

Wine, Nutritional Omega-3 Polyunsaturated Fatty Acids, and Atherosclerosis: Potential Interactions

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ABSTRACT

The complex evolution of atherosclerotic process, from the initial endothelial dysfunction to the plaque formation, includes numerous pathophysiological steps. The association of the well-documented beneficial effect of omega-3 polyunsaturated fatty acids (PUFAs) intake, illustrated by the “Mediterranean diet,” with the still questioned beneficial effects of moderated wine consumption, also illustrated by the so-called “The French Paradox” specific life habit, can be summarized by the “fish-like effect” of wine consumption. In this context, besides direct effects of either increased omega-3 PUFAs or alcohol and polyphenols intakes on biological events involved in atherosclerosis, their interaction can potentiate those effects. After recalling in the first two parts, the main effects of omega-3 PUFAs and wine on atherosclerosis, the third part of this review is dedicated to their interactions in the atherosclerotic process.

Key words: Atherosclerosis, omega-3 polyunsaturated fatty acids, wine

INTRODUCTION

Mediterranean diet and French paradox, two well-known expressions, were used to design the potential cardiovascular protective effect that some alimentary habits can exert. Behind these terms, some controversies appeared mainly regarding the compounds involved in this cardioprotective effects. Actually, it is not only the modification of the type of food consumed that is involved but also a general modification of lifestyle, including inactivity and stress, which can lead to the increase in cardiovascular diseases. When specifically focusing on nutritional habits, “Mediterranean diet” or the “French paradox” principally consist in a modification of lifestyle and can therefore exert their cardioprotective effect. Therefore, the absence in agreement regarding the origin of the cardiovascular protective effect can be summarized by compiling data, suggesting a direct beneficial effect of wine consumption with extra beneficial effects attributed to diet patterns modification, including increased omega-3

polyunsaturated fatty acid (PUFA) consumption. A recent systemic review by da Silva and Rudkowska conclude that, in aged people, a consumption of omega-3 (1–2 g/day) associated with moderate red wine intake (200–400 mL/day) can exert beneficial effects on health.^[1]

Among the cardiovascular diseases, atherosclerosis is a vascular alteration that can lead to heart failure or stroke. In this context, the potential protective effect of omega-3 PUFAs is regularly investigated. However, despite a growing amount of evidences and research works, to date, the insufficient conclusion can be obtained regarding an undoubted beneficial effect of omega-3 PUFA supplementation on peripheral arterial disease.^[2] Moreover this, even if, today, the main explanation regarding this failure to confirm the decreased risk of cardiovascular disease is probably related to the source of PUFAs, the relative content of omega 3 and omega 6 PUFAs, and their precursor. Another key point is the population and the clinical conditions of the studies. This can be illustrated by the findings of Sekikawa *et al.* who focused

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their analysis of PUFA effect on atherosclerosis on the differences between long-term randomized clinical trials in Western countries and Japan. They explain the discrepancies observed, one the one hand, by the differences in doses of PUFAs administered and the other hand by the background dietary intake (of PUFAs) of the populations.^[3] This conclusion can be associated to the one obtained by Michas *et al.* who proposed a higher importance of the total matrix of food than just a modification of fatty acid intake for the prevention of cardiovascular disease.^[4] In this context, as “Mediterranean diet” and “French paradox” are “lifestyle diet modifications,” we can legitimately wonder whether the anti-atherosclerotic protective effect of increased n-3 intake can be modulated by wine consumption. Therefore, the purpose of this review is to summarize the anti-atherosclerotic effect of n-3 PUFAs and wine compounds and to ask the question whether a possible interaction between them can modify their actions.

OMEGA-3 PUFAS AND ATHEROSCLEROSIS

Atherosclerosis is a complex evolving pathology observed in population presenting either primary pathologies or having significant lifestyle modifications. It will induce significant modifications regarding lipidemia, inflammation, and thrombosis and vascular wall associated with macrophage production to peripheral sites including the vessels. Altogether, this will initiate the plaque formation, modulate the plaque stability, and lead to atherosclerosis. Most of the previously mentioned modifications can be counteracted by omega-3 PUFAs.

