing and may contribute to the onset of visceral obesity. Globally, obesity is now considered to be an epidemic phenomenon, and is said to be responsible for the onset of serious and costly metabolic disorders including diabetes mellitus, cardiovascular disease and some types of cancer. The putative benefits associated with wine and alcohol consumption are also argued by some to be offset by a propensity to develop liver dysfunction and cancers of the digestive system. Moreover, in recent years, large-scale longitudinal studies investigating the potential benefits of dietary antioxidants on cardiovascular disease have been quite unspectacular, with modest, or no effect on disease frequency and severity. Indeed, there is now an accumulating body of evidence, which suggests that oxidative stress is a

*Correspondence: S Pal, Nutrition, Dietetics and Food Sciences, School of Public Health, Curtin University of Technology, Bentley 6000, Western Australia.
E-mail: s.pal@curtin.edu.au

consequence and not a requisite for cardiovascular disease. Hence, the very premise on which wine consumption is thought to be beneficial is now in doubt.

Central to the pathology of heart disease is the accumulation of cholesterol in the wall of arterial blood vessels that feed the heart. The cholesterol buildup in the arterial wall is derived from cholesterol-carrying particles called lipoproteins. We have explored how red wine may be beneficial to preventing heart disease by reducing lipoprotein production and increasing its clearance from circulation by the liver. These two points of regulation are critical in decreasing the number of cholesterol-carrying lipoproteins in circulation.

Red wine and heart disease

In humans, lipoproteins can be classified as either intestinally or hepatically derived. The intestinal derived lipoproteins, called chylomicrons (CMs), function to transport all dietary fats from the intestine to peripheral tissues in the body. In addition to dietary lipids, CMs also transport many ingested compounds into the blood stream. These lipoproteins are converted to CM remnants once in circulation. On the other hand, the liver-derived lipoproteins, called very-low-density lipoprotein (VLDL), are packaged in the liver and once in circulation, are converted to low-density lipoproteins (LDL). Central to the pathology of heart disease is the accumulation of cholesterol in the wall of arterial blood vessels that feed the heart. Both LDL and CM remnants can penetrate the arterial wall and deposit their cholesterol, and instigate the development of atherosclerotic plaque.^{7,8}

Primary therapeutic strategies to reduce atherosclerosis rely on reducing the plasma concentration of pro-atherogenic lipoproteins, such as LDL and CM remnants. Statins, the most widely used lipid-lowering agents, are particularly effective because they stimulate clearance pathways (the hepatic LDL receptor), and inhibit secretion of pro-atherogenic lipoproteins (VLDL). We hypothesize that specific red wine phenolic compounds benefit the cardiovascular system the same way as statins. Preliminary evidence from our laboratory suggests that red wine polyphenolics inhibit the lipoprotein production and secretion from the liver and intestines, thereby decreasing circulating concentrations of LDL and CM remnants, respectively. Cell culture experiments in our laboratory show (Figure 1) that exposure of human liver cells to physiological levels of wine polyphenolics generated fewer VLDL particles (as measured by apoB100), and was comparable to the effects of the potent lipid-lowering drug atorvastatin. Similar changes in the number of lipoprotein particles secreted were observed when individual polyphenolics, gallic acid, quercetin and resveratrol were examined.⁹ We have also demonstrated that red wine can also increase hepatic LDL receptor activity and HMG-CoA reductase activity in cultured liver cells.⁹ Consistent with our studies in human liver cells, we found that

red wine phenolics significantly decrease the number of CM particles (as determined by apolipoprotein B48 (apoB48) secretion; the major structural protein of CMs) from cultured human intestinal epithelial cells (CaCo₂) (data not shown). Collectively, our cell culture experiments suggest that wine is equipotent to first-line pharmacotherapies currently being used to combat cardiovascular disease. The next question is whether drinking red wine has the same effect in the whole body system.

Red wine consumption has modest effects on LDL-cholesterol, though often these studies have been done in normolipidemic subjects.^{10,11} It is becoming apparent that reduction of baseline cholesterol levels in healthy normocholesterolemic is difficult to achieve, and therefore this subject group is not appropriate to study the lipid-lowering affects of polyphenolics. Based on our cell culture data, we performed a human intervention pilot study with eight hyperlipidemic postmenopausal women to investigate the acute effects of red wine polyphenolics on lipid levels. Dyslipidemic women each consumed a mixed meal accompanied by either water, dealcoholized red wine or alcoholic red wine on three separate visits, in a random order, 2 weeks apart. One fasting and six hourly postmeal blood samples were taken and analyzed for plasma apoB48 (specific marker

