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Anti-Atherogenic Diets: Observations from Mouse Models

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Abstract

In this article we have summarized our observations on anti-atherogenic properties of a number of functional foods and dietary agents in apolipoprotein E-knockout and low-density lipoprotein receptor-knockout mouse models. Among various diets and dietary agents, our data show strong anti-atherogenic properties for plant sterols, wild rice, germinated brown rice, corn fractions and kgengwe seeds in these animal models. However, fish oil, wheat bran, corn bran, octacosanol and flaxseeds did not show significant anti-atherogenic activities under our experimental conditions in these mouse models. Anti-atherogenic properties of test diets may be mediated through beneficial alterations in lipid metabolism, antioxidant system and inflammatory pathways.

Keywords: Apo E-KO Mice; Atherosclerosis; Corn Bran; Fish Oil; LDL-r-KO Mice; Plant Sterols; Wheat Bran; Wild Rice

Introduction

Cardiovascular disease (CVD) is a chronic metabolic disorder with a significant impact on quality of life along with substantial social and economic burdens. Atherosclerosis is a form of vascular pathology characterized by accumulation of lipids and other substances in sub-endothelial space, leading to narrowing the arterial lumen. Among several non-modifiable risk factors for atherosclerosis, elevated levels of low-density lipoprotein cholesterol have been well established **[1]**. Along with this established risk factor, dietary habits and lifestyle play a crucial role in overall health and disease status **[2]**.

Inadequate levels of physical activity, high intakes of saturated and/or trans-fat, high intakes of simple sugar and the state of obesity or overweight are usually associated with higher concentrations of low-density lipoprotein (LDL) cholesterol **[3-5]**. On the other hand, regular consumption of adequate amounts of dietary fiber, appropriate levels of physical activity, and consumption of certain dietary agents such as plant sterols are usually associated with reductions in LDL cholesterol levels **[6-8]**. In this regard, several dietary and lifestyle strategies have been recommended to reduce atherosclerosis risks through beneficial modifications in lipoprotein metabolism, including reducing LDL cholesterol levels.

Diets rich in dietary fiber and antioxidant agents have been recommended to general population to reduce the overall risk of chronic diseases, including coronary artery disease, diabetes and cancer **[9-11]**. Many clinical studies have reported such benefits. For example, the Mediterranean diet is probably one of the original diets with known cardiovascular benefits **[12, 13]**. This diet primarily consists of fruits and vegetable plus whole grain products and oils rich in monounsaturated fatty acid oleic acid. Another type of diet developed for beneficial effects on cardiovascular system is the population and patient diets developed by the American Heart Association **[14]**. DASH (Dietary Approaches to Stop Hypertension) diet has been also recommended for its benefits towards cardiovascular system **[15]**. A newer diet which was developed and tested for such benefits is Portfolio Eating Plan **[16]**. Cholesterol-lowering effect is the common feature of all of these diets. However, the current clinical literature provides limited evidence on ability of these diets to prevent atherosclerosis. On the other hand, many experimental studies have provided solid evidence on the ability of a number of dietary agents with actual anti-atherogenic properties. In this article, we have summarized our own observations on the prevention of atherogenesis by a number of diets or dietary agents in a couple of commonly-used mouse models.

Materials and Methods

We have used publications from our laboratory in which we have reported presence or absence of anti-atherogenic properties of various diets and/or dietary agents; these reports have been published between 1997 and 2019. All of these studies have been indexed in PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/), and can be located by searching key words such as "Moghadasian MH, mice, atherogenesis, anti-atherogenic, phytosterols, plant sterols, wild rice, corn fraction, fish oil, and flaxseeds" alone and/or in combination.

Reference	Mouse model	Diet/dietary agent	Effect on atherosclerotic lesion size
Moghadasian et al. (1997)	Male Apo E-KO mice	2% (w/w) phytosterols	50% reduction
Moghadasian et al. (1999)	Male Apo E-KO mice	2% (w/w) phytosterols	55% reduction
Zhao et al (2017)	Male Apo E-Ko mice	5% (w/w) corn Aleuron	34% reduction
Masisi et.al (2017)	Male LDL-r-KO mice	5% (w/w) corn Endosperm	34% reduction
Masisi et.al (2017)	Male LDL-r-KO mice	5% (w/w) corn Germ	56% reduction
Moghadasian et al. (2016)	Male LDL-r-KO mice	2% (w/w) phytosterols	83% reductions
Moghadasian et al. (2016)	Male LDL-r-KO mice	60% (w/w) ground wild rice	77% reduction
Moghadasian et al. (2016)	Male LDL-r-KO mice	Combination of 2% (w/w) phytosterol and 60% (w/w) ground wild rice	87% reduction
Surendiran et al. (2013)	Male LDL-r-KO mice	60% (w/w) ground wild rice	71% reduction
Surendiran et al. (2013)	Female LDL-r-KO mice	60% (w/w) ground wild rice	61% reduction
Zhao R et al. (2018)	Male LDL-r-KO mice	60% (w/w) germinated brown rice	35% reduction

Table 1: Summary of anti-atherogenic effects of diets and dietary agents in mouse models.

