Received: 20 May 2018 | Accepted: 21 August 2018
DOI: 10.1002/jcb.27672

PROSPECTS

WILEY Journal of Cellular Biochemistry

The effects of fatty acids consumption on OPG/RANKL/RANK system in cardiovascular diseases: Current status and future perspectives for the impact of diet-gene interaction

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Abstract
Cardiovascular disease (CVD) is an overall term that comprises a number of related pathologies, these include peripheral arterial disease, cerebrovascular disease, coronary heart disease (CHD), venous thromboembolism, and rheumatic and congenital heart diseases. Fatty acids in the diet have been reported to affect CVD. The OPG/RANKL/RANK system appears to have a role in CVD outcomes. However, there have been few studies on the impact of diet-gene interaction for effects of fatty acids consumption on the OPG/RANKL/RANK system in CVD. This review focuses on the effects of fatty acids on OPG/RANKL/RANK in CVD.

KEYWORDS
cardiovascular disease, fatty acids, osteoprotegerin

1 | INTRODUCTION

Cardiovascular disease (CVD) is a general term used for group of related pathologies that include cerebrovascular disease, coronary heart disease (CHD), peripheral arterial disease, venous thromboembolism, and rheumatic and congenital heart diseases. On global level, CVD accounts for 31% of mortality, most of which in the form of cerebrovascular accident and CHD.[1] According to WHO estimations, more than 75% of premature CVD is preventable and the amelioration of risk factors can help decrease the growing CVD burden on providers and individuals.[2] CVD prevention can reduce the rate of important cardiovascular outcomes, so can reduce premature disability and morbidity, on the other hand, can prolong survival and improve quality of life.[3] Preservation of a healthy population has a potential role for comprehensible reduction of economic burden of CVD among asymptomatic patients because the main part of the costs was related to CVD medication use.[4]

The risk of incident stroke is 1.3 times higher in people working 55 hours or more per week than people work standard hours.[5] Blood pressure lowering decreases vascular risk significantly.[6] Hypertriglyceridemia,[7] obesity,[8] and diabetes[9] are CVD risk factors. The risk of CHD in diabetic females is 40% greater than diabetic males.[10] It has also been reported that dietary risk factors contribute to 42.3% of cardiovascular deaths.[11] The American Heart Association recommends the Dietary Approaches to Stop Hypertension eating pattern, which is rich in fruits, vegetables, whole grains, and low in sugar and saturated fat. It is known as a technique of lowering independent CVD risk factors (blood pressure and low-density lipoprotein (LDL) cholesterol, but it does not demonstrate a direct reduction in CVD risk.[12] The European Society of Cardiology recommends that fiber, fruit, vegetable, and fish intake should be increased, shifting to polyunsaturated fatty acids from saturated fatty acids, and avoiding alcohol and adhering to a Mediterranean style diet. These diets reduce CVD risk significantly.[13] The National Institute for Health and Care Excellence (NICE) give advises to reduce consumption of saturated fat, increase monounsaturated fatty acids (MUFA) intake, and consume five serving of vegetables and fruits each day. Two portions of fish and a high-fiber diet each week are also recommended by NICE. They admit that there is not enough evidence to prove that these pieces of advice will affect directly on risk of CVD, but to some extent have benefits on other healthcare areas. It is clear that, most of the studies referenced in this study are from the pre-1990s period. Dietary patterns in this period were considerably different, and almost all their data were concerning CVD risk.[14]

The new update of the 2004 fatty acids and CVD review published by the Agency of Healthcare Research and Quality shows a relatively minor effect of marine oils on LDL-cholesterol and high-density lipoprotein (HDL) cholesterol levels, though a large, dose-dependent effect on serum triglycerides levels.[15] On the contrary, there are evidence demonstrating that α-linolenic acid (ALA) does not influence lipoprotein levels significantly. In addition, ALA and marine oils have not been promising to control blood pressure.[16] On the other hand, current evidence has shown the protective impacts of marine oil intake against the risk of CVD death and other adverse cardiovascular events, but there is insufficient data to demonstrate the relationship between higher marine oil intakes and lower risk of CHD and congestive heart failure. There is an inconsistency regarding the effect of marine oil intake or its association with many different CVD outcomes. Randomized clinical trials have evaluated only patients with known CVD, however, observational studies have generally evaluated healthy population without known CVD. There is always little risk of bias concerning published studies. On the other hand, very few trials have completely evaluated the effects of omega-3 fatty acids (n-3 FA), considering different populations with a variety of diet or other characteristics. Furthermore, few investigations have directly compared the various n-3 FA components, doses, ratios, or duration of intake. As a result, there is insufficient or limited evidence to answer most of the key questions of the review.[15]