In this general context, omega-3 PUFA intake by fish oil consumption has been reported to limit atherosclerosis in animal model including rabbit^[5] and swine.^[6]

Dyslipidemia

The main antiatherogenic effect of omega-3 PUFAs regarding the lipidemia can be associated mainly with the reduction of triglycerides and cholesterol (high-density lipoprotein [HDL] and very-low-density lipoprotein) level and is well documented.^[7] Moreover, in a recent review, da Silva *et al.* reported that fish oil supplementation had either no effect or decreased lipid peroxidation.

Triglycerides

The association between triglyceride level and cardiovascular events is well described.^[8] More specifically epidemiologic studies have described a relationship between the postprandial triglyceride and cardiovascular diseases. In this context, Schirmer *et al.* described in humans that n-3 PUFA supplementation leads to a decrease in both postprandial and fasting triglyceride level, suggesting a possible pathway

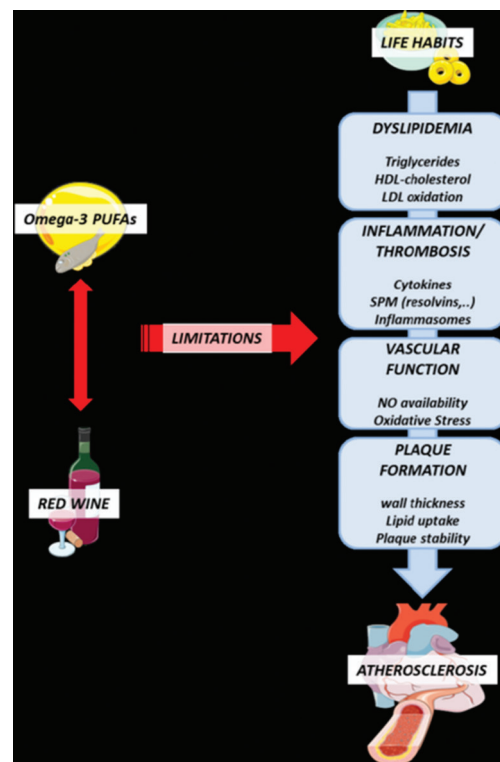


Figure 1: Synthesis of the described triggers involved in atherogenesis, limited either by omega-3 polyunsaturated fatty acids (PUFAs) or wine consumption. The interaction between omega-3 PUFAs and red wine induced a potentiation of the protective effects

to reduced triglyceride-related increase in cardiovascular disease.^[9] This result has to be associated with the ones reported by Oh *et al.* who reported a significant decrease in TG content and an improved vascular function in patients supplemented with omega-3 PUFAs.^[10]

HDL-cholesterol

In a recent review, Pizzini *et al.* reported that it is still unclear whether or not omega-3 PUFAs are able to increase the reverse cholesterol transport and therefore will inhibit or limit the foam cell formation in atherosclerosis process.^[11] They conclude that the omega-3 beneficial effect can be mediated by an HDL remodeling, promoting an hepatic clearance of HDL derived cholesterol.^[12] Finally, only a moderate direct effect of omega-3 PUFAs on HDL-cholesterol has been reported.^[13]

Low-density lipoprotein (LDL) oxidation

Even if lowering the level of total and LDL-cholesterol leads to reduce the coronary heart disease, one trigger of atherosclerosis remains the oxidation of LDL. LDL-oxidation increases their toxicity by promoting the development and progression of atherosclerosis. This has to be related to experimental data from Frémont *et al.* who demonstrates that a high level of dietary PUFAs in rat was leading to a

higher sensitivity to oxidation of LDL.^[14] In this context, an uncontrolled increase in PUFA intake can promote deleterious effect on atherosclerosis.