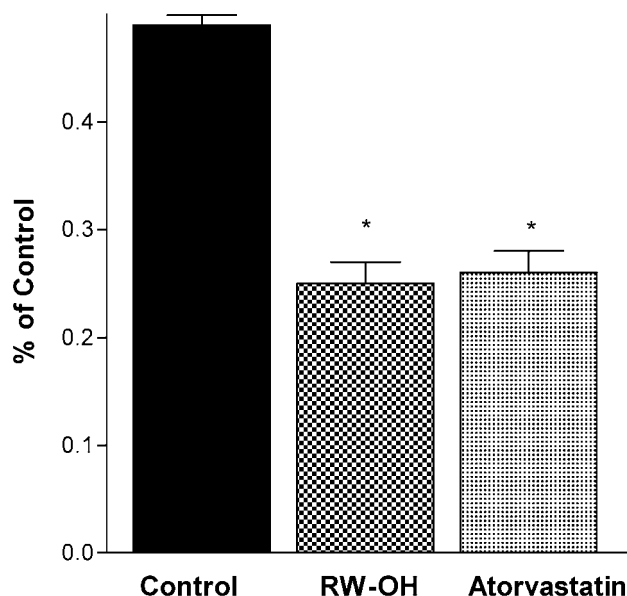


Figure 1 Effect of dealcoholized red wine and atorvastatin on apoB100 secretion from HepG2 cells. HepG2 cells were incubated with 5 μ M dealcoholized red wine (RW-OH) or 10 μ M atorvastatin for 24 h in a background media of serum-free DMEM. The apoB100 was measured in duplicate using Western Blotting ECL detection, as described in 'Methods' section. Each experiment was performed in duplicate and the densities of the apoB100 band on the autoradiograph were quantified using densitometry. ApoB100 concentrations in the media were expressed as a percentage of control \pm s.e.m. of three experiments done with replicates. The average mean of apoB100 secreted into the media by control cells was 0.51 ± 0.054 μ g/mg cell protein/ml media. * denotes values which are significantly different from control values at $P < 0.05$.

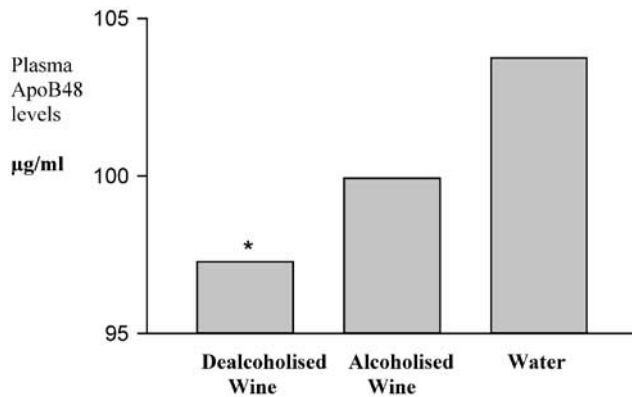


Figure 2 Plasma apoB48 levels in postmenopausal women with the consumption of dealcoholized red wine, alcoholized red wine or water. Eight dyslipidemic postmenopausal women each consumed a mixed meal accompanied by either water, dealcoholized red wine or alcoholic red wine on three separate visits, in a random order, 2 weeks apart. One fasting and six hourly postmeal blood samples were taken and analyzed for plasma apoB48 (specific marker of CMs and their remnants (CMR)) using gel electrophoresis and Western blotting/enhanced chemiluminescence procedure. Data were analyzed by repeated-measures ANOVA and paired *t*-test. * denotes values which are significantly different from control values at $P < 0.05$.

of CMs and their remnants (CMR)); total-, LDL- and HDL-cholesterol; triglycerides (TAG); insulin and glucose at each time point. ApoB48 concentration was determined using gel electrophoresis and Western blotting/enhanced chemiluminescence procedure.

Plasma lipids were assayed by enzymatic colorimetric methods and plasma insulin by ELISA. There was no effect of dealcoholized or alcoholized wine on plasma triglyceride, HDL-, LDL-, total-cholesterol or insulin levels. Circulating CM levels (as measured by apoB48) were significantly attenuated in subjects who consumed a beverage rich in polyphenolics (dealcoholized red wine) with a fat load, compared to water or alcoholized wine (Figure 2). Alcoholized wine also lowered postprandial lipemia (apoB48), but its effect was not as great as dealcoholized wine. Our results demonstrated there was a significant delay in fat absorption (as measured by the apoB48, a marker for CMs and their

remnants) with the consumption of red wine polyphenolics. These preliminary findings suggest that red wine polyphenolics modulate the postprandial response in humans, when consumed with a mixed meal.

We have gained new insights as to how wine or components of wine provide cardiovascular benefits. Acute alcoholic red wine consumption attenuates the levels of postprandial CMs and CMR in plasma, possibly by delaying fat absorption by the intestine. Thus, the reduction of postprandial CM levels with red wine consumption may explain the low CAD mortality rates among the French.

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