The pathophysiology of CVD is multifactorial. Oxidative stress and inflammatory pathways have major roles in pathophysiology of CVD.[17,18] In addition, osteoprotegerin (OPG) is an important factor in the pathophysiology of CVD.[19] This system appears to play a pivotal role on the mortality and morbidity of CVD patients,[20] and OPG is identified as a predictor of CVD and mortality.[21] Today, several studies have evaluated the effects of fatty acids including diet on OPG pathway in CVD. This review focuses on the effects of fatty acids on OPG/RANKL/RANK system in CVD.

2 | OPG/RANKL/RANK SYSTEM

OPG is a cytokine receptor and a member of the tumor necrosis factor (TNF) family. It is a decoy receptor and is expressed by cells of the osteoblastic lineage in competition with receptor activator of nuclear factor-κB (RANK) for receptor activator nuclear factor-κB ligand (RANKL). OPG is encoded by TNFRSF11B. The genes encoding RANK and RANKL are TNFRSF11A and TNFSF11, respectively.[19] Chung et al[22] have shown a relationship between a polymorphism of the TNFRSF11B gene and the presence of coronary artery calcium in systemic lupus erythematosus patients.

It is also known that the GG genotype of the *T245G* (rs3134069) polymorphism, the CC genotype of the *T950C* (rs2073617) polymorphism, and the CC genotype of the *G1181C* (rs2073618) polymorphism are significantly more prevalent in patients with carotid plaque than in control groups and these polymorphisms are related to high serum OPG levels.[23] OPG gene polymorphisms are synergistically effective in peripheral arterial occlusive disease patients and linked with different levels of risk factors for peripheral arterial occlusive disease and critical limb ischemia, and depend on the number of high-risk genotypes carried concomitantly by a given individual.[24] The OPG gene polymorphisms (T245G, T950C, and G1181C) are significantly and independently related to a history of ischemic stroke. They are synergistically effective in patients with history of stroke. The TNFRSF11B gene polymorphisms was related to the ischemic stroke history and synergistic effects between these genotypes might be potential markers for cerebrovascular disorders.[25] An OPG gene polymorphism at position 950 was related to ACS and CAD in Japanese men, and might enhance the CAD development, particularly ACS.[26] The polymorphism at position 950 in the OPG gene linked with cardiovascular morphology and function in healthy people.[27] The RANKL gene rs9594782 polymorphism was associated with aortic calcification in Korean women. This study also showed that the rs2277438 polymorphism was closely related to urine deoxypyridinoline levels, a bone resorption marker, which suggested its role on vascular calcification and bone metabolism in individuals.[28] Another study showed that non-TT genotype of the rs9594782 RANKL single-nucleotide polymorphisms (SNP) was an independent genetic risk factor for the development of ACS.[29] Singh et al[30] reported that OPG rs2073618, RANK rs75404003, and RANKL rs9594782 SNPs may put thalassemia patients at risk of left ventricular hypertrophy.

3 | OPG/RANKL/RANK SYSTEM AND CVD OUTCOMES

The relationship between OPG and a number of risk factors of CVD, such as age, smoking, diabetes, systolic blood pressure, and prevalent CVD was positive. However, there was no association between serum RANKL concentrations and multiple risk factors of CVD, including smoking, diabetes, and antihypertensive treatment.[31] Serum OPG levels was positively associated with serum homocysteine serum levels and negatively associated with serum triglycerides. It was not associated with the body mass index or any other lipid metabolism parameters including total-, LDL- or HDL-cholesterol, cholesterol, Apo AI and Apo B, or lipoprotein (a) and serum levels of creatinine. Serum levels of OPG had tendency to be higher in hypertensive patients in comparison with normotensive patients.[32] It has been reported that OPG was evidently a noticeable atherosclerosis biomarker, which is independently associated with atherosclerosis traditional risk factors, clinical atherosclerotic disease, such as ischemic stroke and ischemic heart disease (IHD), and subclinical peripheral atherosclerosis.[33] This system has a pivotal in mortality and morbidity of CVD patients,[20] and is known as a predictor of CVD and mortality.[21]