INFLAMMATION AND THROMBOSIS

Pro-inflammatory cytokine prothrombotic eicosanoids

The implication of pro-inflammatory cytokines in atherosclerosis has been tremendously studied (for a detailed specific review see Ramji and Davies 2015^[15]). However, to date, no direct effect of omega-3 PUFA intake on pro-inflammatory cytokine has been demonstrated. As discussed below, the indirect effect might be related to a decrease in macrophages infiltration and activation in the plaque.

Prothrombotic and pro-inflammatory eicosanoids are produced from arachidonic acid leading to the generation of prostaglandins and thromboxane. Omega-3 PUFAs are involved in the same enzymatic pathway than arachidonic acid. Therefore, the increase of omega-3 PUFA availability in membranes leads to a competition with arachidonic acid, resulting in a decreased production of prothrombotic factors.

Specialized pro-resolving mediators (SPMs) resolvins, protectins, and maresins

SPMs including resolvins, protectins, and maresins are bioactive molecules produced by lipoxygenase and cyclooxygenase from omega-3 PUFAs. They are not only involved in the limitation of the acute inflammatory response by the reduction of pro-inflammatory cytokine production and macrophage activation but also in tissue repair.^[16,17] In a recent study, Schaller *et al.* have demonstrated in patients with peripheral arterial disease that a supplementation with fish oil for 1 month induced a modification in the omega-3 index strongly correlated with an increase in pro-resolving lipid mediators.^[18]

Inflammasomes

Inflammasomes, multimeric protein complexes from the intracellular NOD-like receptor (NLR) family, are key regulators of the innate immunity and inflammation that are activated by numerous stimuli including advanced glycation products, oxidized LDL, cholesterol crystals, or specific pathogens. This activation induced the secretion of pro-inflammatory cytokines including IL-1 and IL-18. Williams-Bey *et al.* have demonstrated that, in isolated macrophages, omega-3 FFA induced both the suppression of inflammasome activations mediated by NF-kappaB.^[19] More recently, Shen *et al.*^[20] concluded that the PUFA dietary reduction of atherosclerosis is in part associated with the attenuation of inflammasome activation in a mice model through the reduction of the specific NLR protein3. This protein was initially described as a required factor for atherogenesis.^[21]

Interestingly, the limitation of inflammasome activation by omega-3 PUFAs is associated with the enhancing of autophagy leading to a decreased macrophage activity.^[19,20] This effect of omega-3 PUFAs can therefore counterbalanced the progressive deterioration of macrophage autophagy that has been previously described in atherosclerosis.^[22,23]

VASCULAR WALL AND FUNCTION

Atherosclerosis is preceded by structural and functional changes in the vascular wall including the media and endothelium. The structural alteration of the vessel including a remodeling of the media, corresponding to an increased wall thickness, will result in mechanical dysfunction. This is reinforced by the functional alterations of the endothelium which switch from a prorelaxant activity to a procontractile phenotype. As this modification of the endothelium phenotype occurs in a pro-inflammatory and procoagulatory environment, it will largely contribute to the progression of the vascular disease, including atherosclerosis.

In this context, part of the pathways of arterial stiffness development and endothelial dysfunction can be modified by n-3 PUFAs and therefore can modulate atherosclerosis.

NO availability and oxidative stress

The production of NO by the endothelium is associated with a functional endothelium phenotype not only because of its vasodilation effect but also because of its potential antiatherosclerotic properties. Indeed, NO is able to reduce the smooth muscle cell proliferation, to limit the leukocyte adhesion and the platelet aggregation. The reduction of NO bioavailability can either result from a decreased production or by its quenching by reactive oxygen species (ROS).