Results

Studies in Apolipoprotein E-Knockout (apo E-KO) Mice

Apo E-KO mice were first created in 1992 to study lipoprotein metabolism and atherogenesis. These animals develop simultaneous hypercholesterolemia and advanced atherosclerotic lesions over a relatively short period of time. Several studies from our laboratory showed strong cholesterol-lowering and anti-atherogenic activities of plant sterols at 2% (w/w) in these animals **[17, 18]**. This effect of plant sterols was independent of present or absence of dietary cholesterol. Overall, we provided convincing evidence that under our experimental conditions dietary intakes of 2% (w/w) plant sterols consistently result in approximately 50% reductions in atherosclerotic lesion size in male apo E-KO mice over a period of as short as 18 weeks **[17, 18]**. While plant sterols prevented the progression of atherosclerosis in these animals, plant sterols did not result in regression of atherosclerotic lesions **[19]**. Plant sterols also showed efficacy when they were used with other dietary or pharmaceutical agents. For example, we observed that plant sterols could prevent cyclosporine-induced dyslipidemia in apo E-KO mice **[20]**. Plant sterols also showed efficacy when used in combination with wild rice in low-density lipoprotein receptor-knockout (LDL-r-KO) mice **[21]**. We have also tested the anti-atherogenic properties of Hard Red Spring wheat bran at 3.3% (w/w) or Yello Dent corn bran at 1.7% (w/w) in apo E-KO mice **[22]**. In this study, wheat and corn bran treatments resulted in a non-statistically significant reduction of 12% and 7%, respectively. It was interesting to observe that fish oil at 1% (w/w) did not impact atherogenesis in apo E-KO mice **[23]**. Similarly, dietary octacosanols failed to prevent atherogenesis in apo E-KO mice **[24]**.

Studies in LDL-r-KO Mice

Addition of 2% (w/w) plant sterols to an atherogenic diet resulted in approximately 83% reductions in atherosclerotic lesion size in male LDL-r-KO mice **[21]**. In the same study, we observed that the same atherogenic diet containing 60% (w/w) ground wild rice could result in a 77% reduction in atherosclerotic lesion size, while the combination of plant sterols (2% w/w) and ground wild rice (60% w/w) resulted in an 87% reduction in atherosclerotic lesion size **[21]**. In another study, regular consumption of wild rice at 60% (w/w) of the diet resulted in a 71%, and 61% reduction in male and female, respectively, LDL-r-KO mice **[25]**. Germinated brown rice at 60% (w/w) resulted in a 35% reduction in atherosclerotic lesion size in LDL-r-KO mice **[26]**. Similarly, various corn fractions showed anti-atherogenic properties in this animal model. For example, we observed reductions of 34%, 56% and 34% in atherosclerotic lesion size, when LDL-r-KO mice were fed with corn fractions aleuron, endosperm and germ, respectively **[27]**. Kgengwe seed powder at 10% (w/w) also significantly prevented atherogenesis in this animal model **[28]**. On the other hand, neither high doses (10%, w/w) nor moderate doses (5%, w/w) of flaxseeds resulted in prevention of atherogenesis in LDL-r-KO mice **[29]**.

Comments and Conclusions

Atherosclerosis and related abnormalities continue to negatively impact quality of life with enormous burden on health industry in both developed and developing countries. According to a recent report from WHO, 17.9 million people die every year due to CVD; 85% of these deaths are from heart attacks and strokes **[30]**. This overall mortality rate accounts for approximately 31% of the deaths internationally **[30]**. It is reported that overall costs associated with CVD in the United States exceeds $351 billion **[31]**. Therefore, many pharmaceutical, dietary, and surgical/medical protocols have been developed and implemented to reduce the overall CVD mortality and morbidity.

Among many pharmaceutical agents, statins seem to be very efficacious in reducing serum LDL cholesterol levels, and thereby, reduce the overall risk for coronary events, including fatal cardiac events **[32]**. However, these and other drugs may have serious side effects **[33]**. Furthermore, many patients prefer lifestyle and dietary modifications over the drug and/or surgical treatment protocols. It was interesting that a recent study presented at the 2019 American Heart Association provided evidence for effectiveness of dietary and lifestyle modifications in patients with stable angina **[34]**. Such subjects followed professional directions for diet and lifestyle plus took prescribed drugs, but did not undergo stent procedures. Such strong evidence suggests that alternative treatment protocols can be quite effective, if they are used under appropriate conditions. In this short review, we have summarized our own experimental data to support the notion that diets and dietary agents may prevent atherosclerosis through various mechanisms. Although, majority of studies have focused on reductions in serum LDL-cholesterol levels, we have observed that anti-atherogenic diets or dietary agents do not necessary reduce LDL-cholesterol levels in experimental animals.

Apo E-KO and LDL-r-KO mice are two robust mouse models of human dyslipidemia and atherosclerosis **[35, 36]**. While, the apo E-KO mice develop a high degree of hypercholesterolemia mainly in the form of beta-VLDL, the LDL-r-KO mice are a true model of familial hypercholesterolemia. Many studies in our laboratory and others have extensively used these mouse models to understand the mechanisms of atherogenesis and various methods of the prevention of the disease. In particular, we have produced solid evidence that plant sterols can prevent atherogenesis in both animal models. Plant sterols have been recommended for decreasing serum total and LDL-cholesterol levels in moderately hypercholesterolemic subjects. However, thus far, there has been no report on the effectiveness of such dietary agents in the prevention of atherosclerosis. Of other dietary agents with strong anti-atherogenic effects wild rice can be named. We consistently observed that addition of ground wild rice to the feed of LDL-r-KO mice was associated with the prevention of atherosclerosis in both male and female mice. Wild rice has been recognized as a grain product **[37]**, although it does not belong to grains. We have recently presented data that anti-atherogenic properties of wild rice in this animal model may be mediated through alterations, in gut microbiome, inflammatory pathways and metabolomics **[38]**.

In conclusion, there exists strong experimental evidence that certain diets and dietary agents prevent atherogenesis in animal models. Such observations further support benefits of appropriate diets and lifestyle in the prevention of a number of chronic diseases including cardiovascular diseases. One may suggest that such changes in dietary habits and lifestyle might have contributed to, at least in part, in reductions of coronary artery disease death rates. Additional clinical studies are needed to document actual anti-atherogenic effects of diets and dietary agents.

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