According to different biomarkers studies, both subclinical disease and near-term cardiovascular events were only predicted by OPG.[34] OPG independently predicts the combined end-point of hospitalization of IHD, ischemic stroke and all-cause mortality.[35] Jono et al[36] showed that serum OPG levels were much more in patients with clinically significant stenosis of the coronary arteries than in those without. The severity and 10-year progression of carotid atherosclerosis was significantly associated with OPG. In addition, an independent risk factor for incident CVD and vascular mortality was a high level of OPG.[37] Increased hazards of incident CVD and mortality were related to OPG. OPG quartiles nonsignificantly increased the prevalence of coronary artery calcification. But there is no association between coronary artery calcification or incident CVD or mortality with RANKL concentrations.[31] The increased probability of this suggested that OPG may be a reason or a marker for vascular calcification depends on the involvement of serum OPG levels with diabetes and cardiovascular mortality.[38] A study in type 2 diabetic patients showed that there was an independent relationship between serum OPG and asymptomatic CAD.[39]

A 12-year follow-up cohort study showed that future myocardial infarction (MI) risk, total mortality, mortality of IHD, ischemic stroke, stroke and of nonvascular causes independent of traditional cardiovascular risk factors were significantly related to serum OPG.[40] The increase of plasma OPG concentrations was reported in both in the normoalbuminuric and the nephropathic patients with CVD. Consequently, the development of diabetic vascular complications and OPG are related.[41] A cohort study revealed a strong association between the baseline OPG concentration and increased long-term mortality and heart failure hospitalizations and not related to stroke.[42] Abedin et al[43] reported an independent association among plasma OPG, coronary artery calcium, and aortic plaque in an unselected population, which may be a new biomarker for atherosclerosis in human beings. According to Sandberg et al[44] studies, two important feature of unstable disease are increased expression of the OPG/RANKL/RANK system in clinical and experimental atherosclerosis, and increased RANKL expression in T cell. Another study on congestive heart failure patients showed that, OPG was upregulated in symptomatic human carotid atherosclerosis with possible implications for plaque stability.[45] OPG concentrations were increased in rheumatoid arthritis (RA) patients and related to inflammation. In RA patients, OPG is also related to coronary artery calcification independently of cardiovascular risk factors and disease activity.[46] Furthermore, Dessein et al[47] reported that endothelial activation and carotid atherosclerosis in RA was independently related to OPG concentrations. OPG inhibited advanced plaque progression by preventing an increase in lesion size and calcification. OPG also works as a survival factor and may modulate production of MMP9 in vascular cells.[48] Giaginis et al[49] reported that relation of OPG plasma concentrations with risk factors, medical history, and medication intake supported evidence for the potential clinical implication of OPG in carotid atherosclerosis, whereas the clinical utility of RANKL seems uncertain.

OPG protects against atherosclerotic calcification and may be a marker demonstrating the onset of atherosclerosis.[50] Moreover, RANKL is correlated with the number of atherosclerotic plaque lesions.[50] RANKL significantly increases the activity of matrix metalloproteinase (MMP) in vascular smooth muscle cells in people with CVD.[50] The RANKL may activate MMP through the activation of mitogen-activated protein kinases and AP-1.[51,54] Overexpression of activated MMP may promote destabilization and complication of atherosclerotic plaques.[50] In another pathway, RANK activates TNF receptor-associated factor 2 (TRAF2) and TRAF6.[55,56] Then, NF-κB translocate to nucleus leading to the activation of smooth muscle cell gene and osteoblast gene. This pathway also have important role in calcification of vessels.[57] However, OPG inhibits RANK and RANKL[58] (Figure 1).