The enhanced production of NO by omega-3 PUFAs has been evaluated in isolated cell model and in different types of knock-out mice, and the global pathway is well-known today. It includes the limitation of interaction between endothelial nitric oxide synthase (eNOS) and its inhibitors (caveolin and asymmetric dimethylarginine), the increase in eNOS protein expression, and the activation of eNOS by phosphorylation pathway. Moreover, the omega-3 PUFA plasma level has been related to the endothelial function in humans. The reported increase in flow-mediated vasodilation consecutive to fish oil supplementation in human peripheral and coronary arteries has been associated with an increased NO production.^[24,25]

The other aspect associated with NO bioavailability is the oxidative stress. The modulation of oxidative stress by omega-3 PUFAs remains under investigation. Studies have described that omega-3 PUFAs can reduced oxidative stress by the limitation of the ROS production and the final endpoint being the reduction of peroxynitrite formation in the endothelial cell.^[26]

Independently of NO bioavailability, numerous studies reported that fish oil supplementation had either no effect or decreased lipid peroxidation. This apparent oxidative stress limitation can be directly associated with antioxidant properties of fish oil compound rather increase in endogenous antioxidant defenses.^[27]

PLAQUE FORMATION AND STABILITY

Intima Media Thickness

One trigger of the media thickening is the proliferation of smooth muscle cells.^[28] This will lead to a remodeling which can promote atherosclerosis. Both specific omega-3 PUFAs and fish oil have demonstrated the ability to reduce the smooth muscle cell proliferation either by slowing the cell cycle or by reducing the adhesion molecules on the cells. However, the direct association of omega-3 PUFA consumption and a favorable evolution of the intima-media thickness remained under questioning, and the recent results suggest that all the omega-3 PUFAs do not present the same potential.^[29]

Lipid Uptake

Arterial uptake of cholesterol, mainly through LDL, is a major trigger of atherosclerosis. An increased flux of LDL in atherogenic arterial area will result in an increase intake in the vascular wall independently of the usual receptor pathway and lead to lipid accumulation. Chang *et al.* described a limitation of lipid uptake in the media of aorta in mice submitted to a high fat diet and supplemented with omega-3 PUFAs.^[30] These effects are mediated by a decrease in lipoprotein lipase activity.

Plaque Stability

The stability of the plaque that to say its vulnerability to rupture is one of the key determinants of acute cardiovascular events. In this context, all those above-described effects of n-3 PUFAs can be related to their ability to increase the plaque stability, namely the prevention of the rupture of the vulnerable plaque. This mainly mediated by their incorporation into the plaque leads to modification of the plaque physiology.^[31] Thies *et al.* demonstrated a strong association between omega-3 PUFAs and the stability of plaques in a randomized controlled trial.^[32] Actually, they observed a significant increase in plaque stability by adding omega-3 PUFAs in patients with advanced atherosclerotic plaques. This effect is mediated by the incorporation of omega-3 PUFAs into LDL and therefore into the plaque. However, in this important work, they confirmed that this stabilization of the plaques is mediated by general effect mainly on the reduction in inflammatory process and the reduction in metalloprotease activities.^[33] This leads to a more stable plaque characterized by a well-formed fibrous cap and a lower level of infiltrated macrophages.

Regarding the infiltration of macrophages, it has been demonstrated that omega-3 PUFAs are able to reduce the expression of adhesion molecule on both endothelial cells and macrophages and the reduction of chemoattractant molecules.^[33]

However, to date, the total mechanism leading to increase plaque stability by omega-3 PUFAs remains to be fully investigated. Besides the limitation of macrophage infiltration, an increase in cell death can also occur. Indeed, it has been observed that omega-3 PUFAs can exacerbate cell death by both necrosis and apoptosis in human monocyte cells.^[34]

RED WINE AND ATHEROSCLEROSIS

On another side, based on lifestyle modification, the effect of alcohol consumption on cardiovascular disease and therefore on atherosclerosis is largely discussed elsewhere. The question is still under interest. Indeed, from the description of the French paradox in the early 90s to now, no clear conclusion can be made. However, it remains admitted that light-to-moderate consumption of alcoholic beverage can have beneficial effect. More precisely, light-to-moderate red wine is described as given a panel of potentially beneficial effect on several triggers involved in the atherosclerotic process.