4 | FATTY ACID AND CVD OUTCOMES

Fatty acids normally have an even number of carbon atoms from 16 to 26. Fatty acids that have a single bond between adjacent carbon atoms are named "saturated"; those with at least one double bond are called "unsaturated." In chemistry, MUFA are classified as fatty acids containing a single double bond in contrast to polyunsaturated fatty acids (PUFA), which have two or more double bonds but saturated fatty acids (SFA) do not have double bonds.[59,60] In prospective observational studies and adequately powered randomized controlled trials, *n*-3 PUFA seems to be helpful in reducing CHD mortality and sudden cardiac death. Other cardiovascular outcomes such as conflicting evidence from observational studies and/or randomized trials for effects on nonfatal myocardial infarction, ischemic stroke, atrial fibrillation, recurrent ventricular arrhythmias, and heart failure are less effective.[61] The outcome of different studies on omega-3 long-chain PUFAS (*n*-3 PUFAS; fish oil) on CVDs indicate that in secondary prevention, fish oil significantly decreased all-cause mortality, MI, cardiac arrest and sudden death, or stroke.[16] According to a cohort study, fish and dietary *n*-3 PUFA intakes generally have an inverse effect on the increase mortality risks of IHD, MI, heart failure, and total CVD. In *n*-3 PUFA intake and heart failure, these inverse correlations were more noticeable[62] (Figure 2).

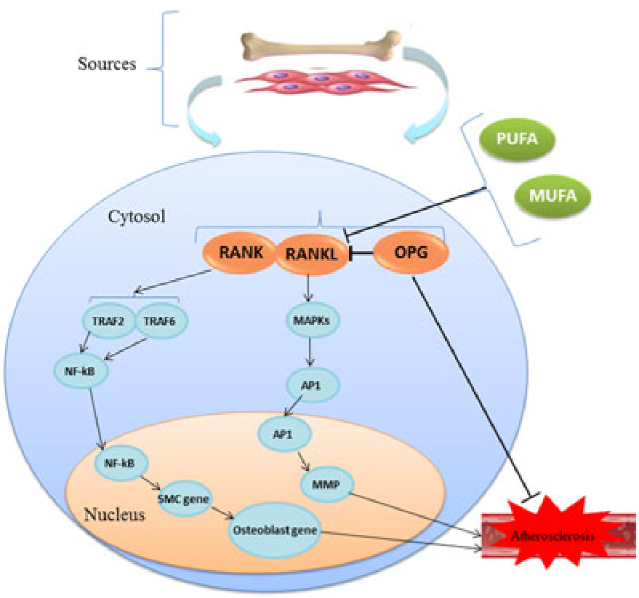

FIGURE 1 Schematic representation of targeting OPG/RANKL/RANK signaling pathway using fatty acids and the prevention of atherosclerosis. AP-1, activator protein-1; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MUFA, monounsaturated fatty acid; NF-κb, nuclear factor-κB; OPG, osteoprotegerin; PUFA, polyunsaturated fatty acid; RANK: receptor activator of nuclear factor-κB; RANKL, receptor activator nuclear factor-κB ligand; SMC, smooth muscle cell; TRAF, TNF receptor-associated factor

It has been reported that individuals taking *n*-3 FA show a significant reduction in the risk of sudden cardiac death and a reduction in all-cause mortality, regardless of using β-blockers and lipid-lowering therapy as secondary prevention drugs. The *n*-3 PUFAs decrease blood viscosity and pressure, and modulate membrane fluidity as well as associated enzyme and receptor functions. The general effects of *n*-3 PUFAs reduce CAD in populations with *n*-3 PUFAs consumption.[63] Johansen and his colleagues revealed hemostatic markers of atherosclerosis are decrease by *n*-3 FA supplementation.[64] In contrast, a meta-analysis indicated that *n*-3 PUFA intake was not effective in lowering the all-cause mortality risk and other negative outcome in CVD[65] (Figure 2).

MUFA supplementation improves the CVD risk factors. MUFA improves healthy blood-lipid profiles, promotes insulin sensitivity, regulates glucose levels and mediates blood pressure.[66] In another study also reported the benefits of MUFA taking on CHD.[67] The effect of MUFAs on decreasing plaque size, collagen and prevent atherosclerotic events in mice with MetS is more than those of SFAs.[68] SFAs intake leads to increased levels of LDL-cholesterol, total cholesterol/HDL-cholesterol ratio, and increased CHD events.[69-71] However, replacement of SFAs with PUFAs or MUFAs can be effective in decreased lipid profiles and CVD risk[72] (Figure 2).