This comes from the observations that wine compounds, including alcohol and polyphenol, have been described to be able to modulate some of the previously described triggers of atherosclerosis.

Oxidative Stress

The limitation of oxidative stress by wine compounds is clearly associated with a limitation of endothelial dysfunction. Those effects are not mediated by alcohol *per se* but by the global red wine content as illustrated by the study of Lassaletta *et al.*^[35] Indeed, in this study, they demonstrated that, despite a global reduction of oxidative stress partly mediated by alcohol, only the red wine consumption was able to induce a protection of the vascular function in swine submitted to an atherogenic diet.

In the specific context of atherosclerosis, Avellone *et al.* reported a limitation of oxidative stress markers in atherosclerosis by moderate Sicilian red wine consumption.^[36]

Anti-inflammatory

Red wine compound has been shown to reduce some aspects of the inflammatory process that are observed in atherosclerosis. It includes the inhibition of an initial trigger of vascular inflammation and the monocyte adhesion by

the down-regulation of the adhesion molecules expression (ICAM-1, VCAM-1,...). This effect is mediated by the inhibition of NF- κ B and AP-1 activation.^[37]

Increasing HDL-cholesterol

The modulation of HDL level by wine consumption is still under investigation. Recently, in a long-term multicentric perspective study, Taborsky *et al.* concluded that they were unable to confirm the hypothesis that wine drinking is associated with an elevation of HDL.^[38] However, in two recent works based on a Mendelian randomized analysis in Japanese populations, Tabara *et al.* associated the beneficial effect of moderate alcohol consumption to a concomitant increase in HDL cholesterol with a decrease in LDL cholesterol.^[39,40] Interestingly, as the molecular basis involved is not fully elucidated, it can be speculated that both ethanol and non-alcoholic components might play a role.^[41]

Besides these results, it is to note that, in the first part, we mentioned that the postprandial hyperlipidemia is a trigger in atherosclerosis process. Interestingly, Natella *et al.* reported that red wine consumption during a meal is able to induce a reduction in the postprandial increase in lipid hydroperoxides and cholesterol oxidation products.^[42] Moreover, the antiatherosclerotic effect can be due to the lower atherogenicity of the macrophages related to a decreased ability to uptake oxidized LDL mediated by polyphenol supplementation.^[43]

Modulation of LDL Oxidation

As previously mentioned, it has been demonstrated that red wine consumption, mainly the non-alcoholic part, was able to limit LDL oxidation in humans.^[44] Similarly, Vinson *et al.* reported that a moderate red wine intake is able to decrease the level of oxidized-LDL in a hamster model, contributing to an inhibition of atherosclerosis.^[45]

However, the modulation of LDL by wine consumption is also related to a decreased in total LDL content.^[46] By comparing wine intake to pure alcohol intake in rats fed with standard diet, the authors demonstrated that a long-term reduction of LDL-cholesterol content can be ascribed to the non-alcoholic components in wine.

Foam Cell Formation

There are no direct evidences on the effect of red wine consumption on the foam-cell formation. Based on the observation, foam cell formation involves ROS and the monocyte chemoattractant protein-1, and Park *et al.* demonstrated that resveratrol, a compound extract from wine, is able to reduce foam-cell formation by both the reduction of the oxidative stress and the production of attractive compound by the macrophages.^[47]

Prevention of Endothelial Dysfunction and Increase in no Bioavailability

It has been demonstrated that wine compounds are able to induce endothelial-mediated vasorelaxation through the NO pathway in both animal and human.^[48,49] The higher polyphenol-induced production of NO has been associated with the prevention of endothelial dysfunction in both experimental animal models and human studies.^[50]