5 | FATTY ACID AND OPG/RANKL/RANK SYSTEM IN CVD

There are few studies reporting the effects of fatty acids on OPG/RANKL/RANK system in different diseases.[73,74] The PUFAs downregulated TNFRSF11B during gestation

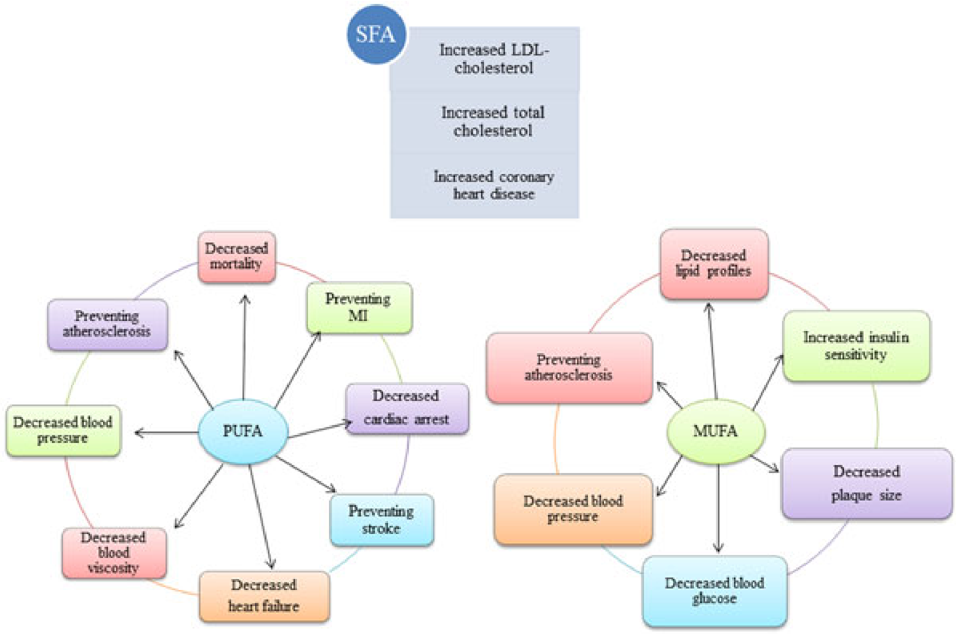

FIGURE 2 Schematic representation of effects of fatty acids on CVD outcomes. CVD, cardiovascular disease; LDL, low-density lipoprotein; MI, myocardial infarction; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acids

and suckling in rats.[75] Another study reported the beneficial effects of *n*-3 PUFAs on TNFRSF11B gene expression in hypercholesterolaemic rabbits.[76] Few studies have estimated the impact of diet-gene interaction on the effects of fatty acids consumption on OPG/RANKL/RANK system in CVD. *N*-3 PUFAs could be effective in prevention of the metabolic syndrome or to the antiarrhythmic effect due to direct effects on different genes including TNFRSF11B.[77] *N*-3 PUFAs suppressed vascular calcification and Tnfsf11 (RANKL) expression in animal model of abdominal aortic aneurysm.[78] Fonolla-Joya and colleagues revealed that administration of *n*-3 PUFAs led to decreased RANKL serum levels in postmenopausal women with moderate cardiovascular risk.[79] Naranjo et al showed that in comparison with dietary MUFAs (from olive oil) prevented atherosclerosis by getting involved in vascular calcification and the use of RANKL/RANK/OPG system in the setting of metabolic syndrome.[80]

6 | CONCLUSIONS

Current evidence shows that the therapeutic effects of fatty acids in CVD may have the beneficial effects on gene expression related to metabolic profiles. OPG/RANKL/RANK system has been introduced as a critical system in CVD. Few studies have investigated the impact of diet-gene interaction for effects of fatty acids consumption on OPG/RANKL/RANK system in CVD. Furthermore, extensive studies including clinical trials and cohort study are needed to evaluate the diet-gene interaction for effects of fatty acids consumption on OPG/RANKL/RANK system in CVD.

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How to cite this article: Tamtaji OR, Borzabadi S, Ghayour-Mobarhan M, Ferns G, Asemi Z. The effects of fatty acids consumption on OPG/RANKL/RANK system in cardiovascular diseases: Current status and future perspectives for the impact of diet-gene interaction. *J Cell Biochem*. 2018;1-8. https://doi.org/10.1002/jcb.27672