Interestingly in humans, Cuevas *et al.* have demonstrated that red wine can counteract a high-fat diet-induced endothelial dysfunction.^[51] They demonstrate that this effect was corresponding to a stable change rather to a simple transient or postprandial response. However, to the best of our knowledge, no direct evidences regarding the effect of red wine on NO bioavailability in the context of atherosclerosis are available. Indirectly in a recent study, in a hypertensive model associated with a low NO availability, the positive effect of red wine extract on eNOS expression associated with a significant increase in NO production has been observed.^[52] Similarly, resveratrol has been associated with a significant NO signaling pathway increase in the reduction of atrial fibrillation, mainly due to the increase in eNOS expression.^[53] The exposition of arteries to disturbed flow can initiate atherosclerosis; this “shear stress-induced atherogenesis” is associated with a reduction in eNOS expression. This reduction can be partly reversed by short-term red wine light consumption in mice.^[54]

However, today in the context of limitation of atherosclerosis by modifying life habits, we can wonder whether the association of the Mediterranean diet observations and the French paradox ones can allow to hypothesis whether a moderate consumption of red wine can modulate the potential antiatherosclerotic effect of omega-3 PUFAs. Indeed in a more general context, Urquiaga *et al.* have shown that moderate wine consumption in healthy volunteers fed with a Mediterranean diet can modify the fatty acid profile and improve the antioxidant status, two triggers of atherosclerosis.^[55,56]

NUTRITIONAL OMEGA-3 PUFAS, RED WINE, AND ATHEROSCLEROSIS

No studies specifically dedicated to the interaction between wine intake and nutritional omega-3 PUFAs in the atherosclerosis context are available. However, some indirect evidences are increasing. To synthesize these data, it appears necessary to separate the described effect of alcohol and non-alcoholic compounds present in wine, in the general context of cardiovascular disease, focusing on vascular diseases when possible.

An initial study by di Giuseppe *et al.* has described that alcohol consumption was positively associated with omega-3 PUFA blood content both in healthy men and women in three European populations.^[57] More precisely, they postulate that both alcohol and non-alcoholic components might exert this effect. Similarly, we reported an interaction of wine drinking with omega-3 PUFAs in patient with coronary heart disease.^[58]

Alcohol Effect

The Lyon Diet Study was one of the first reports investigating the association between ethanol intake and omega-3 PUFA blood content in patients with cardiovascular diseases.^[59,60] Their results can be transposed to wine consumption and omega-3 PUFA content as they clearly report that, among the 353 male patients, 95% of alcohol intake was coming from wine. The data analyses report a positive association between ethanol intake and omega-3 content after controlling for dietary PUFA intakes.

However, based on the available data, non-alcoholic wine compounds may play a significant role in PUFA levels. This was initially described by Pellegrini *et al.* who report a significant increase in omega-3 concentration in platelet phospholipid coming from non-alcoholic compounds of wine.^[61]

Non-alcoholic Compounds

The non-alcoholic wine compounds, large amount of phenolic compounds (mainly flavonoids), are involved in numerous biological mechanisms that can modulate atherosclerosis. It includes the limitation of PUFA oxidation and platelet aggregation.

It is also to note that Frankel *et al.* have demonstrated that the phenolic substances of red wine are able to protect LDL from oxidation. This has to be related to experimental data from Frémont *et al.*^[14] who demonstrate that a high level of dietary PUFAs in rat was leading to a higher sensitivity to oxidation of LDL. Therefore, the proatherogenic potential effect of LDL oxidation that can be increased by high PUFA intake can be modulated by wine consumption.

CONCLUSION

Finally, the limitation of cardiovascular diseases seems today to be approached by the modification of the life's habits. More specifically, the importance of controlling the diet clearly appears as a major issue. In this context, it appears that diet changes including increased intake in omega-3 PUFA lead to fast, meaningful, and lasting results. Although more controversial, the moderate wine consumption also seems to have protective effects. Therefore, considering (1) the biological mechanisms involved in atherosclerosis, (2) the influence of omega-3 and wine compounds on them, and

(3) the interaction between omega-3 and wine compounds, it seems essential to consider an overall change in eating habits in atherosclerosis prevention [Figure 1].

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